Intervencije za liječenje postoperativne boli u djece : analiza dokaza o djelotvornosti, sigurnosti i domenama ishoda

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INTERVENCIJE ZA LIJEČENJE POSTOPERATIVNE BOLI U DJECE: ANALIZA DOKAZA O DJELOTVORNOSTI, SIGURNOSTI I DOMENAMA ISHODA

DOKTORSKA DISERTACIJA

Akademska godina: 2017./2018.

Mentorica:

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U Splitu, listopad 2018. godine

Dio istraživanja u kojem je korišten upitnik financiran je sredstvima projekta „Profesionalizam u zdravstvu“ (HRZZ-IP-2014-09-7672) kojeg je Hrvatska zaklada za znanost (HRZZ) dodijelila prof. Dr. sc. Ani Marušić s Medicinskog fakulteta u Splitu. HRZZ nije na koji način bio uključen u planiranje istraživanja, prikupljanje, obradu podataka ili pisanje rada.

ZAHVALA

Želim se zahvaliti svojoj mentorici i svom uzoru u znanosti, trudu i izvrsnosti, profesorici Puljak bez čije pomoći ovaj doktorat ne bi bio moguć. Obitelji zahvaljujem na svakoj motivaciji, lijepoj riječi i potpori u pisanju doktorata.

1. SADRŽAJ

2. POPIS OZNAKA I KRATICA

ASA	engl. *American Society of Anesthesiologists*
COS	glavni skup ishoda (engl. *core outome set*)
RCT	randomizirani kontrolirani pokus (engl. *randomized controlled trial*)
AMSTAR	engl. A Measurement Tool to Assess Systematic Reviews
PedIMMPACT	engl. the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
PRISMA	engl. Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	engl. International Prospective Register of Systematic Reviews
CDSR	engl. Cochrane Database of Systematic Reviews
CINAHL	engl. Cumulative Index to Nursing and Allied Health Literature
DARE	engl. Database of Reviews of Effect
FPS-R	engl. Faces Pain Scale- Revisited
VAS	vizualno-analogna ljestvica (engl. visual-analogue scale – VAS)

3. POPIS RADOVA NA KOJIMA SE TEMELJI DOKTORSKA DISTERTACIJA:

1. „Interventions for postoperative pain in children: An overview of systematic reviews.“ objavljen u rujnu 2017. godine u *Paediatric Anaesthesia* (2017 JIF 2,389).

2. „Efficacy and Safety Outcomes in Systematic Reviews of Interventions for Postoperative Pain in Children: Comparison Against the Recommended Core Outcome Set.“ objavljen u listopadu 2017. godine u *Pain Medicine* (2017 JIF 2,782).

3. „Outcome domains and pain outcome measures in randomized controlled trials of interventions for postoperative pain in children and adolescents“ objavljenj u rujnu 2018. u online izdanju časopisa *The European Journal of Pain* (2018 EJP 2,991).

4. „Authors' lack of awareness and use of core outcome set on postoperative pain in children is hindering comparative effectiveness research“ objavljen u svibnju 2018. godine u *Journal of Comparative Effectiveness Research* (2017 JIF 1,906)

4. UVOD

Smjernice Američkog udruženja anesteziologa (engl. *American Society of Anesthesiologists – ASA*) za liječenje boli u perioperacijskom razdoblju definiraju postoperativnu akutnu bol kao onu koja je prisutna u kirurškog bolesnika nakon zahvata (1). Bol nakon kirurških zahvata nastaje kao posljedica traume tkiva i može rezultirati fizičkom, kognitivnom i emocionalnom nelagodom, a na ishod oporavka nakon kirurškog zahvata mogu utjecati i promjene povezane s razvojem boli (2). Neprimjereno liječenje postoperativne boli može dovesti do razvoja komplikacija i produženog oporavka koji povećava stope morbiditeta i mortaliteta (3-5). Djelotvornost različitih intervencija za liječenje postoperativne boli objektivno se ispituje randomiziranim kontroliranim pokusima (engl. *randomized controlled trial – RCT*), a sustavni pregledi sažimaju rezultate više takvih pokusa i daju smjernice za praksu i buduća istraživanja.

Dok su RCT-ovi zlatni standard u procjeni djelotvornosti i sigurnosti intervencije, sustavni pregledi predstavljaju najvišu razinu dokaza u medicini te omogućuju kliničarima jednostavan pristup dokazima koje su kritički ocijenili i saželi stručnjaci iz određenih područja. Njihovom se uporabom smanjuje pristranost, odnosno otklon (engl. *bias*) (6). Nadalje, skraćuju vrijeme potrebno za nalaženje i procjenjivanje izvornih znanstvenih članaka (7, 8). Unatoč dobro utemeljenom načinu na koji se provode i temeljitom opisu korištenih strategija za smanjenje pristranosti i povećanja preciznosti, sustavni pregledi mogu se razlikovati u kvaliteti (9). Zbog toga je iznimno važna kritička i pomna procjena metodološke kvalitete postojećih sustavnih preglednih članaka. Da bi se što lakše ocjenjivala i uspoređivala metodološka kvaliteta sustavnih pregleda, godine 2007. Shea i sur. objavili su ljestvicu AMSTAR (engl. *A Measurement Tool to Assess Systematic Reviews*) koja se sastoji od 11 domena važnih za ocjenu metodološke kvalitete sustavnih pregleda (10).

Osim odgovarajuće kvalitete, za sustavne preglede iz pojedinog područja važno je da su primarne studije usporedive, odnosno da mjere iste ishode koji bi trebali biti klinički relevantni. Heterogenost mjera ishoda korištenih u intervencijskim istraživanjima boli otežava usporedbu učinkovitosti trenutno dostupnih načina liječenja. Standardiziranje domena ishoda koje se koriste u RCT-ovima i sustavnim pregledima važno je za postizanje dosljednosti i homogenosti samih rezultata te usporedivosti rezultata između studija. Glavni skup ishoda (engl. *core outcome set* – COS) važan je za sintezu rezultata primarnih studija na klinički značajan način (11). Veća standardizacija domena ishoda dovodi i do značajnijeg povećanja broja kvalitetnih meta-analiza (12).

Kako bi potaknula što veći broj kliničkih studija i sustavnih pregleda o intervencijama za liječenje boli u djece, skupina pedijatara okupljenih u pedijatrijsku inicijativu PedIMMPACT (eng. the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) godine 2008. razvila je glavni skup ishoda za pedijatrijsku bol (13). Osim samih domena ishoda, McGarth i suradnici preporučili su i mjere ishoda, odnosno ljestvice za mjerenje boli koje bi se trebale koristiti u različitim dobnim skupinama djece. Razvili su dvije skupine domena ishoda: za kroničnu i akutnu bol. Glavni skup ishoda za akutnu bol djece koje preporučuje PedIMMPACT inicijativa uključuje 6 domena: 1) intenzitet boli, 2) ocjenu i zadovoljstvo terapijom, 3) nuspojave, 4) tjelesni oporavak, 5) emocionalni odgovor i 6) ekonomske čimbenike (13).

Cilj istraživanja opisanih u ovoj doktorskoj disertacji bio je: analizirati sustavne preglede o učinkovitosti i sigurnosti intervencija za postoperativnu bol u djece, ocijeniti njihovu metodološku kvalitetu, analizirati ishode koje su koristili te na koncu ispitati znanje i stavove znanstvenika iz tog područja o preporučenim domenama i mjerama ishoda. Ova doktorska disertacija temelji se na četiri rada objavljena u međunarodnim medicinskim časopisima.

5. PREGLED METODOLOGIJE OBJEDINJENIH RADOVA

5.1. Prvo istraživanje: pregled sustavnih pregleda

U prvom istraživanju napravljen je sustavni pregled sustavnih pregleda o djelotvornosti i sigurnosti intervencija za liječenje postoperativne boli u djece. Protokol istraživanja je napravljen prema PRISMA (eng. Preferred Reporting Items for Systematic Reviews and Meta-Analyses) smjernicama. Protokol je registriran u registru International Prospective Register of Systematic Reviews – PROSPERO (broj registracije: CRD42015029650). Ispitanici uključenih sustavnih pregleda su morali biti ispitanici mlađi od 18 godina. Uključeni su i oni sustavni pregledi koji su analizirali i starije ispitanike, ali su razdvojili rezultate između djece i odraslih. Podatci su ekstraktirani od strane dva neovisna istraživača. Za ekstrakcijski obrazac korišten je Microsoft Excel program (Microsoft Inc., Redmond, WA, SAD). Nakon kreiranja ekstrakcijskog obrasca testiran je na članovima istraživačkog tima. Razlike u ekstrakciji podataka između dvoje koautora razriješio je treći koautor. Podatci koji su traženi iz svake uključene studije su: karakteristike studije (broj autora, pretraživane elektroničke pismohrane, broj pretraženih elektroničkih pismohrana, datum pretraživanja, jezik studije, zemlja, broj uključenih randomiziranih kliničkih pokusa), karakteristike ispitanika (dob ispitanika i tip kirurškog zahvata), vrsta intervencije i komparatora, postojanje meta-analize, izvor financiranja i izjava o zaključku. Sveobuhvatnom strategijom pretraživanja pretraženo je 6 elektroničkih pismohrana: *Cochrane Database of Systematic Reviews* (CDSR), *Cumulative Index to Nursing and Allied Health Literature* (CINAHL), *Database of Reviews of Effect* (DARE), Embase, MEDLINE i PsycINFO od najranijeg datuma do 24. siječnja 2016. godine. Strategija pretraživanja je prvotno napravljena za MEDLINE pismohranu, a naknadno je prilagođena za ostale elektroničke pismohrane.

Izrađene su prikladne tablice u Microsoft Excel programu u koje su dva autora za svaku studiju neovisno unijeli podatke iz članaka. Analizirana je efikasnost i sigurnost pojedinih intervencija, obilježja sustavnih pregleda kao i njihova metodološka kvaliteta pomoću ljestvice AMSTAR (10). Efikasnost i sigurnost intervencije prikazana je izjavom o zaključcima. Naime korištene su kategorije kojima je ocijenjena efikasnost i sigurnost intervencije i samih dokaza. Kategorije su bile: pozitivno, pozitivno neuvjerljivo, nema dokaza, nema mišljenja, podjednako (za usporedbu više intervencija), podjednako neuvjerljivo, negativno, negativno neuvjerljivo ili nejasno, potrebno je više istraživanja. Intervencija je ocijenjena pozitivnom ako su autori zaključili da je intervencija djelotvorna i sigurna dok su dokazi o djelotvornosti ocijenjeni neuvjerljivim ako su autori smatrali da je potrebno više istraživanja za potvrdu rezultata ili su dokazi ocijenjini lošom kvalitetom. Metodološku kvalitetu uključenih sustavnih pregleda korištenjem ljestvice AMSTAR procijenila su dva autora neovisno.

5.2. Drugo istraživanje: analiza domena ishoda u sustavnim pregledima o postoperativnoj boli u djece

Drugi dio istraživanja je također registriran u PROSPERO (CRD42015029654). Analizirane su domene ishoda korištene u uključenim sustavnim pregledima te napravljena usporedba s preporučenim glavnim skupom ishoda od strane PedIMMPACT inicijative (14). Obnovljena je strategija pretraživanja do 31. siječnja 2017. godine. Za za svaku studiju su dva autora neovisno vadila podatke. Ako su postojala diskrepancije između dva koautora treći je donio konačnu odluku. Isključeni su sustavni pregledi koji su uključivali djecu mlađu od 3 godine jer PedIMMPACT incijativa preporučuje ishode samo za djecu od 3. godine pa nadalje. Osim samih vrsta korištenih ishoda analizirana je i vrsta alata kojima je mjeren intenzitet boli

uključene djece te razlika u korištenju preporučenog glavnog skupa ishoda kod Cochraneovih sustavnih pregleda i ne-Cochraneovih sustavnih pregleda.

5.3. Treće istraživanje: analiza domena ishoda u kliničkim pokusima o postoperativnoj boli u djece

U trećem dijelu istraživanja analizirane su domene ishoda iz RCT-ova koji su uključene u pronađene sustavne preglede te je i za njih provedena usporedba s PedIMMPACT preporučenim glavnim skupom ishoda za akutnu pedijatrijsku bol (14). Istraživanje je provedeno neovisnom ekstrakcijom podataka u tablice. Jedan istraživač je vršio ekstrakciju dok je drugi provjeravao njegov rad, a nesuglasice je razriješio treći istraživač. Istraženo je postoji li razlika u korištenju preporučenog glavnog skupa ishoda prije i nakon objave PedIMMPACT inicijative. Osim domena ishoda analizirani su i alati kojim je mjeren intenzitet boli te su korišteni alati također uspoređeni s preporučenim.

5.4. Četvrto istraživanje: anketa o korištenju preporučenih ishoda za istraživanje postoperativne boli u djece

U četvrti dio istraživanja uključeni su autori sustavnih pregleda i autori u njih uključenih RCT-ova. Istraživanje je odobrilo Etičko povjerenstvo Medicinskog fakulteta u Splitu. Ispitanici su poziv za sudjelovanje u anketi dobili putem elektroničke pošte. Budući da je dopisnih autora sustavih pregleda bilo svega 48, s ciljem povećanja broja ispitanika na međumrežju su tražene i adrese elektroničke pošte ostalih autora uključenih sustavnih pregleda. Za RCT-ove su kontaktirani samo dopisni autori.

Anketa je bila anonimna i imala je 8 pitanja. Napravljena je pomoću SurveyMonkey programa (SurveyMonkey Inc., CA, SAD). Pozivi za sudjelovanje u anketi su poslani u razdoblju od travnja 2017. do srpnja 2017. godine. Svaki sudionik je dobio jedan poziv i četiri podsjetnika u vidu poruke elektroničke pošte. Prije otvaranje anketnog obrasca sudionici su dobili informacije o istraživanju, a zatim su biranjem polja za nastavak sudjelovanja u istraživanju dali svoj informirani pristanak za sudjelovanje u istraživanju. Sudionici istraživanja su odgovarali na pitanja o njihovom znanju o PedIMMPACT inicijativi i njihovim preporukama vezanima za ishode, problemima korištenja preporučenog glavnog skupa ishoda kao i njihovo mišljenje o tome koje bi se domene ishoda trebale koristiti u istraživanjima o postoperativnoj boli u djece. Statistika je napravljena koristeći Microsoft Excel (Microsoft Inc., WA, SAD).

6. SAŽETI PREGLED REZULTATA OBJEDINJENIH RADOVA

6.1. Prvo istraživanje: pregled sustavnih pregleda

Sveobuhvatnom strategijom pretraživanja pronađen je 1318 članak. Nakon uklanjanja duplikata i čitanja sažetaka i naslova izdvojeno je 140 članaka. Proučeni su cjeloviti tekstovi tih članaka te su isključena dodatna 94 članka. Od 45 uključenih sustavnih pregleda samo dva su analizirala ne-farmakološke intervencije te su 33 imali meta-analizu. Sustavni pregledi su objavljivani u razdoblju od 2003. do 2015. godine, a 46% autora dolazi iz Europe. Sustavni pregledi su ukupno uključili 811 RCT-ova s 50 343 sudionika istraživanja; 57% sustavnih pregleda analizirali su postoperativnu bol u djece nakon različitih kirurških intervencija, 20% nakon tonzilektomije i 4% nakon obrezivanja. Također su uključeni i stomatološki postupci koji dovode do postoperativne boli.

Visokom metodološkom kvalitetom ocijenjeno je 38% sustavnih preglednih članaka, 55% srednjom i 7% niskom kvalitetom. Razlika u metodološkoj kvaliteti između sustavnih pregleda s meta-analizom i bez nije bila statistički značajna dok je razlika u metodološkoj kvaliteti između Cochraneovih sustavnih pregleda i ne-Cochraneovih sustavnih pregleda bila statistički značajna. Pozitivno uvjerljiv dokaz o efekasnosti intervencije pronađen je u 18 sustavnih pregleda (40%) koji su analizirali djelovanje diklofenaka (15), ketamina (16-18), kaudalne analgezije (19, 20), deksmedetomidina (21-23), terapije glazbom (24), kortikosteroida (25, 26), epiduralne analgezije (27), paracetamola, nesteroidnih protuupalnih lijekova (28) i abdominalnog bloka (29). Pozitivno uvjerljiv dokaz o sigurnosti intervencije pronađen je u 14 (31%) sustavnih pregleda.

6.2. Drugo istraživanje: analiza domena ishoda u sustavnim pregledima o postoperativnoj boli u djece

Medijan domena ishoda navedenih u metodama (raspon 0-7) i prikazanih u rezultatima (raspon 1-) je bio četiri. Medijan PedIMMPACT domena ishoda je u metodama i rezultatima bio tri (raspon 0-6). Najčešće planirane PedIMMPACT domene ishoda u metodama bile su simptomi i nuspojave (90%) i intenzitet boli (70%) dok su ostale PedIMMPACT domene ishode planirane u manje od 50% metoda. Dodatna analgezija (66%) i dodatna opioidna analgezija (21%) bili su najčešće planirane ne-PedIMMPACT domene ishode u metodama.

U rezultatima su najčešće prikazani ishod bili simptomi i nuspojave (88%), a drugi najčešći bio je intenzitet boli koji je prikazan u 75% rezultata. Dodatna analgezija (65%) najčešća je ne-PediIMMPACT domena ishoda prikazana u rezultatima. Od 48 sustavih pregleda u 13% njih su u rezultatima prikazane domene ishoda koji nisu navedeni u metodama. Cochraneovih sustavih pregleda je bilo 9 od 48. Nije pronađena statistički značajna razlika između učestalosti PedIMMPACT domena ishoda u Cochraneovim i ne-Cochraneovim sustavnim pregledima. Od 34 sustavna pregleda koji su navela intenzitet boli kao ishod u metodama, u njih 19 (56%) su također i naveli vrstu korištenog alata za mjerenje intenziteta boli. U Cochraneovim sustavnim pregledima je statistički značajno češće navedena vrsta alata nego u ne-Cochraneovim sustavnim pregledima. Najčešće naveden alat za mjerenje intenziteta boli je bio vizualno-analogna ljestvica (engl. visual-analogue scale – VAS) (58%).

6.3. Treće istraživanje: analiza domena ishoda u kliničkim pokusima o postoperativnoj boli u djece

Medijan svih prikazanih domena ishoda u uključenim studijama bio je pet (raspon 1-11), a medijan svih PedIMMPACT domena ishoda je bio dva (raspon 0-6). Nakon istraživanja učestalosti korištenja preporučenih domena ishoda od strane PedIMMPACT inicijative u primarnim studijama, pronađeno je da je najčešće analizirana domena ishoda bila intenzitet boli (93%), a slijede je simptomi i nuspojave (83%). Ostali preporučeni ishodi analizirani su u manje od 30% studija. Najčešće analiziran ne-PedIMMPACT ishod bio je dodatna analgezija (71%), dok je na drugom mjesto heterogena skupina specifična za pojedinu intervenciju (65%).

Istraživanje je uključilo 337 RCT-a, od kojih su 221 objavljeni prije objave PedIMMPACT inicijative dok je 116 RTC-ova objavljeno nakon. Medijan PedIMMPACT domena ishoda prije inicijative je bio dva, a nakon inicijative također dva. Razlika u broju PedIMMPACT domena ishoda korištenih prije i poslije objave PedIMMPACT inicijative nije bila statistički značajna ($\chi2=0.102$, $p=0.75$). Najčešće korišteni alat za mjerenje intenziteta boli bila je vizualno-analogna ljestvica (24%).

