SYSTEMATIC REVIEW



Liposomal bupivacaine administration is not superior to traditional periarticular injection for postoperative pain management following total knee arthroplasty: a meta-analysis of randomized controlled trials

Jian-Jiun Chen¹, Yun-Che Wu², Jun-Sing Wang^{3,4,5*} and Cheng-Hung Lee^{2,5,6*}

Abstract

Background Liposomal bupivacaine (LB) is a relatively new formulation that slowly releases bupivacaine to extend its efficacy for 72–96 h. It is inconclusive whether LB offers better efficacy than traditional periarticular injection (TPAI) following total knee arthroplasty (TKA).

Methods Relevant randomized controlled trials (RCTs) were searched using electronic databases, including PubMed, Cochrane Library, EMBASE, and Web of Science. Review Manager 5.4.1 was used for calculations.

Results Sixteen RCTs were included in this meta-analysis. LB had better effects on morphine consumption equivalents during postoperative 24–48 h than TPAI. No significant difference was observed in pain relief, incidence of nausea and vomiting, or length of hospital stay between the two groups.

Conclusion LB administration during TKA is not superior to TPAI. Studies with larger sample size are needed to validate our findings.

PROSPERO registration number: CRD42022355094.

Keywords Total knee arthroplasty, Liposomal bupivacaine, Traditional periarticular injection

*Correspondence:

Jun-Sing Wang

jswang@vghtc.gov.tw

Cheng-Hung Lee

- leechenghung0115@gmail.com
- ¹ Department of Orthopedics, Taipei Veterans General Hospital, Taipei, Taiwan
- ² Department of Orthopedics, Taichung Veterans General Hospital,
- No.1650, Sec. 4, Taiwan Boulevard, Taichung 40705, Taiwan ³ Division of Endocrinology and Metabolism, Department of Internal
- Medicine, Taichung Veterans General Hospital, No.1650, Sec. 4, Taiwan Boulevard, Taichung 40705, Taiwan
- ⁴ Ph.D. Program in Translational Medicine, National Chung Hsing
- University, Taichung, Taiwan

National Chung Hsing University, Taichung, Taiwan



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

 $^{\rm 6}$ Department of Food Science and Technology, Hung Kuang University, Taichung, Taiwan

⁵ Department of Post-Baccalaureate Medicine, College of Medicine,

Introduction

Total knee arthroplasty (TKA) is the most successful and common orthopedic surgery for decreasing pain in patients with osteoarthritis. The number of TKA conducted each year in the USA has been more than 700,000 [1]. Postoperative pain often has negative impact on patient outcomes. Patients with persistent pain cannot undergo early rehabilitation. This results in a decrease in knee joint function, slow recovery time, and delayed hospital discharge [2]. Thus, coping with postoperative pain is critical, but there is currently no gold standard treatment [3].

Kerr and Kohan first described periarticular multimodal drug injection (PMDI), a technique that combines multiple analgesics or anesthetic agents for injection into periarticular spaces during surgery [4–6]. The technique is simple and effective. PMDI can effectively reduce postoperative pain, decrease the demand for systemic analgesics, and consequently decrease the side effects of systemic analgesics [7–12].

Which treatment is the most effective analgesic or anesthetic remains inconclusive. Liposomal bupivacaine (LB; Exparel; Pacira Pharmaceuticals, Parsippany, NJ, USA), a formulation composed of multivesicular liposomes that contain bupivacaine, was approved by the FDA in 2011. The formulation allows bupivacaine to be released more slowly, extending its efficacy to 72-96 h [13]. LB is administered intraoperatively into the surgical wound. This medicine has already been applied safely in several procedures, including TKA and augmentation mammoplasty [14]. LB has been claimed to achieve a better effect on postoperative pain control, lower analgesic rescue dose, lower opioid-related adverse effects (ORAE), and a shorter length of hospital stay than the traditional bupivacaine injection [15]. To analyze the efficacy of LB for TKA and compare it with that of standard agents, the best approach is to use a periarticular injection approach to administer both LB and standard agents following TKA; the advantages are the same administration method and minimal confounding factors [16].

Uncertainty regarding the differences in outcomes between LB and traditional periarticular injection (TPAI) following TKA has been demonstrated in several studies. Only two meta-analyses focused on randomized controlled trials (RCTs) were published in 2019, and there are some data gaps [17, 18]. The conclusion of Yayac et al. [17] revealed that LB offers no advantages over other analgesics, and Liu et al. [18] found no significant difference on the visual analog scale (VAS) after comparing LB to TPAI; however, LB was associated with lower opioid consumption and incidence of nausea and vomiting.

The value of spending more than 10 times the money to use LB rather than TPAI for as-yet-unproven benefits is dubious [19]. As a result, the present study aimed to analyze more valid RCTs, including those published before May 2022, and to fill gaps in the data of previous studies.

Patient and method

This study was conducted per The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20].

Search strategy

PubMed, the Cochrane Library, EMBASE, and Web of Science were searched up to May 2022. The search terms included "total knee arthroplasty OR replacement" AND "liposomal bupivacaine" AND "local infiltration OR periarticular injection OR periarticular infiltration." Furthermore, the reference lists of included studies were searched to identify potentially eligible studies. All the searches were conducted independently by two authors, and disagreements were resolved by the third author.

Study selection

Only "Randomized Controlled Trials" comparing an LB group with a control group were identified. Studies were considered eligible only if they met these criteria: (1) Patient underwent primary TKA. (2) Intervention group received a periarticular LB injection. (3) Control group received TPAI, including standard bupivacaine and cocktail (ropivacaine, morphine, ketorolac, epinephrine, etc.) (4) At least one of the following outcomes was reported: postoperative pain score with rest or activity, opioid consumption, ORAE (nausea and vomiting), and length of hospital stay.

All potentially eligible studies and relevant citations were screened by two authors independently for inclusion. Disagreements were resolved by the third author.

Data abstraction and quality assessment

A standard form was designed by two authors to screen the relevant data in each included study. A Microsoft Excel database was used for data collection. The following data were extracted: (1) patient characteristics (age, sex, and other baseline characteristics), (2) interventions (LB, bupivacaine, or cocktail), (3) outcomes (primary outcome: the VAS score; secondary outcomes: opioid consumption in oral morphine equivalents, the incidence of nausea and vomiting, and the length of hospital stay). Missing data were obtained by contacting corresponding authors. If variability data could not be obtained by studies or authors, the Cochrane Handbook for Systematic Reviews of Interventions was followed to calculate standard deviations by using p values and confidence intervals [21]. Two authors independently assessed the risk of bias associated with the following factors: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other potential sources of bias. Additionally, all authors' conflict of interest statements were assessed. Disagreements were determined by the third author.

The quality of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria [22].

Data analysis

Data were analyzed using the latest version of Review Manager (5.4.1, released in September 2020). The mean differences (MDs) were used to assess the effects of treatment for continuous outcomes. The risk ratios (RRs) were used to weigh the effect size of dichotomous outcomes. The standardized mean difference (SMD) was used to evaluate the morphine consumption equivalents due to the high degree of variability. Significant heterogeneity was considered when $p \le 0.1$ or $I^2 > 50\%$. A fixed-effects model was used for the study groups without significant heterogeneity. A random-effects model was used to ensure the robustness of the model.

In the part of postoperative VAS score, the control group was classified into standard bupivacaine and cocktail groups, and subgroup analyses were performed to eliminate any possible risk of bias.

Results

Search results

A total of 587 citations were identified. Using EndNote software, 101 duplicate citations were excluded. After scanning the titles and abstracts, 454 citations were excluded, and 16 citations were eliminated after reading the full texts. Finally, 16 RCTs met the inclusion criteria of this study (Fig. 1) [15, 19, 23–36].

