

SUPPLEMENTAL DIGITAL CONTENT

A1. SEARCH STRATEGY

We followed the “Preferred reporting items for systematic reviews and meta-analyses” (PRISMA) statement for reporting of this systematic review.¹ Electronic literature searches were performed on April 08, 2013 of Medline, CINAHL, Embase, The Cochrane Library and Web of science. Key words were used to identify the ‘Opioids’ (individual opioid names), ‘setting’ (*e.g.*, surgical procedures, operative, pain, postoperative), ‘outcomes’ (*e.g.*, parent controlled analgesia, opioid consumption, opioid sparing), ‘population’ (*e.g.*, children, pediatric, neonate, child, newborn), and ‘design’ (*e.g.*, randomized controlled trial, controlled clinical trial). The full list of search terms used in the MEDLINE search can be found in Table 1. The full list of search terms are available upon request.

In addition, the references of included articles were reviewed. Eligibility judgments were performed independently by two reviewers (J.K. and C.D.). Inconsistencies were resolved in consensus meetings and confirmed with a third reviewer (C.B.) when necessary.

Table 1. Applied Search Strategies

Terms	MEDLINE search terms
Opioids	"Fentanyl"[mesh] OR "Morphine"[mesh] OR "Codeine"[mesh] OR "Hydromorphone"[mesh] OR "Hydrocodone"[mesh] OR "Oxycodone"[mesh] OR "tramadol"[mesh] OR fentanyl[tiab] OR phentanyl[tiab] OR codeine[tiab] OR methylmorphine[tiab] OR isocodeine[tiab] OR hydromorphone[tiab] OR dihydromorphinone[tiab] OR hydromorphon[tiab] OR palladone[tiab] OR dilaudid[tiab] OR hydrocodone[tiab] OR oxycodone[tiab] OR dihydrone[tiab] OR oxycontin[tiab] OR oxycone[tiab] OR dihydrohydroxycodone[tiab] OR oxycodone[tiab] OR eucodal[tiab] OR morphine[tiab] OR tramadol[tiab]
AND	
Setting	"surgery"[subheading] OR "Surgical Procedures, Operative"[Mesh] OR surgery[tiab] OR surgical[tiab] OR operative[tiab] OR postsurgical[tiab] OR postsurgery[tiab] OR postoperative[tiab]
OR	
Outcomes	"Pain, Postoperative"[Mesh] OR (("Pain"[Mesh] OR pain[tiab]) AND "Analgesia, Patient-Controlled"[Mesh] OR ("Self

	Administration"[Mesh] AND "Analgesia"[mesh]) OR patient controlled analgesia[tiab] OR parent controlled analgesia[tiab] OR nurse controlled analgesia[tiab] OR NCA[tiab] OR PCA[tiab] OR opiate consumption[tiab] OR opioid consumption[tiab] OR morphine consumption[tiab] OR fentanyl consumption[tiab] OR tramadol consumption[tiab] OR codeine consumption[tiab] OR opioid sparing[tiab] OR opiate sparing[tiab] OR morphine sparing[tiab] OR tramadol sparing[tiab] OR fentanyl sparing[tiab] OR rescue medication*[tiab] OR rescue analgesi*[tiab]
AND	
Population	Infant[MeSH Terms] OR Child[MeSH Terms] OR Adolescent[MeSH Terms] OR child*[tiab] OR adolescen*[tiab] OR infan*[tiab] OR neonate*[tiab] OR newborn*[tiab] OR new born*[tiab] OR baby[tiab] OR babies[tiab] OR toddler*[tiab] OR teen*[tiab] OR boy[tiab] OR boys[tiab] OR girl*[tiab] OR pediatric[tiab] OR paediatric[tiab] OR puber*[tiab] OR pubescen*[tiab] OR prepubescen*[tiab] OR prepubert*[tiab]
AND	
Design	"randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "randomized"[tiab] OR "randomised"[tiab] OR "placebo"[tiab] OR "drug therapy"[sh] OR "randomly"[tiab] OR "trial"[tiab] OR "groups"[tiab]

A2. DESCRIPTIVE DATA OF THE STUDIES INCLUDED IN THE STUDY DRUGS

1. Opioids

The majority of included studies evaluated the immediate rescue medication consumption in tonsillectomies/adenoidectomies (33.3%), urological procedures (18.8%) and scoliosis/spinal surgery (12.2%). Most of the studies used placebo controls (60.6%). In 45.5% of the papers, the primary outcome was not clearly stated and 42.4% stated that it was rescue medication. Of the three evaluated outcomes, 67.7% of the papers reported total dose, 50% of studies reported the percentage of patients who needed rescue medication and 48.5% time to first rescue medication. Only 10 papers reported 2 outcomes and 5 papers reported the 3 evaluated outcomes.

In 39.4% of the papers, pain scores were not reported. In those reporting, 40% used observed pain scales (*e.g.*, Children's Hospital of Eastern Ontario Pain Scale, Children and Infants Postoperative Pain Scale and nurses pain scales) and 60% used self-reported pain scales (*e.g.*, Visual Analog Scale, The Wong-Baker FACES Pain Rating Scale, Numeric Rating Scale). In

general, the mean pain score among all the control groups for the chosen time point was 3.4 over 10.

2. Nonsteroidal antiinflammatories (NSAIDs)

The majority of the 29 included studies evaluated the immediate rescue medication consumption in tonsillectomies/adenoidectomies (44.8%), strabismus procedures (10.3%) and orthopedic surgeries (6.9%). Most of the studies used a placebo controls (79.3%). Most papers stated rescue medication as the primary outcome (58.6%), and only 6.9% looked primarily at pain scores. Of the three evaluated outcomes, 65.5% of the papers reported total dose, 62.1% percentage that need rescue medication and 37.9% time to first rescue medication. Thirteen papers reported two outcomes and three papers reported the three evaluated outcomes.

In 17.2% of the papers, pain scores were not reported. In those reporting, 29% used observed pain scales and 70.8% used self-reported pain scales. The mean pain score among all the control groups was 3.1 out of 10.

3. Acetaminophen

The majority of the 11 included studies evaluated the immediate rescue medication consumption in tonsillectomies/adenoidectomies (36.4%), strabismus procedures (10.3%) and orthopedic surgeries (6.9%). Most of the studies used a placebo (63.6%). Most papers stated rescue medication as the primary outcome (54.5%), and only 9.1% looked primarily at pain scores. Of the three evaluated outcomes, 81.8% of the papers reported total dose, 54.5% percentage that need rescue medication and 36.3% time to first rescue medication. Four papers reported two outcomes and two papers reported the three evaluated outcomes.

In 27.3% of the papers, pain scores were not reported. In those reporting, half used observed pain scales and half used self-reported pain scales. The mean pain score among all the control groups was 3.18 out of 10.

