Supplemental Content

Supplemental Content 1: Details of search strategy

Search	Query
#1	bupivacaine OR (bupivacaine hydrochloride) OR (plain bupivacaine) OR (standard bupivcaine) OR (bupivacaine HCl)
#2	(liposomal bupivacaine) OR (liposome bupivacaine) OR depofoam OR exparel OR (extended release bupivacaine)
#3	#1 AND #2

Supplemental Content 2: Details of Risk of Bias Evaluation

author	***year***	**Risk of Bias Evaluation**							
		sequence generation	***allocation concealment***	***blinded performance***	***patient blinding***	***blinded assessment***	***incomplete outcome***	***selective reporting***	***other bias***
Alijanipour	**2017**	determination of the allocation order by an Excel random number generator (low risk)	sequentially numered sealed envelopes that were opened just prior to the intervention (low risk)	surgeon not blinded (high risk)	patients blinded (low risk)	blinded: patients, outcome assessors, data collectors, statistician (low risk)	42 drop-outs (did not complete postoperative questionnaires) + 2 drop-outs retrospectively (did not meet inclusion criteria, error), drop-out rate of 26% (high risk)	all endpoints from the registered protocol are reported (low risk)	did not receive any financial founding (low risk)
Alter	**2017**	randomization by birth date (high risk)	not stated (sequence generation makes an allocation concealment difficult) (high risk)	surgeons not blinded (high risk)	patients blinded (low risk)	observer assessment not stated (unclear risk)	no drop-outs (low risk)	no protocol registered, all endpoints reported (unclear risk)	study was supported through an unrestricted educational grant from Pacira Pharmaceuticals (high risk)

Barron	**2017**	randomization table created by an integer generator, random allocation sequence for 64 patients in blocks of 8 with an equal allocation ratio (low risk)	Randomization sequence housed by the Florida Hospital Investigational Pharmacy (third party) (low risk)	surgeon not blinded (high risk)	patients blinded (low risk)	fully blinded (low risk)	8 drop-outs, explained, equally distributed (unclear risk)	all endpoints from the registered protocol are reported (low risk)	low risk
Bramlett	**2012**	randomization in different equal and unequal ratios via a centralized randomization system (low risk)	central randomization by a third party (low risk)	preperation and administration of study drug not blinded (high risk)	patients blinded (low risk)	fully blinded (low risk)	18 drop-out, insufficient explanation (high risk)	all endpoints from the registered protocol are reported (low risk)	support by Pacira Pharmaceuticals, one author is paid employe by Pacira (high risk)
Bultema	**2016**	random assignment of a 6 digit number from a master list (low risk)	The master list of 6-digit random numbers was not made available to the primary investigator until completion of the study (low risk)	syringes wrapped with opaque tape with the corresponding 6 digit number provided by not involved personnel (low risk)	patients blinded (low risk)	double-blind: patient, primary investigator (low risk)	5 drop-outs, 5 emergency treatments, explained (low risk)	no protocol registered, all endpoints reported (unclear risk)	low risk
Dale	**2019**	Block Randomization in groups of 10 (low risk)	not stated (unclear risk)	single -blinded: (high risk); surgeon who administered the injection was not blinded	patients blinded (low risk)	observer blinded, data collection blinded (low risk)	2 drop-outs, explained (low risk)	More outcomes than in the registered protocol are reported (low risk)	The Exparel used in the study was donated by Pacira Pharmaceuticals (high risk)
Glenn	**2016**	random assignment of a 6 digit number from a master list (low risk)	copy of the master list of the 6 digit numbers was supplied by the lead researcher and was not made known to the investigator during data collection period (third party) (low risk)	anesthetic formulation was drawn into plastic syringes wrapped with opaque tape with the corresponding 6-digit number by trained personnel not involved in the study (low risk)	patients blinded (low risk)	blinded: patient, doctor, investigator (low risk)	13 drop-outs, explained (unclear risk)	no protocol registered, all endpoints reported (unclear risk)	supported by a research grant from the American Association of Endodontists Foundation (low risk)