Characteristics of included studies

A total of 16 RCTs with 1629 participants were involved. Ten RCTs used standard bupivacaine as the control drug [15, 23, 24, 26, 29, 31, 33–36], whereas 6 RCTs used a cocktail. All the RCTs were conducted in the USA. Six RCTs did not perform power analysis to determine the optimal sample size [25, 28, 31, 34–36]. The follow-up period ranged from 24 h to 8 weeks (Table 1).



Fig. 1 Flowchart of literature selection procedure

studies
of included
acteristics o
1 Char
Table

2										
	No.	Age	Male	Female	BMI					
Bramlett 2012 [23] USA 2	25/34	61.1/62.2	13/11	12/23	31.2/31.5	GA	LB 266 mg	Bup 150 mg	36 days	≻
Schroer 2015 [24] USA 5	58/53	67/68.6	24/21	34/32	32/32	SA/GA	LB 266 mg, Bup 75 mg	Bup 150 mg	3 weeks	≻
Collis 2016 [25] USA 5	54/51	63.7/63.5	25/14	29/37	34.1/35.7	GA	LB 266 mg	Rop 246.25 mg, Epi 0.5 mg, Ket 30 mg, Clo 0.08 mg	8 weeks	z
Jain 2016 [26] USA 6	53/62	68.3/67.5	19/17	44/45	33.3/33.3	SA	LB 266 mg	Bup 75 mg, Epi 0.15 mg, Mor 10 mg	MN	≻
Schwarzkopf 2016 [27] USA 2	20/18	63/59	7/10	13/8	29.3/29.5	SA	LB 266 mg, Bup 50 mg	Rop 246.25 mg, Epi 0.5 mg, Clo 80 mg, Tor 30 mg	MN	≻
Snyder 2016 [28] USA 3	35/35	67.3/65.6	22/15	13/20	30.68/31.29	SA/GA	LB 266 mg	Rop 400 mg, Epi 0.6 mg, Ket 30 mg, Mor 5 mg	10 days	z
Alijanipour 2017 [29] USA 5	59/59	64.3/64.9	29/27	30/32	32.3/28.7	SA	LB 266 mg, Epi 0.5 mg	Bup 50 mg, Epi 0.1 mg	6 weeks	≻
Declaire 2017 [30] USA 4	47/49	69.7/67.7	21/21	26/28	31.5/31.9	SA/GA	LB 266 mg, Bup, Epi, Ket, Mor	Rop, Epi, Ket, Mor	MM	≻
Mont 2017 [15] USA 7	10/69	66/66	27/30	43/39	32.4/31.3	SA	LB 266 mg, Bup 100 mg	Bup 100 mg	MN	≻
Smith 2017 [31] USA 1	104/96	66/66	54/28	50/68	31.5/31.6	SA	LB 266 mg	Bup	6 weeks	z
Danoff 2018 [32] USA 2	29/29	62.9/62.9	15/15	14/14	30.4/30.4	SA	LB 266 mg, Bup 75 mg	Rop 250 mg, Epi 0.5 mg, Ket 30 mg, Clo 0.08 mg	6 weeks	≻
Schumer 2018 [36] USA 6	56/64	MM	MN	MN	MN	SA	LB 266 mg, Bup 1 mg/kg	Bup 150 mg	6 weeks	z
Suarez 2018 [33] USA 5	52/52	68.1/67.3	19/26	33/26	30.8/32.01	SA	LB 266 mg, Bup 75 mg	Rop 246.25 mg, Epi 0.5 mg, Ket 30 mg, Clo 0.08 mg	6 weeks	≻
Zlotnicki 2018 [34] USA 3	38/40	63.2/64.3	19/14	19/26	35.5/35.4	SA/GA	LB 266 mg	Bup 100 mg	MM	z
Dysart 2019 [35] USA 7	70/69	66/66	29/28	41/41	MN	SA	LB 266 mg, Bup 100 mg	Bup 100 mg	24 h	z
Hyland 2019 [19] USA 3	30/29	65.0/61.2	14/13	16/16	MN	GA+ACB	LB 266 mg	Rop 40 mg, Ket 30 mg, Mor 10 mg, Methy 40 mg	MN	≻

Study quality

Regarding randomization, three studies used random number tables [28, 31, 33], two studies used Microsoft Excel software [29, 30], four studies used centralized randomization systems [15, 19, 23, 35], and the randomization method was not mentioned in the other studies. Only two studies reported the concealment of allocation [19, 29]. Most studies were blind to participants and outcome assessors but not the surgeons who injected the drugs. Only six studies were blind to the surgeons [15, 23, 30–32, 35].

The methodological quality of the 16 RCTs was summarized using RevMan software. Figure 2 shows the methodological quality of the included studies, and Fig. 3 displays the evaluation of risk of bias by percentage. Figure 4 depicts the funnel plot of the primary outcome, namely the VAS score. One study, VAS POD1 of Declaire 2017 [30], was not included in the funnel plot due to extremely high standard error (MD=0.69, SE=3.08). Asymmetries were noted in postoperative day 0 (POD0), POD1 and POD2, and publication bias cannot be ruled out.

Primary outcome: postoperative pain score

Subgroup analyses of the LB group versus standard bupivacaine group and LB group versus cocktail group were conducted to reduce the possible risk of bias. The assessment time was divided into PODs 0-3 (Fig. 5).

POD 0

A meta-analysis of two studies [23, 31] with 260 participants did not reveal a significant difference between the LB and the bupivacaine subgroups (p = 0.54).

A meta-analysis of three studies [27, 28, 32] with 154 participants did not reveal a significant difference between the LB and the cocktail subgroups (p = 0.93).

POD 1

A meta-analysis of six studies [23, 24, 26, 29, 31, 34] with 691 participants did not reveal a significant difference between the LB and the bupivacaine subgroups (p=0.61).

A meta-analysis of six studies [25, 27, 28, 30, 32, 33] with 459 participants did not report a significant difference between the LB and the cocktail subgroups (p=0.77).



Fig. 2 Methodological quality of included studies

POD 2

A meta-analysis of fie studies [23, 24, 29, 31, 34] with 566 participants did not show a significant difference between the LB and the bupivacaine subgroups (p=0.36).

A meta-analysis of six studies [25, 27, 28, 30, 32, 33] with 459 participants did not reveal a significant



Fig. 3 Risk-of-bias assessment of included studies



Fig. 4 Funnel plot of VAS score. VAS POD1 of Declaire 2017 was not included in the funnel plot due to extremely high standard error (MD = 0.69, SE = 3.08)

difference between the LB and the cocktail subgroups (p = 0.67).

POD 3

A meta-analysis of three studies [24, 29, 31] with 415 participants did not reveal a significant difference between the LB and the bupivacaine subgroups (p=0.99). A meta-analysis of two studies [25, 28] with 175 participants revealed a borderline difference between the LB and the cocktail subgroup (p = 0.05). The VAS score was slightly higher in patients who received LB than in patients who received the cocktail injection.

