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. The authors 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 (milligram per kilogram per hour), (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. **(Anesthesiology 2015; 122:150-71)**

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 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, and the European Union have generated incentives for pharmaceutical companies to test analgesics in children, and some funding mechanisms *via* the Food and Drug Administration 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]

What We Already Know about This Topic

- Traditional approaches to pediatric analgesic trials may leave patients with insufficiently treated pain
- Whether rescue treatments are generally effective in pediatric analgesia trials remains unclear

What This Article Tells Us That Is New

- The investigators performed a meta-analysis of pediatric trials with four classes of analgesics, using rescue/opioid sparing designs
- Average pain scores were low and similar in control and experimental analgesic groups, confirming the ethical basis of opioid-sparing rescue designs
- Opioid-sparing designs also showed good assay sensitivity

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). The first two authors contributed equally to this article.

Submitted for publication April 16, 2014. Accepted for publication August 14, 2014. From the Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts (J.K., C.D., C.B.B.); and Department of Clinical Psychology and Psychotherapy, University of Basel, Basel, Switzerland (J.K.).

 Anesthesiology 2015; 122:150-71

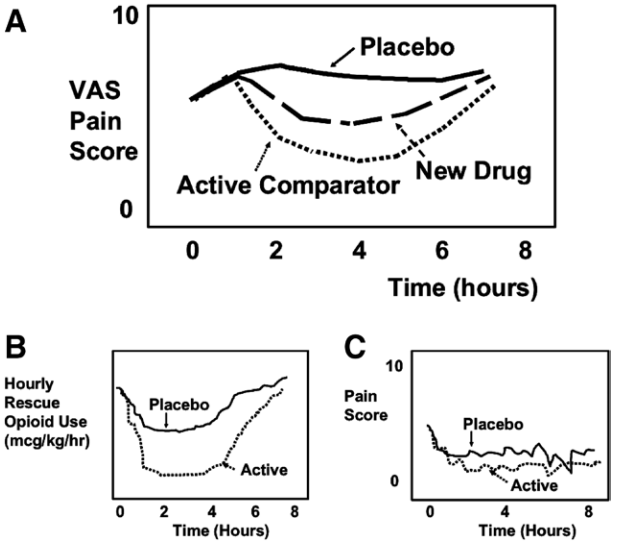

Fig. 1. (*A*) Typical time course of pain scores for a double-blind, parallel-group, placebo-controlled, active comparator analgesic trial. Note that in general, requirement for rescue analgesia results in termination of pain scoring for that subject. (*B*) Idealized time course of hourly rescue dosing 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. Reproduced, with permission, from Berde *et al*. Pediatrics 2012; 129:354–64.[1]

In November 2010, an expert consensus group was convened by the Anesthetic, Analgesic and Addiction Drugs section of the Food and Drug Administration 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 (fig. 1, B 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, http://links.lww.com/ALN/B91).

Materials and Methods

The search strategy is described in detail in Section A1 of Supplemental Digital Content 1, http://links.lww.com/ALN/B91.

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; and (4) assessed rescue medication and/or pain scores in postoperative pain setting.

For the purpose of this study, we included articles only if they (1) included placebo or control groups; (2) used IV opioids as rescue medication; and (3) used opioids, NSAIDs, acetaminophen, or 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: (1) rescue opioid usage (milligram per kilogram per hour), (2) percentage of subjects requiring rescue medication, or (3) 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 articles reporting pain scores, we standardized all the pain scores to a 0 to 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 Hedges' g and the 95% 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

* Available at: www.globalrph.com/narcoticonv.htm. Accessed June 27, 2014.

† Available at: www.meta-analysis.com. Accessed June 27, 2014.

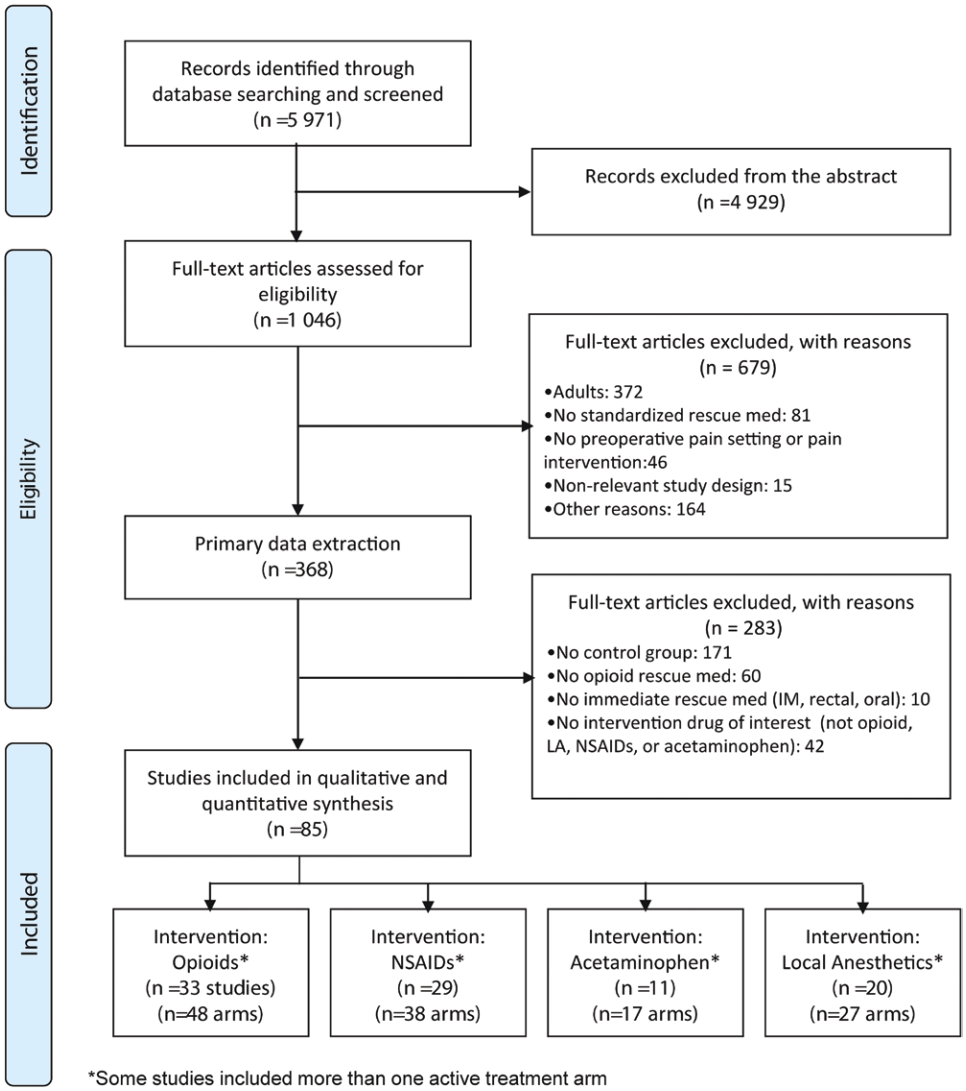

Fig. 2. Flow chart of literature search with summary of excluded and included studies. IM = intramuscular; LA = local anesthetic; NSAIDs = nonsteroidal antiinflammatory drugs.

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 I^2 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 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.

Second, mean opioid sparing by the study drug was expressed as percent of maximum possible effect (placebo – study/placebo),[13] as 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 to 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, http://links.lww.com/ALN/B91.

Opioids as the Study Drug

Details of the 33 included articles (48 active study drug arms) can be seen in Section A2 of Supplemental Digital Content 1, http://links.lww.com/ALN/B91. 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 remifentanil[31] was given intraoperatively as study drug, it produced a significant *negative* postoperative opioid-sparing effect, that is, greater opioid use in patients receiving study drug *versus* placebo, consistent with previous animal and adult human studies showing remifentanil's potential to induce hyperalgesia and acute tolerance.[99]

Total Opioid Usage (Milligram per Kilogram per Hour). 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 of 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 of 32 study drug arms. Intrathecal morphine[25] after spinal fusion showed the highest sparing effect and efficacy–burden relationship.