4. Local Anesthetics

The majority of included studies evaluated the immediate rescue medication consumption in abdominal/urological procedures (45%), tonsillectomies/adenoidectomies (20%), and cleft palate repair (15%). Most of the studies used a placebo control group (71.4%). 35% of the papers reported rescue medication as the primary outcome, the same percentage reported pain scores as

the primary outcome and 25% didn't clearly state the primary outcome. Of the three evaluated outcomes, 65% of the papers reported total dose, 50% percentage that need rescue medication and 50% time to first rescue medication. Only 13 papers reported two outcomes and none of them reported the three evaluated outcomes.

In 35% of the papers, pain scores were not reported. In those reporting, 61.5% used objective pain scales and 38.5% used self-reported pain scales. The mean pain score among all the control groups for the chosen time point was 4.0 out of 10.

A3. ADDITIONAL RESULTS

Table 2 presents detailed information about the effectiveness measures evaluated for each one of the included papers. These measures include: Pain scores in the control/placebo group, mean opioid sparing (placebo—study/placebo), and the Hedge's G with the 95% confidence interval (CI). Table 3 summarizes the results of publication bias and tests of heterogeneity.

In addition to the "Efficacy-burden relationship" graphs, we plotted each one of the outcomes of the treatment arm against the same outcome in the control arm. If the intervention drug is effective in reducing postoperative pain, the postoperative opioid consumption in the treatment groups would be lower (lower total consumption, lower needs of rescue medication and higher time to first rescue medication) than the control groups. If the studies are equally distributed along the line of equality, significant interactions between the intervention drug and the opioid sparing are unlikely. In order to explore possible relationships between the clinical effectiveness of the studies and the pain reported by the children in the control arm, the dots are colored according to the mean pain intensity (scale 0-10) reported in the control arm.

Table 2. Effectiveness Characteristics of Included Studies

	Intervention drug				Opioid Consumption				Percentage needed				Time to first rescue			
Source	Name	Dose	Route	Pain score	placebo-treatment /placebo	Hedges's g	LCI	UCI	placebo-treatment /placebo	Hedges's g	LCI	UCI	placebo-treatment /placebo	Hedges's g	LCI	UCI
Opioids																
Ali (2008) ²	Tramadol	1mg/kg	IV	0.13	n/a	n/a	--	--	0.93	-3.54	-5.21	-1.87	n/a	n/a	--	--
	Dextromethorphan	1mg/kg	ORAL		n/a	n/a	--	--	0.60	-2.45	-4.02	-0.88	n/a	n/a	--	--
Antila (2006) ³	Tramadol	1mg/kg	IV	4.29	-0.18	0.48	-0.23	1.18	n/a	n/a	n/a	n/a	n/a	n/a	--	--
Ayatollahi (2012) ⁴	Tramadol	2mg/kg	INFIL	6.41	n/a	n/a	--	--	0.50	-0.52	-1.92	0.89	n/a	n/a	--	--
Batra (2008) ⁵	Fentanyl	0.25mcg/kg	IT	1.52	0.37	-0.16	-0.88	0.56	n/a	n/a	--	--	0.03	-0.29	-1.01	0.43
	Fentanyl	0.5mcg/kg	IT		0.08	0.00	-0.73	0.73	n/a	n/a	--	--	0.08	-0.97	-1.75	-0.19
	Fentanyl	1mcg/kg	IT		0.01	-0.87	-1.61	-0.12	n/a	n/a	--	--	0.31	-3.94	-5.18	-2.71
