

**M A S A R Y K O V A
U N I V E R Z I T A**

LÉKAŘSKÁ FAKULTA

**Inovace v anesteziologické péči u spondylochirurgických
výkonů pediatrických pacientů: vliv na perioperační
průběh a bezpečnost**

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Klinika anesteziologie, resuscitace a intenzivní medicíny

Habilitační práce dle § 72 odst. 3 písm. b) zákona o vysokých školách

Brno 2026

**M U N I
M E D**

**Klinika anesteziologie,
resuscitace a intenzivní
medicíny**

**Ústav
simulační
medicíny**

Poděkování

Touto cestou bych chtěl poděkovat zejména své rodině, na prvním místě své ženě Zuzce a synovi Honzíkově, za trpělivost a podporu, které mi poskytli při tvorbě této habilitační práce. Poděkování patří i mým rodičům za podporu a směřování v mém životě. Upřímné poděkování patří mým nadřízeným na klinických i teoretických pracovištích, tedy prof. Romanu Gálovi a prof. Petru Štouračovi. Zvláštní díky míří k mým školitelům v průběhu Ph.D. studia, kteří významně ovlivnili moji vědecko-výzkumnou dráhu, a to prof. Martinu Repkovi a doc. Martině Kosinové. Rád bych poděkoval také svým kolegům a spolupracovníkům. Dovolím si vyzdvihnout spondylochirurgický tým v čele s dr. Milanem Filipovičem. I díky jejich pomoci a podpoře mohla vzniknout tato práce. Dále bych chtěl poděkovat, nejen za spolupráci na našich projektech, dr. Tereze Prokopové, ale i za ukázkou zapáleného přístupu k práci i přátelství. V neposlední řadě směřuji své uznání a díky kamarádům, učitelům a trenérům z oblasti školství a sportu, se kterými mám tu čest nadále zůstat v kontaktu. Byli mi a stále jsou inspirací v mnoha životních ohledech, včetně disciplinovanosti či systematického přístupu k různým životním projektům.

Motto

„Lehce dosažené věci nemají žádnou cenu.“

Libor Uher a tým Beskydské sedmičky

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1 Úvod

Předkládaná habilitační práce dle § 72 odst. 3 písm. b) zákona o vysokých školách je souborem uveřejněných vědeckých prací doplněný komentářem. Tato práce se věnuje problematice anesteziologické péče při operacích skoliotických deformit u dětských pacientů. Konkrétně moderních anesteziologických postupů, které ovlivňují perioperační bezpečnost. Předkládaná práce volně navazuje na moji disertační práci [1]. S ohledem na celkový počet publikací je práce rozdělena na tři tematické okruhy, které propojují téma habilitační práce.

Skoliotické deformity páteře představují závažný medicínský problém. V rámci postižení páteře totiž dochází nejen k postižení osového skeletu a přilehlého svalového aparátu, ale často také k ovlivnění funkce kardiovaskulárního, respiračního či gastrointestinálního systému. Alterace těchto orgánových systémů mohou spolu s nepříznivým kosmetickým efektem či bolestí vést k významnému psychickému postižení jedince a celkovému zhoršení kvality života [1-5].

Klinika ortopedie a spondylochirurgie Fakultní nemocnice (FN) Brno a Lékařské fakulty (LF) Masarykovy univerzity představuje tradiční pracoviště, které se věnuje komplexní péči o pacienty se skoliotickými deformitami od roku 1978. FN Brno tak díky komplexnímu interdisciplinárnímu týmu představuje v rámci České republiky největší centrum věnující se problematice skoliotických deformit.

Cílem této habilitační práce je popsat a na základě některých publikací demonstrovat význam interdisciplinární spolupráce v péči o pacienty podstupující korekci skoliotické deformity v celkové anestezii.

1.1 Definice a epidemiologie

Skoliotickou deformitu můžeme definovat jako nefyziologickou deviaci páteře. Zpravidla se jedná o trojdimenzionální zakřivení páteře, které kombinuje vychýlení ve frontální rovině o více než 10°, dále v rovině sagitální (hypo- či hyperkyfóza, hypo- či hyperlordóza) spolu s rotací obratlů, tedy i zakřivení v transversální rovině [2-4].

Z hlediska epidemiologie jde o vůbec nejčastější deformitu páteře u dětských pacientů. Celkově postihuje okolo 2–3 % populace. Dle dostupných dat je popisována rovnoměrná incidence mezi dívkami a chlapci, nicméně v průběhu kostního růstu dochází u dívek k signifikantní progresi skolióz, které jsou v případě idiopatické skoliózy postiženy až osmkrát častěji [3]. Tedy dívky jsou daleko častěji indikovány k operační léčbě. V dětském věku jsou skoliózy relativně flexibilní a u celé řady pacientů mohou být zcela bezpříznakové, lze tak předpokládat vyšší reálnou incidenci v populaci. Postupná progresie zakřivení páteře spolu s jejím „zatuhnutím“ v nefyziologickém postavení vede k významnému postižení jedinců včetně rozvoje bolestí zad, snížení kvality života či invalidizaci. Okolo 10 % postižených jedinců vyžaduje konzervativní léčbu a přibližně 0,1–0,3 % diagnostikovaných případů vyžaduje léčbu operační [2-5].

1.2 Historie skolióz

Skolióza představuje pravděpodobně jedno z nejstarších poznaných onemocnění, především z důvodu patrné změny fyzického vzhledu. Již jeskynní malby z doby kamenné naznačují, že lidé trpěli skoliózou a využívali primitivní formy léčby. První definici, včetně termínu pro zakřivení páteře v sagitální rovině, „ithiscolios“, popsal Hippokrates. Na jeho práci, věnující se definici a léčbě, později navazuje Galén. V 7. století se řecký lékař Pavel z Aeginy pokusil o korekci deformity pomocí korekčních dlah. V roce 1582 Ambroise Paré instruoval zbrojíře k vývoji železných korzetů, které byly specificky tvarovány podle zakřivení páteře postižených. Na konci 19. století byly vyvinuty specifické korzety ke stabilizaci deformit. První operace skoliózy byla provedena roku 1914 v New Yorku. Později, v roce 1946, byla vyvinuta ortéza Milwaukee, která byla po desetiletí jedním ze základních pilířů korzetoterapie, ať už samostatně v rámci konzervativní léčby, tak v kombinaci s chirurgickými postupy. Tyto postupy vycházely ze základní Harringtonovy techniky, která využívala distrakční a kompresní systémy ke korekci skolióz spolu s vložením autogenní kostní tkáně k dosažení fúze páteře. Modernější techniky používají transpedikulární segmentální instrumentaci k provedení preciznější trojrozměrné korekce skoliózy [6].

1.3 Etiologie a klasifikace

Skoliotické deformity rozdělujeme v rámci etiologie na 3 majoritní typy, a to idiopatickou, kongenitální a neuromuskulární skoliózu. Minoritní typy jsou pak zastoupeny skoliózami, které se vyvíjejí v souvislosti s nádorovým postižením páteře, úrazy páteře či skoliózami asociovanými s nějakým vzácným syndromem [3-5].

Nejčastějším typem skoliózy je idiopatická skolióza. Tento typ deformity představuje více než 80 % všech skolióz dětského věku, přičemž jak vyplývá z názvu, příčina skolióz doposud nebyla jednoznačně stanovena. Velmi pravděpodobně se na jejím rozvoji podílí více faktorů, včetně genetické predispozice [3, 5]. Idiopatická skolióza se pak rozděluje na další podtypy podle věku rozvoje deformity. Infantilní idiopatická skolióza bývá diagnostikována do tří let věku dítěte. Mezi třetím a desátým rokem života dítěte hovoříme o juvenilní idiopatické skolióze. Idiopatická skolióza diagnostikovaná po desátém roce života se označuje jako adolescentní [3-6].

Kongenitální skoliózy jsou nejčastější vrozenou vadou páteře, která představuje asi 10 % všech skoliotických deformit, nicméně i toto číslo bude pravděpodobně vyšší, protože kongenitální skolióza může být i zcela asymptomatická [7]. Tyto vývojové poruchy páteře mohou být spojeny s vývojovými poruchami dalších orgánových systémů (srdce, ledviny...). Kongenitální skoliózy jsou asociovány s abnormálním vývojem obratlů nebo poruchami segmentace páteře. V literatuře bývají popisovány nálezy inkompletních obratlů (hemiverterba, motýlovité obratle...) či nesegmentované lišty, v jejichž úseku je normální růst páteře narušen [3, 7, 8].

Skoliotické deformity, které jsou spojeny s různými nervovými či svalovými nemocemi, jsou označovány jako neuromuskulární skoliózy [3]. Jejich výskyt je v literatuře uváděn u méně než 10 % případů skoliotických deviací, přičemž incidence u jednotlivých neuromuskulárních onemocnění bývá variabilní. V některých případech je však výskyt skoliózy značný, například u téměř 90 % pacientů s Duchennovou svalovou dystrofií bývá popisována skolióza [3, 9]. Skoliotické postižení páteře u neuromuskulárních onemocnění představuje daleko komplexnější problém, který se liší od „prosté“ idiopatické skoliózy. V tomto případě totiž dochází k signifikantní progresi skoliotické křivky, která se dále zhoršuje i po skončení kostního růstu. Takto progredující zakřivení páteře ovlivňuje nejen pohybový aparát, ale mohou být těžce postiženy i respirační či kardiovaskulární funkce, které u jiných typů skolióz nebývají tak výrazně alterovány. Typicky bývá popisována restriktivní plicní porucha, která sekundárně vede k rozvoji plicní hypertenze a cor pulmonale chronicum. Významné může být i narušení sedu či pohybového stereotypu, které spolu s bolestmi zad komplikuje běžné denní činnosti či ošetrovatelskou praxi. Z tohoto pohledu představují pacienti s neuromuskulárními skoliózami největší výzvu pro interdisciplinární tým, protože konzervativní terapeutické postupy obvykle zpomalují progresi křivky, nicméně u většiny pacientů dochází k dalšímu zhoršení nálezu. Stejně tak chirurgické techniky jsou i přes značný pokrok nadále spojeny s vysokou mírou komplikací [3, 9, 10].

Minoritní typy jsou vzácnější skoliózy, které se rozvíjejí sekundárně po úraze nebo v souvislosti s nádorovým postižením páteře. Patří sem i tzv. syndromové skoliózy, spojené s některými syndromy, které nejsou primárně neuromuskulární, například v rámci neurofibromatózy, osteogenesis imperfecta či Marfanova syndromu [11].

2 Léčebné postupy

Jak již bylo uvedeno dříve, péče o pacienty trpící skoliózou by měla zahrnovat interdisciplinární tým. Ten je zpravidla tvořen pediatri, ortopedy, neurology, radiology, psychoterapeuty, fyzioterapeuty či protetiky. V dalších fázích mohou být součástí multidisciplinární péče také anesteziologické týmy, neurofyziologové, nutriční specialisti či farmaceuti, vždy individuálně dle potřeb konkrétních pacientů [3, 12, 13].

Samotná volba terapeutického postupu závisí na více faktorech. Ošetřující tým se rozhoduje dle věku pacienta, velikosti či etiologie skoliotické deformity, respektive dle předpokladu dalšího zhoršení skoliotické deformity páteře. Předpoklad největší progresse deformity páteře je dán obdobím růstového spurtu, tedy obdobím nejrychlejšího růstu pacienta. Naopak v období kostní zralosti, tedy po ukončení kostního růstu, již nepředpokládáme významnou progresi křivky, tento trend se pohybuje okolo 1 až 2 stupňů ročně. Toto pravidlo však platí pro idiopatické skoliózy a u dalších typů deformit se jím nelze absolutně řídit [3, 15].

Ačkoli je přístup ke konzervativní, respektive operační léčbě vždy individuální a záleží na více hodnotících faktorech, existuje všeobecně uznávané pravidlo pro stanovení terapeutického přístupu. Toto pravidlo je dáno určením tíže deformity podle tzv. Cobbova úhlu a stanovuje –

- dispenzarizaci pacientů spolu s fyzioterapií u křivek do 20 stupňů,
- fyzioterapii a korzetoterapii v případě deformit v rozsahu od 20 do 40 stupňů,
- operační terapii u progredujících deformit a deformit nad 40 stupňů [3, 14, 15].

Jak vyplývá z výše uvedeného, jedním z prvních kroků je stanovení Cobbova úhlu [3].

2.1 Cobbův úhel

Jedním z nástrojů, pomocí kterého se určuje tíže deformity, respektive se posuzuje dynamika křivky v čase, je Cobbův úhel. Tato metoda byla poprvé použita v roce 1948, přičemž od roku 1966 je měření Cobbova úhlu doporučeno společností Scoliosis Research Society (SRS) jako standardní metoda pro kvantitativní analýzu křivky [16]. Stanovení Cobbova úhlu je oproti jiným metodám hodnocení preferováno z důvodu univerzální aplikace a interpretace, včetně jeho užití u nejtěžších křivek [3, 16].

Tento úhel je definován jako doplňkový úhel, který mezi sebou svírají dvě kolmice na roviny procházející horní krycí plochou horního koncového obratle, respektive dolní krycí plochou dolního koncového obratle [3]. Schéma stanovení ukazuje obrázek 1.

Ačkoli je tato metoda preferována, má své limitace, se kterými musí počítat nejen ortopedický tým. Změna Cobbova úhlu může být způsobena odlišným postavením pacienta při skiagrafii. Stejně jsou popisovány limitace z důvodu chyb při označování koncových obratlů, respektive rovin krycích ploch [16, 17]. Moderní poloautomatické a automatické počítačové softwary se snaží tyto limitace eliminovat [16].

Obrázek 1

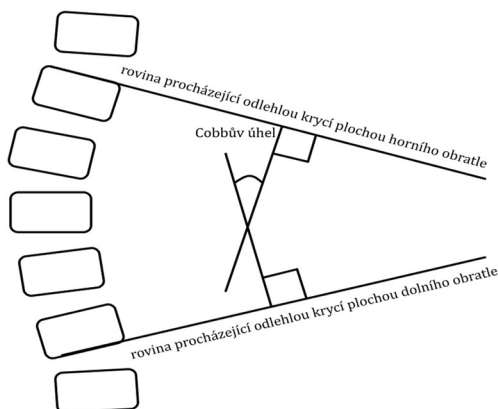


Schéma stanovení Cobbova úhlu:
Nejprve jsou stanoveny horní a dolní koncový obratel, jejichž odlehlými krycími plochami jsou vedeny roviny. Na tyto roviny jsou vyvedeny kolmice, které mezi sebou svírají Cobbův úhel [2].

2.2 Konzervativní léčba

Ze všech diagnostikovaných případů skolióz, tedy 2–3 % populace, vyžaduje konzervativní terapii přibližně 10 % pacientů. Cíle konzervativní terapie vycházejí z ovlivňování morfologických a funkčních aspektů skoliózy [3, 5, 18]. Oba tyto aspekty cílí na zlepšení kvality života a jednotlivé dílčí cíle zahrnují zejména –

- zastavit (případně zmírnit) progresi křivky,
- léčit či působit preventivně na alteraci respiračních funkcí,
- léčit či působit preventivně na bolesti páteře,
- zlepšit držení těla [5, 18].

Jedním z prvních kroků v rámci aktivního přístupu k pacientům se skoliózou je pravidelná dispenzarizace. Intervaly, v rámci kterých jsou pacienti pravidelně klinicky sledováni, jsou individuální a mohou se pohybovat okolo 2 až 3 měsíců u závažnějších případů až po intervaly v horizontu let u méně závažných a „stabilnějších“ případů. V rámci dispenzarizace je individuálně doplňováno skiagrafické vyšetření a důležitou součástí během observací je i dostatečná edukace pacientů a jejich zákonných zástupců o povaze onemocnění a dynamice stavu [3, 5].

Fyzioterapie, respektive rehabilitační péče, je dalším důležitým aspektem konzervativní terapie. V současné době existují specifická cvičení zaměřená na skoliotické deformity, jejichž cílem je ovlivnit svalové asymetrie. Tedy cvičení kombinující protahování zkrácených svalových skupin a posilování ochablých svalů [3, 5]. V závislosti na motivaci pacienta a složitosti cvičících přístupů mohou ambulantní fyzioterapeutická sezení probíhat dvakrát až čtyřikrát týdně a jsou doplňována domácím cvičením. Dále může být

pacientům nabídnuta intenzifikovaná lůžková rehabilitace, která probíhá několik týdnů ve specializovaném zdravotnickém zařízení (rehabilitační ústavy, sanatoria apod.). Tato intenzifikovaná rehabilitace probíhá řádově několik hodin denně. Moderní metody fyzioterapie navíc využívají neurofyziologické modality, které působí nejen na muskuloskeletální systém, ale také na centrální nervový systém [3, 5, 18, 19].

Léčba korzetem, respektive ortézou, představuje další možnost v rámci konzervativní terapie. Jejím cílem je zabránění další progresi deformity páteře, tedy terapie typická pro období kostního spurtu až do dosažení kostní zralosti. Stejně tak slouží korzety k udržení symetrického postavení trupu [3, 5]. V současné době neexistuje standardizovaný léčebný protokol pro korzetoterapii. Jsou užívány různé typy korzetů, individuálně dle zvyklostí pracoviště, etiologie či tíže křivky. Mezi nejznámější typy patří korzety Boston, Charleston, Cheneau, Rosenberger... Podle možností pracoviště jsou dnes vyráběny „hybridní“ korzety, které kombinují výhody jednotlivých výše uvedených typů. Některé práce také popisují možnosti individuálně vyráběných korzetů, designových korzetů pomocí počítačového softwaru a tištěných na 3D tiskárnách. Pro jejich globálnější využití je však třeba více dat, která prokazují jejich benefit [3, 5, 20-22]. Stejně jako jiné přístupy konzervativní terapie vyžaduje nošení korzetů spolupráci a motivaci pacienta. Korzety totiž mohou být nošeny v noci v řádu cca 8 až 12 hodin. Jedním z nejčastěji používaných typů jsou noční polohovací korzety Caen. V indikovaných případech je však nutná korzetoterapie až v režimu 23 hodin denně, kdy pacienti ortézu sundávají prakticky jen na základní hygienu a ošetření kůže [3, 5].

Esenciálním prvkem všech modalit konzervativní terapie jsou edukace, pravidelné hodnocení spolupráce pacientů a případně psychologická podpora. Jejich společným

cílem je motivovat všechny zúčastněné, tedy pacienty i jejich rodiče, aby bylo dosaženo co nejlepších výsledků [5, 23].

2.3 Operační léčba

Operační léčba je všeobecně indikovaná u progredujících, respektive těžších křivek nad 40 stupňů. Dále u deformit, kde je předpoklad dalšího významného zhoršení z důvodu neukončeného kostního růstu. Rámcově se jedná o 0,1–0,3 % diagnostikovaných případů skolióz [3, 5].

Volba operační techniky, včetně operačního přístupu, je v dikci ortopeda, který se rozhoduje zejména podle typu a etiologie křivky a věku pacienta. V naprosté většině případů se volí zadní přístup k páteři. Zadní přístup bývá v rámci raných idiopatických skolióz využíván k instrumentaci pomocí rostoucích tyčí bez kostěné fúze. Stejně tak je indikován u idiopatických adolescentních skolióz či neuromuskulárních skolióz, kde bývá typicky přistupováno k třídimenzionální korekci páteře spolu s instrumentovanou kostěnou fúzí. V případě neuromuskulárních skolióz často spolu se spinopelvickou fixací [3, 24, 25]. V případě kongenitálních skolióz je zadní přístup volen ke krátké prosté kostěné fúzi či k provedení hemivertebrektomie s následnou fúzí [3, 26].

Přední operační přístup je v současnosti volen především u jednodušších hrudních křivek, které bývají ošetřovány moderními instrumentacemi jako tzv. growth-friendly metody. Jedná se o výkony z torakoskopického přístupu bez kostěné fúze. V rámci předního přístupu je typicky využívána selektivní intubace s ventilací jedné plíce, která operačnímu týmu významně zlepšuje operační podmínky. Méně často je přední přístup využíván ke korekci bederních křivek či jako součást kombinovaného zadopředního (transtorakoretroperitoneálního) přístupu při korekci torakolumbálních deformit [3, 24, 27].

3 Anesteziologická a pooperační péče

Chirurgická korekce skoliózy, respektive fúze skoliotické deformity, představuje výzvu nejen pro chirurgický tým, ale také pro anesteziologický tým. Samotný výkon patří mezi invazivní operace s vysokým operačním rizikem, ať už kvůli velkému operačnímu rozsahu, tak kvůli komorbiditám pacientů nebo specifikům anesteziologických postupů souvisejících s intraoperační neurofyzilogickou monitorací (IONM) [1, 28].

Typicky v rámci extenzivního rozsahu dochází během operace k vyšším krevním ztrátám, obtížně hodnotitelné evaporaci tekutin z operační rány či ztrátám tělesné teploty. Komorbidity pacientů mohou být spojeny se základním onemocněním, typicky v případě neuromuskulárních onemocnění vedoucích ke skolióze. Nicméně některé komorbidity, které představují výzvu pro anesteziologický tým, mohou být také důsledkem progresu samotné skoliózy. Pro perioperační péči jsou významné zejména alterace respiračních funkcí, typicky restriktivní plicní porucha, případně z ní vyplývající alterace kardiiovaskulárních funkcí včetně plicní hypertenze či srdečního selhání [28, 29]. Anesteziologický management a specifika související s korekcí skoliózy vyplývají zejména z nutnosti intraoperační monitorace neurologických funkcí, zpravidla IONM. Anesteziologický tým musí ovládat postupy, které minimalizují vliv anestezie na výbavnost a kvalitu IONM, aby bylo dosaženo správné interpretace neurofyziology, respektive operačním týmem při nedostupnosti neurofyzilogů [30, 31].

Na následujících stranách bude anesteziologický management rozdělen do tří základních etap, tedy předanestetického vyšetření a přípravy, anesteziologické péče a pooperační péče [1].

3.1 Předanestetické vyšetření a optimalizace stavu

Předanestetické vyšetření u pacientů před operační korekcí skoliotické deformity vyžaduje komplexní přístup. Cílem je identifikace komorbidit, z nich vyplývajících potenciálních perioperačních rizik, maximální možná optimalizace stavu pacientů, poučení pacientů a osob blízkých s následným získáním informovaného souhlasu. Podkladem předanestetického vyšetření je interní předoperační vyšetření od pediatra včetně klinického vyšetření a základního laboratorního vyšetření, u složitějších případů ne starší než 14 dnů před plánovaným termínem operace [32]. Rozsah vyšetření před zákrokem je přísně individuální, nicméně s ohledem na alteraci více orgánových systémů je vhodné zapojení týmů různých zdravotnických odborností. V závislosti na komorbiditách, klinickém a laboratorním nálezu doplňujeme přípravu o vyšetření kardiologů, pneumologů, neurologů... [32, 33].

Z hlediska vyšetření orgánových systémů, podle přístupu ABCDE, je nutné při vyšetření prvního systému, tedy dýchacích cest (DC), identifikovat pacienty s předpokladem obtížného zajištění DC [1]. Jedná se zejména o pacienty s těžkou deformitou znemožňující adekvátní polohování před úvodem do anestezie, deformitou zasahující do oblasti krční páteře, dále o pacienty s obličejovými abnormalitami či pacienty s předoperačně nasazenou „halo-gravity“ trakcí. U všech těchto patologií musí anesteziologové předpokládat obtížné zajištění DC, které vyžaduje pečlivé plánování, přípravu alternativních pomůcek k zajištění DC nebo využití pokročilejších postupů dle platných doporučení. V rámci tohoto plánování může být využit předoperační rentgen páteře pro získání základních

informací o anatomii DC. Možností je i využití předoperačního ultrazvuku k zobrazení DC [29, 34-36].

V rámci systému „B“ se snažíme získat informace o funkci a rezervách respiračního traktu pacientů, které by mohly být alterovány nejen skoliotickou deformitou, ale také slabostí při základním onemocnění v rámci tzv. syndromových skolióz. Klíčová je identifikace pacientů, u kterých předpokládáme problematické odpojení od umělé plicní ventilace po korekci křivky a změně tlakových poměrů v hrudním koši [37, 38]. Zpravidla se jedná o pacienty, kteří jsou již před operací dependentní na nějaké formě ventilační podpory, nebo pacienty s nedostatečnou expektorací, ale také o pacienty s těžkým restriktivním plicním onemocněním. Podle některých prací bývá tato významná restrikce dána hodnotou forsírované vitální kapacity pod 30 až 40 % náležitých hodnot, u pacientů se svalovou slabostí pak forsírovaná vitální kapacita již pod 50 až 60 % náležitých hodnot [38, 39]. U pacientů před korekcí skoliózy je tak indikováno předoperační vyšetření plicních funkcí. V případě spolupracujících pacientů ideálně spirometrické vyšetření, dle mentálního stavu eventuálně můžeme indikovat polysomnografii s noční kapnografií, analýzu arteriálních krevních plynů či vyšetření maximálních inspiračních/expiračních tlaků [33, 37, 38, 40, 41]. Rizikové pacienti jsou ideálně indikováni k prehabilitaci. Může u nich být zahájen nácvik práce s kašlacím asistentem či neinvazivní ventilací tak, aby byly optimalizovány funkce respiračního traktu a byl usnadněn pooperační weaning [1, 39, 41, 42].

Nemoci kardiovaskulárního systému, systému „C“, mohou být asociovány zejména s těžkou plicní patologií ve smyslu restrikce, kdy dochází sekundárně k rozvoji plicní hypertenze, srdečního selhání a chronického cor pulmonale. Poruchy srdečního rytmu,

kardiomyopatie či vrozené vývojové vady pak bývají popisovány u pacientů s neuromuskulárními nemocemi [38, 43]. Naším cílem je identifikovat rizikové pacienty, u kterých hrozí perioperační dekompenzace jejich chronického kardiovaskulárního onemocnění. Elektrokardiografie (EKG) je rutinně indikována u všech pacientů. Individuálně pak indikujeme kardiologické vyšetření spolu s transtorakální echokardiografií, které nám poskytuje cenné informace pro identifikaci rizikových pacientů a plánování anesteziologické péče včetně stanovení hemodynamických cílů [33, 38, 43].

Vyšetření neurologem je vyžadováno k exaktnímu popisu neurologických funkcí před každou korekcí skoliózy. V indikovaných případech nám může navíc přinést informace o samotném neuromuskulárním onemocnění, včetně patofyziologie, případně informace o potenciálním riziku rozvoje rhabdomyolýzy či maligní hypertermické krize v perioperačním období. Neurologické vyšetření je rovněž nutné k doporučení managementu antiepileptické terapie u pacientů, kteří mají v rámci základního onemocnění epilepsii [38, 44].

V rámci posledního kroku při písmenu „E = everything else“ se zaměřujeme na další konziliární a laboratorní vyšetření nad rámec standardního předoperačního vyšetření, která mohou být zásadní pro plánování anesteziologické či pooperační péče. Patří sem například identifikace rizikových pacientů k realimentaci cestou nutričních specialistů [39, 45]. Součástí multidisciplinárního přístupu může být i psychologická podpora pacientů a jejich blízkých. Strukturované rozhovory by měly nasměrovat očekávání ohledně průběhu výkonu či pobytu na JIP, včetně možných perioperačních komplikací [46].

Důležitou součástí předanestetického vyšetření je důkladné poučení pacienta, v případě dětského pacienta také jeho zákonných zástupců, získání informovaného souhlasu a

předepsání premedikace s ohledem na základní onemocnění, funkční rezervy a komorbiditu pacienta [1, 47].

Jak naznačují některé práce, předoperační optimalizace rizikových pacientů vyžaduje přístup multidisciplinárního týmu, který se snaží identifikovat rizikové faktory u každého pacienta. Maximálně možná kompenzace orgánových dysfunkcí pacientů se skoliotickými deformitami spolu s prehabilitací prokazatelně snižuje incidenci perioperačních komplikací [1, 39].

Na základě těchto dat vznikla ve FN Brno v roce 2025 multioborová komise pro deformity dětské páteře, která se pravidelně setkává u vybraných případů pacientů se skoliotickou deformitou. Multioborový tým tvoří zdravotníci pracovníci z ortopedie, dětské neurologie, pediatrie, anesteziologie a radiologie. Tento tým individuálně hodnotí rizikové pacienty a zvažuje rizika vyplývající z výkonů a komorbidit proti benefitům z úspěšné operace. Na základě rozhodnutí a poučení pacientů, respektive jejich blízkých či zákonných zástupců, jsou pacienti připravováni k operačnímu výkonu prostřednictvím dalších odborností, včetně pneumologů, kardiologů, nutričních specialistů a fyzioterapeutů.

3.2 Anesteziologická péče

Anesteziologický management je zcela zásadní pro bezpečný průběh celé operace, včetně následného pooperačního období. Pro anesteziologický tým může představovat výzvu z mnoha důvodů. Důsledná příprava a plánování anestezie v týmu jsou nezbytné před každým výkonem [28, 38]. Úvod do anestezie se neliší od jiných operací, tedy preferujeme zajištění intravenózního vstupu před samotným úvodem, ideálně v oblasti, kde byla v rámci premedikace aplikována topická anestezie. Po kanylaci periferní žilní kanyly (PŽK) je standardně preferován intravenózní úvod do anestezie kombinací opioidu, hypnotika a nedepolarizujícího svalového relaxans k usnadnění intubačních podmínek. Inhalační anestetika se využívají výjimečně u nespolupracujících agitovaných pacientů bez možnosti zavedení intravenózního vstupu. Součástí úvodu do anestezie je i zajištění DC, typicky endotracheální kanylou, v případě transthorakálního přístupu kanylou s možností selektivní ventilace jedné plíce [28, 36, 38, 48, 49].

Po úvodu je anestezie vedena v naprosté většině případů jako totální intravenózní anestezie (TIVA). Nejčastěji užíváme kombinaci opioidu a propofolu, což představuje zlatý standard při operacích s IONM. Naopak, další dávka svalového relaxans není indikována z důvodu nemožnosti vybavit motorické evokované potenciály. Kombinace propofolu a opioidu může být doplněna o některá koanalgetika, typicky ketamin [30, 31]. Následně probíhá standardní zajištění a monitorace pacienta. Standardní monitoraci tvoří pulzní oxymetrie, EKG, neinvazivní monitorace krevního tlaku. V rámci dalšího zajištění je nutná kanylace druhé PŽK s dostatečným průsvitem, případně dle stavu periferního žilního systému, předpokladu komplikovaného weaningu či nutnosti vazopresorické podpory

kanylujeme pod „real-time“ ultrazvukovou kontrolou centrální žilní katetr (CŽK). U majority spondylochirurgických operačních výkonů je indikováno zavedení arteriálního katetru (AK) ke kontinuální monitoraci krevního tlaku, zejména z důvodu rizika oběhové nestability či významnější krevní ztráty, případně k odběrům v perioperačním období. K monitoraci diurézy a hodnocení tekutinového managementu je při mnohahodinovém výkonu doporučeno zavedení permanentního močového katetru (PMK). Součástí zajištění a monitorace pacienta je i zavedení teploměru [28, 29, 38]. V rámci rozšířené monitorace u spondylochirurgických výkonů vedených TIVA je doporučována také monitorace hloubky anestezie pomocí elektroencefalografie (EEG). Cílem monitorace EEG křivky je vyvarování se příliš hluboké anestezii, ale také minimalizace tzv. bdělé fáze v průběhu operačního výkonu. Česká společnost anesteziologie, resuscitace a intenzivní medicíny (ČSARIM) uvádí monitoraci hloubky anestezie u výkonů v TIVA, zvláště v kombinaci se svalovou relaxací, jako jeden z aspektů bezpečné anestezie [50-52].

Jak již bylo uvedeno výše, propofol a opioid představují zlatý standard pro vedení anestezie během operace s IONM. Propofol je intravenózní anestetikum, které bývá v rámci spondylochirurgie užíváno jak k úvodu, tak k vedení celkové anestezie. Jedná se o agonistu receptorů pro gama-aminomáselnou kyselinu (GABA), čímž dochází ke zvýšení propustnosti pro chloridové ionty, následné hyperpolarizaci neuronů a útlumu centrálního nervového systému (CNS) [38, 53]. Pro výkony ve spondylochirurgii je výhodný nejen z důvodu nejmenšího vlivu na IONM, ale i proto, že TIVA vedená s propofolem oproti jiným způsobům anestezie snižuje krevní ztráty, čímž zlepšuje operační podmínky [54]. Farmakokinetický profil propofolu navíc zkracuje čas do probuzení a extubace, respektive zrychluje probuzení v případě tzv. „wake-up“ testu, tedy perioperačního probuzení

pacienta s cílem posouzení motoriky po operaci páteře. V neposlední řadě snižuje míru pooperační nevolnosti a zvracení (PONV) [54-56].

Druhou nezbytnou komponentou TIVA je intravenózně podávaný opioid. Jednotlivé opioidy se liší podle působení na opioidní receptory, analgetického účinku, ale i délky působení [57]. V současné době je pro korekci skolióz dominantně využíván remifentanil, který lze aplikovat jak pro úvod, tak i pro vedení celkové anestezie. Patří mezi zástupce agonistů μ -opioidních receptorů s ultrakrátkým účinkem. Jeho účinnost je srovnatelná s fentanilem a je asi 100 až 200krát silnější než morfin. Jeho nespornou výhodou, nejen v oblasti spondylochirurgie, je přítomnost esterové vazby, která podléhá hydrolýze nescifickými tkáňovými a plazmatickými esterázami. Díky tomu není farmakokinetika remifentanilu závislá na funkci jater ani ledvin. Tedy bez ohledu na délku infuze a dávkovací schéma nedochází k jeho kumulaci a jeho kontext senzitivní poločas je udáván v délce 3 minut [38, 58-60]. Tím je usnadněno rychlé probouzení pacientů po mnohahodinovém operačním výkonu i v rámci nutnosti provedení wake-up testu. Remifentanil, stejně jako ostatní opioidy, jen minimálně ovlivňuje IONM [61-63].

Po iniciálním zajištění pacientů a nastavení TIVA je nutné pacienta uvést do polohy podle operačního přístupu. Naprostá většina výkonů se provádí v pronační poloze z důvodu zadního přístupu operačního týmu k páteři [24, 25, 28]. Pronační poloha může být spojena s mnoha komplikacemi včetně extrakce zavedených vstupů, proto je třeba jí věnovat adekvátní pozornost, zvláště v případě mnohahodinového výkonu. Pacienti v pronaci jsou položeni na tzv. čtyřbodové lůžko, které uvolňuje tlak na dutinu břišní a hrudní. Tím dochází k redukci tlaků v obou dutinách, což je důležité pro zlepšení srdečního návratu, snížení krevních ztrát při snížení tlaku v epidurálních žilách a zlepšení ventilačních

parametrů. Tedy správná poloha je důležitá pro oběhovou i ventilační kompenzaci pacientů. Neutrální poloha krční páteře, mírný náklon do „antitrendelenburgovy“ polohy spolu s kontrolou tlaku na oči jsou nezbytné pro snížení rizika poškození zraku a slepoty. Specifické polohovací pomůcky je nutné aplikovat pod predilekční místa, zejména oblasti kolen, nártů, loktů, čela... Důležitou součástí anesteziologické péče v souvislosti s pronací je pravidelná kontrola pacienta, umístění na čtyřbodovém lůžku a vypodložení predilekčních míst, protože v souvislosti s manipulací operačního týmu je zvýšené riziko iatrogenního poškození pacientů [1, 28, 38, 64-66].

V průběhu anestezie jsou vitální funkce udržovány individuálně, vždy s ohledem na komorbiditu a věkovou kategorii pacienta. Nicméně pro základní strategii při nastavování protektivních parametrů umělé plicní ventilace a při udržování parametrů kardiovaskulárních funkcí je vhodné vycházet z platných doporučení European Pediatric Advanced Life Support (EPALS) [28, 38, 67]. Obecně můžeme říct, že cílem by mělo být dosažení normoxémie, normokapie a udržování středního arteriálního tlaku minimálně na desátém percentilu pro příslušnou věkovou kategorii dle doporučení EPALS [28, 67]. Naopak koncept permissivní hypotenze u skoliotických výkonů je se zlepšující operační technikou a menšími krevními ztrátami opuštěn. Udržování středního arteriálního tlaku pod desátým percentilem příslušné věkové kategorie se jeví jako velmi rizikové pro potenciální ischemii míchy, tedy pod touto hodnotou bychom se dlouhodobě v průběhu výkonu neměli pohybovat [68-70].

