Local anesthetic dosing and toxicity of pediatric truncal catheters: A narrative review of published practice

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Supplemental Methods

Search Strategy and extraction

Initial search was performed on 11/30/2021 from Pubmed and EuropePMC using the following search strategy: (“Local anesthetic” OR “bupivacaine” OR “ropivacaine” OR “mepivacaine” OR “regional”) AND (“catheter” OR “catheters” OR “infusion” OR “continuous”) AND (“transversus abdominis” OR “transversus abdominis plane” OR “TAP” OR “paravertebral” OR “PVB”) between years 1987 to 2021.

A secondary search for additional pediatric papers was performed on 6/8/2023 on Embase, Web of Science and google scholar using the terms: ('pediatric'/exp OR 'pediatric') AND ('continuous' OR 'infusion'/exp OR 'infusion') AND ('paravertebral' OR 'transversus abdominis'/exp OR 'transversus abdominis') AND ('bupivacaine'/exp OR 'bupivacaine' OR 'ropivacaine'/exp OR 'ropivacaine') filtered for results between the years 1987 and 2021. The top 200 most relevant google-scholar results were pre-screened before entry into Covidence.

Papers were uploaded into Covidence extraction tool where two authors screened. On initial screen, a minimum of two reviewers (MRF, LJ, BB) participated independently in abstract screening, full-text screening, and data extraction (supplemental table S1). In cases of disagreement, the primary text was re-assessed for confirmation of data. Secondary search was moderated by at least one author. Inclusion criteria were transversus abdominis plane or paravertebral blocks or blocks deemed similar enough (modified TAP block, extra-pleural catheter, or proximal intercostal block), use of a catheter, bupivacaine or ropivacaine in a human model. Exclusion criteria included use of an alternative local anesthetic as the primary infusion local anesthetic (e.g. mepivacaine, lidocaine, chloroprocaine), intended use for less than 24 hours, a block explicitly different from TAP or paravertebral (e.g. quadratus lumborum, erector spinae, serratus anterior), dosage unobtainable, animal model, liposomal bupivacaine, review paper or conference abstract.

Data Processing and Synthesis

For assumed start time of the infusion, “… immediately following…” was interpreted as zero minute delay between bolus and infusion when calculating 24-hour total dose. If a bolus occurred at the beginning of surgery, and the infusion was started at the end of surgery or in the PACU, length of surgery was used (or a standardized 2.5-hour time based on operating times for abdominal and thoracic procedures).[1,2] In the case of a missing bolus concentration, the available infusion concentration was used for calculations.

In order to calculate weight based doses, missing weights were added using the median age of patients and weight data from the Centers for Disease Control.[3] For upper and lower limit calculations (including age, weight, and dosing), a 95% confidence interval was calculated based on mean and standard error (e.g. mean – 1.96x std-err. < 95% CI. < mean + 1.96x std-err.) For the ropivacaine group, if bupivacaine was used for the bolus, it was treated as ropivacaine for 24-hour data calculation purposes (and vice-versa for the bupivacaine group).

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Following extraction, data was exported to Microsoft Excel (Redmond, Washington), analyzed with MATLAB (Natick, Massachusetts).

If weight-based bolus dose wasn't available, the dose was calculated:

$$Bolus\ dose\ \left(\frac{mg}{kg}\right) = \frac{Bolus\ concentration\ \left(\frac{mg}{mL}\right) * Bolus\ volume\ (mL)}{Patient\ weight\ (kg)}$$

If a weight-based infusion dose wasn't available, the dose was calculated:

$$Infusion\ dose\left(\frac{mg}{kg * hr}\right) = \frac{Infusion\ concentration\ \left(\frac{mg}{mL}\right) * Infusion\ rate\ (\frac{mL}{hr})}{Patient\ weight\ (kg)}$$

Weight-based intermittent bolus (IB) dose was calculated as:

$$IB\ dose\left(\frac{mg}{kg * hr}\right) = \frac{IB\ concentration\ \left(\frac{mg}{mL}\right) * IB\ volume\ (mL)}{Patient\ weight\ (kg) * {}^{24}/_{IB\ interval\ (hr)}}$$

Total weight-based 24-hour dose was calculated as:

$$24\ hour\ dose\ \left(\frac{mg}{kg}\right) = Bolus\ dose\ \left(\frac{mg}{kg}\right) + [24 - start\ time(hr)] * infusion\ dose\ \left(\frac{mg}{kg * hr}\right) + \frac{additional\ dose\ (mg)}{Patient\ weight(kg)}$$

Mean/median dosing was calculated based on mean/median reported weight and mean/median reported doses, along with a single breakthrough bolus if described, and additional 24-hour dose (e.g. from spinal, local infiltration or other source). Maximum dosing was calculated based on minimum reported weight, maximum reported dose, maximum number of reported breakthrough doses, and any additional dose. Minimum dosing was calculated based on maximum reported weight, minimum reported dose and no breakthrough or additional local anesthetic. Unless otherwise specified, mean/median dose is reported.

Data was compared based on total number of patients so large retrospective cohort studies and randomized trials weight more than case reports or case series. Dosing is plotted as histograms with binning of data for ease of viewing (bolus data is binned into 0.5 mg/kg, infusion data is binned into 0.1 mg/kg/hr, 24-hour data is binned into 2 mg/kg). Data is labeled as mean/median based on variable presentation of mean or median values in original papers.