Ha	**2019**	Randomized block design with five patient blocks (low risk)	study arm allocation only known to the study coordinator until the day of surgery (unclear risk)	surgeons not blinded (high risk)	patients blinded (low risk)	The senior author (T.M.M.) was the only individual aware of which drug was injected because of its different color, but performed none of the pain evaluations or data collation (low risk)	26 drop-outs, explained (drop-out rate 37%) (high risk)	all endpoints from the registered protocol are reported, but the costs. (low risk)	grant from hospital foundation, no industrial sponsorship, one author received unrelated founding (low risk)
Haas	**2012**	patients were randomized in an 1:1:1 ratio (low risk)	not stated (unclear risk)	Because LB and bupivacaine HCl are visually distinguishable, study medications were dispensed via sheathed syringes by study personnel not involved with any protocol-specific postsurgical assessments. (low-risk)	patients blinded (low risk)	staff involved with study-related evaluations remained blinded, low risk	3 drop-outs, explained (low risk)	no protocol registered, all endpoints reported (unclear risk)	supported by Pacira Pharmaceuticals (high risk)
Hutchins	**2015**	randomization with an equal allocation ratio by a random number generator (low risk)	not stated (unclear risk)	practitioner not blinded (high risk)	patients blinded most likely (low risk)	blinded: all sugical, nursing and research personell (low risk)	3 drop-outs, explained (low risk)	all endpoints from the registered protocol are reported (low risk)	grant funding from Pacira Pharmaceuticals (high risk)
Hutchins	**2016**	randomization by random numbers (low risk)	closed envelope (low risk)	practitioner not blinded (high risk)	patients blinded (low risk)	blinded: research personell, patient, not blinded: personell performing the block (low risk)	1 drop-out, explained (low risk)	all endpoints from the registered protocol are reported (low risk)	consultant for Pacira Pharmaceuticals (high risk)
Iwanoff	**2018**	computer generated randomization using REDCap (low risk)	not stated (unclear risk)	single-blinded (high risk)	patients blinded (low risk)	observer not blinded (high-risk)	6 drop-outs, explained (unclear risk)	all endpoints from the registered protocol are reported (low risk)	low risk
Knight	**2015**	Computer-generated block randomization (low risk)	not stated (unclear risk)	surgeon not blinded (high risk)	patients blinded (low risk)	observer not blinded (high risk)	all drop outs explained (low risk)	no study protocol released, no selective reporting within the paper (unclear risk)	low risk

Knudson	**2016**	randomization (unclear risk)	sealed opaque envelope (low risk)	not blinded surgery resident held the information about the anesthetic used and performed the injection (high risk)	patients blinded (low risk)	double blinded, blind: colorectal surgeon, patient (low risk)	6 drop-outs, explained and sensitivity analysis did not change the outcome (low risk)	selective reporting of endpoints (Toradol and Orfimev use?) (unclear risk)	low risk
Motakef	**2017**	randomization by using a computer randomizer (low risk)	not stated (unclear risk)	single- blind (high risk)	patients blinded (low risk)	observer not blinded (high risk)	not drop-outs (low risk)	all endpoints from the registered protocol are reported (low risk)	funding from Plastic Surgery foundation (low risk)
Nadeau	**2016**	Computer generated randomized list, study number (low risk)	sealed envelopes (low risk)	double-blinded: patient, surgeon (low risk)	patients blinded (low risk)	observer blinded (low risk)	3 drop-outs, explained (low risk)	no study protocol released, study not registered (unclear risk)	funded by a resident research grant from Riverside Methodist Hospital (low risk)
Perets	**2017**	document with numbers provided and generated by the hospital pharmacy (low risk)	randomized, sealed and numbered envelopes (low risk)	surgeon not blinded (high risk)	patients blinded (low risk)	observer blinded (low risk)	no drop-outs (low risk)	all endpoints from the registered protocol are reported (low risk)	research support from Pacira Inc (high risk)
Premkumar	**2016**	computer generated random numbers with blocks of 4 (low risk)	sealed envelopes opened in the operating room by the operating staff (low risk)	double-blind: patient and surgeon (low risk)	patients blinded (low risk)	every member of the clinical team involved in the postoperative care (low risk)	3 drop-outs, explained (low risk)	all endpoints from the registered protocol are reported (low risk)	low risk
Schroer	**2015**	randomization by the circulating nurse (unclear risk)	medication used was recorded in the patients' electronical medical record (high risk)	not blinded: surgeon, surgical team (high risk)	patients blinded (low risk)	research collection was blinded (low risk)	no drop-outs (low risk)	no study protocol released, study not registered (unclear risk)	low risk
Schumer	**2018**	Randomization via a computer-generated sequence (low risk)	envelopes (low risk)	single-blind (high risk), patients blinded	patients blinded (low risk)	observer not blinded (high risk)	3 drop-outs, explained (low risk)	no selective reporting within the paper, no study protocol released (unclear risk)	low risk

Vandepitte	**2017**	Randomization via a computer-generated sequence (low risk)	opaque sealed envelopes opened by the primary investigator just before performing (low risk)	double-blinded: staff, surgeons, patients (low risk)	patients blinded (low risk)	blinded staff conducted all patient follow-up assessments (low risk)	2 drop-outs, explained (low risk)	all endpoints from the registered protocol are reported (low risk)	funded by Pacira Pharmaceuticals (high risk)
Wong	2020	Patients were randomized in a 1:1:1 ratio to either receive an intraoperative, laparoscopic-guided TAP block with LB, an TAP block with RB, or NB by a computer program before each operation. (low risk)	not stated (unclear risk)	surgeon not blinded (high risk)	patients blinded (low risk)	In addition, the nursing staff was blinded, which allowed them to record the pain scores as per nursing protocol without bias. The research staff collecting data was blinded. (low risk)	no drop-outs (low risk)	all endpoints from the registered protocol are reported (low risk)	low risk
Zlotnicki	**2018**	Randomization (unclear risk)	not stated (unclear risk)	blinded: patient, staff (nursing and physical therapy), performance not blinded (high risk)	patients blinded (low risk)	observer blinded (low risk)	2 drop-outs, explained (low risk)	no study protocol released, no selective reporting within the paper (unclear risk)	low risk

