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IMMEDIATE RESCUE DESIGNS IN PEDIATRIC ANALGESIC TRIALS: A SYSTEMATIC REVIEW AND META ANALYSIS

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Abstract

Background—Designing analgesic clinical trials in pediatrics requires a balance between scientific, ethical and practical concerns. A previous consensus group recommended immediate-rescue designs using opioid sparing as a surrogate measure of analgesic efficacy. We summarize the performance of rescue analgesic designs in pediatric trials of four commonly used classes of analgesics: opioids, nonsteroidal antiinflammatory drugs, acetaminophen, and local anesthetics.

Methods—Medline, Embase, CINAHL, The Cochrane Library and Web of science were searched in April 2013. The 85 studies selected were randomized or controlled clinical trials using immediate rescue paradigms in postoperative pain settings. A random effects meta-analysis was used to synthesize predefined outcomes using Hedges' G. Difference between the means of the treatment arms were also expressed as a percentage of the corresponding value in the placebo group (placebo-treatment/placebo). Distributions of pain scores in study and control groups and relationships between opioid sparing and pain scores were examined.

Results—For each of the four study drug classes, significant opioid sparing was demonstrated in a majority of studies by one or more of the following endpoints: (1) total dose (mg/kg/h), (2) percentage of children requiring rescue medication and (3) time to first rescue medication (minutes). Pain scores averaged 2.4/10 in study groups, 3.4/10 in control groups.

Conclusions—Opioid sparing is a feasible pragmatic endpoint for pediatric pain analgesic trials. This review serves to guide future research in pediatric analgesia trials, which could test whether some specific design features may improve assay sensitivity while minimizing the risk of unrelieved pain.

Introduction

Clinical trials to evaluate efficacy or effectiveness of analgesics pose ethical and scientific challenges for all ages, but especially for children. For sound scientific reasons, the standard

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approach to adult acute pain trials involves enrollment of patients with moderate to severe pain, randomization between active drug and placebo, and comparison of pain scores over time between active and placebo subjects as the primary measure of analgesic efficacy (fig. 1A).¹ The ethical basis of this approach rests on adults making informed decisions to bear the risk of assignment to a placebo group and potentially to experience continued pain during the study period. Comparative effectiveness trials involving no placebo group are relevant for guiding clinical decision-making, but they pose statistical problems for establishing drug efficacy.²

For children, as vulnerable subjects, there is greater ethical concern about a significant risk of unrelieved pain in clinical trials, particularly where there are existing effective treatments. For ethical and practical reasons, pediatric analgesic trials have proceeded slowly. The U.S. Congress, the Food and Drug Administration (FDA), and the European Union have generated incentives for pharmaceutical companies to test analgesics in children, and some funding mechanisms *via* the FDA and the National Institutes of Health have supported a small number of investigator-initiated pediatric trials for off-patent analgesics that lack commercial incentives.³ Despite these initiatives, enrollment rates in pediatric analgesic trials have been very low.⁴

In November 2010, an expert consensus group was convened by the Anesthetic, Analgesic and Addiction Drugs section of the FDA to address pediatric analgesic trial design issues. Recommendations from this group were published in *Pediatrics* in 2012.¹ One prominent recommendation was to regard rescue-analgesic sparing as a pragmatic surrogate primary endpoint in pediatric analgesic trials. In order to maintain the scientific advantages of the traditional adult design, subjects could still be blinded and randomized between study drug and placebo. By providing immediate access to incremental rescue analgesia, especially *via* patient-controlled analgesia (PCA) or nurse-controlled analgesia (NCA) pumps, we expected that these designs would reduce the odds that subjects, especially those randomized to placebo, would experience unrelieved severe pain (figs. 1B and C). This recommendation was based on committee members' opinions and informal review of a small number of successful trials, but not on any systematic review or quantitative analysis.

With this background, we now attempt a systemic review and quantitative analysis of rescue analgesic designs in pediatric trials of four commonly used classes of analgesics for acute pain: opioids, nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, and local anesthetics. Our hypotheses were: (1) immediate opioid rescue designs provide reasonable assay sensitivity as pragmatic surrogate measures of analgesia efficacy, (2) surrogate efficacy effect sizes vary with drug class and study design, choice of opioid sparing endpoints, method of rescue analgesic administration, and type of surgery, and (3) subjects randomized to either study drug or control/placebo groups with these designs had acceptably low mean pain scores. (Additional technical aspects and details relevant to researchers in the field can be found in Supplemental Digital Content 1).

Materials and Methods

The search strategy is described in detail in Section A1 of Supplemental Digital Content 1

Selection Criteria—Studies were included if they met the following criteria: (1) randomized or controlled clinical trial; (2) children and adolescents aged 18 yr; (3) use of immediate rescue paradigms; (4) assessed rescue medication and/or pain scores in postoperative pain setting.

For the purpose of this study, we included papers only if they (1) included placebo or control groups; (2) used intravenous (IV) opioids as rescue medication; (3) used either a) opioids, b) NSAIDs, c) acetaminophen, or d) local anesthetics as the “study drug,” which was tested for efficacy against a placebo or other control.

We chose to evaluate the following three analgesic sparing outcomes: (a) rescue opioid usage (mg/kg/h), (b) percentage of subjects requiring rescue medication or (c) time to first rescue medication (minutes). No language restrictions were applied. In calculating rescue opioid usage, opioids were converted to morphine equivalents.^{*} In assessing the hourly usage, we chose the shortest reported timeframe over an hour and divided the morphine equivalent by this timeframe. For papers reporting pain scores, we standardized all the pain scores to a 0-10 scale.^{5, 6}

Data Synthesis and Statistical Analysis—Data were extracted independently by two reviewers (J.K. and C.D.). Inconsistencies were resolved in consensus meetings. Additional study variables were extracted and tabulated, including: age range of patients; sample sizes; type(s) of surgery; dose regimes for study drugs and rescue opioid, method of pain assessment; criteria for opioid administration; and duration of follow-up. Each included study was graded for quality and scored using the Jadad criteria.⁷

Two methods of assessing opioid sparing were used. First, we used a meta-analytic approach. We estimated Hedge’s G and the 95% confidence interval (CI) between the study drug and control groups.⁸ Data management and calculations were performed using Comprehensive Meta-Analysis, version 2.0.[†] Since considerable heterogeneity was expected, all analyses were performed with a random-effects model.⁹ We assessed the presence of publication bias using the fail-safe N method.¹⁰ To assess heterogeneity between studies, Q-statistics were calculated. A statistically significant Q indicates a heterogeneous distribution of odds ratios between studies, meaning that systematic differences, possibly influencing the results, are present.¹¹ In addition, the degree of inconsistency was quantified by the I² statistic, which measures the percentage of variation across studies that is due to heterogeneity rather than chance.¹² A 0% value means no heterogeneity, and higher values represent an increase in heterogeneity. Generally, heterogeneity is categorized at 25% (low), 50% (moderate), and 75% (high). Given the large number of possible factors influencing the standardized effect size, we chose not to conduct

^{*} www.globalrph.com/narcoticonv.htm. Last accessed June, 27, 2014.

