

### Kliiniline küsimus nr 13

Kas **postoperatiivses** etapis on **äge valu** ravis tulemuslikum kombineeritud farmakoloogilise valuravi kasutamine vs monoterapia kasutamine?

**Tulemusnäitajad:** *valu tugevus, valu vähenemine, lisavaluvaigisti vajadus (sh opiaadi vajadus), aeg esimese lisavaluvaigisti vajaduseni, ärevuse vähenemine, postoperatiivsete tüsistuste esinemissagedus, valuvaigistitest tingitud kõrvaltoimed, rehospitalseerimine valu tõttu, patsiendi (eestkostja) rahulolu valuraviga, meetodi ohutus, haiglaravi kestus*

### Ravijuhendid

#### Kokkuvõte

**DE-07:** soovib ka lastel kasutada multimodaalset analgeesiat.

**AU-10:** soovib kasutada multimodaalset analgeesiat.

Adjuvantidest manib **deksametasooni** – vähendab PONVi ja annusest sõltuvalt valu tugevust / valuvaigistite koguseid, kuid suurendab samas veritsusriski.

**PEDI-12:** soovib kasutada multimodaalset analgeesiat, ravimite valik (parasetamool, NSAID, LA, opioid jne) lähtub operatioonitüübist.

- **Ketamiin** – tonsillektoomia korral ei ole olulist lisaväärtust kui lisatud morfiinile või bupivakaiini infiltratsioonile. Appendektoomia järgselt ei vähendanud ketamiini morfiinile lisatuna valu tugevust, kuid suurendas kesknärvisüsteemi kõrvaltoimete esinemist. Seljakirurgia korral ei mõjutanud intraoperatiivselt manustatud väikeses annuses ketamiin (0.5 mg/kg küllastusannus ja järgnev infusioon 4 mcg/kg/min) vajaminevat morfiini annust.
- **Deksmedetomidiniin** – tonsillektoomia järgselt võib vähendada vajaminevaid opioidide koguseid. Seljakirurgia korral ei vähenenud deksmedetomidiniini lisamisel PCA morfiinile (0.4mcg/kg/h) oluliselt ei valu tugevus ega ka morfiini annused.
- **Deksametasoon** - vähendab tonsillektoomia järgselt PONVi ja valu tugevust.
- **Iv magnesium** (50 mg/kg) boolusannus ja sellele järgnev infusioon (15 mg/kg/h) vähendas alajäseme operatsioonide korral postop valu tugevust
- **Gabapentiin** - 15 mg/kg operatsioonieelselt jätkates 5 mg/kg tds postoperatiivselt 5 päeva jooksul vähendas seljakirurgia järgselt 1 postop päeval võrreldes platseeboga valu tugevust ja 1-2 postop päeval opioidi annuseid. Peale 2. Postop päeva erinevusi ei olnud. (**Rusy et al.** "Gabapentin use in pediatric spinal fusion patients: a randomized, double-blind, controlled trial." *Anesth & Analg* (2010): 1393-1398.)

### 1.“Behandlung acuter perioperativer und postraumatischer Schmerzen” 2009 (DE-07)

**Non-opioids reduce the doses of opioids** (LoE: 1b) (Anderson et al., 1996; Korpela et al., 1999; Morton und O'Brien, 1999; Pickering et al., 2002; Viitanen et al., 2003),

increase the quality of analgesia (LoE: 1b) (Morton und O'Brien, 1999) and further reduce the opioid-induced adverse effects (LoE: 1b) (Korpela et al., 1999).

## 2. Acute Pain Management: Scientific Evidence 2010 (AU10)

Combining NSAID and PARA has been shown to improve analgesia and/or decrease the need for additional analgesia after adenoidectomy (Viitanen et al. 2003, Level II), tonsillectomy (Pickering et al 2002 Level II), inguinal surgery (Riad and Moussa 2007, Level II), multiple dental extractions (Gazal and Mackie 2007, Level II) and orthopaedic surgery (Hiller et al 2006, Level II).

As a component of multimodal analgesia, nsNSAIDS decrease opioid consumption (Antila et al 2006 Level II, Rygute and Kokki 2007 Level II). A combination of individually titrated intraoperative opioid and regularly administered perioperative mild analgesics (NSAID and/ or paracetamol) is recommended for management of pain following tonsillectomy (Hamunen and Kontinen 2005, Level I).

**Dexamethasone:** single dose of dexamethasone (0,4 to 1mg/kg) reduced pain (by 1 on VAS scale) on the first postoperative day (Afman et al 2006, Level I). A reduction in postoperative analgesic requirements following tonsillectomy and a dose dependent reduction in PONV following dexamethasone 0,05mg/kg, 0,15mg/kg or 0,5mg/kg (max 20mg) has been confirmed. However, the study was terminated after randomisation of 215 children as dexamethasone, but not postoperative use of ibuprofen, was associated with an increased risk of bleeding, which was highest after the largest dose (RR 6,8, 95%CI 1,8 to 16,5) (Czarnetzki et al. 2008 Level II).

**Commented [JL1]:** Kõigis neis uuringutes manustati deksametasooni ühekordseltoperatsiooni ajal aga mitte postop

### Key messages

1. Non-selective NSAIDs do not increase the risk of reoperation for bleeding after tonsillectomy in paediatric patients (**R**) (**Level I** [Cochrane Review]).
2. Dexamethasone reduces post-tonsillectomy pain and postoperative nausea and vomiting (**N**) (**Level I**) but high doses may increase the risk of bleeding (**N**) (**Level II**).
3. Paracetamol and non-selective NSAIDs are effective for moderately severe pain and decrease opioid requirements after major surgery (**U**) (**Level II**).
4. The efficacy of oral codeine in children is variable, individual differences in the ability to generate active metabolites may reduce efficacy (**U**) (**Level II**) or increase side effects (**N**) (**Level IV**).

The following tick boxes ☒ represent conclusions based on clinical experience and expert opinion.

- ☒ Safe dosing of paracetamol requires consideration of the age and body weight of the child, and the duration of therapy (**U**).
- ☒ Aspirin should be avoided in children, but serious adverse events after non-selective NSAIDs are rare in children over 6 months of age (**U**).

### 3. PEDI- 12

Combinations of analgesics should be used unless there are specific contraindications, for example; local anesthetics, opioids, NSAIDs, and paracetamol can be given in conjunction, not exceeding maximum recommended dose.

|                          |                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Tonsillectomy            | <b>NSAID, PARA, opioid</b><br>Combination of individually titrated intraoperative opioids, dexamethasone, and regularly administered periop mild analgesics (NSAIDs and /or PARA) is recommended: Grade A | <b>Adjuvants</b><br>Addition of <b>ketamine</b> 0.25 mg/kg to <b>morphine</b> 0.1 mg/kg <b>did not significantly improve analgesia</b> . Combination of <b>ketamine</b> 0.5 mg/kg IV and topical bupivacaine infiltration - <b>minor reductions in pain scores</b> when compared with LA alone and saline control groups.<br><b>Dexmedetomidine</b> (IV) <b>may reduce opioid requirements</b> and respiratory side effects in children after tonsillectomy. 1 mcg/kg produced less respiratory depression than 100 mcg/kg morphine but less effective analgesia. Higher doses, 2 and 4mcg/kg, lengthened time to rescue opioid analgesia but increased sedation in the early postoperative period when compared to fentanyl 1 or 2 mcg/kg IV.<br>Dexmedetomidine 2 mcg/kg + 0.7 mcg/kg intraoperative reduced early postop opioid requirements and agitation compared with fentanyl 1 mcg/kg.<br><b>Dexamethasone</b> <b>reduces PONV and postoperative pain</b> scores following tonsillectomy. (Steward et al. Steroids for improving recovery following tonsillectomy in children. Cochrane Database Syst Rev 2011; Aug 10;(8): CD003997) |
| <b>Dental procedures</b> | <b>NSAIDs with or without PARA</b> <b>reduce pain</b> following dental extractions: Grade B<br>However, adding PARA to ibuprofen did not improve early analgesia (15 min postop) compared with            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