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Supplemental Figures & Tables

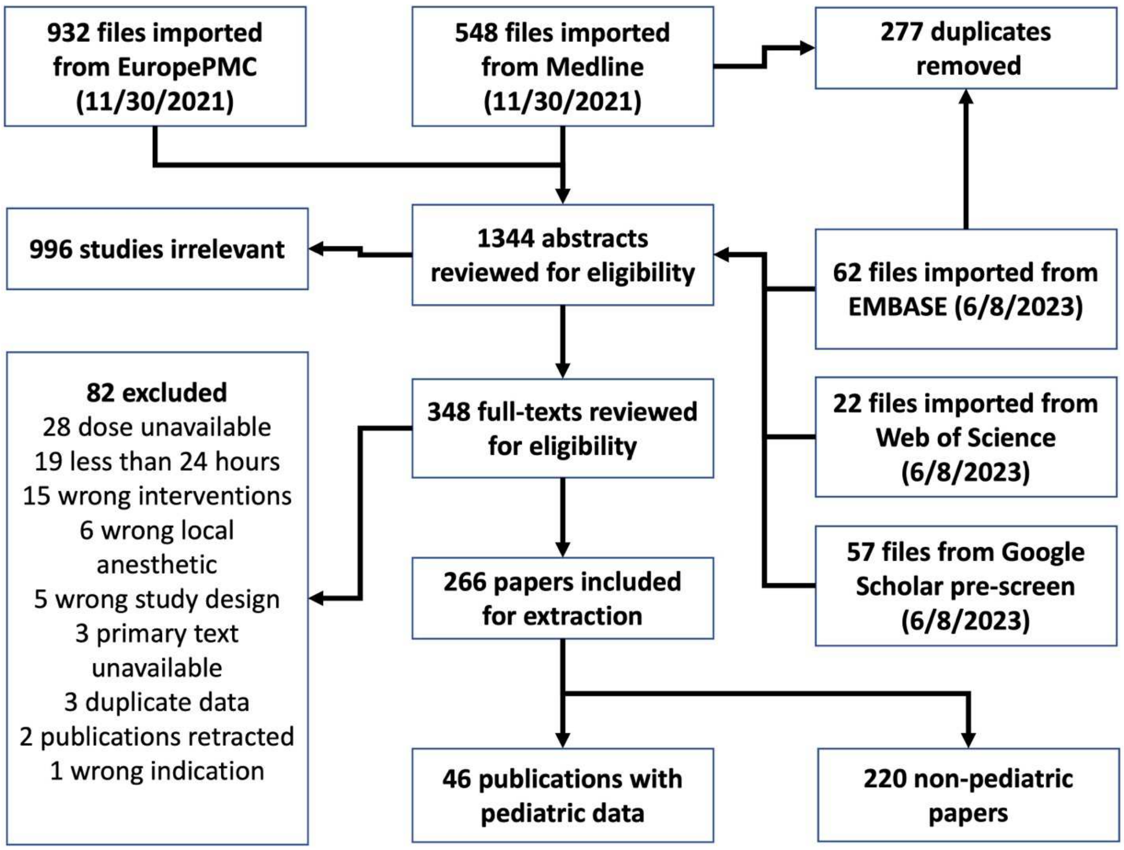

Figure S1: PRISMA screening flow diagram

Table S1: Extraction details

Extraction details
1.) Title 2.) Corresponding author 3.) First author 4.) Country of origin (grouped in USA, UK, Canada, Australia, China, Japan, India, Europe (excluding UK), Middle East, Other Asia (excluding China, Japan and India), and other. 5.) Pubmed ID # 6.) Year of publication 7.) Study design (grouped into randomized controlled trial, retrospective cohort studies, observational studies, Case series, case reports, technical reports and other) 8.) Presence of multiple infusion groups 9.) Number of patients 10.) Mean/median age 11.) Age standard deviation 12.) Minimum age 13.) Maximum age 14.) Mean/median weight 15.) Weight standard deviation 16.) Minimum Weight 17.) Maximum Weight 18.) Mean/median BMI 19.) BMI standard deviation 20.) Minimum BMI 21.) Maximum BMI 22.) Age group (pediatric or adult) 23.) Surgery type 24.) Surgical service (grouped in thoracic, general, orthopedic, plastic, obstetric/gynecological, neurosurgical, urological and other) 25.) Fascial plane block (transversus abdominis of paravertebral) 26.) Laterality (unilateral, bilateral or both) 27.) Infusion drug (Ropivacaine or Bupivacaine) 28.) Delivery method (continuous, intermittent or both) 29.) On-demand delivery (e.g. patient controlled fascial plane infusions) 30.) Bolus concentration (if multiple concentrations used in the bolus, the lower concentration was used) 31.) Mean/Median bolus volume (or weight based-volume) 32.) Bolus volume standard deviation (or weight based) 33.) Min bolus volume (or weight based) 34.) Max bolus volume ((or weight based) 35.) Assumed start time 36.) Infusion concentration (if multiple concentrations used in the bolus, the lower concentration was used) 37.) Mean/median infusion volume (or weight based volume) 38.) Infusion standard deviation (or weight-based) 39.) Min infusion volume (or weight-based) 40.) Max infusion volume (or weight-based) 41.) Intermittent bolus concentration 42.) Intermittent bolus volume (or weight based) 43.) Intermittent bolus standard deviation (or weight-based) 44.) Intermittent bolus minimum

45.) Intermittent bolus maximum
46.) Intermittent bolus interval (hours)
47.) Breakthrough bolus concentration
48.) Breakthrough volume (or weight-based)
49.) Breakthrough bolus interval
50.) Maximum number of breakthrough bolus in 24-hours
51.) Additional dose in 24-hours (e.g. spinal dose or top-up dose if used)
52.) Comments on timing of additional dose
53.) Mean/median infusion duration
54.) Infusion duration standard deviation
55.) Minimum infusion duration
56.) Maximum infusion duration
57.) Proprietary systems used (e.g. OnQ, etc…)
58.) Adjuvants in bolus/infusion (e.g. epinephrine, clonidine, etc…)
59.) Primary outcome
60.) Reported pain benefit
61.) Reported reduction in systemic opioids
62.) If intermittent bolus and continuous infusion used, which was better
63.) Did the authors report local anesthetic systematic toxicity or suspect local anesthetic systemic toxicity
64.) Number of patient with reported toxicity and details
65.) Reports of toxic blood levels (based on details from Knudsen et al)[4]
66.) Complications other than LAST