6.4. Četvrto istraživanje: anketa o korištenju preporučenih ishoda za istraživanje postoperativne boli u djece

Autorima sustavnih pregleda poslano je 114 poziva putem elektroničke pošte za sudjelovanje u anketi. Dvadeset poruka vratilo se neisporučeno. Anketu je ispunilo 15 (16%) autora sustavnih pregleda. Jedna trećina autora je čula za PedIMMPACT inicijativu. Upitani da označe domene ishoda za pedijatrijsku akutnu bol poreporučenu od strane PedIMMPACT

inicijative svi autori su označili intenzitet boli dok su ostalih pet domena ishoda označavali učestalošću od 25 do 83%. Od nepreporučenih domena ishoda najviše su odabrali san. Za najmanje prikladne domene ishode koje treba uvrstiti u glavni skup ishoda odabrali su ekonomske čimbenike i farmakokinetiku. Sedam (70%) autora sustavnih pregleda je reklo da nisu koristili PedIMMPACT prepručeni skup ishoda dok su pripremali svoj sustavni pregled dok su ga ostali koristili djelomično. Kao razlog zašto nisu koristili preporučeni glavni skup ishoda autori su naveli manjak informiranosti o PedIMMPACT inicijativi, velik broj domena te manjak resursa potrebnih za korištenje preporučenog skupa ishoda. Neki su naveli da su publicirali sustavni pregled prije objave PedIMMPACT inicijative dok su drugi naveli da su randomizirani kontrolirani pokusi koje su uključili nisu analizirali preporučene ishode.

Od 300 poslanih poziva autorima RCT-ova za sudjelovanje u anketi 32 su se vratila kao neisporučena. Anketu je ispunilo 27 (10%) autora RCT-ova. Devet (35%) autora je navelo da nikada nisu čuli za PedIMMPACT preporučeni glavi skup ishoda za akutnu pedijatrisku bol, a 66% autora je navelo točan broj domena. Upitani da označe koje domene ishoda pripadaju preporučenom skupu ishoda 94% njih je odabralo intenzitet boli dok je drugi po učestalosti ishod bio simptomi i nuspojave – u 78% ispitanika. Kao najmanje prikladan ishod za uvršavanje u preporučeni skup ishoda autori su naveli ekonomske čimbenike. Prema odgovorima, 47% autora nije koristilo preporučeni skup ishoda dok su pripremali svoju studiju dok ga je 42% autora djelomično koristilo. Dvoje autora je koristilo potpuno preporučeni skup ishoda. Slično kao i autori susavnih pregleda, autora RCT-ova kao razlog slabog korištenja preporučenog skupa ishoda naveli su nedovoljnu informiranost o COS-u. Dvoje autora smatra da je preporučeni skup teško implementirati u praksi.

7. RASPRAVA

U prvom dijelu istraživanja proveden je pregled sustavnih pregleda koji je uključio 45 sustavna pregleda koji su analizirali intervencije za liječenje postoperativne boli u djece. Većina je analizirala farmakološke intervencije i autori su većinom bili iz Europe. U manje od polovine uključenih sustavnih pregleda ponuđeni su uvjerljivi dokazi o djelotvornosti intervencije, dok je uvjerljiv dokaz o sigurnosti intervencije pronađen u manje od trećine sustavnih pregleda.

Broj objavljenih RCT-ova i sustavnih pregleda o postoperativnoj boli u djece zadnjih godina se povećava. Razlog tome je što je postooperativna bol jedan od neugodnijih doživljaja i k tome je još loše liječena (30). Pozitivno uvjerljiv dokaz o djelotvornosti intervencije pronađen je u sustavnim pregledima koji su analizirali djelovanje diklofenaka, ketamina, kaudalne analgezije, deksmedetomidina, terapije glazbom, kortikosteroida, epiduralne analgezije, paracetamola, protuupalnih nesteroidnih lijekova i abdominalnog bloka. Jednaka djelotvornost intervencije i komparatora bila je u sustavnom pregledu koji je analizirao djelotvornost deksmedetomidina nasuprot morfija i fentanila (31). Negativno uvjerljiv dokaz pronašli smo u sustavnom pregledu u kojem se analizirala djelotvornost kaudalne analgezije nasuprot nekaudalne regionale analgezije (32). Sigurnost nije spomenuta ili dokaz nije bio uvjerljiv u skoro pola sustavnih pregleda. Manjak dokaza o sigurnosti intervencije veliki je nedostatak u analizi intervencije. Sve intervencije koje su ocijenjene uvjerljivo pozitivno, osim jedne (19), su u skladu s smjernicama za liječenje akutne postoperativne boli (1, 33). Pouzdanost tih rezultata također ovisi i o metodološkoj kvaliteti uključenih sustavih pregleda. Sustavni pregledi predstavljaju najveću razinu dokaza u medicini, ali mnogi od njih nemaju odgovarajuću metodološku kvalitetu (34). U ovoj disertaciji je AMSTAR ljestica korištena za ocjenu metodološke kvalitete uključenih sustavnih pregleda. Od 45 uključenih pregleda njih deset su bili Cochraneovi sustavi pregledi i imali su bolju metodološku kvalitetu od ne-

Cochraneovih sustavnih pregleda. Bolja metodološka kvaliteta Cochraneovih pregleda dokazana je u mnogim studijama (35, 36), ali je također dokazano da zadnjih godina raste kvaliteta svih sustavnih pregleda (37). Windsor i suradnici smatraju da bi Cochraneovi sustavni pregledi trebali biti zlatni standard informacija za kliničara koji mora donositi odluke (35).

Prvi dio istraživanja iz ove disertacije ima snagu u tome što je napravljen strukturirani protokol koji je registriran prospektivno i na taj način postao javno dostupan. Također je korištena ljestvica za ocjenu metodološke kvalitete studija. Očekuje se da će ova analiza najvećeg stupnja dokaza djelotvornosti i sigurnost liječenja postoperativne boli u djece inspirirati istraživače kliničare da koriste te dokaze u svom pristupu liječenju postoperative boli u djece. Dobiveni rezultati o uspješnosti liječenja boli nakon različitih kirurških zahvata mogu pomoći dječjim kirurzima i anesteziolozima jer djeca zahtijevaju različin pristup od odraslih. Ova sinteza dokaza može biti korisna kliničarima u svakodnevnoj praksi.

Ograničenje prvog istraživanja jest što nisu analizirani dokazi iz primarnih studija nego samo iz sustavnih pregleda što znači da dokaze onih primarnih studija koje nisu uključene u sustavne preglede nisu uzeti u obzir. Pronađen je ograničen broj sustavnih pregleda tako da bi znanstvenici trebali provesti još sustavnih pregleda iz ovog područja. Autori RCT-ova bi trebali u novim kliničkim pokusima analizirati intervencije koje su ocijenjene neuvjerljivim dokazima.

U drugom dijelu istraživanja pokazano je da se autori sustavih pregleda ne pridržavaju preporučenog glavnog skupa ishoda od PedIMMPACT incijative. Dok je medijan svih domena ishoda bio četiri, medijan PedIMMPACT domena ishoda je bio tri. Najčešće analizirana PedIMMPACT domena ishoda bila je simptomi i nuspojave, a druga najčešća intenzitet boli. Nešto više od polovine sustavnih pregleda koji su analizirali intenzitet boli su naveli i alat kojim su ocijenjivali intenzitet boli. Dodatna analgezija je analizirana u više od

polovine sustavnih pregleda. Dodatna analgezija je važan ishod jer također mjeri efikasnost primarne metode analgezije. Dodatna analgezija povećava trošak liječenja i dovodi do većeg broja nuspojava.

Ovo istraživanje je značajno jer je prvi put analiziran broj i vrsta domena ishoda korištenih u sustavim pregledima koji su analizirali postoperativnu bol u djece te ih se usporedilo s preporučenim glavnim skupom ishoda. RCT-ovi se provode da bi se ocijenila djelotvornost i sigurnost intervencija u medicini. Da bi valjano ocijenili intervenciju znanstvenici moraju odabrati ishode koji mjere prednosti i mane intervencije. Biranje valjanih domena ishoda je jedan od težih koraka u provođenju sustavnog pregleda ili primarne studije. Korištenjem preporučenog glavnog skupa ishoda iz određenog područja istraživači smanjuju heterogenost ishoda i omogućuju valjanu sintezu dokaza te provođenje kvalitetne meta-analize (38). Drugi dio ovog istraživanja je dokazao da preporučeni glavni skup ishoda za liječenje pedijatrijske boli nije prepoznat od strane autora sustavnih pregleda iz tog područja.

Za potrebe ovog istraživanja korišten je preporučeni skup ishoda od PedIMMPACT inicijative jer nije bilo moguće pronaći nikakav drugi glavni skup ishoda za akutnu bol u djece.

Samo tri četvrtine sustavnih pregleda analizirali su intenzitet boli kao ishod. To je alarmantan podatak jer pokazuje da autori sustavnih pregleda ne smatraju da je analiza boli važan ishod u sintezi dokaza prilikom procjene intervencija za ublažavanje boli. Rezultati analize također pokazuju da gotovo polovina analiziranih sustavnih pregleda u metodama ne navodi koji alat za mjerenje intenziteta boli namjeravaju analizirati iz primarnih studija. Analiza alata za mjerenje intenziteta boli po dobi nije bila moguća jer su sustavni pregledi uključili razne dobne skupine djece te nisu naveli koju su alat koristili za određenu dobnu skupinu. Vizualno-analogna ljestvica je bila najčešće naveden alat za mjerenje intenziteta boli u metodama, a ta ljestvica je preporučena za djecu u dobi od 8 godina i stariju (14). Numerička ljestvica je drugi najčešće korišten alat, iako nije preporučena za djecu od 3 godine i stariju zbog manjka

dokaza. Svi alati za mjerenje intenziteta boli nisu prikladni za sve dobne skupine (14). Moguće je samo nagađati razloge zašto se numerička ljestica koristi među djecom tako često. Moguće je da autori sustavnih pregleda nisu bili upoznati s glavnim skupom ishoda od strane PedIMMPACT inicijative ili nisu smatrali da su PedIMMPACT preporuke bitne. Odgovori na to pitanje potraženi su u četvrtom dijelu istraživanja.

U okviru drugog istraživanja također je pokazano da su Cochraneovi sustavni pregledi više koristili preproučeni skup ishoda. Međutim, iako je više puta dokazano kako Cochraneovi sustavni pregledi imaju veću metodološku kvalietu od ne-Cochraneovih sustavnih pregleda, važno je napomenuti da i Cochrane sustavni pregledi nisu koristili u potpunosti preporučeni glavni skup ishoda. Nije pronađen niti jedan sustavni pregled koji je koristio svih šest preporučenih domena ishoda.

U trećem dijelu istraživanja analizirane su domene ishoda korištene u RCT-ovima koji su ispitivali djelotvornost i sigurnost intervencija za liječenje postoperativne boli u djece. Istraživanje je pokazalo da se autori ne pridržavaju preporučenog glavnog skupa ishoda i da koriste razne domene ishoda kojima ocijenjuju intervencije. Nije pronađena statistički značajna razlika u vrsti i broju domena ishoda prije i poslije objave skupa ishoda PedIMMPACT inicijative.

Medijan prikazanih domena ishoda u uključenim studijama bio je pet dok je medijan PedIMMPACT domena ishoda bio dva. Taj podatak pokazuje da su se autori analiziranih primarnih studija manje pridržavali PedIMMPACT inicijative od autora sustavnih pregleda koji su analizirani u drugom dijelu istraživanja (39). U drugom dijelu istraživanja je također dokazano da su intenzitet boli i simptomi i nuspojave najčešće prikazane PedIMMPACT domene ishoda, ali u trećem dijelu istraživanja je redoslijed bio obrnut. Naime u analiziranim primarnim studijama najčešće korištena PedIMMPACT domena ishoda bila je intenzitet boli koja je navedena u 93% studija dok su simptomi i nuspojave navedeni u 83%. Ohrabrujuće je

da su autori primarnih studija dali primat mjerenju i analiziranju intenziteta boli jer je drugi dio istraživanja pokazao kako čak 30% sustavnih pregleda nije koristio intenzitet boli kao relevantan ishod, što je teško objašnjivo. Ostala 4 PedIMMPACT ishoda prikazani su u manje od 30% sudija. To je otvorilo novo istraživačko pitanje: jesu li su autori primarnih studija i sustavnih pregleda bili svjesni postojanja preporučenog glavnog skupa ishoda.

U trećem su istraživanju analizirani i alati za procjenu intenziteta boli te su pronađene brojne ljestvice za tu svrhu. PedIMMPACT inicijativa prepručila je upotrebu jedne od tri ljestvice samoprocjene za ocjenu intenziteta akutne boli u djece i adolescenata temeljene prema dobi (14). U djece od tri do četiri godine „Poker Chip Tool“ je preporučena ljestvica (40), u djece od četiri do 12 godina savjetuje se uporaba „Faces Pain Scale- Revisited“ (FPS-R) (41), dok je za djecu stariju od osam godina preporučena vizualno-analogna ljestvica (42). U trećem istraživanju je pokazano kako je 1% autora primarnih studija koristilo Poker Chip Tool dok su drugoj dobnoj skupini njih 12% koristili neku od ljestvica s licima, što pokazuje da postoje mnoge varijante takvih ljestvica.

PedIMMPACT inicijativa eksplicitno preporučuje korištenje FPS-R ljestvice. Međutim, ta ljestvica je korištena u samo 1% studija, u 8% su koristili neku drugu verziju ljestica s licima kao npr. Baker-Wong ili Oucher ljestice, dok su u 3% studija samo naveli da su koristili ljestvicu s licima bez navođenja koje točno. Također PedIMMPACT inicijativa je navela da se numeričke ljestice ne bi trebale koristiti za ocijenjivanje intenziteta boli u djece jer nije dokazana njihova valjanost u toj dobnoj skupini. Drugi dio ovog istraživanja nije mogao dati uvid u punu sliku korištenja i navođenja alata za mjerenje intenziteta boli od strane autora sustavnih pregleda tako da je važno što je proveden treći dio istraživanja gdje su analizirani alati za mjerenje intenziteta boli u primarnim studijama jer se očekuje da bi RCT-ovi trebali navesti informacije o mjerama ishoda koje su koristili.

Osim dokazivanja nedostatnog pridržavanja prepručenom glavnom skupu ishoda, važan rezultat ovog dijela istraživanja je i taj što je pokazano da se autori ne pridržavaju preporučenih ljestica boli za određene dobne skupine. Važno je i napomenuti da su koristili i vitalne znakove kao mjere ishoda unatoč činjenici da su ti znakovi nevjerodostojni. Ovi rezultati važna su poruka budućim autorima primarnih studija za planiranje pokusa iz ovog područja.

Ograničenje trećeg dijela istraživanja je metodološki pristup. U literaturi nisu tražene primarne studije nego su u ovo istraživanje uključeni RCT-ovi koji su uključeni u sustavne preglede pronađene u prvom dijelu istraživanja. Stoga je vjerojatno da noviji RCT-ovi iz ovog područja nisu uključeni u istraživanje jer je potrebno vremena da se provede sustavni pregled. Međutim, budući da je uključen velik broj primarnih studija, realno je očekivati da ovo istraživanje daje odgovarjuću sliku o tendenciji korištenja domena ishoda u primarnim studijama iz analiziranog područja.

U zadnjem dijelu istraživanja provedena je anketa o svjesnosti i prihvaćenosti preporučenog glavnog skupa ishoda među autorima sustavnih pregleda i RCT-ova. Samo trećina ispitanih autora je čula za prepručeni glavni skup ishoda za akutnu pedijatrijsku bol koji preporučuje inicijativa PedIMMPACT. Većina autora nije poznavala šest PedIMMPACT domena ishoda te većina nije koristila preporučeni skup dok su provodili svoju studiju. Kao razloge nedostatnog korištenja glavnog skupa ishoda autori su naveli manjak poznavanja PedIMMPACT preporuka, poteškoće s implementacijom te manjak resursa. Upitani da naznače koje domene bi trebale biti u glavnom skupu ishoda za akutnu pedijatrijsku bol oni su odabrali domene koje se samo djelomično preklapaju s preporučenim glavnim skupom ishoda od strane PedIMMPACT inicijative.

Nedostatak zadnjeg dijela istraživanje je niska stopa odgovora među kontaktiranim autorima. Iako je svakom autoru poslano pet poziva, samo 16% autora sustavnih pregleda i 10% autora

primarnih studija je ispunilo anketu. Tek mali dio poziva vratio se kao neisporučen tako da i taj podatak o nepostojanju želje za sudjelovanjem u anketi može govoriti o manjku znanja o glavnom skupu ishoda. Pretraživanjem literature uočava se da je ovo prva studija gdje je analizirana svjesnost i prihvaćenost preporučenog glavnog skupa ishoda PedIMMPACT inicijative među autorima sustavnih pregleda i RCT-ova.

Inicijativa PedIMMPACT svoje preporuke je objavila još 2008. godine. Deset godina nakon ovim je istraživanjem pokazano da se autori sustavnih pregleda i primarnih studija ne predržavaju tih smjernica. Pretpostavka na početku ovog istraživanja bila je da mogu postojati dva objašnjenja: ili autori smatraju su PedIMMPACT-ove smjernice nedovoljno primjerene ili ne znaju da te smjernice postoje. Testiranjem tih hipoteza pronađeno je da su obje pretpostavke djelomično točne. Jedan ispitanik je naveo da su PedIMMPACT domene teške i kompliciranе za implementaciju, ali nije objasnio zašto. Moguće je da je smatrao da neke PedIMMPACT domene nemaju validirane načine mjerenja. Trebat uzeti u obzir i mogućnost da je inicijativa PedIMMPACT okupila ograničen broj stručnjaka u izradu svoih smjernica pa je moguće da se drugi autori nisu slagali s preporučenim skupom ishoda. Zbog toga razloga su u ovom istraživanju upitani autori smatraju li prikladnima smjernice inicijative PedIMMPACT.

Razvoj glavnog skupa ishoda je složeni proces koji uključuje mnoge korake (38). Objava samog skupa je samo prvi korak. Skup ishoda u pojedinom području istraživanja bi se trebao revidirati povremeno i procijeniti da li autori smatraju da su prvotno preporučene domene ishoda još uvijek relevantne (38). Četvrti dio ovog istraživanja se može smatrati periodičnom reevaulacijom glavnog skupa ishoda. Prema rezultatima istraživanja može se zaključiti da implementacija glavnog skupa ishoda inicijative PedIMMPACT za akutnu bol u djece nije bila uspješna u analiziranom uskom području istraživanja tako da su potrebni daljnji koraci.

Nova istraživanja na ovu temu trebala bi uključiti i druge dionike osim samih autora da se vidi treba li se revidirati glavni skup ishoda za akutnu bol djece.

Mnogi ispitanici su naveli da nisu znali za PedIMMPACT smjerice. Bitno je da se autori informiraju o postojanju takvih smjernica prije provođenja istraživanja. Edukacija o važnosti glavnog skupa ishoda bi se trebala dodati u sve edukacije o planiranju znanstvenih istraživanja. Također bi i članovi etičkih povjerenstava koji odobravaju protokole istraživanja trebali bi biti educirani vezano za postojanje preporučenih skupova ishoda tako da mogu odbiti protokole koji ih ne koriste.