Bean-Lijewski (1996) ⁶	Meperidine	1mg/kg	IM	3.38	0.37	n/a	--	--	0.53	-1.54	-2.43	-0.64	0.70	n/a	--	--
Campbell (1992) ⁷	Fentanyl	1mcg/kg	EPIDUR	n/a	0.00	-0.17	-0.83	0.49	0.14	-0.33	-1.21	0.54	0.21	-0.30	-0.96	0.36
Dawson (2001) ⁸	Dextromethorphan	1mg/kg	ORAL	n/a	0.00	-0.77	-1.41	-0.14	n/a	n/a	--	--	n/a	n/a	--	--
Doyle (1993a) ⁹	Morphine	20mcg/kg/hr	IV	4.09	0.04	-0.17	-0.78	0.44	n/a	n/a	--	--	n/a	n/a	--	--
Doyle (1993b) ¹⁰	Morphine	4mcg/kg/hr	IV	1.30	0.06	-0.10	-0.79	0.60	n/a	n/a	--	--	n/a	n/a	--	--
	Morphine	10mcg/kg/hr	IV		-0.09	0.20	-0.50	0.90	n/a	n/a	--	--	n/a	n/a	--	--
Eschertzhuber (2008) ¹¹	Morphine	5mcg/kg	IT	2.49	0.50	-6.75	-8.66	-4.84	n/a	n/a	--	--	n/a	n/a	--	--
	Morphine	15mcg/kg	IT		0.41	-6.31	-8.11	-4.51	n/a	n/a	--	--	n/a	n/a	--	--
Gall (2001) ¹²	Morphine	2mcg/kg	IT	4.46	0.48	-2.47	-3.60	-1.33	n/a	n/a	--	--	0.38	-1.36	-2.31	-0.42
	Morphine	5mcg/kg	IT		0.48	-2.73	-3.92	-1.53	n/a	n/a	--	--	0.53	-1.36	-2.30	-0.42
Ganesh (2008) ¹³	Fentanyl	2mcg/ml	EPIDUR	2.94	0.31	-1.10	-1.83	-0.38	n/a	n/a	--	--	0.76	-1.01	-1.73	-0.29
Hammer (2005) ¹⁴	Morphine	7mcg/kg	EPIDUR	4.00	0.40	-0.98	-1.63	-0.34	n/a	n/a	--	--	n/a	n/a	--	--
Hasan (2004) ¹⁵	Dextromethorphan	1mg/kg	ORAL	1.93	0.41	-1.08	-1.75	-0.41	n/a	n/a	--	--	n/a	n/a	--	--
Heiba (2012) ¹⁶	Tramadol	2mg/kg	INFIL	7.70	0.12	-3.00	-3.89	-2.10	n/a	n/a	--	--	0.75	-6.57	-8.13	-5.01
Kawaraguchi (2006) ¹⁷	Fentanyl	1mcg/kg	EPIDUR	2.20	n/a	n/a	--	--	0.03	-0.05	-0.80	0.71	-0.14	0.19	-0.46	0.84
Kim (2013) ¹⁸	Remifentanyl	0.3mcg/kg/min	IV	0.76	-0.17	n/a	--	--	n/a	n/a	--	--	n/a	n/a	--	--
	Remifentanyl	0.6mcg/kg/min	IV		-0.48	n/a	--	--	n/a	n/a	--	--	n/a	n/a	--	--
	Remifentanyl	0.9mcg/kg/min	IV		-0.83	n/a	--	--	n/a	n/a	--	--	n/a	n/a	--	--
Krane (1987) ¹⁹	Morphine	0.1mg/kg	EPIDUR	n/a	n/a	n/a	--	--	0.71	-1.92	-3.15	-0.69	0.83	-2.15	-3.04	-1.27
Lawhorn (1994) ²⁰	Butorphanol	40mcg/kg	EPIDUR	n/a	n/a	n/a	--	--	n/a	n/a	--	--	0.02	-0.27	-1.12	0.57
Lawhorn (1997) ²¹	Butorphanol	30mcg/kg	EPIDUR	n/a	n/a	n/a	--	--	0.79	-1.03	-1.51	-0.55	0.70	-5.90	-6.54	-5.26
Mane (2011) ²²	Fentanyl	0.25mcg/kg	BLOCK	n/a	n/a	n/a	--	--	n/a	n/a	--	--	0.24	-1.58	-2.39	-0.78
	Pethidine	0.25mcg/kg	BLOCK		n/a	n/a	--	--	n/a	n/a	--	--	0.49	-4.79	-6.18	-3.39
McDonnell (2008) ²³	Morphine	100mcg/kg	IV	n/a	0.00	-1.94	-2.71	-1.17	n/a	n/a	--	--	n/a	n/a	--	--
Ozcengiz (2001) ²⁴	Tramadol	2mg/kg	EPIDUR	n/a	n/a	n/a	--	--	-0.05	0.00	-0.90	0.90	n/a	n/a	--	--
	Morphine	0.03mg/kg	EPIDUR		n/a	n/a	--	--	0.30	-0.27	-1.28	0.73	n/a	n/a	--	--
Rosen (1989) ²⁵	Morphine	0.075mg/kg	EPIDUR	6.00	0.22	-1.32	-2.06	-0.57	0.83	-1.61	-2.60	-0.62	n/a	n/a	--	--
Rose (1999) ²⁶	Dextromethorphan	0.5mg/kg	ORAL	2.00	0.05	0.70	0.06	1.34	-0.09	0.16	-0.60	0.92	n/a	n/a	--	--
	Dextromethorphan	1mg/kg	ORAL		-0.09	-0.42	-1.05	0.21	-0.09	0.16	-0.60	0.92	n/a	n/a	--	--
Sharma (2011) ²⁷	Methadone	0.1mg/kg	IV	4.24	0.07	-0.28	-0.99	0.42	n/a	n/a	--	--	n/a	n/a	--	--
	Methadone	0.2mg/kg	IV		0.01	0.17	-0.53	0.88	n/a	n/a	--	--	n/a	n/a	--	--
	Methadone	0.3mg/kg	IV		-0.07	-0.09	-0.77	0.59	n/a	n/a	--	--	n/a	n/a	--	--
Suominen (2004) ²⁸	Morphine	20mcg/kg	IT	n/a	0.00	-0.54	-1.01	-0.07	0.13	-0.58	-1.37	0.22	0.29	-0.40	-0.86	0.07
Suski (2010) ²⁹	Dextromethorphan	30-45mg	ORAL	4.83	0.03	-0.10	-0.60	0.40	n/a	n/a	--	--	n/a	n/a	--	--