Supplemental Table S2: Publications with pediatric patients included in the review

Author & Year	**Manuscript details**		**Catheter details**		**Patient details**		**Doing details**			
	Study design (#pts, 945 total)	*Country / Surgical service*	*Location / Laterality / Infusion / On-demand*	Drug	Age (range or std) [years]	Weight (range or std)	Initial Bolus	Infusion OR Intermittent Bolus	Additional / Break-through	24-hour dose (range) [mg/kg]¶
Eng[5] 1992	Case series (6)	UK / Thor.	PVB/Uni/ CI/No	Bupi	10.6 (7 : 16)	-	0.5% 0.2 mL/kg	0.5% 0.2 mL/hr		25
Johnson[6] 1993	Case series (4)	Australia / Thor.	PVB/Uni./ CI/No	Bupi.	6.5 (3 : 10)	NR	0.25% 0.4mL/kg	0.25% 0.2mL/kg/hr		13
Lonnqvist[7] 1995	Obs. (48)	Europe / Thor. & Ortho.	PVB/Both/ CI/No	Bupi.	3 (0.1 : 15)	NR	0.25% 0.5mL/kg	0.25% 0.25mL/kg/hr		16.3
Karmakar[8] 1996	Obs. (20)	UK / Cardiac	PVB/Uni/ CI/No	Bupi	0.1 (0.006 : 0.38)	3.8 (2.5 : 6.2)	0.25% 0.5 mL/kg	0.25% 0.2 mL/kg/hr	1.25 mg /	13.1 (12.75 – 13.25)
Cheung[9] 1997	Obs. (22)	UK / Cardiac	PVB/Uni/ CI/No	Bupi	0.03 (0.003 : 0.39)	3.2 (2.5 : 5.5)	0.25% 0.5 mL/kg	0.125% 0.2 mL/kg/hr		7.25
Downs[10] 1997	Case series (9)	Australia / Thor.	PVB/Uni/ CI/No	Bupi	9, 3, 10, 9, 12, 5, 11, 1, 3	30, 14, 19.5, 52, 33, 15.4, 66, 12, 14.8	0.25% 10mL, 0.5% 5mL, 0.25% 4mL, -, 0.5% 5mL, 0.5% 6mL, 0.5% 15mL, 0.25% 5mL, 0.375% 3mL	0.125% 5mL/hr, 0.1% 3mL/hr, 0.125% 4mL/hr, 0.125% 5mL/hr -, 0.2% 5mL/hr, 0.125% 5mL/hr, 0.125%		5.8, 6.9, 6.7, 2.8, 8.0, 11.7, 4.7, 11, 8.9

								8mL/hr, 0.125% 4mL/hr, 0.125% 4mL/hr		
Karmakar[11] 1997	Case report (1)	UK / Thor.	PVB/Bi/ CI/No	Bupi	0.92	10	0.25% 1mL/kg	0.125% 0.4mL/kg/hr		14
Shah[12] 1997	Obs. (15)	UK / Thor.	PVB/Uni/ CI/No	Bupi	9.8 (2 : 16)	-	0.25% 0.2 mL/kg	0.25% 0.1 mL/kg/hr		6.5
Elder[13] 2010	Retro. Cohort (-)	USA / Neuro.	PVB/Bi/ CI/No	Bupi	55 (16 : 81)	-	0.5% 10 mL	0.5% 4 mL/hr		-
Koyya-lamudi[14] 2010	Case report (1)	USA / Ortho.	PVB/Dual-Uni./ CI/No	Ropi.	10	40	0.5% 20mL	0.2% 8mL/hr	50 mg /	12.4
Rouzrokh[15] 2010	RCT (34)	Middle East / Thor.	PVB/Uni/ CI/No	Ropi	0.007 ±0.0016	3.8+/- 0.36	-	0.5% 0.1 mL/kg/hr		12
Taylor[16] 2010	Case series (1)	USA / General	TAP/Bi/ CI/No	Bupi	5,7	15.7, 17.2	0.125% 8 mL, 0.25% 10mL	0.1% 4 mL/hr	10 mg / 10 mg /	7.4, 7.6
Des-granges[17] 2011	Case report (1)	Europe / General	TAP/Uni/ CI/Yes	Bupi	4	15	0.25% 0.5 mL/kg	0.125% 1.5 mL/hr	/ 0.125% 1.5mL q60	4.35
Ross[18] 2011	Retro cohort (129)	USA / Ortho.	PVB/Uni./ CI/No	Bupi.	14.1±1.8	56.9±12.6	-	0.5% 4mL/hr		8.4 (8 : 8.9)
Visoiu[19] 2011	Case report (1)	USA / General	PVB/Bi/ CI/Yes	Ropi	16	53	0.5% 20 mL	0.2% 18 mL/hr	/ 0.2% 10mL	16.7
Bollag[20] 2012	Case series (1)	USA / Ob/gyne	TAP/Bi/ IB/Yes	Bupi	17	69	0.375% 40 mL	-	12 mg / 0.25% 20mL	2.9