I na kraju je važno napomenuti da ustanove koje financiraju istraživanja, bilo da su iz industrije ili akademske zajednice, ne bi trebale financirati istraživanje ako autori ne namjeravaju koristiti glavni skup ishoda. Pozitivan primjer je britanski Nacionalni institut za istraživanje zdravlja koji u svojim smjernicama za prijavu na istraživačke projekte navodi da se moraju koristiti glavi skupovi ishoda. Također bi registri istraživanja kao npr. Clinicaltrials.gov ili PROSPERO trebali u svojim naputcima za registraciju protokola trebali dati veću važnost COS-u. Unatoč niskoj stopi odgovora, posljednji dio ovog istraživanja donosi važnu poruku znanstvenoj zajednici i autorima PedIMMPACT-ovog glavnog skupa ishoda. Budući da autori ne koriste COS, studije su teško usporedive. Primarne studije koriste heterogene domene ishoda te će autorima sustavnih pregleda biti teško napraviti upotrebljivu sintezu dokaza. Korištenje COS-a je u interesu pacijenata i cijele znanstvene zajednice.

8. ZAKLJUČAK

U prvom dijelu istraživanja provedena je analiza sustavnih pregleda gdje je pokazano da su sve intervencije koje su ocijenjene pozitivno uvjerljivo, osim jedne, u skladu s preporučenim smjernicama za liječenje postoperativne boli. Taj podatak obvezuje kliničare za još strožim pridržavanjem smjernica. Korištenjem AMSTAR ljestvice za ocjenu metodološke kvalitete sustavnih pregleda pokazano je da Cochraneovi sustavni pregledni članci imaju bolju kvalitetu u odnosu na ne-Cochraneove sustavne preglede. U drugom i trećem dijelu istraživanja pokazano je da se autori sustavnih pregleda i RCT-ova o postoperativnoj boli u djece ne drže preporučenog glavnog skupa ishoda. To onemogućuje dobru usporedbu djelotvornosti i sigurnosti intervencija jer autori ne koriste isti način procjene i mjerenja rezultata. Razlog tome istražen je u posljednjem dijelu istraživanja u kojem je provedena aneketa među autorima o svjesnosti i prihvaćenosti glavnog skupa ishoda te su rezultati pokazali da autori analiziranih sustavnih pregleda i kliničkih pokusa uglavnom ne poznaju PedIMMPACT smjernice i da se djelomično ne slažu sa njima. Zbog nekorištenja glavnog skupa ishoda i korištenja različitih domena ishoda dolazi do značajnih poteškoća u sintezi dokaza i komparaciji. Korištenje standardiziranih glavnih skupova ishoda u interesu je pacijenata i cijele znanstvene zajednice. Ova doktorska disertacija je znatno doprinjela znanstvenoj zajednici jer su kroz primarna i sekundarna istraživanja najprije sažeti dokazi o djelotvornosti liječenja postoperativne boli u djece, potom je dokazano da se autori ne pridržavaju glavnog skupa ishoda, a na kraju su istraženi razlozi takvog ponašanja. Osim kliničarima ova doktorska desertacija može pomoći i brojnim znanstvenicima da uvide važnost glavnog skupa ishoda, a također bi bilo očekivano da će inicijativa PedIMMPACT pokrenuti pitanje revidiranja glavog skupa ishoda za liječenje pedijatrijske akutne boli.

9. SAŽETAK

Ciljevi: Ciljevi istraživanja bili su: provesti pregled sustavnih pregleda o djelotvornosti i sigurnosti intervencija za liječenje postoperativne boli u djece te napraviti sintezu dokaza, analizirati domene ishoda u sustavnim pregledima i randomiziranim kontroliranim pokusima (engl. *randomized controlled trial* – RCT) koji su analizirali intervencije za liječenje postoperativne boli u djece te ih usporediti s preporučenim glavnim skupom ishoda inicijative PedIMMPACT (engl. *Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials*) te na koncu provesti anketu o svjesnosti i prihvaćenosti preporučenog glavnog skupa ishoda među autorima sustavnih pregleda i RCT-ova.

Metodologija: U prvom dijelu istraživanja napravljen je pregled sustavnih pregleda o postoperativnoj boli u djece. Sveobuhvatnom strategijom pretraživanja pretraženo je 6 elektroničkih pismohrana. Dva autora su za svaku studiju neovisno vadili podatke iz članaka. Analizirana je efikasnost i sigurnost pojedinih intervencija, obilježja samih studija kao i njihova metodološka kvaliteta pomoću ljestvice AMSTAR. U drugom i trećem dijelu istraživanja su, nakon obnovljene strategije pretraživanja pomoću koje su pronađena 3 nova sustavna pregleda analizirani ishodi korišteni u sustavim pregledima i u RCT-ovima koji su u njih bili uključeni te uspoređeni s preporučenim ishodima inicijative PedIMMPACT. Za ovo istraživanje također su dva autora neovisno vadila podatke. U posljednjem dijelu istraživanja anketirani su autori analiziranih sustavnih preglednih članaka i RCT-ova kako bi se istražilo njihovo znanje i stavovi prema domenama ishoda koje preporučuje PedIMMPACT.

Rezultati: Visokom metodološkom kvalitetom ocijenjeno je 38% sustavnih preglednih članaka o liječenju postoperativne boli u djece, 55% srednjom i 7% niskom kvalitetom. Pozitivno uvjerljiv dokaz o uspješnoj efekasnosti intervencije pronađen je u 18 sustavnih preglednih članaka dok je pozitivno uvjerljiv dokaz o sigurnosti intervencije pronađen u 14 sustavnih preglednih članaka. Medijan broja svih ishoda u uključenim sustavnim preglednim

člancima bio je 4, dok je medijan ishoda preporučenih od strane PedIMMPACT inicijative bio 3. Najčešće opisani PedIMMPACT ishod bio je „nuspojave“, dok je drugi najčešći bio „intenzitet boli“. Nešto više od polovine preglednih članaka koji su analizirali intenzitet boli opisali su alat kojim su mjerili bol. Medijan svih ishoda u uključenim randomiziranim kontroliranim člancima je 5 dok je medijan PedIMMPACT ishoda 2. Najčešće korišten PedIMMPACT ishod bio je „intenzitet boli“ kojeg prate „nuspojave“. Ostala 4 PedIMMPACT ishoda opisana su u manje od 30% uključenih studija. Najčešći ishod koji nije dio preporučenih ishoda PedIMMPACT inicijative bio je „dodatna analgezija“ koja je analizirana u 71% studija. Nije bilo značajne statističke razlike u udjelu PedIMMPACT ishoda u studijama objavljenim prije i poslije objave preporuka. Najčešći alat za mjerenje intenziteta boli bila je vizualno-analogna ljestvica (24%). Samo trećina autora sustavnih preglednih članaka i randomiziranih kontroliranih pokusa o postoperativnoj boli u djece znaju za preporuke PedIMMPACT inicijative. Kao razloge ne korištenja preporučenih ishoda navode nedostatak informiranosti, poteškoće sa implementacijom te manjak resursa.

Zaključak: Pozitivno uvjerljivo ocijenjene su sve intervencije koje su bile u skladu sa smjernicama za liječenje akutne bolni što upozorava na važnost pridržavanja smjernicama. Metodološka kvaliteta pronađenih sustavnih pregleda je varirala, a Cochraneovi pregledi imali su veću kvalitetu pa su samim time i korisniji kliničarima**.** Autori sustavnih pregleda i primarnih studija koje analiziraju intervencije za liječenje postoperativne boli u djece ne predržavaju se preporučenog glavnog skupa ishoda što otežava usporedbu, sintezu rezultata i izradu meta-analiza. Razlog nekorištenja preporučenog skupa ishoda za akutnu bol djece je u tome što većina autora nije nikad čula za inicijativu PedIMMPACT , a oni koji su čuli nedovoljno poznaju njene preporuke. Također su naveli razloge zbog kojih je implementacija smjernica otežana. Nužno je provesti daljnja istraživanja kako bi se vidjelo treba li revidirati preporučeni skup ishoda za akutnu bol djece i kako potaknuti autore da ga koriste.

10. SUMMARY

Aims: The aim of the first part of the study was to conduct an overview of systematic reviews that summarizes the results about efficacy and safety from randomized controlled trials involving the various strategies used for postoperative pain management in children. Second and third goal was to investigate the range of efficacy and safety outcomes used in systematic reviews (SRs) of randomized controlled trials (RCTs) of interventions for postoperative pain in children and compare them with outcome domains recommended in the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (PedIMMPACT). And the last aim was to analyze awareness about and acceptability of core outcome set (COS) for pediatric pain recommended by the PedIMMPACT.

Methods: The first part of the study was an overview of systematic reviews. Six databases were searched from the earliest date to January 24, 2016. Two authors independently assessed the methodological quality of included reviews. A Measurement Tool to Assess Systematic Reviews (AMSTAR) quality assessment tool was used. In the second and third part of the study efficacy and safety outcomes were extracted from included systematic reviews and RCTs. The type and number of outcomes were analyzed and compared against the outcomes recommended by PedIMMPACT. In the last part of the study authors of systematic reviews and RCTs about interventions for postoperative pain in children were surveyed regarding their knowledge, attitudes and usage of the PedIMMPACT COS.

Results: Out of 45 systematic reviews that investigated various interventions for postoperative pain in children, 19 systematic reviews (42%) presented conclusive evidence of efficacy. Positive conclusive evidence was reported in 18 systematic reviews (40%). More than half of systematic reviews included in this overview were rated as having medium methodological quality. Of 45 included systematic reviews, 10 were Cochrane reviews and they had higher methodological quality than non-Cochrane reviews. The median number of

all outcomes in SRs was 4, while the median number of the PedIMMPACT core outcomes was three out of six. The most commonly reported outcome of the PedIMMPACT COS was "symptoms and adverse events," followed by pain intensity, which was reported in 75% of the included SRs. Just over half of the SRs that included a pain intensity outcome also indicated the specific pain assessment tool used in the methods section. Median number of reported outcomes was five (range 1 to 11) for the included RCTs and two (range 0 to 6) for PedIMMPACT. The most commonly analyzed PedIMMPACT outcome domains were pain intensity (93%) and 'symptoms and adverse events' (83%). The remaining four PedIMMPACT outcomes were present in under 30% of included randomized controlled trials. There was no significant difference in the proportion of PedIMMPACT outcome domains' use in RCTs published before or after the PedIMMPACT core outcome set. Only a third of surveyed authors of systematic reviews and randomized controlled trials about postoperative pain in children had heard about the PedIMMPACT COS for acute pediatric pain. Problems indicated as preventing them from using the COS were lack of awareness, difficulties with implementation, and lack of resources.

Conclusion: All analysis of positive conclusive evidence of efficacy in included SRs, except one SR, are in line with guidelines for the management of acute postoperative pain. The superior quality of Cochrane reviews compared to non-Cochrane reviews has already been reported in multiple studies so Cochrane reviews remain the "gold standard" for clinical decision-making. Systematic reviews and RCTs in the field of pediatric pain do not use the recommended COS. This makes comparisons of efficacy and safety across interventions very difficult. Further discussions about the adequacy of COS for acute pediatric pain, as well as interventions to increase the uptake of COS may be warranted.

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Mjesto rada: Klinika za kirurgiju

Datum: svibanj 2016.- veljača 2017.

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Datum: studeni 2015.- ožujak 2016.

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Posao: Stažist

Mjesto rada: KBC Split

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Jezici

Hrvatski (materinji)

Engleski (napredno)

Talijanski (osnovno)

Rad na PC-u.

Microsoft Office, Adobe Illustrator, Adobe Photoshop, End Note, Metamorph, Image

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13. RADOVI OBJEDINJENI U DISERTACIJI

13.1. Prvi rad

Accepted: 13 June 2017
DOI: 10.1111/pan.13203

SYSTEMATIC REVIEW

WILEY Pediatric Anesthesia

Interventions for postoperative pain in children: An overview of systematic reviews

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Summary

The aim of this study was to conduct an overview of systematic reviews that summarizes the results about efficacy and safety from randomized controlled trials involving the various strategies used for postoperative pain management in children. We searched the *Cochrane Database of Systematic Reviews*, CINAHL, Database of Reviews of Effect, Embase, MEDLINE, and PsycINFO from the earliest date to January 24, 2016. This overview included 45 systematic reviews that evaluated interventions for postoperative pain in children. Out of 45 systematic reviews that investigated various interventions for postoperative pain in children, 19 systematic reviews (42%) presented conclusive evidence of efficacy. Positive conclusive evidence was reported in 18 systematic reviews (40%) for the efficacy of diclofenac, ketamine, caudal analgesia, dexmedetomidine, music therapy, corticosteroid, epidural analgesia, paracetamol, and/or nonsteroidal anti-inflammatory drugs and transversus abdominis plane block. Only one systematic review reported conclusive evidence of equal efficacy that involved a comparison of dexmedetomidine vs morphine and fentanyl. Safety of interventions was reported as conclusive in 14 systematic reviews (31%), with positive conclusive evidence for dexmedetomidine, corticosteroid, epidural analgesia, transversus abdominis plane block, and clonidine. Seven systematic reviews reported equal conclusive safety for epidural infusion, diclofenac intravenous vs ketamine added to opioid analgesia, bupivacaine, ketamine, paracetamol, and dexmedetomidine vs intravenous infusions of various opioid analgesics, oral suspension and suppository of diclofenac, only opioid, normal saline, no treatment, placebo, and midazolam. Negative conclusive statement for safety was reported in one systematic review for caudal analgesia vs noncaudal regional analgesia. More than half of systematic reviews included in this overview were rated as having medium methodological quality. Of 45 included systematic reviews, 10 were Cochrane reviews and they had higher methodological quality than non-Cochrane reviews. As evidence concerning efficacy and safety is inconclusive for most of the analyzed interventions, our review points out the need for more rigorous trials concerning pain management in children.

KEYWORDS
analgesia, child, methods, pain management, postoperative pain, review

1 | INTRODUCTION

The guidelines of the American Society of Anesthesiologists (ASA) for the treatment of pain in the perioperative period define postoperative acute pain as pain present in surgical patients following the procedure.[1] Almost 80% of patients undergoing surgery experience postoperative pain, and 80% of them reported moderate to severe pain intensity.[2] Management of postoperative pain has become a major concern in pediatrics.[3,4] Results of many studies in different countries show that treatment of postoperative pain in children is inadequate.[5,6] Lee et al.[7] showed that one of the main reasons of inadequate treatment of postoperative pain in children is due to difficulties with pain assessment and concerns related to side effects of opioid analgesics.

Inadequate management of postoperative pain may lead to development of complications and prolonged recovery time with increased morbidity and mortality rates in adults.[8-10] Although equivalent data for children are not available, this evidence warrants caution in pediatric population too. Appropriate treatment of postoperative pain contributes to shorter time of hospitalization, lower hospital costs, and increased level of patient satisfaction. There is enough evidence that an ineffective treatment of postoperative pain is in positive correlation with delayed wound healing, and the negative development of pain perception and chronic pain in the future.[11,12]

The effectiveness of different interventions for treatment of postoperative pain is objectively examined by randomized controlled trials (RCTs), whereas systematic reviews summarize the results of several experiments and create guidelines for practice and future research. Systematic reviews use scientifically defensible, explicit methods to reduce bias and, if appropriate and possible, meta-analysis to reduce the play of chance. Overview of systematic reviews is a new approach to summarizing evidence, synthesizing results from multiple systematic reviews in a single, useful, and practical document.[13] Overview of systematic reviews aims to provide a summary of evidence from more than one systematic review at a variety of different levels, including the combination of different interventions or the provision of a summary of evidence on the adverse effects of an intervention.[14] This type of research can reduce the time that clinicians and researchers will need to find results from the same area and it may also point out to a lack of clinical trials and systematic reviews in relevant areas.[15]

Children are not small adults and it is known that evidence from clinical trials on children is scarce, not only because fewer of such trials are performed but also because it has been proven that in pediatric RCTs, discontinuation of trials and nonpublication are common, in both academia and industry.[16] The most commonly stated reason for discontinuation of pediatric trials was insufficient patient accrual, followed by "conduct problems", "informative termination", and funding issues. Significant determinants of trial discontinuation were primary funding source and planned sample size. More pediatric trials were discontinued if they had academic affiliations compared to those from industry, and smaller trials were more likely to be discontinued.[16]

Therefore, we hypothesized that evidence about efficacy and safety of interventions for postoperative pain in children is inconsistent and insufficient. By analyzing available evidence from systematic reviews across various surgical conditions, we wanted to inspire clinical researchers to test successful approaches in other postoperative settings as well.

The aim of this study was to conduct an overview of systematic reviews that summarizes the results about efficacy and safety from RCTs analyzing various interventions for postoperative pain in children.

2 | MATERIALS AND METHODS

2.1 | Study design

This was an overview of systematic reviews. The study was reported according to the PRISMA checklist.

2.2 | Study protocol

A protocol for this overview of reviews was developed a priori and registered in the PROSPERO International Prospective Register of Systematic Reviews (No. CRD42015029650).

2.3 | Eligibility criteria

2.3.1 | Types of studies

In this study, we included systematic reviews of randomized controlled trials (RCTs) which evaluated efficacy and safety of interventions for postoperative pain management in children. We excluded studies published as conference abstracts. Only original publication was included if a review was co-published as a duplicate publication in another journal. We included only the latest version of the review if review had an update(s).

2.3.2 | Participants

We included systematic reviews analyzing patients younger than 18 years who underwent any kind of surgery. If adults (age > 18 years) were also included in RCTs within systematic reviews, we included only reviews where results of interventions on children were reported separately.

2.3.3 | Interventions and comparators

Any intervention for postoperative pain (pharmacological or nonpharmacological) and any comparator (placebo, active, and sham) were included.

2.3.4 | Outcomes

Studies were included if they assessed pain intensity, regardless of any other outcome measure(s). Studies in which pain was assessed only as a part of a multifaceted composite assessment were excluded.

2.3.5 | Literature search

We searched the *Cochrane Database of Systematic Reviews* (CDSR), CINAHL, Database of Reviews of Effect (DARE), Embase, MEDLINE, and PsycINFO from the earliest date to January 24, 2016. Search strategy was created for MEDLINE first and then customized for each database. The general principle of the search strategy used for all databases consisted of a combination of indexed and free-text terms to reflect the concepts of "children", "postoperative pain", "surgical procedures", and "systematic reviews" (for MEDLINE, see Table S1). No limits were applied for language and manuscripts written in languages other than English were translated. Search results from all databases were exported into the EndNote library (EndNote X5, Thomson Reuters, New York, NY, USA) and duplicates were removed.

2.3.6 | Screening and study selection

Two authors identified the studies which were included in this overview by using a standardized study eligibility form developed by the authors. Bibliographic records (titles and abstracts) retrieved from all databases were first screened by two authors independently. After that two authors independently examined full texts of potentially eligible studies. If there were disagreements, a third author helped in resolving discrepancies.

2.3.7 | Data collection process

Data were extracted from included studies by two independent reviewer pairs using a data extraction form designed specifically for this review. For extraction form creation, we used MS Excel software (Microsoft Inc., Redmond, WA, USA). The data extraction form was developed in a draft format and piloted by all team members on several studies and modified as required before use. The reviewers abstracted data independently. Differences in extraction were resolved by the involvement of a third reviewer.

2.3.8 | Data items

Information was extracted from each included review on: characteristics of included studies (number of authors, databases searched, number of databases searched, search date, language of searched studies, country, and number of included RCTs), characteristics of participants (including age and type of surgical procedure), type of intervention and comparator, meta-analysis, funding source of included reviews, and conclusion statement. From the full text of systematic reviews, conclusion statement was categorized using a preexisting framework by two authors.

2.3.9 | Conclusiveness of evidence assessment

Conclusion statements were analyzed for conclusiveness. The categories that we used for assessing conclusiveness of systematic reviews regarding efficacy and safety of interventions were: positive, positive inconclusive, no evidence, no opinion, equal (for comparison of multiple interventions), equal inconclusive (for comparison of multiple interventions), negative, negative inconclusive, or unclear, more research is needed. We classified favorable result as positive if the authors concluded that an intervention was effective and/or safe. We categorized a study as inconclusive if the authors indicated that we need more studies to confirm the results or that evidence was of a low quality. Only published opinion of authors of included studies was taken into account for this categorization. A third reviewer verified the categorizations to ensure accuracy and disagreements were resolved through discussion.