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 of 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 article)[15] and smaller for urological procedures (Hedges' g = −0.42; 95% CI, −0.89 to −0.05; $P = 0.08$). Ten of 21 study drug arms demonstrated significant percent opioid-sparing effect.

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 of 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.

NSAID as the Study Drug

Details of the 29 included articles (38 active study drug arms) can be seen in Section A2 of Supplemental Digital Content 1, http://links.lww.com/ALN/B91. The largest number of studies involved adenotonsillectomies (13 articles). Overall the degree of opioid-sparing effect of NSAIDs varied considerably.

Total Opioid Usage (Milligram per Kilogram per Hour). 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 of 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 of 21 study drug arms.

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 of 18 treatment arms (Hedges' g = −0.52; 95% CI, −0.66 to −0.38; $P < 0.001$). Ten out of 17 articles demonstrated significant percent opioid sparing effect.

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

Table 1. Selected Characteristics of Included Studies

			Intervention Drug			Intervention Group		
	Source	Surgery	Name	Dose	Route	N	Mean Age (yr)	SD or Range
Opioids								
	Ali (2008)[15]	Tonsillectomy	Tramadol	1 mg/kg	IV	30	7.53	1.88
			Dextromethorphan	1 mg/kg	Oral	30	7.46	1.85
	Antila (2006)[16]	Tonsillectomy	Tramadol	1 mg/kg	IV	15	11.9	2.40
	Ayatollahi (2012)[17]	Tonsillectomy	Tramadol	2 mg/kg	Infil	42	7.06	2.21
	Batra (2008)[18]	Urological	Fentanyl	0.25 μg/kg	IT	14	0.62	0.24
			Fentanyl	0.5 μg/kg	IT	13	0.57	0.08
			Fentanyl	1 μg/kg	IT	15	0.63	0.29
	Bean-Lijewski (1996)[19]	Other surgeries	Meperidine	1 mg/kg	IM	25	4.10	2.60
	Campbell (1992)[20]	Urological	Fentanyl	1 μg/kg	Epidur	17	5.30	3.30
	Dawson (2001)[21]	Tonsillectomy	Dextromethorphan	1 mg/kg	Oral	19	7.02	1.98
	Doyle (1993a)[22]	Appendectomy	Morphine	20 μg kg^{-1} h^{-1}	IV	20	10.2	(6–12)
	Doyle (1993b)[23]	Appendectomy	Morphine	4 μg kg^{-1} h^{-1}	IV	15	10.4	(6.5–12.9)
			Morphine	10 μg kg^{-1} h^{-1}	IV	15	10.3	(7.2–12.4)
	Eschertzhuber (2008)[24]	Scoliosis	Morphine	5 μg/kg	IT	14	15.0	2.00
			Morphine	15 μg/kg	IT	14	15.0	2.00
	Gall (2001)[25]	Spinal fusion	Morphine	2 μg/kg	IT	10	17.0	3.00
			Morphine	5 μg/kg	IT	10	15.0	2.00
	Ganesh (2008)[26]	Noncardiac thoracic	Fentanyl	2 μg/ml	Epidur	16	0.18	0.07
	Hammer (2005)[27]	Open Heart	Morphine	7 μg/kg	Epidur	20	2.37	1.46
	Hasan (2004)[28]	Tympanomastoid	Dextromethorphan	1 mg/kg	Oral	19	12.2	3.40
	Heiba (2012)[29]	Tonsillectomy	Tramadol	2 mg/kg	Infil	20	15.3	2.20
	Kawaraguchi (2006)[30]	Urological	Fentanyl	1 μg/kg	Epidur	17	4.00	(3–6.92)
	Kim (2013)[31]	Urological	Remifentanil	0.3 μg kg^{-1} min^{-1}	IV	15	2.48	1.18
			Remifentanil	0.6 μg kg^{-1} min^{-1}	IV	15	2.69	1.02
			Remifentanil	0.9 μg kg^{-1} min^{-1}	IV	15	2.72	1.31
	Krane (1987)[32]	Other surgeries	Morphine	0.1 mg/kg	Epidur	15	7.70	NR
	Lawhorn (1994)[33]	Other surgeries	Butorphanol	40 μg/kg	Epidur	10	8.50	5.30
	Lawhorn (1997)[34]	Urological	Butorphanol	30 μg/kg	Epidur	100	4.09	2.57
	Mane (2011)[35]	Cleft palate repair	Fentanyl	0.25 μg/kg	Block	15	16.4	NR
			Meperidine	0.25 μg/kg	Block	15	14.9	NR
	McDonnell (2008)[36]	Ideopathic Scoliosis	Morphine	100 μg/kg	IV	18	14.8	1.70
	Ozcengiz (2001)[37]	Urological	Tramadol	2 mg/kg	Epidur	38	6.85	1.80
			Morphine	0.03 mg/kg	Epidur	40	6.97	1.76
	Rosen (1989)[38]	Open Heart	Morphine	0.075 mg/kg	Epidur	16	2 to 12	NR
	Rose (1999)[39]	Tonsillectomy	Dextromethorphan	0.5 mg/kg	Oral	19	7.80	1.70
			Dextromethorphan	1 mg/kg	Oral	19	7.90	1.60
	Sharma (2011)[40]	Other surgeries	Methadone	0.1 mg/kg	IV	10	14.0	2.00
			Methadone	0.2 mg/kg	IV	10	13.0	2.00
			Methadone	0.3 mg/kg	IV	11	14.0	2.00

(*Continued*)

Control Group				Outcome Variables					
Type of Control	N	Mean Age (yr)	SD or Range	Rescue Opioid	Total Dose	%	Min	Primary Outcome	Pain Scale
Placebo control	30	7.61	1.93	Meperidine		X		"Rescue" medication—number of requests	FACES
Placebo control	15	12.5	1.90	Fentanyl	X			"Rescue" medication—number of rescue	VAS
Placebo control	42	7.40	1.38	Fentanyl		X		Not clearly stated	mCHEOPS
Add on	14	0.56	0.29	Fentanyl	X		X	"Rescue" medication—Time to first rescue	VAS
Placebo control	28	4.20	3.00	Meperidine	X	X	X	Not clearly stated	CHEOPS
Add on	17	4.60	3.80	Morphine	X	X	X	"Rescue" medication—% that need rescue	N/A
Placebo control	21	7.75	2.70	Morphine	X			Not clearly stated	N/A
Placebo control	20	9.60	(6–12)	Morphine	X			Not clearly stated	4 points self-report
Placebo control	15	10.5	(8.70–12.1)	Morphine	X			Not clearly stated	mCHEOPS
Control	14	15.0	1.00	Piritamide	X			Not clearly stated	VAS
Placebo control	10	15.0	4.00	Morphine	X		X	"Rescue" medication—total dose	VAS
Add on	16	0.18	0.14	Nalbuphine	X		X	"Rescue" medication—total dose	FACES
Control	20	2.36	1.56	Fentanyl	X			Pain score	FACES
Placebo control	19	11.5	3.70	Morphine	X			"Rescue" medication—total dose	VAS
Placebo control	20	15.2	3.20	Meperidine	X		X	Not clearly stated	VAS
Add on	18	4.30	(3.00–7.08)	Pentazocine		X	X	"Rescue" medication—Time to first rescue	CHEOPS
Placebo control	15	2.74	1.19	Remifentanil	X			"Rescue" medication—total dose	mCHEOPS
Control	15	7.80	NR	Morphine		X	X	"Rescue" medication—Time to first rescue	N/A
Add on	10	8.60	4.70	Morphine			X	Not clearly stated	N/A
Add on	100	3.97	2.37	Morphine		X	X	Not clearly stated	N/A
Add on	15	14.0	NR	Fentanyl			X	Not clearly stated	N/A
Placebo control	19	14.5	1.90	Morphine	X			"Rescue" medication—total dose	N/A
Control	38	6.76	1.76	Morphine		X		Not clearly stated	N/A
Placebo control	16	2 to 12	NR	Morphine	X	X		Not clearly stated	VAS
Placebo control	19	7.90	1.60	Morphine	X	X		"Rescue" medication—total dose	VAS
Control	30	15.0	2.00	Morphine	X			Pharmacokinetics	Nurses pain scale

(*Continued*)

Table 1. (*Continued*)