Tarkkila (2003) ³⁰	Remifentanyl	1mcg/kg	IV	n/a	0.00	0.62	0.06	1.18	0.20	-0.32	-0.95	0.30	-0.33	0.45	-0.11	1.00
Ugur (2008) ³¹	Tramadol	2mg/kg	IM	2.46	n/a	n/a	--	--	0.56	-0.75	-1.58	0.07	n/a	n/a	--	--
	Tramadol	2mg/kg	INFIL		n/a	n/a	--	--	0.89	-1.61	-2.80	-0.41	n/a	n/a	--	--
Umuroglu (2004) ³²	Morphine	0.1mg/kg	IV	4.25	n/a	n/a	--	--	0.60	-2.05	-3.66	-0.44	0.79	-1.46	-2.24	-0.67
	Tramadol	1.5mg/kg	IV		n/a	n/a	--	--	0.40	-1.64	-3.25	-0.04	0.64	-0.65	-1.36	0.07
Viitanen (2001) ³³	Tramadol	2mg/kg	IV	n/a	0.00	-0.54	-0.98	-0.10	0.35	-0.84	-1.42	-0.25	0.00	0.00	-0.43	0.43
Watcha (1992) ³⁴	Morphine	0.1mg/kg	IV	6.23	n/a	n/a	--	--	0.48	-0.72	-1.29	-0.15	n/a	n/a	--	--
NSAIDs																
Adarsh (2012) ³⁵	Diclofenac	1mg/kg	RECTAL	4.29	0.72	-1.19	-1.73	-0.65	0.67	n/a	--	--	n/a	n/a	--	--
Antila (2006) ³	Ketoprofen	2mg/kg	IV	2.20	0.19	-0.28	-0.98	0.42	n/a	n/a	--	--	n/a	n/a	--	--
Bean-Lijewski (1996) ⁶	Ketorolac	0.75mg/kg	IM	3.38	0.56	n/a	--	--	0.54	n/a	--	--	0.64	n/a	--	--
Bridge (2000) ³⁶	Ketorolac	3mg per eye	OPHTHAL	3.85	n/a	n/a	--	--	0.11	n/a	--	--	0.15	n/a	--	--
Dawson (1996) ³⁷	Ketorolac	1mg/kg + 0.5mg/kg QID	IV	n/a	0.29	-0.33	-0.99	0.34	n/a	n/a	--	--	n/a	n/a	--	--
Kokki (1994) ³⁸	Ibuprofen	40mg/kg/day	RECTAL	0.83	0.40	n/a	--	--	0.29	n/a	--	--	n/a	n/a	--	--
Kokki (1998) ³⁹	Ketoprofen	0.3mg/kg	IV		n/a	n/a	--	--	0.21	-0.49	-0.97	-0.01	0.19	n/a	--	--
	Ketoprofen	1mg/kg	IV	0.50	n/a	n/a	--	--	0.24	-0.56	-1.04	-0.08	0.33	n/a	--	--
	Ketoprofen	3mg/kg	IV		n/a	n/a	--	--	0.35	-0.76	-1.24	-0.29	0.27	n/a	--	--
Kokki (1999a) ⁴⁰	Ketoprofen	1+1mg/kg	IV	0.00	0.30	n/a	--	--	0.22	n/a	--	--	-0.03	n/a	--	--
Kokki (1999b) ⁴¹	Ketoprofen	1+ 4mg/kg	IV	0.00	0.06	-0.26	-0.82	0.31	n/a	n/a	--	--	n/a	n/a	--	--
Kokki (2000) ⁴²	Ketoprofen	25mg/kg	IV		n/a	n/a	--	--	0.21	-0.56	-1.16	0.03	0.28	n/a	--	--
	Ketoprofen	25mg/kg	RECTAL	6.50	n/a	n/a	--	--	0.25	-0.63	-1.22	-0.04	0.34	n/a	--	--
Kokki (2001) ⁴³	Ketoprofen	1+1mg/kg	IV	2.00	n/a	n/a	--	--	0.35	-0.71	-1.21	-0.22	n/a	n/a	--	--
	Ketoprofen	0.3mg/kg	IV		n/a	n/a	--	--	0.24	-0.51	-1.10	0.08	n/a	n/a	--	--
	Ketoprofen	1mg/kg	IV	4.00	n/a	n/a	--	--	0.19	-0.42	-1.03	0.20	n/a	n/a	--	--
	Ketoprofen	3mg/kg	IV		n/a	n/a	--	--	0.34	-0.69	-1.28	-0.10	n/a	n/a	--	--
Kokki (2002) ⁴⁴	Ketoprofen	0.5+3mg/kg preqx	IV		n/a	n/a	--	--	0.06	-0.47	-1.67	0.74	n/a	n/a	--	--
	Ketoprofen	0.5+3mg/kg postqx	IV	1.81	n/a	n/a	--	--	0.09	-0.61	-1.81	0.58	n/a	n/a	--	--
Kokki (2004) ⁴⁵	Ketoprofen	1+1mg/kg	IV	n/a	n/a	n/a	--	--	0.01	n/a	--	--	0.00	0.00	-0.52	0.52
Korpela (2007) ⁴⁶	Naproxen	10mg/kg	ORAL	8.00	0.14	n/a	--	--	0.14	-0.96	-2.17	0.26	0.53	n/a	--	--
Morton (1999) ⁴⁷	Diclofenac	1mg/kg TID	RECTAL	n/a	0.43	n/a	--	--	n/a	n/a	--	--	n/a	n/a	--	--
Munro (2002) ⁴⁸	Ketorolac	0.5mg/kg	IV	5.00	0.33	-0.13	-0.78	0.53	n/a	n/a	--	--	n/a	n/a	--	--
Nikanne (1997) ⁴⁹	Ketoprofen	1+1mg/kg	IV	0.55	0.33	-0.46	-0.77	-0.15	0.17	-0.35	-0.72	0.03	n/a	n/a	--	--
Oztekin (2002) ⁵⁰	Diclofenac	1mg/kg	RECTAL	5.33	0.23	-3.80	-4.83	-2.77	n/a	n/a	--	--	n/a	n/a	--	--
Ryhanen (1994) ⁵¹	Diclofenac	1mg/kg	IM	n/a	0.40	n/a	--	--	0.14	n/a	--	--	0.55	-0.42	-0.75	-0.09
Rugyte (2007) ⁵²	Ketoprofen	1mg/kg	IV	3.59	n/a	-1.21	-1.96	-0.46	n/a	n/a	--	--	n/a	n/a	--	--
Sheeran (2004) ⁵³	Refecoxib	0.5 mg/kg	ORAL	1.02	0.00	0.00	-0.57	0.57	n/a	n/a	--	--	n/a	n/a	--	--
Sims (1994) ⁵⁴	Indomethacin	2mg/kg	RECTAL	4.28	0.28	n/a	--	--	n/a	n/a	--	--	n/a	n/a	--	--
Sutters (1995) ⁵⁵	Ketorolac	1mg/kg	IM	3.41	0.25	-2.83	-3.42	-2.24	0.00	n/a	--	--	n/a	n/a	--	--
Sutters(1999) ⁵⁶	Ketorolac	1mg/kg + 0.5mg/kg QID	IV	2.08	0.58	-0.73	-1.22	-0.24	n/a	0.05	-1.05	1.15	n/a	n/a	--	--
Tuomilehto (2000) ⁵⁷	Ketoprofen	1 mg/kg	IV		n/a	-0.68	-1.12	-0.23	0.00	0.00	-0.67	0.67	0.36	n/a	--	--
	Ketoprofen	1 mg/kg	ORAL	2.50	n/a	n/a	--	--	0.07	-0.14	-0.80	0.53	0.00	n/a	--	--
Tuomilehto (2002) ⁵⁸	Ketoprofen	2mg/kg	IM	1.50	0.41	-0.48	-0.92	-0.04	0.23	-0.66	-1.29	-0.04	n/a	n/a	--	--
	Ketoprofen	2mg/kg	IV		0.30	n/a	--	--	0.29	-0.78	-1.40	-0.16	n/a	n/a	--	--
Vetter (1994) ⁵⁹	Ketorolac	0.8mg/kg	IV	4.55	0.35	-0.92	-1.50	-0.35	n/a	n/a	--	--	0.14	-0.41	-0.96	0.14