2.4 | Study quality

Two authors independently assessed the methodological quality of included reviews. They used A Measurement Tool to Assess Systematic Reviews (AMSTAR) quality assessment tool.[17] Discrepancies were resolved by the third author. We divided total AMSTAR score in three categories: high quality with an AMSTAR score of ≥8 out of maximum 11 points, medium quality with a score between 4 and 7, and low quality with a score between 0 and 3.

2.5 | Data analysis

Data were reported as frequencies and percentages. Differences between two groups were analyzed using Student's *t* test (Graphpad Prism 6, GraphPad Prism Software Inc., San Diego, CA, USA).

3 | RESULTS

3.1 | Literature search

Our search found 1318 articles. After duplicate publications were removed, 974 articles were screened for eligibility using their titles and abstracts. A total of 834 articles were excluded leaving 140 articles to be reviewed in full text. Based on the analysis of full text, we excluded 94 studies (list of excluded studies and their characteristics are available on request). Figure 1 presents flowchart of eligibility of articles. Full text of one manuscript was not available.[18] Forty-five studies met the inclusion criteria and were included in this overview of systematic reviews. Of the 45 included reviews, 33 had meta-analysis. Characteristics of included studies are presented in Table S2.

3.2 | Systematic review characteristics

Reviews were published between 2003 and 2015, with the most recent search date for included studies reported as January 26, 2016. Most of the reviews (80%) were published after 2010 (Table S3). Six systematic reviews (13%) had only two authors and only one systematic review searched a single database.[19] Affiliations of authors of the included systematic reviews were predominantly based in Europe (46%) and Asia (29%). No language restrictions were applied in 30 SRs (67%), and 7 SRs (15%) included RCTs in English only (Table S3).

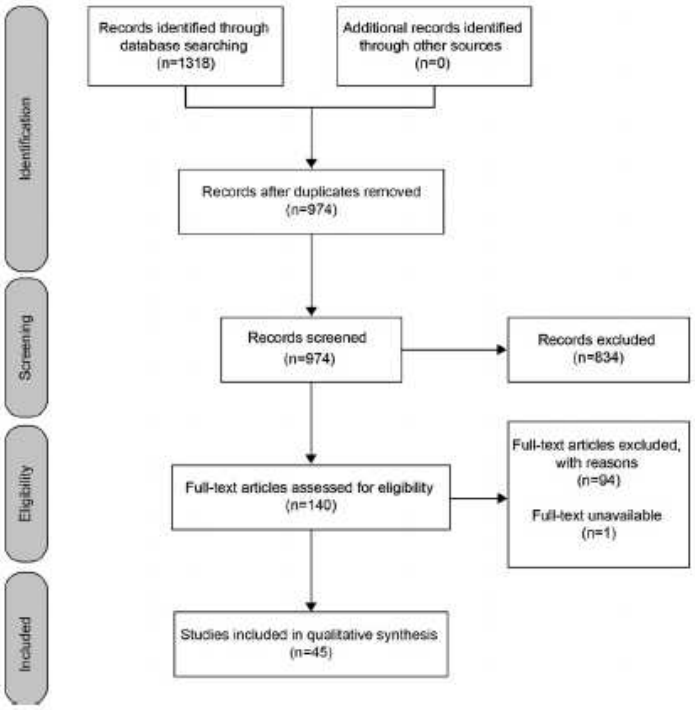

FIGURE 1 Flowchart of eligibility of articles

Total number of RCTs included in the 45 SRs was 811. The individual SRs included between 3 and 73 primary studies, with a total of 50,343 participants. Only six SRs were updated (Table S2), and five of them were published in the *Cochrane Database of Systematic Reviews*. Half of the included Cochrane reviews were updated. More than half (54%) SRs did not report the source of study funding (Table S2).

Of the 45 included SRs, only two SRs analyzed nonpharmacological interventions—therapeutic play[20] and music intervention.[21] One SR analyzed different regimens of providing analgesics, with comparisons of "as required" with "fixed schedule" analgesic administration.[22] Of the 42 SRs that analyzed pharmacological interventions, 14 (33%) SRs analyzed some techniques of regional anesthesia.

Detailed description of interventions and comparators is available in Table 1. Twenty-six SRs (57%) analyzed interventions for postoperative pain after various surgical interventions, 9 SRs (20%) analyzed pain after tonsillectomy, and 4% after circumcision. We also included dental procedures that lead to postoperative pain. The duration of follow-up ranged from 120 minutes in the SR that investigated ketamine peritonsillar infiltration for treating pain after tonsillectomy[23] to 6 months in the SR that investigated continuous epidural infusion for pain management after minimally invasive pectus excavatum repair.[24] Eleven SRs (25%) did not report duration of follow-up.

Characteristics of included studies were summarized in Tables 1, S2 and S3.

3.3 | Methodological quality of the evidence

Methodological quality of the included SRs was analyzed using the 11 domains of AMSTAR. Of the 45 analyzed SRs, 17 (38%) were rated as high quality, 25 (55%) as medium, and 3 SRs (7%) as low methodological quality. Results are reported in Table 1. The 33 SRs with meta-analyses contained a median of 12 primary RCTs (range 3-53), with an average AMSTAR score of 6.4±1.8, while the 12 SRs without meta-analyses included a median of 17 primary RCTs (range 3-73), with an average AMSTAR score of 6.6±2.7. The difference in mean AMSTAR scores between the SRs with or without meta-analysis was not statistically significant ($P=.766$; t test). The 10 Cochrane reviews had average AMSTAR score 8.8±1.2 and 35 non-Cochrane reviews had average AMSTAR score 5.8±1.8, which was significant difference ($P<.001$; t test).

Furthermore, we tested whether SRs with conclusive evidence had better methodological quality. The 19 SRs with conclusive evidence of efficacy had average AMSTAR score 5.9±2.3 and other 26 SRs with inconclusive evidence of efficacy had average AMSTAR score 6.9±1.8, which was not significantly different ($P=.127$; t test). The 14 SRs with conclusive evidence about safety had average AMSTAR score 6.2±2.1 and other 31 SRs with inconclusive

TABLE 1 Conclusions from the full texts and methodological quality of included systematic reviews. The reviews are grouped according to the analyzed interventions

Study	Type of surgical procedure	Route of administration	Interventions	Comparators	Efficacy	Safety	AMSTAR score
van der Heijden (2015)[21]	Orthopedic, cardiac, and day surgery patients	-	Live music therapy	Recorded music, no music interventions	Positive	No opinion	8
He (2015)[20]	Any surgical procedures	-	Therapeutic play	Standard procedure	Unclear, more research is needed	Unclear, more research is needed	5
Hobson (2015)[22]	Tonsillectomy	Any route	As required analgesic administration	Fixed schedule analgesic administration	Unclear, more research is needed	Unclear, more research is needed	11
Michelet (2012)[54]	Not specified	Rectal, oral, intravenous, intramuscular	Balanced analgesia using NSAIDs and opioids	NSAID	Positive, inconclusive	Positive, inconclusive	6
Sun (2010)[40]	Adenotonsillectomy	Local	Bupivacaine	Normal saline	Positive, inconclusive	Equal	5
Lambert (2014)[55]	Any surgical procedures	Intravenous	Clonidine	Placebo, no treatment, higher dose of clonidine, midazolam, fentanyl	Positive, inconclusive	Positive, inconclusive	9
Afman (2006)[33]	Tonsillectomy or adenotonsillectomy	Intravenous, intraoperative	Corticosteroid	Placebo, no treatment	Positive	Positive	8
Steward (2011)[34]	Tonsillectomy or adenotonsillectomy	Intravenous, intraoperative	Corticosteroid (single dose)	Placebo	Positive	Positive inconclusive	9
He (2013)[38]	Tonsillectomy or adenotonsillectomy	Intravenous, intraoperative	Dexmedetomidine	Morphine, fentanyl	Equal	Positive	5
Pasin (2015)[45]	Not specified	Oral, sublingual, intranasal preoperative	Dexmedetomidine	Midazolam	Positive	No opinion	8
Peng (2014)[30]	Dental rehabilitation and tooth extraction, lymph node excision, herniorrhaphy, circumcision, bone marrow biopsy, and others	Oral, rectal, intranasal, sublingual, and buccal preoperative	Dexmedetomidine	Placebo, midazolam, ketamine	Positive, inconclusive	Equal	7
Schnabel (2013)[46]	Not specified	Intravenous, intraoperative	Dexmedetomidine	Placebo, intraoperative opioids	Positive, inconclusive	Unclear, more research is needed	6
Sun (2014)[31]	Not specified	Intranasal, intravenous, sublingual, transmucosal	Dexmedetomidine	Midazolam	Positive	Unclear, more research is needed	5
Zhang (2014)[47]	Not specified	Intravenous	Dexmedetomidine	Placebo	Positive, inconclusive	Unclear more research is needed	7
Zhu (2015)[32]	Not specified	Oral, nasal, intravenous	Dexmedetomidine	Placebo, fentanyl, midazolam	Positive	Unclear, more research is needed	6

(Continues)

TABLE 1 (Continued)

Study	Type of surgical procedure	Route of administration	Interventions	Comparators	Efficacy	Safety	AMSTAR score
Standing (2011)[39]	Not specified	Intravenous	Diclofenac	Oral suspension, suppositories	Positive	Equal	2
Shi (2015)[56]	Not specified	Intravenous, intraoperative	Fentanyl	Placebo	Positive, inconclusive	Negative, inconclusive	8
Duedahl (2007)[57]	Different surgical procedures	Intravenous	Intravenously administered morphine	Control interventions (saline, fentanyl, buprenorphine, bupivacaine, or ketorolac)	Negative, inconclusive	Negative, inconclusive	5
Tong (2014)[23]	Tonsillectomy	Peritonsillar infiltration	Ketamine (perioperative)	Placebo	Unclear, more research is needed	Unclear, more research is needed	6
Cho (2014)[41]	Tonsillectomy	Preoperative, intravenous	Ketamine (perioperative)	No treatment, opioid administration	Positive, inconclusive	Equal	7
Subramaniam (2004)[25]	Not specified	Intravenous	Ketamine added to opioid analgesia	Placebo, only opioid	Positive	Equal	3
Dahmani (2011)[26]	Different surgical procedures	Preoperative, intravenous	Ketamine as a perioperative analgesic	Standard treatment/ placebo	Positive	No opinion	4
Elia (2005)[44]	Different surgical procedures	Intravenous	Ketamine preoperatively and/or postoperatively	Placebo, no treatment	Unclear, more research is needed	Unclear, more research is needed	5
Schnabel (2014)[58]	Not specified	Intramuscular, intravenous	Nalbuphine	Placebo, other opioid	Unclear, more research is needed	Unclear, more research is needed	8
Fedorowicz (2013)[59]	Tonsillectomy or adenotonsillectomy	Local	Oral rinses, mouthwashes, and sprays, used pre- and postoperatively	Placebo	Unclear, more research is needed	Unclear, more research is needed	10
Wong (2013)[36]	Surgery under general anesthesia	Rectal, intravenous	Paracetamol and/or NSAIDs	Placebo	Positive	Positive inconclusive	3
Hamunen (2005)[40]	Tonsillectomy or adenotonsillectomy	Rectal, oral, intravenous, intramuscular	Paracetamol, NSAID, and opioids	Placebo, no intervention	Negative inconclusive	No opinion	6
McNicol (2011)[42]	Any kind of surgery	Intravenous	Paracetamol, propacetamol	Placebo, active comparator (either opioid or NSAID)	Positive, inconclusive	Equal	6
Bu (2015)[61]	Selective operation with general anesthesia	Preoperative, intravenous	Parecoxib sodium	Placebo, standard treatments (opioids or tramadol)	Positive, inconclusive	Positive, inconclusive	8

(Continues)

TABLE 1 (Continued)

Study	Type of surgical procedure	Route of administration	Interventions	Comparators	Efficacy	Safety	AMSTAR score
Brady-Fryer (2004)[62]	The circumcision procedure	Penile block interventions, EMLA	Any intervention intended to relieve pain (lidocaine, acetaminophen, music)	Placebo, no treatment, another active intervention	Positive	Positive	8
Parekh (2014)[63]	Dental treatment under general anesthesia	Local	Any local anesthetic (lignocaine, bupivacaine, lidocaine, prilocaine)	Placebo, no local anesthetic, another local anesthetic	Unclear, more research is needed	Unclear, more research is needed	10
Shanthanna (2014)[43]	Inguinal surgeries	Caudal blockade	Caudal analgesia	Noncaudal regional analgesia techniques (local infiltration INF, iliohypogastric nerve block INB)	Positive	Negative	10
Engelman (2012)[28]	Not specified	Caudal blockade	Caudal analgesia with the same local anesthetic plus one of the additives, clonidine, neostigmine, or tramadol	Caudal analgesia in the control group consisted of bupivacaine, ropivacaine, or levobupivacaine alone	Positive	Negative, inconclusive	4
Lan (2009)[64]	Hypospadias surgery	Caudal blockade	Caudal bupivacaine with neostigmine	Caudal bupivacaine alone	Unclear, more research is needed	Unclear, more research is needed	4
Cyna (2008)[65]	Elective circumcision	Caudal epidural block	Caudal epidural block	Systemic opioids, topical analgesia, subcutaneous ring block, or dorsal nerve block of the penis	Equal, inconclusive	Equal, inconclusive	7
Schnabel (2011)[39]	Urological, lower abdominal, or lower limb surgery	Caudal blockade	Caudally administered clonidine in addition to local anesthetics	Local anesthetics alone	Positive, inconclusive	Positive	7
Stroud (2014)[24]	Minimally invasive pectus excavatum repair	Epidural	Continuous epidural infusion	Intravenous infusions of various opioid analgesics	Equal inconclusive	Equal	8
Tong (2014)[66]	Orchidopexy or lower abdominal surgery	Caudal blockade	Dexmedetomidine in caudal anesthesia	Caudal anesthesia alone	Positive	Positive inconclusive	5

(Continues)

TABLE 1 (Continued)

Study	Type of surgical procedure	Route of administration	Interventions	Comparators	Efficacy	Safety	AMSTAR score
Taenzer (2010)[35]	Scoliosis surgery	Epidural	Epidural analgesia in the form of a continuous infusion of a local anesthetic with or without an opioid in addition to parenteral opioids	The control group was treated with parenteral opioids only.	Positive	Positive	7
Schnabel (2011)[27]	Urological, lower abdominal, or lower limb surgery	Caudal blockade	Ketamine added to caudal local anesthetics	Caudal anesthetics alone, combination of a local anesthetic with other additional drugs	Positive	Positive, inconclusive	8
Ansermino (2003)[29]	Not specified	Caudal blockade	Local anesthetic with nonopioid additives for caudal blockade	Use of local anesthetic	Positive	Negative, inconclusive	4
Suresh (2014)[67]	Different surgical procedures	Perioperative regional block	Skull block, retrobulbar block, subtenon block, peribulbar block, auricular nerve block, glossopharyngeal nerve block,	Local anesthetics	Positive inconclusive	No opinion	4
Guo (2015)[37]	Any type of elective or emergency surgery	Transversus abdominis plane block	Transversus abdominis plane block (ropivacaine, bupivacaine, levobupivacaine)	Local anesthetic wound infiltration	Positive	Positive	5
Jones (2015)[68]	Inguinal herniorrhaphy	Regional	Regional (spinal, epidural, caudal) anesthesia	General anesthesia, combined regional and general anesthesia	Unclear, more research is needed	Unclear, more research is needed	8
Schnabel (2015)[69]	Various	Intramuscular, intravenous	Tramadol	Placebo, other opioids	Unclear, more research is needed	Unclear more research is needed	8

AMSTAR, A measurement tool to assess systematic reviews; EMLA, eutectic mixture of local anesthetics lidocaine and prilocaine; NSAID, nonsteroidal antiinflammatory drug.

evidence about safety had average AMSTAR score 6.6±2, with no significant difference between those two groups (P=.394; *t* test).

3.4 | Conclusiveness of evidence

Conclusions from the full texts of included SRs can be found in Table 1. To facilitate the summary and comparison of a large number of reviews, we have presented conclusions of included studies regarding efficacy and safety using multiple categories related to their conclusiveness. Overall, we found that 10 (22%) conclusion statements were unclear, which means more research is needed.

Safety was not mentioned or it was unclear in 19 (45%) of analyzed conclusions.

3.5 | Summary of evidence

Conclusiveness of evidence in the included SRs is presented in Table 1. Out of 45 SRs that investigated various interventions for postoperative pain in children, 19 SRs (42%) presented conclusive evidence of efficacy. Positive conclusive evidence was reported in 18 SRs (40%) for the efficacy of diclofenac,[19] ketamine,[25-27] caudal analgesia,[28,29] dexmedetomidine,[30-32] music therapy,[21] corticosteroid,[33,34] epidural analgesia,[35] paracetamol and/or NSAIDs,[36] and transversus abdominis plane block.[37] Ketamine routes of administration were intravenous in two SRs,[25,26] and in one SR, ketamine was addition in caudal block.[27] Routes of paracetamol and/or NSAIDs administration in SR with positive conclusive evidence of efficacy were rectal and intravenous. Both SRs with positive conclusive evidence of efficacy of corticosteroids analyzed interventions for postoperative pain after tonsillectomy. The routes of administration of all interventions are presented in Table 1.

Only one SR reported conclusive evidence of equal efficacy for dexmedetomidine vs morphine and fentanyl.[38]

Safety of interventions was reported as conclusive in 14 SRs (31%), with positive conclusive evidence for dexmedetomidine,[38] corticosteroid,[33] epidural analgesia,[35] transversus abdominis plane block,[37] and clonidine.[39] Seven SRs reported equal conclusive safety for epidural infusion, diclofenac intravenous vs ketamine added to opioid analgesia, bupivacaine, ketamine, paracetamol, and dexmedetomidine vs intravenous infusions of various opioid analgesics, oral suspension and suppository of diclofenac, only opioid, normal saline, no treatment, placebo, and midazolam.[19,24,25,30,40-42] Negative conclusive statement for safety was reported in one SR for caudal analgesia vs noncaudal regional analgesia.[43]

3.6 | Discrepancies in results of reviews that analyzed same interventions and comparators

In the 45 included SRs, there were six pairs of the same interventions and comparators that were analyzed in more than one SR. Their results were compared to check whether they report discrepant results.

Four SRs analyzed ketamine vs placebo. Only one indicated conclusive positive evidence about superior efficacy of ketamine,[26] one reported inconclusive positive evidence in favor of ketamine,[41] while two SRs reported that it is unclear which of those two is better and that further research is needed.[23,44]

Three SRs analyzed effect of premedication with dexmedetomidine vs midazolam on the need for postoperative rescue analgesia. All three SRs reported that dexmedetomidine had superior efficacy compared to midazolam, whereas two of them were conclusive.[31,45] One was inconclusive, indicating that dexmedetomidine was superior to midazolam premedication because it resulted in enhanced preoperative sedation and decreased postoperative pain, but that further studies are needed to study dosing schemes and long-term outcomes of dexmedetomidine as a premedication in pediatric anesthesia.[30]

Three SRs investigated efficacy of dexmedetomidine vs placebo. All three of them reported that dexmedetomidine was superior to placebo; one reported that this is conclusive result[32] and two reporting inconclusive evidence that warrants further research.[46,47]

Two SRs compared dexmedetomidine and fentanyl; one SR reported that dexmedetomidine was superior to fentanyl,[32] while the second one reported that efficacy of dexmedetomidine and fentanyl was equal.[38]

Paracetamol vs placebo comparison was analyzed in two SRs; although both of them indicated that paracetamol was superior, one conclusion statement was conclusive[36] and the other inconclusive.[42]

Corticosteroids vs placebo were analyzed in two SRs, and both conclusion statements were positive conclusive in favor of corticosteroids.[33,34]

In these SRs with the same interventions and comparators, conclusions on safety were highly heterogeneous (Table 1).