			Intervention Drug			Intervention Group		
	Source	Surgery	Name	Dose	Route	N	Mean Age (yr)	SD or Range
	Suominen (2004)[41]	Open Heart	Morphine	20 μg/kg	IT	35	1.19	(0.01–16.7)
	Suski (2010)[42]	Ideopathic Scoliosis	Dextromethorphan	30–45 mg	Oral	30	15.9	2.40
	Tarkkila (2003)[43]	Tonsillectomy	Remifentanil	1 μg/kg	IV	25	3.83	2.08
	Ugur (2008)[44]	Tonsillectomy	Tramadol	2 mg/kg	IM	15	8.20	1.70
			Tramadol	2 mg/kg	Infil	15	8.40	1.60
	Umuroglu (2004)[45]	Tonsillectomy	Morphine	0.1 mg/kg	IV	15	7.13	2.51
			Tramadol	1.5 mg/kg	IV	15	6.06	2.08
	Viitanen (2001)[46]	Tonsillectomy	Tramadol	2 mg/kg	IV	40	1 to 3	NR
	Watcha (1992)[47]	Other surgeries	Morphine	0.1 mg/kg	IV	31	8.50	3.70
Nonsteroidal antiinflammatory drugs								
	Adarsh (2012)[48]	Cleft palate repair	Diclofenac	1 mg/kg	Rectal	30	2.80	1.73
	Antila (2006)[16]	Tonsillectomy	Ketoprofen	2 mg/kg	IV	15	12.5	2.30
	Bean-Lijewski (1996)[19]	Other surgeries	Ketorolac	0.75 mg/kg	IM	29	4.00	2.20
	Bridge (2000)[49]	Strabismus	Ketorolac	3 mg per eye	Ophthalm	17	5.25	(4.25–9.75)
	Dawson (1996)[50]	Cleft palate repair	Ketorolac	1 mg/kg + 0.5 mg/kg QID	IV	18	7 to 20	NR
	Kokki (1994)[51]	Elective surgery	Ibuprofen	40 mg kg^{-1} day^{-1}	Rectal	40	2.42	1.11
	Kokki (1998)[52]	Tonsillectomy	Ketoprofen	0.3 mg/kg	IV	55	3.33	(1.5–6.17)
			Ketoprofen	1 mg/kg	IV	55	2.67	(1.25–7.08)
			Ketoprofen	3 mg/kg	IV	55	2.67	(1.25–6.00)
	Kokki (1999a)[53]	Strabismus	Ketoprofen	1 + 1 mg/kg	IV	30	6.92	(4.17–9.33)
	Kokki (1999b)[54]	Major surgery	Ketoprofen	1 + 4 mg/kg	IV	24	6.58	(1.58–14.8)
	Kokki (2000)[55]	Tonsillectomy	Ketoprofen	25 mg/kg	IV	42	3.67	(1.17–8.08)
			Ketoprofen	25 mg/kg	Rectal	42	2.75	(1.42–2.25)
	Kokki (2001)[56]	Tonsillectomy (phase I)	Ketoprofen	1 + 1 mg/kg	IV	54	3.25	1.92
		Tonsillectomy (phase III)	Ketoprofen	0.3 mg/kg	IV	33	3.50	1.75
			Ketoprofen	1 mg/kg	IV	29	3.25	2.17
			Ketoprofen	3 mg/kg	IV	32	3.08	1.83
	Kokki (2002)[57]	Tonsillectomy	Ketoprofen	0.5 + 3 mg/kg preqx	IV	47	10.0	1.00
			Ketoprofen	0.5 + 3 mg/kg postqx	IV	42	12.0	3.00
	Kokki (2004)[58]	Strabismus	Ketoprofen	1 + 1 mg/kg	IV	27	7.92	2.92
	Korpela (2007)[59]	Tonsillectomy	Naproxen	10 mg/kg	Oral	30	1.80	(0.70–6.20)
	Morton (1999)[60]	Appendectomy	Diclofenac	1 mg/kg TID	Rectal	20	10.6	(6.00–13.0)
	Munro (2002)[61]	Ideopathic scoliosis	Ketorolac	0.5 mg/kg	IV	20	14.1	1.20
	Nikanne (1997)[62]	Tonsillectomy	Ketoprofen	1 + 1 mg/kg	IV	80	3.17	(1.00–9.25)
	Oztekin (2002)[63]	Tonsillectomy	Diclofenac	1 mg/kg	Rectal	20	8.40	0.53

(*Continued*)

Control Group				Outcome Variables					
Type of Control	N	Mean Age (yr)	SD or Range	Rescue Opioid	Total Dose	%	Min	Primary Outcome	Pain Scale
Control	36	1.19	(0.03–12.7)	Morphine	X	X	X	"Rescue" medication—% that need rescue	N/A
Placebo control	30	16.5	2.70	Morphine	X			Not clearly stated	NRS
Placebo control	25	2.92	1.83	Oxycodone	X	X	X	Discharge time	N/A
Placebo control	15	8.50	2.10	Meperidine		X		Pain score	VAS
Placebo control	15	6.96	2.08	Meperidine		X	X	Not clearly stated	CHEOPS
Placebo control	40	1 to 3	NR	Meperidine	X	X	X	"Rescue" medication—% that need rescue	N/A
Placebo control	32	10.0	3.60	Morphine		X		Not clearly stated	VAS
Control	30	2.26	1.43	Fentanyl	X	X		"Rescue" medication—total dose	Hannallah
Placebo control	15	12.50	1.90	Fentanyl	X			"Rescue" medication—number of doses	VAS
Placebo control	28	4.20	3.00	Meperidine	X	X	X	Not clearly stated	CHEOPS
Placebo control	13	6.67	(4.17–12.4)	Morphine		X	X	Pain score	CHEOPS
Control	16	7 to 20	NR	Morphine	X			Not clearly stated	N/A
Placebo control	41	2.78	1.32	Morphine	X	X		"Rescue" medication—total dose	Maunuksela
Placebo control	55	3.42	(1.25–6.58)	Fentanyl		X	X	"Rescue" medication—% that need rescue	Maunuksela
Placebo control	29	5.33	(3.83–7.83)	Fentanyl	X	X	X	Vomiting	Maunuksela
Placebo control	23	7.08	(1.25–14.4)	Sulfentanyl	X			"Rescue" medication—total dose	Maunuksela
Placebo control	39	3.75	(1.17–6.08)	Fentanyl		X	X	"Rescue" medication—total dose	Maunuksela
Placebo control	45	3.33	1.92	Fentanyl		X		Lenght of hospital stay	VAS
Placebo control	35	4.00	2.25	Fentanyl		X			
placebo control	20	11.0	1.00	Oxycodone		X		"Rescue" medication—% that need rescue	VAS
Placebo control	29	7.17	3.00	Fentanyl		X	X	"Rescue" medication—number of doses	N/A
Placebo control	29	1.60	(0.80–5.90)	Fentanyl	X	X	X	"Rescue" medication—% that need rescue	OPS
Control	20	10.15	(5–13)	Morphine	X			"Rescue" medication—total dose	N/A
Placebo control	15	13.9	1.30	Morphine	X			Pain score	VAS
Placebo control	84	3.33	(0.83–7.92)	Fentanyl	X	X		"Rescue" medication—% that need rescue	Maunuksela
Control	20	8.90	0.45	Morphine	X			Not clearly stated	VAS

(*Continued*)

Table 1. (*Continued*)