									max 2 times	
El-Morsy[21] 2012	RCT (28)	Middle East / Cardiac	PVB/Uni./ CI/No	Bupi.	11 (3 : 15)	9±2.1	0.25% 0.5mL/kg	0.25% 0.1mL/kg/hr		7.3
Palmer[22] 2012	Obs. (37)	Australia / Thor.	PVB/Uni./ CI/No	Bupi.	neonate*	3 (2.5 : 4.2), 2.3 (1.7 : 4)	0.0625% 0.8mL/kg	0.0625% 0.36mL/kg/hr	- / 0.0625% mL max 12 times	8.3 (3.2 : 12.8),
Visoiu[23] 2012	Case series (6)	USA / General	TAP/Uni/ CI/No	Ropi	0.33, 0.5, 0.583, 1.16, 1.5, 0.16	3.39, 9.58, 10.2, 9.35, 7.69, 2.45	0.2% 0.5mL/kg, 0.2% 0.5mL/kg, 0.2% 0.5mL/kg, 0.2% 0.5mL/kg -, 0.2% 0.5mL/kg, 0.2% 0.5mL/kg	0.05% 2mL/hr, 0.2% 2.5mL/hr, 0.2% 2.5mL/hr, 0.2% 2.5mL/hr -, 0.2% 2mL/hr, 0.05% 1 mL/hr		8.1, 13.5, 12.8, 13.8, 13.5, 5.9
Boretsky[24] 2013	Case series (22)	USA / Thor.	PVB/Uni & Bi/ CI/No	Ropi	4 (0.5 : 15) ; 12 (7 : 17)	17.2 (6.25 : 102) ; 50 (27 : 135)	0.5% 0.5 mL/kg; 0.5% 1 mL/kg	0.2% 0.25 mL/kg/hr; 0.2% 0.25 mL/kg/hr		6.8, 14.5, 17
Yanovski[25] 2013	Case report (1)	Middle East / Plastic	PVB/Uni/ CI/No	Bupi	10	40	0.25% 10 mL	0.1% 5 mL/hr		3.6
Belousova[26] 2014	Obs. (50)	Europe / Cardiac	PVB/Uni./ CI/No	Ropi.	>1 year	NR	0.5% 0.3mL/kg	0.2% 0.1mL/kg/hr		4.9

DiPede[27] 2014	Retro. Cohort (10)	Europe / Thor.	PVB/Uni/ CI/No	Ropi	0.24 (0.126 : 0.32)	6.1 (4.7 : 6.8)	0.4% 0.5 mL/kg	0.125% 0.16 mL/kg/hr		6.8
HallBurton[28] 2014	Retro cohort (10)	USA / Thor.	PVB/Bi./ CI/No	Ropi.	15.5±2.3	55.2 ± 12.5	0.5% 0.6mL/kg	0.2% 0.25mL/kg/hr		15
Kandiah[29] 2014	Case report (1)	USA / General	PVB/Uni/ CI/No	Ropi	0.096	5	0.5% 2 mL	0.1% 1 mL/hr		6.8
Visoiu[30] 2014 (I)	Obs. (6)	USA / Ortho.	PVB/Uni/ CI/No	Ropi	10 (8.75 : 14.75)	31.75 (27.98 : 67.43)	0.5% 0.158 mL/kg	0.2% 0.125 mL/kg/hr		6.8 (3.6 – 8)
Visoiu[31] 2014 (II)	Case series (5)	USA / OMFS	PVB/Uni/ CI/No	Ropi	10 (9 : 17)	33.4 (29.3 : 69.6)	0.5% 8 mL	0.2% 4 mL/hr		7.0 (3.3 – 11)
Bitarafan[32] 2015	Obs. (214)	USA / Thor. & General	PVB/Both/ CI/No	Ropi.	2 (0.003 : 18)	25.3 (1.8 : 113.7)	0.5% 0.5mL/kg	0.2% 0.25mL/kg/hr		14.5 (14.5 : 17)
Cutshall[33] 2015	Case report (1)	USA / Pain	PVB/Uni./ CI/No	Ropi.	15	58		0.2% 10mL/hr		8.3
Salviz[34] 2015	Case report (1)	Middle East / Plastic	PVB/Uni./ CI/Yes	Bupi.	10	30	0.25% 20mL	0.2% 5mL/hr	0.2% 5mL q30 min	9.8 (9.7 : 17.7)
Thompson[35] 2015	Case series (2)	USA / Thor.	PVB/Uni/ CI/No	Ropi	0.005	2.5 (2.3 : 2.7)	-	0.08% 0.25 mL/kg/hr		4.8
Hutchins[36] 2016	Retro. Cohort (17)	USA / General	PVB/Bi/ CI/No	Ropi	13.06 (10.83 : 15.29)	52.33 (40.24 : 64.41)	-	0.2% 0.225 mL/kg/hr		10.8 (9.6 – 12)
Kendigelen[37] 2016	Case report (1)	Middle East / General	PVB/Uni./ IB/No	Bupi.	4	15	0.25% 6mL	0.125% 6mL q4hrs	2.25 mg /	4.2

Murphy[38] 2016	Obs. (83)	UK / Thor.	PVB/Uni/CI/No	Bupi	3.5 (0.42 : 16.7)	16 (6 : 78.6)	0.1% 1.37 mL/kg	0.1% 0.29 mL/kg/hr		8.3 (3 – 15)
Shaffer[39] 2016	Retro. Cohort (10)	USA / ENT	PVB/Uni/ CI/No	Ropi	7.7 (7 : 16.1)	34.7 (21 : 121.5)	0.5% 0.386 mL/kg	0.2% 6.1 mL/hr		9.0 (2.7 – 16.9)
Bakshi[40] 2017	Case series (2)	India / General	TAP/Uni/ IB/No	Bupi	0.5, 4	7, 10	0.25% 5-6 mL	0.25% 5-6mL q8 hrs		7.1 ; 6
Bryskin[41] 2017	RCT (5)	USA / Thor.	PVB/Bi/ CI/No	Ropi	15.6 ±1.1	60.4 ± 2.8	0.35% 0.57 mL/kg	0.2% 0.25 mL/kg/hr		14
Sato[42] 2017	Retro. Cohort (11)	Japan / General	PVB/Uni/ CI/No	Ropi & Bupi	0.231 (0.09 : 0.79)	6 (3.7 : 8.3)	0.2% 1.08 mL/kg, 0.125% 1.7 mL/kg	0.1% 0.3 mL/kg/hr		8.4 (4.6 – 13.3)
Ibrahim[43] 2018	Case report (1)	Middle East / Urology	PVB/Uni/ CI/No	Bupi	8	19	0.25% 10 mL	0.125% 5 mL/hr	30 mg /	9.5
Larsson[44] 2018	Obs. (-)	Europe / Thor.	PVB/Uni/ CI/No	Bupi	68 (14 : 85)	73 (36 : 129)	0.27% 28 mL	0.27% 5 mL/hr		-
Dwivedi[45] 2019	Retro cohort (32)	India / Urology	TAP/Uni./ CI/No	Ropi.	2.1±1.7	14±7.1	0.2% 0.3mL/kg	0.1% 0.2mL/kg/hr		5.4
Muhly[46] 2019	Retro. Cohort (56)	USA / Thor.	PVB/Bi/ CI/No	Ropi	14.9 ±2.5	55.7 ± 11	0.5% 20 mL	0.2% 0.25 mL/kg/hr	25 mg /	14.2 (12 – 15.5)
Tandale[47] 2019	Case Series (3)	India / General	TAP/Uni./ IB/No	Bupi.	neonate*, 7	4 (3.5 : 4.5), 15	0.1% 1mL/kg, 0.2% 1mL/kg	0.1% 1mL/kg q12 hrs, 0.2% 1mL/kg q12 hrs		3,6