Study or Subgroup	Mean	LB SD	Total	Mean	TPAI SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% Cl
1.1.1 bupivacaine 2012 Bramlett	3.1	24	25	43	33	35	8.8%	-1 20 [-2 64 0 24]	
2017 Smith Subtotal (95% CI)	3.46	3.99	104	3.19	4.01	96 131	14.9%	0.27 [-0.84, 1.38]	
Heterogeneity: Chi ² =	2.51, c	df = 1 (P = 0.1	11); I ² =	= 60%	151	23.0%	0.20 [1.10, 0.00]	
Test for overall effect	: Z = 0.	62 (P =	0.54)						
1.1.2 cocktail 2016 Schwarzkopf	7 81	2 5 9	20	7 14	3 33	18	5.0%	0 67 [-1 24 2 58]	
2016 Snyder	2.89	1.81	35	3.6	1.77	35	26.1%	-0.71 [-1.55, 0.13]	
Subtotal (95% CI)	2.2	1.2	23 78	1.9	1	23 76	45.1% 76.2%	-0.02 [-0.51, 0.47]	-
Heterogeneity: Chi ² = Test for overall effect	4.07, c	df = 2 (09 (P =	P = 0.1 0.93)	13); I ² =	51%				
Total (95% CI)			207			207	100.0%	-0.08 [-0.51 0.35]	
Heterogeneity: Chi ² =	6.82, c	if = 4 (P = 0.1	15); I ² =	41%	207	100.070	0.00 [0.51, 0.55]	
Test for overall effect Test for subgroup dif	: Z = 0. ference:	38 (P = s: Chi ²	0.71) = 0.25	, df = 1	1 (P = 0).62), I ²	= 0%		Favours LB Favours TPAI
		LB			ΤΡΑΙ			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2012 Bramlett	3.7	2.3	25	3.8	2.6	35	4.5%	-0.10 [-1.35, 1.15]	
2015 Schroer 2016 Jain	4.5 3.86	2.4 1.8	58 63	4.6 3.97	2.5 1.9	53 62	7.2% 11.2%	-0.10 [-1.01, 0.81] -0.11 [-0.76, 0.54]	
2017 Alijanipour 2017 Smith	2.89	1.87	58	3.45	2.13	59	9.8%	-0.56 [-1.29, 0.17]	
2018 Zlotnicki	5.4	3.03	38	6.9	3.03	40	3.9%	-1.50 [-2.85, -0.15]	
Heterogeneity: Tau ² =	0.31; C	$hi^2 = 1$	2.65, c	if = 5 (P = 0.0	3); I ² =	45.1% 60%	-0.13 [-0.75, 0.45]	
Test for overall effect:	Z = 0.5	1 (P =	0.61)						
1.2.2 cocktail	5 33	0.18	54	5.26	0.19	51	25.1%	0.07 [-0.00, 0.14]	
2016 Schwarzkopf	7.31	3.43	20	7.13	1.46	18	2.8%	0.18 [-1.47, 1.83]	
2016 Snyder 2017 Declaire	4.1	1.27	35 47	3.31	1.55	35 49	0.2%	0.69 [-5.34, 6.72]	· · · · · · · · · · · · · · · · · · ·
2018 Danoff 2018 Suarez	5 2.75	1.3 2.78	23 52	5.1 2.37	1.15 2.78	23 52	10.1% 5.7%	-0.10 [-0.81, 0.61] 0.38 [-0.69, 1.45]	
Subtotal (95% CI) Heterogeneity: Tau ² =	0.03.0	'hi ² = 6	231	= 5 (P	= 0.28	228	54.9%	-0.04 [-0.32, 0.24]	•
Test for overall effect:	Z = 0.2	9 (P =	0.77)			,,			
Total (95% CI)			577			573	100.0%	-0.10 [-0.39, 0.19]	+
Heterogeneity: Tau ² = Test for overall effect:	0.09; C Z = 0.6	Chi² = 1 67 (P =	.9.72, c 0.50)	if = 11	(P = 0.	05); I ² =	= 44%		-2 -1 0 1 2 Favours LB Favours TPAI
Test for subgroup diff	erences	: Chi ² =	= 0.11,	df = 1	(P = 0.	74), I ² =	= 0%		
Study or Subaroup	Mean	LB SD	Total	Mean	TPAI SD	Total	Weight	Mean Difference IV. Random. 95% Cl	Mean Difference IV. Random. 95% Cl
Study or Subgroup	Mean	LB SD	Total	Mean	TPAI SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% Cl
Study or Subgroup 1.3.1 bupivacaine 2012 Bramlett 2015 Schroer	Mean 3.2 4.4	LB SD 2.5 2.1	Total 25 58	Mean 4.1 4.8	2.5 2.1	Total 35 53	<u>Weight</u> 2.0% 4.9%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.40 [-1.18, 0.38]	Mean Difference IV, Random, 95% Cl
Study or Subgroup 1.3.1 bupivacaine 2012 Bramlett 2015 Schroer 2017 Alijanipour 2017 Smith	Mean 3.2 4.4 2.81 3.38	LB SD 2.5 2.1 2.08 3.08	Total 25 58 58 104	Mean 4.1 4.8 3.13 3.3	2.5 2.1 1.87 3.61	Total 35 53 59 96	Weight 2.0% 4.9% 5.7% 3.6%	Mean Difference IV, Random, 95% Cl -0.90 [-2.18, 0.38] -0.40 [-1.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01]	Mean Difference IV, Random, 95% Cl
Study or Subgroup 1.3.1 bupivacaine 2012 Bramlett 2015 Schroer 2017 Alijanipour 2017 Smith 2018 Zlotnicki Subtrail (95% CD	Mean 3.2 4.4 2.81 3.38 3.9	LB SD 2.5 2.1 2.08 3.08 3.55	Total 25 58 58 104 38 283	4.1 4.8 3.13 3.3 3.13	2.5 2.1 1.87 3.61 1.87	Total 35 53 59 96 59 302	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 18.5%	Mean Difference IV, Random, 95% Cl -0.90 [-2.18, 0.38] -0.40 [-1.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.23]	Mean Difference IV, Random, 95% Cl
Study or Subgroup 1.3.1 bupivacaine 2012 Bramlett 2015 Schroer 2017 Alijanjpour 2017 Smith 2018 Zlotnicki Subtotal (95% Cl) Heterogeneity: Tau ² =	Mean 3.2 4.4 2.81 3.38 3.9 0.01; 0	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = 4	Total 25 58 58 104 38 283 4.25, d	4.1 4.8 3.13 3.3 3.13 f = 4 (F	2.5 2.1 1.87 3.61 1.87	Total 35 53 59 96 59 302 7); I ² =	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 18.5% 6%	Mean Difference IV, Random, 95% Cl -0.90 [-2.18, 0.38] -0.40 [-1.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22]	Mean Difference IV, Random, 95% Cl
Study or Subgroup 1.3.1 bupivacaine 2012 Bramlett 2015 Schroer 2017 Alijanipour 2018 Zlotnicki Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect:	Mean 3.2 4.4 2.81 3.38 3.9 0.01; 0 Z = 0.9	LB 2.5 2.1 2.08 3.08 3.55 Chi ² = - 92 (P =	Total 25 58 104 38 283 4.25, d 0.36)	4.1 4.8 3.13 3.3 3.13 f = 4 (F	2.5 2.1 1.87 3.61 1.87 2 = 0.3	Total 35 53 59 96 59 302 7); 1 ² =	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 18.5% 6%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.40 [-1.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.07 [-0.46, 2.00] -0.20 [-0.62, 0.22]	Mean Difference IV, Random, 95% Cl