[†] www.meta-analysis.com. Last accessed June, 27, 2014.

any sensitivity analyses to explain the heterogeneity, except for subgroup analyses with regard to type of surgery to assess its influence on assay sensitivity and choice of outcome.

Secondly, mean opioid sparing by the study drug was expressed as percentage (placebo—study/placebo).¹³ This metric is analogous to use of percent maximum possible effect in pharmacologic studies.¹⁴

A third approach to data synthesis explored the distribution of pain scores in subjects randomized to study drug or control conditions. A “perfect rescue paradigm” should in theory result in low and nearly equal pain scores in both active and placebo groups (fig. 1C).¹ We wanted to evaluate the degree to which this aim is achieved in practice and to depict this balance between assay sensitivity and potential for unrelieved pain in control subjects. To do this we plotted each of these opioid-sparing endpoints against the mean pain scores for subjects in the control/placebo group. We refer to the relationship between these opioid sparing endpoints and the pain in the controls as the “efficacy-burden relationship” for each study. This relationship is meant to assess both how well a study performed in terms of effect size (opioid sparing between test drug and control groups) and how severe the pain was in the group that was randomized not to receive the test drug.

Results

Study Selection

The study selection procedure is summarized in figure 2. The summary of characteristics of the studies is shown in table 1.¹⁵⁻⁹⁸ All included studies were controlled blinded trials with quality scores of 3–5 on the Jadad scale.⁷ Selected results of publication bias and tests of heterogeneity, as well as efficacy measures of the individual studies and the graphical representation of the efficacy-burden relationship are presented in tables 2 and 3 in Section A3 of Supplemental Digital Content 1.

1. Opioids as the Study Drug—Details of the 33 included papers (48 active study drug arms) can be seen in Section A2 of Supplemental Digital Content 1. Two special cases are noteworthy. Trials using intrathecal or epidural opioids as the study drug gave the largest effect sizes and highest efficacy to burden relationships. Intrathecal and epidural opioids, especially morphine and hydromorphone, have markedly higher potency and duration of action compared to the same opioids given systemically. Conversely, when the ultra-short acting opioid remifentanyl³¹ was given intraoperatively as study drug, it produced a significant *negative* postop opioid sparing effect, *i.e.*, greater opioid use in patients receiving study drug *versus* placebo, consistent with previous animal and adult human studies showing remifentanyl’s potential to induce hyperalgesia and acute tolerance.⁹⁹

1.1. Total opioid usage (mg/kg/h): This endpoint was recorded for 32 study drug arms among 22 studies including a wide range of surgeries.

Significant standardized mean differences (reductions in opioid use) were found for 16/28 active study drug arms (Hedges’ $g = -0.84$; 95% CI -1.22 to -0.47 , $p < 0.001$) (fig. 3). Subgroup analyses found a highest effect in scoliosis surgeries (Hedges’ $g = -3.23$; 95% CI

–5.01 to –1.45, $p < 0.001$), intermediate effect sizes in thoracic and cardiac surgeries, (Hedges' $g = -0.90$; 95% CI –1.25 to –0.55, $p < 0.001$), and very modest or insignificant effects in adenotonsillectomies (Hedges' $g = -0.47$; 95% CI –1.16 to 0.22, $p = 0.18$) and urological/abdominal procedures (Hedges' $g = -0.17$; 95% CI –0.43 to 0.09, $p = 0.20$). Significant percent reductions in opioid use were found in 17/32 study drug arms. Intrathecal morphine²⁵ after spinal fusion showed the highest sparing effect and efficacy-burden relationship.

1.2. Percentage requiring rescue medication: This endpoint was recorded for 21 study drug arms among 16 studies. It was used commonly for ambulatory/short-stay surgeries, including urologic surgeries and adenotonsillectomies, not at all for scoliosis surgery or thoracic surgery.

Percentage requiring rescue medication showed significant standardized mean difference from control in 11/21 treatment arms (Hedges' $g = -0.83$; 95% CI –1.15 to –0.52, $p < 0.001$). Subgroup analyses showed that the effect magnitude is higher for the adenotonsillectomies (Hedges' $g = -0.99$; 95% CI –1.53 to –0.44, $p < 0.001$), (driven by one paper¹⁵) and smaller for urological procedures (Hedges' $g = -0.42$; 95% CI –0.89 to –0.05, $p = 0.08$). Ten out of 21 study drug arms demonstrated significant percent opioid sparing effect

1.3. Time to first rescue medication (minutes): This endpoint was recorded for 20 study drug arms among 15 studies. It was used commonly for ambulatory/short-stay surgeries, as well as in one open-heart surgery and one spinal fusion surgery.

Time to first rescue medication shows a strong mean difference in favor of the study drug *versus* control in 11/19 treatment arms (Hedges' $g = -1.64$; 95% CI –2.43 to –0.84, $p < 0.001$). Subanalyses by the type of surgery found small differences in the magnitude of the effect for adenotonsillectomies (Hedges' $g = -1.44$; 95% CI –2.80 to –0.09, $p = 0.04$), and urological procedures (Hedges' $g = -1.86$; 95% CI –3.96 to –0.25, $p = 0.08$). Thirteen out of 20 treatment arms demonstrated significant percentage opioid sparing effect. Overall, time to first rescue seems to be an outcome with high assay sensitivity in single dose opioid studies.

2. NSAID as the Study Drug—Details of the 29 included papers (38 active study drug arms) can be seen in Section A2 of Supplemental Digital Content 1. The largest number of studies involved adenotonsillectomies (13 papers). Overall the degree of opioid sparing effect of NSAIDs varied considerably.

2.1. Total opioid usage (mg/kg/h): This endpoint was recorded for 21 study drug arms among 20 studies. It was used commonly for adenotonsillectomies but also for one study involving idiopathic scoliosis surgery and one involving other types of orthopedic surgery. Significant standardized mean differences (reductions in opioid use) were found for 10/15 active study drug arms (Hedges' $g = -0.92$; 95% CI –1.32 to –0.52, $p < 0.001$) (fig. 4). The effect magnitude was found to be slightly higher in tonsillectomy surgeries than the general mean (Hedges' $g = -1.15$; 95% CI –1.92 to –0.38, $p = 0.003$). No other type of surgery

could be evaluated separately due to the small number of studies. Significant percent reductions in opioid use were found in 11/21 study drug arms.

2.2. Percentage needing rescue medication: This endpoint was recorded for 26 study drug arms among 18 studies. It was used commonly for adenotonsillectomies. Percentage requiring rescue medication showed significant standardized mean difference from control for 8/18 treatment arms (Hedges' $g = -0.52$; 95% CI -0.66 to -0.38 , $p < 0.001$). Ten out of 17 papers demonstrated significant percent opioid sparing effect.