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Visoiu[48] 2019	Case report (1)	USA / General	PVB/Uni./ CI/No	Ropi.	0.4	3.56	0.2% 2mL	0.2% 1mL/hr		14.6
Dwivedi[49] 2020	Case report (1)	India / Urology	TAP/Uni/ CI/No	Ropi	12	35	-	0.1% 0.2 mL/kg/hr		4.8
Xie[50] 2020	Retro. Cohort (34)	USA / Thor.	PVB/Uni/ CI/No	Ropi	16.7 ± 1.9	63.6	0.2% 30 mL	0.2% 0.15 mL/kg/hr		8.1 (7.8 – 8.8)

PVB: paravertebral, *TAP:* Transversus abdominis plane, *RCT:* Randomized controlled trial, *Bupi:* Bupivacaine, *Ropi:* Ropivacaine, *USA:* United States of America, *UK:* United Kingdom, *IB:* Intermittent bolus, *CI:* Continuous infusion, *Uni:* Unilateral, *Bi:* bilateral ‡: For case studies, only a single value is included. If dosing was variable a range is included based on weight and infusion parameters. *: Age only reported as “neonate” NR: Not reported

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Table S3: Details of extracted papers

Publication details			
	Bupivacaine	Ropivacaine	Total
Number of publications	24	23	46*
Year of publication	2010 [1992 – 2018]	2014 [2010 – 2020]	2012 [1992 – 2020]
Patient details			
Number of patients	424	521	945
Under 6 months	91	53	144
Over 6 months	333	468	801
Age	6.9 years (1 day – 17 years)	5.9 years (1 day – 18 years)	6.4 years (1 day – 18 years)
Weight (kg)	27.8 (1.7 – 78.6)	25.7 (2.3 – 135)	26.6 (1.7 – 135)kg
Country of origin (n= 945)			
United States	132	392	524
UK	147	0	147
Europe	49	60	109
Australia	50	0	50
Japan	9	2	11
India	33	5	38
Middle East	32	34	66
Study Design (n= 945)			
RCT	28	39	67
Retrospective Cohort	138	171	309
Observational Trial	225	270	495
Case Series	24	35	59
Case Report	6	6	12
Service (n= 945)			
Thoracic	155	173	328
Multiple unspecified (Thoracic, general, ortho)	48	214	262
Ortho	136	0	136
Cardiac	70	50	120
General	18	28	46
Urology	1	34	35
Plastic/ENT/OMFS	15	2	17
Ob/Gyne	1	0	1

* One publication used both ropivacaine and bupivacaine

Table S4: Details of catheters

Publication details			
	Bupivacaine	Ropivacaine	Total
Block type (n= 945)			
TAP	9	39	48
PVB	415	482	897
Location (n= 945)			
High Thoracic	366	469	835
Abdominal	10	40	50
Thoracic or lumbar	48	0	48
Lumbar	0	11	11
Cervical and Thoracic	0	1	1
Laterality (n= 945)			
Unilateral	372	208	580
Bilateral (or double)	4	99	103
Both	48	214	262
Delivery (n= 945)			
Continuous	417	521	938
Intermittent	7	0	7
Bolus Method (n= 760)			
Fixed-dose	17	99	116
Weight-based dose	277	367	644
Infusion Method (n= 945)			
Fixed-volume continuous	144	26	170
Weight-based continuous	275	495	770
Fixed-volume IB	0	3	3
Weight-based IB	0	3	3
On-demand-delivery	3	1	4
Breakthrough	40	11	51

IB: Intermittent Bolus; PVB: Paravetebral; TAP: Transversus abdominis plane; ENT: Ears, nose & throat; OMFS: Oro-maxillary facial surgery; RCT: Randomized controlled trial

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Table S5: Patient details:

Study ID	# patients	Mean/ median age (years)	Age std	Min age	Max age	Mean weight (kg)	Weight std	Min Weight	Max weight
Rouzrokh 2010	34	0.007	0.0016	0.0064	0.0075	3.8	0.36	3.67	3.92
Dwivedi 2020	1	12		12	12	35		35	35
Desgranges 2011	1	4		4	4	15		15	15
Kandiah 2014	1	0.096		0.096	0.096	5		5	5
Visoiu 2011	1	16		16	16	53		53	53
Boretsky 2013	13	4		0.5	15	17.2		6.25	102
Boretsky 2013	9	12		7	17	50		27	135
DiPede 2014	10	0.24		0.126	0.32	6.1		4.7	6.8
Muhly 2019	56	14.9	2.5	14.24	15.55	55.7	11	52.81	58.58
Xie 2020	34	16.7	1.9	16.06	17.33	63.6		63.6	63.6
Taylor 2010	1	5		5	5	15.7		15.7	15.7
Taylor 2010	1	7		7	7	17.2		17.2	17.2
Bollag 2012	1	17		17	17	69		69	69
Shaffer 2016	10	7.7		7	16.1	34.7		21	121.5
Sato 2017	2	0.231		0.09	0.79	6		3.7	8.3
Sato 2017	9	0.231		0.09	0.79	6		3.7	8.3
Thompson 2015	2	0.005		0.005	0.005	2.5		2.3	2.7
Visoiu 2012	1	0.33		0.33	0.33	3.39		3.39	3.39
Visoiu 2012	1	0.5		0.5	0.5	9.58		9.58	9.58
Visoiu 2012	1	0.583		0.583	0.583	10.2		10.2	10.2
Visoiu 2012	1	1.16		1.16	1.16	9.35		9.35	9.35
Visoiu 2012	1	1.5		1.5	1.5	7.69		7.69	7.69

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Visoiu 2012	1	0.16		0.16	0.16	2.45		2.45	2.45
Hutchins 2016	17	13.06		10.83	15.29	52.33		40.24	64.41
Visoiu 2014	6	10		8.75	14.75	31.75		27.98	67.43
Ibrahim 2018	1	8		8	8	19		19	19
Bakshi 2017	1	0.5		0.5	0.5	7		7	7
Bakshi 2017	1	4		4	4	10		10	10
Bryskin 2017	5	15.6	1.1	14.63	16.56	60.4	2.8	57.94	62.8
Murphy 2016	83	3.5		0.42	16.7	16		6	78.6
Visoiu 2014	5	10		9	17	33.4		29.3	69.6
Yanovski 2013	1	10		10	10	40		40	40
Shah 1997	15	9.8		2	16				
Downs 1997	1	9		9	9	30		30	30
Downs 1997	1	3		3	3	14		14	14
Downs 1997	1	10		10	10	19.5		19.5	19.5
Downs 1997	1	9		9	9	52		52	52
Downs 1997	1	12		12	12	33		33	33
Downs 1997	1	5		5	5	15.4		15.4	15.4
Downs 1997	1	11		11	11	66		66	66
Downs 1997	1	1		1	1	12		12	12
Downs 1997	1	3		3	3	14.8		14.8	14.8
Cheung 1997	22	0.03		0.0027	0.39	3.2		2.5	5.5
Karmakar 1997	1	0.92		0.92	0.92	10		10	10
Karmakar 1996	20	0.1		0.006	0.38	3.8		2.5	6.2
Eng 1992	6	10.6		7	16				
Larsson 2018	454	68		14	85	73		36	129
Elder 2010	24	55		16	81				
Belousova 2014	50	1		1	1				

El-Morsy 2012	28	11		3	15	9		8.2	9.8
Johnson 1993	4	6.5		3	10				
Ross 2011	129	14.1		13.7	14.4	56.9		53.9	59.9
Kendigelen 2016	1	4		4	4	15		15	15
Cutshall 2015	1	15		15	15	58		58	58
Dwivedi 2019	32	2.1		1.5	2.7	14		11.5	16.5
Bitarafan 2015	214	2		0.003	18	13.2		7.6	41
Lonnqvist 1995	48	3		0.1	15				
Palmer 2012	26	0.02		0.02	0.02	3		2.5	4.2
Palmer 2012	11	0.02		0.02	0.02	2.3		1.7	4
Koyyalamudi 2010	1	10		10	10	40		40	40
Tandale 2019	2	0.02		0.02	0.02	4		3.5	4.5
Tandale 2019	1	7		7	7	15		15	15
Salviz 2015	1	10		10	10	30		30	30
Visoiu 2019	1	0.4		0.4	0.4	3.56		3.56	3.56
HallBurton 2014	10	15.5		14	17	55.2		47.2	63.2

Table S6: Bolus details:

Study ID	Mean Bolus conc. (%)	Mean Bolus vol (mL)	Bolus std (mL)	Min Bolus volume (mL)	Max bolus volume (mL)	(alt) Weight bolus dose (mL/kg)	(alt) Weight bolus dose std	(alt) Weight bolus dose min	(alt) Weight bolus dose max
Rouzrokh 2010									
Dwivedi 2020									
Desgranges 2011	0.25					0.5		0.5	0.5
Kandiah 2014	0.5	2		2	2				
Visoiu 2011	0.5	20		20	20				
Boretsky 2013	0.5					0.5		0.5	0.5
Boretsky 2013	0.5					1		1	1
DiPede 2014	0.4					0.5		0.5	0.5
Muhly 2019	0.5	20							0.6
Xie 2020	0.2	30		20	40				
Taylor 2010	0.125	8		8	8				
Taylor 2010	0.25	10		10	10				
Bollag 2012	0.375	40		40	40				
Shaffer 2016	0.5					0.386	0.28	0.21	0.55
Sato 2017	0.2					1.08		0.25	1.5
Sato 2017	0.125					1.728		0.4	2.4
Thompson 2015									
Visoiu 2012	0.2					0.5		0.5	0.5
Visoiu 2012	0.2					0.5		0.5	0.5
Visoiu 2012	0.2					0.5		0.5	0.5
Visoiu 2012	0.2					0.5		0.5	0.5
Visoiu 2012	0.2					0.5		0.5	0.5
Visoiu 2012	0.2					0.5		0.5	0.5
Hutchins 2016									