Study or Subgroup 1.3.1 bupivacaine 2012 Bramlett 2015 Schroer 2017 Alijanipour 2018 Zlotnicki Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect: 1.3.2 cocktail 2016 Collis	Mean 3.2 4.4 2.81 3.38 3.9 • 0.01; 0 Z = 0.9	LB 2.5 2.1 2.08 3.08 3.55 $Chi^2 = -$ 92 (P =	Total 25 58 58 104 38 283 4.25, d 0.36)	4.1 4.8 3.13 3.13 3.13 f = 4 (F	2.5 2.1 1.87 3.61 1.87 9 = 0.3	Total 35 53 59 96 59 302 7); 1 ² =	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 18.5% 6%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.40 [-1.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.07 [-0.46, 2.00] -0.20 [-0.62, 0.22]	Mean Difference IV, Random, 95% Cl
Study or Subgroup 1.3.1 bupivacaine 2012 Bramlett 2015 Schroer 2017 Alijanipour 2018 Zlotnicki Subtotal (95% Cl) Heterogeneity: Tau ² = Test for overall effect: 1.3.2 cocktail 2016 Collis 2016 Schwarzkopf	Mean 3.2 4.4 2.81 3.38 3.9 • 0.01; 0 Z = 0.9 5.02 5.54	LB SD 2.5 2.1 2.08 3.55 Chi ² = - 92 (P = 0.16 1.84	Total 25 58 104 38 283 4.25, d 0.36) 54 20	<u>Mean</u> 4.1 4.8 3.13 3.13 f = 4 (F 4.96 5.25	2.5 2.1 1.87 2 = 0.3 0.16 1.94	Total 35 53 59 96 59 302 7); I ² = 51 18	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 18.5% 6%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.40 [-1.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.29 [-0.92, 1.50]	Mean Difference IV, Random, 95% Cl
Study or Subgroup 1.3.1 bupivacaine 2012 Bramlett 2015 Schroer 2017 Alijanipour 2017 Smith 2018 Zlotnicki Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.3.2 cocktail 2016 Schlwarzkopf 2016 Snyder 2017 Declaire	Mean 3.2 4.4 2.81 3.38 3.9 • 0.01; 0 Z = 0.9 5.02 5.54 2.4 4.44	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = - 92 (P = 0.16 1.84 1.48 1.43	Total 25 58 58 104 38 283 4.25, d 0.36) 54 20 35 47	Mean 4.1 4.8 3.13 3.13 f = 4 (F 4.96 5.25 3.51 4.57	2.5 2.1 1.87 3.61 1.87 9 = 0.3 0.16 1.94 1.54 1.43	Total 35 53 59 96 59 302 $7); I^2 =$ 51 18 35 49	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 18.5% 6% 33.8% 2.3% 5.9% 8.2%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.40 [-1.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.29 [-0.92, 1.50] -1.11 [-1.82, -0.40]	Mean Difference IV, Random, 95% Cl
Study or Subgroup 1.3.1 bupivacaine 2012 Bramlett 2015 Schroer 2017 Alijanipour 2017 Smith 2018 Zlotnicki Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.3.2 cocktail 2016 Schwarzkopf 2016 Schwarzkopf 2016 Schwarzkopf 2016 Schwarzkopf 2016 Schwarzkopf 2016 Schwarzkopf 2016 Schwarzkopf 2017 Declaire 2018 Danoff 2018 Suarez	Mean 3.2 4.4 2.81 3.38 3.9 0.01; C Z = 0.9 5.02 5.54 2.4 4.44 3.57 5.6	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = - 92 (P = 0.16 1.84 1.48 1.43 0.48 1.35	Total 25 58 104 38 283 4.25, d 0.36) 54 20 35 47 52 23	Mean 4.1 4.8 3.13 3.13 f = 4 (F 4.96 5.25 3.51 4.57 3.59 5.25	$\begin{array}{c} \text{TPAI} \\ \text{SD} \\ 2.5 \\ 2.1 \\ 1.87 \\ 3.61 \\ 1.87 \\ P = 0.3 \\ 0.16 \\ 1.94 \\ 1.54 \\ 1.43 \\ 0.48 \\ 1.3 \\ \end{array}$	Total 35 53 59 96 59 302 $7); l^2 =$ 51 18 35 49 52 23	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 18.5% 6% 33.8% 2.3% 5.9% 8.2% 26.2% 5.1%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.40 [-1.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.29 [-0.92, 1.50] -1.11 [-1.82, -0.40] -0.13 [-0.70, 0.44] -0.02 [-0.20, 0.16]	Mean Difference IV, Random, 95% Cl
Study or Subgroup 1.3.1 bupivacaine 2012 Bramlett 2015 Schroer 2017 Alijanipour 2017 Smith 2018 Zlotnicki Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.3.2 cocktail 2016 Schwarzkopf 2016 Schwarzkopf 2016 Snyder 2017 Declaire 2018 Danoff 2018 Suarez Subtotal (95% CI) Heterogeneity: Tau ²	Mean 3.2 4.4 2.81 3.38 3.9 0.01; C Z = 0.9 5.02 5.54 2.4 4.44 3.57 5.6	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = $-$ 92 (P = 0.16 1.84 1.43 0.48 1.35	Total 25 58 104 283 4.25, d 0.36) 54 20 35 47 52 231 231	Mean 4.1 4.8 3.13 3.13 f = 4 (f 4.96 5.25 3.51 4.57 3.59 5.25 df = 5	TPAI SD 2.5 2.1 1.87 3.61 1.87 2 = 0.3 0.16 1.54 1.43 0.48 1.3	Total 35 59 96 59 302 $7); l^2 =$ 51 18 35 49 52 23 223 223 $203y; l^2$	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 18.5% 6% 33.8% 2.3% 5.9% 8.2% 5.9% 8.2% 5.1% 81.5%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.40 [-1.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.29 [-0.92, 1.50] -1.11 [-1.82, -0.40] -0.13 [-0.70, 0.44] -0.02 [-0.20, 0.16] -0.35 [-0.42, 1.12] -0.05 [-0.26, 0.17]	Mean Difference IV, Random, 95% Cl