2.3. Time to first rescue medication (minutes): This endpoint was recorded for 15 study drug arms among 11 studies. It was used commonly for ambulatory/short-stay surgeries, mainly for adenotonsillectomies. Time to first rescue medication shows a moderate mean difference in favor of the study drug *versus* control in 1/4 treatment arms (Hedges' $g = -0.32$; 95% CI -0.53 to -0.10 , $p = 0.004$). Since there were only four studies that could be included, no subgroup analyses could be conducted. Only 2/11 treatment arms demonstrated significant percent opioid sparing effect and one paper had a slightly negative, yet nonsignificant sparing effect.⁵³

Overall, total opioid dose in mg/kg/h seems to be the opioid sparing outcome with the highest assay sensitivity for NSAID trials.

3. Acetaminophen as the Study Drug—Details of the 11 included papers (17 active study drug arms) can be seen in Section A2 of Supplemental Digital Content 1. General conclusions were: (1) rectal acetaminophen showed greatest effect size in all three measures at doses of 40 mg/kg or 60 mg/kg, and variable effects at lower doses; (2) only one oral and two intravenous acetaminophen studies met full inclusion criteria for this review; effect size using intravenous acetaminophen was strongly influenced by study methodology.

3.1. Total opioid usage (mg/kg/h): This endpoint was recorded for 13 study drug arms among 9 studies. It was used commonly for ambulatory/short-stay surgeries. Significant standardized mean differences (reductions in opioid use) were found for 4/8 active study drug arms (Hedges' $g = -2.12$; 95% CI -3.50 to -0.75 , $p = 0.002$) (fig. 5), though this was heavily influenced by the effectiveness of 40 mg/kg and 60mg/kg in the study by Korpela *et al.*⁷⁹ Significant percent reductions in opioid use were found in 4/13 study drug arms.

3.2. Percentage needing rescue medication: This endpoint was recorded for 10 study drug arms among 6 studies. It was used commonly to evaluate rectal acetaminophen in ambulatory/short-stay surgeries. Percentage requiring rescue medication showed significant standardized mean difference from control in 5/10 treatment arms (Hedges' $g = -0.82$; 95% CI -1.20 to -0.44 , $p < 0.001$). Noteworthy, the effects sizes found in Korpela *et al.*⁷⁹ were much smaller compared to the previous outcome and similar to the group mean. Four of six study drug arms demonstrated significant percent opioid sparing effect.

3.3. Time to first rescue medication (minutes): This endpoint was recorded for five study drug arms among four studies. Time to first rescue medication shows no effect in favor of the study drug *versus* control in any arms (Hedges' $g = -0.07$; 95% CI -0.32 to 0.19 , $p =$

0.60). Since there were only four studies that could be included, no subgroup analyses could be conducted. No study found any percent differences between the study drug and control, including even those finding significant differences for 40 mg/kg rectal acetaminophen when assessing total rescue opioid usage.^{59, 73}

Overall, for acetaminophen trials, total opioid dose in mg/kg/h seems to be the outcome with the highest assay sensitivity, yet due to low number of studies, these results should be considered preliminary.

4. Local Anesthetics as the Study Drug—Details of the general characteristic of the 20 included papers (27 active study drug arms) can be seen in Section A2 of Supplemental Digital Content 1.

Total opioid usage (mg/kg/h): This endpoint was recorded for 18 study drug arms among 13 studies. Half of the papers administered the local anesthetics *via* infiltration and the other half *via* peripheral block or epidural. Significant standardized mean differences (reductions in opioid use) were found for 6/14 active study drug arms (Hedges' $g = -0.72$; 95% CI -1.18 to -0.27 , $p = 0.002$) (fig. 6). Abdominal surgeries (including inguinal hernia procedures) showed a nonsignificant effect (Hedges' $g = -0.40$; 95% CI -1.01 to 0.20 , $p = 0.19$). No other type of surgery could be evaluated due to the low number of studies. Single dose studies showed significant standardized mean differences (Hedges' $g = -1.16$ 95% CI: -1.85 to -0.47 , $p = 0.001$) while studies evaluating continuous infusion showed none (Hedges' $g = -0.16$; 95% CI: -0.55 to 0.22 , $p = 0.41$). Significant percent reductions in opioid use were found in 10/18 study drug arms.

4.1. Percentage needing rescue medication: This endpoint was recorded for 15 study drug arms among 10 studies. It was used most commonly for abdominal/urological surgeries. Percentage requiring rescue medication showed significant standardized mean difference from control for 11/15 treatment arms (Hedges' $g = -1.19$; 95% CI -1.56 to -0.82 , $p < 0.001$). Abdominal surgeries (including inguinal hernia procedures) were very close to the mean value (Hedges' $g = -1.21$; 95% CI -1.72 to -0.70 , $p < 0.001$). No other type of surgery could be evaluated due to the small number of studies. Eight of 15 study drug arms demonstrated significant percent opioid sparing effect.

4.2. Time to first rescue medication (minutes): This endpoint was recorded for 12 study drug arms among 10 studies. It was used most commonly for abdominal/urological surgeries. Time to first rescue medication shows a strong difference in favor of the study drug versus control in 9/10 treatment arms (Hedges' $g = -1.55$; 95% CI -2.11 to -0.99 , $p < 0.001$). In subgroup analyses, the urological and abdominal procedures show a smaller magnitude of the effect (Hedges' $g = -1.05$; 95% CI -1.45 to -0.65 , $p < 0.001$). Nine out of 12 treatment arms demonstrated significant percent opioid sparing effect.

Local anesthetic trials were highly variable. They involved wound infiltration (9/20 papers, two of those with continuous subcutaneous infusion), peripheral nerve blocks (5/20 papers), and epidural blocks (4/20 papers, only one of those with continuous infusion). Some involved single injection, others involved continuous infusions.

Pain Scores

Among the entire group of 85 clinical trials, 62 reported pain scores. Mean pain scores were 2.3 ± 1.5 in the study drug arms and 3.4 ± 1.2 in the control arms ($p < 0.001$). Eighteen trials used PCA or NCA, while 44 administered rescue analgesia by nurse-administered boluses. No statistical differences were found between PCA/NCA and nurse-administered rescue trials on pain scores in the study drug arms (2.5 ± 1.3 vs. 2.2 ± 1.6 ; $p = 0.43$) and in the control arms (3.4 ± 1.5 vs. 3.3 ± 2.1 ; $p = 0.84$). Studies using observational measures did not differ from those using self-report measures (3.6 ± 1.7 vs. 3.1 ± 2.1 ; $p = 0.25$). No trial using PCA/NCA had a mean pain score greater than five in either study arm or control arm.

A linear regression found no associations between pain scores in the control group and type of surgery, type of pain scale (objective vs. self-report), and PCA/NCA *versus* nurse-administered boluses.

Efficacy-burden relationships

When opioids were used as the study drug, a positive relationship was found between pain in the control group and time to first rescue medication ($\beta = 0.37$, $R^2 = 0.44$), a small relationship between pain in the control group and total opioid use ($\beta = 0.16$, $R^2 = 0.16$), but no relationship with the percentage requiring rescue medications ($\beta = 0.06$, $R^2 = 0.01$) (figs. 1 and 2 in Supplemental Digital Content 1, which depict the Efficacy-Burden relationship for opioids as the study drug). While time to rescue showed good assay sensitivity for opioid sparing, trials using this endpoint had higher pain scores in control groups compared to trials using the other primary opioid sparing endpoints.