**Commented [JL2]:** "To assess the clinical efficacy of a single intraoperative dose of dexamethasone in reducing post-tonsillectomy morbidity" – minu arust see ei sobi postop multimodaalse valuravi soovituseks

|                                      |             |                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                |
|--------------------------------------|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
|                                      |             | ibuprofen alone in one study.                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                |
| <b>Inguinal hernia repair (open)</b> |             | When using a periop opioid-based regimen (without LA block), <b>multimodal analgesia adding both PARA and NSAID is more effective than either opioid alone or opioid plus either PARA or NSAID.</b>                                                                                                                                                                                                                                    |                                                                                                                                                |
| <b>Umbilical hernia repair</b>       |             | Multimodal analgesic regimen combining LA and simple analgesics perioperatively is <b>recommended</b> , opioid supplementation may be required. PARA and/or NSAID should be continued postoperatively for at least 48 h.                                                                                                                                                                                                               |                                                                                                                                                |
| <b>Intra-abdominal surgery</b>       |             | Multimodal analgesia using parenteral opioids, central neuraxial analgesia together with systemic NSAIDs and PARA should be used.                                                                                                                                                                                                                                                                                                      |                                                                                                                                                |
| <b>Appendicectomy (open)</b>         |             | <b>PCA combined with NSAID is effective for postappendicectomy pain: Grade B</b><br>Iv opioids as a continuous infusion, PCA or NCA, together with a multimodal analgesic strategy including LA wound infiltration, NSAID and PARA is currently suggested practice following appendicectomy. Morphine PCA has been previously shown to be effective, supplementation with NSAID improves analgesia, particularly for pain on movement. | The addition of <b>ketamine</b> to morphine <b>did not improve analgesia</b> in one study and neurobehavioral side effects were increased.     |
| <b>Lower limb surgery</b>            | <b>limb</b> | <b>Systemic PARA and NSAID reduce intravenous opioid requirements: Grade C</b>                                                                                                                                                                                                                                                                                                                                                         | The use of <b>iv magnesium</b> (50 mg/kg) bolus followed by infusion of 15 mg/kg/h <b>reduced postop pain scores</b> and analgesic consumption |

in children with cerebral palsy undergoing femoral osteotomy.

Commented [JL3]: NB! juhendis artiklile viide puudub

## Spinal surgery

The use of **gabapentin** (15 mg/kg) preop followed by 5 mg/kg tds for 5 days **reduced opioid consumption** on postop days 1 and 2 and reduced pain scores on day 1 compared with placebo, no difference was seen beyond day 2 and no difference was seen in side effects.

No difference was seen in pain scores or morphine consumption when **low-dose ketamine** was administered intra-operatively (0.5 mg/kg loading dose followed by an infusion of 4 mcg/kg/min compared with placebo. A retrospective review of the addition of **dexmedetomidine** (0.4mcg/kg/h to PCA morphine was **unable to demonstrate a significant difference in pain scores** or morphine consumption compared with PCA morphine alone.

## Thoracotomy

Multi-modal analgesic approach, including LA technique and/or opioid with NSAID and PARA, is suitable for postthoracotomy pain.

## Neurosurgery

A multi-modal analgesic approach is suitable, which may include the use of LA infiltration, PARA, NSAID, and parenteral or oral opioids.

## SÜSTEMAATILISED ÜLEVAATED / META-ANALÜÜSID

### KOKKUVÕTE

#### • NSAID / PARATSETAMOOL

Süsteemaatiline ülevaade (**Wong et al 2013**) ja meta-analüüs (**Michelet et al. 2012**) - mõlemas leiti, et nsNSAIDi / paratsetamooli lisamine opioididele vähendab vajaminevaid opioidide annuseid.

8 RCT-d:

Rektaalne PARA ei vähenda postop perioodil opioidi annuseid (van der Marel 2007), iv PARA ei vähendanud postop oksükodooni annuseid, kuid vähendas valu tugevust (Hiller et al. 2012), PARA ja ketoprofeeni kombineerimine vähendas valu tugevust peale ortopeedilisi operatsioone kuid mitte peale pehme koe operatsioone (Hiller 2006), rektaalne PARA koos diklofenakiga oli tõhusam kui kumbki ravim monoterapiiana (Mireskandari ja Makarem 2011), ibuprofeeni ja PARA kombineerimine vähendab valu tugevust võrreldes paratsetamooli monoterapiaga peale hamba ekstraktsiooni (Gazal ja Mackie 2007), suukaudne naprokseen aga mitte paratsetamool vähendab lisavaluvaigisti vajadust peale adenoidektoomiat (Korpela 2007), preoperatiivne PARA ja ketorolaki koos manustamine vähendab peale songaoperatsiooni vajaminevat fentanüüli kogust (Hong 2010), postoperatiivne iv PARA kasutamisel oli võrreldes morfiini püsiinfusiooni kasutamisega 48h kumulatiivne morfiini annus väiksem (Ceelie 2013).

- **KETAMIIN**

2 meta-analüüsi (**Dahmani et al. 2011** ja **Cho et al. 2014**) leidsid, et ketamiini lisamine (nii süsteemselt kui ka lokaalselt) multimodaalse valu skeemi vähendab postoperatiivse valu tugevust ja mitte-opioidide annuseid, kuid ei vähenda vajaminevaid opioide annuseid.

RCTd:

Leidus 2 RCTd, mis näitasid ketamiini tõenäolist kasulikku rolli multimodaalses valuravis lastel - ketamiin operatsiooni lõpus manustatult vähendab operatsiooni järgselt valuvaigistite koguseid, valuraviga seotud kõrvaltoimete esinemine ei sagene (Javid 2012, Inanoglu 2009)

Samas leidis 2 RCTd, mis ei leidnud ketamiini kasutamisest multimodaalses valuravis lastel kasu – ei vähenenud postoperatiivne opioidide kasutamine, valu tugevus ega ka sedatsiooniskoor (Bazin 2010, Pestieau 2014).

- **DEKSMEDETOMIDIIN**

2 meta-analüüsi. **Schnabel et al 2013** hindasid operatsiooni ajal manustatud deksmedetomidiini mõju laste postoperatiivsele ägedale valule ja järeldasid 11 RCT alusel, et deksmedetomidiin vähendab postop valu tugevust, kuid mõju operatsiooni järgsele opioidide vajadusele on vähem selge.

**He et al. 2013** hindasid deksmedetomidiini toimet tonsillektoomia või adenoidektoomia järgselt ja leidsid 5-le RCTle tuginedes, et operatsiooniaegne deksmedetomidiin on sama tühus kui opioidid.