Supplemental Content 3: Demographic characteristics of included studies

author, year	number		age (years)		Weight (kg)		BMI (kg/m²)		sex (n)		ASA Status		length of surgery (min)	
	LB	PB	LB	PB	LB	PB	LB	PB	LB	PB	LB	PB	LB	PB
			Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	m/f	m/f	I-IV	I-IV	Mean (SD)	Mean (SD)
Alijanipour, 2017	59	59	65.5 (8.7)	65.4 (7.3)	ns	ns	31.4 (5.5)	30 (6.32)	29/30	27/32	ns	ns	85.9 (17.8)	85.6 (16.7)
Alter, 2017	20	21	63 (15)	57 (15)	ns	ns	ns	ns	4/16	4/17	ns	ns	ns	ns
Barron, 2017	32	32	45 (8.6)	45.4 (9.1)	ns	ns	29 (16)	27.6 (6.1)	0/32	0/32	ns	ns	93 (56)	105 (51)
Bramlett, 2012	52	35	61.3 (7.85)	62.2 (7.2)	94.5 (17.88)	90.9 (16.41)	ns	ns	26/27	11/23	I-III	I-III	ns	ns
Bultema, 2016	47	48	33 (11)	34 (10)	ns	ns	ns	ns	22/25	18/30	I-II	I-II	ns	ns
Dale, 2019	26	26	ns	ns	ns	ns	ns	ns	15/11	14/12	1/15/10	1/15/10	ns	ns
Glenn, 2016	52	48	36 (10)	37 (13)	ns	ns	ns	ns	16/36	21/27	I-II	I-II	ns	ns
Ha, 2019	22	22	49 (9.2)	49 (10)	80.7 (13.6)	76.5 (12.3)	29.1 (4.6)	28.1 (4.5)	ns	ns	II	I-III	ns	ns
Haas, 2012	74	26	43 (11)	44 (11)	81 (20)	80 (16)	ns	ns	55/19	15/11	ns	ns	ns	ns
Hutchins, 2015	28	30	60.5 (10.8)	56.8 (10.0)	89.3 (25.1)	98.5 (34.2)	ns	ns	0/28	0/30	4/15/9	4/13/13	256.5 (49.5)	245.5 (71.25)
Hutchins, 2016	30	29	41.0 (12.5)	38.0 (12.6)	78.7 (12.3)	75.5 (15.5)	ns	ns	14/16	10/20	ns	ns	404 (184)	352 (144)
Iwanoff, 2018	24	33	53.3 (10.8)	51.2 (7.6)	ns	ns	27.8 (5.3)	25.9 (4.1)	0/24	0/33	ns	ns	30.25 (9.25)	30.5 (9)
Knight, 2015	97	94	62 (2.7)	63 (2.7)	ns	ns	28.2 (1.2)	28.9 (1.5)	63/34	57/37	ns	ns	ns	ns
Knudson, 2016	27	30	66.2 (15.7)	67.9 (11.2)	ns	ns	26.9 (5.8)	30.8 (6.2)	15/12	15/15	0/12/14/1	0/9/20/1	ns	ns
Motakef, 2017	12	12	48.7 (12.5)	56.2 (12.6)	ns	ns	25.9 (3.2)	25.3 (4.5)	0/12	0/12	ns	ns	ns	ns
Nadeau 2016	34	34	33 (11.3)	33 (11.3)	ns	ns	21.9 (4)	21.9 (4)	0/34	0/34	ns	ns	ns	ns
Perets, 2017	50	57	61.9 (9.55)	62.4 (12.1)	ns	ns	29.2 (6.85)	31.0 (9.0)	21/29	26/31	8/26/16/0	4/31/21/1	ns	ns
Premkumar, 2016	14	15	24.1 (7.3)	25.5 (6.8)	ns	ns	24.3 (2.5)	26.2 (7.6)	9/5	7/8	ns	ns	87.7 (14.3)	80.2 (14.7)
Schroer, 2015	58	53	67 (8.8)	68.6 (9.2)	ns	ns	32 (5.9)	32 (5.7)	24/34	21/32	1/36/21/0	5/34/14/0	ns	ns
Schumer, 2018	67	64	68.4	68.4	ns	ns	31.3	31.3	ns	ns	ns	ns	ns	ns
Vandepitte, 2017	26	24	61 (11)	57 (12)	ns	ns	28 (4)	27 (5)	13/13	10/14	6/19/1/0	7/17/0/0	ns	ns
Wong, 2020	75	71	42.1 (9.8)	39.4 (10.9)	119.5 (23.8)	121.7 (22.6)	44.5 (7.6)	44.8 (5.5)	15/60	16/55	ns	ns	ns	ns
Zlotnicki, 2018	38	40	63.2 (7.2)	64.3 (8.8)	ns	ns	35.5 (7.4)	35.4 (6.6)	19/19	14/26	ns	ns	ns	ns

Abbreviations: LB: liposomal bupivacaine; PB: plain bupivacaine; SD: standard deviation, ASA: American Society of Anesthesiologist

Supplemental Content 3: Levels of Evidence Table: Liposomal bupivacaine vs plain bupivacaine