When NSAIDs were used as the study drug, a positive strong relationship was found between pain in the control group and time to first rescue medication ($\beta = 0.70$, $R^2 = 0.25$), a small relationship between pain in the control group and percentage requiring rescue medications ($\beta = 0.18$, $R^2 = 0.025$), but no relationship with the total opioid use ($\beta = 0.12$, $R^2 = 0.01$) (figs. 7 and 8).

When acetaminophen was used as the study drug, no relationship was found between pain in the control group and percentage requiring rescue medications ($\beta = 0.007$, $R^2 = 0$), or total opioid use ($\beta = 0.06$, $R^2 = 0.0001$). Since only one study provided pain scores when looking at time to first rescue medication, no association could be assessed (figs. 3 and 4 in Supplemental Digital Content 1, which depict the Efficacy-Burden relationship for acetaminophen as the study drug).

When local anesthetics were used as the study drug, a positive relationship was found between pain in the control group and time to first rescue medication ($\beta = 0.53$, $R^2 = 0.53$), percentage requiring rescue medications ($\beta = 0.29$, $R^2 = 0.40$), and total opioid use ($\beta = 0.29$, $R^2 = 0.40$) (figs. 9 and 10).

Discussion

Our systematic review and quantitative analysis examined rescue analgesic designs in pediatric trials of four commonly used classes of analgesics for acute pain. We considered

these designs from the standpoint of usefulness as a surrogate measure of analgesic efficacy and from the standpoint of burden of unrelieved pain in the subjects, particularly in control groups.

Opioid Sparing as a Surrogate Measure of Analgesic Efficacy

While opioid sparing could be demonstrated in a high percentage of trials in this systematic review, the magnitude of rescue opioid sparing varied greatly. Some sources of variability in these trials appears due to: (1) the test drug (dose, bioavailability, intrinsic efficacy, time course of action relative to the timing of measurements), (2) type of opioid-sparing endpoint (mg/kg/h, time to rescue, percent of subjects needing rescue), (3) method of analysis (Hedges G vs. percent sparing), (4) type of surgery, and (5) a range of additional demographic variables. Despite an initial survey of almost 6,000 abstracts from pediatric analgesic trials using nested search terms, ultimately only 85 trials fit our inclusion criteria for quantitative analysis. Analysis indicated great heterogeneity in each of the five sources of variability. Based on this, recommendations can be only somewhat provisional.

We evaluated the three most common reported rescue-analgesic sparing outcomes: (1) total dose (mg/kg/h), (2) percentage of children requiring rescue medication and (3) time to first rescue medication (minutes). Variations in the design methodologies of the analgesic clinical trial influence the sensitivity for detecting differences in each of these outcomes, making it difficult to designate one of these outcomes as a gold standard for all studies. Total dose seems to be the outcome most often chosen. This parameter can be used in single dose or multiple doses trials. However, this outcome is susceptible to the nonlinear interactions between the study drug and the rescue medication. In addition, for a single dose study drug with strong efficacy but short duration of action, effect size magnitudes will depend on the time period chosen for recording between-group differences, and use of a long acting rescue opioid might wash out between group differences. One recent trial published after we completed the systematic review, used PCA *via* sufentanil as the rescue analgesic to evaluate thoracic paravertebral blockade for the Nuss operation for pectus excavatum. This study showed excellent opioid sparing, but also had high pain scores in the control group.¹⁰⁰ In future studies evaluating rescue opioids with relatively short context-sensitive half-times, we believe that it is important to permit escalation of dosing parameters in the setting of unrelieved pain. Time to first rescue medication appears useful in single dose studies (*e.g.*, nerve blocks, infiltrations) and allows us to have a more clear view of the primary effect of the study drug. However, this parameter appears less useful for very short duration study drugs or multiple dose trials. Finally, percentage requiring rescue medication can be useful in small procedures, when the pain scores and the time and amount of rescue medication needed are low.

Pain Scores, Burden on Control Subjects and Ethical Considerations

From an ethical standpoint, it was noteworthy that, among the 83 studies included in this review, the mean pain scores in the control arm were mild or moderate (averaging 3.4 out of 10 in a standardized scale), and only very rarely severe. PCA/NCA paradigms seem particularly effective for preventing high pain scores among children randomized to control groups.

Previous research indicates that, in routine clinical use, patients and nurses do not dose PCA or NCA, respectively, based solely on pain intensity, but dosing is based also on a range of other factors, including anticipation of future pain and on side-effects. In PCA/NCA trials, dosing was not titrated to give equal scores in the study drug and control groups, but rather mean pain scores were lower in the study drug arms ($p = 0.013$). Based on this, there is a potential for opioid sparing alone to underestimate the analgesic effect of a study drug. Future studies may consider the potential utility of composite efficacy measures based on both pain scores and opioid sparing.

Limitations

As with all quantitative systematic reviews, meta-analyses are only as good as the data that are reported and the description of methods in each study. Data of many studies could not be included due to lack of necessary information. In our meta-analysis, we included multiple treatment arms from a single study. We are aware that duplicating the number of patients in a control group between two comparisons may generate a unit-of-analysis error. This could have been avoided by either splitting the shared group resulting in a smaller sample size and including two or more comparisons, by combining groups to create pairwise comparisons, or by undertaking a multiple treatment analysis. However, the goal of our study was not to test a specific drug's efficacy in either the prevention or treatment of pain but to see if immediate rescue designs are feasible and usable outcomes in both these kinds of studies, over various types of surgeries and intervention drugs, and to consider the utility of different opioid sparing endpoints. It is clear that variability in study design, type of surgery, method of opioid delivery, duration of study drug administration, and reported outcome measures all impact on the likelihood and degree of positive findings and thus our quantitative results should be interpreted as exploratory.

Conclusions and Recommendations for Future Trials

Immediate rescue analgesic trials show reasonable assay sensitivity and tolerably low burden (low-moderate pain scores) for children following surgery. From a clinician's standpoint, opioid sparing matters only if it is associated with meaningful improvements in clinical outcome measures, including pain scores, reductions in side-effects such as nausea, vomiting, itching, bowel dysfunction, *etc.*, as well as in the time course of recovery, rehabilitation, and postoperative behavior. Acetaminophen, NSAIDs, spinal morphine, and a range of types of regional anesthesia are indeed effective at reducing systemic opioid use, but the degree of opioid sparing varies both with drug, dose, technique and type of surgery.