RCT: Olutoye et al 2010 uuringus manustati operatsiooni ajal ühekordselt deksmedetomidiini 0.75 µg/kg või 1 µg/kg, morfiini 50 µg/kg või 100 µg/kg. Suuremate deksmedetomidiini ja morfiini annuste kasutamisel oli keskmine aeg lisavaluvaigisti vajaduseni võrdne, kuid pikem kui samade ravimite väiksemate annuste kasutamisel.

Patel et al. 2010 uurisid deksmedetomidiini kasutamist obstruktiivse uneapnoega lastel adenoidektoomia või tonsillektoomia ajal. Leiti, et postoperatiivne opioidide vajadus vähenes oluliselt ning desaturatsiooniepisoode oli deksmedetomidiini kasutamisel vähem.

**Klonidiini, iv magneesiumi, deksametasooni, gabapentiini / pregabaliini ja lidokaiini** kasutamise kohta lastel postoperatiivse multimodaalse valuravi

komponendina leidis väga vähe informatsiooni. Ei leidunud ühtegi süstemaatilist ülevaadet ega meta-analüüsi.

- **Klonidiin** – vaid 1 RCT 1998 aastast
- **Gabapentiin / pregabaliin** – leidis vaid 1 RCT gabapentiini kohta, kus gabapentinoidiga ravi jätkus ka postoperatiivselt (Rusy et al. 2010). Selles uuringus leiti gabapentiinil olevat postop valu vähendav ja opioidide koguseid vähendav mõju.
- **Lidokaiin** – ei leidunud asjakohaseid artikleid (Until now, lidocaine is only investigated in children in the laryngeal reflex responses to tracheal intubation, and as an adjunct to propofol to prevent or reduce injection pain (Schultz-Machata et al. 2014)).
- **Iv Magneesium** – ei leidunud asjakohaseid artikleid
- **Deksametasoon** – uuritud on ühekordse operatsiooniaegse deksametasooni mõju

## NSAIDS / PARACETAMOL

### Systematic reviews

1. **Wong** I, St John-Green, Walker. "Opioid-sparing effects of perioperative paracetamol and NSAIDs in children." *Pediatric Anesthesia* 23.6 (2013): 475-495.

**Background and Objectives:** Perioperative pain in children can be effectively managed with systemic opioids, but addition of PARA or NSAIDs may reduce opioid requirements and potentially improve analgesia and/or reduce adverse effects.

**Methods:** A [systematic literature search](#) was conducted to identify trials evaluating postoperative opioid requirements in children and comparing NSAID and/or PARA with placebo. Studies were stratified according to design: continuous availability of iv opioid (PCA/NCA) vs intermittent 'as needed' bolus; and single vs multiple dose PARA/NSAIDs. Primary outcome data were extracted, and the % decrease in mean opioid consumption was calculated for statistically significant reductions compared with placebo. Secondary outcomes included differences in pain intensity, adverse effects (sedation, respiratory depression, postoperative nausea and vomiting, pruritus, urinary retention, bleeding), and patient/parent satisfaction.

**Results:** 31 RCTs, with 48 active treatment arms compared with placebo, were included. Significant opioid sparing was reported in 38 of 48 active treatment arms, across 21 of the 31 studies. Benefit was most consistently reported when multiple doses of study drug were administered, and 24 h PCA or NCA opioid requirements were assessed. The proportion of positive studies was less with paracetamol, but was influenced by dose and route of administration. Despite availability of opioid for titration, a reduction in pain intensity by NSAIDs and/or PARA was reported in 16 of 29 studies. Evidence for clinically significant reductions in opioid-related adverse effects was less robust.

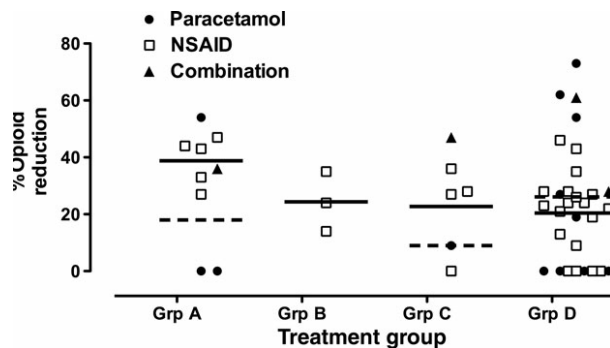


Figure 2 Percentage reduction in opioid requirements in pair-wise comparisons of mean opioid dose requirements in active treatment arms (paracetamol; NSAID; combination = NSAID + paracetamol) vs control/placebo. Studies reporting no statistically significant difference from control are designated as 0% reduction. Solid line = mean of NSAID arms; dotted line = mean of paracetamol arms. Treatment groups comprise Group A = PCA/NCA + study drug \_24 h; Group B = PCA/NCA + study drug \_6 h; Group C: intermittent opioid + study drug \_24 h; Group D = intermittent opioid + study drug \_6 h.

**Conclusion:** This systematic review supports addition of NSAIDs and/or PARA to systemic opioid for perioperative pain management in children.

**2. Michelet,** Daphne, et al. "A meta-analysis of the use of nonsteroidal antiinflammatory drugs for pediatric postoperative pain." *Anesthesia & Analgesia* 114.2 (2012): 393-406.

**BACKGROUND:** NSAIDs have been shown to effectively decrease postop pain, but their opioid-sparing effect is still controversial. In this present meta-analysis, we investigated the postoperative opioid-sparing effect of NSAIDs in children.

**METHODS:** A comprehensive literature search was conducted to identify clinical trials using NSAIDs and opioids as periop analgesic compounds in children and infants. Outcomes measured were opioid consumption, pain intensity, postoperative nausea and vomiting (PONV), and urinary retention. All outcomes were studied during postanesthesia care unit (PACU) stay and the first 24 postop hours. Data from each trial were combined to calculate the pooled odds ratios (ORs) or standardized mean difference (SMD) and their 95% confidence interval.

**RESULTS:** 22 RCTs were analyzed. Periop administration of NSAIDs decreased postoperative opioid requirement (both in the PACU and during the first 24 postop h; SMD = -0.66 [-0.84, -0.48] and -0.83 [-1.11, -0.55], respectively), pain intensity in the PACU (SMD = -0.85 [-1.24, -0.47]), and PONV during the first 24 postoperative hours (OR = 0.75 [0.57-0.99]). NSAIDs did not decrease pain intensity during the first 24 postop hours (OR = 0.56 [0.26-1.2]) and PONV during PACU stay (OR = 1.02 [0.73-1.44]). Subgroup analysis according to the timing of NSAID administration (intraoperative versus postop), type of surgery, or coadministration of PARA did not show any influence of these factors on the studied outcomes except the reduction of pain intensity and the incidence of PONV during the first 24 postop hours, which were influenced by the coadministration of PARA and the type of surgery, respectively.

**CONCLUSION:** This meta-analysis shows that perioperative NSAID administration reduces opioid consumption and PONV during the postoperative period in children.

## RCTs

1. **Van der Marel**, C. D., et al. "Rectal acetaminophen does not reduce morphine consumption after major surgery in young infants." *British journal of anaesthesia* 98.3 (2007): 372-379.

**Background** The safety and value of acetaminophen in addition to continuous morphine infusion has never been studied in newborns and young infants. We investigated the addition of acetaminophen to evaluate whether it decreased morphine consumption in this age group after major thoracic (non-cardiac) or abdominal surgery.