			Intervention Drug			Intervention Group		
	Source	Surgery	Name	Dose	Route	N	Mean Age (yr)	SD or Range
	Ryhanen (1994)[64]	Urological	Diclofenac	1 mg/kg	IM	70	3.80	1.70
	Rugyte (2007)[65]	Pectus	Ketoprofen	1 mg/kg	IV	14	14.00	(13.0–15.0)
	Sheeran (2004)[66]	Tonsillectomy	Rofecoxib	0.5 mg/kg	Oral	23	7.20	1.80
	Sims (1994)[67]	Abdominal	Indomethacin	2 mg/kg	Rectal	13	10.1	1.80
	Sutters (1995)[68]	Tonsillectomy	Ketorolac	1 mg/kg	IM	45	7.06	2.41
	Sutters(1999)[69]	Orthopedic Surgery	Ketorolac	1 mg/kg + 0.5 mg/kg QID	IV	36	12.7	3.51
	Tuomilehto (2000)[70]	Adenoidectomy	Ketoprofen	1 mg/kg	IV	40	2.67	(1.33–6.83)
			Ketoprofen	1 mg/kg	Oral	40	4.17	(1.67–8.42)
	Tuomilehto (2002)[71]	Tonsillectomy	Ketoprofen	2 mg/kg	IM	40	3.50	(1.00–8.33)
			Ketoprofen	2 mg/kg	IV	40	2.50	(1.25–6.25)
	Vetter (1994)[72]	Orthopedics	Ketorolac	0.8 mg/kg	IV	25	13.0	2.00
	Viitanen (2003)[73]	Tonsillectomy	Ibuprofen	15 mg/kg	Rectal	41	3.20	(1.00–6.90)
	Watcha (1992)[47]	Other surgeries	Ketorolac	0.9 mg/kg	IV	32	8.3	3.80
Acetaminophen								
	Bremerich (2001)[74]	Cleft palate	Acetaminophen	10 mg/kg	Rectal	20	0.97	0.73
			Acetaminophen	20 mg/kg	Rectal	20	1.01	0.87
			Acetaminophen	40 mg/kg	Rectal	20	0.79	0.75
	Dashti (2009)[75]	Tonsillectomy	Acetaminophen	40 mg/kg	Rectal	53	10.2	2.84
	Gandhi (2012)[76]	Ophthalmic	Acetaminophen	40 mg/kg	Rectal	48	5.60	3.40
			Acetaminophen	20 mg/kg		47	7.40	3.40
	Hiller (2012)[77]	Spine	Acetaminophen	30 mg/kg	IV	18	15.1	2.00
	Kocum (2013)[78]	Tonsillectomy	Acetaminophen	15 mg/kg	IV	40	4.70	1.00
	Korpela (1999)[79]	Elective surgery	Acetaminophen	20 mg/kg	Rectal	30	3.10	1.90
			Acetaminophen	40 mg/kg	Rectal	30	3.80	2.20
			Acetaminophen	60 mg/kg	Rectal	30	4.20	2.30
	Korpela (2007)[59]	Tonsillectomy	Acetaminophen	10 mg/kg	Oral	30	1.30	(0.80–5.60)
	Mercan (2007)[80]	Inguinal	Acetaminophen	20–25 mg/kg p3	Rectal	65	4.00	2.97
			Acetaminophen	20–25 mg/kg p4	Rectal	78	3.92	2.93
	Morton (1999)[60]	Appendectomy	Acetaminophen	20 mg/kg + 15 mg/kg QID	Rectal	20	9.90	(5.00–12.0)
	Van der Marel (2007)[81]	Abdominal	Acetaminophen	30–40 mg/kg + 20 mg/kg QID	Rectal	29	0.00	(0.00–0.25)
	Viitanen (2003)[73]	Tonsillectomy	Acetaminophen	40 mg/kg	Rectal	40	2.70	(1.00–6.40)
Local anesthetics								
	Carney (2010)[82]	Appendectomy	Ropivacaine 0.75%	2.5 mg/kg	Block	19	NR	(4.00–16.0)
	Chaudhary (2012)[83]	Cardiac	Ropicacine 0.5%	0.05–0.06 mg/kg	Block	14	5.50	1.82
	Coban (2008)[84]	Cleft palate	Ropivacaine	0.2 mg/kg	Infil	10	1.90	1.00
	Edwards (2011)[85]	Appendectomy	Bupivacaine 0.25%	0.5 ml/kg	Infil	29	11.8	(10.8–12.9)
	Giannoni (2001)[86]	Tonsillectomy	Ropivacaine 0.01%	0.15 ml/kg	Infil	21	7.00	2.90
	Heiba (2012)[29]	Tonsillectomy	Lidocaine	2 mg/kg	Infil	20	14.9	2.50
	Hermansson (2013)[87]	Abdominal	Bupivacaine	0.2–0.4 mg kg^{-1} h^{-1}	SC infusion	17	3.40	(0.50–12.6)
	Inanoglu (2009)[88]	Tonsillectomy	Bupivacaine 0.25%	NR	Infil	30	6.00	1.30

(*Continued*)

Control Group				Outcome Variables					
Type of Control	N	Mean Age (yr)	SD or Range	Rescue Opioid	Total Dose	%	Min	Primary Outcome	Pain Scale
Control	73	3.50	1.80	Meperidine		X	X	Not clearly stated	N/A
Placebo control	17	13.0	(10–15)	Morphine	X			"Rescue" medication—total dose	VAS
Placebo control	22	7.60	2.20	Morphine		X		"Rescue" medication—total dose	CHEOPS
Placebo control	15	10.7	2.10	Morphine	X			Not clearly stated	VAS
Placebo control	42	7.08	2.22	Fentanyl	X	X		"Rescue" medication	CHEOPS
Placebo control	32	12.67	4.22	Morphine	X			Not clearly stated	FACES
Placebo control	20	3.83	(1.25–8.42)	Fentanyl		X	X	"Rescue" medication—% that need rescue	Maunuksela
Placebo control	40	2.75	(1.33–7.08)	Fentanyl	X	X		"Rescue" medication—% that need rescue	OPS
Control	25	13.0	2.30	Morphine	X		X	Not clearly stated	VAS
Placebo control	38	2.60	(1.00–6.00)	Meperidine	X		X	"Rescue" medication—% that need rescue	N/A
Placebo control	32	10.0	3.60	Morphine		X		Not clearly stated	VAS
Placebo control	20	1.04	0.97	Piritramide	X			Not clearly stated	CHIPPS
Control	51	9.45	2.22	Meperidine	X	X		Not clearly stated	VAS
Control	30	6.60	4.15	Fentanyl		X	X	Pain score	OPS
Placebo control	18	14.4	1.90	Oxycodone	X	X	X	"Rescue" medication—total dose	N/A
Placebo control	40	4.30	1.00	Meperidine	X			"Rescue" medication—total dose	CHEOPS
Placebo control	30	4.40	2.10	Morphine	X	X		Not clearly stated	VAS
Placebo control	29	1.60	(0.80–5.90)	Fentanyl	X	X	X	"Rescue" medication—% that need rescue	OPS
Control	59	3.97	2.92	Meperidine		X		Not clearly stated	VAS
Control	20	10.15	(5.00–13.0)	Morphine	X			"Rescue" medication—total dose	N/A
Placebo control	25	0.00	(0.00–0.08)	Morphine	X			"Rescue" medication	VAS
Placebo control	38	2.60	(1.00–6.00)	Meperidine	X		X	"Rescue" medication—% that need rescue	N/A
Placebo control	21	NR	(5–16)	Morphine	X		X	"Rescue" medication—total dose	CHIPPS
Placebo control	13	5.70	1.58	Fentanyl	X			Pain score	mOPS
Control	10	1.80	0.80	Morphine		X	X	Not clearly stated	CHIPPS
Placebo control	29	12.3	(11.3–13.3)	Morphine	X	X		Pain score	FACES
Control	30	11.9	(10.8–13.1)						
Placebo control	21	7.40	3.70	Fentanyl		X		Pain score	VAS
Placebo control	20	15.2	3.20	Meperidine	X		X	Not clearly stated	VAS
Placebo control	15	2.80	(0.6–5.8)	Morphine	X			"Rescue" medication—number of doses	N/A
Placebo control	30	6.20	1.60	Fentanyl		X	X	Pain score	CHEOPS

(*Continued*)

Table 1. (*Continued*)