PCA/NCA paradigms seem ideal for more extensive surgeries, repeated dosing of the study drug, or trials involving long-acting study drugs. Surrogate efficacy measures are important for guiding analgesic prescribing in infants and children, but they are not the only outcome measures that are essential components of pediatric analgesic trials. As outlined by previous consensus groups, including the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials,¹⁰¹ measures of safety, side-effects, hospital stay, complications, behavioral measures, and functional recovery parameters are essential as well. The

combination of these elements will allow for ethical and feasible study designs in future pediatric analgesic trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A. Typical time course of pain scores for a double-blind, parallel-group, placebo-controlled, active comparator analgesic trial. Note that in general, requirement for rescue analgesia result in termination of pain score in for that subject. **B.** Idealized time course of hourly rescue dosing of a short – acting opioid. **C.** Idealized time course of the pain. Note that, depending on the dosing schedule for rescue analgesics, in some trials of this design, pain scores remain lower in the active group than in the placebo group. VAS – Visual analog scale. (Taken from Berde *et al.* 2012¹, with permission).

Figure 2.
Flow chart of literature search with summary of excluded and included studies.

Figure 3.

Forest plot for opioids as study drug. Expressed as Hedges' G score and 95% Confidence Intervals. Negative scores favors study drug over control. *Study included more than one active treatment arm.

Figure 4.

Forest plot for nonsteroidal anti-inflammatory drugs as study drug. Expressed as Hedges' G score and 95% Confidence Intervals. Negative scores favors study drug over control. *Study included more than one active treatment arm.

Figure 5. Forest plot for acetaminophen as study drug. Expressed as Hedges' G score and 95% Confidence Intervals. Negative scores favors study drug over control. *Study included more than one active treatment arm.

Figure 6.

Forest plot for local anesthetics as study drug. Expressed as Hedges' G score and 95% Confidence Intervals. Negative scores favors study drug over control. *Study included more than one active treatment arm.

Figure 7.

Efficacy – Burden relationship for nonsteroidal anti-inflammatory drugs as the study drug.

A. Rescue opioid usage (mg/kg/h) as the outcome. **B.** Percentage requiring rescue medication as the outcome. **C.** Time to first rescue medication (minutes) as the outcome. Opioid Sparing: placebo— study/placebo.

Figure 8. Nonsteroidal antiinflammatory drugs as the study drug. **A.** Rescue opioid usage (mg/kg/h) as the outcome. **B.** Percentage requiring rescue medication as the outcome. **C.** Time to first rescue medication (minutes) as the outcome. Colorless circles indicate studies without pain scores.

Figure 9.

Efficacy – Burden relationship for local anesthetics as the study drug. **A.** Rescue opioid usage (mg/kg/h) as the outcome. **B.** Percentage requiring rescue medication as the outcome. **C.** Time to first rescue medication (minutes) as the outcome. Opioid Sparing: placebo—study/placebo.

Figure 10. Local anesthetics as the study drug. **A.** Rescue opioid usage (mg/kg/h) as the outcome. **B.** Percentage requiring rescue medication as the outcome. **C.** Time to first rescue medication (minutes) as the outcome. Colorless circles indicate studies without pain scores.

Selected characteristics of included studies.

Table 1

Intervention drug			Intervention group			Control group			Outcome variables							
Source	Surgery	Name	Dose	Route	Mean age (years)		SD or range	Type of control	Mean age (years)		Total dose			Primary outcome	Pain Scale	
					N				N		SD or range	Rescue opioid	%			Mins
Opioids																
Ali (2008) ¹⁵	Tonsillectomy	Tramadol Dextromethorphan	1mg/kg IV	30	7.53	1.88	Placebo control	30	7.61	1.93	Meperidine	X		"Rescue" medication - number of requests	FACES	
			1mg/kg ORAL	30	7.46	1.85										
Anila (2006) ¹⁶	Tonsillectomy	Tramadol	1mg/kg IV	15	11.9	2.40	Placebo control	15	12.5	1.90	Fentanyl	X		"Rescue" medication - number of rescue	VAS	
Ayatollahi (2012) ¹⁷	Tonsillectomy	Tramadol	2mg/kg INFL	42	7.06	2.21	Placebo control	42	7.40	1.38	Fentanyl	X		No clearly stated	mCHEOPS	
Batra (2008) ¹⁸	Urological	Fentanyl Fentanyl Fentanyl	0.25mcg/kg IT	14	0.62	0.24	Add on	14	0.56	0.29	Fentanyl	X	X	"Rescue" medication - Time to first rescue	VAS	
			0.5mcg/kg IT 1mcg/kg IT	13 15	0.57 0.63	0.08 0.29										
Beau-Ljowski (1996) ¹⁹	Other surgeries	Meperidine	1mg/kg IM	25	4.10	2.60	Placebo control	28	4.20	3.00	Meperidine	X	X	No clearly stated	CHEOPS	
Campbell (1992) ²⁰	Urological	Fentanyl	1mcg/kg EPIDUR	17	5.30	3.30	Add on	17	4.60	3.80	Morphine	X	X	"Rescue" medication - % that need rescue	N/A	
Dawson (2001) ²¹	Tonsillectomy	Dextromethorphan	1mg/kg ORAL	19	7.02	1.98	Placebo control	21	7.75	2.70	Morphine	X		No clearly stated	N/A	
Doyle (1993a) ²²	Appendectomy	Morphine	20mcg/kg/hr IV	20	10.2	(6-12)	Placebo control	20	9.60	(6-12)	Morphine	X		No clearly stated	4 points self-report	
Doyle (1993b) ²³	Appendectomy	Morphine Morphine	4mcg/kg/hr IV 10mcg/kg/hr IV	15 15	10.4 10.3	(6.5–12.9) (7.2-12.4)	Placebo control	15	10.5	(8.70-12.1)	Morphine	X		No clearly stated	mCHEOPS	
Escherzhuber (2008) ²⁴	Scoliosis	Morphine Morphine	5mcg/kg IT 15mcg/kg IT	14 14	15.0 15.0	2.00 2.00	Control	14	15.0	1.00	Piritamide	X		No clearly stated	VAS	
Gall (2001) ²⁵	Spinal fusion	Morphine Morphine	2mcg/kg IT 5mcg/kg IT	10 10	17.0 15.0	3.00 2.00	Placebo control	10	15.0	4.00	Morphine	X	X	"Rescue" medication - total dose	VAS	
Gunesh (2008) ²⁶	Non-cardiac thoracic	Fentanyl	2mcg/ml EPIDUR	16	0.18	0.07	Add on	16	0.18	0.14	Nalbuphine	X	X	"Rescue" medication - total dose	FACES	
Hammer (2005) ²⁷	Open Heart	Morphine	7mcg/kg EPIDUR	20	2.37	1.46	Control	20	2.36	1.56	Fentanyl	X		Pain score	FACES	
Hasan (2004) ²⁸	Tympanomastoid	Dextromethorphan	1mg/kg ORAL	19	12.2	3.40	Placebo control	19	11.5	3.70	Morphine	X		"Rescue" medication - total dose	VAS	
Heiba (2012) ²⁹	Tonsillectomy	Tramadol	2mg/kg INFL	20	15.3	2.20	Placebo control	20	15.2	3.20	Pethidine	X	X	No clearly stated	VAS	
Kawaraguchi (2006) ³⁰	Urological	Fentanyl	1mcg/kg EPIDUR	17	4.00	(3-6.92)	Add on	18	4.30	(3.00-7.08)	Pentazocine	X	X	"Rescue" medication - Time to first rescue	CHEOPS	
Kim (2013) ³¹	Urological	Remifenutril Remifenutril Remifenutril	0.3mcg/kg/min IV	15	2.48	1.18	Placebo control	15	2.74	1.19	Remifenutril	X		"Rescue" medication - total dose	mCHEOPS	
			0.6mcg/kg/min IV 0.9mcg/kg/min IV	15 15	2.69 2.72	1.02 1.31										
Krane (1987) ³²	Other surgeries	Morphine	0.1mg/kg EPIDUR	15	7.70	NR	Control	15	7.80	NR	Morphine	X	X	"Rescue" medication - Time to first rescue	N/A	
Lawhorn (1994) ³³	Other surgeries	Butorphanol	40mcg/kg EPIDUR	10	8.50	5.30	Add on	10	8.60	4.70	Morphine	X		No clearly stated	N/A	
Lawhorn (1997) ³⁴	Urological	Butorphanol	30mcg/kg EPIDUR	100	4.09	2.57	Add on	100	3.97	2.37	Morphine	X	X	No clearly stated	N/A	
Mune (2011) ³⁵	Cleft palate repair	Fentanyl Pethidine	0.25mcg/kg BLOCK	15	16.4	NR	Add on	15	14.0	NR	Fentanyl		X	No clearly stated	N/A	
			0.25mcg/kg BLOCK	15	14.9	NR										
McDonnell (2008) ³⁶	Ideopathic Scoliosis	Morphine	100mcg/kg IV	18	14.8	1.70	Placebo control	19	14.5	1.90	Morphine	X		"Rescue" medication - total dose	N/A	