Perioperační období je spojeno s vyššími krevními ztrátami a asociovanou koagulopatií, především v průběhu operačního výkonu. Krevní ztráty souvisejí s velikostí operační rány, počtem operovaných segmentů, délkou operačního výkonu, ale i typem a tíží

deformity. Neuromuskulární skoliózy jsou prokazatelně spojeny s vyššími krevními ztrátami nejen z výše uvedených důvodů, ale i z důvodu řidší kostní tkáně [29, 38, 71]. Strategie k redukci krevních ztrát zahrnují předoperační korekci anémie po identifikaci její příčiny, odběr autologní krevní transfúze a, dle možností, realimentaci pacientů s úpravou malnutrice. Intraoperační strategie zahrnují prevenci a korekci hypotermie, udržování euvolémie, perioperační rekuperaci krve s použitím „Cell-saveru“, časné využití viskoelastických metod s cílenou korekcí koagulopatie či intravenózní aplikaci antifibrinolytik. Současné práce podporují podávání kyseliny tranexamové, nicméně neexistují jednoznačná data pro iniciační a následnou udržovací dávku [28, 29, 38, 71, 72]. Dávkování kyseliny tranexamové se podle dostupných zdrojů liší, ale úvodní bolus se pohybuje v rozmezí 10–30 mg/kg intravenózně, případně doplněný o pokračující kontinuální infuzi v rozmezí 1–5 mg/kg/h [71, 73-76]. Transfúzní trigger bývá pro většinu pacientů uváděn v rozmezí hemoglobinu 70–80 g/l, pokud není nutné individuálně posouvat trigger k vyšším hodnotám u pacientů s komorbiditami [29, 77].

Další esenciální složkou anesteziologického managementu je péče o tělesnou teplotu pacientů. Operační rána představuje významný zdroj úniku tepla. Rizikovými faktory pro rozvoj hypotermie jsou nízká tělesná hmotnost, diagnóza neuromuskulární skoliózy nebo větší skoliotická křivka [78]. Hypotermie pacientů je asociována s prodlouženým metabolismem léků, vyššími krevními ztrátami, ale i dalšími pooperačními komplikacemi. Účinnými postupy vedoucími k prevenci hypotermie jsou „prewarming“, aktivní zahřátí pacienta před úvodem do celkové anestezie, poté aktivní zahřívání pacienta pomocí zahřívacích pomůcek aplikovaných na pacienta, ohřívačky tekutin i vyšší teplota operačního sálu v průběhu operace [78-80].

Vyvedení pacientů z celkové anestezie probíhá v naprosté většině případů na operačním sále po skončení výkonu a nijak zásadně se neliší od weaningu pacientů po jiných operacích. Předpokladem je stabilizace respiračních a kardiovaskulárních funkcí a normotermie pacienta. Jedním z důležitých aspektů časného probuzení pacienta po mnoha-hodinové operaci je prevence hluboké anestezie prostřednictvím monitorace EEG. Stejně tak je vhodné pro TIVA využít systém „Target Controlled Infusion“ (TCI). Jedná se o software pro cílenou řízenou infuzi ke stabilnímu podávání anestezie v operačním období a udržování adekvátní hloubky anestezie, který tak urychluje vyvedení z celkové anestezie [1, 28, 29, 33, 38]. Problematika weaningu rizikových pacientů, pacientů se svalovou slabostí, je zmíněna v kapitole věnující se pooperační péči a anestezii pacientů s neuromuskulárními typy skolióz.

3.3 Pooperační péče

Pooperační péče pacientů po korekci skoliotické deformity je ve většině případů, s ohledem na rozsah, délku i invazivitu operace, směřována na jednotku intenzivní péče (JIP) [81].

Jedním z cílů pooperační péče je bezpečné odpojení rizikových pacientů od umělé plicní ventilace spolu s extubací, časná identifikace rizika respiračního selhání. Aplikace lokálních protokolů pro weaning pacientů využívajících intenzivní dechovou rehabilitaci či neinvazivní ventilaci prokazatelně zkracuje délku pooperační umělé plicní ventilace, četnost reintubace či riziko ventilátorové pneumonie [1, 82-85].

Stabilizace kardiovaskulárních funkcí u nestabilních pacientů je dalším cílem péče, která využívá kombinaci klinického vyšetření, EKG, invazivní monitoraci krevního tlaku, případně pokročilejší monitoraci hemodynamiky včetně echokardiografie. Prostřednictvím těchto modalit by mělo být dosaženo stavu eurolémie a adekvátní titrace vazopresorické podpory, kterou se snažíme dle vývoje stavu časně vysadit [28, 38, 86-88].

V rámci systému „D = disability“ jsou důležitými kroky zhodnocení neurologických funkcí a léčba akutní pooperační bolesti. Korekce skoliózy je výkon, při kterém předpokládáme vysokou intenzitu bolesti, zejména v prvních 48 až 72 hodinách po operaci. Pro management akutní bolesti je klíčový koncept multimodální analgezie, která kombinuje některé fyzikální techniky s farmakologickými. V rámci farmakologických modalit se uplatňuje kombinace neopioidů, opioidní analgezie, koanalgetik (ketamin, dexmedetomidin) a v současnosti stále více techniky regionální analgezie, ať už ve formě intratrácheální aplikace morfinu či blokády erector spinae plane [38, 89-93].

Řešení pooperačních komplikací již bylo částečně zmíněno v předchozím textu a patří sem obtížné odpojování od umělé plicní ventilace, oběhová nestabilita, pooperační anémie či akutní bolest. Vůbec nejčastěji komplikace v pooperačním průběhu představují infekční komplikace, poztrátová anémie a poruchy trávicího traktu. Ošetřující tým by tak měl pravidelně pátrat po známkách infekce, včetně rutinních mikrobiologických odběrů. Zpravidla se jedná o infekce močového systému, zápal plic či rané infekce [1, 38, 94-96]. Z poruch trávicího traktu se nejčastěji můžeme setkat s pooperační nevolností, vomitem či ileózními stavy, typicky v souvislosti se změnami nitrobršních poměrů [97-98].

4 Tematické okruhy habilitační práce

První tematický okruh mé habilitační práce obsahuje soubor prací, které se věnují anesteziologickému managementu pacientů s neuromuskulární skoliózou. Anestezie pacientů s neuromuskulárními skoliózami představuje ještě větší výzvu než u pacientů se skoliózami idiopatickými [1, 3, 9, 10]. Kromě všech dříve uvedených komorbidit a rizikových faktorů spojených se skoliotickou deformitou a operačním výkonem, je u těchto pacientů anesteziologický management komplikován základním onemocněním, tedy neuromuskulární nemocí [9, 10, 38]. Skoliotická zakřivení jsou u pacientů s neuromuskulární skoliózou většího rozsahu, tedy i postižení dalších orgánových systémů, zejména respiračního a kardiovaskulárního, jsou závažnější. Operace jsou tedy daleko invazivnější, zpravidla doprovázeny významnějšími krevními ztrátami [33, 38]. V rámci prvního tematického okruhu byly použity práce zahrnující přehledový článek, tři kazuistiky a dvě mezinárodní doporučení věnující se anesteziologickému managementu pacientů s extrémně vzácnými syndromy.

Druhý tematický okruh obsahuje soubor prací, které se věnují anestezii k operačním výkonům s IONM, konkrétně transkraniálních motorických evokovaných potenciálů (MEP). Cílem IONM je časná identifikace potenciálně reverzibilního poškození CNS, ale i periferního nervového systému (PNS). Časná identifikace takového poškození v průběhu operačního výkonu umožňuje změnit operační postup a tím minimalizovat riziko nevratného poškození neurologických struktur. IONM zahrnuje více modalit, které lze využívat v průběhu výkonů s rizikem iatrogenního neurologického poškození, tedy i v průběhu operací skoliotických deformit. Anestezie může některé z těchto modalit ovlivňovat, proto

je nutné u operací s IONM přizpůsobit anesteziologický management s cílem minimalizovat vliv na výbavnost a kvalitu IONM [30, 31, 99, 100]. Ve druhém tematickém okruhu budou prezentovány jedna původní práce, dopis redakci a přehledový článek.

Třetí tematický okruh se věnuje ovlivňování krevních ztrát v perioperačním období prostřednictvím profylaktické aplikace fibrinogenu. Krevní ztráty v průběhu operace vedou k potřebě podání krevních transfúzí. Podle zdroje je tato potřeba udávána v rozmezí 30–60 % případů [101, 102]. Strategie vedoucí k redukci krevních ztrát byly popsány výše v kapitole Anesteziologický management. Nicméně profylaktické podávání fibrinogenu, jakožto postupu vedoucího ke snížení krvácení u pacientů podstupujících korekci skoliózy, zatím nebylo popsáno [28, 29, 38]. Třetí tematický okruh obsahuje práci prezentující studijní protokol a jednu původní práci.

Předkládané práce představují 10 prvoautorských prací, respektive 1 práci s pozicí korespondenčního autora, které jsou publikovány v recenzovaných časopisech evidovaných v databázi Web of Science (WoS).

5 Práce vzniklé v souvislosti s anestezií pacientů s neuromuskulárními skoliózami

Jak již bylo uvedeno výše, operační výkon i samotná anestezie pacientů s neuromuskulární skoliotickou deformitou mohou představovat podstatně těžší zkoušku pro celý tým pečující o tyto pacienty na sále [1, 33, 38]. Tato forma skoliózy vzniká v souvislosti s progredující svalovou slabostí a ztrátou svalové postury při základním onemocnění, přičemž deformita progreduje i po ukončení kostního růstu [10, 33, 103].

Alterace více orgánových systémů typická pro pacienty s neuromuskulární skoliózou ovlivňuje jejich management, a to od předoperační přípravy přes anestezii až po pooperační péči. Samotná příprava zahrnuje extenzivnější rehabilitaci, včetně nácviku užití neinvazivní ventilace, kašlacího asistenta či konzultace nutričních specialistů. V rámci předanestetického vyšetření je aplikován komplexnější multidisciplinární přístup. Podávání sedativní premedikace je nutné volit přísně individuálně dle orgánových dysfunkcí, zejména z důvodu zvýšené senzitivity vůči sedaci s rizikem hypoventilace či dechové zástavy [10, 21, 33, 38, 39, 46, 104]. Anestezie je zatížena vyšší četností komplikací vyplývajících z neuromuskulárního onemocnění nebo z důsledků skoliózy. Některé syndromy mohou být asociovány s obličejovými deformitami a předpokládaným obtížným zajištěním DC [1, 10, 33, 38]. Anestezie a operační výkon zpravidla trvají déle z důvodu delší a těžší deformity. To spolu s nižší denzitou kostí u pacientů s omezenou hybností signifikantně zvyšuje krevní ztráty [29, 38, 71]. Navíc celá řada neuromuskulárních onemocnění je spojena se zvýšeným rizikem život ohrožujících stavů, maligní hypertermické krize či rhabdomyolýzy [105-108]. Stejně tak pooperační péče je spojena s vyšší mírou infekčních

komplikací, prolongovaným a obtížným weaningem, oběhovou nestabilitou či pooperační anémií s koagulopatií [1, 33, 38, 109].

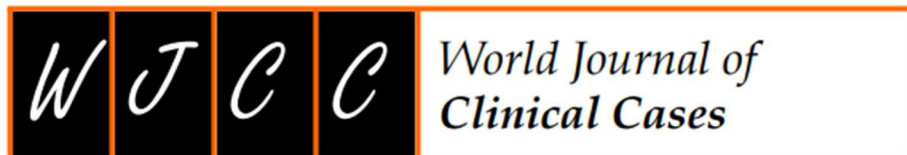
Ačkoliv představuje podíl pacientů operovaných pro neuromuskulární skoliózu méně než 10 %, jedná se o jednu z nejtěžších anestezií vůbec. Kromě relativně běžných neuromuskulárních onemocnění, jako jsou dětská mozková obrna či myastenia gravis, se v naší klinické praxi můžeme setkat i s extrémně vzácnými, doposud blíže nepopsanými syndromy. Na základě těchto poznatků a výzev jsem se rozhodl věnovat problematice anesteziologické péče pacientů podstupujících operační korekci neuromuskulárních skolióz podrobněji. Jako anesteziolog jsem se i díky tomu v roce 2025 stal členem týmu multioborové komise pro deformity dětské páteře FN Brno.

5.1 Anesthesia of a patient with congenital cataract, facial dysmorphism, and neuropathy syndrome for posterior scoliosis: A case report

První kazuistické sdělení pojednává o anestezii 13leté pacientky k operaci skoliotické deformity s extrémně vzácným neuromuskulárním onemocněním. Naše kazuistika byla celosvětově teprve druhou kazuistikou popisující anestezii u tohoto syndromu [1, 110]. Syndrom Congenital cataract, facial dysmorphism, and neuropathy (CCFDN) představuje autozomálně recesivně dědičné onemocnění způsobené mutací genu CTDP1, poprvé popsané v roce 1999 [110, 111].

Dominující příznaky onemocnění zahrnují četné obličejové deformity, mentální retardaci a periferní neuropatii. V naší publikaci jsme se podrobněji věnovali provedené anestezii vedené formou TIVA s bezpečnou kombinací propofolu a remifentanilu. Dále byla akcentována problematika obtížného zajištění DC, omezené spolupráce při opožděném psychomotorickém vývoji či specifika vedení anestezie u syndromů s rizikem rozvoje rhabdomyolýzy. S ohledem na omezená data jsme v sekci diskuze podrobněji rozvedli typické příznaky onemocnění a z nich vyplývající rizika a komplikace pro anesteziologický tým. Tato rizika byla porovnána s údaji zmíněnými v doposud jediné publikované práci a na jejich základě jsme vytvořili doporučení pro optimální vedení anestezie u pacientů s CCFDN syndromem [110, 112].

Popis úspěšné a bezpečné anestezie byl publikován v časopise World Journal of Clinical Cases (IF 1,1; Q4 v kategorii MEDICINE, GENERAL & INTERNAL dle WoS) v roce 2022 [1, 110].



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World J Clin Cases 2022 May 6; 10(13): 4207-4213

DOI: 10.12998/wjcc.v10.i13.4207

ISSN 2307-8960 (online)

CASE REPORT

Anesthesia of a patient with congenital cataract, facial dysmorphism, and neuropathy syndrome for posterior scoliosis: A case report

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Specialty type: Anesthesiology

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Higa K, Japan

Received: September 9, 2021

Peer-review started: September 9, 2021

First decision: December 9, 2021

Revised: December 17, 2021

Accepted: March 16, 2022

Article in press: March 16, 2022

Published online: May 6, 2022



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Abstract

BACKGROUND

Congenital cataract, facial dysmorphism, and neuropathy (CCFDN) syndrome is an extremely rare multiorgan disorder. Characteristics include congenital cataracts, facial deformation, extremity deformities, and demyelinating neuropathy. CCFDN syndrome is associated with increased risk during anesthesia including rhabdomyolysis or epileptic seizures. There is a lack of published information about difficult airways in these patients. Difficult airways during intubation represent one of the most dreaded anesthesia complications: A "can not intubate, can not oxygenate" scenario. Presented herein is the first described successful endotracheal intubation of a CCFDN syndrome patient.

CASE SUMMARY

We report the anesthetic management of a 13-year-old girl with CCFDN syndrome scheduled for posterior neuromuscular scoliosis correction surgery. The patient suffered from extensive progressive neuromuscular scoliosis with a Cobb angle of 83°. Her limitations included neuropathy and a scoliotic curve. This condition negatively impacted her quality of life. This case reflects the potential anesthetic complications for posterior scoliosis correction and CCFDN syndrome. The challenge for our anesthetic team was the limited amount of data about anesthetic management of this condition. In total, one case report without any

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data about endotracheal intubation of patients with this condition was available. Endotracheal intubation in our case was uncomplicated. Another focus of our case was the prevention of possible complications associated with this syndrome, including rhabdomyolysis and seizures. Rhabdomyolysis can be triggered by some types of anesthetic agents like suxamethonium or volatile anesthetics, especially in patients with certain types of myopathies.

CONCLUSION

Adequate understanding of the anesthetic management of CCFDN syndrome can reduce perioperative complications and improve patient outcome after surgery.

Key Words: CCFDN syndrome; Neuromuscular scoliosis; Anesthetic management; Total intravenous anesthesia; Endotracheal intubation; Case report

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Core Tip: We report on a rare case of anesthetic management of a patient with congenital cataract, facial dysmorphism, and neuropathy (CCFDN) syndrome for posterior neuromuscular scoliosis correction. Additionally, this case report is unique as it for the first time presents successful endotracheal intubation in a patient with CCFDN syndrome associated with facial dysmorphism.

Citation: Hudec J, Kosinova M, Prokopova T, Filipovic M, Repko M, Stourac P. Anesthesia of a patient with congenital cataract, facial dysmorphism, and neuropathy syndrome for posterior scoliosis: A case report. *World J Clin Cases* 2022; 10(13): 4207-4213

URL: <https://www.wjgnet.com/2307-8960/full/v10/i13/4207.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v10.i13.4207>

INTRODUCTION

Congenital cataract, facial dysmorphism, and neuropathy (CCFDN) syndrome is an extremely rare multiorgan disorder. It is an autosomal recessive disease with unknown prevalence, described in Roma ethnicity[1]. The diagnosis is based on clinical examination. Typical abnormalities include ophthalmic problems like bilateral congenital cataracts, nystagmus, microphthalmia or microcornea, facial dysmorphism with micrognathia, scoliosis or extremity deformities, hypo/demyelinating symmetric peripheral neuropathy, and developmental delay[2-6].

CCFDN syndrome is associated with increased risk during anesthesia. Rhabdomyolysis, pulmonary oedema, inspiratory stridor after anesthesia, or epileptic seizures are described in the literature. Although there is no literature about difficult airways in these patients, difficult airway management (DAM) should be expected due to facial dysmorphism and irregular anatomy. There is no convincing data about an association with malignant hyperthermia[3,8].

Only one case study was published regarding the anesthetic management of a patient with CCFDN syndrome. That case involved a 9-year-old boy from the Czech Republic who underwent surgery at Birmingham, UK and repeatedly at a younger age in Czech that was not published. In that case, a laryngeal mask was used for airway management[8].

We report on the first orthopedic case of a 13-year-old girl with CCFDN syndrome for posterior correction and fusion for neuromuscular scoliosis in which the first successful endotracheal intubation and anesthesia by total intravenous anesthesia (TIVA) in a major orthopedic surgery on a patient suffering from CCFDN syndrome is documented.

CASE PRESENTATION

Chief complaints

Our patient is a 13-year-old Roma girl (ASA physical status III) prepared for T₁-L₂ posterior scoliosis correction and fusion.

History of present illness

The patient suffered from mild mental retardation; however, communication was unhindered. She walked without support for a distance of approximately 20 m, but had limitation in movement of the upper extremities due to peripheral neuropathy. Facial dysmorphism was presented by prominent nasal

philtrum and upper incisors.

The progressive curve of scoliosis limited the possibility of rehabilitation, therefore brace treatment was not prescribed for our patient. The Cobb angle was 83°.

Previous general anesthesia for cataract operation at the University Hospital in Prague was uncomplicated. We could not obtain more information about the course of anesthesia used.

History of past illness

The patient was diagnosed with a patent foramen ovale and pulmonary valve stenosis, both hemodynamically insignificant without contraindication to the procedure in the prone position.

Personal and family history

The patient had no significant family history. Rhabdomyolysis, seizure, or CCFDN syndrome was not present in her family relatives.

Physical examination

The patient's body weight was 45 kg and her height was 136 cm; however, the scoliosis curve reduced her actual height. Her Mallampati score was 1. The cardiovascular system was not affected and valve disease was insignificant. Her ASA score was III.

Laboratory examinations

On admission, laboratory test results were within normal limits. There was no abnormality in blood count, biochemical tests, or coagulation.

Pulmonary functions were dominantly limited by restrictive lung disease (forced vital capacity, 54%; forced expiratory volume in 1 s, 62%).

Imaging examinations

Chest X-ray was limited by chest scoliosis and revealed no abnormal lung and heart pathology. Echocardiography found hemodynamically insignificant valve disease. X-ray demonstrated a significant and progressive scoliosis curve with a Cobb angle 83° (Figure 1).

FINAL DIAGNOSIS

The final diagnosis was extensive progressive neuromuscular scoliosis in a patient with CCFDN syndrome indicated for surgical correction and fusion.

TREATMENT

Anesthetic management

Total intravenous anesthesia was the preferred anesthesia technique due to the possibility of motor evoked potential (MEP) monitoring and to minimize the higher risk of rhabdomyolysis described in these patients that is associated with other types of anesthesia. We prepared two infusion pumps, first with 1% propofol and a second with remifentanyl (4 mg/20 mL).

Along with standard vital sign monitoring, we monitored the bispectral index (BIS) to prevent propofol overdosing as the patient presented with abnormal body proportions due to the disfigurement of disease. We cannulated a peripheral IV line G20 before anesthesia induction through which we performed the total IV anesthesia. For induction, we administered a bolus of 120 mg propofol followed by the continuous infusion of 3 mg/kg IV after 2 min pre-oxygenation. We gave a single bolus dose of 0.6 mg/kg rocuronium for intubation relaxation. For analgesia, a remifentanyl infusion was used at a dose of 0.1 µg/kg/min. The patient's airway was evaluated as having a Cormack-Lehane score of 1 during direct laryngoscopy with a Macintosh blade size of 3. The airway was secured with a cuffed 6.5 mm endotracheal tube on the first attempt. No complications were experienced during either pre-intubation mask ventilation or intubation.

Post intubation, we targeted the dose of propofol and remifentanyl to a BIS value between 40-60. Before MEP monitoring, the patient had no residual neuromuscular blockade (TOF ratio more than 90%). We cannulated a second peripheral IV line G18 and an arterial line G20 for invasive blood pressure monitoring. A dose of 700 mg tranexamic acid was given IV before the start of the operation for expected blood loss. The patient was pronated for surgery. Special gel pads were placed to position the patient to prevent iatrogenic trauma since patients with CCFDN syndrome suffer from osteoporosis and pose a higher risk of iatrogenic trauma. The body temperature was maintained between 36.5-34.7 °C with warming blankets applied on the upper and lower extremities. Total blood loss was 1600 mL (36 mL/kg). We administered blood derivatives based on the thromboelastometry results and complete

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Figure 1 X-ray before surgery. Large curve limiting lung functions.

blood count. Perioperative fluid management, considering evaporation from the large wound, was performed according to pulse pressure variation. The patient received 754 mL of red blood cells, 200 mL of purified plasma and 4000 mg of fibrinogen, 3500 mL of balanced crystalloids, and 500 mL of 4% gelatine. We administered paracetamol 700 mg IV and piritramide 7.5 mg SC prior to the end of the procedure. No fluctuation in MEP occurred during the duration of the procedure.

The propofol infusion was suspended approximately 30 min before the skin suture with continual BIS monitoring. Remifentanyl continued until positioning to the supine position. We extubated the patient 4 min after positioning. Perioperative rhabdomyolysis or seizures did not develop in our patient.

Postoperative care in the intensive care unit was without cardiorespiratory complications. The patient's rehabilitation was uneventful, the surgical wound healed "per primam intentionem". The spine instrumentation was without dislocation on the control X-ray. The patient recovered without new neurological deficit and was discharged home on the eleventh day post surgery.

OUTCOME AND FOLLOW-UP

The 6-mo outcome was favorable. The patient arrived with compensated scoliosis and a nearly immeasurable curve. The spine instrumentation was sufficient (Figure 2). There was no new neurological deficit present. The patient visits a physiotherapist regularly.

DISCUSSION

CCFDN syndrome is a rare multisystem disorder. The most typical abnormalities include ophthalmic problems, facial dysmorphism, scoliosis, extremity deformities, and hypo/demyelinating symmetric peripheral neuropathy (Table 1). This syndrome has similar clinical manifestations to Marinesco-Sjögren syndrome. However, molecular testing revealed that these syndromes are genetically different. The definitive diagnosis is confirmed by genetic testing. There is a mutation in the CTDP1 gene on chromosome 18q23 with a homozygous mutation 863+389C>T. Today we know that the best prevention of the repetition of the disease in affected families is molecular testing of all Roma children with congenital cataracts[1].

Anesthesiologists usually manage these patients for skeletal corrections or ophthalmic operations of the cataract and rarely for gonad abnormality correction[8]. Only one case report mentions anesthetic management of these patients for orchidopexy of the patient with CCFDN syndrome where a laryngeal mask was used for airway management[8]. We report the first case of successful, uncomplicated endotracheal intubation of a patient with CCFDN syndrome without need of using any special equipment for DAM. Anesthesiologists should always anticipate possible difficult airway management in patients with facial dysmorphism[3]. A clear plan for airway management is necessary, including preparation of anticipated equipment in accordance with local or international guidelines for difficult airway management. In this case, we managed to secure the airway with our first-choice device - a size

Table 1 The most frequent clinical signs and symptoms of congenital cataract, facial dysmorphism, and neuropathy syndrome and associated possible anesthetic complications

Clinical sign	Possible anesthetic complication
Cataract	Iatrogenic eye damage
Microcornea	Iatrogenic eye damage
Microphthalmia	Iatrogenic eye damage
Malar prominence	Difficult airway management
Micrognathia	Difficult airway management
Prominent upper incisors	Difficult airway management
Prominent nasal philtrum	Difficult airway management
Cervical spine abnormality	Difficult airway management
Development delay	Limited cooperation for invasive procedures
Peripheral neuropathy	Rhabdomyolysis
Scoliosis	Restrictive lung disease
Osteoporosis	Iatrogenic injury



DOI: 10.12998/wjcc.v10.i13.4207 Copyright ©The Author(s) 2022.

Figure 2 X-ray 6-mo after surgery. Instrumentation in correct position.

6.5 mm cuffed endotracheal tube.

Scoliosis is one of the most frequent deformities in patients with neuromuscular disease. The effect of scoliosis is complex with multiorgan involvement, greater than just the motor system of the patients affecting daily care, walking, and sitting. Other systems have secondary involvement, dominantly the cardiovascular and respiratory systems depending on the curve's severity and progression[9-13]. Perioperative care during posterior scoliosis procedures is unique due to the patient's prone positioning, evoked potential monitoring[9], higher blood loss, body temperature loss, and increased evaporation from the large wound[10]. Positioning, especially in patients with CCFDN syndrome, is complicated from peripheral neuropathy with osteoporosis. There is a higher risk of iatrogenic injury with these patients, therefore the manipulation and positioning must be done with extreme care[11]. TIVA is the preferred method for procedures with MEP monitoring[12]. Non-depolarising muscle relaxants should be used only during intubation. Another dose of relaxant is contraindicated to enable MEP monitoring. Neuromuscular blockade monitoring is strictly recommended when non-depolarising muscle relaxants are used. The blockade can be prolonged in patients with a neuromuscular disease like CCFDN syndrome, therefore rocuronium is preferred as the antidote sugammadex can be used to suspend

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muscle relaxation to avoid prolonged neuromuscular blockade[13,14]. Evoked potentials can be altered, and the amplitudes can be lower in CCFDN syndrome with progressive peripheral neuropathy. The adequate depth of anesthesia excludes the adverse effect of deep anesthesia on MEP reproducibility [15]. We decided to avoid volatile anesthetics as the risk of rhabdomyolysis and malignant hyperthermia is elevated with those agents. The association with malignant hyperthermia is unlikely from the different gene locations of CCFDN syndrome and malignant hyperthermia[8]. Rhabdomyolysis presents an acute crisis associated with exposure to suxamethonium or volatile anesthetics and it is known as "anesthesia-induced rhabdomyolysis." Rhabdomyolysis may present as sudden bradycardia with peaked T waves on ECG or cardiac arrest. Hyperkalemia and raised creatine kinase levels are present, especially in patients with neuromuscular disease[1]. Myoglobinuria monitoring is used to detect rhabdomyolysis postoperatively. Controlled awakening, especially in patients with a neuromuscular disorder, can reduce the length of mechanical ventilation required for anesthesia. Managing the depth of anesthesia according to BIS value can shorten the awakening from general anesthesia[8]. The dose of propofol and remifentanyl was managed by targeting administration to BIS values from 40 to 60. The patient was extubated 4 min after postoperative supine positioning. Regional analgesia in patients with CCFDN syndrome is described in the literature[8]; however, the mental status of the patient is of grave concern during regional anesthesia of a developmentally delayed patient. Regional blockade is preferably combined with general anesthesia, especially in children with development delay[16]. There is no specific access or contraindications for regional anesthesia in patients with CCFDN syndrome although there can be anatomical abnormalities due to peripheral neuropathy and contractions. Ultrasound-guided regional anesthesia is the method of choice. In this case, the large extent of the procedure from T₂ to L₂ and the risk of local anesthetic toxicity prevented the use of regional analgesia techniques. Postoperative care depends on the patient's comorbidities and the type of surgery. There is a higher risk of postoperative complications as prolonged neuromuscular blockade or respiratory insufficiency are potential complications. Intensive care of the patient is indicated after prolonged or high-risk surgeries. These patients will profit from early mobilization and rehabilitation[14].

Anesthesia for posterior scoliosis correction can be challenging for anesthesia and the orthopedic team. In this case, the anesthesiologist should know specifics for posterior scoliosis correction and CCFDN syndrome. TIVA and reported perioperative management with safety measures respecting the specifics of both the patient and procedure helped reduce risks described in the CCFDN syndrome and provided early recovery of our patient from the procedure.

CONCLUSION

A rare case of anesthetic management of a patient with CCFDN syndrome undergoing general anesthesia for posterior neuromuscular scoliosis correction has been described. Understanding this syndrome eliminates perioperative complications and enables excellent postoperative patient outcome.

The publication of the first successful endotracheal intubation and uncomplicated perioperative period in major surgery in a patient with CCFDN syndrome is presented. Although airway management was uncomplicated in the end, DAM should be expected in these patients. It is recommended that DAM should be anticipated and advanced equipment for DAM should be available.

ACKNOWLEDGEMENTS

The figures were used with permission of the Department of Radiology and Nuclear Medicine, University Hospital Brno. This case report was presented as a poster at the World Congress of Anaesthesiologists in September 2021.

FOOTNOTES

Author contributions: Hudec J performed anesthesia on the patient; Hudec J, Kosinova M, Prokopova T, and Stourac P had a significant contribution in writing the manuscript; Repko M and Filipovic F operated on the patient, and analyzed and interpreted the patient data regarding motor evoked potentials; all authors read and approved the final manuscript.

Informed consent statement: The legal representative provided informed consent for this publication.

Conflict-of-interest statement: The authors declare no conflict of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Ma YJ

L-Editor: Wang TQ

P-Editor: Ma YJ

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5.2 Anesthesia of the Patient with Zhu-Tokita-Takenouchi-Kim (ZTTK) Syndrome: A Case Report

Druhou kazuistikou z oblasti anestezie pacientů s neuromuskulární skoliózou je případ 7letého chlapce s extrémně vzácným ZTTK syndromem [1, 113]. Tento syndrom patří mezi autozomálně dominantně dědičná genetická onemocnění, způsobená mutací genu SON, a poprvé byl popsán v roce 2015 [113, 114].

Podobně jako v první kazuistice jsme kromě samotného anesteziologického managementu popsali a diskutovali typické rysy tohoto vzácného syndromu. Pro ZTTK syndrom jsou charakteristické obličejové dysmorfie, které by měly zvyšovat obezřetnost anesteziologického týmu v souvislosti s předpokládaným obtížným zajištěním DC. Dalšími typickými znaky jsou vrozené vývojové vady CNS, kardiovaskulárního, gastrointestinálního či močového systému. Konkrétně pacient v naší kazuistice v mladším věku podstoupil operaci Fallotovy tetralogie, dále byly u pacienta diagnostikovány abnormality mozku vedoucí k mentální retardaci a centrální hypotonii. Všechny tyto příznaky jsou diskutovány v naší publikaci spolu se souvisejícími anesteziologickými komplikacemi, včetně opatření k jejich minimalizaci [113, 115].

Popis anesteziologického managementu u pacientů se syndromem ZTTK byl publikován roku 2022 v časopise Children (IF 2,4; Q2 v kategorii PEDIATRICS dle WoS) [1, 113].



Case Report

Anesthesia of the Patient with Zhu-Tokita-Takenouchi-Kim (ZTTK) Syndrome: A Case Report

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Citation: Hudec, J.; Kosinova, M. Anesthesia of the Patient with Zhu-Tokita-Takenouchi-Kim (ZTTK) Syndrome: A Case Report. *Children* **2022**, *9*, 869. <https://doi.org/10.3390/children9060869>

Academic Editor: Brenda Golianu

Received: 19 April 2022

Accepted: 9 June 2022

Published: 11 June 2022

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Abstract: Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome is an extremely rare multiorgan disorder, first described in 2015. Nowadays, about 50 patients with ZTTK syndrome have been reported, but there are no data about management during anesthesia. ZTTK syndrome patients can be indicated for surgery of musculoskeletal deformations and corrections of cardiovascular or urogenital malformations. This syndrome can be challenging for the anesthetic team based on the clinical manifestation of the syndrome. Because there are no recommendations for the management of these patients, anesthesiologists have to study typical symptoms, anatomy and possible expected changes in pathophysiology in perioperative period. One of the most dreaded anesthetic complications, the scenario “can not intubate, can not ventilate” could occur in these patients. The goal of this publication is to show options for anesthetic and perioperative management of this new rare syndrome with no published studies about management and approach in the perioperative period. The anesthetic team should choose the safest available approach. We present the first case report of anesthesia of a patient with ZTTK syndrome, a 7-year-old boy indicated for posterior neuromuscular scoliosis correction and fusion. This case describes the author's experiences with anesthetic management and mentions possible early postoperative complications. Adequate understanding of this syndrome can reduce perioperative complications and improve patient outcomes after surgery.

Keywords: ZTTK syndrome; neuromuscular scoliosis; anesthesia; case report

1. Introduction

Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome is an extremely rare multiorgan disorder, first described in 2015. ZTTK syndrome represents a recent diagnosis, described in about 50 patients up to this date. Just few articles about ZTTK syndrome were published from 2015 to 2022, and most of them are focused on describing clinical and molecular findings. The authors present a unique publication from clinical practice about a patient suffering from ZTTK syndrome, because there are no published data about the perioperative management of these patients including anesthesia management. It is an autosomal dominant hereditary disorder, which affects many organ systems, caused by a heterozygous mutation in the SON gene (21q22.11). This mutation leads to abnormal RNA splicing [1–3]. The typical symptoms include intellectual development disorders, seizures, and brain malformation such as corpus callosum abnormality. Facial dysmorphism includes facial asymmetry with macrocephaly, midface retrusion, short philtrum, or abnormality of the nasal bridge. Musculoskeletal abnormalities are represented by hypotonia, short stature, skull abnormality, scoliosis or hemivertebrae, rib abnormalities or joint hypermobility, and contractures. Typical visceral malformations are urogenital abnormalities such as a horseshoe or unilateral kidney, cardiac abnormalities such as an atrial or ventricular septal defect, and gastrointestinal abnormalities [4–6]. The occurrence

of these symptoms can lead to possible difficulties during perioperative management (IV line or arterial line cannulation and difficult airway management). Other rarer perioperative complications associated with this orphan disease can include the occurrence of rhabdomyolysis with hyperkalemia. This potentially lethal complication triggered by suxamethonium or volatile agents is described especially in patients with neuromuscular diseases [7]. Anesthesiologists have to study and understand these specific problems prior to any anesthesia performance.

The goal of this publication is to show possible options for anesthetic and perioperative management of this new rare syndrome with no published studies about management and approach in the perioperative period. The anesthetic team should choose the safest available approach to prevent possible adverse events. We present the first case report about the anesthesia of a patient suffering from ZTTK syndrome.

2. Case Presentations

Our patient is a 7-year-old boy admitted for T₄–L₅ neuromuscular scoliosis surgery. He weighed 14.5 kg, and he was 112 cm high, ASA physical status III.

The boy was born at full term via Caesarean section due to intrauterine growth restriction. He underwent surgery for Tetralogy of Fallot and another transventricular correction at a younger age before the ZTTK syndrome diagnosis. Detailed information about past anesthesia is not available. However, the mother did not mention significant complications. He had a psychomotor development delay with the central hypotonic syndrome. Magnetic resonance imaging showed an anomaly of the cortex and thin corpus callosum. He has suffered from hypopituitarism with hypothyroidism and epileptic seizures since 2020. His medication included levothyroxine and somatropin, as hormonal substitution, and vigabatrin was indicated due to the anamnesis of epileptic seizures. The differential diagnosis focused on genetic examination with the result of ZTTK syndrome.

He was able to walk with support for a short distance before the surgery. His speech was limited to a few words. Facial dysmorphism was presented by a small mouth, broad nasal bridge, and strabismus. Pulmonary functions were limited by a progressive scoliosis curve. The Cobb angle was 95° (Figure 1). Spirometry was not performed because of insufficient cooperation. ECG, echocardiography (Normal systolic function with right heart dilatation, pulmonary valve regurgitation grade III, and mild stenosis of the left branch of the pulmonary artery), and other cardiovascular findings were without contraindication to the surgery. According to the endocrinologist's recommendation, hormone substitution with hydrocortisone, levothyroxine, and somatropin was administered. The actual EEG was without epileptic activity on the chronic medication.