4 | DISCUSSION

This overview included 45 systematic reviews that evaluated interventions for postoperative pain in children. The majority of the reviews analyzed pharmacological interventions; the majority were published after 2010 and almost half were conducted in Europe. Less than half of the included SRs presented conclusive evidence about efficacy of analyzed interventions. Safety of interventions was reported as conclusive in one-third of the SRs; almost half of the SRs either did not provide conclusion of safety or the safety issue was unclear.

The number of published original studies and systematic reviews about postoperative pain in children has increased in recent years. The reason is that the postoperative pain is one of the most harmful stimuli experienced by children but it is often undertreated.[48]

Based on our findings, positive conclusive evidence of efficacy in postoperative pain in children was reported for diclofenac intravenous vs oral suspension or suppository,[19] ketamine vs opioid or placebo,[25-27] caudal analgesia with additives vs without additives,[28,29] dexmedetomidine vs midazolam or ketamine,[30-32] live

music therapy vs recorded or no music,[21] corticosteroid vs placebo,[33,34] epidural analgesia vs parenteral opioids only,[35] paracetamol and/or NSAIDs vs placebo,[36] and transversus abdominis plane block vs local anesthetic wound infiltration.[37] Equal efficacy was reported in SR for dexmedetomidine vs morphine and fentanyl.[38]

Negative conclusive statement for safety was reported in one SR for caudal analgesia vs noncaudal regional analgesia.[43] Safety was not mentioned or it was unclear in almost half of the analyzed SR conclusions. Lack of safety information for many of the investigated interventions is a major limitation of the available evidence.

All analysis of positive conclusive evidence of efficacy in included SRs, except one SR,[28] are in line with guidelines for the management of acute postoperative pain.[1,49] However, reliability of these results also depends on the methodological quality of included studies. Systematic reviews provide the strongest level of evidence in medicine, but many of them do not have adequate methodologies and cannot provide comprehensive evidence to decision-makers.[50]

The AMSTAR scale was used to assess various aspects of the methodological quality of SRs. More than half of SRs included in this overview were rated as having medium methodological quality. Of 45 included SRs, 10 were Cochrane reviews and they had higher methodological quality than non-Cochrane reviews. The superior quality of Cochrane reviews compared to non-Cochrane reviews has already been reported in multiple studies,[51,52] but it has also been recently reported that overall quality of systematic reviews is improving over time.[53] Windsor et al.[51] considered that Cochrane reviews can be the "gold standard" for clinical decision-making, which is supported by current evidence-base about SR quality.

This overview has several strengths because we created structured and explicit protocol with a comprehensive search strategy, and this protocol was prospectively registered and publicly available. We also used a quality assessment checklist to evaluate the methodological quality which increases the validity of our overview. We did not limit our inclusion criteria based on the publication date of reviews because even if a systematic review was published recently, it might contain evidence from trials conducted and published long time ago. Therefore, our overview presents the full picture about the SRs conducted in the analyzed field, but we still need to take into account that pertinence of outcomes and data developed long time ago must be considered on a case by case basis.

We hope that our analysis of the highest level of available evidence of safe and efficacious interventions for pediatric pain across various surgical conditions can inspire clinical researchers to test successful approaches in other postoperative settings as well. Various surgical procedures are performed in children and information about successful pain alleviation therapies tested in children can be useful to pediatric surgeons and anesthesiologists because children require different approach than adults.

We expect that our evidence synthesis will also be useful for clinicians in their daily practice. Critical appraisal of our evidence synthesis about interventions for postoperative pain in children provides reliable and accessible information to clinicians and decision-makers. By using information from this paper, clinicians can decide to choose the optimal postoperative pain management and have insight into safety of those interventions. Overviews of SRs are an efficient way to critically appraise prior reviews and gather the best available evidence in a single source to provide broad, cumulative statements that summarize the current evidence and knowledge on the effectiveness of interventions. All of our findings related to positive conclusive evidence of efficacy in included reviews, except in one SR, are in line with guidelines for the management of acute postoperative pain so clinicians can confidently rely on the guidelines of the ASA.

This overview also has some limitations. Due to our study design, we did not retrieve data from primary trials and therefore the presented evidence is limited to the information and judgments of the authors who conducted and reported systematic reviews. Interventions for postoperative pain in children that were not analyzed in systematic reviews could not be included in the present study. We found a limited number of SRs on this topic. Therefore, it would be desirable to conduct more systematic reviews about interventions for treating pediatric postoperative pain. We need more RCTs that will test interventions whose efficacy and safety for pediatric population are unclear.

To summarize, we found conclusive evidence from 19 systematic reviews indicating that there are multiple effective interventions for management of postoperative pain in children. More systematic reviews are needed to summarize evidence from primary studies about efficacy of other interventions for postoperative pain in children, as well as more randomized controlled trials on the subjects, as for many interventions there is inconclusive evidence of their efficacy and safety.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Boric K, Dosenovic S, Jelicic Kadic A, et al. Interventions for postoperative pain in children: An overview of systematic reviews. *Pediatr Anesth*. 2017;00:1–12. https://doi.org/10.1111/pan.13203

13.2. Drugi rad

Pain Medicine 2017; 00: 1–6
doi: 10.1093/pm/pnx255

OXFORD

Review Article

Efficacy and Safety Outcomes in Systematic Reviews of Interventions for Postoperative Pain in Children: Comparison Against the Recommended Core Outcome Set

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Conflicts of interest: Krste Boric and co-authors have no known conflicts of interest. There are no sources of external support supplied.

Abstract

Objective. To investigate the range of efficacy and safety outcomes used in systematic reviews (SRs) of randomized controlled trials (RCTs) of interventions for postoperative pain in children and compare them with outcome domains recommended in the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (PedIMMPACT).

Methods. Five electronic databases were searched: MEDLINE, Cochrane Database of Systematic Reviews, DARE, CINAHL, and PsycINFO. Two review authors extracted outcome data independently. Efficacy and safety outcomes were extracted and categorized. The type and number of outcomes were analyzed and compared against the outcomes recommended by PedIMMPACT. The study protocol was registered in PROSPERO (CRD42015029654).

Results. We included 48 systematic reviews with data from 816 trials. The median number of all outcomes was 4, while the median number of the PedIMMPACT core outcomes was three out of six. The most commonly reported outcome of the PedIMMPACT Core Outcome set (COS) was "symptoms and adverse events," followed by pain intensity, which was reported in 75% of the included SRs. Just over half of the SRs that included a pain intensity outcome also indicated the specific pain assessment tool used in the methods section.

Conclusions. Systematic reviews in the field of pediatric pain do not use the recommended COS. Nor do they consistently include pain as an outcome. This makes comparisons of efficacy and safety across interventions very difficult. Future studies should explore whether the authors are aware of the COS and whether the recommended COS is appropriate.

Key Words. Pain; Systematic Review; Core Outcome Set; Outcomes; Assessment Tools

Introduction

Standardizing the outcomes that are used in clinical trials and systematic reviews is important for ensuring consistency and homogeneity of findings and comparability of results between the studies. Core outcome sets (COS) are an agreed-upon standardized collection of outcomes that should be measured and reported for a specific area of health. These sets represent the minimum that should be measured and reported in all

clinical trials of a specific condition. Utilizing a COS allows for the synthesis of the results of primary studies in a clinically meaningful way [1]. It has been suggested that COS should be routinely used in systematic reviews. The most important advantages of COS are the increase in the amount of usable data for meta-analyses and the improvement in the comparability of studies from the same field [2].

In 2003, Turk et al. [3] recommended core outcome domains for chronic pain clinical trials within the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), and in 2005, Dworkin et al. [4] recommended specific measures for assessment of those domains. The Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (PedIMMPACT) was developed for children age three years and older [5] to encourage standardization of outcome domains in clinical trials of pediatric pain. PedIMMPACT defined two core outcome domains, one for acute pain and another for chronic and recurrent pain in children and adolescents [5].

To our best knowledge, there are no reports about compliance of systematic reviews on pediatric pain with the COS recommended by PedIMMPACT. Therefore, the aim of this study was to investigate the number and variety of outcomes used in systematic reviews on interventions for postoperative pain and to compare them against the outcomes for acute pain recommended by the PedIMMPACT initiative.

Methods

Study Design

An overview of systematic reviews was conducted. Study was reported according to the PRISMA checklist.

Study Protocol

A protocol for this overview of reviews was developed a priori and registered in the PROSPERO International Prospective Register of Systematic Reviews (No. CRD42015029654).

Searches

Searches were conducted in five electronic databases (MEDLINE, Cochrane Database of Systematic Reviews, DARE, CINAHL, and PsycINFO) from the earliest date to January 31, 2017. Studies in any language were eligible. A complex search strategy was developed for each database.

Types of Studies to Be Included

We analyzed systematic reviews with or without meta-analysis of randomized and quasi-randomized controlled trials evaluating any therapeutic intervention for postoperative pain in children. Participants were defined as patients younger than age 18 years who underwent surgical procedures. Any therapeutic intervention was eligible, pharmacological or nonpharmacological. All comparators were eligible. We excluded the studies that included only children younger than age three years because PedIMMPACT refers to children age three years and older.

Outcomes

All reported efficacy and safety outcomes were analyzed and compared against the outcome domains recommended in the PedIMMPACT [5]. The six outcomes for acute pain defined by the PedIMMPACT COS are pain intensity, global judgment of satisfaction with treatment, symptoms and adverse events, physical recovery, emotional response, and economic factors [5]. Outcomes in Cochrane and non-Cochrane SRs were compared.

Pain Assessment Tools

All SRs, including pain as an outcome, were analyzed to determine if a specific pain assessment tool was indicated in the methods section.

Data Extraction (Selection and Coding)

Titles and abstracts of retrieved records were initially screened independently by two authors (KB, AJK). If at least one author suggested inclusion, the full-text article was retrieved and assessed by two authors (KB, AJK) independently. Disagreements were resolved by the third author (LP). Bibliographic details, primary and secondary outcome measures for efficacy and safety, measurement tools, and follow-up time were extracted by two independent authors (MJ, MB). Discrepancies were resolved by the third author (LP). Outcomes were analyzed and categorized.

Strategy for Data Synthesis

A descriptive data synthesis was performed, and data were presented as frequency and percentage. Pearson's chi-square test was used to calculate differences in proportions. Analyses were conducted with MedCalc statistical software, v. 15.2.1 (MedCalc Software bvba, Ostend, Belgium). Statistical significance was set at $P < 0.05$.

Results

Literature Search

Search strategy retrieved 1,518 bibliographic records (titles and abstracts). After removing duplicates, we analyzed 1,028 records. We performed duplicate independent screening of those bibliographic records and chose 155 records to analyze in full text. The full text of one manuscript was not available. We found 50 systematic reviews about interventions for pediatric pain, which

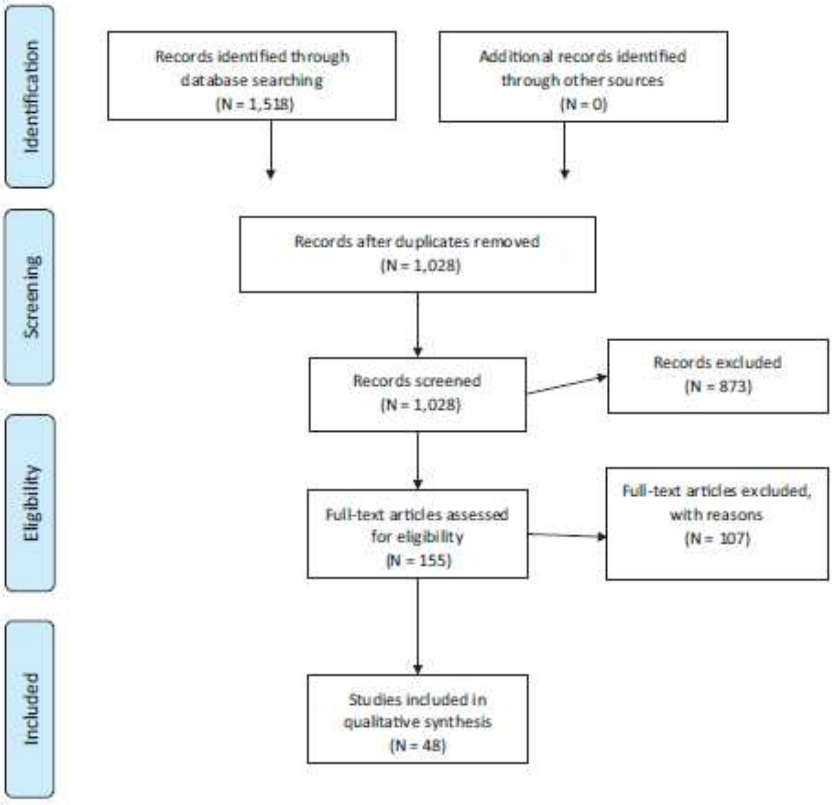

Figure 1 Study PRISMA flow diagram.

included 866 RCTs. Two SRs included exclusively children under three years [6,7]. Therefore, these two studies were excluded. The remaining 48 studies included children of various age ranges, and their outcomes were analyzed. A flow diagram of the study selection process is presented in Figure 1.

Included Studies

The 48 included systematic reviews that matched our inclusion criteria presented data from 816 RCTs. The trials were performed between 2003 and 2017, comprising data on 52,570 participants. Pharmacological interventions were analyzed in 46 systematic reviews, and nonpharmacological in two reviews. List of included studies is presented in the Supplementary Table S1.

Outcomes Specified in Methods and Reported in Results

The median number of all outcomes was four in both methods (range = 0–7) and results (range = 1–7) sections. The median number of the PedIMMPACT core outcome domains was three (range = 0–6) in both methods and results sections. A detailed analysis of the presence of six PedIMMPACT core outcomes in the methods section showed that the majority of included reviews indicated in the methods that they planned to analyze symptoms and adverse events (90%) and pain intensity (70%), while the remaining four outcomes were mentioned in less than 50% of methods sections in the included reviews. Among non-PedIMMPACT outcomes identified in the methods, additional analgesia was specified in more than 50% of the SRs, followed by additional opioid analgesia in 21% of SRs. A widely heterogeneous category of outcomes specific to certain interventions was found in half of the SRs; examples are sedation, return of bowel function, time to opening of eyes, procedural time, etc. (Table 1). In the results section, the most commonly reported outcome was "symptoms and adverse events" (88%). Pain intensity was the second most frequently reported outcome (75%). The remaining four PedIMMPACT core outcomes were reported in less than 50% of results in the

Table 1 Type and frequency of outcomes in methods and results of systematic reviews about interventions for pediatric pain

Outcome	Methods, No. (%)	Results, No. (%)
PedIMMPACT outcomes		
Pain intensity	34 (70)	36 (75)
Global judgment of satisfaction with treatment	6 (13)	7 (15)
Symptoms and adverse events	43 (90)	42 (88)
Physical recovery	10 (21)	10 (21)
Emotional response	10 (21)	9 (19)
Economic factors	14 (29)	14 (29)
Other outcomes		
Additional analgesia	32 (66)	31 (65)
Additional opioid analgesia	10 (21)	10 (21)
Pain free	1 (2)	1 (2)
Duration of postoperative analgesia	6 (13)	6 (13)
Pharmacokinetics	1 (2)	1 (2)
Outcomes specific only for certain interventions	23 (48)	20 (42)
Role functioning	4 (8)	3 (6)
Sleep	3 (6)	3 (6)

included reviews. Additional analgesia (65%) was the most frequently reported non-PedIMMPACT outcome (Table 1). Six of the 48 included SRs (13%) reported one or more outcomes in the results section that were not specified in the methods.

Cochrane vs Non-Cochrane SRs

Among the 48 included SRs, there were nine Cochrane reviews and 39 non-Cochrane reviews. The nine Cochrane reviews had a total of 50 outcomes prespecified in the methods, and 31 of those were consistent with the PedIMMPACT recommendations (62%). In the 39 non-Cochrane reviews, a total of 148 outcomes were prespecified in the methods, and 88 (59%) were in accordance with PedIMMPACT. The median number of PedIMMPACT outcomes in the methods of Cochrane reviews was three (range = 2–5), and in the non-Cochrane reviews it was two (range = 0–4).

There was no significant difference in the proportion of PedIMMPACT outcomes between the two groups ($\chi^2 = 0.025$, $P = 0.87$). In the results section of the Cochrane SRs, 27 out of 43 reported outcomes (63%) were in accordance with PedIMMPACT, while in the non-Cochrane reviews, 91 out of 151 reported outcomes (60%) were in line with PedIMMPACT. The median number of PedIMMPACT outcomes in the results of Cochrane reviews was three (range = 1–5), and in the non-Cochrane reviews it was two (range = 0–4). This difference in proportion of PedIMMPACT outcomes in the results between Cochrane and non-Cochrane SRs was not significant ($\chi^2 = 0.022$, $P = 0.88$).

Table 2 Type and frequency of pain assessment tools specified in the methods section of included systematic reviews

Pain assessment tool types	
Neonatal infant pain scale (NIPS)	1
Visual analog scale (VAS)	11
The face, legs, activity, cry, consolability (FLACC) scale	2
Numeric rating scale (NRS) or verbal numerical scale (VNS)	8
FPS-R	2
Color analogue scale (CAS)	2
Objective pain scale (OPS)	2
Children's and infant's postoperative pain scale (CHIPPS)	1
Modified CHEOPS (mCHEOPS) score	1

Pain Assessment Tools Prespecified in the Methods of Systematic Reviews

Among the 34 SRs that specified pain as an outcome in the methods, 19 (56%) also specified pain assessment tools in the methods section. Of eight Cochrane SRs, seven (88%) specified pain assessment tools in the methods, while 12 of 26 non-Cochrane SRs (46%) indicated pain assessment tools that would be extracted. This difference in proportions was significantly different ($\chi^2 = 42.4$, $P < 0.001$). The most commonly specified pain assessment tool (Table 2) in the methods section was the visual analog scale (58%). The numeric rating scale was the second most frequently specified pain assessment tool in the methods (42%).

Discussion

Our results indicate that the authors of SRs on interventions for pediatric pain do not adhere to the COS recommended by the PedIMMPACT initiative. While the median number of all reported outcomes was four, the median number of the PedIMMPACT core outcomes was three out of six. The most commonly reported outcome of the PedIMMPACT COS was "symptoms and adverse events," followed by pain intensity, which was reported in 75% of included SRs. Just above half of the SRs that had pain intensity outcomes also specified pain assessment tools that would be extracted in the methods section. Additional analgesia was reported in more than half of the SRs among non-PedIMMPACT outcomes. Researchers may find this outcome very

relevant because it is a secondary measure of the effectiveness of the primary analgesic method. Additional analgesics increase both the cost to the health care system and the risk of adverse drug events.

To our knowledge, this is the first attempt to determine the type and number of outcomes used in systematic reviews of interventions for postoperative pain in children and to compare them with a recommended COS. Clinical trials are conducted to determine the efficacy and safety of interventions in medicine. To conduct such assessments, researchers need to choose outcomes that will measure the benefits and harms of an intervention. The outcomes may be specific to a certain condition or intervention, or they may include broad aspects of health such as pain. Choosing appropriate outcomes and measurement tools is critical in designing clinical trials and systematic reviews of clinical trials in order to allow comparisons of effects across different studies and different interventions [8].