Viitanen (2003) ⁶⁰	Ibuprofen	15mg/kg	RECTAL	n/a	0.23	n/a	--	--	n/a	n/a	--	--	0.17	-0.32	-0.76	0.12
Watcha (1992) ³⁴	Ketorolac	0.9mg/kg	IV	6.23	n/a	-1.32	-2.12	-0.52	0.48	n/a	--	--	n/a	n/a	--	--
Acetaminophen																
Bremerich (2001) ⁶¹	Acetaminophen	10mg/kg	RECTAL		-0.11	0.21	-0.40	0.82	n/a	n/a	--	--	n/a	n/a	--	--
	Acetaminophen	20mg/kg	RECTAL	1.90	-0.18	0.32	-0.29	0.93	n/a	n/a	--	--	n/a	n/a	--	--
	Acetaminophen	40mg/kg	RECTAL		-0.27	0.51	-0.11	1.13	n/a	n/a	--	--	n/a	n/a	--	--
Dashti (2009) ⁶²	Acetaminophen	40mg/kg	RECTAL	6.11	0.64	-0.99	-1.40	-0.59	0.30	-0.40	-0.83	0.03	n/a	n/a	--	--
Gandhi (2012) ⁶³	Acetaminophen	40mg/kg	RECTAL	3.20	n/a	n/a	--	--	0.92	-1.57	-2.76	-0.38	-0.05	-0.06	-0.51	0.40
	Acetaminophen	20mg/kg	RECTAL		n/a	n/a	--	--	0.68	-0.74	-1.46	-0.03	0.04	-0.04	-0.49	0.42
Hiller (2012) ⁶⁴	Acetaminophen	30mg/kg	IV	n/a	0.00	n/a	--	--	0.46	-0.75	-1.50	0.00	-0.26	n/a	--	--
Kocum (2013) ⁶⁵	Acetaminophen	15mg/kg	IV	3.03	0.00	n/a	--	--	n/a	n/a	--	--	n/a	n/a	--	--
Korpela (1999) ⁶⁶	Acetaminophen	20mg/kg	RECTAL		0.25	-2.77	-3.47	-2.07	0.30	-0.91	-1.67	-0.14	n/a	n/a	--	--
	Acetaminophen	40mg/kg	RECTAL	1.97	0.52	-5.52	-6.62	-4.41	0.48	-1.26	-2.02	-0.50	n/a	n/a	--	--
	Acetaminophen	60mg/kg	RECTAL		0.75	-10.90	-12.9	-8.89	0.74	-1.85	-2.65	-1.06	n/a	n/a	--	--
Korpela (2007) ⁴⁶	acetaminophen	10mg/kg	ORAL	8.00	-0.14	n/a	--	--	0.00	0.00	-1.55	1.55	-0.07	n/a	--	--
Mercan (2007) ⁶⁷	Acetaminophen	20-25mg/kg p3	RECTAL		n/a	n/a	--	--	0.12	-0.07	-1.61	1.47	n/a	n/a	--	--
	Acetaminophen	20-25mg/kg p4	RECTAL	0.94	n/a	n/a	--	--	-0.53	0.24	-1.09	1.56	n/a	n/a	--	--
Morton (1999) ⁴⁷		20mg/kg														
	Acetaminophen	+15mg/kg QID	RECTAL	n/a	0.17	n/a	--	--	n/a	n/a	--	--	n/a	n/a	--	--
Van der Marel (2007) ⁶⁸	Acetaminophen	30-40mg/kg +	RECTAL	0.30	-0.10	0.14	-0.39	0.67	n/a	n/a			n/a	n/a		
		20mg/kg QID									--	--			--	--
Viitanen (2003) ⁶⁰	Acetaminophen	40mg/kg	RECTAL	n/a	0.17	n/a	--	--	n/a	n/a	--	--	-0.10	-0.11	-0.55	0.33
Local Anesthetics																
Carney (2010) ⁶⁹	Ropivacaine 0.75%	2.5mg/kg	BLOCK	5.00	0.78	n/a	--	--	n/a	n/a	--	--	0.71	n/a	--	--
Chaudhary (2012) ⁷⁰	Ropivacaine 0.5%	0.05-0.06mg/kg	BLOCK	4.83	0.64	-2.80	-3.84	-1.75	n/a	n/a	--	--	n/a	n/a	--	--
Coban (2008) ⁷¹	Ropivacaine	0.2mg/kg	INFIL	3.50	n/a	n/a	--	--	0.67	-0.95	-2.00	0.11	n/a	n/a	--	--
Edwards (2011) ⁷²	Bupivacaine 0.25%	0.5ml/kg	INFIL	2.14	0.08	-0.04	-0.55	0.46	0.07	-0.05	-0.67	0.56	0.07	n/a	--	--
					0.07	-0.04	-0.55	0.46	0.20	-0.18	-0.78	0.42	n/a	n/a	--	--
Giannoni (2001) ⁷³	Ropivacaine 0.01%	0.15ml/kg	INFIL	4.31	n/a	n/a	--	--	0.50	-1.12	-1.93	-0.31	n/a	n/a	--	--
Heiba (2012) ¹⁶	Lidocaine	2mg/kg	INFIL	7.70	0.54	-2.82	-3.68	-1.95	n/a	n/a	--	--	0.75	-7.53	-9.28	-5.77
Hermansson (2013) ⁷⁴	Bupivacaine	0.2 to	SC	n/a	0.59	-0.96	-1.68	-0.24	n/a	n/a	--	--	n/a	n/a	--	--
		0.4mg/kg/hr	INFUSION													
Inanoglu (2009) ⁷⁵	Bupivacaine 0.25%	NR	INFIL	5.75	n/a	n/a	--	--	0.57	-1.63	-2.49	-0.77	0.74	-1.99	-2.60	-1.37
Jagannathan (2009) ⁷⁶	Bupivacaine 0.25%	0.1ml/kg	BLOCK	1.92	n/a	n/a	--	--	0.77	-0.88	-2.11	0.35	0.37	-0.76	-1.34	-0.18
Klamt (2003) ⁷⁷	Ropivacaine 0.1%	0.2ml/kg/hr	EPIDUR	n/a	-0.64	0.39	-0.27	1.04	n/a	n/a	--	--	0.01	-0.01	-0.66	0.64
Krane (1987) ¹⁹	Bupivacaine 0.25%	0.1ml/kg	EPIDUR	n/a	n/a	n/a	--	--	0.46	-1.41	-2.64	-0.18	0.70	-1.68	-2.53	-0.84
Kundra (2006) ⁷⁸	Bupivacaine 0.25%	0.25ml/kg	IM BLOCK		0.51	n/a	--	--	0.77	-2.93	-4.51	-1.35	n/a	n/a	--	--
	Bupivacaine 0.25%	0.25ml/kg	M BLOCK	5.64	0.50	n/a	--	--	0.82	-3.12	-4.71	-1.52	n/a	n/a	--	--
	Bupivacaine 0.25%	0.25ml/kg	SM BLOCK		0.54	n/a	--	--	0.77	-2.93	-4.51	-1.35	n/a	n/a	--	--
Meara (2010) ⁷⁹	Bupivacaine 0.25%		SC	2.48	0.08	0.00	-0.48	0.48	n/a	n/a	--	--	n/a	n/a	--	--
		1ml/h	INFUSION													
Muthukumar (2012) ⁸⁰	Lignocaine	7mg/kg	INFIL	4.50	1.00	-1.25	-1.62	-0.87	n/a	n/a	--	--	n/a	n/a	--	--
	Lignocaine	7mg/kg	INFIL		0.90	-1.18	-1.88	-0.49	n/a	n/a	--	--	n/a	n/a	--	--
O'hara (2004) ⁸¹	Bupivacaine 0.1%	4ml/hr	EPIDUR	4.22	0.26	-0.41	-0.96	0.14	n/a	n/a	--	--	n/a	n/a	--	--
	Bupivacaine 0.065%	4ml/hr	EPIDUR		-0.19	0.29	-0.25	0.84	n/a	n/a	--	--	n/a	n/a	--	--
Park (2004) ⁸²	Ropivacaine 0.5%	30mg	INFIL	2.23	-0.03	0.04	-0.42	0.50	n/a	n/a	--	--	n/a	n/a	--	--
Ryhanen (1994) ⁵¹	Bupivacaine 0.25%	1ml/kg	EPIDUR	n/a	n/a	n/a	--	--	0.40	-1.29	-1.86	-0.72	0.88	-1.53	-1.92	-1.14