		Intervention Drug			Intervention Group		
Source	Surgery	Name	Dose	Route	N	Mean Age (yr)	SD or Range
Jagannathan (2009)[89]	Urological	Bupivacaine 0.25%	0.1 ml/kg	Block	25	3.62	1.87
Klamt (2003)[90]	Abdominal	Ropivacaine 0.1%	0.2 ml kg^{-1} h\$^{-1}$	Epidur	17	2.82	2.67
Krane (1987)[32]	Other surgeries	Bupivacaine 0.25%	0.1 ml/kg	Epidur	13	6.20	NR
Kundra (2006)[91]	Inguinal hernia	Bupivacaine 0.25%	0.25 ml/kg	ILIH-I	34	6.10	3.60
		Bupivacaine 0.25%	0.25 ml/kg	ILIH-M	34	5.80	3.10
		Bupivacaine 0.25%	0.25 ml/kg	ILIH-S	34	5.80	3.70
Meara (2010)[92]	Cleft palate	Bupivacaine 0.25%	1 ml/h	SC infusion	32	6 to 9	NR
Muthukumar (2012)[93]	Cleft palate	Lidocaine	7 mg/kg	Infil	25	2.10	1.70
		Lidocaine	7 mg/kg	Infil	25	2.60	1.90
O´hara (2004)[94]	Spinal	Bupivacaine 0.1%	4 ml/h	Epidur	10	13 to 21	NR
		Bupivacaine 0.065%	4 ml/h	Epidur	12	13 to 21	NR
Park (2004)[95]	Tonsillectomy	Ropivacaine 0.5%	30 mg	Infil	66	7.00	2.00
Ryhanen (1994)[64]	Urological	Bupivacaine 0.25%	1 ml/kg	Epidur	57	3.90	1.80
		Bupivacaine 0.25% + Epinephrine	1 ml/kg	Epidur	50	3.90	1.80
Splinter (2010)[96]	Appendectomy	Ropivacaine 0.2%	0.25–0.5 ml/kg	Block	18	10.2	3.00
Tirotta (2009)[97]	Cardiac	Bupivacaine 0.25% / Levobupivacaine	0.5–5 ml/h	SC infusion	35	4.47	(0.25–14.7)
Usmani (2009)[98]	Urological	EMLA cream	5%	Topical	30	6.00	2.00
		Lidocaine 1%	0.5 ml/kg	IV	30	7.00	2.00

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; ILIH-I = inferomedial approach to ilioinguinal–iliohypogastric nerve block; ILIH-M = medial approach to ilioinguinal–iliohypogastric nerve block; ILIH-S = superomedial approach to ilioinguinal–iliohypogastric nerve block; IM = intramuscular; Infil = infiltration; IT = intrathecal; IV = intravenous; mCHEOPs = modified CHEOPs; mOPS = modified OPS; N/A = not applicable; NRS = numeric rate scale; Ophthalm = ophthalmological drops; OPS = Observational Pain Scale; SC infusion = subcutaneous infusion; VAS = visual analog scale.

shows a moderate mean difference in favor of the study drug *versus* control in one of four 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 of 11 treatment arms demonstrated significant percent opioid-sparing effect and one article had a slightly negative, yet nonsignificant sparing effect.[53]

Overall, total opioid dose in milligram per kilogram per hour seems to be the opioid-sparing outcome with the highest assay sensitivity for NSAID trials.

Acetaminophen as the Study Drug

Details of the 11 included articles (17 active study drug arms) can be seen in Section A2 of Supplemental Digital Content 1, http://links.lww.com/ALN/B91. General conclusions were (1) rectal acetaminophen showed greatest effect size in all three measures at doses of 40 or 60 mg/kg, and variable effects at lower doses; and (2) only one oral and two IV acetaminophen studies met full inclusion criteria for this review; effect size using IV acetaminophen was strongly influenced by study methodology.

Total Opioid Usage (Milligram per Kilogram per Hour). 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 four of eight 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 and 60 mg/kg in the study by Korpela *et al.*[79] Significant percent reductions in opioid use were found in 4 of 13 study drug arms.

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 of 10 treatment arms (Hedges' g = –0.82; 95% CI, –1.20 to –0.44; $P < 0.001$). Noteworthy, the effects sizes found in the study reported by

Control Group				Outcome Variables					
Type of Control	N	Mean Age (yr)	SD or Range	Rescue Opioid	Total Dose	%	Min	Primary Outcome	Pain Scale
Add on	23	4.14	1.89	Morphine		X	X	Pain score	CHIPPS
Add on	18	3.53	2.83	Tramadol	X		X	Not clearly stated	N/A
Control	15	7.80	NR	Morphine		X	X	"Rescue" medication—Time to first rescue	N/A
Placebo control	34	5.20	3.30	Fentanyl	X	X		"Rescue" medication—total dose	APDS
Placebo control	33	6 to 9	NR	Morphine	X			Pain score	FACES
Placebo control	25	2.70	2.10	Fentanyl	X			Cardiovascular response	FLACC
	25	2.90	2.10						
Placebo control	9	13 to 21	NR	Morphine	X			Not clearly stated	VAS
Placebo control	64	7.00	3.00	Fentanyl	X			Pain score	OPS
Control	73	3.50	1.80	Meperidine		X	X	Not clearly stated	N/A
Placebo control	18	10.6	2.90	Morphine	X		X	"Rescue" medication—total dose	N/A
Placebo control	37	3.51	(0.25–16.7)	Morphine	X	X		"Rescue" medication—total dose	N/A
Placebo control	30	7.00	3.00	Fentanyl		X	X	"Rescue" medication—number of doses	N/A

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.

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 milligram per kilogram per hour seems to be the outcome with the highest assay sensitivity, yet due to low number of studies, these results should be considered preliminary.

Local Anesthetics as the Study Drug

Details of the general characteristic of the 20 included articles (27 active study drug arms) can be seen in Section A2 of Supplemental Digital Content 1, http://links.lww.com/ALN/B91.

Total Opioid Usage (Milligram per Kilogram per Hour). This endpoint was recorded for 18 study drug arms among 13 studies. Half of the articles 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 of 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), whereas studies evaluating continuous infusion showed none (Hedges' g = –0.16; 95% CI, –0.55 to 0.22; P = 0.41).