Study or Subgroup 1.3.1 bupivacaine 2012 Bramlett 2013 Schroer 2017 Alijanipour 2017 Shiith 2018 Zlornicki Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect: 1.3.2 cocktail 2016 Schwarzkopf 2016 Snyder 2016 Snyder 2016 Snyder 2017 Declaire 2018 Danoff 2018 Suarez Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect:	Mean 3.2 4.4 2.81 3.38 3.9 0.01; C Z = 0.9 5.02 5.54 2.4 4.44 3.57 5.6 0.03; C Z = 0.9	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = - 0.16 1.84 1.43 0.48 1.43 0.48 1.35 Chi ² = - 2 (P =	Total 25 58 58 283 4.25, d 0.36) 54 200 35 47 52 231 12.07, 0.67)	Mean 4.1 4.8 3.13 3.13 f = 4 (F 4.96 5.25 3.51 4.57 3.59 5.25 3.51 4.57 3.59 5.25 5.25	TPAI SD 2.5 2.1 1.87 3.61 1.87 9 0.16 1.54 1.94 1.43 0.48 1.3 (P = 0.) 1.3	Total 35 59 96 59 302 7); 1 ² = 51 18 35 49 52 228 03); 1 ² =	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 18.5% 6% 33.8% 2.3% 5.9% 8.2% 5.1% 81.5%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.40 [-1.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.29 [-0.92, 1.50] -1.11 [-1.82, -0.40] -0.13 [-0.70, 0.44] -0.02 [-0.20, 0.16] -0.35 [-0.42, 1.12] -0.05 [-0.26, 0.17]	Mean Difference IV, Random, 95% Cl
Study or Subgroup 1.3.1 bupivacaine 2012 Bramlett 2013 Schroer 2017 Snith 2018 Zlotnicki Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.3.2 coctail 2016 Schwarzkopf 2016 Snyder 2018 Danoff 2018 Suarez Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI)	$\begin{array}{c} \mbox{Mean} \\ 3.2 \\ 4.4 \\ 2.81 \\ 3.38 \\ 3.9 \\ 0.01; (2 \\ -0.5 \\ 5.02 \\ 5.54 \\ 4.4 \\ 4.44 \\ 3.57 \\ 5.6 \\ 0.03; (2 \\ -0.4 \\ 2 \\ -0.4 \\ 0.03; (2 \\ -0.4 $	LB SD 2.5 2.1 2.08 3.08 3.55 $Chi^2 = -202$ (P = 0.16 1.84 1.48 1.43 0.48 1.35 $Chi^2 = -32$ C	Total 25 58 104 38 283 4.25, d 0.36) 54 20 35 47 52 23 231 12.07, 0.67) 514	Mean 4.1 4.8 3.13 3.3 3.13 4.96 5.25 3.51 4.57 3.59 5.25 df = 5	$\begin{array}{c} \text{TPAI} \\ \text{SD} \\ 2.5 \\ 2.1 \\ 1.87 \\ 3.61 \\ 1.87 \\ 0.16 \\ 1.94 \\ 1.54 \\ 1.43 \\ 0.48 \\ 1.3 \\ (P = 0. \end{array}$	Total 35 53 99 59 302 7); 12 = 51 18 35 223 228 03); 12 = 530	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 18.5% 6% 33.8% 2.3% 5.9% 8.2% 26.2% 5.1% 81.5% 10.0%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.40 [-1.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.29 [-0.92, 1.50] -1.11 [-1.82, -0.40] -0.13 [-0.70, 0.44] -0.02 [-0.20, 0.16] -0.35 [-0.42, 1.12] -0.05 [-0.26, 0.12]	Mean Difference IV, Random, 95% Cl
Study or Subgroup 1.3.1 bupivacaine 2012 Bramlett 2013 Schroer 2017 Snith 2018 Zlotnicki Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.3.2 cocktail 2016 Schwarzkopf 2016 Schwarzkopf 2016 Subwarzkopf 2016 Subwarzkopf 2016 Subwarzkopf 2016 Subwarzkopf 2016 Subwarzkopf 2016 Subwarzkopf 2018 Danoff 2018 Danoff 2018 Suarez Est for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for overall effect:	Mean 3.2 4.4 2.81 3.38 3.9 0.01; (Z = 0.1 5.02 5.54 2.4 4.44 3.57 5.6 0.03; (Z = 0.2 0.03; (Z = 0.2 0.03; (Z = 0.2) 0.03;	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = - 4.5 Chi ² = - 2.5 Chi	Total 25 58 58 283 4.25, d 0.36) 54 4.25, d 0.36) 54 233 231 12.07, 0.67) 514 17.71, 0, d5)	Mean 4.1 4.8 3.13 3.13 4.96 5.25 5.25 5.25 5.25 5.25 5.25 5.25 4.57 3.59 5.25 5.25 4.57 4.57 3.59 5.25 5.25 5.25 5.25 5.25 5.25 5.25 5	$\begin{array}{c} \text{TPAI} \\ \text{SD} \\ 2.5 \\ 2.1 \\ 1.87 \\ 3.61 \\ 1.87 \\ P = 0.3 \\ 0.16 \\ 1.54 \\ 1.43 \\ 0.48 \\ 1.3 \\ (P = 0. \\ (P = 0. \\ 0 \\ (P = 0. \\ (P = 0. \\ 0 \\ (P = 0. \\ (P$	Total 35 59 96 59 302 77; 1² = 51 18 35 223 228 03); 1² = 5300 0.06); 1²	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 18.5% 6% 33.8% 2.3% 5.9% 8.2% 5.1% 81.5% 81.5% 100.0% = 44%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.40 [-1.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.29 [-0.92, 1.50] -1.11 [-1.82, -0.40] -0.13 [-0.70, 0.44] -0.02 [-0.20, 0.16] -0.35 [-0.42, 1.12] -0.05 [-0.26, 0.12]	Mean Difference IV, Random, 95% CI
Study or Subgroup 1.3.1 bupivacaine 2012 Branmett 2013 Schroer 2017 Snith 2018 Zlotnicki Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.3.2 cocktail 2016 Schwarzkopf 2016 Schwarzkopf 2016 Snyder 2016 Snyder 2016 Subarot 2018 Danoff 2018 Suarez Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for overa	Mean 3.2 4.4 2.81 3.38 3.9 0.01; (Z = 0.3 5.02 5.54 4.44 4.3.57 5.6 0.03; (Z = 0.3 0.03; (Z = 0.3) 0.03; (Z = 0.3)	LB SD 2.5 2.1 2.08 3.08 3.55 5.5 2.1 2.08 3.05 5.5 2.1 2.08 3.05 5.5 2.1 2.08 3.05 5.5 2.1 2.1 2.08 3.05 5.1 2.1 2.08 3.05 5.1 2.1 2.08 3.05 5.1 2.08 3.05 5.1 2.08 3.05 5.1 2.08 3.05 5.1 2.08 3.05 5.1 2.08 3.05 5.1 2.08 3.05 5.1 2.08 3.05 5.1 2.08 3.05 5.1 2.08 3.05 5.1 2.08 3.05 5.1 2.08 3.05 5.1 2.08 3.05 5.1 2.08 3.05 5.1 2.08 3.05 5.1 2.08 3.05 5.1 2.09 2.09 2.09 2.09 2.09 2.09 2.09 2.09	Total 25 58 58 283 4.25, d 0.36) 54 20 35 47 72 23 231 12.07, 0.67) 514 0.45) = 0.40	Mean 4.1 4.8 3.13 3.13 f = 4 (f 4.96 5.25 3.51 4.95 5.25 3.51 4.96 5.25 3.51 4.96 5.25 df = 5 df = 10 , df = 1	$\begin{array}{c} \text{TPAI} \\ \text{SD} \\ 2.5 \\ 2.1 \\ 1.87 \\ 3.61 \\ 1.87 \\ P = 0.3 \\ 0.16 \\ 1.94 \\ 1.54 \\ 1.3 \\ 1.3 \\ (P = 0.0 \\ 0.48 \\ 1.3 \\ 0.48 \\ 0.48 \\ 1.3 \\ 0.48 \\ 0.48 \\ 1.3 \\ 0.48 \\ 0.48 \\ 1.3 \\ 0.48 \\ 0.48 \\ 1.3 \\ 0.48 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.3 \\ 1.3 \\ 0.48 \\ 1.3 \\ $	Total 35 59 96 59 302 7); I² = 51 18 35 49 52 23 203); I² = 530 0.06); I² .53), I²	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 18.5% 6% 33.8% 2.3% 8.2% 26.2% 81.5% 81.5% = 59% 100.0% = 44% = 0%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.29 [-0.92, 1.50] -1.11 [-1.82, -0.40] -0.02 [-0.20, 0.16] 0.35 [-0.42, 1.12] -0.05 [-0.26, 0.12] -0.07 [-0.26, 0.12]	Mean Difference IV, Random, 95% CI