	Bupivacaine 0.25% +Adrenaline	1ml/kg	EPIDUR		n/a	n/a	--	--	0.38	-1.25	-1.83	-0.67	0.89	-1.64	-2.05	-1.23
Splinter (2010) ⁸³	Ropivacaine 0.2%	0.25-0.5ml/kg	BLOCK	n/a	0.65	-1.85	-2.89	-0.80	n/a	n/a	--	--	0.65	-1.36	-2.07	-0.65
Tirotta (2009) ⁸⁴	Bupivacaine /Levobupivacaine	0.5 -5 ml/hr	SC INFUSION	n/a	0.75	-0.51	-1.36	0.33	0.18	-1.14	-2.26	-0.01	n/a	n/a	--	--
Usmani (2009) ⁸⁵	EMLA cream	5%	TOPIC	n/a	n/a	n/a	--	--	0.67	-0.98	-1.60	-0.35	0.50	-0.93	-1.46	-0.40
	Lidocaine 1%	0.5ml/kg	IV		n/a	n/a	--	--	0.72	-1.10	-1.75	-0.44	0.52	-0.91	-1.43	-0.38

EPIDUR = Epidural; IM = Intramuscular; IM BLOCK = Inferior-medial block; INFIL = Infiltration; IT = Intrathecal; IV = Intravenous; LCI = Lower Confidence Interval; M BLOCK

= Medial Block; n/a = Not applicable; NSAIDS = nonsteroidal antiinflammatory drugs; OPTHAL = Ophthalmological drops; QID = quater in die (4x a day); SC INFUSION =

subcutaneous infusion; SM BLOCK = superior-medial block; UCI = upper confidence interval.

TABLE 3. Selected Results of Publication Bias and Tests of Heterogeneity

<i>Outcome</i>	<i>Study Drug</i>			
	<i>Opioids</i>	<i>NSAIDs</i>	<i>Acetaminophen</i>	<i>Local Anesthetics</i>
Total Opioid Usage				
Classic Fail-Safe N	726	498	213	193
Heterogeneity [†] (df)	88**(27)	87**(14)	97**(7)	88**(13)
Heterogeneity [†]	0.86	0.53	3.7	0.63
Hedges' G (95%CI)	-0.84 (-1.2 to -0.47)	-0.92 (-1.3 to -0.52)	-2.1 (-3.5 to -0.75)	-0.72 (-1.2 to -0.27)
% requiring medication				
Classic Fail-Safe N	375	210	78	415
Heterogeneity [†] (df)	62**(20)	0 (17)	48*(9)	64**(14)
Heterogeneity [†]	0.30	0.00	0.16	0.31
Hedges' G (95%CI)	-0.83 (-1.2 to -0.52)	-0.52 (-0.66 to -0.38)	-0.82 (-1.2 to -0.44)	-1.2 (-1.6 to -0.82)
Time to first rescue				
Classic Fail-Safe N	1115	4	0	573
Heterogeneity [†] (df)	96**(18)	0 (3)	0 (2)	89**(9)
Heterogeneity [†]	3.0	0.00	0.00	0.68
Hedges' G (95%CI)	-1.6 (-2.4 to -0.84)	-0.32 (-0.53 to -0.10)	-0.07 (-0.32 to 0.19)	-1.6 (-2.1 to -0.99)

[†] Variance between studies as a proportion of the total variance; heterogeneity tested using the I^2 statistic. Low heterogeneity = 25%; moderate

heterogeneity=50%; high heterogeneity=75%. The *p* values indicated in this column refer to whether the Q statistic is significant (the I^2 statistic does not include a test of significance).

‡ Heterogeneity tested using the T^2 (Tau-squared) statistic, which estimates the between-study variance.

* $p \leq 0.05$. ** $p \leq 0.01$.

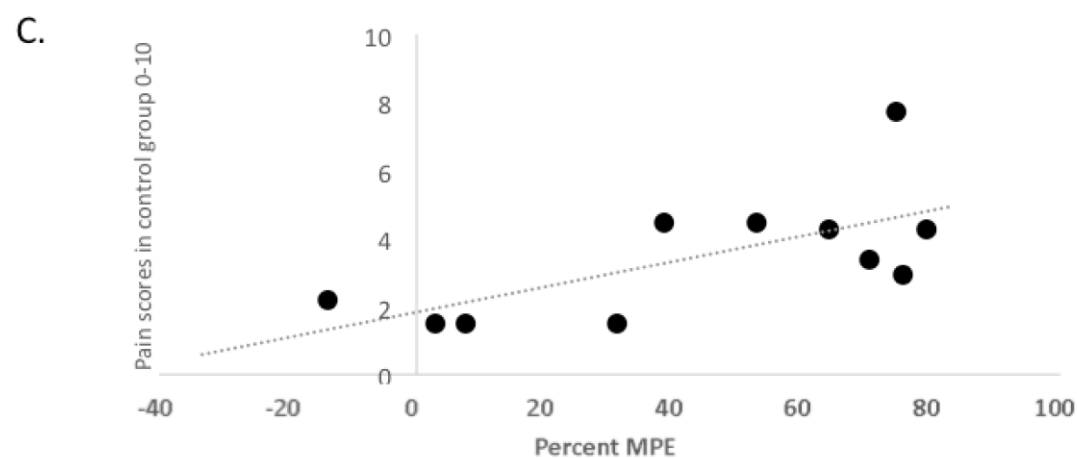
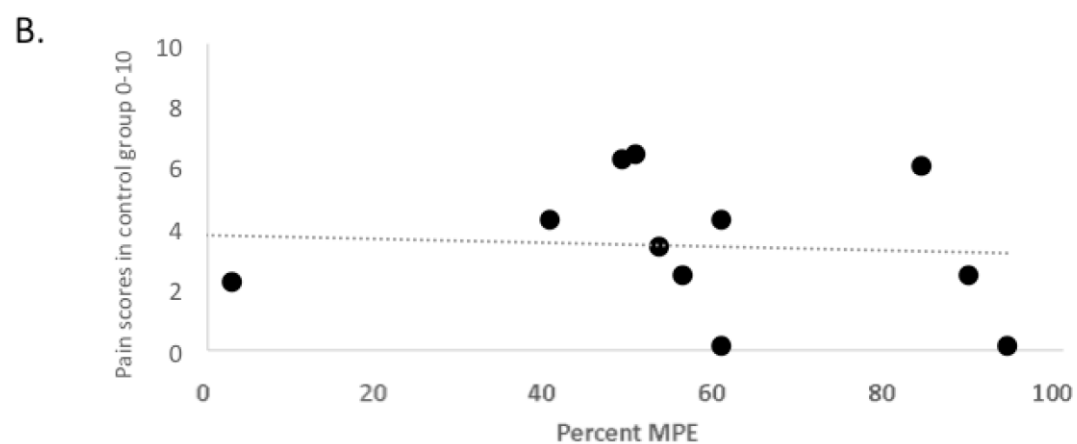
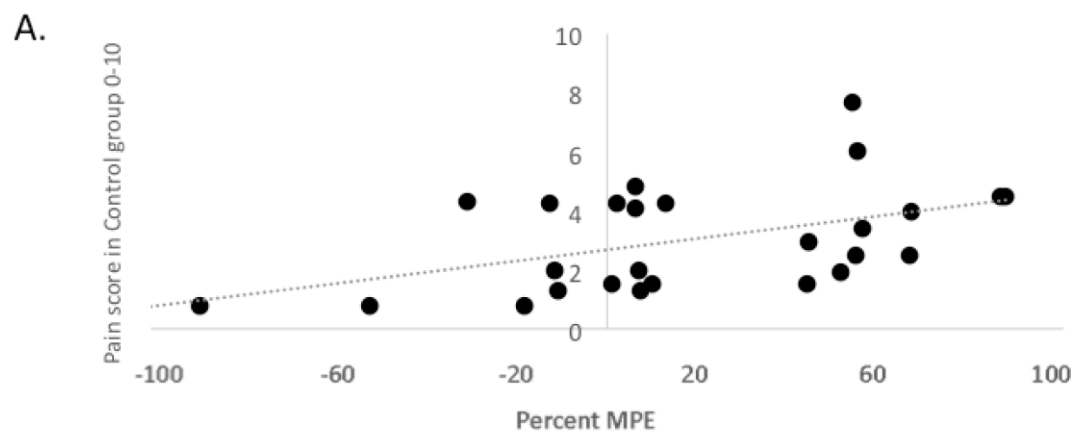