By using a standardized COS for a specific clinical area, researchers reduce heterogeneity in reported outcomes across trials and enable meaningful evidence synthesis and meta-analyses in systematic reviews. The outcomes do not have to be restricted to the COS; instead, the COS should be used, together with additional relevant outcomes that can be explored [8]. Our findings indicate that recommended COS for pediatric pain did not catch the attention of researchers conducting systematic reviews in this field.

Subgroup analysis for different time periods was not conducted in this study because the PedIMMPACT recommendations were published in 2003 and only one of the included SRs was published in the same year, with no SRs published before that year. The SRs published in the following year might have used COS recommended by the PedIMMPACT. We used PedIMMPACT as a reference for this study because we could not find other published recommendations about the suggested COS for acute pain in children and adolescents. Not all of the outcome domains suggested by the PedIMMPACT have validated measurement tools, and this was clearly emphasized by the PedIMMPACT authors [5]. The lack of specific and validated measures leaves clinical trialists in the field of pediatric pain in a dilemma as to whether to use measures of unknown reliability and validity or to ignore outcome domains that could be relevant for patients and practice. This situation can be remedied only with development and testing of appropriate measurement tools. It has been recommended that trialists in this area of research should test the reliability and validity of various instruments together with primary data collection [5].

Only three-quarters of the SRs analyzed pain as an outcome. This result is alarming because it means that the SR authors do not find analyzing pain to be an important outcome in evidence synthesis of interventions for pediatric postoperative pain. Almost half of those SRs did not specify in the methods which pain assessment tools would be extracted from the included trials. An analysis of pain assessment tools according to the age of children included in the SRs was not possible because the SRs included very wide ranges of children's ages and did not specify which pain assessment tools were used for different age groups of children.

VAS was the most commonly prespecified pain measurement tool in the methods, and this tool has been recommended for children for age eight years and older [5]. The numeric rating scale was the second most frequently specified pain assessment tool in the methods even though this tool has not been recommended for children age three years and older because of the lack of psychometric studies with the NRS in children and adolescents [5]. All pain assessment tools are not appropriate for all ages. We can only speculate that this scale was used this frequently because the study authors were not familiar with information about the validity of various pain assessment tools in children.

It is possible that the authors of SRs did not use COS defined by PedIMMPACT because they were not familiar with it, or perhaps they did not find the PedIMMPACT COS to be relevant and appropriate.

A comparison of Cochrane vs non-Cochrane SRs revealed that Cochrane SRs had slightly higher compliance with the PedIMMPACT COS. It has been already reported that Cochrane SRs use more rigorous methodology than non-Cochrane SRs [9] and that they are of higher quality and are less biased on average than other systematic reviews [10]. However, even the Cochrane SRs did not comply with the PedIMMPACT COS completely. We did not find a single SR that used all of the six recommended PedIMMPACT outcomes.

Future studies in this field should explore outcomes used in clinical trials about pediatric pain. Authors of systematic reviews and clinical trials in the field of pediatric pain should be queried to understand why they do not use the PedIMMPACT COS and whether they find the COS appropriate. Parents and children should also be involved in studies assessing the relevance and acceptability of recommended outcomes. If necessary, the COS defined by the PedIMMPACT should be revised.

In conclusion, we found that systematic reviews in the field of pediatric pain did not use recommended COS and that they did not even consistently include pain as an outcome. This makes comparisons of efficacy and safety across interventions very difficult. Future studies should explore whether the authors are aware of the COS and whether the recommended COS is appropriate.

Acknowledgments

We are grateful to Ms. Dalibora Behmen for language editing.

Supplementary Data

Supplementary Data may be found online at http://painmedicine.oxfordjournals.org.

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13.3. Treći rad

Received: 14 December 2017 | Revised: 20 August 2018 | Accepted: 24 August 2018

DOI: 10.1002/ejp.1313

ORIGINAL ARTICLE

WILEY EJP

Outcome domains and pain outcome measures in randomized controlled trials of interventions for postoperative pain in children and adolescents

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Abstract

Background: We analysed outcome domains and pain outcome measures in randomized controlled trials of interventions for postoperative pain management in children and adolescents and compared them to the core outcome set recommended by the Pediatric Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (PedIMMPACT).

Methods: Systematic literature search was conducted in MEDLINE, CDSR, DARE, CINAHL and PsycINFO up to 31 January 2017. One author extracted data and second verified the extraction. Outcome domains and pain outcome measures were analysed and compared with the PedIMMPACT core outcome set.

Results: We included 337 trials. Median number of reported outcomes was five (range 1–11) for the included trials and two (range 0–6) for PedIMMPACT. The most commonly analysed PedIMMPACT outcome domains were pain intensity (93%) and "symptoms and adverse events" (83%). The remaining four PedIMMPACT outcomes were present in under 30% of included randomized controlled trials. Proportion of PedIMMPACT outcome domains did not change after the PedIMMPACT was published in 2008. Of the 312 trials that reported pain intensity, 303 (97%) also specified pain assessment tools, in which the most common was the visual analogue scale (24%) followed by the Children's Hospital of Eastern Ontario Pain Scale (18%).

Conclusion: Analysed trials about interventions for pediatric postoperative pain insufficiently used the recommended core outcome set for acute pain in children. Relevance of the PedIMMPACT core outcome set, as well as the reasons behind its limited uptake, need to be further evaluated.

Significance: Recommended core outcomes have been insufficiently used in randomized controlled trials about postoperative pain in children, which hinders comparability of studies and makes synthesis of evidence difficult.

1 | INTRODUCTION

According to the Core Outcome Measures in Effectiveness Trials (COMET) Initiative website, a core outcome set is "an agreed minimum set of outcomes or outcome measures" (COMET 2017). Nonetheless, the existence of core outcome set for a certain research field does not prevent trialists from using additional outcome domains that they consider relevant. Development and usage of a core outcome set as an agreed standardized set of outcome domains are recommended as they enable a simple comparison and permit contrasting and meta-analysing of trial results (COMET 2017). Therefore, using core outcome sets is desirable both in randomized controlled trials and in systematic reviews.

Previously, we analysed outcome domains used in systematic reviews concerning paediatric postoperative pain (Boric, Dosenovic, Jelicic Kadic, Batinic, et al., 2017; Boric, Dosenovic, Jelicic Kadic, Boric, 2017). Our results show that the outcomes used in those systematic reviews did not adhere with the available recommended core outcome set for paediatric acute pain, which was published by the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (PedIMMPACT) (McGrath et al., 2008). One of the reasons might include unfamiliarity of the authors with the PedIMMPACT recommendations. Furthermore, there is also a possibility that these authors did not agree with the core outcome set proposed by the PedIMMPACT initiative. We assumed that it is also possible that some authors of randomized controlled trials do not include core outcome set, which is then reflected in the systematic reviews from this field, so we decided to test this hypothesis. Although our previous work demonstrated that outcomes reported in systematic reviews did not adhere to the core outcomes set, it is possible that selection of outcomes to be included in these reviews may not be representative of the primary studies. Thus, in this study we report on the outcome domains and pain outcome measures included in primary randomized controlled trials and compare these domains to those recommended by the PedIMMPACT initiative.

This study aimed to analyse outcome domains and pain outcome measures used in randomized controlled trials regarding interventions for postoperative pain in children and adolescents, as well as to compare them with core outcome domains recommended by the PedIMMPACT initiative.

2 | METHODS

2.1 | Study design

We conducted a methodological study of RCTs published in peer-reviewed journals.

2.2 | Included trials

We analysed RCTs that were included in the 50 systematic reviews concerning interventions used in management of postoperative pain in children and adolescents. The systematic reviews were retrieved from the five electronic databases (MEDLINE, Cochrane Database of Systematic Reviews, DARE, CINAHL and PsycINFO). We set the search dates from the inception of databases to 31 January 2017. RCTs in all available languages were included. Furthermore, we did not impose any limits regarding the therapeutic interventions studied in the trials. Eligible participants included children and adolescents younger than 18 years. RCTs that included children younger than three years were excluded because the PedIMMPACT core outcome set specifically excluded children up to three years of age.

2.3 | Analysis of outcome domains and pain outcome measures

We analysed all efficacy and safety outcome domains and pain outcome measures reported in the included RCTs. They were then compared to the core outcome set recommended in the PedIMMPACT regarding acute pain in children and adolescents (McGrath et al., 2008). The PedIMMPACT core outcome set for acute pain includes the following six domains: (a) pain intensity, (b) global judgement of satisfaction with treatment, (c) symptoms and adverse events, (d) physical recovery, (e) emotional response and (f) economic factors (McGrath et al., 2008). We also analysed whether there was a difference in the number of outcome domains and outcome measures used before and after the publication of the PedIMMPACT. The pre-PedIMMPACT cohort was defined as RCTs published up to 2008, while the post-PedIMMPACT cohort included RCTs published from 2008 onwards.

2.4 | Data extraction

A data extraction form was specifically designed for this study and was tested on five RCTs by two authors independently. One author extracted the data while the second author verified these extractions. Disagreements were resolved by a third author, when necessary.

Variables included in the data extraction form were: Study name (first author), Year of publication, Number of outcomes, Number of PedIMMPACT outcomes, Pain intensity (y/n), Global judgement of satisfaction with treatment (y/n), Symptoms and adverse events (y/n), Physical recovery (y/n), Emotional response (y/n), Economic factors (y/n), Additional analgesia (y/n), Outcome specific only for certain interventions (y/n), Additional opioid analgesia

(y/n), Pain-free (y/n), The duration of postoperative analgesia (y/n), Pharmacokinetics (y/n), Biochemical variables (y/n), Role functioning (y/n), Sleep (y/n) and Vital signs monitoring during analgesic (y/n).

2.5 | Statistics

We conducted descriptive statistics and presented data as frequencies and percentages. We used a chi-squared test to analyse differences in proportions of PedIMMPACT-recommended outcome domains between pre- and post-PedIMMPACT core outcome set publication. For the statistical analysis, we used the MedCalc statistical software, v 15.2.1 (©MedCalc Software bvba, Ostend, Belgium).

3 | RESULTS

3.1 | Literature search and included RCTs

Our search found 1,518 systematic reviews. After duplicate publications were removed, 1,028 articles were screened for eligibility using their titles and abstracts. We performed duplicate independent screening of those bibliographic records and chose 155 records to analyse in full text. The full text of one manuscript was not available. We found 50 systematic reviews regarding interventions for postoperative paediatric pain, which included 816 studies. After removing duplicates, 509 studies were analysed and 172 were excluded because they were not RCTs, or because they included adults or children below the age of 3, for which the PedIMMPACT is not relevant. The remaining 337 RCTs (Supporting Information Table S1) and their outcome domains/measures were analysed (Figure 1).

3.2 | Reported outcomes

The median number of reported outcome domains in the included RCTs was five (range 1–11), while the median number of the PedIMMPACT outcome domains was two (range 0–6). After analysing whether some of the six PedIMMPACT outcome domains were included in the RCTs, we found that the most commonly analysed PedIMMPACT outcomes were pain intensity (93%) and "symptoms and adverse events" (83%). The remaining four outcomes were present in <30% of included RCTs. After analysing non-PedIMMPACT outcome domains reported in the selected RCTs, we found that usage of additional analgesia was reported in 240 RCTs (71%). Outcome domains specific to certain interventions were used in 220 RCTs (65%); this was a very heterogeneous category of outcomes, such as sedation, return to normal bowel function, time to first opening of eyes, procedural time (Table 1).

3.3 | Outcomes reported in RCTs published before and after PedIMMPACT initiative

Our study included 337 RCTs, 221 of which were published before the PedIMMPACT initiative, while 116 RCTs were published after (Table 2). The 221 trials published in the pre-PedIMMPACT period comprised of a total of 1048 outcomes analysed and 530 were included in the PedIMMPACT core outcome set (50%). The 116 trials published after the PedIMMPACT initiative reported a total of 588 outcome domains, 289 (49%) of which were in accordance with the PedIMMPACT core outcome set.

Of the 221 trials published in the pre-PedIMMPACT period, 139 (63%) studies included from zero to two PedIMMPACT outcome domains and 82 (37%) included three or more domains. Of the 116 trials published after the PedIMMPACT initiative, 67 (58%) included from zero to two PedIMMPACT outcome domains, while 49 (42%) included three or more (Table 3).

The median number of PedIMMPACT outcome domains was two (range 0–6) in the pre-PedIMMPACT cohort of RCTs and two (range 0–5) in the post-PedIMMPACT cohort of RCTs. This difference in the proportion of PedIMMPACT outcome domains included in the pre- and post-PedIMMPACT cohorts was not significant ($\chi^2 = 0.102$, $p = 0.75$).

3.4 | Pain assessment tools

Of the 312 trials that reported pain intensity as an outcome domain, 303 (97%) also reported additional pain assessment. In 303 of these trials, as many as 33 pain assessment tools were used. The most commonly specified pain assessment tool (Table 4) was the visual analogue scale (VAS) (24%) followed by the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) (18%).

4 | DISCUSSION

In this study, we analysed outcome domains and pain outcome measures in RCTs of interventions regarding postoperative paediatric pain management. We found that the trialists generally did not adhere to the recommended PedIMMPACT core outcome set and used a wide range of outcome measures to evaluate postoperative interventions for paediatric pain. There was no significant difference in the number of outcome domains recommended by the PedIMMPACT initiative in the pre-PedIMMPACT and post-PedIMMPACT cohort of trials.

The median number of reported outcome domains in the included RCTs was five, while the median number of the PedIMMPACT outcome domains was two. These

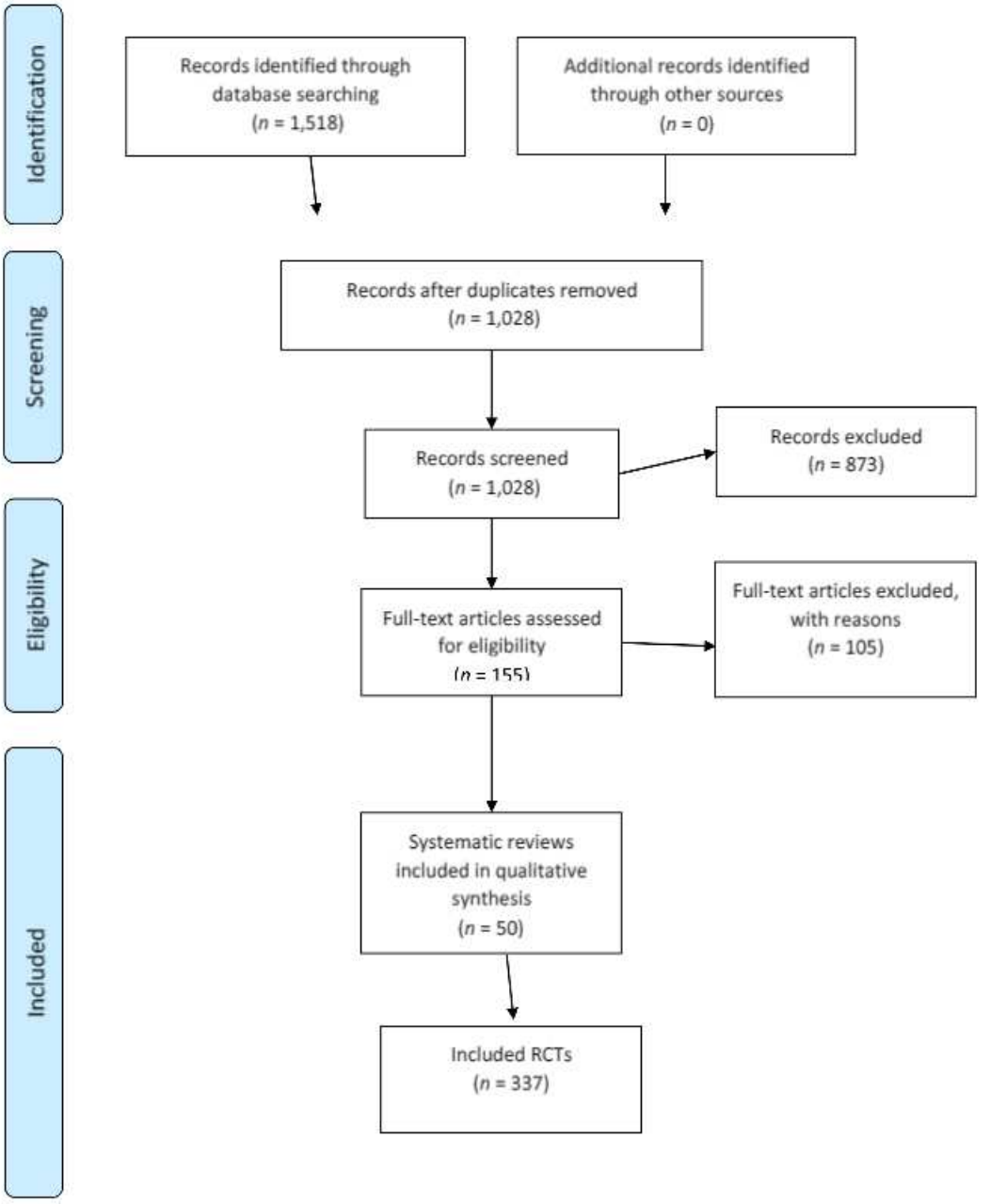

FIGURE 1 Study PRISMA flow diagram

results are poorer than the findings of our previous study, in which we analysed outcome domains and outcome measures for pain in systematic reviews about postoperative paediatric pain, where we found that the median number of all outcome domains in those systematic reviews was four, while the median number of the PedIMMPACT-

TABLE 1 Type and frequency of outcomes of randomized controlled trials about interventions for postoperative paediatric pain

Outcome	*N* (%)
PedIMMPACT outcomes	
Pain intensity	312 (93)
Symptoms and adverse events	281 (83)
Economic factors	71 (21)
Physical recovery	54 (16)
Global judgement of satisfaction with treatment	51 (15)
Emotional response	50 (15)
Other outcomes	
Additional analgesia	240 (71)
Outcomes specific only for certain interventions	220 (65)
Vital signs monitoring during analgesic administration	171 (50)
Duration of postoperative analgesia	71 (21)
Additional opioid analgesia	54 (16)
Sleep	24 (7)
Pharmacokinetics	15 (4)
Pain-free	10 (3)
Role functioning	2 (1)

TABLE 2 Type and frequency of outcomes of randomized controlled trials about interventions for postoperative paediatric pain published before and after the publication of PedIMMPACT core outcome set

Outcome	*N* (%) before	*N* (%) after
PedIMMPACT outcomes		
Pain intensity	205 (93)	107 (92)
Symptoms and adverse events	182 (82)	99 (85)
Economic factors	44 (20)	27 (23)
Physical recovery	37 (17)	17 (15)
Global judgement of satisfaction with treatment	31 (14)	20 (17)
Emotional response	31 (14)	19 (16)
Other outcomes		
Additional analgesia	157 (71)	83 (72)
Outcomes specific only for certain interventions	137 (61)	83 (72)
Vital signs monitoring during analgesic administration	102 (46)	69 (59)
Duration of postoperative analgesia	44 (20)	27 (23)
Additional opioid analgesia	35 (16)	19 (16)
Sleep	17 (7)	7 (6)
Pharmacokinetics	11 (5)	4 (4)
Pain-free	8 (3)	2 (1)
Role functioning	2 (1)	0 (0)

TABLE 3 The number of RCTs that included exact number of PedIMMPACT outcome domains before and after the publication of PedIMMPACT core outcome set

Number of PedIMMPACT outcome domains	*N* (%) before	*N* (%) after
0	3 (1)	1 (1)
1	19 (9)	5 (4)
2	117 (53)	61 (52)
3 or more	82 (37)	49 (42)

recommended outcome domains was three out of six. This would imply that systematic reviews are more likely to use recommended outcome domains compared to RCTs from the same field (Boric, Dosenovic, Jelicic Kadic, Boric, 2017).