Outcomes	Limitations	Inconsistency/ Heterogeneity	Indirectness	Imprecision	Publication bias	Mean difference (MD) or Ratio of Means (ROM) [95% Confidence Interval]	Number of participants (studies)	Quality or certainty of the evidence (GRADE)
Pain Scores 24h [NRS 0-10] (MD)	Potential overestimation due to unblinded performance	*Low, I^2* of 0% p-value for heterogeneity: p= 0.84	None (pairwise meta-analysis, fully direct)	No serious imprecision	Not detected	MD -0.37 (95%-CI -0.56; -0.19)	1348 (17 studies)	⊕⊕⊕⊕ HIGH (homogenous results)
MEQ 24h [mg] (ROM)	Potential serious limitation due to risk of bias	*moderate, I^2* of 44% p-value for heterogeneity: p= 0.04	None	No serious imprecision	Not detected	ROM 0.85 (95%-CI 0.82; 0.89)	1086 (14 studies)	⊕⊕⊕⊕ HIGH (homogenous results)
Pain Scores 72h [NRS 0-10] (MD)	Potential serious limitation due to risk of bias	*substantial, I^2* of 74% p-value for heterogeneity: p < 0.01	None	No serious imprecision	Not detected	MD -0.25 (95%-CI -0.71; 0.20)	1203 (15 studies)	⊕⊕⊕ MODERATE (substantial heterogeneity)
MEQ 72h [mg] (ROM)	Potential serious limitation due to risk of bias	*Low, I^2* of 32 % p-value for heterogeneity: p= 0.16	None	No serious imprecision	Not detected	ROM 0.85 (95%-CI 0.77; 0.95)	680 (9 studies)	⊕⊕⊕⊕ HIGH (homogenous results)

Time to first analgesic request	Potential serious limitation due to risk of bias	NA	None	NA	NA	NA	NA	NA
Adverse events	Potential serious limitation due to risk of bias	NA	None	NA	NA	NA	NA	NA

Supplemental Content 4:

Study	year	Drug approved by the FDA for this indication	Off-label use	Study performed with an Investigational New Drug (IND)
Alijanipour	2017	x		
Alter	2017	x		
Barron	2017	x		
Bramlett	2012	x		
Bultema	2016	x		
Dale	2019	x		
Glenn	2016	x		
Ha	2019	x		
Haas	2012	x		
Hutchins	2015	x		
Hutchins	2016	x		
Iwanoff	2018	x		
Knight	2015	x		
Knudson	2016	x		
Motakef	2017	x		
Nadeau	2016	x		
Perets	2017	x		
Premkumar	2016	x		
Schroer	2015	x		
Schumer	2018	x		
Vandepitte	2017			x, Liposomal bupivacaine was used as investigational drug in this study before its approval for interscalene nerve block in 2018
Wong	2020	x		
Zlotnicki	2018	x		