Fig. 1. Efficacy– Burden relationship for opioids as the study drug. **A.** Rescue opioid usage (mg/kg/h) as the outcome. **B.** Percentage requiring rescue medication as the outcome. **C.** Time to first rescue medication (minutes) as the outcome. Percent MPE= Percent maximum possible effect: placebo—study/ placebo.

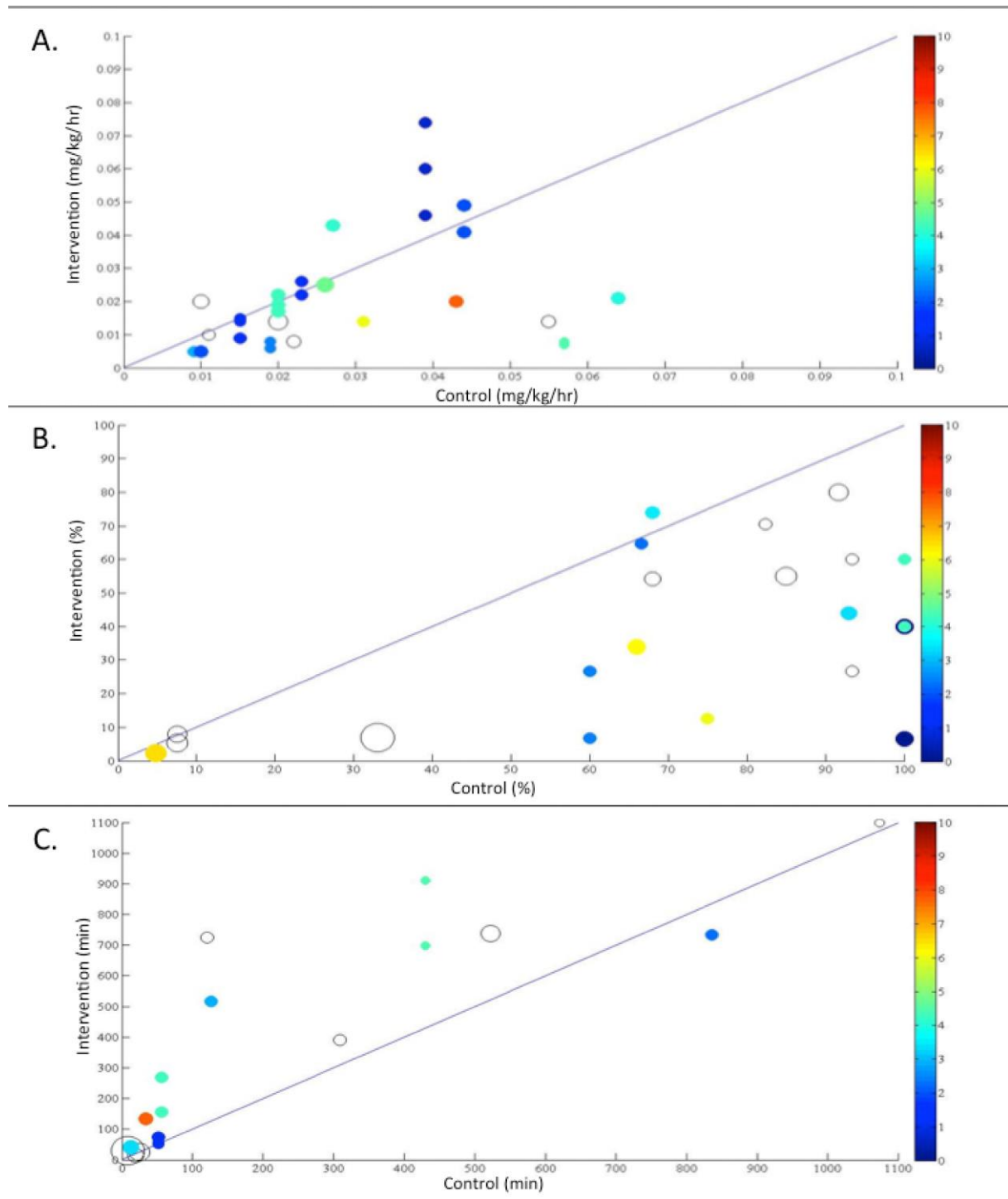


Fig. 2. Opioids as the study drug. **A.** Rescue opioid usage (mg/kg/h) as the outcome. **B.** Percentage requiring rescue medication as the outcome. **C.** Time to first rescue medication (minutes) as the outcome. Colorless circles indicate studies without pain scores.