Intervention drug			Intervention group			Control group			Outcome variables				
Source	Surgery	Name	Dose	Route	Mean age (years)		SD or range	Type of control	Mean age (years)		SD or range	Total dose	
					N	N			N	N		Rescue opioid	%
Ozengiz (2001) ³⁷	Urological	Tramadol Morphine	2mg/kg EPIDUR 0.03mg/kg EPIDUR	38 40	6.85 6.97	1.80 1.76	Control	38	6.76	1.76	Morphine	X	X
Rosen (1989) ³⁸	Open Heart	Morphine	0.075mg/kg EPIDUR	16	2 to 12	NR	Placebo control	16	2 to 12	NR	Morphine	X	X
Rose (1999) ³⁹	Tonsillectomy	Dextromethorphan Dextromethorphan	0.5mg/kg ORAL 1mg/kg ORAL	19 19	7.80 7.90	1.70 1.60	Placebo control	19	7.90	1.60	Morphine	X	X
Sharma (2011) ⁴⁰	Other surgeries	Methadone Methadone Methadone	0.1mg/kg IV 0.2mg/kg IV 0.3mg/kg IV	10 10 11	14.0 13.0 14.0	2.00 2.00 2.00	Control	30	15.0	2.00	Morphine	X	
Suominen (2004) ⁴¹	Open Heart	Morphine	20mcg/kg IT	35	1.19	(0.01-16.7)	Control	36	1.19	(0.03-12.7)	Morphine	X	X
Suski (2010) ⁴²	Ideopathic Scoliosis	Dextromethorphan	30-45mg ORAL	30	15.9	2.40	Placebo control	30	16.5	2.70	Morphine	X	
Takkila (2003) ⁴³	Tonsillectomy	Remifentanyl	1mg/kg IV	25	3.83	2.08	Placebo control	25	2.92	1.83	Oxycodone	X	X
Ugur (2008) ⁴⁴	Tonsillectomy	Tramadol Tramadol	2mg/kg IM 2mg/kg INHL	15 15	8.20 8.40	1.70 1.60	Placebo control	15	8.50	2.10	Meperidine	X	
Umuroglu (2004) ⁴⁵	Tonsillectomy	Morphine Tramadol	0.1mg/kg IV 1.5mg/kg IV	15 15	7.13 6.06	2.51 2.08	Placebo control	15	6.96	2.08	Pethidine	X	X
Vitunen (2001) ⁴⁶	Tonsillectomy	Tramadol	2mg/kg IV	40	1 to 3	NR	Placebo control	40	1 to 3	NR	Pethidine	X	X
Watch (1992) ⁴⁷	Other surgeries	Morphine	0.1mg/kg IV	31	8.50	3.70	Placebo control	32	10.0	3.60	Morphine	X	
Non-steroidal anti-inflammatory drugs (NSAID)													
Adarsh (2012) ⁴⁸	Cleft palate repair	Diclofenac	1mg/kg RECTAL	30	2.80	1.73	Control	30	2.26	1.43	Fentanyl	X	X
Antila (2006) ⁴⁶	Tonsillectomy	Ketoprofen	2mg/kg IV	15	12.5	2.30	Placebo control	15	12.50	1.90	Fentanyl	X	
Beun-Lijewski (1996) ⁴⁹	Other surgeries	Ketonalac	0.75mg/kg IM	29	4.00	2.20	Placebo control	28	4.20	3.00	Meperidine	X	X
Bridge (2000) ⁴⁹	Strabismus	Ketonalac	3mg per eye OPHTHALM	17	5.25	(4.25-9.75)	Placebo control	13	6.67	(4.17-12.4)	Morphine	X	X
Dawson (1996) ⁵⁰	Cleft palate repair	Ketonalac	1mg/kg + 1mg/kg 0.5mg/kg QID	18	7 to 20	NR	Control	16	7 to 20	NR	Morphine	X	
Kokki (1994) ⁵¹	Elective surgery	Ibuprofen	40mg/kg/day RECTAL	40	2.42	1.11	Placebo control	41	2.78	1.32	Morphine	X	X
Kokki (1998) ⁵²	Tonsillectomy	Ketoprofen Ketoprofen Ketoprofen	0.3mg/kg IV 1mg/kg IV 3mg/kg IV	55 55 55	3.33 2.67 2.67	(1.5-6.17) (1.25-7.08) (1.25-6.00)	Placebo control	55	3.42	(1.25-6.58)	Fentanyl	X	X
Kokki (1999) ⁵³	Strabismus	Ketoprofen	1+1mg/kg IV	30	6.92	(4.17-9.33)	Placebo control	29	5.33	(3.83-7.83)	Fentanyl	X	X
Kokki (1999) ⁵⁴	Major surgery	Ketoprofen	1+4mg/kg IV	24	6.58	(1.58-14.8)	Placebo control	23	7.08	(1.25-14.4)	Sulfentanyl	X	
Kokki (2000) ⁵⁵	Tonsillectomy	Ketoprofen Ketoprofen	25mg/kg IV 25mg/kg RECTAL	42 42	3.67 2.75	(1.17-8.08) (1.42-2.25)	Placebo control	39	3.75	(1.17-6.08)	Fentanyl	X	X
Kokki (2001) ⁵⁶	Tonsillectomy (phase I) Tonsillectomy (phase III)	Ketoprofen Ketoprofen Ketoprofen	1+1mg/kg IV 0.3mg/kg IV 1mg/kg IV	54 33 29	3.25 3.50 3.25	1.92 1.75 2.17	Placebo control	45 35	3.33 4.00	1.92 2.25	Fentanyl Fentanyl	X X	
Kokki (2002) ⁵⁷	Tonsillectomy	Ketoprofen	0.5+3mg/kg preqx IV)5+3mg/kg postqx IV	47 42	10.0 12.0	1.00 3.00	placebo control	20	11.0	1.00	Oxycodone	X	