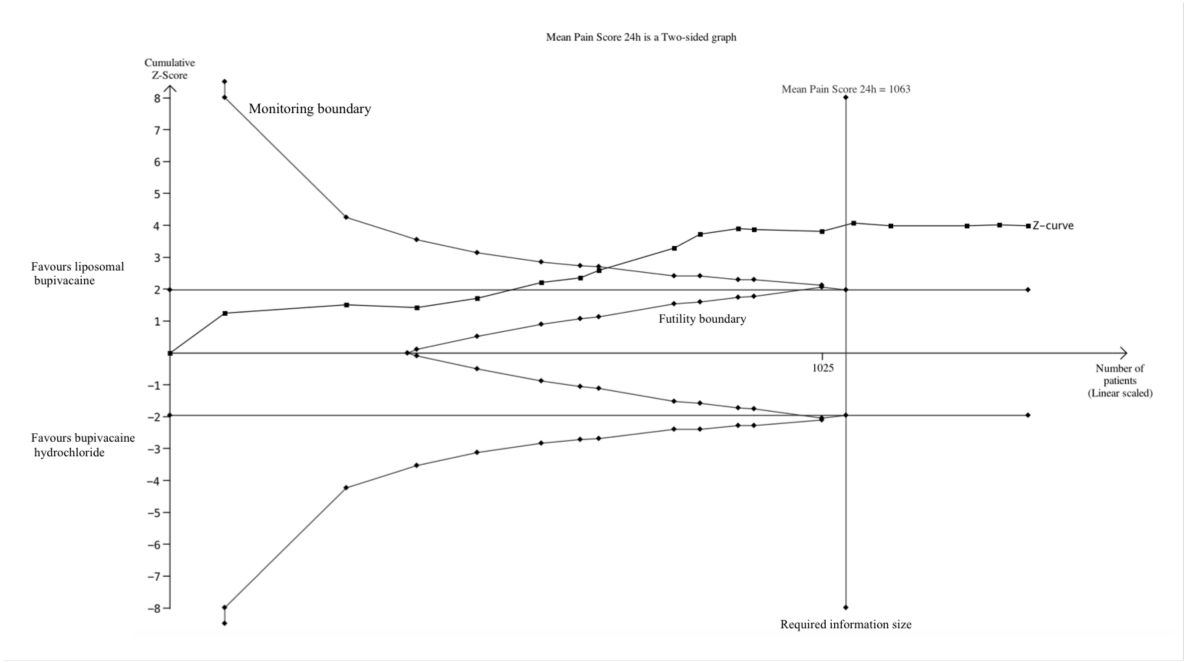
Supplemental Content 5: Adverse event

author, year	nausea/vomiting				dizziness				Pruritus				urinating difficulties				thrombembolic complications				neurologic complications				local anesthetic systemic toxicity				wound healing complications				hypesthesia/ numbness			
	LB		PB		LB		PB		LB		PB		LB		PB		LB		PB		LB		PB		LB		PB		LB		PB		LB		PB	
	e	*n*	*e*	*n*	*e*	*n*	*e*	*n*	*e*	*n*	*e*	*n*	*e*	*n*	*e*	*n*	*e*	*n*	*e*	*n*	*e*	*n*	*e*	*n*	*e*	*n*	*e*	*n*	*e*	*n*	*e*	*n*	*e*	*n*	*e*	*n*
Alijanipour, 2017																	1	87	1	75	2	87	0	75					1	87	0	75				
Alter, 2017																																	16	20	11	21
Barron, 2017	4	16	6	25	1	16	3	25					2	16	5	25	2	16	5	25																
Bramlett, 2012	20	53	23	34	6	53	6	34	6	53	6	34	1	53	0	34																	2	53	0	34
Bultema, 2016																																				
Dale, 2019																																				
Glenn, 2016																																				
Ha, 2019																																				
Haas, 2012	7	73	3	26					1	73	1	26																								
Hutchins, 2015	7	28	17	30																																
Hutchins, 2016	7	30	15	30																																
Iwanoff, 2018																	0	24	0	33																
Knight, 2015																																				
Knudson, 2016	9	27	14	30																																
Motakef, 2017	3	12	2	12																																
Nadeau 2016																																				
Perets, 2017	12	43	8	48																																
Premkumar, 2016																																				
Schroer, 2015	3	58	2	53																																
Schumer, 2018	19	66	14	64	2	66	0	64	9	66	7	64	1	66	2	64	1	66	1	64																
Vandepitte, 2017					5	26	4	24									1	26	0	24					4 a	25	3 a	24								
Wong, 2020	27	75	41	71																																
Zlotnicki, 2018																																				

total (n)	118	481	145	422	14	161	13	147	16	192	14	124	4	135	7	123	5	219	7	221	2	87	0	75	4	25	3	24	1	87	0	75	18	73	11	55
percentage (%)	24.5		34.4		8.7		8.8		8.3		11.3		3		5.7		2.3		3.2		2.3		0		16		12.5		1.5		0		24.7		20	

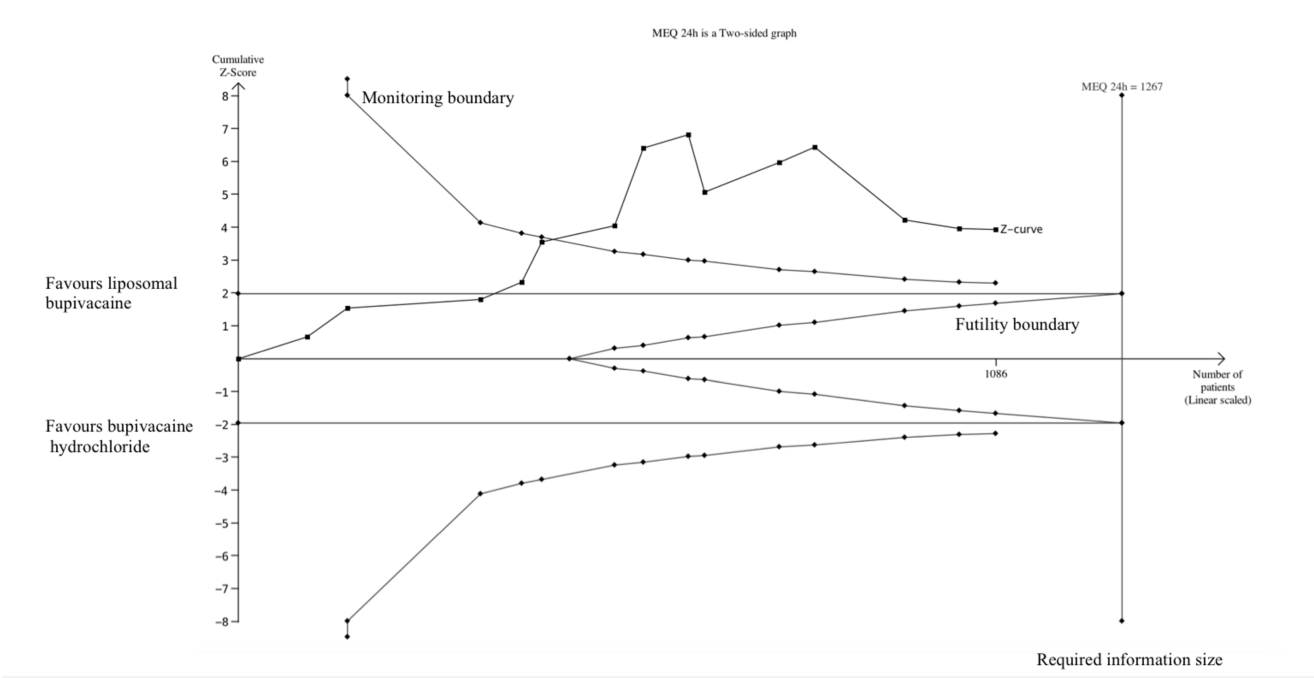
Abbreviations: LB: liposomal bupivacaine; PB: plain bupivacaine; e: event; n: number
a: ear ringing, metallic taste