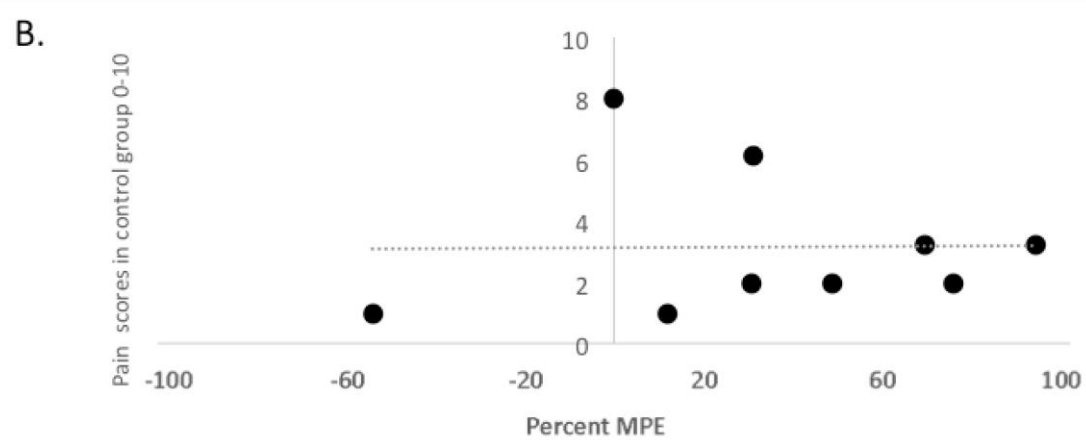
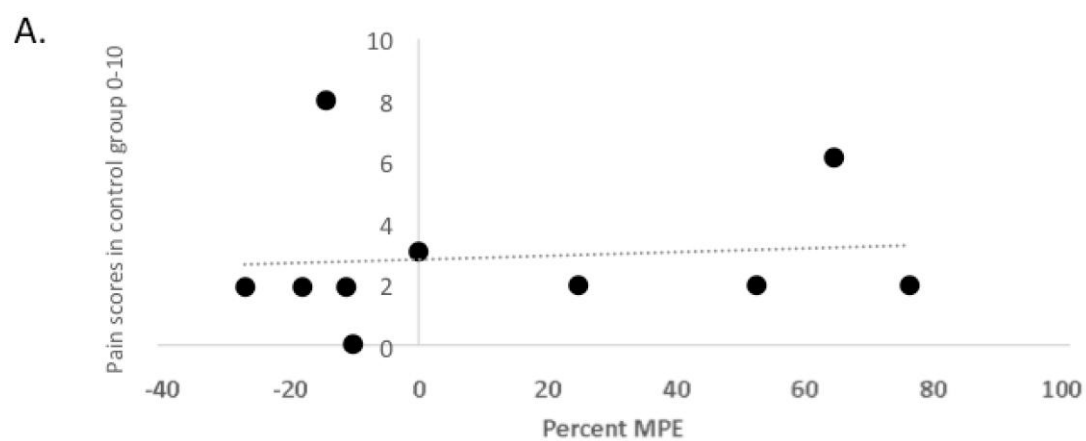


Fig. 3. Efficacy – Burden relationship for acetaminophen as the study drug. **A.** Rescue opioid usage (mg/kg/h) as the outcome. **B.** Percentage requiring rescue medication as the outcome. Percent MPE= Percent maximum possible effect: placebo—study/placebo.

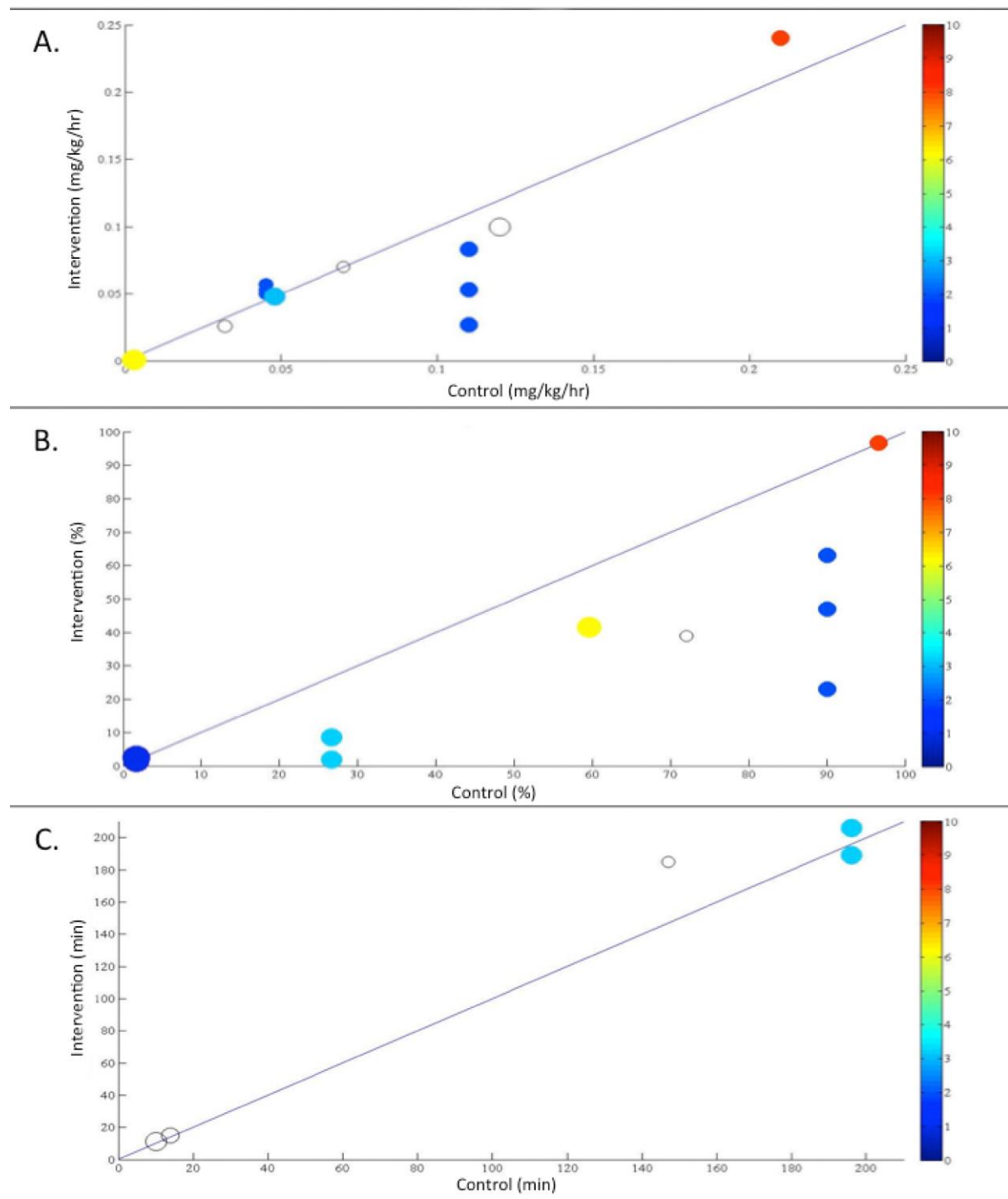


Fig. 4. Acetaminophen as the study drug. **A.** Rescue opioid usage (mg/kg/h) as the outcome. **B.** Percentage requiring rescue medication as the outcome. **C.** Time to first rescue medication (minutes) as the outcome. Colorless circles indicate studies without pain scores.

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