In summary, our patient's typical ZTTK syndrome abnormalities included development delay, seizures, thin corpus callosum with cortex abnormality, central hypotonic syndrome, and facial dysmorphism with a small mouth and a broad nasal bridge. Scoliosis was presented from musculoskeletal abnormalities; heart abnormalities were represented by Tetralogy of Fallot. Endocrine dysfunction included hypopituitarism with hypothyroidism.

We chose total intravenous anesthesia (TIVA) because of the monitoring of motor evoked potentials (MEP), unconvincing data about malignant hyperthermia, and the possible risk of rhabdomyolysis. We used propofol, remifentanyl, and cisatracurium for anesthesia induction. We continued with propofol and remifentanyl infusion. Face mask ventilation was without complications. We evaluated airways with a Cormack–Lehane score of 1 and secured airways with a cuffed endotracheal tube, size 5.0 mm. There were no complications with the intubation. After the intubation, we targeted the dose of propofol (target dose between 5–7 mg/kg/h, respectively, 70–110 mg/h) and remifentanyl (target dose between 0.4–0.5 µg/kg/min, respectively, 360–450 µg/h) to a bispectral index (BIS) value between 40–60. In addition, the accelerometer was used for neuromuscular blockade monitoring before the MEP monitoring, and the patient had no residual blockade (TOF ratio above 90 %).



Figure 1. X-ray before surgery with progressive scoliosis, Cobb angle 95°.

We turned the patient to the prone position after arterial catheter and central venous catheter cannulation. The cannulation was ultrasound-guided and uncomplicated. We used specific gel pads to prevent iatrogenic trauma. Self-warming blankets with warming pads were applied to upper and lower extremities to prevent hypothermia. Body temperature was monitored with an esophageal thermometer regularly, and the temperature did not fall below 35.9 °C. The surgery took 5.5 h. The total dose of propofol was 480 mg and the total dose of remifentanyl was 1350 µg. Total blood loss was about 200 mL (13.3 mL/kg).

We extubated the patient 10 min after turning him back to the supine position. The inspiratory stridor and desaturation developed after extubation. We administered oxygen via a face mask and 50 mg of hydrocortisone with sufficient reaction and further normal peripheral oxygen saturation. The inspiratory stridor duration was about 10 min. Then, the patient was admitted electively to the ICU. Early postoperative care was complicated by metabolic alkalosis and hypokalemia due to compensation of the respiratory acidosis after scoliosis correction. Potassium was substituted intravenously. This condition normalized over 10 days. Other functions normalized spontaneously. Postoperative pain management was administered with a combination of non-opioid painkillers, such as paracetamol and metamizole with a dose of 15 mg/kg IV every 6 h, and opioid therapy with piritramide with a dose of 0.1 mg/kg SC every 6 h. Regional anesthesia was not administered due to the large scoliotic curve and the potential risk of local anesthetic toxicity. The rest of the postoperative care was uncomplicated. Instrumentation was in the correct position (Figure 2). The patient was discharged home 13 days after surgery.

The 5-month follow-up after the surgery was a favorable outcome for the patient. The scoliosis was compensated with a nearly immeasurable curve. The spine instrumentation was in the correct position and the patient was without a new neurological deficit.



Figure 2. X-ray after surgery with instrumentation in the correct position.

3. Discussion

To the best of our knowledge, there are no data about anesthesia and possible perioperative complications in patients suffering from ZTTK syndrome, a newly described orphan disease. As this is a newly described rare disease, it is very unlikely that strong data exist about the perioperative management of ZTTK patients due to the extremely low incidence in the population. One of the possibilities is the presentation of a rare case report focused on individual management highlighting the specifics associated with this syndrome. In this article, we reported expected challenges for the anesthetic team on one case report.

ZTTK patients can be anesthetized for the corrections of the musculoskeletal, urogenital, or cardiovascular system. Brain abnormalities and psychomotor development delay are described in most patients. Although there are no specific contraindications for regional anesthesia, general anesthesia is a method of choice in patients with limited cooperation and altered mental status [4,5].

There are no data about the risk of rhabdomyolysis or malignant hyperthermia. The incidence of malignant hyperthermia is unlikely. These two syndromes have different gene localization (chromosome 19 for malignant hyperthermia and chromosome 21 for ZTTK syndrome) [8]. However, we decided to avoid volatile agents and succinylcholine. TIVA is a safe method for the possible risk of rhabdomyolysis. Nondepolarising muscle relaxants can be used safely. Rocuronium with the available antidote sugammadex is another safe combination to avoid a prolonged neuromuscular blockade, especially in short surgeries [9]. Neuromuscular blockade monitoring is essential in patients with hypotonia, due to the risk of residual neuromuscular blockade. Urine myoglobin level monitoring can be used to diagnose rhabdomyolysis postoperatively [7,10].

Depth of anesthesia monitoring is recommended for TIVA. It shortens the time of awakening from anesthesia and reduces the risk of sedative overdosing [11]. We targeted the dose of sedative and opioid to a BIS value of 50 ± 10 to prevent overdosing. Due to proper dosing, we managed to extubate the patient 10 min after positioning him back to the supine position.

Patients with ZTTK syndrome are of short stature with small hands and short feet. Joint hypermobility, scoliosis, or contractures are described in these patients [6]. Abnormal body proportions associated with this syndrome can lead to difficult invasive access cannulation.

Ultrasound-guided insertion can be helpful, especially if any anatomical deformity is present. It reduces the incidence of insertion failure [12]. In addition, body disfigurement, skull abnormalities, and hypotonia can be associated with osteoporosis. The positioning must be performed extremely carefully because of the higher risk of iatrogenic injury [13].

Mild or moderate facial dysmorphism is presented in all patients. The signs include facial asymmetry, midface retraction, short philtrum, broad nasal bridge, or small mouth with a high-arched palate. Dental abnormalities are described in the literature [4]. Although airway management was not described in the literature, these factors should lead to an expectation of difficult airway management (DAM). However, we did not have a problem with face mask ventilation and intubation. Special equipment for DAM should be prepared before every airway securing [14].

Postoperative care can be burdened by the risk of life-threatening complications in patients with neuromuscular disease, especially after major or high-risk surgery [15,16]. There is a risk of respiratory insufficiency, prolonged muscle blockade, or a potential risk of rhabdomyolysis. Vital signs in patients with ZTTK syndrome should be monitored until stabilization after surgery.

Adequate preparation and understanding of this syndrome can eliminate possible complications and improve postoperative patient outcomes. Possible anesthetic complications are mentioned in Table 1.

Table 1. The frequent clinical signs and symptoms of Zhu-Tokita-Takenouchi-Kim syndrome and associated possible anesthetic complications.

Clinical Sign	Possible Anesthetic Complication
Facial asymmetry	Difficult airway management
Midface retrusion	Difficult airway management
Abnormality of the nasal bridge	Difficult airway management
Intellectual disability	Limited cooperation for invasive procedures
Development delay	Limited cooperation for invasive procedures
Neurological abnormality, hypotonia	Rhabdomyolysis
Scoliosis	Restrictive lung disease
Skull abnormality, contractures	Difficult invasive access
Contractures, joint hypermobility	Difficult positioning, iatrogenic trauma

4. Conclusions

We describe the first case of anesthetic management of a patient with ZTTK syndrome. Our patient underwent total intravenous anesthesia for posterior neuromuscular scoliosis correction and fusion with no major complications. Describing this case and understanding this syndrome can help anesthetic teams to improve the perioperative management of these patients.

Author Contributions: Conceptualization, J.H. anesthetized the patient, collected data, and wrote the manuscript. M.K. reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Specific University Research provided by the Ministry of Education, Youth and Sports (MUNI/A/1178/2021)—support of research groups; Supported by MHCR-DRO (FNBr, 65269705)—Start-up grant (J.H.).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: The legal representative signed the informed consent for this publication.

Data Availability Statement: The data presented in this case report are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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5.3 OrphanAnesthesia – doporučení pro anestezii pacientů s vzácným onemocněním

Významnost našich dvou kazuistických sdělení dokládá spolupráce s redaktory projektu OrphanAnesthesia. Tento ambiciózní projekt byl založen v roce 2005 a v současné době se jedná o společnou iniciativu skupiny pro dětskou anestezii v rámci Německé společnosti anesteziologie a intenzivní medicíny, projektu Orphanet a Evropské společnosti pro pediatrickou anestezii (European Society for Paediatric Anaesthesia). Cílem tohoto projektu je vytvoření strukturovaných, recenzovaných mezinárodních doporučení pro perioperační péči pacientů se vzácnými onemocněními. Tato stručná doporučení mají za cíl zvýšit perioperační bezpečnost u pacientů a odrážejí nejlepší dostupnou evidenci. Všechna tato doporučení jsou volně přístupná v anglickém jazyce na webu <https://www.orphananesthesia.eu/en/> a dále jsou publikována také v časopise *Anästhesiologie & Intensivmedizin* [116].

Výše uvedené dvě kazuistiky byly zpracovány dle struktury OrphanAnesthesia a v roce 2023 publikovány v časopise *Anästhesiologie & Intensivmedizin* (IF 0,5; Q4 v kategorii ANESTHESIOLOGY dle WoS) [1, 117, 118].

5.3.1 Anaesthesia recommendations for Congenital cataracts, facial dysmorphism and neuropathy syndrome

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Anaesthesia recommendations for Congenital cataracts, facial dysmorphism and neuropathy syndrome

Disease name: Congenital cataracts, facial dysmorphism and neuropathy syndrome

ICD 10: Q87.8

Synonyms: CCFDN syndrome

Disease summary: The congenital cataracts, facial dysmorphism and neuropathy (CCFDN) syndrome is an extremely rare autosomal recessive disorder with unknown prevalence. This multiorgan disorder is typically described in Roma ethnicity. The first case was described in 1999 in Roma patients from Bulgaria. It is caused and diagnosed by a mutation in CTFP1 gene on chromosome 18q23. This mutation causes an altered transcription process, affecting many cellular processes and functions. The clinical manifestation of the CCFDN syndrome is similar to that of the Marinesco-Sjögren syndrome, but molecular testing has already shown that these syndromes are different. Disease abnormalities include ophthalmic problems, especially bilateral congenital cataract, nystagmus or microcornea, facial dysmorphism with micrognathia, mild development delay, musculoskeletal deformities caused by demyelinating peripheral neuropathy and hypogonadism. These patients undergo ophthalmic surgery of cataracts, corrective orthopaedic surgery like scoliosis or extremities correction. Perioperative management includes close anaesthetic monitoring, postoperative care in ICU is appropriate, except for short noncomplicated surgery, due to potentially life-threatening complications like epileptic seizures, rhabdomyolysis, pulmonary oedema or inspiratory stridor. The main postoperative complication of patients with CCFDN syndrome is rhabdomyolysis, so we should limit using volatile anaesthetics and depolarising muscle relaxants. Total intravenous anaesthesia, eventually nondepolarising muscle relaxants, are preferred.

Medicine is in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong



Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

► **Citation:** Hudec J, Kosinová M: Congenital cataracts, facial dysmorphism and neuropathy syndrome. Anästh Intensivmed 2023;64:S446–S453 DOI: 10.19224/ai2023.S446

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Typical surgery

Most frequent procedures include ophthalmic surgery, typically cataract, orthopaedic surgery like scoliosis or extremities correction and tendon transfers. Rarer procedures are corrections of gonad abnormalities.

Type of anaesthesia

Both kinds of anaesthesia, general or regional anaesthesia, are possible. General anaesthesia is the preferred method for a patient suffering from mental retardation and poor compliance.

The specific contraindications for regional anaesthesia associated with CCFDN syndrome are unknown, there is just one published report about regional anaesthesia in these patients. Ultrasound-navigated peripheral blocks are useful as part of postoperative analgesia, but cannulation can be difficult due to deviant anatomical proportions in patients with musculoskeletal deformations.

General anaesthesia is a method of choice in patients with altered mental status. Depolarising muscle relaxants and volatile anaesthetics should be limited. A high risk of severe rhabdomyolysis and hyperkalaemia has been described. However, rhabdomyolysis is probably triggered by stress and ineffective postoperative pain control. Inhalational induction of anaesthesia may be considered in case of a difficult IV access to reduce patient stress. The best choice consists in total intravenous anaesthesia, eventually with non-depolarising muscle relaxants in case of intubation or to facilitate surgery. Rocuronium and sugammadex administration is the preferred combination for neuromuscular blockade control, as there is a potential to full recovery from the neuromuscular blockade. There are unconvincing data about malignant hyperthermia, but the association with malignant hyperthermia is unlikely due to the separate gene localisations of these disorders.

Analgo-sedation is not contraindicated, but should be considered in each individual case, especially if patients display altered respiratory functions due to scoliosis, mental retardation or muscular weakness. In addition, facial dysmorphism, specifically mandibular hypoplasia can cause upper airway obstruction after sedation.

Necessary additional preoperative testing (beside standard care)

The spectrum of preoperative assessment should be considered individually according to the severity of symptoms and the type of surgery. The CCFDN syndrome is characterised by a demyelinating peripheral neuropathy with skeletal muscle weakness. It can result in scoliosis with an alteration of cardiopulmonary functions. Pre-anaesthesia evaluation should focus on the signs of difficult airway management in the first place and on the identification of cardiovascular and pulmonary disorders and neurological deficits, respectively muscle weakness.

Cardiovascular assessment includes electrocardiography. There are no data on serious cardiac disease, but in cases of doubt (severe scoliosis), echocardiography should be considered.

Respiratory function evaluation should be considered in patients with severe muscular weakness or severe scoliosis. It includes arterial blood-gas analysis and spirometry. This

testing can be complicated by the noncompliant patient with mental retardation, but it can be helpful for predicting the need for postoperative ventilatory support.

Neurological examination is recommended in patients with neurological deficit, severe muscle weakness, extremity deformations and before spine surgery. In addition, it can be helpful for juridical reasons in these patients for a clear description of neurological deficit in case of possible iatrogenic harm of patients.

Particular preparation for airway management

The CCFDN syndrome is a multiorgan disorder. Facial dysmorphism is a typical sign of this syndrome, especially in late childhood or adult males. Dysmorphism is presented by a prominent nasal philtrum with upper incisors, thickening of the perioral tissues and micrognathia. Two studies reported of different types of airway securement. A laryngeal mask was used in the case first published, endotracheal intubation in the second. Both cases did not report of problems with bag-mask ventilation or airway securing.

There are no more data about airway securing. As there is a possibility of difficult airways due to facial dysmorphism, equipment for difficult airway management should be available before every anaesthetic care.

Particular preparation for transfusion or administration of blood products

Data on transfusion management have not been published. A higher blood loss and a need for blood products must be expected in patients with CCFDN syndrome during invasive procedures, e.g., spine surgery or extremities correction. Some data presented higher blood losses in patients with a neuromuscular disorder compared to patients without any neuromuscular deficit. Osteoporosis might be accountable for the higher blood loss in these patients.

Particular preparation for anticoagulation

There is no case about thrombotic complications that has been reported in the literature. Recommendations for an anticoagulation therapy is not available. But higher risks of thrombosis in patients with limited mobility may be expected. In these patients we should consider the risk-benefit ratio of anticoagulation during the perioperative period.

Particular precautions for positioning, transportation and mobilisation

CCFDN syndrome patients might suffer from osteoporosis due to peripheral neuropathy with a low mobility level or endocrine deficiency. There is a higher risk of iatrogenic injury in these patients. It is recommended to use specific positioning pads in these patients, especially in the prone position.

Interactions of chronic disease and anaesthesia medications

Not reported.

Anaesthetic procedure

Regional anaesthesia, neuraxial techniques including, are possible with respect to the mental status of these patients. However, regional techniques can be combined with general anaesthesia. There is no specific approach, but there could be different anatomical proportions in patients with neuromuscular disease. Ultrasound is the preferred method for regional anaesthesia navigation.

General anaesthesia is preferred in a patient with severe mental alteration. Total intravenous anaesthesia is a method of choice.

Volatile anaesthetics and depolarising muscle relaxants should be limited. There is a higher risk of hyperkalaemia and rhabdomyolysis.

Non-depolarising muscle relaxants can be used in patients with CCFDN syndrome. We recommend neuromuscular blockade monitoring due to the higher risk of a prolonged neuromuscular blockade.

A good pain control will prevent the risk of an excessive stress reaction and rhabdomyolysis. Regional anaesthesia and paracetamol have been used without complications.

Particular or additional monitoring

Depth of anaesthesia should always be monitored during TIVA. It can reduce the total dose of anaesthetics, and it shortens the time of recovery from anaesthesia.

We should always monitor the depth of neuromuscular blockade. There is a risk of prolonged neuromuscular blockade in patients with demyelinating peripheral neuropathy.

Invasive blood pressure monitoring is recommended in more extensive surgery, major fluid shifts or in patients with altered cardiovascular functions.

Possible complications

Patients with the CCFDN syndrome have a higher risk of rhabdomyolysis. Volatile anaesthetics should be limited. A potential rhabdomyolysis can be detected postoperatively by myoglobinuria monitoring.

Other complications have been described, e.g., seizures, pulmonary oedema or inspiratory stridor. These complications should be treated according to respective standards.

A peripheral neuropathy could result from a prolonged neuromuscular blockade. A residual neuromuscular blockade might impair recovery.

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Postoperative care

Postoperative monitoring depends on the type of surgical procedure and the patient's comorbidities. Intensive care should be provided in high-risk surgeries to patients with a disability of high degree.

The potential rhabdomyolysis can be detected postoperatively by myoglobinuria monitoring.

Patients could profit from early weaning and mobilisation after surgery. Immobilisation can worsen the neuropathy and the outcome after surgery.

Disease-related acute problems and effect on anaesthesia and recovery

There are limited data about airway management. Difficult airways should always be expected as a result of facial dysmorphism.

There are unconvincing data about malignant hyperthermia. But an association with malignant hyperthermia is unlikely because of the separate gene localisations of the CCFDN syndrome and malignant hyperthermia.

Ambulatory anaesthesia

Not reported.

Obstetrical anaesthesia

Not reported.

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Date last modified: November 2022

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Disclosure The authors have no financial or other competing interest to disclose. This recommendation was unfunded.

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Disclosure The reviewers have no financial or other competing interest to disclose.

Please note that this recommendation has not been by an anaesthesiologist and a disease expert but by two anaesthesiologists instead.

5.3.2 Anaesthesia recommendations for Zhu-Tokita-Takenouchi-Kim syndrome

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Anaesthesia recommendations for Zhu-Tokita-Takenouchi-Kim syndrome

Disease name: Zhu-Tokita-Takenouchi-Kim syndrome

ICD 10: Q87.8

Synonyms: ZTTK syndrome

Disease summary: Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome is a rare multi-organ disease. First cases were mentioned in 2015. This syndrome is typically inherited in an autosomal dominant manner (typically de novo) and is caused by heterozygous mutations in the SON gene (21q22.11). Mutations in this gene lead to abnormal RNA splicing processes, which are essential for metabolic functions and neurodevelopment, including neural cell migration and/or renal development.

This disorder can be suspected prenatally through intrauterine growth retardation. ZTTK syndrome abnormalities include a delay of global development, brain abnormalities like corpus callosum abnormalities, ventriculomegaly or cerebellar abnormalities, seizures, and generalised hypotonia. Facial dysmorphism is presented by short philtrum, microcephaly, wide nasal bridge, and midface retrusion. Other abnormalities include scoliosis, joint and muscle contractures, joint hypermobility, visceral malformations like a horseshoe or unilateral kidney, gastrointestinal malformations, or cardiac disorders like an atrial or ventricular septal defect.

Patients suffering from ZTTK syndrome can be indicated for corrections of cardiovascular or urogenital abnormalities in addition to surgery for musculoskeletal deformations. Anaesthesiologists have to focus on continual close monitoring due to the potential risk of perioperative complications like difficult airway management (DAM), anaesthesia-induced rhabdomyolysis (AIR), or inspiratory stridor after extubation. Rhabdomyolysis represents a potentially life-threatening complication, especially in these patients suffering from a neuromuscular disorder. Anaesthesiologists should prefer total intravenous anaesthesia (TIVA), eventually with nondepolarising myorelaxants and, avoid volatile anaesthetics and succinylcholine.

Medicine is in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong



Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

► **Citation:** Hudec J, Kosinová M: Zhu-Tokita-Takenouchi-Kim syndrome.
Anästh Intensivmed 2023;64:S332-S339. DOI: 10.19224/ai2023.S332

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Typical surgery

Typical procedures include musculoskeletal corrections for scoliosis or extremities deformations, invasive and minimally invasive corrections of cardiovascular defects, or surgical repair of visceral malformations. Patients with development delay require sedation for a central venous access or MRI.

Type of anaesthesia

Anaesthesia of patients suffering from Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome can be challenging for all members of a perioperative team. Theoretically, general and regional anaesthesia is possible. However, only general anaesthesia has been described in the literature so far. There are no data about the use of regional anaesthesia in these patients.

Regional anaesthesia in patients with ZTTK syndrome has no specific contraindications. Cardiovascular abnormalities can be contraindications when it comes to a neuraxial blockade. The same applies to patients with heart disease. Anaesthesiologists must be ready to deal with the limited cooperation of patients with developmental delay. Intravenous access, neuraxial blockade, or peripheral blocks can also be challenging due to musculoskeletal deformations. Ultrasound-navigated venous cannulation or regional anaesthesia can improve the success rate.

General anaesthesia, concretely total intravenous anaesthesia (TIVA), is a method of choice in patients with psychomotor development delay. Volatile anaesthetics as well as succinylcholine should be avoided because of the potential risk of severe rhabdomyolysis or hyperkalemia. TIVA, also in combination with non-depolarising muscle relaxants, has been described in the literature. The benefit of rocuronium in combination with sugammadex in patients with neuromuscular disease has been described. This combination allows a complete recovery from muscle relaxation. The data about the risk of malignant hyperthermia are not available, however, the association between these syndromes is unlikely. They have different gene localization (SON gene located on chromosome 21).

Analgosedation has no specific contraindications to this syndrome. This anaesthetic approach should be considered individually by all members of the perioperative team. The sedation is unsuitable for patients with a restrictive lung disease due to scoliosis, mental retardation, or muscular weakness with the risk of hypoventilation. But then, the potential benefits must be weighed against the risk of difficult airway management, especially in patients with facial dysmorphism.

Necessary additional preoperative testing (beside standard care)

The patient's case history and the type of surgery are essential for determining the spectrum of preoperative assessment. ZTTK syndrome is typically associated with multi-organ involvement and anaesthesiologists must consider indications for each examination individually to identify cardiovascular, pulmonary, or visceral disorders and neurological deficits.

Neurological examination is a necessity, eventually including electroencephalography and a detailed description of the neurological deficit. Also, the neurologist should recommend any specific therapy needed for patients suffering from epileptic seizures. In addition, a

neurological examination can be helpful for juridical reasons in patients with neurological deficits before surgery.

Electrocardiography is a standard part of the preoperative assessment. Patients with ZTTK syndrome can suffer from heart disease. Cardiologist examination with echocardiography should be indicated in patients with heart disease symptoms before high-risk surgery or, in case of doubts, e.g., a large scoliotic curve with possible pulmonary hypertension.

The evaluation of respiratory functions includes arterial blood-gas analysis by spirometry. This examination should be considered in patients with altered respiratory functions, for example, patients with restrictive lung disease due to musculoskeletal abnormalities, scoliosis, or muscle weakness. On the other hand, this examination will not be helpful in case of noncompliant patients.

Other specific preoperative testing includes patients with a hormonal imbalance and the recommendation of hormone substitution by an endocrinologist. Magnetic resonance imaging (MRI) to identify brain abnormalities can be helpful but is not strictly necessary before surgery.

Particular preparation for airway management

ZTTK syndrome is a disorder that typically involves dysmorphic features in patients. Typical facial dysmorphism includes macrocephaly with midface retrusion, short philtrum, and a wide nasal bridge. There is only one case that reports airway management. Endotracheal intubation was used in this case. The authors mentioned uncomplicated bag-mask ventilation. There were no complications with any airway securing method mentioned.

There is no more data about airway securing. Anaesthesiologists must expect possible difficult airway management (DAM) due to facial dysmorphism in patients with ZTTK syndrome. Authors recommend preparing the equipment for DAM and devising more alternative plans for airway securing before every anaesthetic care.

Particular preparation for transfusion or administration of blood products

One case report indicated a relatively high blood loss, about 20% of the total blood volume during long-time and extensive surgery. No other data about the administration of blood products are available. Some studies presented a higher blood loss in patients with neuromuscular disease compared to patients without these syndromes. Hence anaesthesiologists must expect higher blood losses in patients suffering from ZTTK syndrome with limited mobility and general hypotonia.

Particular preparation for anticoagulation

There are no data on thrombotic complications and the administration of anticoagulation therapy in the literature. However, patients with ZTTK syndrome often have limited mobility. Therefore, the perioperative team should expect a higher risk of thrombotic complications during the perioperative period and individually consider the potential risk-benefit ratio of anticoagulation therapy with higher blood loss as compared to thrombosis in low-mobility patients.

Particular precautions for positioning, transportation and mobilisation

Patients with ZTTK syndrome can suffer from a low mobility associated with a neuromuscular disorder, endocrine dysfunction, and/or secondary osteoporosis. There is often an abnormal body constitution or contractures in these patients. The perioperative team should expect a higher risk of iatrogenic damage. We recommend using specific positioning pads and careful, coordinated positioning of patients with ZTTK syndrome.

Interactions of chronic disease and anaesthesia medications

There could be possible interaction with antiepileptic drugs, heart rhythm drugs, or other neurological medication, e.g., some interactions can cause prolonged QT symptoms, deepening the sedation. The perioperative team, in case of uncertainty, should consider consulting a neurologist or pharmacologist to plan the administration of drugs before surgery and in the postoperative period.

Anaesthetic procedure

General anaesthesia, especially total intravenous anaesthesia, is the preferred method for a patient with a severe mental alteration. The combination of propofol, opioid, and non-depolarising muscle relaxants was used safely in a patient with ZTTK syndrome. In case of need for muscle relaxation, rocuronium is a preferred relaxant because a prolonged neuromuscular blockade can be reversed by sugammadex.

On the contrary, depolarising muscle relaxants or volatile anaesthetics should be avoided due to the potential risk of rhabdomyolysis and severe hyperkalemia.

There are no specific contraindications for any type of regional anaesthesia. An anaesthetic team must consider a limited cooperation in patients with altered mental status. The usual places for invasive access can be modified due to the changed body proportions, joint contractures, or scoliosis. Ultrasound-guided cannulation can significantly reduce the incidence of invasive access insertion failure.

Particular or additional monitoring

There is a potential risk of prolonged muscle relaxation in patients with general hypotonia. The anaesthetic team should always monitor the depth of a neuromuscular blockade.

Invasive haemodynamic monitoring should be considered in high-risk or more extensive surgeries with major fluid shifts and in case of patients having undergone cardiovascular corrections.

TIVA should be administered according to the depth of anaesthesia monitoring. Standard doses of sedatives can lead to overdosing and wake-up time prolongation after anaesthesia in patients with an abnormal habitus. Monitoring the depth of anaesthesia is helpful, and it also shortens the time of anaesthesia.

Possible complications

Difficult airway management should be expected in patients with facial abnormalities. The anaesthetic team has to be prepared for this life-threatening complication and have alternative plans for airway securing, e.g., awake fibre-optic intubation, or have a prepared kit with invasive techniques ready for securing the airways, such as bougie-assisted cricothyrotomy.

The inspiratory stridor with desaturation after extubation has been described in the literature. This complication has been treated as a standard.

There is a potential risk of rhabdomyolysis as well as other neuromuscular disorders, especially during long-time surgical procedures with a risk of muscle damage. Volatile anaesthetics or depolarising muscle relaxants should be avoided. Stress factors, like pain, should be eliminated. The rhabdomyolysis can be detected postoperatively by plasma creatine kinase and myoglobinuria monitoring.

postoperative care

Patients suffering from ZTTK syndrome will profit from monitoring in ICUs after surgery, especially in cases of high-risk or extensive surgery.

Rhabdomyolysis, as a possible postoperative complication, can be diagnosed by clinical examination in combination with the laboratory results.

Disease-related acute problems and effect on anaesthesia and recovery

There is no data about the risk of malignant hyperthermia. There are different gene localisations in these two syndromes, so the association between ZTTK syndrome and malignant hyperthermia is unlikely.

Other complications and problems are mentioned above.

Ambulatory anaesthesia

Ambulatory anaesthetic care has not been reported. The anaesthetic team should consider the potentially higher risk in ambulatory care settings for these patients.

Obstetrical anaesthesia

Not reported.

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Date last modified: November 2022

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Disclosure The authors have no financial or other competing interest to disclose. This recommendation was unfunded.

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Disclosure The reviewers have no financial or other competing interest to disclose.

5.4 Perioperative Management of the Patient With Chromosome 6p Duplication: A Case Report And a Narrative Review of Literature

Poslední z kazuistik pacientů s neuromuskulární skoliózou pojednává o 9leté dívce s vzácným genetickým onemocněním, syndromem duplikace chromozomu 6p [119]. Jedná se o vzácné onemocnění poprvé popsané v 70. letech 20. století. Doposud bylo u tohoto syndromu popsáno přibližně u 50 pacientů [119, 120].

Mezi typické příznaky tohoto onemocnění patří nízká porodní hmotnost, mentální retardace, obličejové abnormality, vrozené vývojové vady srdce, močových cest nebo svalová hypotonie [119, 121]. V této publikaci jsme se, kromě samotného popisu anesteziologického případu, zaměřili na podrobnou revizi literatury, na jejímž základě jsme akcentovali typické příznaky i návrh na optimalizaci perioperační péče o pacienty se syndromem duplikace chromozomu 6p [119]. Oproti výše zmíněným kazuistikám je tato práce pojata komplexněji, včetně přístupu ortopedů, fyzioterapeutů a dalších zdravotnických odborností. Na základě rešerše literatury byl rovněž vytvořen doporučený postup v rámci projektu OrphanAnesthesia, nicméně tento postup prochází recenzním řízením a v době tvorby habilitační práce nebyl přijat k další publikaci.

Tato kazuistika byla publikována v časopise Bratislava Medical Journal (IF 1,1; Q2 v kategorii MEDICINE, GENERAL & INTERNAL dle WoS) v roce 2025 [119].



Perioperative Management of the Patient With Chromosome 6p Duplication: A Case Report And a Narrative Review of Literature

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Received: 5 November 2024 / Accepted: 23 December 2024 / Published online: 5 February 2025
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Abstract

Chromosome 6p duplication syndrome represents a rare genetic disorder. About 50 patients have been described till now. The syndrome is also called trisomy 6p, and it is clinically characterized by short stature with microcephaly, mental retardation, congenital heart defects, or kidney tract anomalies. Epileptic seizures and spine deviations have also been described in a few children. Perioperative management of patients with chromosome 6p duplication can be challenging for all healthcare providers due to the multiorgan disability of the patients. To our knowledge, we report the first case of comprehensive perioperative management of patients with chromosome 6p duplication. Our case report is about a 9-year-old girl scheduled for scoliosis surgery. It discusses individual steps in the preoperative examination, surgery, and postoperative care, including preventing possible complications. This publication aims to show possible options for comprehensive perioperative management of patients with extremely rare syndrome because there are no published studies about perioperative management. Understanding the 6p duplication syndrome may improve the patient's outcome in the perioperative period.

Keywords 6p duplication syndrome · Perioperative management · Total intravenous anaesthesia · Scoliosis · Case report

1 Introduction

6p duplication syndrome, also called trisomy 6p, is an extremely rare genetic disorder. It was first described in the 1970s, and to date, about 50 patients have been reported worldwide. The actual incidence is unknown [1, 2]. As the name indicates, this chromosomal aberration is characterised by an extra genetic material on the short arm of chromosome 6. The duplication usually arises as a balanced translocation, insertion, or de novo mutation [1–3]. The clinical signs are variable and depend on the duplicated segment of chromosome 6. The typical symptoms include low birth weight, short stature with disproportionate extremities, microcephaly, intellectual disability with speech delay, congenital heart

defects, or kidney tract anomalies with renal complications. A prominent forehead and nose bridge, microstomia, thin lips, small eyes, or ear anomalies characterise microcephaly. Epileptic seizures, spine deviations, or minor genital anomalies have been described in several children [1–4]. To our knowledge, about 50 cases of 6p duplication syndrome have been published. We summarized these cases, clinical findings including, in Table 1.

Perioperative management can be highly challenging for all multidisciplinary team members who take care of patients with chromosome 6p duplication. We report the first comprehensive perioperative management of a patient with this rare disorder and discuss possibilities for improving patients' outcomes.

2 Case Report

A 9-year-old girl was admitted to our hospital for elective scoliosis surgery. She weighed 29 kg, and she was 128 cm tall. The baby girl was born at 34 weeks gestation via spontaneous labour. The pregnancy was complicated by intrauterine growth restriction, the girl weighed only 1795 g. Apgar's score was 8–9–10. However, she required CPAP for 15 h

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Table 1 Reported cases of 6p duplication syndrome with clinical features (from 1971 to 2023)

Case	Author	Year	Phenotypic features
1	Therkelsen et al. [5]	1971	Not applicable
2	Chiyo et al. [6]	1975	Low birth weight, short stature, blepharoptosis, strabismus, short bulbous nose, hearing loss, syndactyly
3	Breuning et al. [7]	1977	Low birth weight, psychomotor retardation, blepharoptosis, small kidneys
4	Côté et al. [8]	1978	Low birth weight, psychomotor retardation, feeding problems, micrognathia, cataracts, proteinuria
5	Bernheim et al. [9]	1979	Psychomotor retardation, blepharoptosis, high nasal bridge, nystagmus, small mouth, systolic murmur
6	Rosi et al. [10]	1979	Low birth weight, psychomotor retardation, blepharoptosis, micrognathia
7	Pagano et al. [11]	1980	Not applicable
8	Ferrando et al. [12]	1981	Low birth weight, psychomotor retardation, low-set ears, blepharoptosis, high forehead, clinodactyly
9	Eden et al. [13]	1985	Low birth weight, psychomotor retardation, microcephaly, blepharoptosis
10	Smith et al. [14]	1985	Low birth weight, small brain, no olfactory bulbs, interventricular septal defect, no uterus and vagina
11	Scarborough et al. [15]	1986	Microcephaly, blepharoptosis, mild hypertelorism, holosystolic murmur, syndactyly
12	Burd et al. [16]	1988	Low birth weight, psychomotor retardation, prominent forehead, low-set ears, prominent nasal bridge
13	Lytle et al. [17]	1989	Low birth weight, microcephaly, low-set ears, pulmonary stenosis, ventriculoseptal defect, patent ductus arteriosus
14	Nakajima et al. [18]	1995	Low birth weight, microcephaly, broad forehead, blepharoptosis, small mouth, atrial septal defect
15	Rudnik-Schöneborn et al. [19]	1997	Low birth weight, psychomotor retardation, small mouth, low-set ears, muscular hypotonia
16	Röthlisberger et al. [20]	1999	Low birth weight, psychomotor retardation, microcephaly, blepharoptosis, abnormal ears
17	Villa et al. [21]	2000	Low birth weight, psychomotor retardation, seizures, microcephaly, narrow forehead, low-set ears
18	Ng et al. [22]	2001	Low birth weight, psychomotor retardation, prominent forehead, microstomia, low-set ears
19	Giardino et al. [23]	2002	Low birth weight, psychomotor retardation, hypertrophy, strabismus, proteinuria, reduced number of glomeruli
20	Domínguez et al. [2]	2003	Low birth weight, hypotrophy, microcephaly, prominent forehead, blepharoptosis, small mouth, low-set ears
21	Stohler et al. [24]	2007	Hearing loss, low-set ears, pulmonary stenosis, atrial septal defect, hydronephrosis
22	Andrieux et al. [25]	2008	Low birth weight, psychomotor retardation, epilepsy, epicanthus, hypertelorism
23	Bart et al. [26]	2011	Psychomotor retardation, tracheomalacia, micrognathia, macroglossia, feeding problems
24	Berner et al. [27]	2013	Low birth weight, psychomotor retardation, blepharoptosis, proteinuria
25	Castiglione et al. [28]	2013	Psychomotor retardation, hearing loss, heart defects, renal dysfunction
26	Varvagiannis et al. [29]	2013	Psychomotor retardation, prominent forehead, micrognathia, strabismus, scoliosis
27	Yoshimura-Furuhata et al. [4]	2015	Psychomotor retardation, hydronephrosis, proteinuria, glomerular sclerosis
28	Jankauskienė et al. [1]	2016	Low birth weight, psychomotor retardation, hearing loss, hypotonia, hydrocephalus, microstomia, pulmonary stenosis, proteinuria
29	Sivasankaran et al. [30]	2016	Low birth weight, psychomotor retardation, low-set ears, macrocephaly
30	Morinaga et al. [31]	2017	Short stature, psychomotor retardation, pulmonary stenosis, atrial septal defect
31	Peterman et al. [3]	2020	Psychomotor retardation, seizures, microcephaly, hydrocephalus, corpus callosum agenesis, scoliosis
32	Türkylmaz et al. [32]	2023	Low birth weight, psychomotor retardation, hearing loss, structural brain anomalies, prominent forehead, blepharoptosis, low-set ears, hypothyroidism

due to the grunting and an incubator for eight days during postpartum adaptation. Furthermore, she remained in the hospital for a feeding disorder with the need for enteral nutrition through a nasogastric tube.