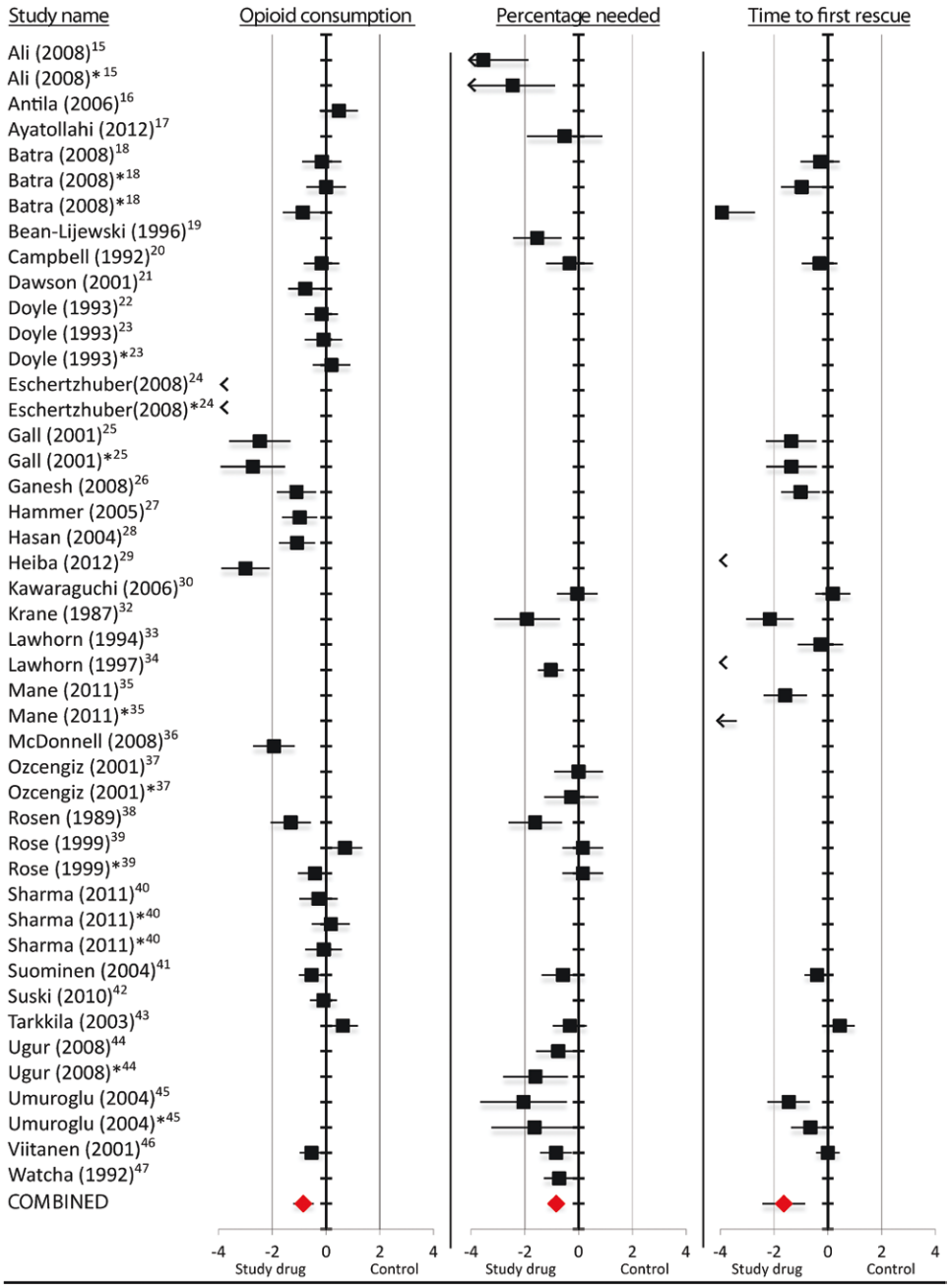

Fig. 3. Forest plot for opioids as study drug. Expressed as Hedges' g score and 95% CIs. Negative scores favor study drug over control. *Study included more than one active treatment arm.

Significant percent reductions in opioid use were found in 10 of 18 study drug arms.

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 of 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.

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 of 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'

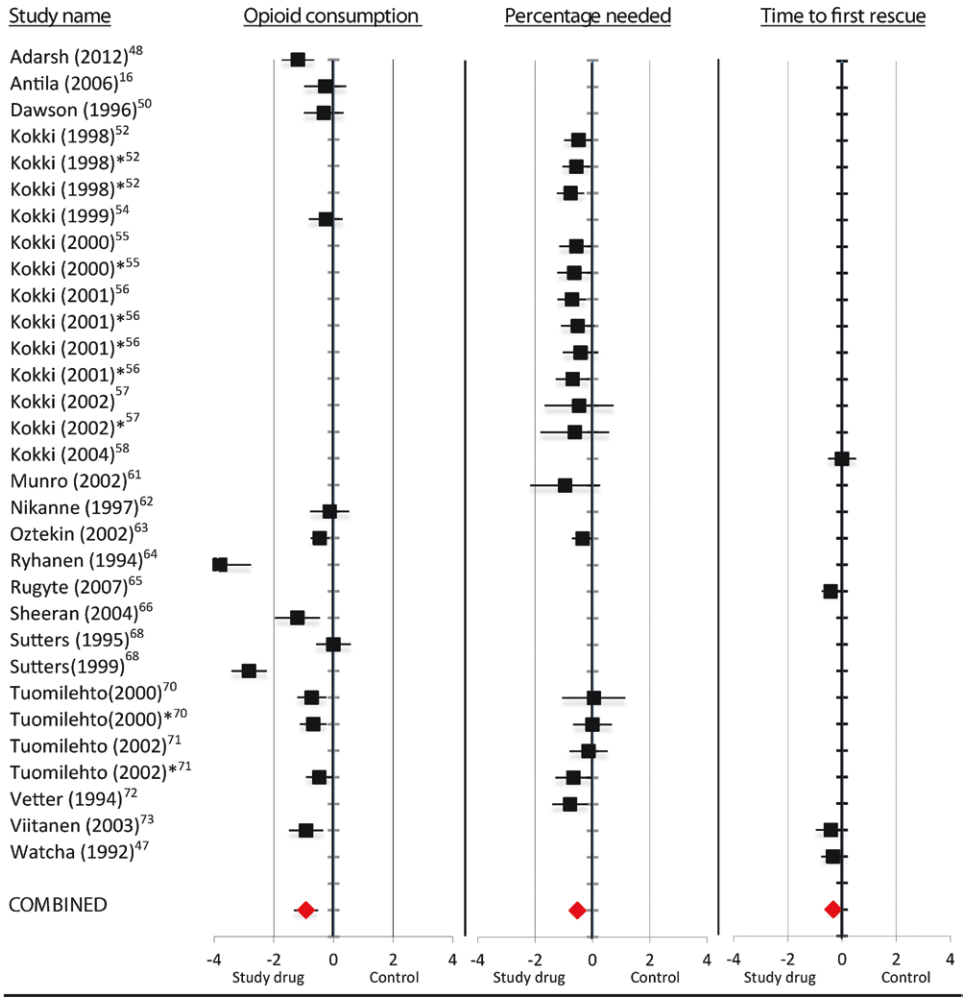

Fig. 4. Forest plot for nonsteroidal antiinflammatory drugs as study drug. Expressed as Hedges' g score and 95% CIs. Negative scores favor study drug over control. *Study included more than one active treatment arm.

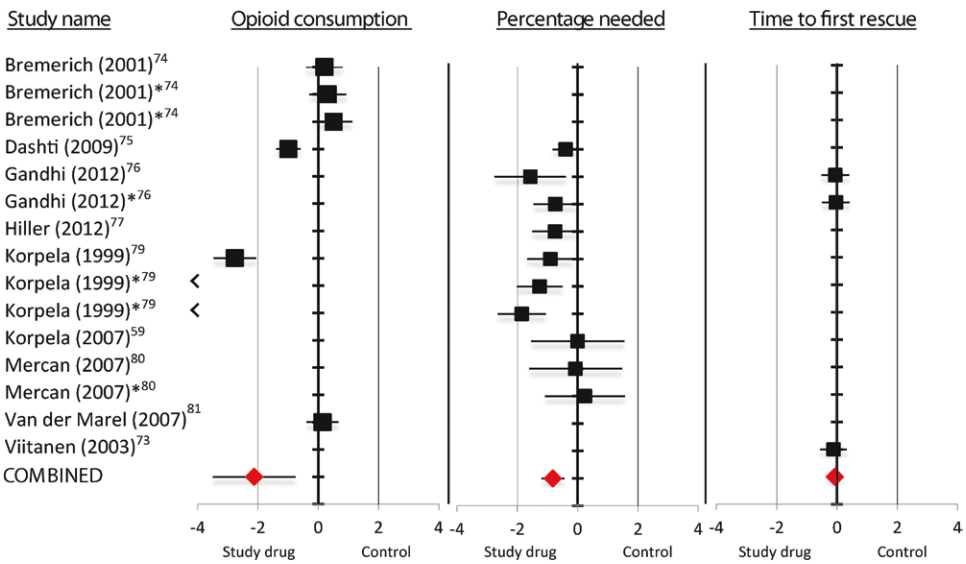

Fig. 5. Forest plot for acetaminophen as study drug. Expressed as Hedges' g score and 95% CIs. Negative scores favor study drug over control. *Study included more than one active treatment arm.