Study or Subgroup 1.3.1 bupivacaine 2012 Branmett 2015 Schroer 2017 Srinth 2018 Zlotnicki Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 2016 Schwarzkopf 2016 Schwarzkopf 2016 Snyder 2017 Declaire 2018 Danoff 2018 Suarez Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diff	Mean 3.2 4.4 2.81 3.38 3.9 0.01; (Z = 0.9 5.02 5.02 2.5,4 4.44 3.57 5.6 0.03; (Z = 0.03; (Z = 0.03; (Z = 0.9) 0.03; (Z = 0.9)	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = $-$ 2(P = - 0.16 1.84 1.43 0.48 1.35 Chi ² = $-$ 2 Chi ² = $-$ Chi ² = $-$ Chi ² = $-$ 2 Chi ² = $-$ Chi ² = $-$ C	Total 25 58 58 283 4.25, d 0.36) 54 20 35 47 72 233 231 12.07, 0.67) 514 17.71, 0.45) = 0.40	Mean 4.1 4.8 3.13 3.3 3.13 f = 4 (f 5.25 3.51 4.57 3.59 5.25 df = 5 df = 10 , df = 1	TPAI SD 2.5 2.1 1.87 3.61 1.94 1.54 0.48 1.3 (P = 0. (P = 0) (P = 0)	Total 35 53 59 302 7); I² = 51 18 35 49 52 228 03); I² 530 0.06); I² .53), I²	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 18.5% 6% 33.8% 2.3% 5.6% 33.8% 2.3% 5.1% 81.5% 5.5% 100.0% = 0%	Mean Difference [V, Random, 95% CI -0.90 [-2.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.29 [-0.92, 1.50] -1.11 [-1.82, -0.40] -0.13 [-0.70, 0.44] -0.02 [-0.20, 0.16] 0.35 [-0.42, 1.12] -0.05 [-0.26, 0.12] -0.07 [-0.26, 0.12]	Mean Difference IV, Random, 95% CI
Study or Subgroup 1.3.1 bupivacaine 2012 Brandlett 2015 Schroer 2017 Snith 2018 Zlotnicki Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.3.2 cocktail 2016 Schwarzkopf 2016 Snyder 2018 Danoff 2018 Suarez Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diff	$\begin{array}{c} \mbox{Mean} \\ 3.2 \\ 4.4 \\ 2.81 \\ 3.38 \\ 3.9 \\ 0.01; (\\ Z = 0.3 \\ 5.54 \\ 2.4 \\ 4.44 \\ 3.57 \\ 5.6 \\ 0.03; (\\ Z = 0.3 \\ 2 = 0.3 \\ $	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = - 0.16 1.84 1.43 0.48 1.43 0.48 43 (P = Chi ² = 1 76 (P = S: Chi ² = -	Total 25 58 58 104 38 28 28 28 28 28 28 28 28 28 2	Mean 4.1 4.8 3.13 3.3 3.13 f = 4 (f 5.25 3.51 4.57 3.59 5.25 df = 5 df = 10 df = 11	TPAI SD 2.5 2.1 1.87 P = 0.3 0.16 1.94 1.54 1.3 0.48 1.3 0.48 1.3 0.48 1.3 0.48 1.3 0.48 1.3 0.48 1.3 0.48 1.3 0.48 1.3 0.48 1.3 0.48 1.3 0.48 1.3 0.48 1.54 1	Total 35 53 59 302 7); I² = 51 18 35 23 223 23 23 23 23 23 530 .066); I² .53), I²	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 18.5% 6% 33.8% 2.3% 5.9% 33.8% 2.3% 5.9% 18.5% 6% 18.5% 18	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.06 [-0.00, 0.12] 1.11 [-1.82, -0.40] -0.13 [-0.70, 0.44] -0.02 [-0.20, 0.16] 0.35 [-0.42, 1.12] -0.05 [-0.26, 0.12] -0.07 [-0.26, 0.12] Mean Difference	Mean Difference IV, Random, 95% CI
Study or Subgroup 1.3.1 bupivacaine 2012 Brandlett 2015 Schroer 2017 Jaijanipour 2017 Smith 2018 Zlotnicki Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 2016 Schwarzkopf 2018 Danoff 2018 Suare2 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diff	$\begin{tabular}{lllllllllllllllllllllllllllllllllll$	LB SD 2.5 2.1 2.08 3.55 5 5 2.1 2.08 3.55 5 5 2.1 2.08 4.08 4.048 1.43 0.48 1.43 0.48 1.43 0.48 1.43 0.48 1.45 5 Chi ² = - 2 (P = 0.16 0.16 0.18 4.1 0.28 0.20 0.20 0.20 0.20 0.20 0.20 0.20	Total 25 58 58 283 4.25, d 0.36) 54 420 0.35 47 72 23 231 12.07, 0.67) 514 17.71, 0.45) = 0.40 Total	Mean 4.1 4.8 3.13 3.13 f = 4 (f 4.96 5.25 5.25 5.25 df = 5 6.25 df = 5 df = 1(, df = 1	TPAI SD 2.5 2.1 1.87 P = 0.3 0.16 1.94 1.54 1.3 0.48 1.3 (P = 0. 0.(P = 0) 0.(P = 0) TPAI SD	Total 35 53 59 302 77); I² = 51 18 35 90 52 23 2303); I² = 530 0.06); I² 530 530, I² 530, I² 530, I²	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 2.2% 3.6% 3.8% 2.3% 5.9% 3.6% 5.1% 5.1% 5.1% 81.5% 5.9% 100.0% = 0% Weight	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.06 [-0.00, 0.12] 1.11 [-1.82, -0.40] -0.13 [-0.70, 0.44] -0.02 [-0.20, 0.16] 0.035 [-0.42, 1.12] -0.05 [-0.26, 0.12] -0.07 [-0.26, 0.12] Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Random, 95% CI