**Methods** RCT was performed in 71 patients given either acetaminophen 90–100 mg kg<sup>-1</sup> day<sup>-1</sup> or placebo rectally, in addition to a morphine loading dose of 100 µg kg<sup>-1</sup> and 5–10 µg kg<sup>-1</sup> h<sup>-1</sup> continuous infusion. Analgesic efficacy was assessed using Visual Analogue Scale (VAS) and COMFORT scores. Extra morphine was administered if VAS was ≥4.

**Results** We analysed data of 54 patients, of whom 29 received acetaminophen and 25 received placebo. Median (25–75th percentile) age was 0 (0–2) months. Additional morphine bolus requirements and increases in continuous morphine infusion were similar in both groups (P = 0.366 and P = 0.06, respectively). There was no significant difference in total morphine consumption, respectively, 7.91 (6.59–14.02) and 7.19 (5.45–12.06) µg kg<sup>-1</sup> h<sup>-1</sup> for the acetaminophen and placebo group (P = 0.60). COMFORT [median (25–75th percentile) acetaminophen 10 (9–12) and placebo 11 (9–13)] and VAS [median (25–75th percentile) acetaminophen 0.0 (0.0–0.2) and placebo 0.0 (0.0–0.3)] scores did not differ between acetaminophen and placebo group (P = 0.06 and P = 0.73, respectively).

**Conclusions** Acetaminophen, as an adjuvant to continuous morphine infusion, does not have an additional analgesic effect and should not be considered as standard of care in young infants, 0–2 months of age, after major thoracic (non-cardiac) or abdominal surgery.

2. **Hiller**, Arja, et al. "Acetaminophen improves analgesia but does not reduce opioid requirement after major spine surgery in children and adolescents." *Spine* 37.20 (2012): E1225-E1231.

**Study Design.** A randomized, placebo-controlled, double-blind study to evaluate the effect of IV administered acetaminophen on postoperative pain in children and adolescents undergoing surgery for idiopathic scoliosis or spondylolisthesis.

**Objective.** To evaluate effectiveness of IV-administered acetaminophen on postoperative analgesia, opioid consumption, and acetaminophen concentrations after major spine surgery in adolescents.

**Summary of Background Data.** Scoliosis surgery is associated with severe postoperative pain, most commonly treated with IV-administered opioids. NSAIDs, as adjuvant to opioids, improve analgesia and reduce the need for opioids. However, by inhibiting cyclo-oxygenase enzymes peripherally, NSAIDs may inhibit bone healing. Acetaminophen, a centrally acting analgesic, does not have the adverse effects of NSAIDs and has improved analgesia in children after another orthopedic surgery.

**Methods.** In an institutional review board approved study, 36 American Society of Anesthesiology patient classification I to III patients of 10 to 18 years of age were analyzed. Acetaminophen 30 mg/kg, administered IV or 0.9% NaCl was administered at the end of scoliosis or spondylolisthesis surgery, and thereafter twice at 8-hour intervals. Timed blood samples for acetaminophen determination were taken between 0.25 and 20 h after the first dose. All patients received standard propofol-remifentanyl anesthesia. Pain scores (VAS 0–10), opioid consumption, and adverse effects were recorded.

**Results.** In the surgical ward, 7 (39%) patients in the acetaminophen and 13 (72%) in the placebo group had a VAS pain score 6 or more ( $P < 0.05$ ). There were fewer hours with VAS score 6 or more in the acetaminophen group compared with the placebo group (8.7% vs. 17.8% of the hours,  $P < 0.05$ ). There was no difference in oxycodone consumption during the 24-h follow-up between the 2 groups.

**Conclusion.** IV-administered acetaminophen 90 mg/kg/day, adjuvant to oxycodone, did improve analgesia, but did not diminish oxycodone consumption during 24 h after major spine surgery in children and adolescents. All acetaminophen concentrations were in nontoxic levels.

3. **Hiller**, Arja, et al. "The analgesic efficacy of acetaminophen, ketoprofen, or their combination for pediatric surgical patients having soft tissue or orthopedic procedures." *Anesthesia & Analgesia* 102.5 (2006): 1365-1371.

The combined use of acetaminophen and a NSAID has been shown to provide better postoperative analgesia than either drug alone in several adult studies. However, there are no pediatric studies analyzing similar effects when the currently recommended doses of acetaminophen are used.

**Method:** In a double-blind, placebo-controlled design we randomized 120 children, aged 1–9 yr, undergoing orthopedic or soft tissue surgery, into 3 groups to receive either acetaminophen 60 mg/kg rectally and 40 mg/kg orally, ketoprofen 2 mg/kg IV twice, or the combination of the active drugs. The first drug doses were given at anesthetic induction and the second doses 8 h thereafter. During anesthesia all children received sevoflurane and a continuous infusion of remifentanyl. Postop pain was evaluated by the behavioral objective pain scale (0–9) for 24h. The rescue medication was morphine 0.05 mg/kg IV. The primary outcome variable was morphine consumption.

**Results:** Morphine requirement was less in the combination than in the acetaminophen group both in the postanesthesia care unit ( $2.5 \pm 1.7$  versus  $3.9 \pm 2.1$  morphine doses) and during the 24-h postoperative follow-up ( $4.1 \pm 2.5$  versus  $5.9 \pm 2.9$  morphine doses) ( $P < 0.05$ ). No differences existed between the ketoprofen and the acetaminophen groups. The objective pain scale scores were lowest in the combination group both in the postanesthesia care unit and in the postoperative ward ( $P < 0.05$ ). When children were divided based on their surgery, opioid requirement and pain scores were less in the combination than in the parent drug groups only after orthopedic surgery.

**Conclusion:** The combination of acetaminophen 100 mg/kg and ketoprofen 4 mg/kg in a day provided better analgesia and lower pain scores after orthopedic, but not soft tissue, surgery in children.

4. **Mireskandari and Makarem.** "Effect of rectal diclofenac and acetaminophen

alone and in combination on postoperative pain after cleft palate repair in children." *Journal of Craniofacial Surgery* 22.5 (2011): 1955-1959.

Acetaminophen and diclofenac are prescribed as postop analgesic agents in children. However, the efficacy of their combination is not studied sufficiently. We compare the analgesic effects of acetaminophen, diclofenac, and their combination after cleft palate surgery.

**Methods:** In this randomized clinical trial, 120 children (1.5-5 y) who were scheduled for cleft palate repair were studied. Children were randomized to receive placebo, acetaminophen (40 mg/kg), diclofenac (1 mg/kg), or acetaminophen (40 mg/kg) plus diclofenac (1 mg/kg) rectally just after surgery. Acetaminophen (30 mg/kg) and diclofenac (1 mg/kg) were administered every 8 hours until 48 hours. Postoperative pain was assessed regularly with the Children Hospital of Eastern Ontario Pain Scale, and rescue analgesia was provided if scores were 7 or greater. Time to the first prescription of meperidine, total postoperative meperidine consumption, and adverse effects were the main outcomes.

**Results:** After surgery, pain scores were higher in placebo than in other groups in all time intervals. In the first 12 hours, pain scores in the combined group were less than those in the acetaminophen ( $P < 0.05$ ) and diclofenac ( $P < 0.05$ ) groups. Postoperative meperidine consumption was the highest in placebo and was the least in combined group ( $P < 0.05$ ). It was significantly higher in the acetaminophen group than in the diclofenac group ( $P < 0.05$ ). Time to the first prescription of meperidine was significantly different among all groups. Adverse effects were comparable among groups.

**Conclusion:** Rectal acetaminophen plus diclofenac was found to be the most effective in pain control. However, both rectal acetaminophen and diclofenac were more effective than placebo, whereas diclofenac was more effective than acetaminophen.