Neurologists have dispensed the patient because of psychomotor development delay, especially gross motor skills, affected speech, and epilepsy treated with valproic acid. The

differential diagnosis included magnetic resonance imaging and endocrinologic examination, which were negative. However, genetic testing diagnosed chromosome 6p duplication. Except for the symptoms described above, her clinical manifestations were short stature, microcephaly with facial dysmorphism, specifically hypertelorism, a broad nasal bridge, a small mouth, and scoliosis with the Cobb angle of

105° (Fig. 1). Early-onset scoliosis (EOS) is a special group of spinal deformities, including patients who developed the deformity before 10 years of age. EOS involves the whole etiological spectrum of deformities, from idiopathic, congenital, and syndromic to neuromuscular curves [33].

Our patient was diagnosed with EOS at six months of age. The treatment started conservatively, so a brace was prescribed. The patient tolerated and wore the brace for 15 h daily; however, a significant progression of the curve was observed. At the time of surgery, our patient was classified as 9S4 + p2 according to the Classification of Early Onset Scoliosis introduced by Williams et al. Considering the patient's young age and further predictable progression of the curve based on the natural history of EOS, surgical treatment was indicated. The goal of the surgery in these patients is not only to restore normal alignment of the spine but also to prevent patients from developing Thoracic Insufficiency Syndrome, which is associated with increased morbidity and mortality due to cardiovascular deterioration. Most significant lung and alveolar development occur in the first ten years of life and is dependent, among other factors, on the dimensions of thorax cavities, which can be considerably affected by spine and trunk deformity [34]. Therefore, so-called growth-friendly techniques are used at this age. Non-fusion surgical procedures allow for deformity correction and, at the same time, further growth of the spine and trunk, which is crucial for preventing thoracic insufficiency syndrome. In this case, orthopaedists performed the modified Shilla technique [35]. If no complications during growth occur, this patient will undergo just one more surgery after reaching skeletal maturity, which is convenient in

comparison to the traditional growing rods technique that requires multiple surgeries and repetitive general anaesthesia during childhood.

The preoperative examination included paediatric, cardiological, neurologic, and anaesthetic evaluation. The 12-lead electrocardiography (ECG) and echocardiography revealed no structural or functional heart pathology. Spirometry yielded minimally due to limited cooperation. The chest X-ray showed no significant pathology on chest organs, except for the spine deviation. Neurologist examination, electroencephalography (EEG) included, recommended the standard administration of the antiepileptic medication before the surgery because the last focal seizures were three months ago, and the blood level of acid valproic was in the recommended range. Lab results were without significant deviation, liver enzymes and renal functions included. The previous anaesthesia was uncomplicated, ASA physical status was III, and the Mallampati score was evaluated as 2. Atropine, midazolam, and promethazine were administered PO before surgery as a premedication.

The girl was indicated for scoliosis surgery in the prone position. We chose total intravenous anaesthesia (TIVA) in a combination of propofol and remifentanyl because of the motor evoked potentials (MEP) monitoring. Rocuronium, the non-depolarising muscle relaxant, was administered to facilitate the intubation. Bag-mask ventilation and endotracheal intubation via direct laryngoscopy were uncomplicated, and the anaesthesiologist evaluated airways with a Cormack-Lehane score of II. The arterial line for invasive blood monitoring was cannulated like two IV lines. The bispectral index (BIS) for depth of anaesthesia monitoring extended the standard vital function monitoring during anaesthesia, such as ECG, invasive blood pressure, pulse oximetry, capnography, and body temperature. The anaesthesiologist targeted the doses of propofol and remifentanyl to a recommended range of depth of anaesthesia measured by BIS. The surgeons performed T₃ – L₅ scoliosis correction from the posterior approach. The surgery time was 420 min, and it was successful, without complications. She received 2000 ml of balanced crystalloids, and the urine output was 700 ml. The blood loss was 450 ml (15.5 ml/kg). Tranexamic acid was administered before skin incision at a dose of 15 mg/kg IV, and red blood cells with fibrinogen were administered based on blood count and coagulation test. The MEP monitoring was not suggestive of new neurological injury development. The acetaminophen was administered before the end of the surgery. The anaesthesiologist weaned from artificial ventilation and extubated the patient 15 min after the end of surgery. The patient was admitted to the intensive care unit (ICU), and the respiratory and cardiovascular functions were stable during admission.

The postoperative care was favourable. No new neurological deficit was observed postoperatively. The pain was



Fig. 1 X-ray before scoliosis surgery, Cobb angle of 105°

well controlled with a combination of opioids and non-opioid pain medication so the patient could start rehabilitating on the first postoperative day. New organ dysfunction, kidney disease development, seizures, significant lab results deviation, or infections did not develop. The patient was transferred to a standard ward on the third postoperative day. Further postoperative care was uncomplicated. The instrumentation was in the correct position, and the wound healed per primam intentionem. The patient was discharged on the seventh postoperative day. The six-month outcome was favourable, without any complications.

3 Discussion

Chromosome 6p duplication syndrome is a sporadic genetic disorder. Clinically severe organ disorders associated with this syndrome can significantly affect the perioperative period and postoperative outcomes. Due to the lack of patients, there is no robust data on perioperative management. One way to improve these patients' outcomes is to present case reports. In this article, we describe the first comprehensive perioperative management and discuss the challenges expected from this syndrome. The article may help all members of a perioperative multidisciplinary team caring for patients with chromosome 6p duplication.

The preoperative assessment should focus on identifying and optimising potential organ dysfunctions. Congenital heart disease, such as atrial or ventricular septal defects, and pulmonary stenosis with right ventricular hypertrophy are some of the common disorders associated with 6p duplication syndrome. Cardiologists should perform 12-lead ECG and echocardiography to diagnose potential heart pathology [13, 31]. Neurologist examination with EEG should be indicated in patients with a history of epilepsy to recommend antiepileptics perioperative administration. However, the neurological exam and other examinations required can yield minimally due to developmental delay [25]. Renal involvement, such as glomerulopathy, proteinuria, hydronephrosis, or other congenital urinary tract abnormalities, has been described in most patients. The monitoring of kidney functions should be recommended as a standard part of the preoperative assessment [1, 4].

General anaesthesia with volatile anaesthetics was described in the literature [31]. We report another possibility of anaesthesia maintenance, TIVA, possibly with non-depolarising muscle relaxants administration. Of the most dreaded complications in anaesthesiology is the scenario "cannot intubate, cannot oxygenate". Although uncomplicated bag-mask ventilation, successful nasotracheal, and, at this point, orotracheal intubations have been reported, the authors recommend being prepared for difficult airway

management due to facial dysmorphism and dental abnormalities [31, 36]. Vital function monitoring should be extended compared to healthy patients because the anaesthetic drugs can significantly affect cardiovascular functions in patients with heart pathology [31]. The authors recommend invasive blood pressure and BIS monitoring to titrate the anaesthetics more easily, especially in high-risk surgeries.

Except for the standard postoperative approach, postoperative care should closely monitor 6p duplication syndrome-associated complications. These complications include especially a new kidney disease development or seizure exacerbation. The authors recommend regular monitoring of renal functions and antiepileptic drug administration as soon as possible after the surgery [1, 4, 25].

4 Conclusion

We describe the first case of comprehensive perioperative management of a patient with chromosome 6p duplication. Our patient underwent posterior scoliosis correction under total intravenous anaesthesia. In this case, we report the multidisciplinary approach to managing these patients and minimizing the complications of the perioperative period. Describing this case and understanding the syndrome can help all care team members improve the outcome of patients with chromosome 6p duplication.

Acknowledgements The authors thank all HCPs who cared for this patient in the perioperative period, especially Marcela Matýšková and Milan Filipovič. They also thank the patient and parents for agreeing to this publication.

Author Contributions J.H., T.P., M.G., M.P. wrote the main manuscript text. J.H., T.P., M.G., M.P. prepared figures R.G., M. R. revised it critically for important intellectual content. All authors whose names appear on the submission: approved the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding Open access publishing supported by the institutions participating in the CzechELib Transformative Agreement.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interest The authors have no competing interests to declare that are relevant to the content of this article.

Financial Interest The authors declare they have no financial interests.

Non-Financial Interests None.

Informed Consent Statement The legal representative signed the informed consent for this publication.

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5.5 Anesthesia and Perioperative Management for Surgical Correction of Neuromuscular Scoliosis in Children: A Narrative Review

Poslední prací, která vznikla v rámci tématu anestezie u pacientů podstupujících operační výkon pro neuromuskulární skoliózu, je přehledový článek věnující se komplexně celé anesteziologické problematice [1, 38].

Jak již bylo zmíněno výše, pacienti s neuromuskulárními syndromy tvoří významně heterogenní skupinu, a to od relativně běžných nemocí až po extrémně vzácné syndromy, které svou náročností představují jednu z nejtěžších populací v rámci anesteziologické a perioperační péče. Interdisciplinární přístup by měl být aplikován již od fáze indikace k operačnímu výkonu až do propuštění pacientů domů [1, 33, 38]. V naší přehledové práci se věnujeme jednotlivým etapám anesteziologické péče. Tedy předoperační optimalizaci stavu a přípravě pacientů s neuromuskulárními syndromy. Dále samotnému anesteziologickému managementu. V poslední části publikace pak identifikujeme specifika a výzvy, na které je potřeba se zaměřit v průběhu pooperační péče [1, 38].

Ačkoli se jedná o relativně okrajové téma v rámci anesteziologické péče, naše práce byla v roce 2023 publikována v časopise Journal of Clinical Medicine (IF 3,0, Q1 v kategorii MEDICINE, GENERAL & INTERNAL dle WoS). O přínosu naší publikace pro klinickou praxi svědčí i poměrně velký počet citací, konkrétně v době psaní této habilitační práce byl přehledový článek citován již 16krát dle databáze WoS [1, 38].

Review

Anesthesia and Perioperative Management for Surgical Correction of Neuromuscular Scoliosis in Children: A Narrative Review

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Abstract: Scoliosis is the most frequent spinal deformity in children. It is defined as a spine deviation of more than 10° in the frontal plane. Neuromuscular scoliosis is associated with a heterogeneous spectrum of muscular or neurological symptoms. Anesthesia and surgery for neuromuscular scoliosis have a higher risk of perioperative complications than for idiopathic scoliosis. However, patients and their relatives report improved quality of life after the surgery. The challenges for the anesthetic team result from the specifics of the anesthesia, the scoliosis surgery itself, or factors associated with neuromuscular disorders. This article includes details of preanesthetic evaluation, intraoperative management, and postoperative care in the intensive care unit from an anesthetic view. In summary, adequate care for patients who have neuromuscular scoliosis requires interdisciplinary cooperation. This comprehensive review covers information about the perioperative management of neuromuscular scoliosis for all healthcare providers who take care of these patients during the perioperative period, with an emphasis on anesthesia management.

Keywords: neuromuscular scoliosis; anesthesia; total intravenous anesthesia; children; spondylosurgery; spine



Citation: Hudec, J.; Prokopová, T.; Kosinová, M.; Gál, R. Anesthesia and Perioperative Management for Surgical Correction of Neuromuscular Scoliosis in Children: A Narrative Review. *J. Clin. Med.* **2023**, *12*, 3651. <https://doi.org/10.3390/jcm12113651>

Academic Editor: Won Ho Kim

Received: 5 May 2023

Revised: 17 May 2023

Accepted: 20 May 2023

Published: 24 May 2023



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1. Introduction

Scoliosis is the most common spinal deformity in children. It is an abnormal lateral deviation of the spine, greater than 10° in the frontal plane. The lateral curvature is typically in combination with deviation in the sagittal plane (hyper/hypokyphosis or hyper/hypolordosis) and vertebral rotation [1,2]. The pathophysiological effect of scoliosis is complex and multiorgan. Besides musculoskeletal disturbances, cardiovascular, pulmonary, or psychosocial effects are described [1–4]. Scoliosis is categorized according to the etiology. The most frequent types include idiopathic (80%), congenital, and neuromuscular scoliosis [1,3]. Neuromuscular scoliosis, scoliosis associated with any neuromuscular syndrome, can be followed by alterations of vital functions by underlying diseases. Patients are at higher risk of curve progression to a significant deviation, which can lead to ventilation/perfusion (V/Q) mismatching, respiratory failure, and cor pulmonale [3,5–7]. The surgical correction of any scoliosis is indicated to prevent curve progression or the progression of restrictive lung disease. Other indications, especially in neuromuscular scoliosis, include improving posture and nursing care. Although there is a higher rate of perioperative complications in neuromuscular scoliosis surgery, patients and their relatives report improvements in quality of life after the surgery [7–9].

Scoliosis surgery is a major surgery associated with a high possibility of serious complications, particularly in patients with neuromuscular scoliosis. According to our experience, the management of patients undergoing surgery for idiopathic scoliosis is well described in many articles. This narrative review is focused on the differences and specifics of pediatric patients with neuromuscular scoliosis. Our goal is to bring relevant and comprehensive information to all perioperative team members, such as anesthesiologists, pediatricians, surgeons, or neurophysiologists, since interdisciplinary cooperation could be crucial for the patient outcome. We highlight the challenges both in the perioperative management of scoliosis surgery itself and in high-risk anesthesia for patients with neuromuscular disease [9–11].

2. Methods

The main limitation for the research was the diversity and rareness of some neuromuscular syndromes and the fact that neuromuscular scoliosis correction is a serious surgery but also a marginal topic requiring specialized care. For this reason, we choose an extended time frame of 1995–2022. The Google Scholar (<https://scholar.google.com>, Access time: 1–31 August 2022) [12], PubMed (<https://pubmed.ncbi.nlm.nih.gov/>, Access time: 1–31 August 2022) [13], Embase (<https://www.embase.com/>, Access time: 1–31 August 2022 [14] and Web of Science databases (<https://www.webofscience.com/wos/author/search>, Access time: 1–31 August 2022) [15] were used to search the literature. The aim was to map the whole perioperative process (preanesthetic assessment, anesthesia, and postoperative care).

We used a combination of terms, such as “anesthesia”, “anesthetic management”, “neuromuscular disease”, “neuromuscular disorders”, “neuromuscular scoliosis”, “pediatric”. Besides this, we focus on specific issues in each section of this article.

Preanesthetic assessment Medical Subject Headings (MeSH) terms: “airway management”, “respiratory functions examination”, “cardiovascular examination”, “neurological examination”, “invasive access”, “nutrition”, “prehabilitation”.

Anesthesia and intraoperative MeSH terms: “air embolism”, “blood management”, “intraoperative neurophysiological monitoring”, “malignant hyperthermia”, “orphan anesthesia”, “perioperative monitoring”, “prone position”, “rhabdomyolysis”, “temperature management”, “total intravenous anesthesia”, “vital functions monitoring”.

Postoperative care MeSH terms: “intensive care unit”, “postoperative care”, “respiratory insufficiency”, “ventilator weaning”, “hemodynamic monitoring”, “emergence delirium”, “pain management”, “postoperative pain”, “fluid therapy”, “acute kidney injury”, “nutritional support”, “postoperative hemorrhage”, “postoperative complication”, “postoperative wound infection”, “rehabilitation”.

3. Results

3.1. Preanesthetic Assessment

The preanesthetic evaluation requires a multidisciplinary approach. An integral part of this assessment is the identification of decompensated functions or organ reserves that could bring possible perioperative complications and its maximal preoperative optimization [9,10]. Anesthesiologists should individually consider the extent of preoperative testing according to the risks and benefits, scoliotic curvature severity, mental state or physical status with comorbidities, and type of planned surgical technique. The administration of pharmaceutical premedication has to be considered individually in patients with neuromuscular disorders. There are no precise data about dose restriction; it should be decided with respect to the neurological status and other associated aspects, such as the vagus stimulator, Lioresal pump, or severity of lung disease [10,16–18]. We list the specifics of preanesthetic assessment divided according to the ABCDE approach. This represents a widely respected approach to seriously ill patients, including the pediatric population. This approach could be used to anticipate and systematically prevent life-threatening complications [19].

3.1.1. Airways

Difficult airway management should be expected with a higher rate in patients with neuromuscular disorders as some syndromes are associated with facial dysmorphism, abnormal habitus, or limited mobility, especially limited neck mobility [17,19]. Anesthesiologists should search for risk factors for difficult airway management during the preanesthesia visit and prepare for airway securing, including advanced airway techniques such as video laryngoscopy or awake fiber optic intubation [20–22].

3.1.2. Breathing

The evaluation of respiratory function should be extended to chest X-radiation (X-ray), peripheral capillary oxygen saturation (SpO₂) measurement, and pulmonary function tests such as spirometry. Chest X-ray can provide information about airway deviations or signs of recurrent gastric content aspiration [10,18]. Spirometry quantifies the type and severity of lung dysfunction, typically restrictive lung disease. However, a development delay may impair the feasibility of spirometry. Severe restrictive lung disease (forced vital capacity <50% of normal values in patients with muscle weakness and symptoms of hypoventilation, or forced vital capacity <30% of normal values without muscle weakness) predicts a higher risk of respiratory complications such as pneumonia or prolonged weaning from ventilatory support [10,23]. Another method to determine high-risk patients (when spirometry is not available) is carbon dioxide monitoring during sleeping. However, this method is unreliable to detect hypoventilation and it is not preferred nowadays. Non-invasive bioelectrical impedance is available for clinicians. These monitors measure the tidal volume, minute ventilation, or respiratory rate to detect hypoventilation. It is essential to reduce the risk of perioperative complications and respiratory failure by optimizing respiratory function. Prehabilitation in cooperation with physiotherapists and pneumologists can improve patients' outcomes. This prehabilitation includes preoperative training in non-invasive ventilation or assisted coughing [23–25].

3.1.3. Circulation

Electrocardiography (ECG) is a standard part of preoperative assessment that can detect arrhythmias potentially associated with autonomic dysfunction [9–11]. Careful cardiologist examination with echocardiography is recommended in patients with myocardial dysfunction, because many neuromuscular syndromes are associated with heart disease, such as cardiomyopathy, valve disease, congenital heart disease, or limited stress tolerance. Preoperative cardiologic evaluation should be suggested in patients without myocardial dysfunction if pulmonary hypertension is suspected [10,20,26,27].

3.1.4. Disability (Neurology)

The neurological examination must provide a precise diagnosis with the known pathophysiology of a neuromuscular disorder. It helps with individualized anesthesia planning, which should reduce the risk of many anesthetic complications (see below). Exact neurological status description is suitable for juridical reasons, in case of postoperative neurological deficit development [27]. In addition, neurological deficit description helps with physiotherapy planning [26,27]. Epilepsy is diagnosed more frequently in patients with neuromuscular disorders [28]. Actual electroencephalography (EEG) should be considered, and perioperative antiepileptic drug administration must respect neurologist recommendations, taking into account possible interactions with anesthetic drugs [26,27].

3.1.5. Exposure (Environment)

Signs of difficult invasive access and suitable places for cannulation should be actively searched for. The signs of difficult access include muscle contractures or abnormal body proportions [27]. Other specific examinations should be indicated individually, e.g., nutritionists' recommendations in patients with signs of malnutrition [9,29]. Except for standard blood tests, plasma levels of myoglobin or creatine kinase should be obtained. These

markers are often altered in patients with neuromuscular disease. However, plasma levels before surgery are helpful to determine the baseline and monitor these levels' dynamics after surgery when suspecting rhabdomyolysis development [27,30,31].

3.2. Anesthesia and Intraoperative Management

Anesthesia for neuromuscular scoliosis is a challenge for the anesthetic team. Intraoperative management is specific and unique due to neuromuscular disease in children with its possible associated complications, such as intraoperative neurophysiological monitoring (IONM), high blood loss, patient positioning—typically pronation—fluid shift, long surgical times, and body temperature loss [10,27,31].

3.2.1. Anesthetic Management

Anesthesia and the choice of anesthetic drugs have to respect the pathophysiological category of the syndrome. Data on orphan syndromes are scarce. However, anesthesiologists can obtain information about the syndromes and anesthetic management from internet sources, e.g., published unique case reports, Orphananesthesia [32]. Total intravenous anesthesia (TIVA), most often the combination of propofol and remifentanyl, is the most suitable and safe method, especially in the case of IONM. It requires a sufficient intravenous (IV) line. However, cannulation can be difficult due to the joint contractures or abnormal habitus [33,34]. The indication of a central venous catheter should be considered individually according to the comorbidities and expectation of the need for vasopressors [10,27]. Ultrasound-guided cannulation can reduce the incidence of unsuccessful attempts and also increases the safety of the procedure [10,20]. Depth of anesthesia monitoring is recommended for TIVA to prevent overdosing and shorten the time of awakening after the surgery [10,18,27].

Non-depolarizing muscle relaxants can be administered safely. The effect of these drugs is variable, typically prolonged in patients suffering from neuromuscular disorders. Therefore, any administration of neuromuscular blocking agents should be followed by monitoring of the depth of neuromuscular blockade [26,27,32]. Rocuronium with available antagonist sugammadex represents a safe combination to provide complete recovery after the blockade and allow reliable IONM [35].

Anesthesia and vital functions should be managed individually with consideration of the age and comorbidities of each patient. The aim of ventilation and oxygenation is normoxia and normocapnia [9,10]. Anesthesiologists can manage perioperative vital functions according to vital function levels mentioned in the European Pediatric Advanced Life Support (EPALS) Guidelines 2021 [36]. The target blood pressure is not strongly recommended in children during scoliosis surgery. However, some data recommend maintaining a mean arterial blood pressure (MAP) near 65 mmHg, but approximately the fifth percentile of the mean and systolic arterial blood pressure for the relevant age group can be used safely. Transesophageal echocardiography should be considered in high-risk patients, e.g., patients with myocardial dysfunction or pulmonary hypertension. In addition, intraoperative transesophageal echocardiography helps to evaluate the volume status and manage goal-directed fluid therapy [10,33,37].

3.2.2. Neuromuscular Disease and Associated Complications—Malignant Hyperthermia and Rhabdomyolysis

Perioperative complications in patients with neuromuscular syndrome are observed at a higher rate compared to patients without neuromuscular disorders [9]. The most severe complications are malignant hyperthermia (MH) and rhabdomyolysis. Their development depends on the pathophysiology category of concrete neuromuscular disease, e.g., myopathies represent a high risk for MH or rhabdomyolysis [38].

MH is a syndrome caused by the hypermetabolic response with increased carbon dioxide production to suxamethonium or volatile anesthetics exposure. Early diagnosis and treatment with cooling of the patient are essential. It is recommended to use local pro-

protocols (personalized guidelines with particular locations of, e.g., dantrolene and emergency numbers) for the treatment of malignant hyperthermia. These protocols should be available in the operation room, where surgeries for high-risk patients are performed. To manage the crisis, the elimination of triggers (mentioned anesthetic drugs), hyperventilation with 100% oxygen, treatment of hyperkalemia (calcium administration for membrane stabilization, salbutamol, and insulin/glucose administration for kalemia reduction) are necessary. Dantrolene administration and symptomatic therapy, such as arrhythmia treatment, should be managed according to the actual guidelines [38–40].

Rhabdomyolysis is a condition associated with muscle damage. Myoglobin, potassium, and creatine kinase are released from the intracellular space [41]. Rhabdomyolysis was described after succinylcholine or volatile anesthetics exposure as anesthesia-induced rhabdomyolysis. Moreover, it was reported after muscle injury during a long surgery with inadequate patient positioning [38,42]. The differential diagnosis of MH can be complicated, and both syndromes can initially present with similar clinical signs. Rhabdomyolysis is typical of hyperkalemia, creatine kinase elevation, or myoglobinuria with “cola-colored urine”. Myoglobinuria can be monitored postoperatively. Therapy has to focus on hyperkalemia treatment, hyperventilation with 100% oxygen, the prevention of acute kidney injury development, volume therapy, and the elimination of triggers [38,41,42].

3.2.3. Intraoperative Neurophysiological Monitoring

IONM represents an important and, in recent years, rising method for neural structure injury monitoring. Anesthetic management, including oxygenation, ventilation, massive blood loss, or hypotension, can influence the IONM reproducibility. IONM reproducibility can be limited in patients with neuromuscular disorders. The anesthetic team has to create the best conditions for IONM. The most common anesthetic technique is TIVA, typically in a combination of propofol and remifentanyl. This combination is suitable for patients with neuromuscular disorders and allows early awakening from anesthesia if surgeons require the wake-up test. Other intravenous agents can be applied considering their adverse effect profiles and contraindications. Modern trends show the use of ketamine in combination as a co-analgesic, which reduces the total dose of propofol and remifentanyl. All neuromuscular relaxants interfere with motor evoked potential (MEP) monitoring. They are administered in the phase of induction to the anesthesia to facilitate airway securing. Other anesthesiological aspects include maintaining normoxia with normocapnia, preventing severe hypothermia (more than 2.5 °C from the baseline), and ensuring adequate blood flow to the spinal cord. This means maintaining normotension during surgery (see above), namely increasing MAP above 85 mmHg when MEP is decreased. Anesthesiologists must consider the transfusion trigger to ensure adequate perfusion and oxygenation (see below) [43,44].

3.2.4. Positioning and Associated Complications

The prone position is the most frequent position for scoliosis surgery to facilitate access to the spine. This position is associated with several complications caused by raised intra-abdominal or thoracic pressure. In addition, prone positioning is associated with a higher risk of postoperative visual loss [45–48].

Patients with neuromuscular disorders can suffer from joint and muscle contractures, and some syndromes can be associated with low bone density. There is a potential risk of iatrogenic injury. These conditions represent increased demands for exact positioning. Correct but considerate prone positioning, respecting joint mobility, and the pressure distribution on the chest and pelvis decrease the rate of complications. Aside from careful positioning on the operating room table, the anesthesia team should elevate the upper part of the body to decrease the intraocular pressure and reduce the risk of visual loss. Other factors in reducing the risk of postoperative visual loss are avoiding anemia, hypotension (see above), and preventing venous return obstruction due to malpositioning. Besides ensuring appropriate positioning before surgery, the anesthetic team should control the

body position during surgery. The patient may be harmed by manipulation by the operating team during surgery [45,46].

Advanced cardiopulmonary resuscitation with chest compressions is possible in a prone position. External cardiac massage may be performed with the palms placed over the patient's scapulae. Internal cardiac massage and direct defibrillation were performed successfully via left posterior thoracotomy in a patient with Duchenne's muscular dystrophy during scoliosis correction in a prone position [48]. However, anesthesiologists should consider turning the patient to a supine position in the case of a stabilized spine without prominent orthopedic tools for manipulation with instrumentation (rod pushers, connect ratchets, downtubes, etc.) [10,47,48].

3.2.5. Blood Loss and Patient Blood Management

Patients with neuromuscular disease are at a high risk of extensive blood loss because of prolonged and extensive procedures or bones with lower density. Strategies to reduce blood loss are still being discussed. Antifibrinolytics' effect in reducing blood loss and transfusion administration has been described in scoliosis surgery, especially in patients with neuromuscular disorders. Tranexamic acid is one of the most widely used antifibrinolytics. The recommended prophylactic dose is about 15 mg/kg IV. The optimal maintenance dose is unclear; current data mention infusions of 1–20 mg/kg/h. The risk of adverse events, thromboembolism included, has not been increased in prophylactic administration during scoliosis surgery [49–51].

Another means to reduce allogeneic blood transfusion is intraoperative cell salvage (Cell Saver). The blood is collected from the wound into a reservoir. Red blood cells can be re-infused to the patient after purification of the collected blood. It is a preferred method, especially in high-risk patients with neuromuscular disorders and a presumed low bone density [52,53].

Desmopressin increases von Willebrand factor and factor VIII levels. However, it does not have an effect in reducing blood loss. Prophylactic administration is not recommended [54].

Protocols for red blood cell transfusion triggers describe the administration of Red Blood Cells (RBC) at levels between 7 and 8 g Hb/dL. Other coagulation factors should be administered according to the laboratory or viscoelastic hemostatic assays ideally [54,55].

Patients with neuromuscular disorders or immobilization after extensive surgery, in combination with a post-surgical inflammatory state, are at a higher risk of deep vein thrombosis and pulmonary embolism. Early mobilization and mechanical prevention are recommended. Data on pharmacological prophylaxis are scarce. Low-molecular-weight heparin administration in the perioperative period until the normalization of the patient's condition should be considered after the validation of risk factors [56].

3.2.6. Body Temperature Management

As mentioned above, severe hypothermia, with a decrease in temperature of more than 2.5 °C from the baseline, interferes with IONM. Patients with neuromuscular disease, a lower body mass index, or a larger Cobb angle (the angle between the extension line of the upper and lower end plate of the most inclined vertebral bodies) are at a higher risk of hypothermia [5]. Other adverse effects include prolonged metabolism of anesthetic agents, coagulopathy with higher blood loss, and wound or respiratory infections. Preoperative and intraoperative active warming, or prewarming before surgery, is recommended to prevent hypothermia in patients with neuromuscular disorders [57,58].

3.3. Postoperative Care

3.3.1. Admission to Intensive Care Unit (ICU)

According to studies, most of the patients require admission to the ICU or pediatric ICU. However, the decision should be made individually, e.g., the recovery after surgeries with a duration under 4 h can be, in some cases, manageable at a postanesthesia care

unit. The possible predicting factors for ICU admission are a low weight, neuromuscular scoliosis, pre-existing respiratory pathology, and other comorbidities. A higher number of operated segments or a higher degree of spine curvature is not associated with ICU admission [59,60].

3.3.2. Airway and Breathing

Patients with neuromuscular scoliosis often suffer from preexisting respiratory diseases such as muscle weakness (e.g., Duchenne's muscular dystrophy) or restrictive disorders, most often caused by chest deformities, which leads to a risk of postoperative respiratory failure [61,62]. Facial dysmorphism in some syndromes is associated with difficult airways. Proper equipment for difficult airway management should be available at the ICU in case of the need for emergent reintubation. Reintubation or prolonged weaning is associated with a risk of ventilator-associated pneumonia or tracheal stenosis, so early successful weaning should be one of the main goals [63]. Bulbar weakness can also be part of some syndromes and lead to dysphagia, gastric regurgitation, dysphonia, or difficult expectoration [62]. Protocols for weaning and monitoring diaphragm function can help to achieve early extubation, leading to better patient outcomes [64,65]. Implementing non-invasive ventilation into weaning processes in high-risk patients can prevent prolonged intubation and tracheostomy [62,66–68].

3.3.3. Circulation

Early after the operation, at least ECG, non-invasive blood pressure, and peripheral oxygen saturation should be monitored. For patients without signs of hemodynamic instability (hypotension, arrhythmias, altered mental status, low diuresis, etc.), standard monitoring is sufficient. In cases of hemodynamically unstable patients, invasive blood pressure should be monitored. Hypotension should be treated with volumotherapy and vasopressors according to its severity. For the prediction of volume responsiveness in hemodynamically unstable children, unresponsive to initial fluid therapy, cardiac output monitoring with echocardiography is recommended if available. Cardiac output could be monitored also with non-invasive or invasive pulse waveform analysis, although the data on the use of these methods in children are limited. Central venous pressure monitoring and central venous oxygen saturation monitoring could provide a more complex view of the patient's status and its trend, but these types of monitoring should not be used as the sole method [69]. In children with pre-existing cardiac disease, transthoracic echocardiography could be helpful to determine the cardiac contractility, preload, signs of pulmonary hypertension, or a possible worsening of valvular diseases. The sources for this topic are rare, and the authors highlight the potential for further research in this area [9,36].

3.3.4. Disability (Neurology, Analgesia)

Dexmedetomidine sedation, in patients who require sedation after surgery, decreases the use of opioids and the risk of postoperative delirium when compared to midazolam [70].

Scoliosis correction is a type of surgery with an anticipated high postoperative pain level [70–72]. Patients with neuromuscular diseases are at a greater risk of undertreated pain [71,72]. Undertreated pain could lead to prolonged hospitalization, patient psychological trauma, and persistent postoperative pain [71]. The location of the most intense pain is the surgical wound. For most patients, it becomes tolerable after four days [71–73]. For this time period, the patient should be actively screened for their pain level and sufficiently treated. Multimodal analgesia should be chosen and started already during surgery to decrease opioid use. The most frequent opioid during surgery is remifentanyl. Remifentanyl's conversion to longer-acting opioids, such as sufentanil or piritramide, is necessary before the end of the surgery. Postoperative continuous opioid administration by a patient-controlled analgesia (PCA) pump is the gold standard for patients after idiopathic scoliosis correction. Neuromuscular scoliosis is sometimes associated with syndromes characteristic

of mental or severe physical impairments. Depending on the pain severity, the safe and effective use of PCA delivery may require the assistance of the pediatric patient's parents and/or a nurse. Epidural analgesia and regional analgesia (bilateral erector spinae plane block) initiated at the operating theater reduce postoperative opioid use [71–76]. Epidural analgesia could achieve better analgesia than PCA. The patient's neurologic status should be assessed before the administration bolus of local anesthetics because a sensory or motor blockade could occur. The risks associated with epidural analgesia do not differ from those of other surgery types [71,72]. For patients with idiopathic scoliosis, the intrathecal opioid (most often morphine or sufentanil) administration at the operation theater before the skin incision is associated with reduced intravenous opioid use during anesthesia and sufficient postoperative analgesia for the first 24 h. If morphine is lower than 20 µg/kg, the risk of respiratory depression is not higher than in the intravenous PCA method. Data on intrathecal morphine administration are limited in patients with neuromuscular scoliosis [71]. The bilateral erector spinae block in both the single-shot and catheter techniques has been successfully performed. The maximum dose of local anesthetic per 24 h needs to be respected to avoid systemic toxicity. Continuous wound infiltration seems to be an option for postoperative analgesia, but more research on this topic is required. Regional analgesia is often combined with non-steroidal anti-inflammatory drugs (NSAIDs) if needed [70–72,77]. Perioperative and postoperative low-dose ketamine infusion can also be an efficient part of multimodal pain management [77,78]. The intravenous use of local anesthetics (e.g., lidocaine) or gabapentinoids is controversial [70,77]. The indication, timing, and dosing scheme should undergo further research. The use of glucocorticoids should be explored more, but a single dose of dexamethasone after surgery seems to reduce the pain level without a higher risk of infection [70,77].

3.3.5. Electrolytes

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) can occur after spinal fusion in neuromuscular and idiopathic scoliosis. The therapy is not different compared to that for patients without neuromuscular disorders [79].

3.3.6. Fluids (Kidneys)

Acute kidney injury (AKI) was detected in children after spine surgery. Different stages of AKI were diagnosed in 17% (35 of 208) of patients. The risk factors include nephrotoxic medications (e.g., aminoglycosides, NSAIDs) and a low amount of fluids intraoperatively. The management of NSAIDs is often needed in the postoperative period. However, their administration should be reconsidered daily because NSAIDs reduce prostaglandin synthesis. This can lead to kidney hypoperfusion or nephritis. Moreover, other nephrotoxic medication administration risks versus benefits should be reevaluated every day [80].

3.3.7. Gastrointestinal Tract (GIT) and Nutrition

Preexisting dysphagia or gastroesophageal reflux can be worsened in patients with neuromuscular diseases. Tests and monitoring of dysphagia before postoperative realimentation can be helpful. Early postoperative nutrition should be started in malnourished patients prior to surgery. A good nutritional status can reduce the risk of postoperative infection [81]. Neuromuscular disease is also the leading risk factor for postoperative ileus, which is more likely in patients with extended bed rest. Monitoring symptoms of ileus (e.g., nausea, vomiting, abdomen distension) and early interventions can shorten the length of the hospital stay [81,82]. The risk of pancreatitis rises in cases of prolonged postoperative fasting. No cases of pancreatitis with organ failure, shock, or death have been reported. The impaired mental status or diminished pain due to high doses of analgesics and atypical clinical symptoms can make diagnostics difficult. Liver enzymes, amylase, and lipase measurement can help in obtaining a diagnosis. If pancreatitis develops, the standard treatment should be started immediately [82].

3.3.8. Hematology

The more significant depletion of coagulation factors is present in patients suffering from neuromuscular disorders. Routine control of the thrombin time, prothrombin time, partial thromboplastin time, and fibrinogen in combination with viscoelastic hemostatic assays should be done in postoperative care. In prolonged postoperative bleeding, extended tests should be considered (e.g., factor XIII level), and the standard treatment for coagulopathy should be started [83].

3.3.9. Infections

Infection is a leading complication in postoperative care after scoliosis surgery, with higher incidence in patients with neuromuscular disease. Urinary infection and pneumonia are the most frequent infections. The most common causes of urinary infections in hospitals are urinary catheters. Indications for the insertion and maintenance of urinary catheters should be reconsidered every day. Proper insertion techniques and maintenance care are a solution to reduce the risk of urinary infection [84]. The prevention of pneumonia is mostly the same as in other patients in the ICU. The specifics for patients with neuromuscular diseases are described above. Patients should also be routinely monitored for signs of wound infection [85,86]. The prevention of postoperative wound infection does not differ from standard care for wounds after spinal surgery.