Study or Subgroup 1.3.1 bupivacaine 2012 Brandlett 2015 Schroer 2017 Snith 2018 Zlotnicki 2018 Zlotnicki Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 1.3.2 cocktail 2016 Schwarzkopf 2018 Danoff 2018 Suaref Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for overall effect: Test for subgroup diff Study or Subgroup diff Study or Subgroup L4.1 bupivacaine 2015 Schroer	Mean 3.2 4.4 2.81 3.38 3.9 0.01; (; 2.4, 4 2.4 2.57 5.62 5.54 3.57 5.6 0.03; (; 2.4, 4, 44 4.44 3.57 5.6 0.03; (; 2.9, 0.03; (; 2.9, 0.03; (; 2.9, 0.03; (; 2.9, 0.03; (; 0.03; (; 2.9, 0.03; (; 0.03; (; 2.9, 0.03; (; 3.91 3.91	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = $-\frac{1}{2}$ 0.16 1.84 1.43 0.48 1.43 0.49 1.43 0.49 1.43 0.49 1.43 0.49 1.43 0.48 1.43 0.48 1.43 0.48 1.43 0.48 1.43 0.49 1.43 0.56 1.43 0.56 1.43 0.56 1.43 0.57 1.43 0.57 1.43 0.57 1.43 0.57 1.43 0.57 1.43 0.57 1.43 0.57 1.43 0.57 1.43 0.57 1.43 0.57 1.43 0.57 1.43 0.57 1.43 0.57 1.43 0.57 1.5	Total 25 58 104 283 4.25, d 20 35 47 52 231 12.07, 0.67) 514 17.71, 0.45) = 0.40 Total 51	Mean 4.1 4.8 3.13 3.3 3.13 f = 4 (f 4.96 5.25 3.51 4.96 5.25 3.59 5.25 df = 5 df = 10 Mean 4.91	TPAI SD 2.5 2.1 1.87 3.61 1.87 9 0.16 1.94 1.54 0.48 1.3 (P = 0.) 0.0 (P = 0.) 0 (P = 0.) 1.88 1.3 1.90 (P = 0.) 0.0 (P = 0.) 1.88 1.3 1.90 (P = 0.) 1.88	Total 35 53 59 96 59 302 7); 1 ² = 51 18 35 228 03); 1 ² = 530 0.06); 1 ² 530 0.06); 1 ² Total	Weight 2.0% 4.9% 4.9% 5.7% 5.7% 2.3% 6% 33.8% 2.3% 5.9% 33.8% 5.9% 9% 5.1% 8 2.6% 5.9% 5.1% 900.000% 4.4% 0.9% 0.9%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.06 [-0.00, 0.12] 0.02 [-0.20, 0.42] -0.31 [-0.70, 0.44] -0.35 [-0.26, 0.0, 0.16] 0.35 [-0.26, 0.17] -0.07 [-0.26, 0.12] Mean Difference IV, Fixed, 95% CI -0.19 [-0.88, 0.50]	Mean Difference IV, Random, 95% CI
Study or Subgroup 1.3.1 bupivacaine 2012 Brandlett 2015 Schroer 2017 Snith 2018 Zlotnicki 2018 Zlotnicki Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 2018 Danoff 2018 Suaref 2018 Danoff 2018 Suaref 2018 Obanoff 2018 Suaref 2018 Obanoff 2018 Suaref 2018 Chonoff 2018 Suaref 2015 Schroer 2017 Anijanipour 2017 Snith	Mean 3.2 4.4 2.81 3.38 3.9 0.01; Z = 0.1 5.54 2.4 4.44 4.44 3.57 5.60 2 = 0.1 0.03; 2 = 0.2 0.03; 2 = 0.3 0.03; Z = 0.3 0.03; 3.91 2.7 3.91 2.7 3.91 2.7	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = $-\frac{1}{2}$ 0.16 1.84 1.43 0.48 1.43 1.4	Total 25 58 104 4.25, d 283 4.25, d 0.360 54 47 52 231 12.07, 0.670 514 17.71, 0.450 = 0.400 Total 51 51 53 54 54 54 54 54 54 54 54 54 54	Mean 4.1 4.8 3.13 3.3 3.13 f = 4 (f 4.96 5.25 3.51 5.25 df = 5 df = 10 Mean 4.96 4.97 3.9 5.25	TPAI SD 2.5 2.1 1.87 3.61 1.87 $= 0.3$ 0.16 1.94 1.54 1.3 (P = 0.) $= 0.2$ 0.) (P = 0.) $= 0.2$ (P = 0.) $= 0.2$ 1.8 1.3 1.62 $= 0.3$ 1.8 1.62 1.8 3.16	Total 35 53 96 59 96 59 302 7); i² = 51 18 35 228 03); i² = 530 0.06); i² 530, i² 530, i² Total 47 96 96	Weight 2.0% 4.9% 4.9% 5.7% 5.7% 3.6% 2.3% 2.2% 18.5% 6% 33.8% 2.3% 5.9% 5.1% 5.1% 5.1% 9.9% 2.4% 100.0% = 44% Weight 0% 0.9% 1.0% 0.6% 0.6%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.20 [-0.22, 1.50] -0.20 [-0.20, 0.16] 0.35 [-0.42, 1.12] -0.05 [-0.26, 0.12] -0.07 [-0.26, 0.12] -0.07 [-0.26, 0.12] -0.07 [-0.26, 0.12] -0.09 [-0.76, 0.94]	Mean Difference IV, Random, 95% CI
Study or Subgroup 1.3.1 bupivacaine 2012 Brannett 2015 Schroer 2017 Snith 2018 Zlotnicki Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect: 2016 Schwarzkopf 2018 Danoff 2018 Suares Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect: 2015 Schroer 2017 Snith Subtotal (95% CI)	Mean 3.2 4.4 2.81 3.38 3.90 0.01; (Z 5.02 5.54 2.4 3.38 3.90 0.01; (Z 5.02 5.54 2.4 3.57 5.60 0.03; (Z 2 0.03; (Z 0.10; (Z	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = - 0.16 1.84 1.43 1.43 1.44 1.43 1.43 1.44 1.43 1.44 1.43 1.44 1.43 1.44 1.43 1.44 1.43 1.44 1.43 1.44 1.43 1.44 1.43 1.44 1.43 1.44 1.43 1.44 1.43 1.44 1.43 1.44 1.43 1.44 1.43 1.44 1.43 1.44 1.43 1.44 1.45 Chi ² = - 76 (P = - Chi ² = - 76 (P = - 2.97 (P = - 76 (P = - 2.97 (P = - 76 (P = - 2.97	Total 25 58 104 38 283 283 40 35 47 52 231 112.07, 0.67) 514 10.405) = 0.400 51 104 51 58 104 213 104 213	$\begin{array}{c} \text{Mean} \\ 4.11 \\ 4.8 \\ 3.13 \\ 3.3 \\ 3.13 \\ f = 4 (f \\ 5.25 \\ 3.51 \\ 4.57 \\ 3.59 \\ 5.25 \\ df = 5 \\ df = 10 \\ df = 10 \\ df = 11 \\ 1.57 \\ 3.9 \\ 7.57 \\ 7$	TPAI SD 2.5 2.1 1.87 3.61 1.87 P = 0.3 0.16 1.94 1.54 1.34 1.34 (P = 0.48 1.3 (P = 0.48 0.48 1.3 (P = 0.48 1.3 (P = 0.48) (P =	Total 35 59 96 59 50 27); $l^2 =$ 51 18 35 49 52 23 228 003); $l^2 =$ 530 0.060; l^2 530 10 530 10 530 10 53 53 59 59 59 59 59 59 59 59 59 59	Weight 2.0% 4.9% 5.7% 3.6% 2.3% 8.2% 5.9% 5.9% 26.2% 5.9% 2.3% 9.5% 9.9% 0.9% 0.6% 0.6% 2.6%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.20 [-0.92, 1.50] -0.20 [-0.02, 0.20, 0.16] 0.33 [-0.42, 1.12] -0.02 [-0.20, 0.16] 0.35 [-0.26, 0.17] -0.07 [-0.26, 0.12] Mean Difference IV, Fixed, 95% CI -0.19 [-0.88, 0.50] 0.31 [-0.54, 0.80] 0.39 [-0.76, 0.94] 0.09 [-0.76, 0.94] 0.09 [-0.76, 0.94]	Mean Difference IV, Random, 95% CI