Supplemental Content 6: Trial Sequential Analysis (TSA) for Mean Pain Scores after 24 hours



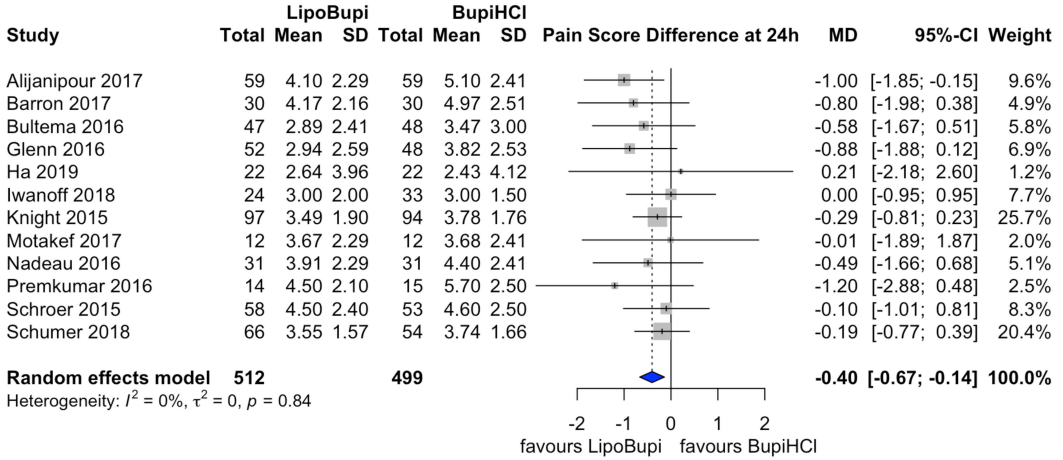
Supplemental Content 6: Trial sequential analysis for the Mean Pain Score 24 hours postoperatively.
The y-axis depicts the required information size. The horizontal lines depict the conventional threshold for statistical (not clinical) significance at Z= 1.96/ -1.96 (i.e. p = 0.05). The threshold for clinical relevance of the effect size is not shown in this figure._The outer and the inner curved diagonal lines, represent the adjusted threshold for statistical significance and the futility boundaries. The Z-curve refers to the statistical summary of the accrued data. If a Z-curve crosses the futility boundaries before the required information size is reached, the likelihood of finding a significant effect is negligible. If a Z-curve crosses the monitoring boundary (threshold of statistically significant treatment effect) before the information size is reached, further studies are unlikely to change the treatment effect.

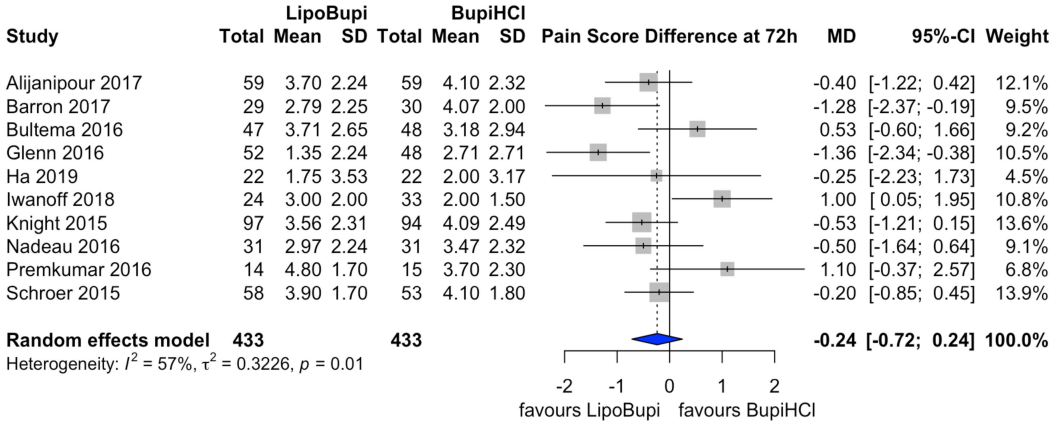
Supplemental Content 7: Trial Sequential Analysis (TSA) for cumulative morphine equivalents (MEQ) after 24 hours