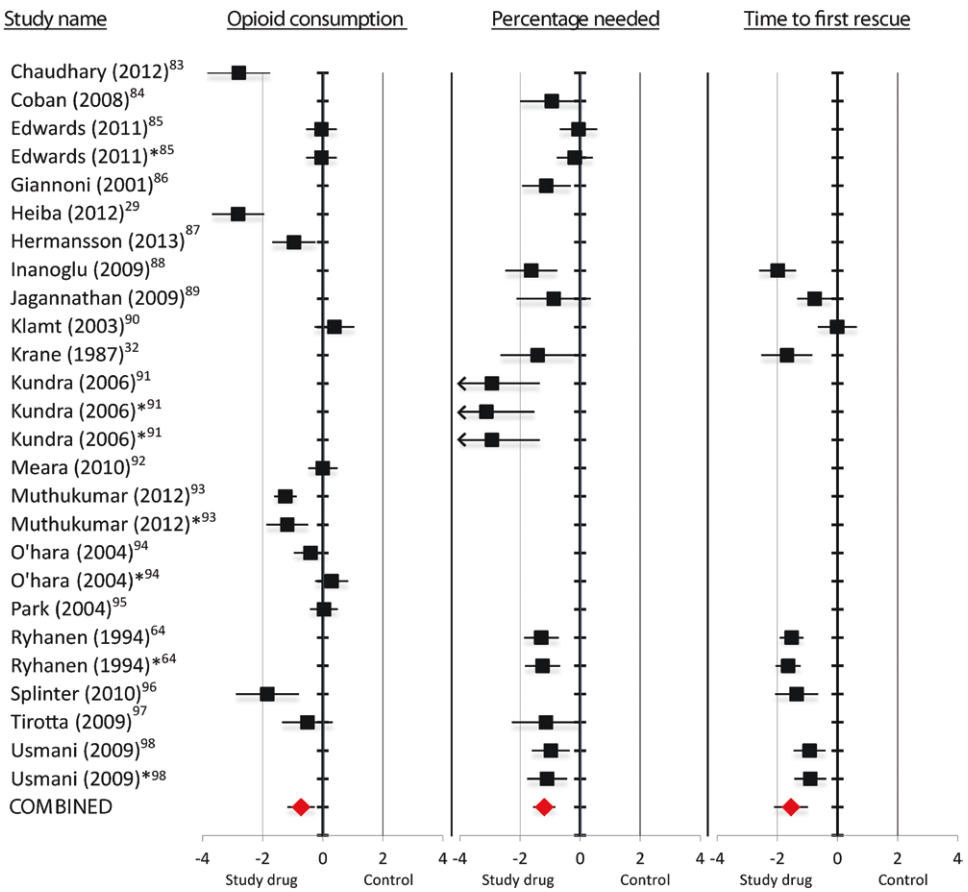

Fig. 6. Forest plot for local anesthetics as study drug. Expressed as Hedges' g score and 95% CIs. Negative scores favor study drug over control. *Study included more than one active treatment arm.

g = −1.05; 95% CI, −1.45 to −0.65; $P < 0.001$). Nine of 12 treatment arms demonstrated significant percent opioid-sparing effect.

Local anesthetic trials were highly variable. They involved wound infiltration (9 of 20 articles, two of those with continuous subcutaneous infusion), peripheral nerve blocks (5 of 20 articles), and epidural blocks (4 of 20 articles, 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, whereas 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. Similar results for the pain score measures were found when using parametric and nonparametric methods.

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 (β = 0.37, $R^2 = 0.44$), a small relationship between pain in the control group and total opioid use (β = 0.16, $R^2 = 0.16$), but no relationship with the percentage requiring recue medications (β = 0.06, $R^2 = 0.01$) (figs. 1 and 2 in Supplemental Digital Content 1, http://links.lww.com/ALN/B91, which depict the efficacy–burden relationship for opioids as the study drug). Although time to rescue showed good assay sensitivity for opioid sparing, trials using this endpoint had higher pain scores in control groups compared with 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 (β = 0.70, $R^2 = 0.25$),

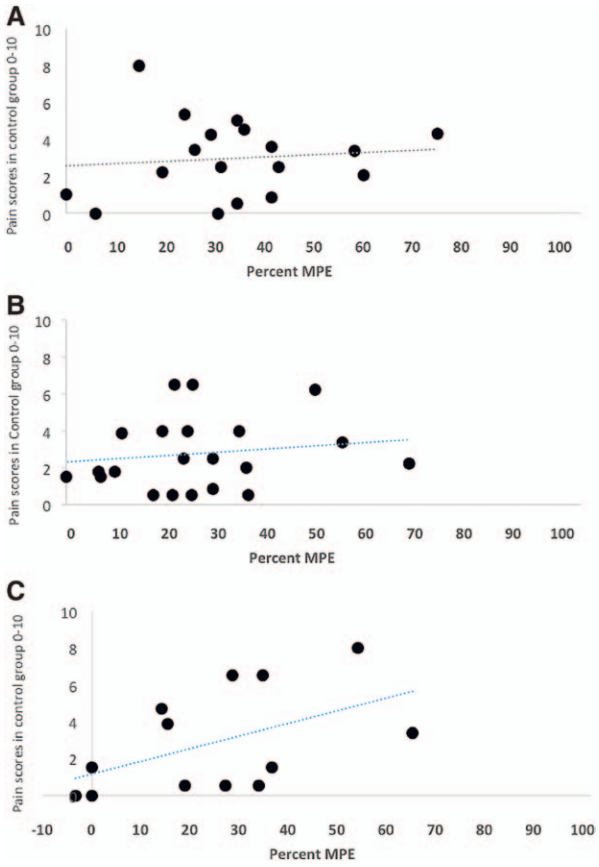

Fig. 7. Efficacy—burden relationship for nonsteroidal antiinflammatory drugs as the study drug. (*A*) Rescue opioid usage (milligram per kilogram per hour) as the outcome. (*B*) Percentage requiring rescue medication as the outcome. (*C*) Time to first rescue medication (minutes) as the outcome. Percent MPE = percent maximum possible effect: placebo—study/placebo.

a small relationship between pain in the control group and percentage requiring recue 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 recue 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, http://links.lww.com/ALN/B91, which depict the efficacy–vurden 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 recue 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

Although 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 (milligram per kilogram per hour, 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 (milligram per kilogram per hour), (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 an accepted 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,

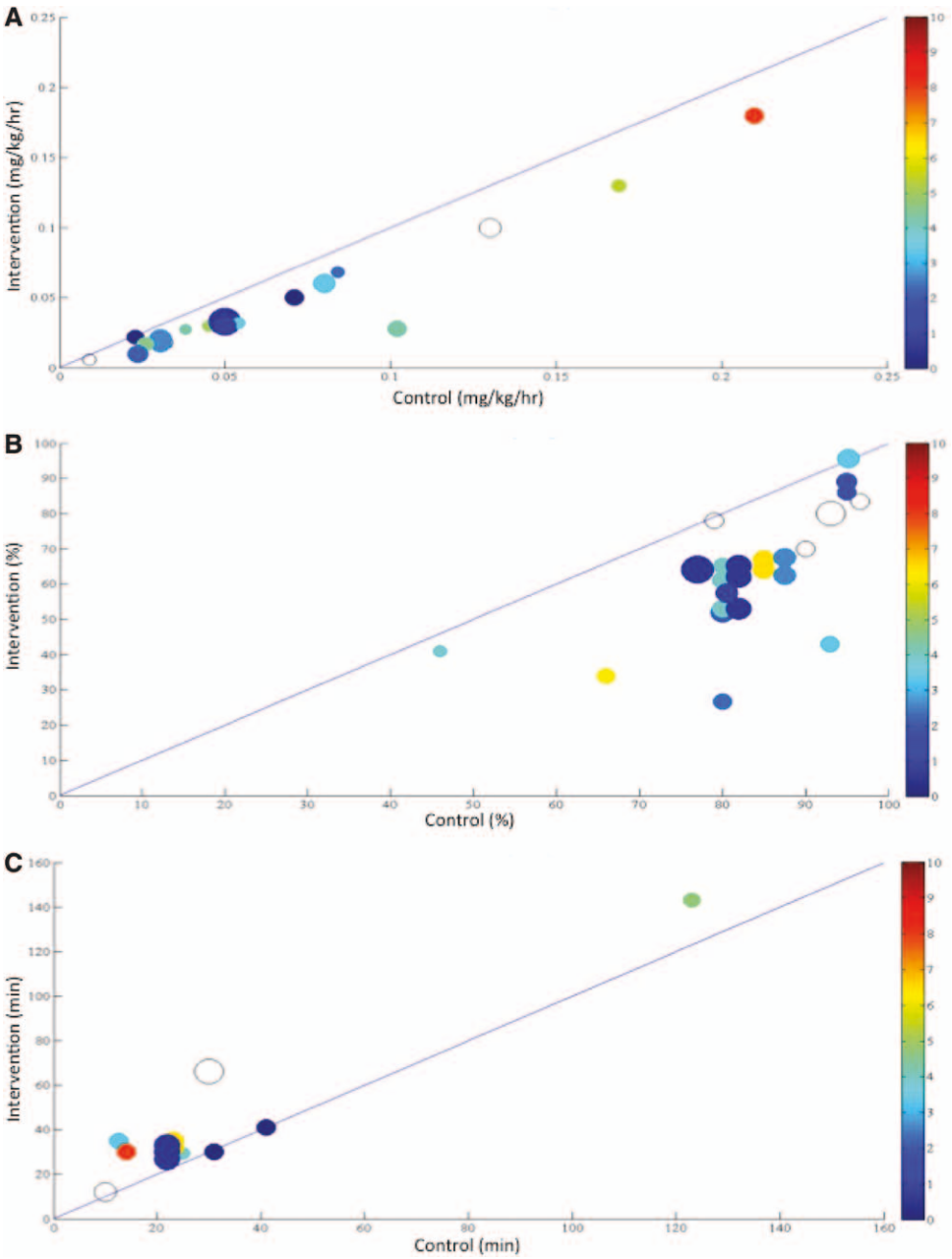

Fig. 8. Nonsteroidal antiinflammatory drugs as the study drug. (*A*) Rescue opioid usage (milligram per kilogram per hour) as the outcome. (*B*) Percentage requiring rescue medication as the outcome. (*C*) Time to first rescue medication (minutes) as the outcome. *Colorless circles* indicate studies without pain scores.