3.3.10. Rehabilitation

Patients with neuromuscular diseases are supposed to have complex physiotherapy. A very important part of rehabilitation is breathing and coughing exercises because of the high incidence of preoperative respiratory complications and weak cough. The pre-rehabilitation should start prior to the surgery to train high-risk patients to breathe with NIV or use a cough assistant. Chest physiotherapy should be maximized one week prior to surgery [24].

4. Conclusions

Anesthesia and the perioperative management of pediatric patients for neuromuscular scoliosis surgery represent a significant challenge for all healthcare providers. This heterogeneous team involves surgeons, anesthesiologists, neurophysiologists, pediatricians, nurses, nutritionists, and physiotherapists. Every part of the management should be adequately planned because of the higher risk of perioperative complications compared to idiopathic scoliosis. Healthcare providers have to consider all risks arising from the surgery, anesthesia, and the nature of the disease as a multidisciplinary and individual approach to each patient can improve the postoperative outcome. Firstly, mentioned data focus on the maximal optimization of altered functions before surgery and patients' complex multidisciplinary prehabilitation. Secondly, adequate preparation of the anesthetic management regarding the specifics of neuromuscular syndromes, surgery, or anesthesia is essential for safety in the perioperative period. Thirdly, postoperative care in the ICU with adequate prevention, early identification, and treatment of possible complications can improve the postoperative outcome. All the described steps can lead to improved quality of life in patients with neuromuscular scoliosis.

Author Contributions: Conceptualization, search of the data, writing, J.H. and T.P.; supervision, M.K.; data analysis and review, M.K. and R.G. All authors have read and agreed to the published version of the manuscript.

Funding: This work was funded by the Specific University in Research provided by MŠMT, grant number MUNI/A/1105/2022, and MH CZ—DRO, grant number FNBr, 65269705.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: A narrative review with references retrieved from the databases of Embase, Google Scholar, Web of Knowledge, and PubMed was performed to obtain the related literature published.

Conflicts of Interest: The authors declare no conflict of interest.

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6 Práce vzniklé v souvislosti s anestezií u operačních výkonů s MEP

Motorické evokované potenciály představují jednu z modalit IONM. IONM zahrnuje soubor technik, mezi které řadíme kromě MEP také EEG, elektromyografii (EMG) a somatosenzorické evokované potenciály (SSEP), respektive zrakové či sluchové evokované potenciály (VEP, BAEP). Cílem IONM je posouzení zachování integrity CNS či PNS, respektive časná diagnostika jejich potenciálně reverzibilního poškození během operačního výkonu. Díky časně diagnostice tak minimalizujeme riziko ireverzibilního poškození neurologických struktur [1, 100]. Kombinace více technik IONM se využívá jako tzv. multimodální neuromonitorace. V rámci spondylochirurgie je to zpravidla kombinace SSEP a MEP. Z dalších rizikových výkonů, kromě operací páteře, kde je IONM využíván, jsou například operace aorty. [1, 100, 122, 123].

IONM ve spondylochirurgii, respektive u korekce skolióz u dětských pacientů, dnes představuje zlatý standard tak, jak jej doporučuje společnost Scoliosis Research Society (SRS) [124]. Před rutinní implementací IONM do klinické praxe byl využíván test probuzení pacienta, tzv. „wake-up“, který však neumožňuje reálně v čase identifikovat neurologické postižení, navíc vyžaduje spolupráci pacientů a je spojen s rizikem extrakce invazivních vstupů v pronační poloze. Proto je dnes využíván pouze v případech, kdy intraoperační nález nekoreluje s nálezem na IONM [125-127].

Multimodální neuromonitorace, tedy aplikace více modalit v průběhu výkonu, je tou nejlepší variantou IONM. Vyžaduje však erudované neurofyziology, kteří jsou celosvětově velmi omezeně dostupní, a proto ne vždy lze využít výhody multimodálního monitoringu.

I z tohoto důvodu jsou akceptovatelné jednodušší varianty neuromonitorace, např. operačním týmem řízená monitorace MEP, jak ji připouští SRS. V tomto případě však musí být neurofyziolog dostupný ke konzultaci pro řešení perioperačních nejasností [1, 124, 128, 129].

Anesteziologický tým poskytující anestezii pacientům v průběhu operačních výkonů s monitorací MEP musí ovládat anesteziologické techniky, respektive disponovat znalostmi, jak vytvořit optimální podmínky pro monitoraci MEP. Celá řada patofyziologických vlivů či anestetik totiž může negativním způsobem významně ovlivnit kvalitu snímání MEP, a tím i komfort operačního týmu a v neposlední řadě pak bezpečnost pacienta [1, 30, 31, 100].

Základními fyziologickými aspekty, kterými se ve spondylochirurgii snažíme optimalizovat podmínky pro monitoraci MEP, jsou udržení normální saturace hemoglobinu kyslíkem, respektive normoxémie, a dále normální ventilace, tedy normoxémie. Dále bychom měli udržovat fyziologické funkce pacienta v adekvátním rozmezí, tedy je třeba se vyhnout významné hypotenzi, anémii či hypotermii. Všechny tyto aspekty mohou ovlivňovat perfúzi míchy, tedy sekundárně i výbavnost MEP, aniž by došlo k iatrogennímu poškození neurologických struktur [1, 30, 31, 130]. Pokud jde o způsob vedení anestezie, zlatým standardem pro výkony s monitorací MEP je TIVA kombinující propofol a opioid, typicky remifentanil. Propofol ze všech běžně dostupných anestetik vede k nejmenšímu poklesu amplitudy MEP. To z něj činí nejrozšířenější anestetikum pro výkony s MEP. Druhou esenciální složkou TIVA jsou opioidy, které mají jen nevýznamný vliv na kvalitu MEP. Naopak benzodiazepiny, podobně jako thiopental, vedou k signifikantnímu poklesu amplitudy a prodloužení latence MEP. V kombinaci s prodlouženým metabolismem tak nejsou

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preferovány pro výkony vyžadující monitoraci MEP. Ketamin je anestetikum se zcela odlišným mechanismem účinku, které bylo úspěšně užíváno v anestetické dávce i jako koanalgetikum s menším efektem na kvalitu MEP a je tedy vhodnou součástí TIVA pro výkony s touto monitorací. Další léčiva, která nejsou vhodná během operačních výkonů s MEP, jsou inhalační anestetika a svalová relaxancia. Tato léčiva svým myorelaxačním účinkem významně ovlivňují kvalitu MEP. Svalová relaxancia je však možné použít v rámci úvodu do celkové anestezie k usnadnění intubačních podmínek, nicméně další dávka by neměla být podána. Inhalační anestetika by pro svůj silný inhibiční účinek na amplitudu MEP neměla být vůbec užita [1, 30, 31, 130, 131].

Remimazolam je nové léčivo ze skupiny benzodiazepinů s ultrakrátkým účinkem. Poprvé byl schválen a úspěšně použit pro celkovou anestezii v roce 2020 v Japonsku. Vyznačuje se vysokou afinitou k receptorům pro kyselinu gama-aminomáselnou typu A (GABA-A), kde vede k hyperpolarizaci membrány [132, 133]. Jedním z prvních pracovišť v Evropě, kde byl remimazolam použit v rámci celkové anestezie, se stala FN Brno. Do budoucna by remimazolam mohl představovat bezpečnou alternativu k ostatním sedativům/anestetikům, která kombinuje výhody farmakodynamických vlastností benzodiazepinů a farmakokinetických vlastností remifentanilu. Tedy díky přítomnosti esterové vazby ve své struktuře je rychle hydrolyzován plazmatickými esterázami. Od svého schválení byl úspěšně aplikován jako sedativum či anestetikum, zejména v asijských zemích. V Evropě byl schvalovací proces zpomalen během pandemie COVID-19 a ještě nedávno byl dostupný pouze jako sedativum, v současnosti však již jako anestetikum k celkové anestezii [132-134].

Úspěšné použití remimazolamu u pacientů podstupujících operační korekci skoliotické deformity jsme v roce 2025 prezentovali formou posteru na kongresu ČSARIM. Tento poster získal ocenění za nejlepší poster v kategorii kazuistik. Naše kazuistická série korespondovala se závěry prací z asijských zemí, kde byl remimazolam úspěšně aplikován v rámci výkonů s IONM, včetně dětských pacientů. Remimazolam tak velmi pravděpodobně poskytuje vhodné podmínky pro IONM [135, 136].

Úspěšné použití remimazolamu, bezpečný a nekomplikovaný perioperační průběh s úspěšnou monitorací MEP jsme publikovali v časopise Biomedical Papers-Olomouc (IF 0,8; Q4 v kategorii MEDICINE, RESEARCH & EXPERIMENTAL) v roce 2026. Tato práce však t. č. prochází formálními úpravami a autorskou korekturou, z tohoto důvodu nemůže být citována ani dále prezentována.

6.1 Základní principy anesteziologické péče k perioperační monitoraci transkraniálních motorických evokovaných potenciálů

Jedním z prvních projektů, na který jsme se zaměřili při optimalizaci péče o pediatrické pacienty podstupující korekci skoliózy, byla práce věnující se jednotlivým aspektům anesteziologické péče a jejich vlivu na kvalitu a výbavnost IONM, respektive MEP [1, 131]. Jak již bylo výše zmíněno, správně vedená anestezie může zásadním způsobem ovlivnit podmínky pro IONM. Erudovaný anesteziologický tým tak díky znalosti této problematiky vytváří bezpečné prostředí nejen pro pacienta, ale také pro operační tým, čímž zvyšuje pocit jistoty tohoto týmu během operace. To vše významně zlepšuje pooperační outcome našich pacientů [1, 30, 31, 131].

V rámci pochopení specifik anesteziologické péče jsme se rozhodli pro hlubší prostudování této problematiky. V naší přehledové práci jsme analyzovali jednotlivé typy anestetik a jejich vliv na kvalitu parametrů MEP. Druhá část přehledového článku se pak věnovala aspektům vnitřního prostředí, kterým je při výkonech s monitorací MEP třeba věnovat zvýšenou pozornost. Z analýzy vyplynulo obecné doporučení o nutnosti vedení anestezie formou TIVA, kombinací propofolu a remifentanilu, s péčí o vnitřní prostředí ve smyslu normoxémie, normokapie, normotermie, eurolémie, bez těžké anémie či hypotenze [1, 31, 131]. Na základě tohoto článku byl vytvořen lokální protokol pro vedení anestezie během výkonů s IONM.

Přehledový článek byl publikován v časopise Česká a Slovenská Neurologie a Neurochirurgie (IF 0,5; Q4 v kategorii NEUROSCIENCES dle WoS) v roce 2022 [1, 131].

Základní principy anesteziologické péče k perioperační monitoraci transkraniálních motorických evokovaných potenciálů

Basic principles of anaesthetic care for intraoperative transcranial motor evoked potentials monitoring

Souhrn

Intraoperační sledování evokovaných potenciálů představuje v současnosti významnou neurofyzilogickou metodu používanou v rámci operačních výkonů, u kterých hrozí riziko narušení funkční integrity CNS. Jednou z nejvýznamnějších monitorovacích modalit jsou transkraniální motorické evokované potenciály (MEP), které mohou být efektivně sledovány proškoleným operačním týmem pod dohledem neurofyzilogů. Pro správný neuromonitoring je potřeba efektivní spolupráce mezi operačním týmem, anesteziologickým týmem a neurofyzilogem. Cílem tohoto článku je vytvořit ucelený přehled všech potenciálních faktorů, jež mohou ovlivnit výbavnost MEP v intraoperačním období. Autoři se zaměřují nejen na vliv jednotlivých léčiv používaných v rámci anestezie, ale i na samotnou formu anestezie či nefarmakologické faktory s možným vlivem na výbavnost MEP. Tento přehledový článek poskytuje základní informace všem, kteří se podílejí na perioperační péči o pacienty podstupující výkony s monitorací MEP, a může tak usnadnit spolupráci a zefektivnit komunikaci napříč zainteresovanými obory.

Abstract

Intraoperative evoked potentials monitoring is an essential neurophysiological modality used in surgeries with a risk of CNS functional integrity damage. Transcranial motor evoked potentials (MEPs) are one of the most important modalities. Trained surgeons can effectively monitor MEPs under the supervision of a neurophysiologist. Effective cooperation among all operating team members, anaesthesiologists, and neurophysiologist is essential for proper neuromonitoring. The aim of this article is to comprehensively summarize all possible factors that can affect the quality of intraoperative MEPs monitoring. The authors focus on the effect of anaesthetic drugs and anaesthetic management, including anaesthesia maintenance or non-pharmacological factors, which can affect the MEPs' reproducibility. This review provides essential information to all members of a perioperative team that take care for patients during surgery with MEPs monitoring. This information can facilitate cooperation and streamline communication across all related disciplines.

Úvod

Intraoperační monitorace transkraniálních motorických evokovaných potenciálů (MEP) v současné době představuje standardní součást operačních výkonů, u kterých hrozí riziko perioperačního neurologického defi-

citu. Jedná se zejména o výkony v neurochirurgii, spondylochirurgii, případně o operace aorty, které mohou být spojeny s mechanickým či ischemickým poškozením míchy vedoucím k iatrogennímu poškození pacientů. Monitorace MEP poskytuje velmi cenné in-

Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.
The Editorial Board declares that the manuscript met the ICMJE "uniform requirements" for biomedical papers.

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Přijato k recenzii: 18. 7. 2022
Přijato do tisku: 18. 10. 2022

Klíčová slova

celková anestezie – motorické evokované
potenciály – neurofyzilogický
monitoring – totální intravenózní anestezie

Key words

general anaesthesia – motor evoked poten-
tials – neurophysiological monitoring – total
intravenous anaesthesia

formace operačnímu týmu o zachování funkční integrity v operované oblasti a zásadně tak přispívá ke zvýšení bezpečnosti pacientů. Současně s tím vede ke zvýšení jistoty celého týmu [1–3]. Transkraniální elektrická stimulace vedoucí k vybavení MEP na-

hradila dříve běžně užívaný wake-up test. Díky tomu není nutné rutinní probuzení pacientů v průběhu operačního výkonu se zvýšeným rizikem selfextubace, poškození invazivních vstupů či narušení operační polohy spojené s motorickým neklidem pacienta. Další nevýhodou je nemožnost stanovení porušení integrity nervového systému reálné v čase, ale až s latencí, v době probuzení [4,5].

K adekvátní neurofyziologické monitoraci je klíčová týmová spolupráce mezi operačním týmem, neurofyziologem a anesteziologickým týmem. Peroperační anesteziologické postupy mohou mít zásadní vliv na výbavnost MEP a nepřímo ovlivnit výsledný neurologický stav operovaných pacientů. Anesteziologický tým tak musí zvládnout management výkonů s neurofyziologickou monitorací, neboť je známo, že farmaka užívaná v anestezii více či méně ovlivňují výbavnost MEP. Stejně tak musí být zajištěny stabilita vnitřního prostředí, adekvátní oxygenace, ventilace či teplotní komfort pacienta [6,7]. V případě jakýchkoli pochybností při omezené výbavnosti MEP musí být anesteziolog připraven vyloučit potenciální anesteziologické vlivy. Proto je nezbytné vybudování důvěry mezi jednotlivými členy operačního týmu a adekvátní komunikace, která prokazatelně zlepšuje pooperační výsledný stav pacientů [8,9].

Tento přehledový článek je zaměřen na základní aspekty anesteziologické péče, která může ovlivnit výbavnost peroperační monitorace MEP. Zaměříme se na vytvoření adekvátních podmínek správnou volbou anestetik, monitoraci hloubky anestezie a péči o stabilitu vnitřního prostředí.

Transkraniální motorické evokované potenciály

Motorické evokované potenciály jsou používány při posuzování funkční integrity motorického systému. Tyto potenciály jsou vybaveny prostřednictvím elektrické stimulace s užitím podkožních elektrod v pozici C1 a C2, resp. C3 a C4, které jsou umístěny na skalpu podle standardního systému EEG 10/20, přičemž stimulovaný kortex se typicky nachází pod anodou v důsledku vyšší stimulační účinnosti ve srovnání s katodou [10].

Původně bylo v průběhu celkové anestezie obtížné vybavit a správně reprodukovat MEP, zvláště při užití inhalačních anestetik. Nicméně novější anesteziologické postupy s užitím totální intravenózní anestezie (TIVA), stejně tak jako vývoj stimulačních metod, vedly k rozšíření této metody do praxe i v prů-

běhu celkové anestezie. Sled krátkých stimulačních pulzů umožňuje vybavit a snímat MEP ze svalů horních i dolních končetin s užitím povrchových nebo jehlových elektrod [10,11].

V souvislosti s aplikací elektrického impulzu panují obavy ohledně rizika vyvolání epileptických záchvatů, popálenin hlavy či srdečních arytmií. V některých pracích bylo popsáno snadné vyvolání záchvatů po kontinuální, několik vteřin trvající stimulaci mozku o frekvenci 50–60 Hz [10]. Nicméně při standardním použití v průběhu operace nebylo prokázáno, že by transkraniální stimulace vedla k vyvolání záchvatů. Z tohoto hlediska je použití MEP bezpečnou metodou [12].

Interpretace MEP je obtížná a vyžaduje zkušenosti. Některé studie prokazují výskyt motorického deficitu navzdory žádné či nesignifikantní změně v parametrech MEP. To může být způsobeno poškozením jednotlivého nervového kořene, které se neprojeví změnou neurofyziologické monitorace. V některých případech byla naopak popsána alterace MEP, ačkoli nebyl pozorován motorický deficit [13,14].

Při interpretaci MEP se jako signifikantní změna považuje jejich ztráta (vymizení, absence), která znamená pooperační parézu. Některé retrospektivní studie však za tzv. cut-off, vyžadující zvýšenou obezřetnost a komunikaci mezi členy týmu, považují kombinaci poklesu amplitudy o více než 70 % a prodloužení latence o více než 10 %. Pro tyto arbitrární hranice je však potřeba více studií [15,16].

Inhalační anestezie

Inhalační anestetika prokazatelně vedou ke snížení excitability motorických neuronů. Užití volatálních anestetik může být kontraindikováno u pacientů s určitým preexistujícím neurologickým onemocněním pro riziko maligní hypertermie či rhabdomyolýzy, jakou jsou např. myopatie [17]. Mechanismus účinku inhalačních anestetik není dosud zcela jasný. Předpokládá se ovlivnění propustnosti buněčných membrán či působení na některých iontových kanálech. Použití sevofluranu i desfluranu vede v závislosti na dávce k poklesu amplitudy a prodloužení latence MEP, podle některých prací má desfluran silnější inhibiční efekt oproti sevofluranu. Ačkoli lze zvýšením stimulačního impulzu dosáhnout alespoň parciální výbavnosti MEP v průběhu výkonu, inhalační anestetika vedou k falešně pozitivním změnám ve výbavnosti MEP. Z toho důvodu není jejich užití vhodné [18,19].

Použití oxidu dusného (N₂O) do nosné směsi vedlo u zdravých dobrovolníků ke snížení amplitudy MEP [20]. Expozice N₂O u dlouhých výkonů (operace aorty, skolióza, ...) navíc významně zvyšuje riziko pooperační nevolnosti a zvracení (PONV), není tedy vhodnou součástí celkové anestezie pro dlouhé výkony s monitorací MEP [21].

Zlatým standardem pro operace s monitorací MEP je TIVA, dle možností s použitím režimu Target Controlled Infusion (TCI) a s monitorací hloubky anestezie [10].

Totální intravenózní anestezie

Totální intravenózní anestezie je definována jako forma celkové anestezie s aplikací jednotlivých složek anestezie výhradně intravenózní cestou, tedy bez užití inhalačních anestetik. Ve srovnání s doplňovanou inhalační anestezii se jedná o méně používanou techniku, nicméně anesteziologové by tuto techniku měli rutinně ovládat, protože ne všichni pacienti mohou být exponováni inhalačním anestetikům (maligní hypertermie, rhabdomyolýza). U některých pacientů je pak TIVA preferovanou metodou (nitrolební hypertenze, hypovolémie, vysoké riziko PONV). TIVA přináší výhody v podobě redukce PONV nebo právě u výkonů s monitorací MEP. Při této monitoraci je však vhodné minimalizovat podávání bolusů anestetik. Pokud musíme aplikovat bolus anestetik, např. z důvodu rizika poškození pacienta, je nutné o této skutečnosti informovat všechny členy týmu na operačním sále. Standardní součástí TIVA, zvláště při současném použití svalových relaxancií, by měla být monitorace hloubky anestezie pro vyšší riziko peroperační bdělosti ve srovnání s anestezii vedenou inhalačními anestetiky. Česká společnost anesteziologie, resuscitace a intenzivní medicíny (ČSARIM) doporučuje monitoraci hloubky anestezie vedené prostřednictvím TIVA [22,23].

Propofol

Propofol představuje v současnosti nejrozšířenější intravenózní anestetikum používané jak k úvodu, tak vedení anestezie. Mechanismus anestetického účinku spočívá v aktivaci receptorů A₁ a γ -aminomáselnou kyselinu (receptor GABA_A). Výhodou užití je rychlá eliminace především v játrech i při kontinuálním podávání. Jeho nežádoucí účinky jsou alterace kardiiovaskulárních funkcí a arteriální hypotenze, útlum dechového centra či tzv. syndrom propofolové infuze (PRIS), který zpravidla vzniká při aplikaci dávky vyšší

než 5 mg/kg/h po dobu delší než 48 h. Operační výkony takové délky bývají popisovány vzácně, nicméně je potřeba s touto komplikací počítat při pokračující sedaci po operačním výkonu na JIP [24]. Propofol v závislosti na dávce snižuje amplitudu MEP, mechanismus tohoto poklesu není dosud známý. Pokles amplitudy je však ve srovnání s inalačními anestetiky nižší a anestezie vedená kontinuální infuzí propofolu je vhodnou metodou k monitoraci MEP [25].

Benzodiazepiny

Benzodiazepiny působí rovněž prostřednictvím aktivace receptorů GABAA. Délka působení benzodiazepinů je přímo úměrná délce jejich podávání, nicméně délka jejich působení i po jednorázovém podání anestetické dávky je podstatně delší oproti výše zmíněnému propofolu. Proto může být u delších výkonů prodloužené vyvedení z celkové anestezie, zvláště u pacientů s alterací jaterních či renálních funkcí. Benzodiazepiny jsou tudíž v rámci úvodu a vedení anestezie užívány v monoterapii spíše zřídka [26]. Podobně jako u propofolu dochází v závislosti na dávce k poklesu amplitudy MEP, nicméně nízké dávky benzodiazepinů, t. j. nejčastěji zastoupených midazolamem, sloužící k premedikaci či anxiolyze neovlivňují signifikantně MEP [27].

Etomidát

Dalším intravenózním hypnotikem je etomidát, který působí jako modulator receptorů GABAA a tím zesiluje inhibiční účinek GABA. Jeho výhodou je, že mezi ostatními hypnotiky vyvolává nejmenší kardiiovaskulární a respirační depresi. Z tohoto důvodu je preferován u kardiálně kompromitovaných pacientů. Stále diskutovaným tématem je vliv etomidátu na inhibici syntézy kortizolu. Etomidát je rychle metabolizován jaterními esterázami, předpokládá se i vliv metabolizace plazmatickými esterázami, díky čemuž může být alternativou pro vedení anestezie při kontraindikaci propofolu [28]. Limitace prací zkoumající vliv etomidátu na výbavnost MEP jsou dány nižším počtem pacientů. Nicméně etomidát byl úspěšně aplikován u výkonů s neurofyzilogickou monitorací. Parametry MEP byly velmi variabilní, od vzestupů amplitudy až po nevýznamný pokles. Signifikantní pokles amplitudy byl zaznamenán jen ojediněle, po aplikaci bolusu. Navíc podle některých prací byly pooperačně monitorované hladiny kortizolu po kontinuální infuzi etomidátu v normě [29,30].

Ketamin

Ketamin představuje zcela unikátní anestetikum, které působí dominantně jako antagonist receptoru N-methyl-D-asparagové (NMDA) kyseliny a tím navozuje tzv. disociativní anestezii. Mezi jeho výhody patří sympatomimetický účinek a minimální vliv na dechové centrum. Pro jeho analgetický účinek je ketamin v současnosti stále více využíván anesteziology k terapii jak akutní, tak i chronické bolesti. Pro analgetický účinek bývají aplikovány nižší, subanestetické dávky [31]. Vliv ketaminu na výbavnost MEP byl zkoumán jak v anestetických, tak v subanestetických dávkách. Současná literatura uvádí, že ketamin má příznivé účinky a může být bezpečně aplikován u operací s monitorací MEP. V subanestetických dávkách byly dokonce naměřeny vyšší amplitudy MEP bez vlivu na latenci [32,33].

Thiopental

Thiopental patří mezi nejdéle používané barbituráty. Mechanismus účinku spočívá rovněž v aktivaci receptorů GABAA. Jeho zásadní nevýhodou je prodloužená eliminace po kontinuálním podávání, nicméně kontinuální infuze thiopentalu není v rámci anestezie běžnou praxí. Ačkoli thiopental negativně ovlivňuje výbavnost MEP, může být bezpečně použit k úvodu do celkové anestezie, neboť jednorázová dávka k úvodu nepředstavuje problém při další monitoraci MEP [34,35].

Dexmedetomidin

Dexmedetomidin patří do skupiny vysoce selektivních α -2 agonistů, který snadno přestupuje do CNS a tam inhibuje uvolnění zejména noradrenalinu, méně pak acetylcholinu či serotoninu. Dominantně je užíván k sedaci pacientů na JIP. Nicméně v posledních letech je stále více zkoumán jeho vliv v perioperačním období pro jeho možný koanalgetický efekt, dále snižuje výskyt pooperačního třesu. Použití dexmedetomidinu k vedení anestezie u intubovaných zatím nemá schválenou indikaci, a tudíž se jedná o podání off-label. Jeho aplikace v kombinaci s dalšími anestetiky však umožňuje snížit celkové dávky opioidů i anestetik. Z nežádoucích účinků, jaké jsou popisovány v průběhu tzv. bdělé sedace neintubovaných pacientů, je třeba počítat s rizikem arteriální hypotenze a bradykardie [36,37]. Ve studiích zkoumajících vliv dexmedetomidinu na MEP byl dexmedetomidin aplikován ke standardní kombinaci propofol/opioid za

monitorace hloubky anestezie. Dexmedetomidin v závislosti na dávce signifikantně ovlivňuje amplitudu MEP a podle současných dat nelze jeho užití v průběhu celkové anestezie u operací s neurofyzilogickou monitorací MEP doporučit [38,39].

Opioidy

Opioidy zajišťují analgezii prostřednictvím opioidních receptorů v CNS a periferním nervovém systému (PNS). Jsou důležitou součástí doplňované anestezie, tlumí adrenergní autonomní reakci na chirurgickou stimulaci. V současné době je u dlouhých výkonů preferována kontinuální infuze remifentanilu. Jedná se o silný opioid, který je metabolizován tkáňovými a plazmatickými esterázami. Bez ohledu na délku trvání infuze či farmakokinetickou variabilitu našich pacientů je jeho kontext senzitivní po dobu 3 min. Je možné použít i další opioidy se stejným mechanismem účinku, např. sufentanil, nicméně je nutné znát farmakokinetické vlastnosti jednotlivých opioidů. Použití opioidů má jen nesignifikantní vliv na výbavnost MEP v průběhu operace [27,40,41].

Svalová relaxancia

Periferní myorelaxancia navozují svalovou relaxaci obsazením nikotinového receptoru nervosvalové ploténky. V anestezii jsou využívány především pro usnadnění endotracheální intubace či optimalizaci operačních podmínek. V závislosti na dávce snižují výbavnost MEP až po úplnou absenci jejich vybavení, čímž mohou zásadně ovlivnit až znemožnit neurofyzilogickou monitoraci. Proto je doporučeno aplikovat svalovou relaxancia s krátko- či střednědobým účinkem, a to při úvodu do anestezie k zajištění dýchacích cest, bez další aplikace v průběhu operace. Monitorace reziduální svalové blokády pomocí akcelerometrie zvyšuje bezpečnost pacientů. Obnovení plné svalové síly (TOFr nad 90 %) umožňuje získat výchozí parametry MEP před začátkem operace bez vlivu myorelaxancií. Další možností je aplikace sugammadexu, kterým lze během 3 min zvrátit vliv reziduální nervosvalové blokády navozené rocuroniem či vekuroniem [27,42,43].

Vnitřní prostředí a fyziologické změny

Péče o vnitřní prostředí v rámci výkonů s monitorací MEP musí cílit na zajištění adekvátní dodávky kyslíku do mycí, která má vysoké nároky na přísuv kyslíku a dalších metabolitů potřebných pro správnou funkci nervové

Tab. 1. Anesteziologické kroky při signifikantní změně motorických evokovaných potenciálů.

Vedení anestezie	Vnitřní prostředí
úprava hloubky anestezie	optimalizace oxygenace, ventilace
výměna anestetik	korekce volémie, anemie
přidání adjuvancií (ketamin, ...)	korekce hypotermie při změně o min. 2,5 °C
vyloučit vliv svalové relaxace	korekce arteriální hypotenze

tkáně. Ideální anesteziologická péče tak cílí na optimalizaci oxygenace, ventilace, perfuze míchy a teplotního managementu [27].

Extrémní hypoxémie či hyperoxémie, stejně tak jako hypokapnie, respektive hyperkapnie vedou k alteraci MEP. Mírné vychýlení těchto fyziologických funkcí nepovede ke změně amplitudy či latence [44,45].

Adekvátní dodávka kyslíku do tkání souvisí s hrazením krevních ztrát a respektováním transfuzního triggeru dle aktuálních doporučení. V současné době je preferován restriktivní přístup s indikací transfuze při hladině hemoglobinu mezi 70–80 g/l [27,46].

Perfuzi míchy je zajišťována prostřednictvím autoregulačních mechanismů, ale i u zdravých jedinců při běžném rozmezí středního arteriálního tlaku (MAP) je třeba počítat s rizikem ischemie míchy způsobené lokálními faktory, a tím se změnami v neuromonitoringu. Preventivní aplikace permissivní hypotenze proto není doporučována. Naopak někdy může být nutné zvýšit MAP k zajištění adekvátní perfuze míchy na podkladě zhoršení neuromonitorace. Navíc je třeba respektovat věk pacienta, komorbidity, jako jsou arteriální hypertenze či diabetes mellitus, které mohou dále posouvat autoregulační práh směrem nahoru [27,44].

S dodávkou kyslíku do míchy také souvisí adekvátní náplň cévního řečiště. Hypovolémie může vést k arteriální hypotenzii a nedostatečné perfuzi míchy, hypervolémie může způsobit otok nervových obalů, případně otok skalpu, kde jsou umístěny stimulační elektrody. Prodlužuje se tak dráha nutná ke stimulaci, což se projeví sníženou výbavností MEP [45].

Teplotní management hraje zásadní roli nejen v rámci perioperačních komplikací, jako jsou ranné infekce, prodloužená eliminace léků s prolongovaným probouzením či rozvoj koagulopatie [47]. Hypotermie vede k poruše axonálního vedení ve smyslu snížení rychlosti, hypertermie má opačný efekt. Změny v monitoraci MEP byly prokázány

při změně tělesné teploty o více než 2,5 °C oproti výchozí tělesné teplotě. V tomto rozmezí bychom se tak měli pohybovat při monitoraci MEP [27,44,45].

Anesteziologické kroky při alteraci MEP

V případě signifikantních změn MEP je nutná vzájemná spolupráce a komunikace mezi anesteziologickým týmem, operačním týmem a neurofyziologem s cílem včasné identifikace problému. Při těchto situacích je vhodné přechodně přerušit operativu a ověřit funkčnost a správné nastavení neurofyziologické monitorace. V případě, že se jedná o změny MEP pod neurotopickou úrovní chirurgické manipulace, se zachováním výbavnosti MEP nad touto úrovní, bude se jednat pravděpodobně o příčinu chirurgickou [27].

Při globální alteraci MEP je třeba hledat příčinu systémovou, respektive anesteziologickou. Anesteziologický tým by se měl zaměřit na vedení anestezie, kontrolu polohy pacienta a korekci vnitřního prostředí (tab. 1). Při příliš hluboké anestezii je nutné upravit hloubku anestezie. Případně lze zvážit přidání ketaminu do kombinace s cílem snížení dávky ostatních anestetik a s tím spojeného zlepšení výbavnosti MEP. Po úvodu do anestezie je v neposlední řadě nezbytné vyloučit vliv neuromuskulární blokády a případně zvážit farmakologickou antagonizaci či vyčkání spontánního zotavení z nervosvalové blokády. Kontrola polohy pacienta je nutná jednak z důvodu možného pohybu pacienta při práci operačního týmu, jednak z důvodu změny polohy při motorické odpovědi na transkraniální stimulaci. Změna polohy pacienta může ovlivnit prokrvení operované oblasti a tím může být změněna výbavnost MEP. Dle potřeby je vhodné korigovat krevní tlak k zajištění adekvátní perfuze míchy a podat krevní deriváty při hladině hemoglobinu pod 70 g/l. Důležitou součástí anesteziologické péče je zajistit vy-

hívání pacienta s cílem prevence hypotermie z důvodu výše zmíněných nežádoucích účinků. V rámci monitorace MEP je dostačující zabránit výkyvům tělesné teploty o více než 2,5 °C oproti výchozí teplotě. Posledním krokem při selhání těchto postupů je provedení wake-up testu k posouzení motorické deficity u bdělého pacienta [27,44,45,48].

Závěr

S přibývajícím počtem operací s možností monitorace zachování funkční integrity nervové tkáně (operace mozku, páteře či aorty) stoupají nároky na všechny členy týmu pečující o pacienta na operačním sále. Výhodou této monitorace je vyšší bezpečnost pro pacienty, ale i vyšší jistota pro operátory. MEP představují v současnosti nejvýznamnější metodu intraoperační neurofyziologické monitorace. Pro správnou a kvalitní monitoraci je nezbytná spolupráce operačního týmu, neurofyziologa a anesteziologického týmu.

Tento přehledový článek se zaměřuje na základní principy, ze kterých by měl každý anesteziologický tým vycházet, aby byl schopen zajistit co nejlepší podmínky pro monitoraci MEP. Současně podává informace o anesteziologických krocích, které jsou nezbytné při signifikantní poruše výbavnosti MEP.

Konflikt zájmů

Autoři prohlašují, že nemají žádný konflikt zájmů v souvislosti s předmětem práce.

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6.2 Challenging anesthesia of the patient on ketogenic diet therapy scheduled for scoliosis surgery under motor evoked potentials monitoring: a case report

Naše další práce byla publikována jako dopis redakci, jedná se však o další kazuistiku prezentující poměrně vzácné metabolické onemocnění, které vyžadovalo komplexní interdisciplinární přístup. Popsali jsme případ 19leté pacientky trpící syndromem GLUT-1 deficiencie (Glut1-DS), onemocněním charakterizovaným poruchou příjmu glukózy v mozku v důsledku postižení glukózového transportéru 1 [1, 132, 138].

Pacienti s tímto onemocněním trpí častými epileptickými záchvaty, typicky rezistentními k farmakologické terapii. Jednou z terapeutických možností vedoucích k signifikantní redukci záchvatů je ketogenní dieta s cílem tvorby ketoláték jako alternativního zdroje energie pro mozek [137, 138]. Problémem perioperačního managementu pacientů na ketogenní dietě je progres acidózy s poruchou vnitřního prostředí či tzv. ztráta ketózy s následnou exacerbací epileptických záchvatů. Cílem interdisciplinární péče je minimalizovat vliv perioperačního lačnění a vyhnout se prolongované infuzi propofolu, jejíž délka však není jasně stanovena ani doporučena [137, 139].

V naší práci popisujeme proces předoperační přípravy, od konzultace dětských epileptologů, kteří se specializují na ketogenní diety, až po samotnou anestezii a pooperační péči. Epileptologové pacientce rozepsali parenterální nutrici o přesně definovaném poměru tukové a netukové energie, která byla pacientce aplikována ve fázi předoperačního i pooperačního lačnění cestou ČŽK. Anestezie byla vedena formou TIVA, nicméně namísto propofolu byl použit midazolam v redukováné dávce. Naopak byla signifikantně navýšena dávka remifentanilu, to vše za přísné monitorace indexu hloubky anestezie a frontálního

EEG. Vyšší intenzita transkraniální stimulace umožnila detekci kvalitních MEP při aplikaci nižších dávek midazolamu a vyšších dávek remifentanilu. Pooperační péče byla komplikována poklesem ketolátek v krvi, nicméně bez rozvoje epileptogenní aktivity. Po opětovné konzultaci s dětskými neurology byla přerušena parenterální alimentace pacientky a zahájeno cílené hladovění, v rámci kterého došlo opět k zahájení ketogeneze a úpravě stavu. Popis tohoto specifického anesteziologického přístupu ukázal alternativní možnosti vedení anestezie v případě nemožnosti použít propofol [1, 137].