Furthermore, in our previous study that analysed systematic reviews about postoperative paediatric pain, we also found that pain intensity and "symptoms and adverse events" were the most commonly used PedIMMPACT outcome domains, but in a reverse order when compared to our current study. In the analysed RCTs, pain intensity was the most commonly used PedIMMPACT outcome domain, found in 93% of the trials, while "symptoms and adverse events" were reported in 83% of the trials. However, in the systematic reviews from this field, "symptoms and adverse events" were the most commonly reported PedIMMPACT outcome domain, found in 90% of the systematic reviews, followed by pain intensity that was reported in 70% of the trials (Boric, Dosenovic, Jelicic Kadic, Boric, 2017). We were pleased to see that the RCTs indeed give preference to measuring and reporting pain intensity, as the finding that 30% of systematic reviews about interventions for alleviating postoperative paediatric pain do not find pain intensity to be relevant was very unexpected (Boric, Dosenovic, Jelicic Kadic, Boric, 2017).

The remaining four PedIMMPACT outcome domains were reported in <30% of the trials analysed in this study and systematic reviews analysed in our previous study, with economic factors being most common between these four—in 21% of trials and 29% of systematic reviews (Boric, Dosenovic, Jelicic Kadic, Boric, 2017). This prompts the question regarding whether authors of systematic reviews and RCTs are aware of the PedIMMPACT core outcome set, and if they are, whether they find them to be useful and pertinent.

We recently conducted a survey among the authors of the RCTs and systematic reviews published in the field of postoperative paediatric pain to analyse their awareness

TABLE 4 Type and frequency of pain assessment tools specified in the included RCTs

Pain assessment tool types	*N* (%)
Visual Analogue Scale (VAS)	73 (24)
Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)	54 (18)
Objective Pain Scale (OPS)	40 (13)
Numerical Rating Scale (NRS)	34 (11)
The Face, Legs, Activity, Cry, Consolability Scale (FLACC)	18 (6)
Baker-Wong FACES Pain	17 (6)
Modified pain score as described by Hannallah	17 (6)
Children's and Infants' Postoperative Pain Scale (CHIPPS)	13 (4)
Faces Pain Scale (FPS)	9 (9)
Maunuksela pain scores	9 (3)
Modified CHEOPS	8 (2)
Modified OPS	8 (2)
Oucher Faces Pain Scale (OFPS)	7 (2)
Verbal Rating Scale (VRS)	7 (2)
Poker Chips Tool (PCT)	4 (1)
Toddler-Preschooler Postoperative Pain Scale (TPPPS)	4 (1)
Faces Pain Scale—Revised (FPS-R)	3 (1)
Pain discomfort scale (ADPS)	3 (1)
Other pain assessment tool types	16 (5)

about the PedIMMPACT core outcome set and whether they find these recommendations appropriate (Boric et al., 2018). The responses of the surveyed authors indicated that some authors were indeed not aware of the PedIMMPACT core outcome set, while others stressed that the core outcome sets were too complicated, that they encompass too many domains, and that they are difficult to implement in practice. When asked which outcome domains they would personally include in a core outcome set for acute paediatric pain, more than half of the surveyed authors indicated that they would use the following in order of frequency: pain intensity, additional analgesia, additional opioid analgesia, pain-free, symptoms and adverse events, physical recovery, emotional response and sleep (Boric et al., 2018).

Some authors may find the core outcome set difficult to implement because not all outcome domains recommended by the PedIMMPACT initiative have validated measures (McGrath et al., 2008). Furthermore, issues related to gaps in knowledge translation and difficulties in guideline implementation should be considered when proposing core outcome sets. Literature on barriers and facilitators to practice change, and recommended practice change strategies should be considered by stakeholders involved in planning and implementing core outcome sets (Gagliardi & Alhabib, 2015; Gagliardi, Marshall, Huckson, James, & Moore, 2015). We consider that future studies should examine the barriers and facilitators to use of the PedIMMPACT guidelines and design targeted interventions to increase their uptake. It is also important to emphasize that we did not find a difference in the frequency of usage of the PedIMMPACT core outcome sets before and after its publication. We used the year 2008 as a cut-off, since the PedIMMPACT core outcome set was published in 2008. It is possible that a different cut-off year may yield different results regarding compliance to the core outcome set.

In this study, outcome measures used for pain assessment were also analysed and numerous scales used for this purpose were discovered. However, the PedIMMPACT initiative recommended using one of three self-reporting measures to analyse acute pain intensity in clinical trials in children and adolescents based on their age. In children aged three–four years, Poker Chip Tool was recommended (Hester, Foster, & Kristensen, 1990), in children aged four to 12 years, Faces Pain Scale—Revisited (FPS-R) was used (Hicks, von Baeyer, & McGrath, 2006), and in those aged eight years and above, VAS was recommended (Scott, Ansell, & Huskisson, 1977).

In our study, only one per cent of trials used the Poker Chip Tool. Regarding the second age bracket, 12% of studies reported using some version of the "faces" scale, reflecting the fact that there are many different varieties to the "faces" scale. In the PedIMMPACT, the FPS-R was explicitly recommended (McGrath et al., 2008). This scale was only used in one per cent of trials included in our analysis; eight per cent used another specific version of the "faces" scale, such as Baker-Wong or Oucher faces scale, while 3% of the studies simply indicated that they used the Faces Pain Scale, without any specifications.

The PedIMMPACT also recommends using observational pain scales in acute pain trials. Namely, they recommended using the following five observational measures: Face, Legs, Arms, Cry, Consolability (FLACC) (Merkel, Voepel-Lewis, Shayevitz, & Malviya, 1997), Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) (McGrath et al., 1985), Parents' Postoperative Pain Measure (PPPM) (Chambers, Reid, McGrath, & Finley, 1996), COMFORT Scale (Ambuel, Hamlett, Marx, & Blumer, 1992) and Toddler-Preschooler Postoperative Pain Scale (TPPPS) (Tarbell, Cohen, & Marsh, 1992). CHEOPS, or its modified version, was used in 20% of the trials, FLACC in 6% and TPPPS in 1%. PPPM was used in one trial and COMFORT was not used in any of the analysed trials.

The PedIMMPACT core outcome set explicitly recommended that NRS should not be used in children as it was not validated in this group of individuals (McGrath et al., 2008). More recently, von Baeyer et al. studied NRS in

three data sets and concluded that NRS could be considered as a functional equivalent to VAS and FPS-R, exception made for very mild pain, which is equivalent to values lower than 1 (out of 10). They concluded on page 223 of their manuscript that the use of NRS is "tentatively supported for clinical practice with children of 8 years or older," and recommended for further research regarding usage of scales with children (von Baeyer et al., 2009).

Our previous analysis of systematic reviews could not provide a full picture of specific pain assessment tools that their authors consider relevant, simply because more than half of the systematic reviews did not specify in their methods which outcome measures they will take into account. Therefore, we considered important to do a separate analysis about pain assessment tools in RCTs included in those systematic reviews, because we hypothesized that RCTs ought to provide information about the measures they used.

In terms of knowledge translation, messages of this manuscript are primarily relevant for individuals involved in planning new RCTs—authors, editors, peer reviewers of protocols and grants, ethics committees. Findings related to systematic reviews, presented in our previous manuscript, will probably not be considered by all those individuals involved in RCT planning and protocol reviewing. Without proving that actually RCTs are also insufficient regarding the consistent use of core outcome set, we do not have direct evidence that actions are needed to either increase compliance with core outcome set in RCTs from this field of research, or alternatively, actions that will reassess whether the only existing core outcome set in this field is appropriate for the community it is targeting.

Besides showing lack of regard for the relevant core outcome set in the analysed RCTs, another major result of this study, significant for clinical practice, is that there was little regard in RCTs for using age-appropriate pain assessment tools. Trialists should provide rationale for using specific outcome measure for pain intensity, in terms of age of included children. Furthermore, it is worth noting that vital signs are being used as an outcome measure, despite the fact they are unreliable. These findings warrant attention of trialists when designing new trials in this research field.

A limitation to this study was the methodological approach. We did not search literature for RCTs directly; instead, we searched for systematic reviews on this subject and then screened all trials that those reviews included; therefore, it is possible we did not include some relevant RCTs, particularly if they were more recent, because it takes time to produce a systematic review. Therefore, this subset of trials, which concerns interventions for postoperative pain in children, does not have to be an exhaustive list of all trials published on the subject thus far. However, considering the large number of trials included, we are confident that our study gives a clear picture regarding the current tendency of outcome domain usage in the trials from this field.

Future studies should be focused on the relevance of the PedIMMPACT core outcome set. It may be pertinent to revisit the core outcome set and recommend changes. Development of a core outcome set needs to be followed by periodic review to ensure that the recommended outcome domains remain relevant, as well as to assess whether additional domains need to be included (Williamson et al., 2012). Likewise, implementation of the core outcome set needs to be periodically evaluated to make sure that it is adequately used, and to shed light on the reasons behind insufficient use if they are neglected (Williamson et al., 2012). This study can be considered as part of the effort that needs to be given to evaluate the usage of the PedIMMPACT core outcome set, even though our research group did not participate in its development.

Furthermore, relevant stakeholders need to be involved in promoting the uptake of the current core outcome set, such as funders and ethics committees responsible for evaluating protocols of trials before their commencement. Clinical trial registers may also play an active role in this process, as already proposed (Clarke & Williamson, 2015). It would also be worthwhile to study interventions that would increase awareness of available core outcome sets and their approval and usage in the trialists' research community.

In conclusion, analysed trials about interventions for paediatric postoperative pain insufficiently use the current single recommended core outcome set for acute pain in children. Further interventions that will assess the relevance of the PedIMMPACT core outcome set are required in order to shed some light on the reasons behind its insufficient uptake among trialists.

CONFLICT OF INTEREST

The authors report no conflict of interests in this work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Boric K, Jelicic Kadic A, Boric M, et al. Outcome domains and pain outcome measures in randomized controlled trials of interventions for postoperative pain in children and adolescents. *Eur J Pain*. 2018;00:1–8. https://doi.org/10.1002/ejp.1313

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Research Article

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Journal of **Comparative Effectiveness Research**

Authors' lack of awareness and use of core outcome set on postoperative pain in children is hindering comparative effectiveness research

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Aim: To analyze awareness about and acceptability of core outcome set (COS) for pediatric pain recommended by the PedIMMPACT. **Methods :** We invited authors of systematic reviews and randomized controlled trials about interventions for postoperative pain in children to participate in a survey. **Results:** Only a third of surveyed authors of systematic reviews and randomized controlled trials about postoperative pain in children had heard about the PedIMMPACT COS for acute pediatric pain. Problems indicated as preventing them from using the COS were lack of awareness, difficulties with implementation, and lack of resources. **Conclusion:** Further discussions about the adequacy of COS for acute pediatric pain, as well as interventions to increase the uptake of COS may be warranted.

First draft submitted: 30 September 2017; Accepted for publication: 27 November 2017; Published online: 18 May 2018

Keywords: children • core outcome set • outcome • outcome domain • pain • PedIMMPACT

A need for a greater attention to alleviation of postoperative pain in children has been recognized ever since Eland and Anderson published their seminal study in which they reported that children do not receive analgesics after major surgical procedures [1]. Different measures for postoperative analgesia in children were developed, therapies have been evaluated and practice has changed. However, many children and adolescents still suffer because of inadequate pain management [2,3].

Randomized controlled trials (RCTs) are a standard method for studying efficacy and safety of interventions in medicine. Standardization of outcome domains and outcome measures in RCTs and systematic reviews (SRs) from the field of pediatric pain would enable simpler design and review of research protocols, simplify and improve production of SRs and help clinicians in decision-making. To encourage clinical trials in pediatric population and enable easier interpretation and data collection in trials and reviews on pediatric pain, the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (PedIMMPACT) was developed, and in 2008 published the recommended core outcome domains and measures for clinical trials to treat pain in children and adolescents [4].

The manuscript describing PedIMMPACT indicated that the COS was based on an SR of literature and consensus of experts, described as stakeholders representing *"academic research, government funding and regulatory agencies, and the pharmaceutical industry"* [4]. The consensus group that published the COS consisted of 26 authors who mainly had affiliations from the USA; three affiliations were from Canada and only three from Europe,

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including two from Sweden and one from the UK [4]. Finally, their findings were disseminated and reviewed by the international pediatric pain community consisting of clinicians and researchers from more than 45 countries, whose suggestions were included within the PedIMMPACT recommendations [4].

The PedIMMPACT initiative first reached consensus about domains that should be used for acute and chronic pain in age groups 3–6 years, and 7 years and older. Pain in neonates and infants was not included in their considerations due to considerable developmental differences between children in that age group and other age groups. Additionally, the PedIMMPACT did not consider pain in children with cognitive disabilities because of challenges associated with assessment of pain in that group of children. The next step was to assess adequate measures for each core outcome domain. The PedIMMPACT has finally recommended a core outcome set (COS) for analyzing acute and chronic pain in clinical trials and SRs about pediatric pain with the primary aim of standardizing outcomes in research from that field [4].

The COS for pediatric acute pain recommended by the PedIMMPACT includes the following six outcome domains: pain intensity, global judgement of satisfaction with treatment, symptoms and adverse events, physical recovery, emotional response and economic factors [4].

In our previous work, we systematically searched for SRs and RCTs about postoperative postoperative treatment of pain in children, and analyzed whether they use the COS suggested by the PedIMMPACT [5,6]. Analysis of COS in those SRs indicated that the use of the PedIMMPACT COS was insufficient and that some SRs did not even analyze pain intensity as an outcome domain [5,6].

The aim of this study was to analyze awareness and acceptability of COS for acute pediatric pain recommended by the PedIMMPACT among authors of RCTs and SRs about interventions for postoperative pain in children.

Methods

Based on a previous overview of SRs, we identified 48 SRs with data from a total of 576 unique RCTs [5,6]. These SRs were published between 2003 and 2017 and analyzed interventions for postoperative pain in children. Analyzed interventions were both pharmacological and nonpharmacological; any intervention and comparator were eligible for inclusion [5,6].

We downloaded full text articles of all those studies, extracted email addresses of corresponding authors of those SRs and RCTs and sent them an email with an invitation to participate in our survey. Since there were only 48 SRs, we also searched the internet to find email addresses of other SR authors in order to increase the number of potential participants. For RCTs we contacted only corresponding authors; if the email address was not indicated we tried to find it online, and if we could not find it, we were not able to contact those authors in this study.

Survey

For the purpose of this study we designed an eight-item survey in English language. The survey was designed by the authors of the study, which are methodologists and clinicians.

The participants were asked about their awareness of PedIMMPACT COS. Then we asked for the number of outcomes recommended by the COS, and which core outcomes were recommended by the PedIMMPACT. For this the authors were shown a list of outcome domains of which six belong to the PedIMMPACT COS, and the other six do not. The non-COS domains that we used were outcome domains that were most frequently used in the SRs used for this study [5].

The study participants were asked which of the shown domains belong to the PedIMMPACT COS. Participants had the possibility to skip question about reasons for personally not using the COS, in case their study was published before the PedIMMPACT COS was published and this is why they are not aware of it.

In the second set of questions, participants were asked to rate the relevance of the PedIMMPACT outcome domains and other non-PedIMMPACT outcome domains we found in the SRs on the topic [5,6], whether they used the PedIMMPACT COS for preparing their review, any difficulties associated with using the PedIMMPACT COS, their personal opinion about outcomes that should be included in COS for pediatric pain and any comments they might have about the study topic.

Survey administration

The survey was administered via SurveyMonkey, a web-based survey software (SurveyMonkey Inc., CA, USA). The survey was set as anonymous and we did not collect IP addresses of the responders. The email invitations for

Table 1. Respondents' recognition of the PedIMMPACT core outcomes.

Outcomes	Responses of SR authors, n (%) of 12‡	Responses of trial authors, n (%) of 18
Pain intensity†	12 (100)	17 (94)
Global judgment of satisfaction with treatment†	6 (50)	9 (50)
Symptoms and adverse events†	10 (83)	13 (78)
Physical recovery†	10 (83)	10 (56)
Emotional response†	9 (75)	11 (61)
Economic factors†	3 (25)	7 (39)
Sleep	7 (58)	8 (44)
The duration of postoperative analgesia	6 (50)	10 (56)
Additional analgesia	5 (42)	12 (67)
Role functioning	4 (33)	4 (22)
Pain free	4 (33)	8 (44)
Additional opioid analgesia	4 (33)	7 (39)
Outcome specific only for certain interventions	2 (16)	4 (22)
Pharmacokinetics	1 (8)	5 (28)

†These six outcomes are recommended by the PedIMMPACT as the core outcome set for acute pediatric pain.
‡The participants had option to skip questions; this question was answered by 12 authors of SRs.
SR: Systematic review.

participation in the study were sent from April to July 2017. Each participant received initial invitation and four subsequent reminders.

Ethics

The study was approved by the Ethics Committee of the University of Split School of Medicine. Before accessing the survey, the participants were provided information about the study and asked to click on a dedicated button on the SurveyMonkey page indicating that they are giving their informed consent and are willing to proceed with the survey.

Statistics

Descriptive statistics was performed using the Microsoft Excel (Microsoft Inc., WA, USA).

Results

SR authors

We sent 114 email invitations. Of these, 20 email invitations bounced back as not deliverable. 15 authors (16%) of SRs completed our survey.

Five SR authors (33%) indicated that they heard about the PedIMMPACT initiative. When asked how many core outcome domains for pediatric pain are recommended by the PedIMMPACT initiative, three SR authors chose six domains, while one chose eight domains.

When asked which of the listed core outcome domains for pediatric pain are recommended by the PedIMMPACT initiative, all SR authors marked the outcome 'pain intensity' as a recommended outcome. The other five domains were chosen by 25–83% of the SR authors (Table 1). From the list of six outcome domains that do not belong to the COS for acute pediatric pain, the majority chose 'sleep', while only one author chose 'pharmacokinetics' (Table 1).

From the list of the offered outcome domains, the SR authors rated as the most appropriate outcomes 'pain intensity', 'symptoms and adverse events' and 'sleep'. They marked 'economic factors' and 'pharmacokinetics' as the least appropriate outcomes for inclusion in a COS for assessing intervention for pediatric pain (Table 2).

Seven (70%) SR authors answered that they did not use the PedIMMPACT COS while preparing their SR; 30% answered that they used the COS partially. No one indicated that they used full recommended outcome set.

Seven SR authors provided problem/reason that may have prevented them to use the PedIMMPACT COS. They stated lack of information about the PedIMMPACT initiative, complained that the COS has too many domains and that they lack resources needed to use the COS. Some of the SR authors stated that they published their SRs before the COS was created or that RCTs that they analyzed did not include those outcomes.

Table 2. Systematic review authors' opinion about appropriateness of the listed outcome domains for acute pediatric pain.