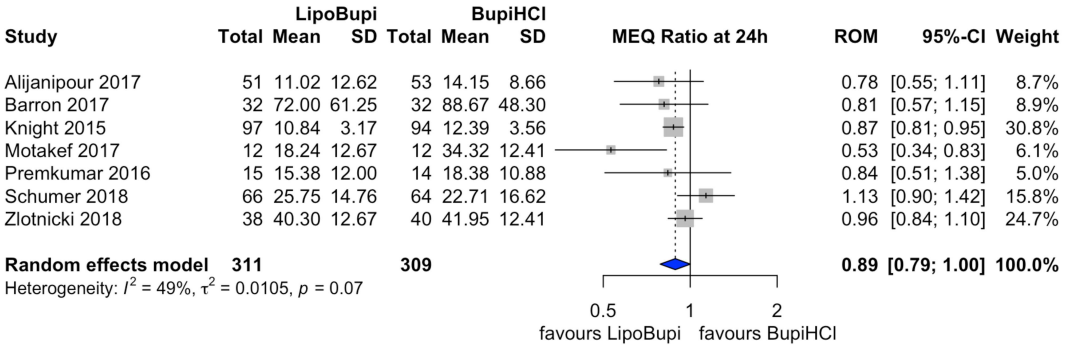
Supplemental Content 7: Trial sequential analysis for the cumulative morphine equivalents 24 hours postoperatively.
The y-axis depicts the required information size. The horizontal lines depict the conventional threshold for statistical (not clinical) significance at Z= 1.96/ -1.96 (i.e. p = 0.05). The threshold for clinical relevance of the effect size is not shown in this figure. The outer and the inner curved diagonal lines, represent the adjusted threshold for statistical significance and the futility boundaries. The Z-curve refers to the statistical summary of the accrued data. If a Z-curve crosses the futility boundaries before the required information size is reached, the likelihood of finding a significant effect is negligible. If a Z-curve crosses the monitoring boundary (threshold of statistically significant treatment effect) before the information size is reached, further studies are unlikely to change the treatment effect.

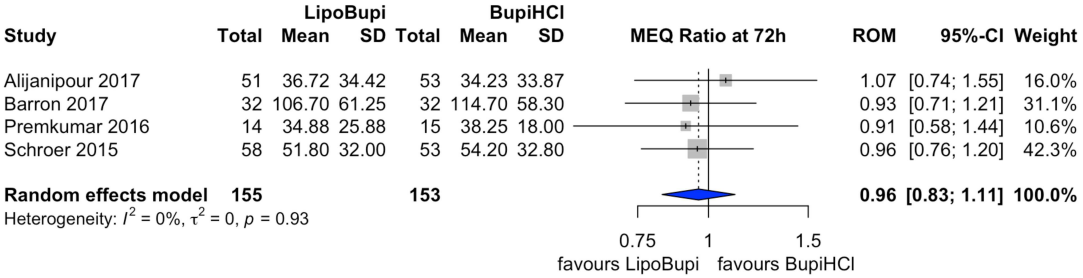
Supplemental Content 8: Not-predefined subgroup analysis for the influence of funding. (all forest plots include only non-industrial sponsored studies). Mean Pain Score 24 h and 72 h.



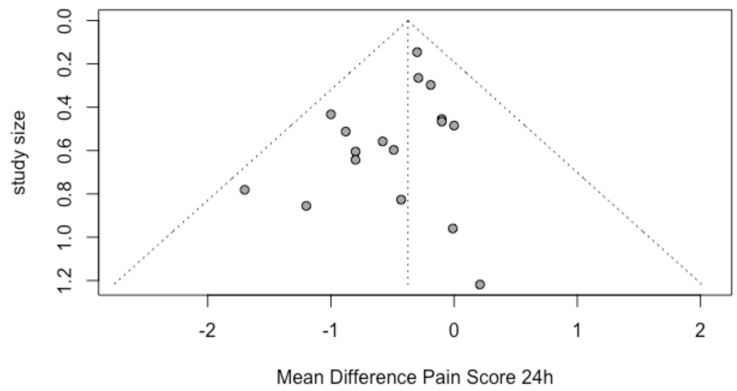


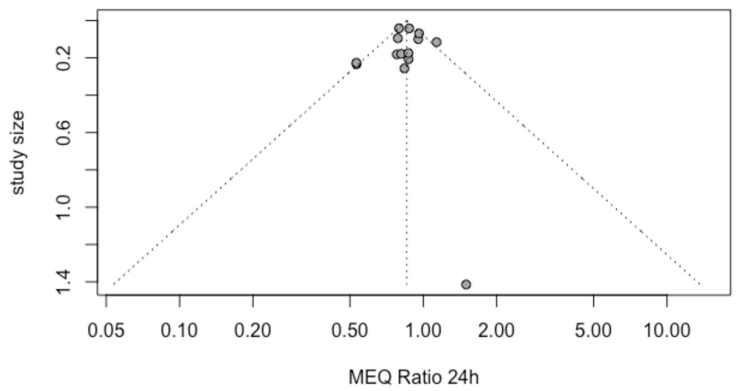
Supplemental Content 9: Not-predefined subgroup analysis for the influence of funding. (all forest plots include only non-industrial sponsored studies). Ratio of Morphine Equivalent Consumption 24 h and 72 h.