Dopis redakci byl publikován v časopise Journal of Anesthesia (IF 2,8; Q2 v kategorii ANESTHESIOLOGY dle WoS) v roce 2023 [1, 137].



Challenging anesthesia of the patient on ketogenic diet therapy scheduled for scoliosis surgery under motor evoked potentials monitoring: a case report

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Received: 14 May 2023 / Accepted: 9 July 2023 / Published online: 9 August 2023
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Keywords Motor evoked potentials · Midazolam · Remifentanyl · Total intravenous anesthesia · Case report

To the Editor:

Although propofol represents a “gold standard” from anesthetic drugs for total intravenous anesthesia (TIVA) with intraoperative neurophysiological monitoring (IONM), the anesthetic team should have an alternative plan in rare cases when the propofol is contraindicated, and remifentanyl, a new ultra-short-acting benzodiazepine, is not available [1, 2]. We describe a patient suffering from glucose transporter type 1 deficiency syndrome (Glut1DS) with the history of epilepsy treated by ketogenic diet therapy (KDT) scheduled for scoliosis surgery under IONM. The prolonged propofol administration was contraindicated due to high doses of carbohydrates contained in propofol that may worsen epilepsy. In rare cases, prolonged propofol infusion can lead to propofol infusion syndrome (PRIS) in patients on KDT,

and that is why anesthetic team has to prepare an alternative management to allow quality IONM [3].

The patient provided informed consent for this case. A 19-year-old girl (height 160 cm, weight 52 kg) was scheduled for progressive T3–L2 scoliosis surgery, ASA physical status III. The girl was born at full term, and the adaptation in the postpartum period was without problems. She has suffered from hypopituitarism and Glut1DS on KDT, diagnosed at age six after a series of epileptic seizures. The KDT ratio was 3:1, which means 3 g of fat to 1 g of carbohydrate plus protein. Most of the calorie intake was delivered from fats, specifically 216 g of fats per day, and other calorie intake was delivered from 30 g of carbohydrates and 42 g of proteins. Total energy intake was 2233 kcal per day.

The patient has been observed with scoliosis from 13 years. The deformity worsened after growth hormone substitution. Back pain worsened the quality of life. Finally, she was indicated for surgical correction. The Cobb angle was 83°. Except for standard preanesthetic assessment, the neurological examination from Children's University Hospital was indicated to recommend KDT administration in the perioperative period. Specific preoperative measures included central venous line insertion a day before surgery to administer 1/3 of the calculated daily energy intake in the morning before the surgery and the remaining 2/3 after the surgery in the intensive care unit (ICU).

We chose TIVA for intraoperative monitoring of motor evoked potentials (MEP). However, propofol should be avoided because carbohydrates in its solvent may induce loss of ketosis and increase the risk of postoperative seizures [3]. We administered 1.5 mg/kg of ketamine, 0.1 mg/kg of midazolam, and 1 µg/kg of remifentanyl for anesthesia induction. The depth of anesthesia was monitored by the bispectral index (BIS). We administered remifentanyl 0.4–0.5 µg/kg/min and midazolam 0.2 mg/kg/h for maintaining BIS

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between 50 and 60 after tracheal intubation. MEP were reproducible before skin incision with the application of increased stimulation intensity. The higher doses of remifentanyl without hemodynamic deterioration during the surgery allowed reduce the total dose of midazolam. Lower doses of midazolam and anesthesia maintained to higher BIS levels (50–60) allowed sufficient MEP monitoring. MEP latency and amplitude were reproducible during the whole surgery. The surgery was uncomplicated, and MEP parameters were without significant alteration. After the surgery, we administered 10 µg of sufentanil and transferred the patient to the ICU. The patient was extubated about 30 min after the admission to ICU.

Postoperative care was complicated by excessive stress response associated with high-extensive surgery. It led to low serum ketone levels, specifically β-hydroxybutyrate serum level. However, epileptic seizures did not occur. We did not administer parenteral nutrition in the first two postoperative days to start ketogenesis. On the 3rd postoperative day, the patient started with PO nutrition after fasting when the ketone level rose. Further postoperative care was uneventful, and the patient was discharged home 11 days after the surgery without a new neurological deficit. The 4-month follow-up was a favorable outcome for the patient without a new neurological deficit or seizures.

Perioperative management of children on KDT is a challenge for all healthcare providers in the perioperative period. KDT is indicated in children with drug-resistant epilepsy and other metabolic or neurological disorders, such as Glut1DS. The basic principle is ketone production, an alternative energy source for the brain. It is assumed that ketone (β-hydroxybutyrate, acetoacetate, and acetone) production and caloric restriction probably decrease cerebral glucose utilization and reduce neuronal excitability. These metabolic changes reduce the incidence of seizures, although the exact mechanism remains unknown. However, KDT has many adverse effects, and the perioperative period can be associated with a higher risk of metabolic complications, such as worsening acidosis or loss of ketosis and exacerbating seizures. Complex preoperative planning is essential for a good postoperative outcome. Unfortunately, the recommendations for anesthetic management are based on a low number of patients. In addition, these recommendations include avoiding high doses of propofol for a prolonged period due to the risk of PRIS [3].

Propofol is the dominant anesthetic drug for TIVA with IONM. However, all anesthetists should be prepared for “plan B” in rare cases when the propofol is contraindicated [2, 4]. Benzodiazepines were routinely used for TIVA before the propofol era. However, benzodiazepine perioperative administration was reduced significantly. In addition, higher doses of benzodiazepines can lead to a significant decrease in MEP amplitude. This side effect

can be reduced by increased MEP stimulation intensity and benzodiazepine administration in a low doses, as possible, e.g., with a combination of ultra-short-acting opioid, remifentanyl, in higher doses [2, 4]. Short-acting benzodiazepines, such as midazolam in our case, can be considered in case of propofol contraindication. The authors recommend a depth of anesthesia monitoring, an essential condition to avoid overdosing with a negative influence on MEP monitoring and on the other hand the periods of awareness.

Remimazolam is a promising new ultra-short-acting benzodiazepine that could reduce anesthesiologists' concerns associated with the side effects of benzodiazepines. Remimazolam-based anesthesia was described during surgery with IONM and in pediatric surgery with MEP monitoring. However, remimazolam was approved for clinical use recently, and it is not available worldwide [1, 5, 6]. Its administration for TIVA with IONM needs further studies to confirm its promising profile. It could extend the spectrum of safe anesthetic drugs used for TIVA.

Author contributions JH and MK drafted the manuscript. JH, MK and OH analyzed the data. OH, MR and RG revised the manuscript. All authors have read and approved the final manuscript.

Funding This work was supported by the [Specific University in Research provided by MŠMT] under Grant [MUNI/A/1105/2022] and [MH CZ—DRO] under Grant [FNBr. 65269705].

Declarations

Conflict of interest All authors declare no conflict of interest.

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6.3 The influence of depth sedation on motor evoked potentials monitoring in youth from 4 to 23 years old: preliminary data from a prospective observational study

Hlavní část výzkumu v oblasti anestezie u operačních výkonů s monitorací MEP jsme zaměřili na posouzení vlivu hloubky anestezie na výbavnost, kvalitu a interpretaci MEP operačním týmem, to vše u dětí a mladistvých. Jak již bylo uvedeno dříve, vliv jednotlivých anestetik na kvalitu MEP byl dobře popsán, nicméně jasná data o vlivu hloubky anestezie stále chybí. Designovali jsme tedy prospektivní observační studii (SCOL studie), v rámci které byl zkoumán vliv hloubky anestezie, definované indexem hloubky anestezie, na MEP. Důležitým aspektem byla interpretace MEP operačním týmem, nikoliv neurofyziology, aby byl akcentován klinický význam při prakticky celosvětovém nedostatku neurofyziků [1, 124, 128, 140].

Naše studie byla schválena etickou komisí FN Brno a po registraci na Clinical-Trials.gov byla zahájena v září 2020. Hlavním cílem studie SCOL bylo testovat hypotézu, zda různé úrovně hloubky anestezie, podle indexu hloubky anestezie měřeného bispektrálním indexem (BIS), ovlivňují výbavnost MEP a jejich interpretaci operatéry. V rámci sekundárních cílů jsme pak popsali dílčí parametry MEP, tedy latenci a amplitudu, při různých úrovních hloubky anestezie [1, 140].

Počet pacientů nutný k potvrzení hypotézy byl stanoven „power analýzou“ na 150. Zařazováni byli děti a mladiství (biologický věk byl stanoven nejen datem narození, ale i kostním věkem z RTG pánve) indikovaní k operaci skoliotické deformity v TIVA (propofol a remifentanil) s operačním týmem monitorovanými MEP. Naopak, vyřazovacími kritérii byli pacienti s kontraindikací podávání propofolu či remifentanilu, pacienti bez možnosti

umístění elektrod k monitoraci MEP či BIS do standardní pozice nebo pacienti podstupující korekci skoliózy s MEP monitorovanými neurofyziology. První MEP byly monitorovány dle lokálního protokolu při „mělčí“ anestezii (BIS 55–65) po uspání, zajištění pacienta a otočení do pronace. Tyto MEP byly nastaveny jako výchozí a sloužily k porovnání s dalšími MEP měřeními v pozdějších fázích. Před kožní incizí byla prohloubena anestezie k BIS 35–45 a byly zaznamenány druhé MEP. V průběhu výkonu byla hloubka anestezie udržována v rozmezí BIS 35–65 dle lokálního protokolu pro anestezii při operacích skolióz. MEP byly vždy monitorovány dle lokálního protokolu pro monitoraci MEP operačním týmem po instrumentaci šroubů, tyčí a korekci křivky [1, 140].

S ohledem na omezení operativy v důsledku pandemie COVID-19 jsme se rozhodli zpracovat předběžná data prvních 50 pacientů. Již tento počet pacientů je v celosvětovém ohledu u studií skoliotických deformit dětských pacientů unikátní. MEP byly úspěšně vybaveny u všech 50 pacientů při obou úrovních hloubky anestezie. Amplitudy MEP při BIS 35–45 dosahovaly průměrně 84,5 % velikosti výchozích amplitud při BIS 55–65. Latence MEP při BIS 35–45 dosahovaly průměrně 104 % doby výchozích latencí při BIS 55–65. Tyto alterace byly hodnoceny jako statisticky významné, nicméně žádná z nich nebyla dle lokálního protokolu klinicky významná. Tedy tyto změny neovlivňovaly interpretaci MEP operačním týmem [1, 140].

Ačkoli bylo iniciálně prezentováno 50 pacientů, získané výsledky naznačují, že při hlubší úrovni anestezie dochází k poklesu amplitudy a prodloužení latence ve srovnání s „mělčí anestezí“, tedy při BIS 55–65. Alterace parametrů MEP však nebyla klinicky relevantní, a tedy vedení hloubky anestezie v doporučeném rozmezí pro index hloubky anestezie pravděpodobně neovlivňuje interpretaci MEP operatéry. Udržování anestezie

v doporučeném rozmezí indexu hloubky anestezie je tak pravděpodobně optimálním způsobem vedení anestezie u operací dětských pacientů s IONM [1, 140].

Hlavní limitací naší práce byla prezentace předběžných výsledků, tedy 50 pacientů. Nicméně v tuto chvíli můžeme konstatovat, že v srpnu roku 2024 bylo úspěšně zařazeno všech 150 pacientů tak, jak bylo stanoveno „power analýzou“. Po zpracování dat byla připravena původní práce, jejíž výsledky definitivně potvrzují a korespondují s daty z původní práce s třetinovým počtem pacientů [1, 140]. Tato práce byla v době psaní této habilitační práce přijata v roce 2026 do časopisu *Anesthesia & Analgesia* (IF 4,7; Q1 v kategorii ANESTHESIOLOGY dle WoS). T. č. prochází formálními úpravami a autorskou korekturou, z tohoto důvodu nemůže být citována ani podrobněji prezentována [1].

Původní práce s předběžnými výsledky byla publikována v časopise *Frontiers in Medicine* (IF 3,0; Q1 v kategorii MEDICINE, GENERAL & INTERNAL) v roce 2024 [1, 140].



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RECEIVED 27 July 2024
ACCEPTED 14 October 2024
PUBLISHED 29 October 2024

CITATION
Hudec J, Kosinová M, Prokopová T,
Zelinková H, Hudáček K, Repko M, Gál R and
Štourač P (2024) The influence of depth of
sedation on motor evoked potentials
monitoring in youth from 4 to 23 years old:
preliminary data from a prospective
observational study.
Front. Med. 11:1471450.
doi: 10.3389/fmed.2024.1471450

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The influence of depth of sedation on motor evoked potentials monitoring in youth from 4 to 23 years old: preliminary data from a prospective observational study

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Introduction: The influence of various levels of sedation depth on motor evoked potentials (MEP) reproducibility in youth is still unclear because of a lack of data. We tested the hypothesis that a deeper level of total intravenous anesthesia (TIVA) [bispectral index (BIS) 40 ± 5 compared to 60 ± 5] can affect surgeon-directed MEP and their interpretation in youths.

Methods: All patients received TIVA combined with propofol and remifentanyl. TIVA was initially maintained at a BIS level of 60 ± 5 . The sedation anesthesia was deepened to BIS level 40 ± 5 before the skin incision. MEP were recorded and interpreted at both BIS levels. The primary endpoint was to evaluate the effect of the depth of sedation on the MEP reproducibility directed and interpreted by the surgical team in each patient separately. The secondary endpoint was to compare the relativized MEP parameters (amplitude and latency) in percentage at various levels of sedation in each patient separately. We planned to enroll 150 patients. Due to the COVID-19 pandemic, we decided to analyze the results of the first 50 patients.

Results: The surgical team successfully recorded and interpreted MEP in all 50 enrolled patients in both levels of sedation depth without any clinical doubts. The MEP parameters at BIS level 40 ± 5 , proportionally compared with the baseline, were latency 104% (97–110%) and the MEP amplitudes 84.5% (51–109%).

Conclusion: Preliminary data predict that deeper sedation (BIS 40 ± 5) does not affect the surgical team's interpretation of MEP in youth patients. These results support that surgeon-directed MEP may be an alternative when neurophysiologists are unavailable.

KEYWORDS

bispectral index, intraoperative neurophysiological monitoring, motor evoked potentials, remifentanyl, scoliosis surgery, total intravenous anesthesia

1 Introduction

The intraoperative neurophysiological monitoring (IONM) technique has become a standard in many surgical fields. This commonly used method enables high-risk surgeries by decreasing the potential risk of neurological injury. IONM includes motor evoked potentials (MEP), somatosensory evoked potentials (SSEP), brainstem auditory evoked potentials (BAEP), electromyography (EMG), and electroencephalography (EEG) (1–3).

The application of IONM has increased in the pediatric population, e.g., in scoliosis surgery, which is challenging for the perioperative team, especially for the risk of neurological injury (4–8). IONM is indicated to decrease the risk of new neurological deficit development. The Scoliosis Research Society strongly recommends its use during spinal deformity surgery (9). MEP and SSEP are IONM modalities commonly used in pediatric scoliosis surgery (10), and their monitoring replaced the intraoperative clinical examination, the wake-up test (11). The great advantage of IONM is that it detects possible nerve injuries during the instrumentation in time, which could more efficiently prevent them. Additionally, the wake-up test can be performed on a limited basis in pediatric patients. There is generally more difficulty in cooperation with pediatric patients, especially with developmental delays or neuromuscular disorders (10, 12).

Multimodal monitoring (SSEP and MEP) directed by neurophysiologists is an optimal way to detect neurological injury during surgeries (9, 13). It decreases the incidence of false-negative reports. Furthermore, the application of SSEP with MEP allows some level of neurophysiological monitoring even in cases when one of the mentioned modalities is not suitable or suspended for different reasons (e.g., MEP may not be suitable for patients with severe motor deficit; in contrast, SSEP could provide at least information about sensory pathways) (14, 15). On the other hand, surgeon-directed transcranial MEP monitoring represents a possible and safe alternative in cases when neurophysiologists are unavailable. However, the final decision for a particular type of monitoring should be made individually for each patient (14, 16).

During anesthesia, anesthetic agents and several pathophysiological conditions (severe hypoxia, hypercapnia, or hypotension) can significantly affect the IONM (17). The anesthetic team should ensure the conditions for optimal MEP monitoring. Total intravenous anesthesia (TIVA) with a combination of propofol and opioids represents the “gold standard” for IONM. The influence of anesthetic or analgesic agents on MEP was studied in several studies (18–20). However, the overall influence of the depth of TIVA sedation maintained at recommended levels is still unclear, especially in pediatric patients (2, 17).

This study aims to evaluate and describe the influence of the sedation depth guided by bispectral index (BIS) and targeted to recommended levels ($BIS 40 \pm 5$ versus 60 ± 5) on MEP interpretation by surgeons and measured parameters (amplitude and latency) in youth. We aimed to assess the hypothesis that a deeper level of TIVA can affect surgeon-directed MEP and their interpretations by a surgical team. This hypothesis includes prolonged MEP latencies and decreased MEP amplitudes on a deeper level of sedation, $BIS 40 \pm 5$.

2 Materials and methods

2.1 Study design

The Scoliosis (SCOL) study was designed as a prospective, monocentric before-after-trial. It was approved by the Ethics Committee of the University Hospital Brno, Czech Republic, on 24th June 2020 (No. 90/20, chair PharmD. Sarka Kozakova). We registered the study on the [ClinicalTrials.gov](https://clinicaltrials.gov) registry (NCT04423146) on 5th June 2020. The project was managed according to international regulations and guidelines (Helsinki Declaration). We used the STROBE checklist to publish this article (21). According to the power analysis, the planned sample size was 150 patients. Power analysis was created with the following settings. We evaluated the width of the 95% confidence interval (CI) for the endpoint occurrence (non-reproducibility of MEP). The expected occurrence of the endpoint was 10%. However, due to the prolonged recruitment during the COVID-19 pandemic, we decided to perform a post-hoc power analysis and publish the results of the first 50 patients. The sample size of 50 produces a two-sided 95% confidence interval with a width equal to 0.185 when the sample proportion is 0.100.

2.2 Participants

The inclusion criteria were all children and youth diagnosed with congenital, neuromuscular, infantile idiopathic, juvenile idiopathic, adolescent idiopathic, or other syndromic scoliosis scheduled for elective scoliosis surgery in TIVA with surgeon-directed MEP monitoring. We determined childhood and teenage age according to orthopedic diagnostic criteria for not adult scoliosis surgery, according to skeletal maturity, specifically the Risser sign, because bone age better indicates biological maturity than chronological age (22). All participants or legal representatives could withdraw from the SCOL study at any time without giving any reason. Exclusion criteria were scoliosis surgery without surgeon-directed MEP monitoring, known contraindications for propofol or remifentanyl administration (e.g., soy, egg lecithin, or peanut allergy), and inability to attach BIS or MEP electrodes to the standard positions. We excluded patients with known motor disease with no possibility of provoking MEP. All enrolled patients were managed according to the anesthesia and MEP monitoring local protocols (see below). The influence of depth of sedation on MEP was evaluated for each patient separately.

2.3 Anesthesia protocol

Before surgery, all enrolled patients were evaluated and premedicated with 0.1–0.2 mg/kg of midazolam *per os* (PO), eventually in combination with promethazine PO or atropine PO administered about 60 min before surgery. An intravenous (IV) bolus of propofol in dose 1.5–3 mg/kg, remifentanyl in dose 1–2 µg/kg, and 0.6 mg/kg of rocuronium (or other intermediate-acting neuromuscular agents in appropriate dosing in case of rocuronium outage) were administered for the induction to anesthesia. Sevoflurane was administered for induction to anesthesia in case of

a patient's limited cooperation and the impossibility of IV line cannulation. Muscle relaxants could only be administered to facilitate endotracheal intubation. The anesthesia maintenance was performed with TIVA: propofol and remifentanyl. The initial remifentanyl infusion rate was about 0.1–0.2 µg/kg/min, and the initial propofol infusion rate started at about 4–5 mg/kg/h with titrating to BIS level 60 ± 5. The second IV line, arterial line, and permanent urine catheter were inserted after endotracheal intubation. In case of peripheral venous system insufficiency, the central venous catheter was administered. Also, surgeons applied electrodes for MEP monitoring after the anesthesia induction and airway securement. We used a BIS with standard frontotemporal EEG electrodes for depth of sedation anesthesia monitoring (BIS™ complete 2-channel Monitor, Covidien/Medtronic GmbH, Germany). The adequate level of sedation for surgery was targeted with BIS in combination with monitoring signs of light sedation (patients' movements, increased heart rate and blood pressure or interference with artificial ventilation). The quantitative measurement of neuromuscular blockade, particularly Train-of-four ratio, was used to determine residual blockade (23). All the above was applied before turning the patient to the prone position. The remifentanyl infusion rate was raised to 0.5–0.6 µg/kg/min, and the propofol infusion rate was raised to 5–7 mg/kg/h with titrating to BIS level 40 ± 5 before skin incision. The dosages of propofol and remifentanyl were chosen according to the recommendations and pharmacokinetic studies (24–26). We titrated the TIVA between the BIS levels 40–60 during the surgery. The depth of the sedation and blood loss influence patients' cardiovascular stability. Children's vital functions, such as saturation, end-tidal CO₂, heart rate, invasive blood pressure, and body temperature, were monitored and managed (e.g., administering vasopressors, fluid therapy, blood products, coagulation factors...) to maintain the values recommended in European Pediatric Advanced Life Support (EPALS) guidelines and EBM (27, 28).

2.4 Motor evoked potentials monitoring

Surgeon-directed MEP were monitored according to the local protocol. Transcranial electric stimulation was achieved and monitored using the Medtronic NIM-ECLIPSE (NIM-ECLIPSE® IONM system, Medtronic, MN, USA, Minneapolis). The MEP were evoked using needle electrodes placed in position C3/C4, and the stimulated cortex was below the anode. This positioning was according to the EEG standards, the international 10/20 system. A train of 5 pulses, with a duration of 0.20–1.00 ms, amplitude of max. 2×100 mA and an interstimulus interval of 2–3 ms with a frequency of 1 Hz were applied for stimulation. MEP were recorded with surface electrodes placed according to the standard approach muscle/tendon from both lower extremities (m. tibialis anterior and m. abductor hallucis). The correct placement of electrodes for MEP was checked in the prone position. The essential condition for MEP monitoring was recovery from neuromuscular blockade. First, baseline MEP parameters were recorded on the BIS level of 60 ± 5 and a train-of-four ratio of more than 90% before the commencement of surgery. The second MEP parameters were recorded when we deepened the sedation anesthesia to the BIS level of 40 ± 5 just before the skin incision. These two points were based on the recommended boundaries of a range of BIS index values to achieve an adequate

depth of sedation in children and youth (29, 30). Other MEP were recorded after screws insertion, rods insertion, and spine correction (contraction, distraction). Surgeons' interpretation was based on the local protocol. The protocol defines a significant change in MEP monitoring as MEP absence after stimulation. The absence of MEP is a warning criterion that informs about the possible risk of new neurological deficit development. We relativized all MEP parameters in percentage for the interindividual variability in MEP parameters among patients. The baseline amplitudes and latencies (BIS level 60 ± 5) were determined as 100%. Other amplitudes and latencies during the surgery were counted as percentages from the baselines. Figure 1 shows the MEP recording timeline. It is a graphical presentation of the electronic case report form (CRF).

2.5 Study objectives

The study's primary objective was to evaluate the influence of the depth of sedation on the MEP reproducibility and interpretation by the surgical team in each patient separately. The secondary goal was to compare the relativized MEP parameters in percentage, latency, and amplitude at different levels of depth of sedation. These parameters were monitored in defined surgery phases. The initial MEP parameters were set as a baseline (100%), and other parameters were expressed as percentages. We evaluated MEP parameters and interpretations by surgeons for each patient separately. We did not compare the results of individual patients with those of other patients. So, the influence of different age groups on BIS varying values was excluded. We measured the incidence of new neurological deficits after surgery.

2.6 Statistical analysis

Standard descriptive statistics were applied in the analysis: absolute frequencies for categorical variables and mean, median, minimum, and maximum for continuous variables. We used the Statistica 13.5 software (STATISTICA software TIBCO Software, OK, USA, Tulsa). A non-parametric Wilcoxon Signed Ranks Test was performed to compare MEP parameters' dependence on the BIS level 60 vs. 40.

3 Results

We started recruiting patients in September 2020. However, the recruitment was prolonged by a limited number of elective surgeries during the COVID-19 pandemic. The most frequent type of scoliosis was idiopathic scoliosis in 62% (n = 31) patients. Demographic and epidemiologic data are shown in Table 1. We achieved the appropriate depths of sedation in all children and youth before the skin incision.

Surgeons successfully recorded MEP in all patients during all phases of the surgery. The influence of a deeper level of sedation was not clinically significant, and MEP interpretation by a surgical team was not affected as a primary outcome.

The MEP parameters at BIS level 40 ± 5, proportionally compared with the baseline, were prolonged latencies 104% (97–110%), median (minimum – maximum), and decreased amplitudes 84.5% (51–109%).

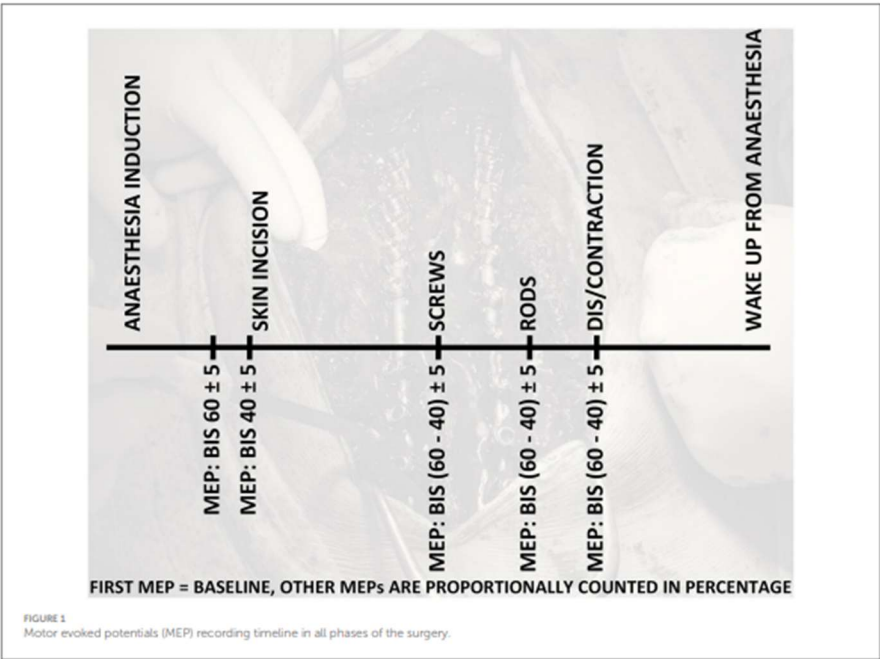


TABLE 1 Patient's characteristics, demographic, and epidemiologic data.

Patient's characteristics	
	n = 50
Age, years, median (min-max)	15 (4-23)
Sex, F, n (%)	37 (74%)
Weight, kg, median (min-max)	50 (12-94)
Height, cm, median (min-max)	160 (97-188)
ASA* physical status:	
ASA I, n (%)	20 (40%)
ASA II, n (%)	18 (36%)
ASA III, n (%)	12 (24%)
Scoliosis type:	
Idiopathic scoliosis, n (%)	31 (62%)
Neuromuscular scoliosis, n (%)	11 (22%)
Congenital scoliosis, n (%)	4 (8%)
Other scoliosis, n (%)	4 (8%)
Cobb's angle, °, median, (min-max)	52 (0-109)
Operated segments, n, median, (min-max)	11 (3-18)

*ASA, American Society of Anesthesiologists.

The absence of MEP was not observed at any level of sedation, BIS 40 ± 5 included. New neurological deficits did not develop in any of

the patients. MEP parameters in all phases of surgery are illustrated in Table 2. We proved the statistically significant difference in latency and amplitude in dependence on the sedation depth. Results are presented in Table 3.

4 Discussion

This prospective study describes the influence of sedation depth on MEP. To the best of our knowledge, this is one the largest and most significant sample of MEP parameters recorded in youth, so we decided to share these exciting data from the first 50 patients. Very few studies were completed on the influence of sedation depth on MEP. In the adult population, mostly during brain surgeries, the difference in sedation levels also resulted in MEP alteration. However, the number of studies and patient cohorts is very small, and further research should be performed to verify these results. Moreover, based on post-hoc power analysis, the data provided clinically significant results (31). In addition, our study is interesting because of the enrollment of all scoliosis types, not only the idiopathic, which is studied the most. The results apply to other types of scoliosis.

Although we described the statistically significant difference in MEP parameters in dependence on the sedation depth, the statistical alteration does not correlate with clinical alteration. These results imply that sedation depth in the recommended BIS range (40-60) ± 5 does not interfere with MEP interpretation by the

surgical team, which is our most clinically significant finding. It supports the statement that surgeon-directed MEP are safe, feasible, and relatively simple method with high sensitivity and specificity (13, 16, 32). Although neurophysiologist-directed multimodal monitoring is the safest and preferred method, there is a limitation: a need for more skilled staff responsible for overseeing IONM. Many centers worldwide support the MEP monitoring certification not only for neurophysiologists but also for neuro-anesthesiologists or spinal surgeons. The advantage is that a skilled surgeon can record it alone without significant engagement during surgery (32–34). For these reasons, we consider this finding as the most clinically important.

Another clinically exciting result is that we could not prove the significant influence of the sedation depth in the recommended BIS

range (60–40) $\pm$ 5 on the MEP amplitude and latency. The SCOL study's strength is that it was designed to measure MEP in optimal conditions without significant influence of other variables, such as physiological or vital function status and surgical instrumentation. The only significant variables are the researched ones, e.g., defined doses of propofol and remifentanyl, which affect the depth of sedation (17, 28, 35). The patients enrolled for the SCOL study were monitored as mentioned above. Appropriate ventilation, vasopressors, hemo/volume substitution, and body temperature management according to EBM were maintained within the normal values of vital function during the surgery (28).

As previous studies describe, most drugs used during anesthesia in children affect the IONM. Neuromuscular blocking agents should not be used during IONM except for the initial dose for intubation. Other unrecommended drugs are volatile anesthetics, benzodiazepines, or thiopental. These drugs in anesthetic doses significantly impair IONM (14, 36). A gold standard for maintaining general anesthesia during operations with IONM is considered a combination of propofol and opioids, which in clinically relevant doses reduce MEP amplitude and prolong the latency of SSEP, both insignificantly (19, 20). Although we have sufficient information about the influence of anesthetic agents on IONM, the exact effect of the depth of TIVA sedation on MEP is still unclear. BIS monitoring limitations result from using referential data from adult patients, and the suitability of EEG monitoring in pediatrics needs to be better described. However, when we set our research, we followed the most relevant studies at that time describing the influence of propofol on EEG changes in children. These changes were described as age dependent. However, the oscillations in the propofol-induced EEG were qualitatively similar among patients from 1 year old till adulthood, and BIS monitoring was commonly used off-label in children. In addition, some studies found no significant differences in BIS monitoring practice between pediatric and adult patients. In contrast, applying these devices to children younger than 1 year is not recommended (37–41). As scoliosis surgery is not indicated in children under 1 year, the most problematic group in BIS monitoring, we decided to use BIS in the same way as in adults. We decided to address the topic about the influence of depth of TIVA sedation on MEP in the SCOL study. As our findings show, the decrease of the amplitude was, on average, 15.5% (–9–49%), and the latency delay was, on average, 4.0% (–3–10%) at BIS level 40 $\pm$ 5. These results imply a minimal clinically significant influence on MEP amplitude and latency of sedation depth in the recommended range of BIS value 40–60 in youth. As BIS monitoring is considered a standard in surgeries under TIVA, and BIS in the range of 40–60 should be maintained, the effect of sedation probably should not be the

TABLE 2 Motor evoked potentials parameters (amplitude and latency) recorded in all phases of the surgery.

Motor evoked potentials	
	n = 50
Baseline (BIS* 60 $\pm$ 5)	
Reproducibility, n (%)	50 (100%)
Amplitude, %, median (min–max)	100 (100–100)
Latency, %, median (min–max)	100 (100–100)
Before incision (BIS 40 $\pm$ 5)	
Reproducibility, n (%)	50 (100%)
Amplitude, %, median (min–max)	84.5 (51–109)
Latency, %, median (min–max)	104 (97–110)
Screws (BIS (60–40) $\pm$ 5)	
Reproducibility, n (%)	50 (100%)
Amplitude, %, median (min–max)	94 (53–451)
Latency, %, median (min–max)	103 (85–109)
Rods (BIS (60–40) $\pm$ 5)	
Reproducibility, n (%)	50 (100%)
Amplitude, %, median (min–max)	96 (44–556)
Latency, %, median (min–max)	100 (78–108)
Dis/contraction (BIS (60–40) $\pm$ 5)	
Reproducibility, n (%)	50 (100%)
Amplitude, %, median (min–max)	96 (61–659)
Latency, %, median (min–max)	100 (81–110)

*BIS, Bispectral index.

TABLE 3 Statistically significant difference in motor evoked potentials parameters in dependence on the sedation depth.

	BIS* 60	BIS 40	BIS 40 x 60 difference	p-values
Amplitude (μ V)	532.22 (345.37)	439.34 (290.45)	–92.88 (130.64)	< 0.001
Amplitude (%)	100 (0)	82.96 (14.28)	–17.04 (14.28)	< 0.001
Latency (ms)	31.06 (8.91)	32.24 (10.05)	1.18 (1.49)	< 0.001
Latency (%)	100 (0)	103.52 (3.49)	3.52 (3.49)	< 0.001

Mean (SD).

*BIS, Bispectral index.

leading cause of a sudden drop in amplitude or latency of MEP. On the other hand, as sedation levels of BIS under 40 are not recommended, these levels of sedation were not investigated. From other studies, we can assume that deeper sedation could significantly decrease amplitudes and prolonged latencies (31).

We could find a congruence for alarm points if we compare our results with studies by Benuska et al. and Kobayashi et al. The minor alarm points could be defined as a combination of an amplitude decrease of $\geq 70\%$ and a latency delay of $\geq 10\%$ from the baseline (42, 43). Although combined alterations of MEP parameters can reduce false positive values, these studies' results are based on a small number of patients. A recent study by Magampa and Dunn and Polly et al. still recommend comparing amplitudes from legs and hands. It seems the loss of signal from the lower extremities and maintenance of signal from the upper extremities represent the most reliable method (13, 44). This claim is in consensus with the recommendation of the Scoliosis Research Society for IONM. The absence of signal both from the upper and lower extremities is likely due to technical issues or anesthetic implications. However, we did not measure this ratio because it was not our study outcome (9). If anesthetists maintain TIVA between the recommended range for sedation depth, the sudden drop in signal is more likely to be a technical issue and can be solved sooner to maintain patient safety (17).

A major study limitation was the number of enrolled patients. The COVID-19 pandemic limited elective surgery and recruitment of patients. The number of 50 patients from a planned sample size of 150 reduces the statistical analysis's power. However, according to our research, this number represents a large sample of youths, and the presentation of the first 50 patients brings us interesting results, which could suggest ways to improve patient outcomes (42, 45). Another limitation is that we did not have target-controlled infusion (TCI) software for patients of all age and weight groups when we set this study protocol. Nevertheless, the EEG monitoring and maintenance of sedation between recommended levels is crucial for patient safety with both TCI and the calculated speed of continuous infusion. These are both possible ways to administer the propofol infusion (29). In addition, no significant differences were detected between continuous infusion guided by the BIS and TCI systems. We aimed to reduce the bias due to the choice of different models for different age groups (Kataria vs. Schnider). This study was designed when BIS monitoring was highly recommended during TIVA to prevent patients' awareness during surgeries. These days, the reliability of the BIS value in predicting anesthesia that is too light is in question. Our study used a combination of BIS and clinical signs of patients responding to painful stimuli during surgery, such as elevation in heart rate, blood pressure, interference with artificial ventilation and patients' movement to prevent the patients' awareness. We had no suspicion of light sedation, and no intraoperative patient awareness was reported. Finally, although the EEG waveform in children varies with age, the BIS monitoring is not calibrated individually to age. However, based on previous studies in children and youth, we set these two points of the recommended range for BIS monitoring (29, 30). Regarding the reliability of BIS monitoring in children, the trend in sedation level could be described well with BIS. Also, the trend in sedation, thus in BIS, is important for the MEP trend.