5. Gazal and Mackie. "A comparison of PARA, ibuprofen or their combination for pain relief following extractions in children under general anaesthesia: RCT." *Int J Paedi Dentistry* 17.3 (2007): 169-177.

**Objective.** This study was designed to compare the effectiveness of different oral analgesics for relieving pain and distress in children following the extraction of teeth under general anaesthesia (GA).

**Methods.** 201 subjects were randomly allocated to one of 4 groups. 47 children were included in the ibuprofen alone ( $5 \text{ mg kg}^{-1}$ ) group, 51 in the PARA/ibuprofen combination ( $15/5 \text{ mg kg}^{-1}$ ) group, 48 in the high-dose PARA ( $20 \text{ mg kg}^{-1}$ ) group, and 55 children were included in the usual-dose PARA ( $15 \text{ mg kg}^{-1}$ ) group (control group). Evaluation of distress for children was made immediately pre-operatively, on recovery from anaesthesia and again after 15 min by using a five-point face scale. Furthermore, each child was observed immediately postop and 15 min postop for signs of pain using the Children's Hospital of Eastern Ontario Pain Scale.

**Results.** There were significant decreases in the mean pain and distress scores for both the ibuprofen alone and PARA/ibuprofen combination groups compared to the control group (usual-dose PARA) at 15 min postop.

**Conclusions.** This study provides evidence to support the oral administration of ibuprofen alone or in combination with paracetamol for postoperative analgesia in children who are having teeth extracted under GA.

6. **Korpela**, R., et al. "Oral naproxen but not oral PARA reduces the need for rescue analgesic after adenoidectomy in children." *Acta Anaesthesiol Scand* 51.6 (2007): 726-730.

**Background:** Our aim was to show the efficacy of naproxen and PARA with and without pethidine on pain and nausea and vomiting after adenoidectomy. The primary outcome was the requirement of rescue analgesic for post-operative pain and the secondary outcome was PONV.

**Methods:** A randomized, double-blind, placebo-controlled study design was used. Thirty minutes before anaesthesia induction, patients ( $n=180$ ) received either a single oral dose analgesic (naproxen 10 mg/kg or paracetamol 20 mg/kg) or a placebo. Half of the children received pethidine 1 mg/kg i.v. at the induction of anaesthesia. Post-op pain was evaluated using an objective behavioural pain scale (OPS 0–9) and rescue medication, i.v. fentanyl 1 µg/kg, was administered if the child suffered from moderate or severe pain ( $OPS \geq 4$ ).

**Results:** When pethidine was not used, 83% of the children in the naproxen group vs. 97% in the other two groups required rescue fentanyl ( $P < 0.05$ ). The use of pethidine reduced the incidence of fentanyl requirement by 30% and the number of fentanyl doses by 50% ( $P < 0.001$ ). It also equalized the effects of naproxen, paracetamol and the placebo making the pain model invalid for this kind of study. The drawback associated with better analgesia was a doubling of the incidence of PONV ( $P < 0.001$ ).

**Conclusions:** Oral naproxen (10 mg/kg), but not oral paracetamol (20 mg/kg), reduces the need for rescue analgesic after adenoidectomy in children. The sensitivity of the pain model is crucial for these types of studies.

7. **Hong et al.** "Fentanyl sparing effects of combined ketorolac and acetaminophen for outpatient inguinal hernia repair in children." *Journal of urology* 183.4 (2010): 1551-1555.

In this prospective, randomized, double-blinded study we sought to evaluate the efficacy and safety of combined use of iv ketorolac and acetaminophen in small children undergoing outpatient inguinal hernia repair.

**Materials and Methods:** We studied 55 children 1-5 years old who were undergoing elective repair of unilateral inguinal hernia. After induction of general anesthesia children in the experimental group (28 patients) received 1 mg/kg ketorolac and 20 mg/kg acetaminophen iv. In the control group (27 patients) the same volume of saline was administered. All patients received 1 µg/kg fentanyl iv before incision. We also evaluated the nr of patients requiring postop rescue fentanyl, total fentanyl consumption, pain scores and side effects.

**Results:** Significantly fewer patients receiving ketorolac-acetaminophen received postoperative rescue fentanyl compared to controls (28.6% vs 81.5%). A significantly lower total dose of fentanyl was administered to patients receiving ketorolac-acetaminophen compared to controls (0.54 vs 1.37 µg/kg). Pain scores were significantly higher in the control group immediately postoperatively but eventually decreased. The incidences of sedation use (55.6% vs 25.0%) and vomiting (33.3% vs 10.7%) were significantly higher in controls.

**Conclusions:** Preoperative iv coadministration of ketorolac and acetaminophen is a simple, safe and effective method for relieving postoperative pain, and demonstrates highly [significant fentanyl sparing effects](#) in small children after outpatient inguinal hernia repair.

8. [Ceelie et al.](#) "Effect of [iv PARA](#) on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: RCT." *JAMA* 309.2 (2013): 149-154.

**Objective** To [determine whether IV PARA would significantly \(>30%\) reduce morphine requirements in neonates and infants](#) after major surgery.

**Design, Setting, and Patients:** Single-center, randomized, double-blind study conducted in a level 3 PICU in Rotterdam, the Netherlands. Patients were [71 neonates or infants <1y](#) undergoing major thoracic (noncardiac) or abdominal surgery between March 2008 and July 2010, with follow-up of 48 hours.

**Interventions** All patients received a loading dose of morphine 30 min before the end of surgery, followed by [continuous morphine or intermittent iv PARA up to 48 h](#) postsurgery. Infants in both study groups received morphine (boluses and/or continuous infusion) as rescue medication on the guidance of the validated pain assessment instruments.

**Main Outcome Measures** Primary outcome was cumulative morphine dose (study and rescue dose). Secondary outcomes were pain scores and morphine-related adverse effects.

**Results** The cumulative median morphine dose in the first 48 hours postop was 121 (interquartile range, 99-264) µg/kg in the PARA group (n = 33) and 357 (interquartile range, 220-605) µg/kg in the morphine group (n = 38),  $P < .001$ , with a between-group difference that was 66% (95% CI, 34%-109%) lower in the PARA group. Pain scores and adverse effects were not significantly different between groups.

**Conclusion and Relevance** [Among infants undergoing major surgery, postoperative use of intermittent iv paracetamol compared with continuous morphine resulted in a lower cumulative morphine dose over 48 h.](#)

## KETAMINE

### Systematic reviews / meta-analyses

1. [Dahmani et al.](#) "Ketamine for perioperative pain management in children: a [meta-analysis](#) of published studies." *Pediatric Anesthesia* 21.6 (2011): 636-652.

**Introduction:** Ketamine, a compound with analgesic and antihyperalgesic properties, has been shown to decrease postop pain and opioid requirements in adults. The goal of the present meta-analysis was [to investigate postoperative analgesic properties of ketamine in pediatric patients](#).

**Material and methods:** A comprehensive literature search was conducted to identify clinical trials that used ketamine as a perioperative analgesic compound in children and infants. Outcomes measured were postop analgesic consumption, pain intensity and duration of sensory block (when ketamine was used by caudal route)

during the postoperative care unit (PACU) stay and the early postoperative period (6–24 h after leaving the operative room). The data from each trial were combined to calculate the pooled odds ratios or standard mean differences and their 95% confidence intervals.