Intervention drug			Intervention group			Control group			Outcome variables					
Source	Surgery	Name	Dose	Route	Mean age (years)		SD or range	Type of control	Mean age (years)		Total dose			
					N	N			N	N	SD or range	Rescue opioid	%	Primary outcome
Kokki (2004) ⁵⁸	Strabismus	Ketoprofen	1+1mg/kg IV	27	7.92	2.92	Placebo control	29	7.17	3.00	Fentanyl	X	X	"Rescue" medication - number of doses
Korpela (2007) ⁵⁹	Tonsillectomy	Naproxen	10mg/kg ORAL	30	1.80	(0.70-6.20)	Placebo control	29	1.60	(0.80-5.90)	Fentanyl	X	X	"Rescue" medication - % that need rescue
Morton (1999) ⁶⁰	Appendectomy	Diclofenac	1mg/kg TID RECTAL	20	10.6	(6.00-13.0)	Control	20	10.15	(5-13)	Morphine	X		"Rescue" medication - total dose
Munro (2002) ⁶¹	Ideopathic scoliosis	Ketorolac	0.5mg/kg IV	20	14.1	1.20	Placebo control	15	13.9	1.30	Morphine	X		Pain score
Nikamie (1997) ⁶²	Tonsillectomy	Ketoprofen	1+1mg/kg IV	80	3.17	(1.00-9.25)	Placebo control	84	3.33	(0.83-7.92)	Fentanyl	X	X	"Rescue" medication - % that need rescue
Ozskin (2002) ⁶³	Tonsillectomy	Diclofenac	1mg/kg RECTAL	20	8.40	0.53	Control	20	8.90	0.45	Morphine	X		No clearly stated
Ryhänen (1994) ⁶⁴	Urological	Diclofenac	1mg/kg IM	70	3.80	1.70	Control	73	3.50	1.80	Petidine	X	X	No clearly stated
Rugye (2007) ⁶⁵	Pectus	Ketoprofen	1mg/kg IV	14	14.00	(13.0-15.0)	Placebo control	17	13.0	(10-15)	Morphine	X		"Rescue" medication - total dose
Sheeran (2004) ⁶⁶	Tonsillectomy	Refecoxib	0.5 mg/kg ORAL	23	7.20	1.80	Placebo control	22	7.60	2.20	Morphine	X		"Rescue" medication - total dose
Sims (1994) ⁶⁷	Abdominal	Indomethacin	2mg/kg RECTAL	13	10.1	1.80	Placebo control	15	10.7	2.10	Morphine	X		No clearly stated
Sutars (1995) ⁶⁸	Tonsillectomy	Ketorolac	1mg/kg IM	45	7.06	2.41	Placebo control	42	7.08	2.22	Fentanyl	X	X	"Rescue" medication
Sutars (1999) ⁶⁹	Orthopedic Surgery	Ketorolac	1mg/kg + iv 0.5mg/kg QID	36	12.7	3.51	Placebo control	32	12.67	4.22	Morphine	X		No clearly stated
Tuomilehto (2000) ⁷⁰	Adenoidectomy	Ketoprofen Ketoprofen	1 mg/kg IV 1 mg/kg ORAL	40 40	2.67 4.17	(1.33-6.83) (1.67-8.42)	Placebo control	20	3.83	(1.25-8.42)	Fentanyl	X	X	"Rescue" medication - % that need rescue
Tuomilehto (2002) ⁷¹	Tonsillectomy	Ketoprofen Ketoprofen	2mg/kg IM 2mg/kg IV	40 40	3.50 2.50	(1.00-8.33) (1.25-6.25)	Placebo control	40	2.75	(1.33-7.08)	Fentanyl	X	X	"Rescue" medication - % that need rescue
Vetter (1994) ⁷²	Orthopedics	Ketorolac	0.8mg/kg IV	25	13.0	2.00	Control	25	13.0	2.30	Morphine	X	X	No clearly stated
Virtanen (2003) ⁷³	Tonsillectomy	Ibuprofen	15mg/kg RECTAL	41	3.20	(1.00-6.90)	Placebo control	38	2.60	(1.00-6.00)	Meperidine	X	X	"Rescue" medication - % that need rescue
Wacha (1992) ⁴⁷	Other surgeries	Ketorolac	0.9mg/kg IV	32	8.3	3.80	Placebo control	32	10.0	3.60	Morphine	X		No clearly stated
Acetaminophen														
Brennerich (2001) ⁷⁴	Cleft palate	Acetaminophen Acetaminophen Acetaminophen	10mg/kg RECTAL 20mg/kg RECTAL 40mg/kg RECTAL	20 20 20	0.97 0.73 0.79	0.73 0.73 0.75	Placebo control	20	1.04	0.97	Priritamide	X		No clearly stated
Dashti (2009) ⁷⁵	Tonsillectomy	Acetaminophen	40mg/kg RECTAL	53	10.2	2.84	Control	51	9.45	2.22	Petidine	X	X	No clearly stated
Gandhi (2012) ⁷⁶	Ophthalmic	Acetaminophen Acetaminophen	40mg/kg RECTAL 20mg/kg	48 47	5.60 7.40	3.40 3.40	Control	30	6.60	4.15	Fentanyl	X	X	Pain score
Hiller (2012) ⁷⁷	Spine	Acetaminophen	30mg/kg IV	18	15.1	2.00	Placebo control	18	14.4	1.90	Oxycodone	X	X	"Rescue" medication - total dose
Kocum (2013) ⁷⁸	Tonsillectomy	Acetaminophen	15mg/kg IV	40	4.70	1.00	Placebo control	40	4.30	1.00	Petidine	X		"Rescue" medication - total dose
Korpela (1999) ⁷⁹	Elective surgery	Acetaminophen Acetaminophen Acetaminophen	20mg/kg RECTAL 40mg/kg RECTAL 60mg/kg RECTAL	30 30 30	3.10 3.80 4.20	1.90 2.20 2.30	Placebo control	30	4.40	2.10	Morphine	X	X	No clearly stated
Korpela (2007) ⁵⁹	Tonsillectomy	Acetaminophen	10mg/kg ORAL	30	1.30	(0.80-5.60)	Placebo control	29	1.60	(0.80-5.90)	Fentanyl	X	X	"Rescue" medication - % that need rescue
Mercun (2007) ⁸⁰	Inguinal	Acetaminophen Acetaminophen	20-25mg/kg p3 RECTAL 20-25mg/kg p4 RECTAL	65 78	4.00 3.92	2.97 2.93	Control	59	3.97	2.92	Meperidine	X		No clearly stated