Our results did not show a significant drop in MEP, when the drop in BIS from 60 to 40 by deepening the sedation was performed. These results imply that drops in BIS in the recommended range should not clinically influence the MEP. The effect of the level of sedation which causes the burst suppression pattern on EEG was not part of this study, as this level of sedation is considered too deep and not recommended for general anesthesia. The more accurate monitoring of sedation levels in relation to MEP for example analysis of raw EEG or density spectral array analysis could be the theme for further research.

In conclusion, based on our preliminary data, it seems reasonable that surgeon-directed MEP may probably represent a promising way of neuromonitoring during scoliosis surgery in youth between the ages of 4 and 23 years. This method probably allows simple IONM alternatives when traditional neurophysiologist-led IONM is unavailable. However, our preliminary results should be interpreted cautiously because only a third of the patients were enrolled from the planned sample size, and we will continue with recruitment. The surgical team should always consider the pros and cons of the possibilities of IONM recording, especially in more complex cases with severe deformities, and choose the best option individually to maximize patient outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of the University Hospital Brno, Czech Republic. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

JH: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. MK: Formal analysis, Writing – original draft, Writing – review & editing, Conceptualization, Methodology, Supervision. TP: Formal analysis, Writing – original draft, Writing – review & editing. HZ: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. KH: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. MR: Methodology, Project administration, Writing – original draft, Writing – review & editing. RG: Project administration, Writing – original draft, Writing – review & editing. PS: Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

INOVACE V ANESTEZIOLOGICKÉ PÉČI U SPONDYLOCHIRURGICKÝCH VÝKONŮ PEDIATRICKÝCH PACIENTŮ: VLIV NA PERIOPERAČNÍ PRŮBĚH A BEZPEČNOST

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10.3389/fmed.2024.1471450

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Specific University Research provided by MŠMT under Grant [MUNI/IVV/0770/2023] and MH CZ - DRO under Grant [FNBr, 65269705].

Acknowledgments

The authors thank all the HCPs who cared for enrolled patients during the perioperative period, Lenka Dobrovolná for administrative assistance, and Martin Nemec for his help in understanding the IONM problems. These preliminary data were presented as a poster at the Euroanaesthesia Congress in June 2023.

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INOVACE V ANESTEZIOLOGICKÉ PÉČI U SPONDYLOCHIRURGICKÝCH VÝKONŮ PEDIATRICKÝCH PACIENTŮ: VLIV NA PERIOPERAČNÍ PRŮBĚH A BEZPEČNOST

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7 Práce vzniklé v souvislosti s managementem krevních ztrát během operací skoliotických deformit

Jak jsem již popisoval v kapitole věnující se anesteziologické péči, korekce skoliotických deformit jsou zpravidla spojeny s vyššími krevními ztrátami, eventuelně koagulopatií v perioperačním období [29, 38]. Některé zdroje uvádějí nutnost podání krevních derivátů a transfúzních přípravků v přibližně 30–60 % případů [101, 102]. Krvácivé komplikace, stejně jako komplikace spojené s podáváním transfúzních přípravků a krevních derivátů, prokazatelně zvyšují morbiditu i mortalitu pacientů a celkové náklady na hospitalizaci [142]. Mezi prokázané strategie vedoucí k redukci ztrát patří předoperační optimalizace hemokoagulace, tedy korekce anémie, zajištění autologní krevní transfúze či adekvátní alimentace pacientů. Z perioperačních kroků jsou to udržování normovolémie a normotermie, užití „Cell-saveru“, intravenózní podávání antifibrinolytik a cílená korekce koagulopatie dle viskoelastických metod [29, 38, 71, 72].

Další vědecko-výzkumná činnost bude věnována právě problematice redukce krevních ztrát v průběhu operační korekce skoliózy.

7.1 Effect of Prophylactic Fibrinogen Concentrate In Scoliosis Surgery (EFISS)

Podání kyseliny tranexamové je dnes již rutinní praxí u řady výkonů s předpokládanými velkými krevními ztrátami, tedy včetně oblasti spondylochirurgie. V mnoha operačních oborech je tak součástí doporučení již v rámci profylaktického podání, nicméně mohou se lišit pohledy na dávkovací schémata pro úvodní bolus a následnou pokračující infúzi. V rámci dávkování nejsou data jednotná [1, 71, 73-76, 141, 142].

Fibrinogen (faktor I) je jedním ze základních faktorů krevního srážení. Některé studie věnující se problematice fibrinogenu naznačují vyšší krevní ztráty perioperačně u pacientů se vstupní hypofibrinogenémií či dysfibrinogenémií, a to i ve spondylochirurgii. Stejně tak některé práce popisují nižší krevní ztráty u pacientů s předoperačně vyšší hladinou fibrinogenu [143-145]. Profylaktické podávání fibrinogenu je v současnosti hojně diskutovaným tématem. Jeho účinnost byla studována u menšího počtu pacientů v oblasti kardiovaskulární chirurgie či transuretrální resekce prostaty. Diskutována byla i problematika podávání fibrinogenu v pediatrii. V jedné studii vedl liberální přístup při podávání fibrinogenu k redukci krevních ztrát během operací kraniosynostózy. Nicméně data jednoznačně prokazující účinnost profylaktického podání fibrinogenu, které by vedlo k signifikantní redukci krevních ztrát, jsou velmi omezená. V budoucnu tak bude potřeba v této oblasti provést další výzkumy [146-148].

Studie EFISS byla navržena jako prospektivní randomizovaná studie, v rámci které jsme chtěli zhodnotit proveditelnost a bezpečnost profylaktického podávání fibrinogenu u dětských pacientů podstupujících operační korekci skoliotické deformity [149, 150].

Do naší pilotní studie bylo zařazeno celkem 32 pacientů mladších 18 let, kteří byli indikováni k operaci skoliózy. Vyřazovacími kritérii byly antikoagulační farmakoterapie, preexistující koagulopatie, anamnéza hluboké žilní trombózy či plicní embolie, přecitlivělost na fibrinogen a nesouhlas zákonných zástupců, kteří tak nepodepsali informovaný souhlas s účastí ve studii [149, 150].

Kromě standardní perioperační péče pro pacienty podstupující operaci skoliózy dle lokálního protokolu bylo pacientům randomizovaným do intervenční skupiny intravenózně podáno 20–30 mg/kg fibrinogenu. Primárním cílem bylo posouzení bezpečnosti, tedy zkoumána byla četnost a typ nežádoucích účinků a reakcí včetně velmi závažných reakcí a úmrtí v souvislosti s účastí ve studii. V rámci sekundárních cílů jsme se věnovali posouzení proveditelnosti a účinnosti [149, 150].

Při porovnání intervenční skupiny a skupiny se standardní péčí nebyl pozorován statisticky významný rozdíl v incidenci či závažnosti nežádoucích účinků. Rovněž nebyly pozorovány statisticky významné rozdíly v aplikaci krevních derivátů či transfúzních přípravků. Výsledky naší studie naznačují, že profylaktické podání fibrinogenu u dětských pacientů podstupujících korekci skoliózy je proveditelné a jeví se jako bezpečné. Závěry ohledně klinického účinku však nelze při počtu 32 pacientů vyvodit [149, 150].

Naše práce byla přijata v podobě protokolu studie v časopise BMJ Open (IF 2,4; Q1 v kategorii MEDICINE, GENERAL & INTERNAL) v roce 2023. Ukončená pilotní studie byla pak publikována ve stejném časopise (IF 2,3; Q2 v kategorii MEDICINE, GENERAL & INTERNAL) v roce 2025 [149, 150].

7.1.1 Effect of Prophylactic Fibrinogen Concentrate In Scoliosis Surgery (EFISS): a study protocol of two-arm, randomised study

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Protocol

BMJ Open Effect of Prophylactic Fibrinogen Concentrate In Scoliosis Surgery (EFISS): a study protocol of two-arm, randomised trial

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To cite: Vrbica K, Hudec J, Hrdy O, et al. Effect of Prophylactic Fibrinogen Concentrate In Scoliosis Surgery (EFISS): a study protocol of two-arm, randomised trial. *BMJ Open* 2023;13:e071547. doi:10.1136/bmjopen-2022-071547

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-071547>).

Received 02 January 2023
Accepted 07 May 2023



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ABSTRACT

Introduction Fibrinogen is one of the essential coagulation factors. Preoperative lower plasma fibrinogen level has been associated with higher blood loss. Scoliosis surgery presents a challenge for the anaesthetic team, one of the reasons being blood loss and transfusion management. Recently, the prophylactic fibrinogen administration has been a debated topic in various indications. It has been described for example, in urological or cardiovascular surgery, as well as in paediatrics. This pilot study is focused on verifying the feasibility of potential large randomised trial and verifying the safety of prophylactic fibrinogen administration in paediatric scoliosis surgery.

Methods and analysis A total of 32 paediatric patients indicated for scoliosis surgery will be recruited. Participants will be randomised into study groups in a 1:1 allocation ratio. Patients in the intervention group will receive prophylactic single dose of fibrinogen, in addition to standard of care. Patients in the control group will receive standard of care without study medication prior to skin incision. The primary aim is to assess the safety of prophylactic fibrinogen administration during scoliosis surgery in children, the incidence of any adverse events (AEs) and reactions will be monitored during participation in the study. The secondary objective is to investigate the additional safety information, feasibility and efficacy of a prophylactic fibrinogen administration. The incidence of AEs and reactions according to selected adverse events of special interest will be monitored. All collected data will be subjected to statistical analysis according to a separate statistical analysis plan.

Ethics and dissemination This trial follows the applicable legislation and requirements for good clinical practice according to the International Conference on Harmonisation E6(R2). All essential trial documents were approved by the relevant ethics committee and national regulatory authority (State Institute for Drug Control) and their potential amendments will be submitted for approval.

Trial registration number NCT05391412.

BACKGROUND

Scoliosis is defined as an abnormal lateral deviation of the spine of $>10^\circ$ in the frontal

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Results of this study might improve knowledge about prophylactic fibrinogen administration in the paediatric population during scoliosis surgery.
- ⇒ The results of this feasibility study will provide data to plan a fully powered randomised trial.
- ⇒ Results of this study might support the claim about the safety of the fibrinogen administration before surgery.
- ⇒ The participants are younger than 18 years at the time of recruitment, according to national legislation, the informed consent must be signed by both parents or legal guardians.
- ⇒ The feasibility assessment may indicate a lack of data to determine the influence on blood loss and bleeding management.

plane, with deviation in the sagittal plane and vertebral rotation. It is one of the most common spinal deformities in children.¹⁻³ The approach to the treatment is multidisciplinary and depends on the scoliotic curve severity and progression.⁴ The surgery is commonly indicated in patients with progressive curves and Cobb angle $>40^\circ$ to stop further progression of the curve and prevent the development of multiple organ disease.⁴ Except for musculoskeletal disorders, cardiovascular, respiratory, gastrointestinal or psychosocial problems are described in patients with scoliosis.⁵ Anaesthesia for scoliosis surgery is a highly challenging task for the whole team. The specifics of such anaesthesia include long operation time, body temperature decrease, high blood losses, positioning or intraoperative neurophysiological monitoring.^{6,7}

During scoliosis surgery, high blood loss and the necessity of blood transfusions are described, while allogeneic derivatives are necessary in the perioperative period in about

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30%–60% of cases.⁸ Bleeding complications and adverse events (AEs) associated with blood transfusions prolong and increase the cost of hospitalisation and increase the mortality.⁹ Well-known and commonly applied approaches to reduce blood loss include antifibrinolytics, such as tranexamic acid, which can be administered before surgery,^{10,11} permissive hypotension, which can be used to reduce blood loss. Prevention of hypothermia is another way to reduce bleeding, and cell salvage, especially in high-risk patients, where it is preferred to minimise allogeneic blood transfusions.¹²

Fibrinogen is essential for clot formation and stopping bleeding.^{13,14} Hypofibrinogenemia or dysfibrinogenemia leads to more severe bleeding during high-extensive surgery.^{15–17} Moreover, some studies describe less blood loss in patients with higher preoperative fibrinogen levels.¹⁸ Prophylactic administration of fibrinogen is a widely discussed theme, but to date, the data are limited.¹⁹ Some studies described a significant reduction in blood loss and a secondary reduction in allogeneic derivatives administration. Prophylactic fibrinogen administration has been described in cardiovascular or urological surgery.^{20–22} Additionally, early administration has been reported to be safe in the paediatric population.²³

However, the effect of prophylactic fibrinogen administration in paediatric scoliosis surgery remains unclear. We designed this study to verify the feasibility of prophylactic fibrinogen administration in paediatric scoliosis surgery. The results will be used to plan a sufficiently large randomised trial with the aim to clarify the impact of prophylactic fibrinogen application on the magnitude of blood loss and the need for transfusion. This study is focused on the safety, efficacy and feasibility of prophylactic administration of fibrinogen in scoliosis surgery. The clinical outcome of each participant is studied, particularly the incidence of potential AEs such as thromboembolism, allergic reactions or fevers. The results of this study may improve knowledge about prophylactic fibrinogen application. All participants in this study will contribute to this socially beneficial knowledge.

METHODS AND ANALYSIS

Study design

The setting of the study is two-arm, prospective, monocentric, randomised, double-blind pilot trial with a 1:1 allocation ratio testing safety, efficacy and feasibility of prophylactic fibrinogen administration during scoliosis surgery in the paediatric population. The pilot study started on 1 June 2022 and the estimated end of the study is planned on 30 September 2023. The study protocol is compiled according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist.²⁴

Aims and objectives

This pilot study is conducted before designing a fully powered study and it aims to assess the safety, feasibility and efficacy of prophylactic fibrinogen administration during scoliosis surgery in the paediatric population. Results will be used to optimise the fully powered study design and determine the final sample size.

The primary aim of a pilot study is to assess the safety of perioperative infusion of fibrinogen during scoliosis surgery in children. The incidence of any AEs, adverse drug reactions, serious AEs, serious adverse reactions, unexpected adverse reactions and suspected unexpected serious adverse reactions will be monitored during participation in the study. These primary outcomes monitoring respects European directive 2001/20/EC.²⁵

The secondary aim is to investigate the additional safety information, feasibility and efficacy of a prophylactic administration of fibrinogen. The incidence of AEs and reactions according to the following adverse events of special interest (AESI) will be monitored. Monitored AESI include deep vein thrombosis verified on ultrasound imaging, pulmonary embolism confirmed on CT scan and infection or healing disorder requiring resurgery and/or the initiation of antibiotic therapy. Additional safety information include intensive care unit (ICU) and hospital length of stay (days) and 28-day mortality.

Other end points and monitored parameters, such as additional safety information, demographic characteristics, laboratory values, comparison of blood loss or feasibility assessment, are mentioned in the section 'Data collection'.

Participants

Eligibility criteria

All patients admitted to the hospital for scoliosis surgery will be screened for inclusion criteria. When inclusion criteria will be met, the exclusion criteria will be checked. Only patients with fulfilled all inclusion criteria and without all exclusion criteria will be considered for participation in the study.

Inclusion criteria

- ▶ Elective scoliosis surgery.
- ▶ Age <18 years at the time of enrolment.
- ▶ Signed the relevant informed consent form (ICF).
- ▶ Sexually active participants (aged ≥15 years) must agree to the use of following methods of contraception for the duration of this clinical trial:
 - Women—proper use of a highly reliable method of contraception, that is, combined hormonal contraception (oral, vaginal or transdermal form), gestagen hormonal contraceptives associated with ovulation inhibition (oral or injectable form) or sexual abstinence.
 - Men—sexual abstinence or the use of an adequate contraceptive method (ie, condom) in case of sexual intercourse.



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Exclusion criteria

- ▶ Diagnosed congenital or acquired coagulopathy.
- ▶ Use of anticoagulants with the exception of perioperative prophylactic administration of low molecular weight heparin to prevent venous thromboembolism.
- ▶ Known hypersensitivity to the active substance or to any of the excipients of investigational medicinal product (IMP).
- ▶ History of deep vein thrombosis or pulmonary embolism.
- ▶ Pregnancy and lactation.

Recruitment and withdrawal

The study is conducted at University Hospital Brno, Czech Republic, in cooperation with the Department of Anaesthesiology and Intensive Care Medicine and the Department of Orthopaedic Surgery. The study is controlled by research infrastructure CZECRIN. All patients eligible for the study and the patient's parents/legal guardians will be asked to participate in the Effect of Prophylactic Fibrinogen Concentrate In Scoliosis Surgery (EFISS) study. The informed consent has to be signed by both parents or legal guardians. For patients who reach the age of 12 years at the time of enrolment, adapted written information and an informed consent is prepared considering the level of knowledge and the age of patients. All participants or their parents/legal guardians can withdraw at any time without giving any reason, but they must notify the investigator.

Sample size

Since this is a pilot study, a power calculation to determine sample size is not required. The sample size was defined in consensus by the State Institute of Drug Control of the Czech Republic, statisticians and investigators. Thirty participants (15 in both arms) were defined as a sample size according to standard guidelines for pilot studies and recommendation of good practice.²⁶⁻²⁸ Considering a 5% dropout rate, 32 participants will be recruited.

Randomisation and blinding

Patients will be randomised in a 1:1 ratio to receive fibrinogen or standard of care without further study medication. Randomisation will be performed electronically in the electronic case report form (eCRF) Research Electronic Data Capture (REDCap) database. This eCRF was created by study statisticians and study data managers and contains a randomisation list. Unblinded person will perform the randomisation after controlling all inclusions and exclusions criteria before induction to the anaesthesia. Based on the randomisation process, an unblinded person indicates IMP application/non-application before skin incision.

The study medication will be prepared by the unblinded study nurse outside the operating theatre. It will be administered after induction of anaesthesia before the beginning of surgery under the supervision of an unblinded investigator. The study nurse and investigator

will be unblinded for the duration of this study and will not be part of the operating team. The blinded surgical team (orthopaedist, anaesthesiologist and anaesthesiology nurse) will be outside the theatre during the IMP application/non-application. The unblinded study team maintains the anaesthesia respecting local protocol for paediatric scoliosis anaesthesia during the IMP application/non-application. After IMP application/non-application, unblinded study nurse and unblinded investigator will leave the operating room, and the blinded operating team will enter back to the theatre. Based on these blinding measures, we are able to ensure absolute blinding of the surgical team.

The data management group and statisticians will work with a pseudo-anonymised data set. Emergency unblinding before the end of the study should occur only in exceptional circumstances when knowledge of the actual treatment is necessary for further management of the patient's treatment. This activity can be performed directly in the REDCap electronic database. The investigator must report all unblindings (with reason) as they occur on the corresponding eCRF page.

Intervention

Choice of comparators

Bleeding and coagulopathy are present during scoliosis surgery, and lack of fibrinogen plays a crucial role in it. We decided to reduce blood loss and coagulopathy development, the fibrinogen will be administered preventively in the intervention arm. The standard of care presents respecting local protocol based on international guidelines (see section 'Standard of care'). This standard approach will be compared with the intervention.

Standard of care

All study participants will receive standard of care in blood and coagulation management for scoliosis surgery. Blood tests including haemoglobin (Hb), haematocrit (Htc), platelet count (Plt), fibrinogen level (Fbg), activated partial thrombin time (aPTT), prothrombin time (PT) and thrombin time (TT) will be performed before the surgery. Values will be checked before surgery, and in case of significant pathology, the surgery will be delayed and the haematologist will be invited. Tranexamic acid will be administered to all patients before the skin incision in a dose of 10–15 mg/kg. The standard of care includes the restrictive administration of blood transfusion, plasma derivative and fluids during the perioperative period. The anaesthesiologist or attending physician in the ICU will administer fluids, blood transfusions and derivatives depending on clinical judgement, blood loss, blood count, coagulation tests and vital signs. This administration is directed by the local protocol of the investigator's hospital which respects international guidelines. 'Goal-directed therapy' approach is preferred in case of bleeding in perioperative period. When the blood loss exceeds about 25% of estimated total blood volume of the patient, blood samples (blood count,

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coagulation status and/or viscoelastic haemostatic assay) are performed and blood transfusions and derivatives are managed according to the results. The goals during bleeding are Hb 70–90 g/L, fibrinogen >2 g/L, platelets >50×10⁹/L and normalisation of coagulation status. In case of life-threatening bleeding, the transfusion strategy of fibrinogen concentrate with red blood cells or fresh frozen plasma with red blood cells in ratio of at least 1:2 is performed. The local protocol respects international guidelines.²⁹

Intervention description

Participants in the intervention group will receive the standard of care, and in addition, a single dose of fibrinogen prior to the skin incision. IMP is administered intravenously and is immediately available at a plasma concentration corresponding to the dose. It is in a powder form in a vial, and it is necessary to solve this powder carefully. The reconstitution procedure should follow the instructions in the package leaflet. Patients in the intervention group will receive a single dose of IMP intravenously, 20–30 mg/kg. This dose range is based on the package leaflet and investigators will administer IMP in doses of hundreds of mg in this range (rounded to closest hundred in dose range). The medicinal product will be diluted in a 100 mL infusion bag and will be administered after induction to anaesthesia before surgery. The infusion rate should not exceed approximately 5 mL/min. The IMP will be administered according to the above study blinding rules.

Comparison

Participants in the intervention group will receive standard of care and IMP before skin incision. Participants in the control group will receive standard of care without study medication before skin incision. In the control group, the placebo will not be administered. It is caused by the requirements of the national regulatory authority (State Institute of Drug Control of the Czech Republic), which does not allow the administration of a placebo in the paediatric population unless it has therapeutic or preventive effect.

The blinded operating team will manage both groups according to the standard of care after the initial intervention/non-intervention. Therefore, fibrinogen can be administered to all patients if indicated in perioperative period according to the local protocol for bleeding management (see section Standard of care).

Primary and secondary outcomes will be compared between intervention and control groups to assess the potential feasibility of a large-scale study.

Trial feasibility

The trial feasibility assessment is one of the secondary aims of this study. We will monitor the recruitment rate of eligible patients who will be approached for consent to participate. The feasibility criterion is >75% of enrolled participants. We will also evaluate the percentage of missing outcomes and clinical data. The goal is to have

<10% missing outcome data, including ICU and hospital length of stay (LOS) and survival, and <10% missing clinical data obtained from clinical medical notes and electronic patient records.

Clinical outcomes

The clinical outcome focuses on reducing blood loss and transfusions in paediatric patients after prophylactic fibrinogen administration during scoliosis surgery. Blood loss and plasma derivatives management will be reported for each participant. Blood count and coagulation parameters will be monitored before surgery, in the end and 24 hours after the surgery. All parameters will be recorded in the eCRF database.

Data collection

During the course of the trial, subjects will be monitored during hospitalisation and after discharge. According to medical records, all data will be collected in an eCRF. Data of blood count (Hb, Hct, Plt) and coagulation status (PT, aPTT, TT, Fbg) will be filled in eCRF before surgery, after surgery and 24 hours after surgery. Information about inclusion and exclusion criteria, informed consent and demographic data will be obtained on the day of enrolment. Collected participant demographic data will be age (years), sex (male, female), weight (kg) and Cobb's angle (°). Blood samples will be taken before surgery according to standard of care, postoperative blood samples will be taken immediately after surgery and 24 hours after surgery. We will record operative time, blood loss, the volume of blood loss for the surgical segment of the spine and urinary output during surgery and 24 hours after surgery. We will track the number, type and volume of administered transfusion products, plasma derivatives, crystalloid solutions and colloid solutions during surgery and in 24 hours postoperative period. The critical part of monitored data will be the incidence of AEs and reactions according to the following AESI. These reactions will include deep vein thrombosis verified on ultrasound imaging, pulmonary embolism confirmed on CT, infection or healing disorder requiring resurgery and/or the initiation of antibiotic therapy. Ultrasound imaging or CT scan will be indicated individually, only in patients with suspicion of AESI according to the clinical condition.

Other monitored additional safety information will be:

- ▶ Hospital LOS.
- ▶ ICU LOS (day of admission and day of discharge will be counted as 1 day).
- ▶ Twenty-eight-day mortality (number of patients who are not alive 28 days after randomisation).

According to the SPIRIT checklist, the schedule of enrolment, interventions and assessments is summarised in table 1.²⁴

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books and

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Table 1 Clinical trial schedule

Timepoint	Study period						
	Screening	Allocation	Postallocation		Hospital discharge	Follow-up	Premature termination
	D_0	D_{0-1}	D_1	D_2	D_{2-28}	D_{28}	Anytime
Enrolment							
Inclusion/Exclusion criteria	X						
Informed consent	X						
Pregnancy testing*	X						
Randomisation		X					
Intervention							
Study medication application†			X				
Assessments							
Demographic data‡	X						
Adverse events			X	X	X	X	X
Laboratory testing§			X	X			
Blood loss¶			X	X			
Urinary output**			X	X			
Transfusion products consumption††			X	X			
Fluid therapy††			X	X			
ICU LOS (days)					X		
LOS (days)					X		
28-day mortality						X	
Reason for premature termination							X

*Urine pregnancy testing.

†Fibrinogen infusion or standard of care.

‡Age, sex, weight, Cobb's angle.

§Haemoglobin, haematocrit, platelet count, fibrinogen, aPTT, PT, TT.

¶Volume (mL) during surgery and in the 24-hour postoperative period and volume (mL) related to the surgical segment of the spine.

**Volume (mL) in the 24-hour postoperative period.

††Type and volume (mL) during surgery and in the 24-hour postoperative period.

aPTT, activated partial thrombin time; ICU, intensive care unit; LOS, length of stay; PT, prothrombin time; TT, thrombin time.

other listings that link participant ID numbers to additional identifying information will be stored in a locked file in an area with limited access. No later than 3 years after the collection of the 1-year postrandomisation, we will deliver a completely blinded data set to an appropriate data repository for sharing purposes. Statistical codes will be archived in accordance with standard operating procedures.

Statistical analysis

A separate statistical analysis plan (SAP) will be prepared to provide details on the approach to analyses. The SAP will be finalised before the database lock. All eventual deviations from the SAP will be described and justified in the relevant part of the Clinical Trial Report. As a general approach for the descriptive analysis, the following statistics will be provided for continuous variables: the number of subjects with available data (n), mean, SD, median,

minimum and maximum. The number and percentage of patients will be provided for categorical variables. For a comparison of continuous variables between treatment groups, two-sample t-test or its non-parametric alternative Mann-Whitney U test will be used, where appropriate. Pearson's χ^2 test or Fisher's exact test will be used to compare categorical variables, where appropriate. All statistical tests will be two-sided. P values <0.05 will constitute statistically significant differences. During the pilot study, the interim analysis is not planned.

Protocol non-adherence will be assessed by the principal investigator case by case. Patients with major deviations from the study protocol will be excluded from the analysis. Missing data are not planned to be imputed. However, in the event of substantial missing data for any parameter, a sensitivity analysis using any method of imputation could also be used.

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Patient and public involvement

Patients or the public will not be involved in the study development. This EFiSS study was proposed and designed by an expert team of University Hospital Brno and the Faculty of Medicine, Masaryk University Brno in the Czech Republic.

Monitoring and auditing

The trial centre will be monitored according to the monitoring plan provided by research infrastructure CZECRIN. The objectives of the monitoring are to ensure that the trial participant's safety and rights are respected, that accurate, valid and complete data are collected and that the trial is conducted in accordance with the trial protocol, the principles of good clinical practice (GCP) and national legislation. Sponsor, regulatory authority and ethics committees have the right to inspect/audit the trial site.

ETHICS AND DISSEMINATION

This trial follows the applicable legislation and requirements for GCP according to the ICH E6(R2). Compliance with this standard provides public assurance that the rights, safety and well-being of trial participants are protected and that the clinical trial data are credible.

All essential trial documents were approved by the relevant ethics committee and national regulatory authority (State Institute for Drug Control) and their potential amendments will be submitted for approval. The study was approved by University Hospital Brno's Ethics Committee (No.: 24/22MONO) and by State Institute for Drug Control (No.: suks11048/2022). This clinical study includes patients belonging to the category of vulnerable subjects, namely children and adolescents under 18 years of age.

Informed consent procedure

The parents/legal guardians will receive written information and an ICF. The investigator will inform in a comprehensible manner about the nature, purpose and significance of the clinical trial simultaneously. This procedure will take place before enrolling the child in the study. Parents/Legal guardians will also be informed of the measures to protect personal data. That liability insurance has been arranged for investigators and sponsors in the event of health damage due to a clinical trial, including possible compensation for trial subjects. Paediatric patients will receive from the investigator information on the clinical trial adapted to their level of knowledge and intellectual abilities, including details on the benefits and risks of participating in this clinical trial. The explicit wish of instructed paediatric patients to refuse to participate or to withdraw from a clinical trial at any time is always respected. Written information and an informed assent form are prepared for patients who reach the age of 12 years at the time of enrolment. Paediatric patients and their parents/legal guardians will get

sufficient time to study the written information and the ICF carefully and will ask additional questions to which the investigator must respond satisfactorily. All legal representatives (both parents) must sign the ICF at the end of the process.

Supervision of the informed consent procedure

The process of obtaining informed consent from the patient's parents/legal guardians, or patients, must always be adequately documented by the investigator using valid forms and the patient's medical records. The clinical trial monitor will check the process during monitoring visits. Significant deviations in the process will lead to the termination of the patient's participation in the trial.

DISCUSSION

Prophylactic fibrinogen administration before high-risk surgeries is a widely discussed topic across medical fields. Preoperative lower levels of fibrinogen are associated with higher blood loss in adolescent idiopathic scoliosis surgery. However, if the effect of prophylactic fibrinogen administration will lead to blood loss reduction in these patients is unclear.^{16 17 30}

The safety of fibrinogen administration in the paediatric population has been demonstrated in several studies.^{25 31} However, in these studies, fibrinogen was substituted during the surgery according to the viscoelastic haemostatic assays, the substitution was not prophylactic. In addition, the number of participants was low. In summary, data on prophylactic administration in children and adolescents are insufficient, more studies are needed.

We can see some similarity with tranexamic acid administration. In recent years, tranexamic acid has been commonly used in scoliosis surgery to reduce blood loss.³²⁻³⁴ The efficacy of tranexamic acid is unambiguous, it reduces blood loss, the need for blood transfusions and the length of hospitalisation.³² The use of tranexamic acid is incorporated in orthopaedic recommendations for blood management.³⁵ However, some studies have provided evidence of the thromboembolic potential of tranexamic acid.^{36 37} In contrast, fibrinogen is not associated with higher thromboembolic risk repeatedly.³⁸ It is appropriate to study fibrinogen concentrate to see if it has the same positive properties as tranexamic acid without possible side effects.

This pilot study also has some limitations. The sample size is designed according to standard guidelines for pilot studies, so it is limited to 32 patients. Participants are under the age of 18 years, so informed consent has to be signed by both parents or legal guardians, which may lead to limited enrolment. Data are collected 28 days after randomisation, which may not be an adequate interval to evaluate safety and feasibility. And final limitation is the absence of placebo administration in the standard of care group. This absence is mainly caused by the requirements of the national regulatory authority, which does not allow



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the administration of a placebo without a therapeutic or preventive effect in the paediatric population.

CONCLUSION

This pilot study should demonstrate the safety and feasibility of the intended intervention and form the basis for a later large study which could have extensive impact in scoliosis surgery and bleeding management. But the results will not prove most likely the efficacy of prophylactic administration of fibrinogen in scoliosis surgery.

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Acknowledgements The authors thank everyone involved in the study, concretely the participants, assessors and all healthcare providers taking care for participants.

Contributors OH and RG first conceived this protocol after revision from the other authors. KV, JH and MG are the main authors and editors of this manuscript. MG and MR are responsible for patient involvement. JH, KV and HH provide standards of care. CZECRIN (MK and RD) assisted in the development of the study protocol and is responsible for statistical analysis. All authors read and approved the final version of the manuscript.

Funding The project was supported by Specific University Research provided by MSM (J15/98:1431/0002) and by the Ministry of Health, Czech Republic—conceptual development of research organisation (FNBr, 65269705). The project was supported by the national budget through MEYS, RI CZECRIN (LM2018128).

Disclaimer The sponsor has no role in the design of this trial and will not have any role during its execution, analyses, interpretation of the data, or the decision to submit results.

Competing interests In the past 5 years, KV and RG have received honoraria for lecturing from CSL Behring.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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7.1.2 Effect of prophylactic fibrinogen concentrate in scoliosis surgery (EFISS): a randomised pilot trial

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Original research

BMJ Open Effect of prophylactic fibrinogen concentrate in scoliosis surgery (EFISS): a randomised pilot trial

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To cite: Hudec J, Vrbica K, Hrdy O, et al. Effect of prophylactic fibrinogen concentrate in scoliosis surgery (EFISS): a randomised pilot trial. *BMJ Open* 2025;15:e100137. doi:10.1136/bmjopen-2025-100137

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<https://doi.org/10.1136/bmjopen-2025-100137>).

JH and KV contributed equally.

Received 03 February 2025
Accepted 22 August 2025

ABSTRACT

Objectives The goal of this study is to assess the safety, feasibility and clinical outcomes of prophylactic fibrinogen administration in paediatric scoliosis surgery.

Design Prospective, two-arm, randomised, double-blind pilot trial.

Setting Single-centre study conducted at a tertiary care hospital specialising in scoliosis surgery.

Participants 32 children undergoing scoliosis surgery entered and completed the study. The inclusion criteria were elective scoliosis surgery, age <18 years, provision of a signed informed consent form by both parents and consent to contraception use for the duration of this clinical trial among sexually active (≥15 years of age) participants. The exclusion criteria were diagnosed congenital or acquired coagulopathy, use of anticoagulants other than perioperative prophylactic administration of low molecular weight heparin to prevent venous thromboembolism, known hypersensitivity to the active substance or any excipients in the investigated medicinal product, history of deep vein thrombosis or pulmonary embolism, pregnancy and lactation.

Interventions Participants were randomised 1:1 to a standard group, receiving standard blood and coagulation management, or a fibrinogen group, receiving a single prophylactic dose of fibrinogen concentrate in addition to standard care.

Primary and secondary outcome measures Safety, the primary objective, was assessed according to adverse events, serious adverse events and other safety parameters. Secondary objectives included feasibility and clinical outcomes.

Results In the fibrinogen group, 101 adverse events across 19 types were observed, whereas in the standard group, 95 adverse events across 21 types ($p>0.9999$) and one serious adverse event were observed. No adverse events of special interest or deaths occurred in either group. Blood loss did not significantly differ between the fibrinogen (1021.88 mL (SD 473.63)) and standard (859.38 mL (SD 713.03)) groups ($p=0.1677$). The mean length of hospital stay was 8.88 (SD 0.81) days in the fibrinogen group and 9.25 (SD 1.88) days in the standard group ($p=0.9210$). No statistically significant differences in the use of blood transfusions, blood derivatives, crystalloids or colloids were observed between groups.

Conclusions This study demonstrates that the prophylactic administration of fibrinogen during scoliosis surgery in children is feasible and appears to be safe.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study was designed as a two-arm, single-centre, randomised, double-blind trial.
- ⇒ This study focuses on paediatrics, a population that remains relatively under-researched.
- ⇒ The requirement for informed consent from both parents limited participant enrolment and may have introduced selection bias.
- ⇒ The intervention study was designed without placebo administration in order to avoid the risk of potential adverse events associated with placebo use.
- ⇒ The study limitation is its short 28-day follow-up period.

Due to the limited sample size, no conclusions can be drawn regarding the efficacy of pre-emptive fibrinogen administration on clinical outcomes. However, the results provide valuable data to inform sample size calculation for a future full-scale randomised controlled trial.

Trial registration number ClinicalTrials.gov
NCT05391412.

BACKGROUND

Scoliosis, one of the most common spinal deformities in paediatrics, has an average prevalence of 2–3% worldwide.^{1,2} Scoliosis is usually defined as a lateral curvature of the spine measuring $>10^\circ$ in the coronal plane on an X-ray. However, this condition is a complex multidimensional structural spine deformity resulting from rotation, angulation and curvature abnormalities in all three axes.^{3–5} The progression of the scoliotic curve over time, particularly during rapid growth periods, changes the shape and size of the rib cage and thorax, thus leading to respiratory, cardiovascular, gastrointestinal and psychosocial disorders affecting multiple organs. Scoliotic curve progression is also associated with back pain.⁶ Scoliosis treatments are aimed at stopping the progression of curve deviation and thus preventing the development of multiple-organ diseases.⁷ Treatment options



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Hudec J, et al. *BMJ Open* 2025;15:e100137. doi:10.1136/bmjopen-2025-100137

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for scoliosis include observation, physiotherapy, bracing and surgery. The choice of treatment method depends on the severity and progression of the scoliotic curve. A common indication for surgical treatment is progressive deviation of the scoliotic curve and a Cobb angle $>40^\circ$.