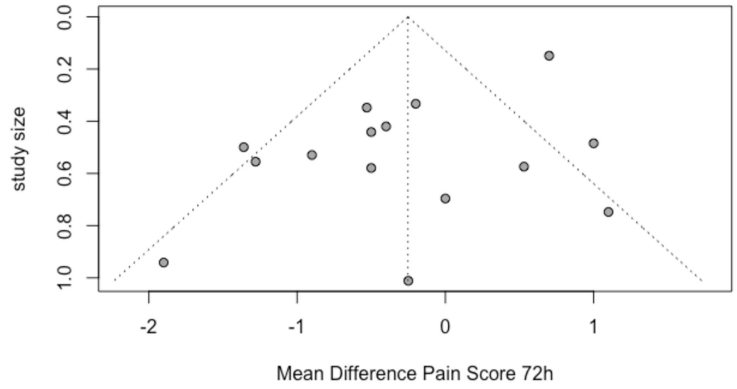


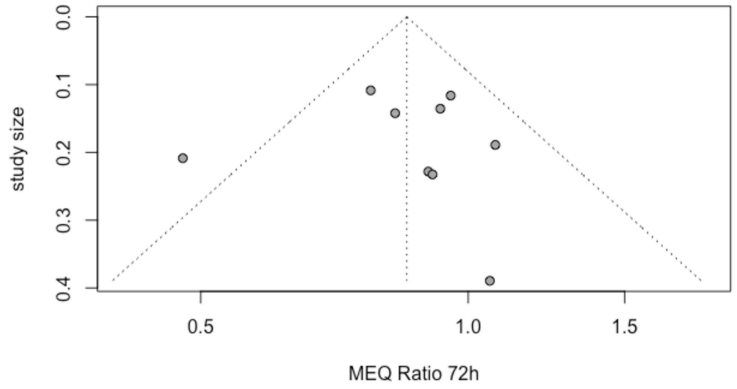


Supplemental Content 10: Funnel Plots to identify possible publication bias.

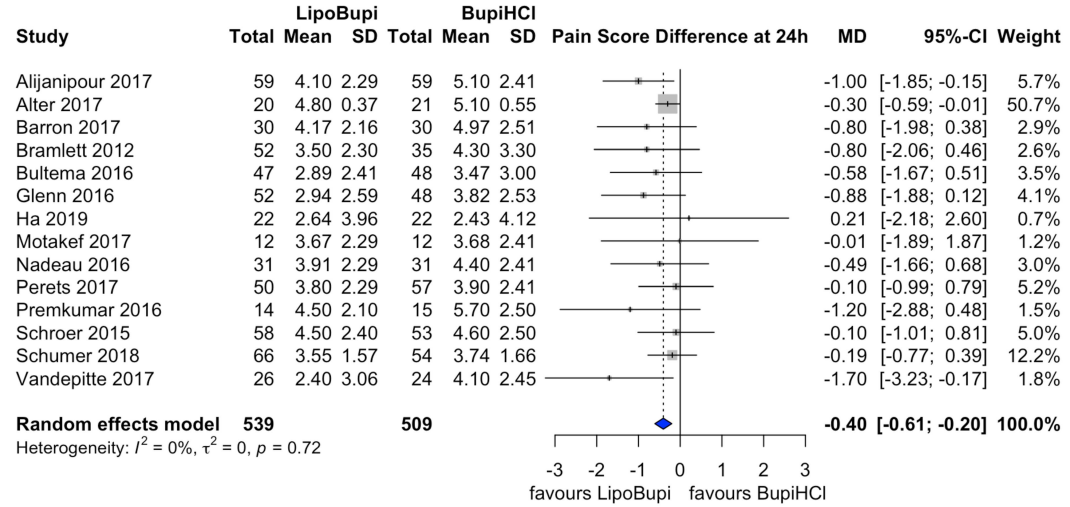


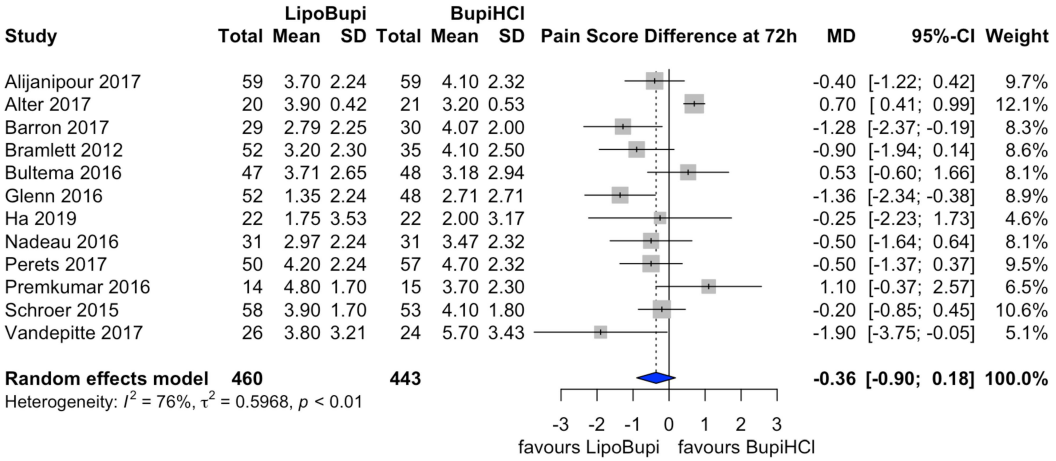






Supplemental Content 11: Not-predefined subgroup analysis for the influence of calculating mean (SD) from median (interquartile range or total range). (all forest plots include only studies that reported means in the original data). Mean Pain Score at 24 h and 72 h.





Supplemental Content 12: Not-predefined subgroup analysis for the influence of calculating mean (SD) from median (interquartile range or total range). (all forest plots include only studies that reported means in the original data). Ratio of Morphine Equivalents (MEQ) at 24 h and 72 h.