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.

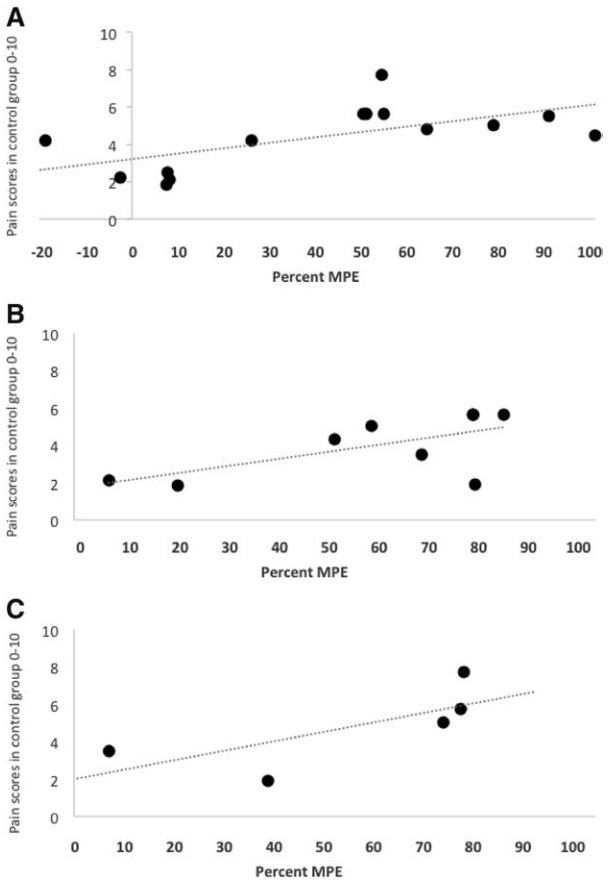

Fig. 9. Efficacy–burden relationship for local anesthetics as the study drug. (*A*) Rescue opioid usage (milligram per kilogram per hour) as the outcome. (*B*) Percentage requiring rescue medication as the outcome. (*C*) Time to first rescue medication (minutes) as the outcome. Percent MPE = percent maximum possible effect: placebo—study/placebo.

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 after 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.

Patient-controlled analgesia/nurse-controlled analgesia 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.

Acknowledgments

The authors thank Paul A. Bain, Ph.D. (Countway Library of Medicine, Harvard University, Boston, Massachusetts), and Alison Clapp, M.L.I.S. (Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts), for their assistance in searching the literature, and Ted Kaptchuk, B.A. (Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts), for providing mentoring, which was supported by National Institutes of Health grant no. 2K24AT004095 (Bethesda, Maryland).

This study was supported by a grant project (P2BSP1_148628) awarded to Dr. Kossowsky by the Swiss National Science Foundation (Bern, Switzerland) and by the Sara Page Mayo Endowment for Pediatric Pain Research, Education and Treatment (Boston, Massachusetts) to Dr. Berde.

Competing Interests

The authors declare no competing interests.

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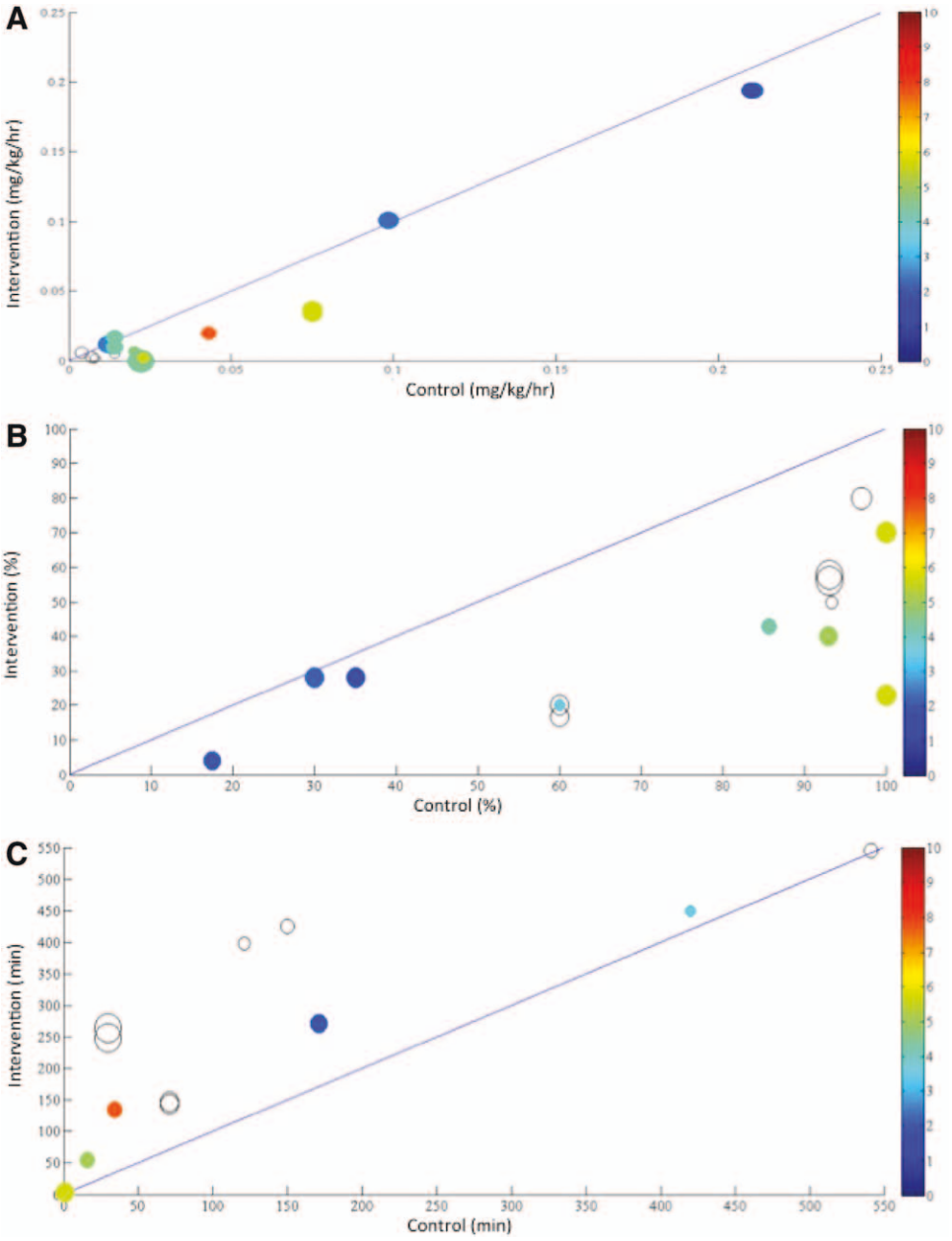

Fig. 10. Local anesthetics as the study drug. (*A*) Rescue opioid usage (milligram per kilogram per hour) as the outcome. (*B*) Percentage requiring rescue medication as the outcome. (*C*) Time to first rescue medication (minutes) as the outcome. *Colorless circles* indicate studies without pain scores.

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