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Visoiu 2014	0.5					0.158		0.14	0.254
Ibrahim 2018	0.25	10		10	10				
Bakshi 2017	0.25	5		5	5				
Bakshi 2017	0.25	6		6	6				
Bryskin 2017	0.35					0.57		0.57	0.57
Murphy 2016	0.1					1.37		0.37	3.13
Visoiu 2014	0.5	8		8	8				
Yanovski 2013	0.25	10		10	10				
Shah 1997	0.25					0.2		0.2	0.2
Downs 1997	0.25	10		10	10				
Downs 1997	0.5	5		5	5				
Downs 1997	0.25	4		4	4				
Downs 1997	0.5								
Downs 1997	0.5	5		5	5				
Downs 1997	0.5	6		6	6				
Downs 1997	0.5	15		15	15				
Downs 1997	0.25	5		5	5				
Downs 1997	0.375	3		3	3				
Cheung 1997	0.25					0.5		0.5	0.5
Karmakar 1997	0.25					1		1	1
Karmakar 1996	0.25					0.5		0.5	0.5
Eng 1992	0.5					0.2		0.2	0.2
Larsson 2018	0.27	28		28	28				
Elder 2010	0.5	10		10	10				
Belousova 2014	0.5					0.3		0.3	0.3
El-Morsy 2012	0.25					0.5		0.5	0.5
Johnson 1993	0.25					0.4		0.4	0.4

Ross 2011									
Kendigelen 2016	0.25	6		6	6				
Cutshall 2015									
Dwivedi 2019	0.2					0.3		0.3	0.3
Bitarafan 2015	0.5					0.5		0.5	1
Lonnqvist 1995	0.25					0.5		0.5	0.5
Palmer 2012	0.0625					0.8		0.36	3.5
Palmer 2012	0.0625					0.8		0.36	3.5
Koyyalamudi 2010	0.5	20		20	20				
Tandale 2019	0.1					1		1	1
Tandale 2019	0.2					1		1	1
Salviz 2015	0.25	20		20	20				
Visoiu 2019	0.2	2		2	2				
HallBurton 2014	0.5					0.6		0.6	0.6

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Table S7: Infusion Dosing

Study ID	Start time (hr)	Mean CI conc. (%)	Hourly CI Vol (mL* Hr^{-1})	CI Vol std (mL* Hr^{-1})	Min hourly CI Vol (mL* Hr^{-1})	Max hourly CI Vol (mL* Hr^{-1})	Mean CI dose (mL* kg^{-1} hr^{-1})	Min CI dose (mL* Kg^{-1} hr^{-1})	Max CI dose (mL* Kg^{-1} hr^{-1})	IB conc (%)	Mean IB volume (mL) or (mL/kg)	Min IB vol (mL) or (mL/kg)	Max IB Vol (mL) or (mL/kg)	IB interval (hr)
Rouzrokh 2010	0	0.5					0.1	0.1	0.1					
Dwivedi 2020	0	0.1					0.2	0.2	0.2					
Desgranges 2011	0	0.125	1.5		1.5	1.5								
Kandiah 2014	0	0.1	1		1	1								
Visoiu 2011	2.5	0.2	18		16	20								
Boretsky 2013	0	0.2					0.25	0.25	0.25					
Boretsky 2013	0	0.2					0.25	0.25	0.25					
DiPede 2014	0	0.125					0.16	0.16	0.16					
Muhly 2019		0.2					0.25	0.25	0.25					
Xie 2020	0	0.2				10	0.15	0.15	0.15					
Taylor 2010		0.1	4		4	4	0.25	0.25	0.25					
Taylor 2010		0.1	4		4	4	0.23	0.23	0.23					
Bollag 2012	0													
Shaffer 2016	3.83	0.2	6.1	2	4.86	7.33								
Sato 2017	3.3	0.1					0.3	0.2	0.5					

Sato 2017	3.3	0.1					0.3	0.2	0.5					
Thompson 2015	0	0.08					0.25	0.25	0.25					
Visoiu 2012	0	0.05	2		2	2								
Visoiu 2012	0	0.2	2.5		2.5	2.5								
Visoiu 2012	0	0.2	2.5		2.5	2.5								
Visoiu 2012	0	0.2	2.5		2.5	2.5								
Visoiu 2012	0	0.2	2		2	2								
Visoiu 2012	0	0.05	1		1	1								
Hutchins 2016	0	0.2					0.225	0.2	0.25					
Visoiu 2014	0	0.2					0.125	0.06	0.145					
Ibrahim 2018	4	0.125	5		5	5								
Bakshi 2017										0.25	5mL	5 mL	5 mL	8
Bakshi 2017										0.25	6mL	6 mL	6 mL	8
Bryskin 2017	0	0.2					0.25	0.25	0.25					
Murphy 2016	0	0.1					0.29	0.11	0.5					
Visoiu 2014	0	0.2	4		4	6								
Yanovski 2013	0	0.1	5		5	5								
Shah 1997	0	0.25					0.1	0.1	0.1					

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Downs 1997	0	0.125	5		5	5								
Downs 1997	0	0.1	3		3	3								
Downs 1997	0	0.125	4		4	4								
Downs 1997	0	0.125	5		5	5								
Downs 1997	0	0.2	5		5	5								
Downs 1997	0	0.125	5		5	5								
Downs 1997	0	0.125	8		8	8								
Downs 1997	0	0.125	4		4	4								
Downs 1997	0	0.125	4		4	4								
Cheung 1997	0	0.125					0.2	0.2	0.2					
Karmakar 1997	1	0.125					0.4	0.4	0.4					
Karmakar 1996	1	0.25					0.2	0.2	0.2					
Eng 1992	0	0.5					0.2	0.2	0.2					
Larsson 2018	2.5	0.27	5		5	5								
Elder 2010	0	0.5	4		4	4								
Belousova 2014	7	0.2					0.1	0.1	0.1					
El-Morsy 2012	0	0.25					0.1	0.1	0.1					
Johnson 1993	0	0.25					0.2	0.2	0.2					
Ross 2011	0	0.5	4		4	4								