**Results:** 35 randomized, blinded controlled studies were retrieved from the literature. Systemic ketamine was effective in decreasing PACU pain intensity and analgesic requirement but failed to influence early (6–24 h) pain intensity and analgesic requirement. Ketamine administered locally during tonsillectomy, decreased PACU and early (6–24 h) pain intensity and PACU analgesic requirements. Used as an adjuvant for caudal analgesia, ketamine increased the duration of sensory block and PACU analgesic requirement without impacting PACU pain intensity. Ketamine failed to exhibit a postoperative opioid-sparing effect.

**Conclusions:** administration of ketamine was associated with decreased PACU postoperative pain intensity and nonopioid analgesic requirement. However, ketamine failed to exhibit a postoperative opioid-sparing effect.

## 2. Cho et al. "Efficacy of Ketamine in Improving Pain after Tonsillectomy in Children: Meta-Analysis." *PloS one* 9.6 (2014): e101259.

**Background and objectives:** The goal of this meta-analysis study was to perform a systematic review of the literature on the effects of ketamine on postoperative pain following tonsillectomy and adverse effects in children.

**Subjects and Methods:** Two authors independently searched three databases (MEDLINE, SCOPUS, Cochrane) from their inception of article collection to February 2014. Studies that compared preoperative ketamine administration (ketamine groups) with no treatment (control group) or opioid administration (opioid group) where the outcomes of interest were postoperative pain intensity, rescue analgesic consumption, or adverse effects (sedation, nausea and vomiting, bad dream, worsening sleep pattern, and hallucination) 0–24 hours after leaving the operation room were included in the analysis.

**Results:** A total of 24 studies with 1257 participants were included and reviewed for the meta-analysis

The pain score reported by the physician during first 4 hours and need for analgesics during 24 hours postoperatively was significantly decreased in the ketamine group versus control group and was similar with the opioid group. In addition, there was no significant difference between ketamine and control groups for adverse effects during 24 hours postoperatively. In the subgroup analyses (systemic and local administration) regarding pain related measurements, peritonsillar infiltration of ketamine was more effective in reducing the postoperative pain severity and need for analgesics.

**Conclusion:** Preoperative administration of ketamine systemically or locally could provide pain relief without side-effects in children undergoing tonsillectomy. However, considering the insufficient evaluation of efficacy of ketamine according to the administration methods and high heterogeneity in some parameters, further clinical trials with robust research methodology should be conducted to confirm the results of this study.

**RCT**

1. Javid et al. "Evaluation of a low dose ketamine in post tonsillectomy pain relief: a randomized trial comparing intravenous and subcutaneous ketamine in pediatrics." *Anesthesiology and pain medicine* 2.2 (2012): 85.

**Objectives:** Despite employing different surgical and anesthetic strategies in post-tonsillectomy pain relief, this is still a clinical problem. The study was designed to evaluate the efficacy of a low dose ketamine in post tonsillectomy pain relief.

**Patients and Methods:** Our prospective randomized double blinded study enrolled 75 pediatric patients (3-10 years old) who were scheduled for a tonsillectomy procedure. Patients were randomly assigned to one of three groups receiving; intravenous (IV) ketamine 0.5mg/kg, subcutaneous (SC) ketamine 0.5 mg/kg and placebo at the end of the operation. Post-operative pain score was assessed using modified CHEOPS.

**Results:** In our study we did not find any significant difference among the three groups regarding sex, age, and weight, duration of operation, hemodynamic stability, and nausea and vomiting. However, in ketamine groups, pain score and analgesic consumption were significantly lower ( $P < 0.00$ ). The efficacy of the both ketamine groups was similar.

**Conclusions:** The study demonstrated that the both subcutaneous and intravenous injections of ketamine, at the end of the operation, were safe and effective for post-tonsillectomy pain control. Ketamine reduced postoperative analgesic medications consumption without increasing the risk of complications.

2. Bazin, et al. "Effects of perioperative intravenous low dose of ketamine on postoperative analgesia in children." *European Journal of Anaesthesiology* (EJA) 27.1 (2010): 47-52.

**Background and objective:** Low dose of ketamine reduces postoperative pain and opioid consumption in adult studies. However, there are only a few data with controversial results in the paediatric population. The aim of this randomized controlled trial was to evaluate the use of low doses of intravenous ketamine on postoperative pain in children after surgery on the lower part of the body.

**Methods:** 37 children with ASA 1 or 2 from 6 to 60 months of age, undergoing scheduled surgery, were prospectively enrolled in a double blind sequential trial using a triangular test, with analysis every 10 patients treated. The children were randomly assigned to iv saline or 0.15 mg kg<sup>-1</sup> ketamine before surgery, followed by a continuous infusion of 1.4 µg kg<sup>-1</sup> min<sup>-1</sup> over 24 h. After sevoflurane induction and tracheal intubation, a caudal anaesthesia was performed in all children (1 ml kg<sup>-1</sup> of bupivacaine 0.25% with epinephrine). The postoperative analgesic technique was standardized with iv paracetamol 15 mg kg<sup>-1</sup> 6 h<sup>-1</sup>, rectal morniflumate (20 mg kg<sup>-1</sup> 12 h<sup>-1</sup>) and iv nalbuphine infusion 1.2 mg kg<sup>-1</sup> 24 h<sup>-1</sup> for 24 h. The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) scores, additional bolus of nalbuphine (if CHEOPS >7) and side effects were recorded from eye opening every 2 h over 24 h. The primary endpoint was the CHEOPS area under the curve.

**Results:** There was no difference in terms of additional bolus of nalbuphine as well as CHEOPS score area under the curve between groups, that is, 76 ± 10 in the ketamine group versus 74 ± 7 in the control group. No psychomimetic side effects were noted.

**Conclusion:** The study failed to show any evidence of benefit of ketamine to improve analgesia in children when given in addition to a multimodal analgesic therapy with paracetamol, a NSAID and an opiate.

3. **Inanoglu, et al.** "Intravenous ketamine and local bupivacaine infiltration are effective as part of a multimodal regime for reducing post-tonsillectomy pain." *Medical Science Monitor* 15.10 (2009): CR539-CR543.

**Background:** The aim of this study was to investigate the effects of a multimodal analgesic regimen, including iv ketamine and peritonsillar infiltration of bupivacaine, on post-tonsillectomy pain in children.

**Material and Method:** Ninety children aged 2-12 years, undergoing tonsillectomy, were enrolled in this randomized, controlled and double-blinded study. Group I (n=30) received iv and peritonsillar saline, group II (n=30) received iv saline and peritonsillar bupivacaine, and group III (n=30) received iv 0.5 mg/kg ketamine and peritonsillar 0.25% bupivacaine (3-5 ml per tonsil). Pain was evaluated using a modified Children's Hospital of Eastern Ontario Pain Scale (mCHEOPS) recorded 15 min and 1, 4, 12, 16, and 24 h postoperatively.

**Results:** No difference was found in the demographic data among the groups. Group I patients had higher pain scores at 15th min, and 1st and 4th h than group II, and at all time intervals, than group III ( $P<0.05$ ). Patients in group III also had significantly lower pain scores than group II at all time intervals except at 15th min ( $P<0.05$ ). Analgesic requirements and the time to first analgesia were also significantly ( $P<0.05$ ) better in the ketamine group.

**Conclusions:** Iv ketamine and peritonsillar infiltration with bupivacaine are safe and effective as part of a multimodal regime in reducing post-tonsillectomy pain.