Intervention drug			Intervention group			Control group			Outcome variables				
Source	Surgery	Name	Dose	Route	Mean age (years)		SD or range	Type of control	Mean age (years)		SD or range	Total dose	
					N	N			N	N		%	Primary outcome
Morton (1999) ⁶⁰	Appendectomy	Acetaminophen	20mg/kg RECTAL +15mg/kg QID	20	9.90	(5.00-12.0)	Control	20	10.15	(5.00-13.0)	Morphine	X	"Rescue" medication - total dose
Van der Marel (2007) ⁸¹	Abdominal	Acetaminophen	30-40mg/kg + RECTAL 20mg/kg QID	29	0.00	(0.00-0.25)	Placebo control	25	0.00	(0.00-0.08)	Morphine	X	"Rescue" medication
Vitnanen (2003) ⁷³	Tonsillectomy	Acetaminophen	40mg/kg RECTAL	40	2.70	(1.00-6.40)	Placebo control	38	2.60	(1.00-6.00)	Meperidine	X	"Rescue" medication - % that need rescue
Local Anesthetics													
Clamey (2010) ⁸²	Appendectomy	Ropivacaine 0.75%	2.5mg/kg BLOCK	19	NR	(4.00-16.0)	Placebo control	21	NR	(5-16)	Morphine	X	"Rescue" medication - total dose
Chaudhury (2012) ⁸³	Cardiac	Ropivacaine 0.5%	0.05-0.06mg/kg BLOCK	14	5.50	1.82	Placebo control	13	5.70	1.58	Fentanyl	X	Pain score
Coban (2008) ⁸⁴	Cleft palate	Ropivacaine	0.2mg/kg INFIL	10	1.90	1.00	Control	10	1.80	0.80	Morphine	X	No clearly stated
Edwards (2011) ⁸⁵	Appendectomy	Bupivacaine 0.25%	0.5ml/kg INFIL	29	11.8	(10.8-12.9)	Placebo control Control	29 30	12.3 11.9	(11.3-13.3) (0.8-13.1)	Morphine	X	Pain score
Giannoni (2001) ⁸⁶	Tonsillectomy	Ropivacaine 0.01%	0.15ml/kg INFIL	21	7.00	2.90	Placebo control	21	7.40	3.70	Fentanyl	X	Pain score
Heiba (2012) ²⁹	Tonsillectomy	Lidocaine	2mg/kg INFIL	20	14.9	2.50	Placebo control	20	15.2	3.20	Petidine	X	No clearly stated
Hermansson (2013) ⁸⁷	Abdominal	Bupivacaine	0.2 to SC INFUSION 0.4mg/kg/hr	17	3.40	(0.50-12.6)	Placebo control	15	2.80	(0.6-5.8)	Morphine	X	"Rescue" medication - number of doses
Imanoglu (2009) ⁸⁸	Tonsillectomy	Bupivacaine 0.25%	NR INFIL	30	6.00	1.30	Placebo control	30	6.20	1.60	Fentanyl	X	Pain score
Jagannathan (2009) ⁸⁹	Urological	Bupivacaine 0.25%	0.1ml/kg BLOCK	25	3.62	1.87	Add on	23	4.14	1.89	Morphine	X	Pain score
Klann (2003) ⁹⁰	Abdominal	Ropivacaine 0.1%	0.2ml/kg/hr EPIDUR	17	2.82	2.67	Add on	18	3.53	2.83	Tramadol	X	No clearly stated
Krane (1987) ³²	Other surgeries	Bupivacaine 0.25%	0.1ml/kg EPIDUR	13	6.20	NR	Control	15	7.80	NR	Morphine	X	"Rescue" medication - Time to first rescue
Kundra (2006) ⁹¹	Inguinal hernia	Bupivacaine 0.25% Bupivacaine 0.25% Bupivacaine 0.25%	0.25ml/kg IM BLOCK 0.25ml/kg IM BLOCK 0.25ml/kg SM BLOCK	34 34 34	6.10 5.80 5.80	3.60 3.10 3.70	Placebo control	34	5.20	3.30 z	Fentanyl	X	"Rescue" medication - total dose
Meatra (2010) ⁹²	Cleft palate	Bupivacaine 0.25%	1ml/h. SC INFUSION	32	6 to 9	NR	Placebo control	33	6 to 9	NR	Morphine	X	Pain score
Muthukumar (2012) ⁹³	Cleft palate	Lignocaine Lignocaine	7mg/kg INFIL 7mg/kg INFIL	25 25	2.10 2.60	1.70 1.90	Placebo control	25 25	2.70 2.90	2.10 2.10	Fentanyl	X	Cardiovascular response
O'hara (2004) ⁹⁴	Spinal	Bupivacaine 0.1% Bupivacaine 0.065%	4ml/hr EPIDUR 4ml/hr EPIDUR	10 12	13 to 21 13 to 21	NR NR	Placebo control	9	13 to 21	NR	Morphine	X	No clearly stated
Park (2004) ⁹⁵	Tonsillectomy	Ropivacaine 0.5%	30mg INFIL	66	7.00	2.00	Placebo control	64	7.00	3.00	Fentanyl	X	Pain score
Ryhanen (1994) ⁶⁴	Urological	Bupivacaine 0.25% Bupivacaine 0.25% +Adrenaline	1ml/kg EPIDUR 1ml/kg EPIDUR	57 50	3.90 3.90	1.80 1.80	Control	73	3.50	1.80	Petidine	X	No clearly stated
Spliner (2010) ⁹⁶	Appendectomy	Ropivacaine 0.2%	0.25-0.5ml/kg BLOCK	18	10.2	3.00	Placebo control	18	10.6	2.90	Morphine	X	"Rescue" medication - total dose
Trotta (2009) ⁹⁷	Cardiac	Bupivacaine 0.25% /Levobupivacaine	0.5 -5 ml/hr SC INFUSION	35	4.47	(0.25-14.7)	Placebo control	37	3.51	(0.25-16.7)	Morphine	X	"Rescue" medication - total dose
Usmani (2009) ⁹⁸	Urological	EMLA cream Lidocaine 1%	5% TOPIC 0.5ml/kg IV	30 30	6.00 7.00	2.00 2.00	Placebo control	30	7.00	3.00	Fentanyl	X	"Rescue" medication - number of doses

APDS = All India Institute of Medical Sciences pain discomfort scale; CHEOPs = Children’s Hospital of Eastern Ontario Pain Scale; CHIPPS = Children and Infants Postoperative Pain Scale; EPIDUR = Epidural; FACES = The Wong-Baker FACES® Pain Rating Scale; FLACC = The Face, Legs, Activity, Cry, Consolability scale; IM = Intramuscular; IM BLOCK = Inferior-medial block; INFIL = Infiltration; IT = Intrathecal; IV = Intravenous; M BLOCK = Medial Block; mCHEOPs = Modified CHEOPs; mOPS = Modified OPS; N/A = Not apply; NRS = Numeric Rate Scale; OPTHALM = Ophthalmological drops; OPS Observational Pain Scale; SC INFUSION = Subcutaneous infusion; SM BLOCK = Superior-medial block; VAS = Visual Analog Scale.