Scoliosis surgery is challenging because of long operation times, body temperature management, positioning, intraoperative neurophysiological monitoring and high blood losses.⁸⁻⁹ Blood transfusions in the perioperative period are required in approximately 30%–60% of cases and are associated with prolonged hospital stays, increased costs and mortality.¹⁰⁻¹¹ Strategies to decrease blood loss and the need for transfusions are therefore warranted; these strategies include antifibrinolytic treatment (eg, tranexamic acid), hypothermia prevention and cell salvage.¹²⁻¹⁴

Recently, attention has been paid to fibrinogen, a coagulation factor essential for clot formation during haemostasis.¹⁵⁻¹⁶ Hypo/dysfibrinogenaemia can lead to severe bleeding during high-risk surgeries.¹⁷⁻²⁰ Moreover, some studies have reported less blood loss in patients with higher preoperative fibrinogen levels.²¹⁻²² The effects of prophylactic fibrinogen administration have been reported in cardiovascular or urological surgery, and decreased blood loss and transfusion requirements have been observed.²³⁻²⁵ Early intraoperative fibrinogen administration, compared with late administration, has been found to decrease transfusion volume and blood loss in children undergoing surgery for craniosynostosis but not for scoliosis. However, the scoliotic population in the trial was small.²⁶ The effects of prophylactic fibrinogen administration in the paediatric population undergoing scoliosis surgery, particularly regarding safety and the magnitude of blood loss, remain unclear. This study was aimed at assessing the safety, efficacy and feasibility of prophylactic fibrinogen administration in paediatric scoliosis surgery.

METHODS

Study design and participants

This two-arm, single-centre, randomised, double-blind trial was conducted between June 2022 and October 2023 at a tertiary teaching hospital in the Czech Republic. All patients admitted for elective scoliosis surgery were screened for eligibility. The inclusion criteria were elective scoliosis surgery, age <18 years at the time of enrolment, provision of a signed informed consent form by both parents and consent to contraception use for the duration of this clinical trial among sexually active (≥ 15 years of age) participants.

The exclusion criteria were diagnosed congenital or acquired coagulopathy, use of anticoagulants other than perioperative prophylactic administration of low molecular weight heparin to prevent venous thromboembolism, known hypersensitivity to the active substance or any excipients in the investigated

medicinal product, history of deep vein thrombosis or pulmonary embolism, pregnancy and lactation. After provision of informed consent, each patient was randomised to one of the trial arms. The randomisation procedure was implemented in an electronic case report form with a randomisation ratio of 1:1. The study statistician generated the randomisation list, which the study data manager implemented in the electronic case report form. Allocation concealment was ensured with a web-based randomisation system. The generation of the allocation sequence was embedded in the trial website. The study investigator enrolled participants and randomised them with the web-based randomisation system. The patient and treating physicians and nurses were blinded to the study intervention. An unblinded investigator performed the randomisation before induction to the anaesthesia, and the study medication was prepared by the unblinded study nurse outside the operating theatre. It was administered/non-administered after induction of anaesthesia before the beginning of surgery under the supervision of an unblinded investigator. The blinded surgical and anaesthesia team was outside of the operating theatre during the administration/non-administration of fibrinogen. The data management group and statisticians worked with a pseudo-anonymised data set. The detailed methods of this study have been published as a protocol.¹⁶ No interim safety analysis was conducted, as the study was designed to explore safety. The study is reported according to CONSORT guidelines.²⁷

Interventions

Standard of care

In one arm of the study (STANDARD), all participants received standard of care blood and coagulation management for scoliosis surgery according to the local protocol, which adheres to international guidelines.²⁸ Standard blood and coagulation tests were performed before the surgery. Tranexamic acid was administered intravenously before the skin incision at a dose of 10–15 mg/kg. A restrictive approach was used to administer blood transfusions, plasma derivatives and fluids. The indications for administration depended on clinical judgement, according to assessment of blood loss, blood test results and vital signs. The thresholds were set to Hb at 70–90 g/L, fibrinogen at >2 g/L and platelets at $>50 \times 10^9$ /L. In the event of life-threatening bleeding, the transfusion strategy of fibrinogen concentrates and red blood cells or fresh frozen plasma in a ratio of at least 1:2 was used.

Intervention group

Participants randomised to the second arm (FIBRINOGEN) received the standard of care. In addition, a single dose of 20–30 mg/kg of fibrinogen was administered intravenously before the skin incision.

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Table 1 Demographic characteristics

Characteristic	Statistic	FIBRINOGEN	STANDARD	P value
Sex				
Male	n (%)	5 (31.3)	4 (25)	>0.9999
Female	n (%)	11 (68.7)	12 (75)	
Age (years)	Mean (SD)	14.06 (1.61)	13.56 (2.76)	0.8926
	Median (min,max)	15 (11,16)	14 (6,17)	
ASA score	Mean (SD)	1.63 (0.62)	1.25 (0.45)	0.0688
	Median (min,max)	2 (1,3)	1 (1,2)	
Weight (kg)	Mean (SD)	50.53 (11.6)	51.51 (13.45)	0.8082
	Median (min,max)	48.5 (34.4,75)	55 (20,77)	
Height (cm)	Mean (SD)	164.38 (10.73)	158.06 (16.27)	0.3956
	Median (min,max)	162 (143,192)	162 (110,179)	
Fused levels (N)	Mean (SD)	10.44 (2.56)	10.75 (2.57)	0.7325
	Median (min,max)	10 (6,15)	11.5 (6,15)	
Cobb angle (°)	Mean (SD)	56.81 (14.42)	58.63 (15.76)	0.8800
	Median (min,max)	54 (39,90)	51 (44,91)	

ASA, American Society of Anesthesiologists.

ASA, American Society of Anesthesiologists.

Outcome measures

Primary outcome

The primary outcome of the study was the safety assessment of prophylactic fibrinogen administration in scoliosis surgery in children.

This primary outcome monitoring followed European directive 2001/20/EC.²⁹ According to this directive, the safety assessment included the incidence of adverse events (AEs), adverse drug reactions, serious AEs, serious adverse reactions, unexpected adverse reactions and suspected unexpected serious adverse reactions, which were compared between study groups.

Secondary outcomes

Additional safety information

AEs of special interest (AESI), including deep vein thrombosis verified on ultrasound imaging, pulmonary embolism confirmed on CT scan and infection or healing disorder requiring re-surgery and/or the initiation of antibiotic therapy, were monitored. Intensive care unit (ICU) and hospital length of stay (LOS) and 28-day mortality were also assessed.

Feasibility

The following parameters were analysed in the study feasibility assessment: the recruitment rate of eligible patients approached for consent to participate (with a feasibility criterion of >75% of enrolled participants), the percentage of missing outcomes and clinical data (with an aim of <10% missing outcome data and <10% missing clinical data obtained from patient records).

Clinical outcomes

The analysed clinical outcomes included demographic data, total volume blood loss, blood loss per one fused

level, number of patients receiving transfusion products or blood derivatives, number of administered transfusions and blood derivatives (red blood cells, thrombocytes of apheresis, fresh frozen plasma, fibrinogen concentrate, prothrombin complex concentrate), volume of administered fluids (crystalloid or colloids), urine output within the 24 hours after the surgery, blood counts (haemoglobin, haematocrit and platelets) and coagulation parameters (fibrinogen, activated partial thromboplastin time (aPTT), prothrombin time (PT) and thrombin time (TT)) before surgery, at the end of surgery and 24 hours after surgery.

Sample size and power considerations

Because this study was a pilot study, a power calculation to determine sample size was not required. By considering pilot study standards and guidelines, we set the sample size to 30 participants, with 15 per study arm.^{30–32} According to the expectation of a 5% dropout rate, the final sample size was set to 32 participants (16 per arm).³³

Statistics

The statistical analyses were performed according to a previously published protocol.¹⁶ Categorical data are presented as numbers and percentages. For continuous data, the mean, SD, median, minimum and maximum were calculated. Test for normality (Shapiro-Wilk test) was used together with visual inspection of data (histograms and Q-Q plots were used) for continuous parameters. For comparison of continuous variables between treatment groups, the two-sample t-test or its non-parametric alternative, the Mann-Whitney U test, was used, as appropriate. For categorical parameters, Fisher's exact test was used when assumptions for Pearson's χ^2 test

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Table 2 Adverse events

	Total (N=32)			FIBRINOGEN (N=16)			STANDARD (N=16)			P value
	AE	n	%	AE	n	%	AE	n	%	
Number of patients with at least one AE		32	100		16	100		16	100	>0.9999
Total number of AEs	196			101			95			
General disorders	57	32	100	29	16	100	28	16	100	>0.9999
Pain	32	32	100	16	16	100	16	16	100	>0.9999
Fever	25	25	78.13	13	13	81.25	12	12	75.00	>0.9999
Surgical disorders	2	2	6.25	–	–	–	2	2	12.50	>0.9999
Drain self-extraction	1	1	3.13	–	–	–	1	1	6.25	>0.9999
Re-surgery	1	1	3.13	–	–	–	1	1	6.25	>0.9999
Gastrointestinal disorders	42	23	71.88	25	11	68.75	17	12	75.00	>0.9999
Flatulence	4	4	12.50	2	2	12.50	2	2	12.50	>0.9999
Nausea	16	16	50.00	9	9	56.25	7	7	43.75	0.7244
Vomiting	9	9	28.13	6	6	37.50	3	3	18.75	0.4331
Diarrhoea	1	1	3.13	1	1	6.25	–	–	–	>0.9999
Constipation	12	12	37.50	7	7	43.75	5	5	31.25	0.7160
Blood and haemostasis disorders	80	32	100	41	16	100	39	16	100	>0.9999
Anaemia	31	31	96.88	15	15	93.75	16	16	100	>0.9999
Coagulopathy	32	32	100	16	16	100	16	16	100	>0.9999
Leucocytosis	10	10	31.25	5	5	31.25	5	5	31.25	>0.9999
Thrombocytopenia	7	7	21.88	5	5	31.25	2	2	12.50	0.3944
Skin and soft tissue disorders	2	1	3.13	–	–	–	2	1	6.25	>0.9999
Face oedema	1	1	3.13	–	–	–	1	1	6.25	>0.9999
Soft tissue oedema	1	1	3.13	–	–	–	1	1	6.25	>0.9999
Urogenital disorders	2	2	6.25	1	1	6.25	1	1	6.25	>0.9999
Urinary infection	2	2	6.25	1	1	6.25	1	1	6.25	>0.9999
Homeostasis and metabolism disorders	4	4	12.50	2	2	12.50	2	2	12.50	>0.9999
Hypokalaemia	2	2	6.25	1	1	6.25	1	1	6.25	>0.9999
Hyponatraemia	1	1	3.13	–	–	–	1	1	6.25	>0.9999
Loss of appetite	1	1	3.13	1	1	6.25	–	–	–	>0.9999
Nervous system disorders	6	6	18.75	3	3	18.75	3	3	18.75	>0.9999
Paraesthesia	1	1	3.13	1	1	6.25	–	–	–	>0.9999
Vertigo	5	5	15.63	2	2	12.50	3	3	18.75	>0.9999
Respiratory disorders	1	1	3.13	–	–	–	1	1	6.25	>0.9999
Cough	1	1	3.13	–	–	–	1	1	6.25	>0.9999

%, percentage of patients with at least one adverse event in the category; AE, adverse events; n, number of patients with at least one adverse event in the category; P value, p value of Fisher exact test.

were not met (ie, at least one expected frequency was <5 in contingency table). All statistical tests were two-sided, and p values <0.05 were considered to indicate statistically significant differences. Analyses were conducted on an intention-to-treat basis and missing data were not imputed. The statistical analyses were performed in SAS version 9.4. The study statistical analysis plan is available in online supplemental file 1.

Ethical considerations and data protection

The study was approved by University Hospital Brno's Ethics Committee (No 24/22MONO) and by State Institute for Drug Control (No suks11048/2022), and was conducted in accordance with the principles of the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (NCT05391412, date of approval 6 May 2022). No later than 3 years after the collection of the 1-year

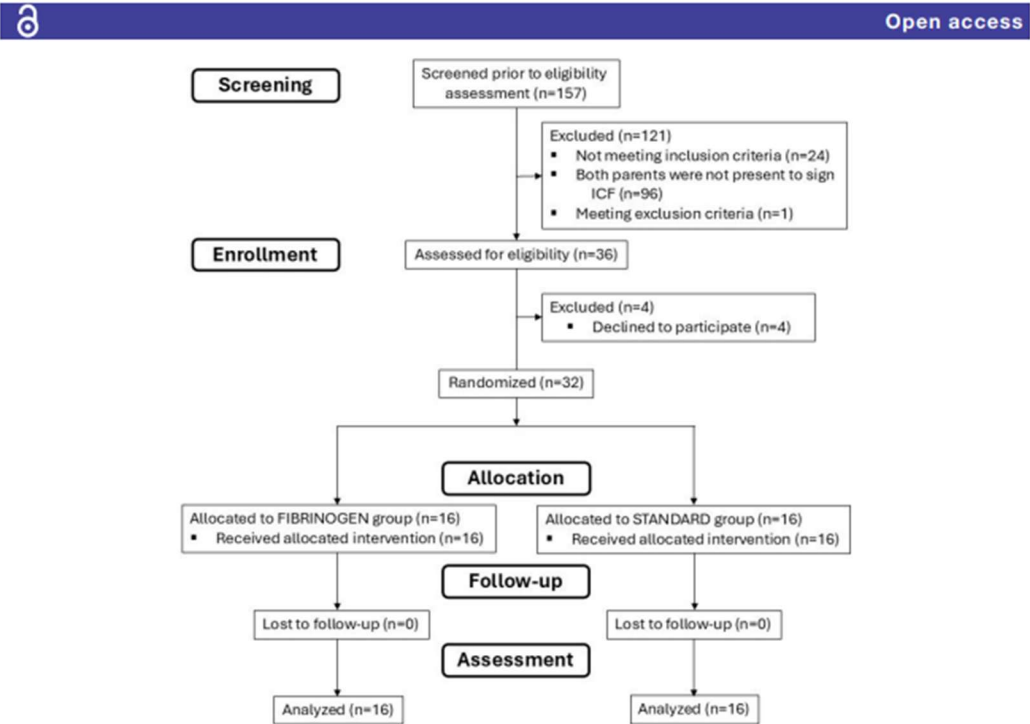


Figure 1 Flowchart diagram. ICF, Informed Consent Form.

post-randomisation, a completely blinded data set will be delivered to an appropriate data repository for sharing purposes.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

RESULTS

Characteristics of the study sample

Between 8 June 2022 and 14 June 2023, a total of 32 children with adolescent idiopathic scoliosis undergoing scoliosis surgery were enrolled in this study. The mean age was 13.8 years, and nine (28.1%) participants were boys. The demographic characteristics between groups were comparable, except for the American Society of Anesthesiologists (ASA) score, which showed a difference that was not statistically significant, as demonstrated in table 1.

Primary outcome

Regarding the primary outcome, safety, all patients in both groups showed some AEs. A total of 101 AEs of 19 types were observed in the FIBRINOGEN group. In the STANDARD group, 95 AEs of 21 types were observed. These AEs were of grades 1–3, whereas no AEs of grades

4 and 5 were observed. In the STANDARD group, one serious AE occurred, which required reoperation because of breakage of the implanted rod. Throughout the study, we observed no adverse drug reactions, serious adverse reactions, unexpected adverse reactions or suspected unexpected serious adverse reactions. The detailed list of individual AEs is presented in table 2. The difference in AEs between groups was not statistically significant.

Secondary outcomes

No AESI were observed in both groups. The mean LOS was 8.88 (SD 0.81) days in the FIBRINOGEN group and 9.25 (SD 1.88) days in the STANDARD group (p=0.9210). The mean ICU LOS was 3.38 (SD 1.09) days in the FIBRINOGEN group and 3.63 (SD 1.63) days in the STANDARD group (p=0.9069). No significant differences were observed between groups in either measure. No patients died during the 28-day observation period.

Feasibility

The patient enrolment process is shown in figure 1. Ultimately, 32 participants were enrolled, and the recruitment rate of eligible patients approached for consent was 88.9%, exceeding the required threshold of 75%. The percentage of missing outcome data (LOS, ICU LOS and 28-day survival) was 0%, a value well below the required threshold of 10%. The percentage of missing clinical data

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Table 3 Haematological parameters and blood loss

	N	Time	Mean	SD	Median	Minimum	Maximum	P value
Haemoglobin (g/L)								
FIBRINOGEN	16	Before surgery	132.75	9.14	135.5	118	147	0.5849
STANDARD	16		134.69	10.65	135	115	155	
FIBRINOGEN	16	End of surgery	103.24	13.5	104	76	121	0.6452
STANDARD	16		105.39	12.71	109	79.3	127	
FIBRINOGEN	16	24 hours after surgery	100	5.91	101.5	93	113	0.7877
STANDARD	16		100.81	10.37	98.5	88	127	
Haematocrit (%)								
FIBRINOGEN	16	Before surgery	39.56	2.73	39.5	35	43	0.6843
STANDARD	16		39.99	3.11	40.5	34	46	
FIBRINOGEN	16	End of surgery	29.69	3.84	30	22	36	0.4029
STANDARD	16		30.81	3.66	31.5	23	37	
FIBRINOGEN	16	24 hours after surgery	29.13	1.78	29	26	33	0.8362
STANDARD	16		29.31	3.11	28.5	26	37	
Platelets (10 ⁹ /L)								
FIBRINOGEN	16	Before surgery	271.69	60.52	254	165	396	0.115
STANDARD	16		304.94	55.24	305	190	440	
FIBRINOGEN	16	End of surgery	184.5	46.75	174	105	284	0.0379
STANDARD	16		222.88	53.03	220	117	304	
FIBRINOGEN	16	24 hours after surgery	170.5	32.56	168	116	236	0.0251
STANDARD	16		202.44	43.31	198	121	289	
Fibrinogen (g/L)								
FIBRINOGEN	16	Before surgery	2.77	0.51	2.68	2.12	3.89	0.5097
STANDARD	16		2.67	0.31	2.68	2.17	3.1	
FIBRINOGEN	16	End of surgery	2.56	0.39	2.46	1.89	3.48	0.2336
STANDARD	16		2.39	0.41	2.42	1.44	3.03	
FIBRINOGEN	16	24 hours after surgery	4.01	0.58	3.97	3.35	5.6	0.3034
STANDARD	16		4.19	0.38	4.21	3.53	4.98	
aPTT (s)								
FIBRINOGEN	16	Before surgery	34.14	2.59	34.9	30.4	39.2	0.8723
STANDARD	16		34.28	2.42	34.3	30.1	39.5	
FIBRINOGEN	16	End of surgery	41.14	4.7	40.8	31.8	50.2	0.2767
STANDARD	16		39.38	4.29	39.1	33.2	49	
FIBRINOGEN	16	24 hours after surgery	37.16	2.98	36.8	33.1	43.8	0.8913
STANDARD	16		37.02	2.66	38.1	31.3	40.8	
PT (s)								
FIBRINOGEN	16	Before surgery	15.33	1.3	15.1	13.6	17.9	0.1161
STANDARD	16		14.69	0.86	14.6	13.3	15.9	
FIBRINOGEN	16	End of surgery	19.38	2.17	19.6	15.1	24.4	0.0371
STANDARD	15		17.83	1.73	17.6	15	20.6	
FIBRINOGEN	16	24 hours after surgery	21.2	2.04	21.4	17.8	25.2	0.1348
STANDARD	16		19.89	2.74	20	16.2	27.6	
TT (s)								
FIBRINOGEN	16	Before surgery	17.67	1.30	17.5	14.9	21.3	0.6401
STANDARD	16		17.49	0.7	17.4	16.5	19.2	

Continued

Continued

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Table 3 Continued							
	N	Time	Mean	SD	Median	Minimum	P value
FIBRINOGEN	16	End of surgery	18.78	0.81	18.7	17.6	0.1778
STANDARD	16		18.39	0.75	18.3	17.3	
FIBRINOGEN	16	24 hours after surgery	15.95	0.8	15.8	14.9	0.076
STANDARD	16		15.45	0.73	15.6	13.4	
Total blood loss (mL)							
FIBRINOGEN	16	During surgery	1021.88	473.63	1000	200	0.1677
STANDARD	16		859.38	713.03	675	200	
FIBRINOGEN	15	24 hours after surgery	290	79.55	300	120	0.4983
STANDARD	14		326.43	93.86	290	230	
Blood loss per one fused level (mL/fused level)							
FIBRINOGEN	16	During surgery	98.16	38.49	111.11	26.67	0.1008
STANDARD	16		76.61	52.03	64.58	21.43	
FIBRINOGEN	15	24 hours after surgery	28.01	9.47	30	13.33	0.5948
STANDARD	14		29.77	7.98	28.08	17.86	

aPTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time.

(clinical medical notes and electronic patient records) was 0.0047% (7 of 1504), a value also below the required threshold of 10%.

Clinical outcomes

Another aspect of the secondary outcomes was the comparison of selected haematological parameters before, during and 24 hours after surgery, and the comparison of blood loss during and 24 hours after surgery between groups (table 3). A statistically significant difference was observed in platelet count, which was higher in the STANDARD group at the end of surgery (mean 222.88 (SD 53.03) vs 184.50 (SD 46.75); $p=0.0379$) and 24 hours after surgery (mean 202.44 (SD 43.31) vs 170.50 (SD 32.56); $p=0.0251$). Another statistically significant difference was observed in PT at the end of surgery: in the STANDARD group (mean 17.83s (SD 1.73) vs 19.38s (SD 2.17); $p=0.0371$), PT was shorter than the standard range of 11.0–17.0s. Blood loss did not differ significantly between the FIBRINOGEN and STANDARD groups during surgery (mean 1021.88mL (SD 473.63) vs 859.38mL (SD 713.03); $p=0.1677$) and 24 hours after surgery (mean 290.0mL (SD 79.55) vs 326.43mL (SD 93.86); $p=0.4983$). The administration of blood transfusions, blood derivatives, crystalloids and colloids showed no statistically significant differences between groups (table 4).

DISCUSSION

Here, we present the results of a pilot study exploring the safety and feasibility of prophylactic fibrinogen administration in paediatric scoliosis surgery. Supplementation with fibrinogen, an essential coagulation factor, is currently a discussed topic. However, the

influence of prophylactic administration, particularly in the paediatric population before high-risk surgery, remains unclear. To our knowledge, this study is the first trial examining the safety and feasibility of prophylactic fibrinogen administration in this population. Regarding safety, the incidence of AEs of grades 1–3 was comparable and showed no statistically significant differences between groups. Most monitored AEs, such as anaemia, leukocytopenia, tachycardia or high body temperature, were complications of the major surgery with blood loss and are part of postoperative systemic inflammatory response syndrome, as previously described.^{34–36} No AEs of grades 4 or 5 occurred in either group. A comparison of the incidence of serious AEs in both groups revealed only one case of a patient with a prolonged hospital stay and need for reoperation in the STANDARD group. However, a second surgery was indicated for rod breakage, a surgical complication. The observed need for reoperation in 1 of 16 patients was comparable to that in the most extensive study published in 2022, in which the reoperation rate was 6.0%.³⁷ Thus, the authors did not assume a significant effect of fibrinogen on the occurrence of AEs, as confirmed by our findings of no AESI in either the FIBRINOGEN STANDARD group. The differences in ICU LOS and hospital LOS were not statistically significant in both groups. Our hospital LOS findings were comparable to those in a study from Syracuse, USA, in which the average hospital LOS between 1997 and 2012 was 8 days.³⁸ Another study from Denmark has reported a mean LOS of 8 days in more than 1300 patients.³⁹ In contrast, other studies have described shorter hospital LOS of 4.9 days and 5.4 days.^{40–41} The

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Table 4 Total of blood transfusions, blood derivatives and fluids during surgery and 24 hours after surgery

	During surgery				24 hours after surgery				Total			
	FIBRINOGEN (N=16)		STANDARD (N=16)		FIBRINOGEN (N=16)		STANDARD (N=16)		FIBRINOGEN (N=16)		STANDARD (N=16)	
	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total
Blood transfusions and/or blood derivatives	13 (81.25)		11 (68.75)		6 (37.50)		6 (37.50)		13 (81.25)		13 (81.25)	
					0.6851							
Blood transfusions	13 (81.25)		10 (62.50)		6 (37.50)		6 (37.50)		13 (81.25)		13 (81.25)	
					0.4331							
Erythrocytes (mL)	13 (81.25)	6773 mL	10 (62.50)	5009 mL	6 (37.50)	1558 mL	6 (37.50)	1474 mL	13 (81.25)	8331 mL	13 (81.25)	6483 mL
					0.6851							
Blood derivatives	13 (81.25)		11 (68.75)		-		-		13 (81.25)		11 (68.75)	
					0.6851							
Fibrinogen(g)	13 (81.25)	32 g	11 (68.75)	34 g	-		-		13 (81.25)	32 g	11 (68.75)	34 g
					0.6851							
PIP(n)	1 (6.25)	1	2 (12.50)	2	-		-		1 (6.25)	1	2 (12.50)	2
					>0.9999							
Colloids	10 (62.50)	5000 mL	6 (37.50)	3000 mL	0.2890		1 (6.25)	400 mL	10 (62.50)	5000 mL	7 (43.75)	3400 mL
					0.9999							
Crystalloids	16 (100.00)	37 100 mL	16 (100.00)	40 000 mL	0.9999		16 (100.00)	36 650 mL	16 (100.00)	74 860 mL	16 (100.00)	76 650 mL
					>0.9999							
PIP, pathogen inactivated plasma.												

variations among studies are likely to be due to the different surgical approaches, healthcare systems or methods for counting days of hospitalisation. Therefore, we conclude that the prophylactic fibrinogen administration appears safe and to have no effect on LOS. Our study demonstrated 0% mortality in both groups at 28 days. This finding is in accordance with those from prior studies, although the number of patients included in our study did not allow for a relevant comparison.^{38, 39} Thus, the prophylactic fibrinogen administration before scoliosis surgery is likely to be safe.

In terms of feasibility, most patients met the inclusion criteria, and fibrinogen was able to be administered. The main challenge arose from national legislation requiring both parents of each patient to provide signed informed consent in studies of paediatric patients. Because University Hospital Brno is one of the largest scoliotic centres in Central Europe, the travel distance to Brno is long, and both parents are often unable to travel with their children to admission. However, the requirement to obtain the signatures of both parents ended after the enforcement of EU Regulation 536/2014.⁴² We therefore assume that easier patient recruitment in the future will enable more extensive studies to be conducted. The missing outcomes and clinical data percentages were both below the pre-set threshold of 10%. Therefore, on the basis of the above considerations, we conclude that a future large study would be feasible.

Regarding clinical outcomes, the measured blood loss during surgery was higher in the FIBRINOGEN group than in the standard group, but the difference was not statistically significant. The blood loss was comparable to that in a study by Wang *et al* in 765 adolescent patients with idiopathic scoliosis undergoing posterior spinal fusion surgery, in which the measured blood loss reached 926.8 ± 521.1 mL.⁴³ Our study population showed variability in blood loss, with a minimum value as much as 10 times lower than the maximum. Therefore, we adjusted the measurements by converting absolute blood loss to relative blood loss per fused level. Although higher mean blood losses per fused level were observed in the FIBRINOGEN group than the STANDARD group during surgery, the differences were not statistically significant. The mean blood loss in both groups in the present study was lower than the reported mean blood loss of 123.9 mL per fused level in a study by Modi *et al*, which used a similar normalisation method.⁴⁴ Blood loss may be influenced by several external factors. Differences in bone age, bone density and intraoperative haemodynamic parameters contribute to patient variability.⁴⁴ The surgeon's experience also plays a role, and inaccuracies in measuring blood loss may exist.⁴⁵ We note the nearly significant difference in ASA scores between the groups, with a mean of 1.63 in the FIBRINOGEN group vs 1.25 in the STANDARD group ($p=0.068$). The monitored haematological parameters revealed that



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the platelet count was statistically significantly higher in the STANDARD group than the FIBRINOGEN group at the end of surgery and 24 hours postoperatively. Studies focused on preoperative prophylactic administration of fibrinogen have often not reported platelet count dynamics. However, a study by Kwapisz *et al.*, which focused on high-risk cardiac surgery, did not demonstrate this phenomenon.⁴⁶ In a study by Karlsson *et al.*, platelet aggregability increased in the group that received prophylactic fibrinogen before cardiac surgery, but no trend toward a platelet count decrease was observed in this group.⁴⁷ This finding might potentially explain our findings; however, further research is required to comprehensively elucidate this phenomenon.

Like any clinical study, this research has certain limitations that must be acknowledged for accurate interpretation of the results. First, the inability to include children without both parents present to provide informed consent substantially restricted patient enrolment and might potentially have exacerbated selection bias. This limitation might have been further accentuated by the small sample size, which was nevertheless expected, given the pilot study context. Second, AEs were not specifically predefined but were recorded at the discretion of the investigators; consequently, either an overestimation or underestimation of the reported number of AEs might have resulted. Another limitation of this study was the short 28-day follow-up, as some thromboembolic events or wound complications can emerge after 4 weeks. Furthermore, clinical outcomes, including laboratory values and blood loss, can be influenced by multiple factors. A notable strength of this study is that all participants had idiopathic scoliosis, and the demographics were largely uniform across groups (except for ASA scores, which present an additional limitation). The authors assume that our sample is worldwide representative as scoliosis surgery is primarily focused in a limited number of hospitals. Specifically, there are only two centres in the Czech Republic. In addition, our centre, with almost 300 scoliosis surgeries per year, is one of the largest centres in Europe. From this perspective, our sample is assumed to be demographically and characteristically representative. Although the single-centre design ensured strong adherence to protocols and standardised procedures, it could not completely eliminate interindividual differences among the attending anaesthesiologists and attending surgeons.

CONCLUSIONS

In conclusion, this study demonstrates that the prophylactic administration of fibrinogen during scoliosis surgery in children is feasible and appears to be safe. Due to the limited sample size, no conclusions can be drawn regarding the efficacy of pre-emptive fibrinogen administration on clinical outcomes. However, the results provide valuable data to inform sample size calculation

and feasibility considerations for a future full-scale randomised controlled trial.

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Acknowledgements We would like to thank Hana Horáková, Petra Agalarevova, Martina Colonova, Yvona Vypelova and the staff of the Orthopaedic Department at University Hospital Brno for their collaboration and support throughout the study.

Contributors OH, RG, MK and RD conceived and designed the study. Data were collected and assembled by JH, KV, MG, MR and OH. JH, KV, OH and RS performed the data analysis and interpretation. JH, KV and OH prepared the manuscript with assistance from MG, MR, MK, RD, RG and RS. All authors read and approved the final manuscript. OH is the guarantor.

Funding The publication was written with the support of the Specific University Research (MUNI/A/1568/2024) provided by MSM. The project was supported by the Ministry of Health, Czech Republic—conceptual development of research organisation (FNBr, 65269705) and by the national budget through MEYS, LRI CZECRIN (LM2023049).

Competing interests In the past 3 years, KV and RG have received honoraria for lecturing from CSL Behring. All other authors have no competing interest to declare.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval This study involves human participants and was approved by University Hospital Brno's Ethics Committee (No 24/22MONO) and by the State Institute for Drug Control (No sukds11048/2022) and was conducted in accordance with the Declaration of Helsinki and all applicable good clinical practice rules. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. No later than 3 years after the collection of the 1-year post-randomisation a completely blinded data set will be delivered to an appropriate data repository for sharing purposes. Until this moment, the complete datasets used and/or analysed during the current study including additional files are available from the corresponding author on reasonable request.

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10 Seznam literatury se vztahem k tématu habilitační práce

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Další vědeckovýzkumné aktivity

1. **TAČR grant: TQ15000324:** Development of artificial intelligence and virtual persons for a training of difficult communication between healthcare professionals, patients and family members in the intensive care units.

Hlavní řešitel.

11 Abecední seznam zkratek

AK – arteriální katetr

BAEP – brainstem auditory evoked potentials, sluchové evokované potenciály

BIS – bispektrální index

CCFDN – Congenital cataract, facial dysmorphism, and neuropathy

CNS – centrální nervový systém

COVID-19 – koronavirové onemocnění 2019, angl. coronavirus disease 2019

CŽK – centrální žilní katetr

ČSARIM – Česká společnost anesteziologie, resuscitace a intenzivní medicíny

DC – dýchací cesty

doc. – docent

EEG – elektroencefalografie

EFISS – Effect of Prophylactic Fibrinogen Concentrate In Scoliosis Surgery

EKG – elektrokardiografie

EMG – elektromyografie

FN – Fakultní nemocnice

Glut1-DS – Glucose transporter-1 deficiency syndrome

IF – impakt faktor, angl. impact factor

IONM – intraoperační neurofyzilogický monitoring

JIP – jednotka intenzivní péče

LF – Lékařská fakulta

MEP – motorické evokované potenciály

MU – Masarykova univerzita

MUDr. – Medicinae universae doctor

Ph.D. – Philosophiae doctor

PMK – permanentní močový katetr

PNS – periferní nervový systém

prof. – profesor

PŽK – periferní žilní kanyla

SCOL – Scoliosis, skolióza

SRS – Scoliosis Research Society

SSEP – somatosenzorické evokované potenciály

TCI – target controlled infusion, řízená cílová infúze

TIVA – totální intravenózní anestezie

Tzv. – takzvaný

VEP – visual evoked potentials, zrakové evokované potenciály

WoS – Web of Science

ZTTK – Zhu-Tokita-Takenouchi-Kim

12 Použité zdroje

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13 Komentář

Název práce: **Inovace v anesteziologické péči u spondylochirurgických výkonů pediatrických pacientů: vliv na perioperační průběh a bezpečnost**

Habilitační práce je předkládána jako komentovaný soubor vybraných publikací rozdělený na tři tematické okruhy.

Prvním tematickým okruhem je anesteziologická péče o pacienty podstupující korekci neuromuskulární skoliózy. Publikace v tomto okruhu tvoří soubor tří kazuistických sdělení zaměřených na anestezii raritních syndromů a onemocnění, z nichž u některých byl anesteziologický management v celosvětovém měřítku popsán vůbec poprvé. Význam těchto kazuistik dokládá navazující tvorba dvou mezinárodních doporučení v rámci projektu OrphanAnesthesia, která popisují nejen možnosti bezpečné perioperační péče u pacientů s extrémně vzácnými syndromy. Přehledový článek věnující se anestezii pacientů podstupujících operace neuromuskulárních skolióz je mnohonásobně citovaný i v databázi WoS. Významným klinickým dopadem tohoto okruhu je vznik multioborové komise pro deformity dětské páteře ve FN Brno.

Ve druhém tematickém okruhu se věnuji problematice anestezie a intraoperační neurofyziologické monitorace, konkrétně motorickým evokovaným potenciálům. Specifika anestezie jsou popsána v přehledovém článku, nicméně hlavní část tohoto okruhu je zaměřena na vliv hloubky anestezie na kvalitu a výbavnost motorických evokovaných

potenciálů. Výsledky naší prospektivní observační studie rozšiřují pohled na možnosti anesteziologického managementu u výkonů s neurofyzilogickou monitorací u dětí. Tento tematický okruh navíc rozšiřuje práce popisující interdisciplinární přístup k pacientce se syndromem GLUT-1 deficiencie.

Třetí tematický okruh mé habilitační práce se věnuje profylaktickému podání fibrinogenu u dětských pacientů podstupujících operační korekci skoliotické deformity. Nosnou oblastí tohoto okruhu byla bezpečnost a proveditelnost takové studie. Výsledky naší pilotní práce u 32 pacientů naznačují, že profylaktická aplikace fibrinogenu je bezpečná a proveditelná, nicméně jakékoli klinické důsledky jsme z této studie vyvodit nemohli.

14 Habilitation Thesis Abstract

Title: Innovations in anaesthesia for paediatric spinal surgery: the impact on peri-operative outcomes and safety

This habilitation thesis is being presented as a synthesis of previously published scholarly works. It is divided into three separate parts.

The first part of the habilitation thesis focuses on the anaesthesia for patients undergoing surgery for neuromuscular scoliosis. The publications in this area comprise three case reports describing anaesthesia for rare syndromes and diseases, some of which have been reported worldwide for the first time. The significance of these case reports is underscored by the subsequent publication of two international recommendations, as part of the OrphanAnesthesia project, that describe options for safe perioperative care for patients with extremely rare syndromes. A review article on the anaesthesia of patients undergoing surgery for neuromuscular scoliosis has been cited numerous times in the Web of Science database. A significant clinical outcome of this work is the establishment of a multidisciplinary committee for paediatric spinal deformities at Brno University Hospital.

In the second part of the habilitation thesis, I address the issue of anaesthesia and intraoperative neurophysiological monitoring, specifically motor evoked potentials. The specifics of anaesthesia are described in a review article. However, the main focus of this section is the effect of anaesthesia depth on the quality and reproducibility of motor evoked potentials. The results of our prospective observational study broaden the

perspective on the possibilities of anaesthesia during surgeries with neurophysiological monitoring in children. Furthermore, the second part brings a unique interdisciplinary approach to the patient with GLUT-1 deficiency syndrome.

The third part is dedicated to the prophylactic administration of fibrinogen in paediatric patients undergoing scoliosis surgery. The main focus of this section was the study's safety and feasibility. The results of our pilot study involving 32 patients suggest that prophylactic fibrinogen administration is safe and feasible. However, we were unable to conclude any clinical implications from this study.