4. **Pestieau, et al.** "Prolonged perioperative infusion of low-dose ketamine does not alter opioid use after pediatric scoliosis surgery." *Pediatric Anesthesia* 24.6 (2014): 582-590.

**Background:** Opioid consumption after posterior spinal fusion is known to be high and often exceeds those reported in other major surgical procedures. A number of clinical trials provide evidence that the perioperative use of subanesthetic doses of ketamine reduces pain and opioid requirements in some surgical procedures, but the effect of prolonged perioperative low-dose ketamine infusion in patients undergoing posterior spinal fusion for pediatric scoliosis surgery is unknown.

**Objective:** To test the hypothesis that a 72-h perioperative low-dose ketamine infusion would decrease opioid use in pediatric patients undergoing posterior spinal fusion.

**Methods:** In a double-blind prospective controlled trial, patients undergoing posterior spinal fusion for scoliosis were randomized to receive perioperative low-dose ketamine or placebo control. Patients received general anesthesia, intraoperative remifentanyl, and morphine patient-controlled analgesia postoperatively. Daily opioid consumption, self-reported pain scores, and sedation scores were measured.

**Results:** Fifty-four patients were enrolled and 50 completed the study. Contrary to our hypothesis, ketamine- and control-treated patients had similar postoperative opioid use, pain scores, and sedation scores measurements. In contrast, ketamine-

treated patients required less intraoperative remifentanyl compared with control (mean 2.9 mg vs. 4 mg,  $P = 0.0415$ ). Number of vertebrae instrumented, time between end-of-surgery and 24 h assessment, or remifentanyl doses did not impact on postoperative opioid use. Over 96-h postoperatively, morphine-equivalent consumption was lower ( $-0.40$ ,  $P = 0.006$ ) and sedation score was higher ( $0.47$ ,  $P = 0.0211$ ) in male patients, compared with female patients.

**Conclusions:** These findings do not support the use of perioperative low-dose ketamine to decrease opioid use in children with scoliosis undergoing posterior spinal fusion.

## DEXMEDETOMIDINE

### Systematic reviews / meta-analyses

1. Schnabel et al. "Efficacy and safety of intraoperative dexmedetomidine for acute postoperative pain in children: a meta-analysis of randomized controlled trials." *Pediatric Anesthesia* 23.2 (2013): 170-179.

#### Background

Aim of the current meta-analysis was to assess the effects of intraoperative dexmedetomidine on postoperative pain, analgesic consumption, and adverse events in comparison with placebo or opioids in children undergoing surgery.

#### Methods

This meta-analysis was performed according to the recommendations of the PRISMA statement and the Cochrane collaboration. For dichotomous and continuous outcomes of efficacy and adverse events, the Revman® (The Nordic Cochrane Centre, Copenhagen, Denmark) statistical software was used to calculate relative risk (RR), mean difference (MD), and 95% confidence intervals (CI).

#### Results

We included 11 randomized controlled trials – 434 children received dexmedetomidine, 440 received control. In comparison with placebo, children receiving dexmedetomidine showed a reduced RR for postoperative opioids (0.4; 95% CI: 0.26–0.62;  $P < 0.00001$ ) and postoperative pain (0.51; 95% CI: 0.32–0.81;  $P = 0.004$ ). Similar results were obtained for the comparison with intraoperative opioids: reduced RR for postoperative pain (0.49; 95% CI: 0.25–0.94;  $P = 0.03$ ) and the need for postoperative opioids (0.77; 95% CI: 0.60–1.09;  $P = 0.05$ ).

#### Conclusions

This meta-analysis revealed a lower risk for postoperative pain and the need for postoperative opioids following intraoperative dexmedetomidine in comparison with placebo or opioids in children undergoing surgery; however, the influence of dexmedetomidine on postoperative opioid consumption is less clear. Although there were only a limited number of adverse events, further studies focusing on procedure specific dexmedetomidine dosing and adverse events are urgently needed.

5. He, Xing-Ying, et al. "Dexmedetomidine versus morphine or fentanyl in the management of children after tonsillectomy and adenoidectomy: a meta-analysis

of randomized controlled trials." *Annals of Otology, Rhinology & Laryngology* 122.2 (2013): 114-120.

**Objectives:** The primary objective of this review was to evaluate and compare the efficacy and safety of dexmedetomidine hydrochloride with the efficacy and safety of opioids for postoperative management of children after tonsillectomy and adenoidectomy.

**Methods:** We searched the Cochrane Central Register of Controlled Trials (Central) in the Cochrane Library (most recent issue), Medline (1966 to date) through Ovid, Embase (1980 to date), and Web of Science (1945 to date). The number of patients who required rescue analgesics (morphine or fentanyl) in the postanesthesia care unit, the number of patients with emergence agitation, the number of patients with postoperative nausea and vomiting, the time to eye-opening in response to verbal stimuli, and the time to extubation were analyzed.

**Results:** We included 5 trials, consisting of 482 patients in total. There were no significant differences in the number of patients who required rescue analgesics in the postanesthesia care unit, the number of patients with emergence agitation, the number of patients with postoperative nausea and vomiting, or the time to extubation between patients who received dexmedetomidine and those who received opioids. Compared with opioids, dexmedetomidine was associated with a significantly decreased time to eye-opening in response to verbal stimuli (mean difference, -2.11 minutes; 95% confidence interval, -3.32 to -0.91 minutes;  $p = 0.0006$ ).

**Conclusions:** Intraoperative use of dexmedetomidine was as effective as opioids in preventing postoperative pain and emergence agitation in children who had undergone tonsillectomy and adenoidectomy.

## RCT

1. **Olutoye**, Olutoyin A., et al. "The effect of intraoperative dexmedetomidine on postoperative analgesia and sedation in pediatric patients undergoing tonsillectomy and adenoidectomy." *Anesthesia & Analgesia* 111.2 (2010): 490-495.

**BACKGROUND:** We designed a prospective, double-blind, randomized controlled study to determine the effects of intraoperative dexmedetomidine on postoperative recovery including pain, sedation, and hemodynamics in pediatric patients undergoing tonsillectomy and adenoidectomy.

**METHODS:** 109 patients were randomized to receive a single intraoperative dose of dexmedetomidine 0.75 µg/kg, dexmedetomidine 1 µg/kg, morphine 50 µg/kg, or morphine 100 µg/kg over 10 minutes after endotracheal intubation.

**RESULTS:** There were no significant differences among the 4 groups in patient demographics, ASA physical status, postoperative opioid requirements, sedation scores, duration of oxygen supplementation in the postanesthetic care unit, and time to discharge readiness. The median time to first postoperative rescue analgesic was similar in patients receiving dexmedetomidine 1 µg/kg and morphine 100 µg/kg, but significantly longer compared with patients receiving dexmedetomidine 0.75 µg/kg or morphine 50 µg/kg ( $P < 0.01$ ). In addition, the number of patients requiring >1 rescue analgesic dose was significantly higher in the dexmedetomidine 0.75 µg/kg group compared with the dexmedetomidine 1 µg/kg and morphine 100 µg/kg groups, but not

the morphine 50 µg/kg group. Patients receiving dexmedetomidine had significantly slower heart rates in the first 30 minutes after surgery compared with those receiving morphine ( $P < 0.05$ ). There was no significant difference in sedation scores among the groups.