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Kendigelen 2016	0									0.125	6 mL	6 mL	6 mL	4
Cutshall 2015	0	0.2	10		10	10								
Dwivedi 2019	0	0.1					0.2	0.2	0.2					
Bitarafan 2015	0	0.2					0.25	0.25	0.25					
Lonnqvist 1995	0	0.25					0.25	0.25	0.25					
Palmer 2012	0	0.0625					0.36	0.2	0.55					
Palmer 2012	0	0.0625					0.36	0.2	0.55					
Koyyalamudi 2010	2.5	0.2	8		8	8								
Tandale 2019	0									0.1	1mL/kg	1mL/kg	1mL/kg	12
Tandale 2019	0									0.2	1mL/kg	1mL/kg	1mL/kg	12
Salviz 2015	0	0.2	5		5	5								
Visoiu 2019	0	0.2	1		1	1								
HallBurton 2014	0	0.2					0.25	0.25	0.25					

CI: Continuous infusion; *IB:* Intermittent bolus; *Conc:* Concentration; *Hr:* Hour; *Vol:* Volume ; *Std:* Standard deviation

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Table S8: Breakthrough and duration

Study ID	Breakthru bolus conc (%)	Breakthru bolus vol (mL)	Breakthru bolus dose (mL/kg)	Breakthru int (min)	Breakthru total bolus in 24 hours (#)	Extra mg in first 24 hrs. (mg)	Dose comments	Mean dur (hrs)	Std dur (hrs)	Min dur (hrs)	Max dur (hrs)
Rouzrokh 2010								48		48	48
Dwivedi 2020								48		48	48
Desgranges 2011	0.125	1.5		60				48		48	48
Kandiah 2014								72		72	72
Visoiu 2011	0.2	10						120		120	120
Boretsky 2013								72		24	120
Boretsky 2013								72		48	120
DiPede 2014								72		72	72
Muhly 2019						25	given at the end of the case if the patient was stable	84		72	96
Xie 2020								72		48	120
Taylor 2010						10	During surgery	92		92	92
Taylor 2010						10	During surgery	48		48	48
Bollag 2012	0.25	20		0	2	12	for spinal block	30		30	30
Shaffer 2016	0.2						"clinician administered boluses" no mention of how much or how frequently	52.5		18	87

Sato 2017								48		48	48
Sato 2017								48		48	48
Thompson 2015								108		96	120
Visoiu 2012								60		48	72
Visoiu 2012								60		48	72
Visoiu 2012								60		48	72
Visoiu 2012								60		48	72
Visoiu 2012								60		48	72
Visoiu 2012								60		48	72
Hutchins 2016								168		96	168
Visoiu 2014								96		72	102
Ibrahim 2018						30	During surgery.	144		144	144
Bakshi 2017								72		72	72
Bakshi 2017								48		48	48
Bryskin 2017								72		72	72
Murphy 2016								39.3		2.3	221
Visoiu 2014							initial infusion in first case was started at 6 ml/hr then decreased	96		72	120
Yanovski 2013								72		72	72
Shah 1997							Beginning of surgery	120		120	120
Downs 1997								68		68	68
Downs 1997								41		41	41
Downs 1997								75		75	75

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Downs 1997								86		86	86
Downs 1997								90		90	90
Downs 1997								62		62	62
Downs 1997								89		89	89
Downs 1997								69		69	69
Downs 1997								72		72	72
Cheung 1997								48		48	48
Karmakar 1997								60		60	60
Karmakar 1996						1.25	Test dose	24		24	36
Eng 1992								120		120	120
Larsson 2018								72		72	72
Elder 2010								72		72	72
Belousova 2014								48		48	48
El-Morsy 2012								24		24	24
Johnson 1993								24		24	24
Ross 2011								100		100	100
Kendigelen 2016						2.25		48		48	48
Cutshall 2015								192		192	192
Dwivedi 2019								24		24	24
Bitarafan 2015								72		48	120
Lonnqvist 1995								24		24	24
Palmer 2012	0.0625		0.2		12			43		1.5	72
Palmer 2012	0.0625		0.2		12			43		1.5	72
Koyyalamudi 2010						50		72		72	72
Tandale 2019								72		72	72
Tandale 2019								48		48	48
Salviz 2015	0.2	5		30				36		36	36

Visoiu 2019								72		72	72
HallBurton 2014								72		72	72

Brk-thru: Breakthrough

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Table S9: Doses from USA versus International

	Ropivacaine			Bupivacaine		
	All	<6 months	>6 months	All	< 6 months	>6 months
			Bolus			
USA Bolus- mg/kg (range) [#pts]	**2.5 (0.8 – 5) [n=372]**	1 (1-2) [n=5]	2.5 (0.8 – 5) [n=367]	**1.5 (0.6 – 2.2) [n=3]**	-	1.5 (0.6 – 2.2) [n=3]
International Bolus – mg/kg (range) [#pts]	**1.5 (0.6 – 2.2) [n=94]**	2 (2-2.2) [n=12]	1.5 (0.6 – 1.5) [n=82]	**1.25 (0.5 – 2.5) [n = 291]**	1.25 (0.5 – 2.2) [=91]	1.25 (0.5 – 2.5) [n=200]
			Infusion			
USA infusion - mg/kg/hg (range) [# pts]	**0.5 (0.2 – 0.68) [n=392]**	0.2 (0.2 – 0.56) [n=7]	0.5 (0.24 – 0.68] n=385]	0.35 (0.23 – 0.35) [n=131]	-	0.35 (0.23 – 0.35) [n=131]
International infusion - mg/kg/hg (range) [# pts]	**0.2 (0.2 – 0.5) [n=129]**	0.5 (0.2 - 0.5) [n=46]	0.2 (0.2 - 0.2) [n=83]	0.29 (0.08 – 1.0) [n=292]	0.25 (0.08 – 0.5) [n=91]	0.29 (0.12 – 1.0) [n=201]

Data presented as median (range) [n]

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