Outcomes	1: Totally inappropriate	2: Inappropriate	3: Neutral	4. Appropriate	5: Totally appropriate	Rating average	Response count
Pain intensity[†]	0	0	1	2	7	4.60	10
Global judgment of satisfaction with treatment[†]	0	2	2	4	2	3.60	10
Symptoms and adverse events[†]	0	0	0	5	5	4.50	10
Physical recovery[†]	0	0	2	5	4	4.18	11
Emotional response[†]	0	0	2	3	6	4.36	11
Economic factors[†]	1	5	2	2	0	2.50	10
Sleep	0	0	0	6	5	4.45	11
Additional analgesia	0	1	1	3	5	4.20	10
Role functioning	1	1	4	2	1	3.11	9
Pain-free	2	2	2	2	2	3.00	10
Additional opioid analgesia	0	2	0	6	3	3.91	11
Outcome specific only for certain interventions	1	1	3	2	3	3.50	10
Pharmacokinetics	2	2	5	0	1	2.60	10

[†]These six outcomes are recommended by the PedIMMPACT as the core outcome set for acute pediatric pain.

When asked whether they can indicate some problems/reasons that somebody else might experience, which may prevent consistent use of all COS domains that are recommended by the PedIMMPACT, the SR authors listed the same reasons as in the previous question.

Finally, the SR authors were asked to select one or more outcome domains from the list of offered domains that they personally feel that should be part of the COS for assessing the efficacy and safety of interventions in pediatric pain (in children aged 3 years and older). None of the outcome domains that are in the PedIMMPACT COS for acute pediatric pain were chosen by all the SR authors.

Most of the SR authors (77%) indicated that outcomes 'symptoms and adverse events' and 'sleep' should be part of the COS. These were followed by 'pain intensity', 'additional analgesia' and 'physical recovery' that were chosen by 67% of the SR authors. 'Emotional response' and 'additional opioid analgesia' were another two outcome domains that were selected by more than 50% of the SR authors (Table 3).

RCT authors

Among 300 email invitations that were sent, 32 bounced back as undelivered. Twenty-seven (10%) authors of RCTs completed our survey.

Nine (35%) RCT authors answered that they have heard about the PedIMMPACT COS for acute pediatric pain.

Six (66%) RCT authors indicated that PedIMMPACT COS has six domains, two respondents chose four domains while one respondent answered that it has eight domains.

When offered outcome domains to choose those that belong to the PedIMMPACT COS for acute pediatric pain, 17 (94%) RCT authors chose the outcome 'pain intensity'. The second most commonly chosen outcome (78%) was 'symptoms and adverse events' (Table 1). As the most appropriate for the COS for pediatric pain, RCT authors rated 'pain intensity', 'symptoms and adverse events' and 'additional analgesia'. 'Economic factors' was rated as the least appropriate (Table 4).

Nine (47%) RCT authors answered that they did not use the PedIMMPACT COS while preparing their trial, while 42% answered that they used the set partially. Two respondents used the full recommended outcome set to prepare their trial.

Table 3. Authors' opinion about outcome domains that should be part of the core outcome set for assessing the efficacy and safety of interventions in pediatric pain (in children aged 3 years and older).

Outcomes	Responses of SR authors, n (%) of 9	Responses of trial authors, n (%) of 18
Pain intensity[†]	6 (67)	15 (83)
Global judgment of satisfaction with treatment[†]	3 (33)	6 (33)
Symptoms and adverse events[†]	7 (78)	12 (67)
Physical recovery[†]	6 (67)	11 (61)
Emotional response[†]	5 (55)	10 (56)
Economic factors[†]	3 (33)	5 (28)
Sleep	7 (78)	10 (56)
Additional analgesia	6 (67)	15 (83)
Role functioning	1 (11)	4 (22)
Pain-free	2 (22)	12 (67)
Additional opioid analgesia	5 (55)	13 (72)
Outcome specific only for certain interventions	1 (11)	6 (33)
Pharmacokinetics	0 (0)	8 (44)

[†]These six outcomes are recommended by the PedIMMPACT as the core outcome set for acute pediatric pain.
SR: Systematic review.

Table 4. Trial authors' opinion about appropriateness of the listed outcome domains for acute pediatric pain.

Outcomes	1: Totally inappropriate	2: Inappropriate	3: Neutral	4. Appropriate	5: Totally appropriate	Rating average	Response count
Pain intensity[†]	1	0	1	3	14	4.53	19
Global judgment of satisfaction with treatment[†]	1	1	1	8	8	4.11	19
Symptoms and adverse events[†]	1	0	2	5	11	4.32	19
Physical recovery[†]	0	1	4	5	9	4.16	19
Emotional response[†]	0	1	7	5	6	3.84	19
Economic factors[†]	1	4	8	4	2	3.11	19
Sleep	0	1	6	5	7	3.95	19
Additional analgesia	0	0	1	5	13	4.63	19
Role functioning	0	1	9	2	5	3.65	17
Pain-free	0	2	4	1	12	4.21	19
Additional opioid analgesia	0	1	4	4	10	4.21	19
Outcome specific only for certain interventions	0	2	4	5	6	3.88	17
Pharmacokinetics	0	1	1	6	10	4.39	18

[†]These six outcomes are recommended by the PedIMMPACT as the core outcome set for acute pediatric pain.

As problems that they have experienced and that may have prevented consistent use of all COS domains, the RCT authors indicated a lack of information about COS. One person indicated that more presentations on this topic should be conducted among scientific population. Two RCT authors consider that domains are complicated and difficult to implement in practice. One author wrote that their RCT was published before the COS was published.

As a major problem that might prevent use of all COS, the RCT authors indicated lack of human resources and time. They also stated that the COS is too complicated and difficult to implement in practice.

'Pain intensity' and 'additional analgesia' were chosen by 83% of the RCT authors when they were asked to select one or more outcome domains from the list of offered domains that they personally feel that should be part of the

COS for assessing the efficacy and safety of interventions in pediatric pain (in children aged 3 years and older). 'Additional opioid analgesia', 'pain-free', 'symptoms and adverse events' and 'sleep' were other outcome domains that were chosen by more than half participating RCT authors (Table 3).

Discussion

Only a third of surveyed authors of SRs and RCTs about postoperative pain in children had heard about the PedIMMPACT COS for acute pediatric pain. Most of them showed lack of knowledge about six domains of that COS, and the majority did not use the COS while preparing their studies. Problems indicated as preventing them from using the COS were lack of awareness, difficulties with implementation and lack of resources. When asked to indicate which outcome domains should be part of the COS for acute pediatric pain, they chose domains that only partly overlap with outcome domains of the PedIMMPACT for acute pain.

A limitation of our study is low response rate. Even after five email messages, only 16% of SR authors and 10% of RCT authors participated in the survey. A minority of emails bounced back as undelivered, so lack of willingness of authors to participate in such survey may also be an indication about insufficient awareness about the COS.

To our best knowledge, this is the first study that analyzed the knowledge, utilization and opinion of SR and RCT authors about the PedIMMPACT COS for acute pediatric pain. It has been reported that adherence to the IMMPACT COS for pain in adults is also insufficient [7]. In 2015, Mulla *et al.* published analysis of 156 trials about opioids for chronic noncancer pain. They found that reporting of the IMMPACT recommended COS was very variable, ranging from 99% for 'pain' to 7% for 'interpersonal functioning'. They also conducted regression analysis to study factors that could be associated with using recommended IMMPACT outcome domains. Identified factors were associated with reporting of certain individual outcome domains, not the COS [7].

The PedIMMPACT was published in 2008, and it is the only published recommended COS for acute pediatric pain [4]. Ten years later, we found out that SR and RCT authors have not been using this COS since it was published [6]. We hypothesized that there could be two explanations; either the authors do not find the PedIMMPACT COS appropriate, or they are not aware of it. Therefore, we decided to test these hypotheses, and we found that both explanations are part of the story. One of the study participants indicated that the PedIMMPACT COS was complicated and difficult to implement. The participant did not elaborate this further. It is possible that the participant is referring to the fact that the PedIMMPACT COS recommended some outcome domains which did not have validated measures [4].

The consensus required was not reported in the manuscript that described the PedIMMPACT COS. We agree that any consensus involves the possibility that not all of the authors agree, and that also not all the authors will agree with the suggested COS. For this reason we studied whether they find it appropriate.

Developing a COS is a complex process that involves multiple steps [8]. However, developing a COS is only the first step. It has been recommended that the COS should be reviewed periodically, as a very important part of validation of a COS. Such periodic evaluations can ensure that the outcome domains in a COS are still relevant, to review the possibility of adding new outcomes, to analyze whether implementation of the COS was successful and to make sure that new stakeholders are engaged when appropriate [8]. Our study can be considered as part of this periodic evaluation of the PedIMMPACT COS for acute pediatric pain. Based on our findings, implementation of that COS was not successful, and this situation calls for different actions and interventions.

New studies in this field could focus on other stakeholders as well, not only published authors, to see whether there is a need for revision of the COS. We plan to submit these results to the developers of the PedIMMPACT COS so that they can be used for audit and potential update of the COS, as recommended by the experts in the field of COS development and the COMET handbook [9].

In 2013, Kirkham *et al.* published analysis of outcome measures used in trials about rheumatoid arthritis (RA) over the period of 50 years, and within the study they contacted authors of trials published after publication of the RA COS in 1994. Their study had different aims than ours. They asked trialists whether they were aware of COS during designing of their study and choosing outcome domains, and whether they would consider using the RA COS in their future trials. They also included a small sample of authors. Among the 38 authors that responded, 13 did not use the full RA COS, and the majority of them indicated that they were not aware of it at the time they designed their study [10]. In this study we did not intend to ask the same questions; instead, we mainly wanted to know whether authors of SRs and trials in a particular field were aware of the relevant COS and did they find it appropriate; only one question was about whether they used the COS for their study.

Multiple surveyed authors indicated that they are not aware of the PedIMMPACT COS. This lack of knowledge could be addressed at several levels, but only before the study begins. Once the authors submit their manuscript to a journal is already too late because the study was completed and the authors cannot analyze new outcomes now from the beginning. First, education about the importance of COS can be added to research methodology courses, particularly in graduate schools. Second, members of ethics committees, or internal review boards should be aware of the COS and reject protocols for trials that do not use COS if they exist in a given research area. Third, research funders, both from industry and academia, should not fund trials or SRs that do not use relevant COS. As a commendable example, the UK's National Institute for Health Research has the following guidance in their guidance notes for applicants of full proposals: *"Where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise"* [11].

Fourth, public registries of clinical trials such as Clinicaltrials.gov and PROSPERO for SRs should introduce relevant sections that ask whether the protocol uses relevant COS. Already in 2015, Clarke and Williamson proposed that trial registries *"should encourage researchers to note their use of the core outcome set and to specify each of the outcomes from the core set, as well as any additional outcomes, that they will measure"* [12].

Resources available via COMET initiative website should be used as a part of the solution [13]. The COMET is an initiative that brings together individuals that are interested in developing and applying agreed COSs. The initiative's website enables search of the COMET's database where studies about COS that are planned, ongoing or completed are collated [13]. Registries can provide links to the COMET website [13], where authors can check whether there are COS for any given research field, if they are not aware of it already. It is encouraging that the ISRCTN registry has already done this; on their website with instructions about primary outcome measures authors are instructed that they should refer to the COMET about the core outcome measures that should be used [14].

Furthermore, as one surveyed author suggested, interventions for raising awareness about the relevant COS in the academic community are necessary. This is the part of action defined as engaging new stakeholders when appropriate after development of COS [8]. All relevant stakeholders should be identified and included in discussion and action that will aim to improve awareness about and acceptance of the relevant COS. Industry is particularly important stakeholder in this respect because many trials are funded by producers of drugs and medical devices.

Although the number of authors participating in the study was low, this number is comparable with the overall number of authors that participated in the study of Kirkham *et al.*, which had 38 authors that responded to their email message about their usage of RA COS [10].

Furthermore, due to low number of SRs identified, we invited more than one author per SR to participate in the survey. It is likely that responses of authors that participated in the same SR were not the same, and therefore they would represent their personal opinion, and not representing the SR as the unit of analysis.

Despite the low response rate, our study still brings important message to the research community and developers of the PedIMMPACT COS. Since the authors do not use the COS, the studies are not comparable. Trials will use heterogeneous outcome domains, and SRs will have trouble synthesizing evidence if there are many outcome domains measured. Using standardized COS is in the interest of patients and entire research community to ensure that evidence can be justly compared and synthesized in SRs.

In conclusion, interventions are needed that will increase authors' awareness about the relevant COS. Additionally, further discussion about the most relevant outcome domains for pediatric pain may be warranted, considering that the majority of surveyed authors gave preference to outcome domains that do not completely overlap with PedIMMPACT COS. Insufficient use of the COS is hindering comparative effectiveness research because it is difficult to assess relative performance among competing interventions.

Acknowledgements

We are grateful to I Buljan for assistance with the SurveyMonkey interface. We would also like to thank the anonymous peer reviewers, who provided particularly constructive feedback, for contributing their time, effort and engagement to make this manuscript better.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Summary points

- This study analyzed awareness about the core outcome set (COS) for pediatric pain recommended by the PedIMMPACT initiative among researchers in this field.
- We surveyed authors of systematic reviews (SRs) and randomized controlled trials (RCTs) about interventions for postoperative pain in children.
- The survey was administered via SurveyMonkey, a web-based survey software.
- 15 authors of SRs and 27 authors of RCTs completed our survey.
- Only a third of the surveyed authors heard about the PedIMMPACT COS.
- Most of the authors showed lack of knowledge about six domains of that COS, and the majority did not use the COS while preparing their studies.
- When asked to recommend which outcome domains should be part of the COS for acute pediatric pain, the suggested outcome domains were partly different from the PedIMMPACT COS.
- Using standardized core outcome set is in the interest of patients and entire research community to ensure that evidence can be justly compared and synthesized in SRs.
- The PedIMMPACT COS should be revisited to make sure that it still contains the most relevant outcome domains for pediatric pain.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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14. DODATCI

14.1. Strategija pretraživanja za elektroničku pismohranu MEDLINE

1 exp child/ (1633037)
2 exp Infant/ (989361)
3 exp adolescent/ (1690068)
4 exp Pediatrics/ (48086)
5 (child* or adolescen* or kid or kids or youth* or youngster* or minor or minors or teen* or juvenile* or student* or pupil or pupils or boy or boys or girl or girls or under 18* or underage 18* or under eighteen* or under age* or pediatric* or paediatric*).ti,ab,kw. (1809226)
6 1 or 2 or 3 or 4 or 5 (3654104)
7 exp Surgical Procedures, Operative/ (2597866)
8 exp Analgesia/ (37911)
9 analge$.ti,ab,kw. (100089)
10 8 or 9 (118227)
11 7 and 10 (30199)
12 Pain, Postoperative.sh. (29597)
13 ((postoperative adj4 pain$) or (post-operative adj4 pain$) or post-operative-pain$ or (post$ adj4 pain$) or (postoperative adj4 analgesi$) or (post-operative adj4 analgesi$) or post-operative analgesi$).ti,ab,kw. (39803)
14 ((post-surgical adj4 pain$) or (post surgical adj4 pain$) or (post-surgery adj4 pain$)).ti,ab,kw. (418)
15 ((pain$ adj4 after surg$) or (pain$ adj4 after operat$) or (pain$ adj4 follow$ operat$) or (pain$ adj4 follow$ surg$)).ti,ab,kw. (3143)
16 (pain-relief after surg$ or pain following surg$ or pain control after).ti,ab,kw. (683)
17 (("post surg$" or post-surg$) and (pain$ or discomfort)).ti,ab,kw. (1471)
18 (analgesi$ adj4 surg$).ti,ab,kw. (3704)
19 (analgesi$ adj4 operat$).ti,ab,kw. (1843)
20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (56811)
21 11 or 20 (72780)
22 (review or review,tutorial or review, academic).pt. (2048774)
23 (medline or medlars or embase or pubmed or cochrane).tw,sh. (114184)
24 (scisearch or psychinfo or psycinfo).tw,sh. (10744)
25 (psychlit or psyclit).tw,sh. (880)
26 cinahl.tw,sh. (12942)
27 ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh. (8559)
28 (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh. (18413)
29 (pooling or pooled or mantel haenszel).tw,sh. (63719)
30 (peto or dersimonian or der simonian or fixed effect).tw,sh. (4193)
31 (retraction of publication or retracted publication).pt. (8416)
32 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 (187350)
33 22 and 32 (87721)
34 meta-analysis.pt. (60105)
35 meta-analysis.sh. (60105)
36 (meta-analys$ or meta analys$ or metaanalys$).tw,sh. (105772)
37 (systematic$ adj5 review$).tw,sh. (81907)
38 (systematic$ adj5 overview$).tw,sh. (1131)

39 (quantitativ$ adj5 review$).tw,sh. (5139)
40 (quantitativ$ adj5 overview$).tw,sh. (206)
41 (quantitativ$ adj5 synthesis$).tw,sh. (1572)
42 (methodologic$ adj5 review$).tw,sh. (3843)
43 (methodologic$ adj5 overview$).tw,sh. (270)
44 (integrative research review$ or research integration).tw. (100)
45 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 (164349)
46 33 or 45 (203299)
47 6 and 21 and 46

14.2. Anketni obrazac korišten u četvrtom dijelu istraživanja

1. *Have you ever heard about the core set of outcomes for acute pediatric pain recommended by the PedIMMPACT initiative?*

Yes

No

2. *How many core outcome domains for acute pediatric pain are recommended by the PedIMMPACT initiative?*

4

6

8

10

3. *What do you think, which of these core outcome domains for pediatric pain are recommended by the PedIMMPACT initiative (check all answers that apply):*

Pain intensity

Pain-free

Additional analgesia

Global judgment of satisfaction with treatment

Symptoms and adverse events

Physical recovery

Emotional response

Role functioning

Sleep

Economic factors

Pharmacokinetics

Outcome specific only for certain interventions

Additional opioid analgesia

The duration of postoperative analgesia

4. *Please rate on the scale from 1 to 5 (1 = totally inappropriate, 5 = totally appropriate) your perception of appropriateness of each of the following outcomes for inclusion in a core outcome set for assessing interventions for pediatric pain (in children aged 3 years and older):*

Pain intensity

Global judgment of satisfaction with treatment

Symptoms and adverse events

Physical recovery

Emotional response

Economic factors

Sleep

Additional analgesia

Role functioning

Pain-free

Additional opioid analgesia

Outcome specific only for certain interventions

Pharmacokinetics

5. *While you were preparing your randomized controlled trial about intervention(s) for pediatric pain, did you use the core outcome set recommended by the PedIMMPACT initiative?*

Yes

Partially

No

While searching the literature, we found a large number of systematic reviews that evaluated interventions for pain relief in pediatric patients but none of those systematic reviews that were published after the year 2008 (after publication of the core outcome set recommended by the PedIMMPACT initiatives) have used all the outcomes recommended by the PedIMMPACT initiative.

6. *Can you indicate some problems/reasons that you have personally experienced and which may have prevented consisted use of all the core outcome set domains that are recommended by the PedIMMPACT?*

7. *Can you indicate some problems/reasons that somebody else might experience, which may prevent consisted use of all the core outcome set domains that are recommended by the PedIMMPACT?*

8. *Please select from the available list of outcomes one or more of those that you personally feel that should be part of the core outcome set for assessing the efficacy and safety of interventions in acute pediatric pain (in children aged 3 years and older):*

Pain intensity

Global judgment of satisfaction with treatment

Symptoms and adverse events

Physical recovery

Emotional response

Economic factors

Sleep

Additional analgesia

Role functioning

Pain-free

Additional opioid analgesia

Outcome specific only for certain interventions

Pharmacokinetics

9. *If you have any comments about this survey or questions about core outcome set that was recommended by PedIMMPACT initiatives, please indicate so:*

10. *If you would like to get results of this survey after the study is completed, please leave your email address. We would like to emphasize that leaving your email is not necessary for participation in the study and that the survey is designed as anonymous.*