**CONCLUSIONS:** The total postoperative rescue opioid requirements were similar in tonsillectomy patients receiving intraoperative dexmedetomidine or morphine. However, the use of dexmedetomidine 1 µg/kg and morphine 100 µg/kg had the advantages of an increased time to first analgesic and a reduced need for additional rescue analgesia doses, without increasing discharge times.

2. Patel, et al. "Dexmedetomidine infusion for analgesia and prevention of emergence agitation in children with obstructive sleep apnea syndrome undergoing tonsillectomy and adenoidectomy." *Anesthesia & Analgesia* 111.4 (2010): 1004-1010.

**BACKGROUND:** Dexmedetomidine, a specific  $\alpha_2$  agonist, has an analgesic-sparing effect and reduces emergence agitation. We compared an intraoperative dexmedetomidine infusion with bolus fentanyl to reduce perioperative opioid use and decrease emergence agitation in children with obstructive sleep apnea syndrome undergoing adenotonsillectomy (T&A).

**METHODS:** 122 patients with obstructive sleep apnea syndrome undergoing T&A, ages 2 to 10 years, completed this prospective, randomized, U.S. Food and Drug Administration–approved study. After mask induction with sevoflurane, group D received IV dexmedetomidine 2 µg · kg<sup>-1</sup> over 10 minutes, followed by 0.7 µg · kg<sup>-1</sup> · h<sup>-1</sup>, and group F received IV fentanyl bolus 1 µg · kg<sup>-1</sup>. Anesthesia was maintained with sevoflurane, oxygen, and nitrous oxide. Fentanyl 0.5 to 1 µg · kg<sup>-1</sup> was given to subjects in both groups for an increase in heart rate or systolic blood pressure 30% above preincision values that continued for 5 minutes. Observers in the postanesthesia care unit (PACU) were blinded to treatment groups. Pain was evaluated using the objective pain score in the PACU on arrival, at 5 minutes, at 15 minutes, then every 15 minutes for 120 minutes. Emergence agitation was evaluated at the same intervals by 2 scales: the Pediatric Anesthesia Emergence Delirium scale and a 5-point scale described by Cole. Morphine (0.05 to 0.1 mg · kg<sup>-1</sup>) was given for pain (score >4) or severe agitation (score 4 or 5) lasting more than 5 minutes.

**RESULTS:** In group D, 9.8% patients needed intraoperative rescue fentanyl in comparison with 36% in group F ( $P = 0.001$ ). Mean systolic blood pressure and heart rate were significantly lower in group D ( $P < 0.05$ ). Minimum alveolar concentration values were significantly different between the 2 groups ( $P = 0.015$ ). The median objective pain score was 3 for group D and 5 for group F ( $P = 0.001$ ). In group D, 10 (16.3%) patients required rescue morphine, in comparison with 29 (47.5%) in group F ( $P = 0.002$ ). The frequency of severe emergence agitation on arrival in the PACU was 18% in group D and 45.9% in group F ( $P = 0.004$ ); at 5 minutes and at 15 minutes, it was lower in group D ( $P = 0.028$ ). The duration of agitation on the Cole scale was statistically lower in group D ( $P = 0.004$ ). In group D, 18% of patients and 40.9% in group F had an episode of SPO<sub>2</sub> below 95% ( $P = 0.01$ ).

**CONCLUSIONS:** An intraoperative infusion of dexmedetomidine combined with inhalation anesthetics provided satisfactory intraoperative conditions for T&A without adverse hemodynamic effects. Postoperative opioid requirements were

significantly reduced, and the incidence and duration of severe emergence agitation was lower with fewer patients having desaturation episodes.

## CLONIDINE

### RCT

1. **Reimer, et al.** "The effectiveness of clonidine as an analgesic in paediatric adenotonsillectomy." Canadian journal of anaesthesia 45.12 (1998): 1162-1167.

To compare the analgesic effects of preoperative oral clonidine with intraoperative intravenous fentanyl in children undergoing tonsillectomy or adenotonsillectomy.

**METHODS:** This randomized, controlled, double-blind study of 36 ASA I-II children, age 7-12 yr undergoing adenotonsillectomy was conducted at a tertiary care paediatric teaching hospital. Either 4 micrograms.kg-1 clonidine po was given 60-90 min preoperatively or 3 micrograms.kg-1 fentanyl i.v. was given intraoperatively. Postoperatively visual analog pain scores (VAS) were recorded at rest and on swallowing every 10 min for the first 30 min and then every 15 min for two hours. Morphine 0.05 mg.kg-1 i.v. was given for VAS > or = 5. If > 3 doses were required, 1.5 mg.kg-1 codeine po and 20 mg.kg-1 acetaminophen po were given. Sedation and anxiety scores were recorded preoperatively. Haemodynamic changes, blood loss, recovery scores, and the incidence of vomiting, hypotension, and airway obstruction were recorded.

**RESULTS:** Children who received clonidine had a higher incidence of preoperative sedation (63%) than those receiving fentanyl (6%). Preinduction mean arterial pressure was lower in the clonidine group but required no intervention. VAS scores were similar throughout the observation period. There was no difference either in the number of morphine or codeine rescue doses administered or in the incidence of side effects.

**CONCLUSION:** Oral clonidine is an effective analgesic and sedative for children undergoing tonsillectomy or adenotonsillectomy.

## GABAPENTIN / PREGABALIN

### RCT

1. **Rusy, Lynn M., et al.** "Gabapentin use in pediatric spinal fusion patients: a randomized, double-blind, controlled trial." Anesthesia & Analgesia 110.5 (2010): 1393-1398.

**BACKGROUND:** Gabapentin has opioid-sparing effects in adult surgical patients, but no reported studies have involved children and adolescents. In a double-blind, randomized, controlled trial, we examined whether gabapentin decreases postoperative opioid consumption for pediatric spinal fusion patients with idiopathic scoliosis.

**METHODS:** Patients, aged 9 to 18 years, received preoperative gabapentin (15 mg/kg, treatment) or placebo. Anesthesia was standardized. After surgery, all patients received standardized PCA opioid and continued on either gabapentin (5 mg/kg) or

placebo 3 times per day for 5 days. Opioid use was calculated in mg/kg/time intervals. Pain scores and opioid side effects were recorded.

**RESULTS:** Data from 59 patients (30 placebo and 29 gabapentin) did not differ in demographics. Total morphine consumption (mg/kg/h  $\pm$  SD) was significantly lower in the gabapentin group in the recovery room ( $0.044 \pm 0.017$  vs  $0.064 \pm 0.031$ ,  $P = 0.003$ ), postoperative day 1 ( $0.046 \pm 0.016$  vs  $0.055 \pm 0.017$ ,  $P = 0.051$ ), and postoperative day 2 ( $0.036 \pm 0.016$  vs  $0.047 \pm 0.019$ ,  $P = 0.018$ ). In addition, gabapentin significantly reduced first pain scores in the recovery room ( $2.5 \pm 2.8$  vs  $6.0 \pm 2.4$ ,  $P < 0.001$ ) and the morning after surgery ( $3.2 \pm 2.6$  vs  $5.0 \pm 2.2$ ,  $P < 0.05$ ), but otherwise pain scores were not significantly different. There were no differences in opioid-related side effects over the course of the study.

**CONCLUSION:** Perioperative oral gabapentin reduced the amount of morphine used for postoperative pain after spinal fusion surgery, but not overall opioid-related side effects. Initial pain scores were lower in the treatment group. Perioperative use of gabapentin seems to be an effective adjunct to improve pain control in the early stages of recovery in children and adolescents undergoing spinal fusion.