Study or Subgroup 1.3.1 bupivacaine 2012 Brannett 2015 Schroer 2017 Snith 2018 Zlotnicki Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 2016 Schwarzkopf 2018 Danoff 2018 Suares Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for overall effect: Test for overall effect: 2015 Schroer 2017 Snith Subtotal (95% CI)	Mean 3.2 4.4 2.81 3.38 3.90 0.01; (Z 5.02 5.54 2.4 3.38 3.90 2.554 2.4 3.57 5.02 5.02 5.02 5.03 2.4 3.57 5.62 2.0.03; (Z 0.03; (Z 3.91 2.7, 7 3.99 0.47, c : Z = 0.	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = - 0.16 1.84 1.43 1.43 1.43 1.43 1.43 1.44 1.43 1.43 Chi ² = - 2.7 Chi ² = - 2.97 ff = 2.0 (P = - 2.97 Chi ² = -	Total 25 58 88 283 283 38 283 112.07, 0.67) 514 231 117.71, 0.45) = 0.400 514 112.07, 0.45) = 0.400 514 112.07, 0.45) = 0.400 514 112.07, 0.400 514 112.07, 0.400 514 112.07, 0.400 514 112.07, 0.400 514 112.07, 112.07, 0.400 511 52 531 54 54 54 54 54	$\begin{array}{c} \text{Mean} \\ 4.11 \\ 4.8 \\ 3.13 \\ 3.3 \\ 3.13 \\ f = 4 (f \\ 5.25 \\ 3.51 \\ 4.57 \\ 3.59 \\ 5.25 \\ df = 5 \\ df = 10 \\ df = 10 \\ df = 11 \\ 1.57 \\ 3.9 \\ 79); l^2 = 0 \\ \end{array}$	$\begin{array}{l} \textbf{TPAI} \\ \textbf{SD} \\ 2.5 \\ 2.1 \\ 1.87 \\ 3.61 \\ 1.87 \\ 9 = 0.3 \\ 0.16 \\ 1.94 \\ 1.54 \\ 1.3 \\ (P = 0.048 \\ 1.3 \\ (P = 0.048 \\ 0.48 \\ 1.3 \\ (P = 0.048 \\ 0.48 \\ 1.3 \\ (P = 0.048 \\ 0.48 \\ 1.3 \\ 1.94 \\$	Total 355 59 96 59 302 27); $l^2 =$ 51 18 35 49 52 23 302; $l^2 =$ 530 0.06); l^2 530 0.06); l^2 530 100; l^2 100; l^2	Weight 2.0% 4.9% 5.7% 8.8% 2.3% 8.5% 5.9% 100.0% = 59% 100.0% = 0% Weight 0.9% 0.0% 2.3%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.20 [-0.92, 1.50] -0.20 [-0.02, 0.20, 0.16] 0.35 [-0.42, 1.12] -0.02 [-0.20, 0.16] 0.35 [-0.26, 0.12] -0.07 [-0.26, 0.12] -0.07 [-0.26, 0.12] -0.07 [-0.26, 0.12] -0.09 [-0.76, 0.94] 0.09 [-0.76, 0.94] 0.09 [-0.42, 0.42]	Mean Difference IV, Random, 95% CI
Study or Subgroup	$\begin{tabular}{lllllllllllllllllllllllllllllllllll$	LB SD 2.5 2.1 2.08 3.08	Total 25 58 58 88 233 54 20 35 231 12.07, 0.45) = 0.40 514 17.71, 514 17.8 10.47 51 58 104 213 20 20 21 22 23 24 251 58 104 213 24 251 58 251 58 26 21	$\begin{array}{c} \textbf{Mean} \\ 4.1 \\ 4.8 \\ 3.13 \\ 3.3 \\ 3.3 \\ 1.13 \\ f = 4 (f \\ 5.25 \\ 3.51 \\ 4.96 \\ 5.25 \\ 3.59 \\ 5.25 \\ 5.25 \\ df = 1 \\ df = 10 \\ df = 1 \\ df = 1 \\ df = 1 \\ 4.1 \\ 2.57 \\ 3.79 \\ 79); l^2 = 1 \\ \end{array}$	$\begin{array}{c} \text{TPAI} \\ \text{SD} \\ 2.5 \\ 2.1 \\ 1.87 \\ 3.61 \\ 1.94 \\ 1.54 \\ 1.94 \\ 1.54 \\ 1.94 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.3 \\ 1.6 \\ 0.0 \\ P = 0. \\ 0.0 \\ P = 0. \\ 0.0 \\ P = 0. \\ 1.8 \\ 1.62 \\ 3.16 \\ 0.0 \\ 0.$	Total 35 59 96 59 302 7); I² = 51 18 35 223 230 223 303); I² = 530 0.06); I² 530, I² 530, I² Total 47 59 96 202	Weight 2.0% 4.9% 5.7% 3.76% 2.3% 2.3% 2.3% 5.9% 100.0% = 59% 100.0% weight 0.% 2.3% 2.3% 2.3% 5.9% 100.0% 0% 2.3% 2.3% 2.3% 3.3.8% 2.3% 3.3.8% 5.9% 100.0% 0.6% 2.6%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.32 [-1.04, 0.40] .0.8 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.92, 1.50] 0.06 [-0.00, 0.12] 0.20 [-0.92, 1.50] -0.20 [-0.20, 0.40] -0.35 [-0.42, 1.12] -0.05 [-0.26, 0.12] Mean Difference IV, Fixed, 95% CI -0.19 [-0.88, 0.50] 0.31 [-0.54, 0.84] 0.09 [-0.76, 0.94] 0.00 [-0.42, 0.42]	Mean Difference IV, Random, 95% CI
Study or Subgroup	$\begin{array}{c} \textbf{Mean} \\ 3.2 \\ 4.4 \\ 2.81 \\ 3.38 \\ 3.9 \\ 0.01; (z = 0.3 \\ 2.4 \\ 4.44 \\ 4.57 \\ 5.6 \\ 0.03; (z = 0.3 \\ 2 = 0.3 \\ 2 = 0.3 \\ 2 = 0.3 \\ 2 = 0.3 \\ 2 = 0.3 \\ 3.57 \\ 3.99 \\ 0.47, cz \\ 2 = 0.4 \\ 3.91 \\ 2.7 \\ 3.99 \\ 0.47, cz \\ 2 = 0.4 \\ 4.36 \\ 4 \\ 4 \\ 4 \\ 4 \\ 4 \\ 4 \\ 4 \\ 4 \\ 4 \\ $	LB SD 2.5 2.1 2.08 3.08 3.35 Chi ² = - 92 (P = 0.16 1.44 1.43 0.48 1.42 0.48 1.42 0.48 1.42 0.48 1.42 0.48 1.42 0.48 1.7 2.05 1.7 1.7 2.97 ff (P = 2 (0) 0.8 0.88	Total 25 58 58 8 283 425, d 0.36) 54 223 231 112.07, 52 231 112.07, 514 117.71, 0.45) = 0.400 Total 51 58 104 213 0.45) = 0.400	$\begin{array}{c} \textbf{Mean} \\ 4.11 \\ 4.8 \\ 3.13 \\ 3.3 \\ 3.13 \\ f = 4 (f \\ 5.25 \\ 3.51 \\ 4.96 \\ 5.25 \\ 3.51 \\ 5.25 \\ 5.25 \\ df = 5 \\ df = 10 \\ df = 10 \\ df = 11 \\ 2.57 \\ 3.79 \\ 79); l^2 = \\ 4.29 \\ 4.29 \\ 4 \end{array}$	$\begin{array}{c} \text{TPAI} \\ \text{SD} \\ 2.5 \\ 2.1 \\ 1.87 \\ 3.61 \\ 1.94 \\ 1.54 \\ 1.3 \\ (P=0.3) \\ 0.16 \\ 1.94 \\ 1.3 \\ (P=0.3) \\ 0.0 \\ 0.0 \\ (P=0.3) \\ 0.0 \\ (P=0.3) \\ 0.0 \\ 0.0 \\ 1.8 \\ 3.16 \\ 0.18 \\ 1.83 \\ 0.18 \\ 0.1$	Total 35 53 59 96 57 51 18 35 228 03); 1² = 530 0.06); 1² 530; 1² 530 0.06); 1² 530 0.06); 1² 530 0.06); 1² 530 0.06); 1² 530 530 530 530 530 530 530 531 35	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 1.85% 6% 33.8% 2.2% 8.2% 5.9% 2.2% 8.2% 5.9% 100.0% 4.4% = 0% Weight 0.9% 0.6% 2.6% 100.0% 0.6% 100.0%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.92, 1.50] 0.06 [-0.00, 0.12] 0.20 [-0.92, 1.50] -0.20 [-0.02, 0.20] -0.35 [-0.42, 1.12] -0.05 [-0.26, 0.12] -0.05 [-0.26, 0.12] -0.05 [-0.26, 0.12] -0.07 [-0.26, 0.12] -0.19 [-0.88, 0.50] 0.13 [-0.54] 0.09 [-0.76, 0.94] 0.00 [-0.42, 0.42] 0.00 [-0.42, 0.42]	Mean Difference IV, Random, 95% CI
Study or Subgroup	$\begin{array}{c} \textbf{Mean} \\ 3.2 \\ 4.4 \\ 2.81 \\ 3.38 \\ 3.9 \\ 0.01; (z = 0.5, 0.2 \\ 2.4 \\ 4.44 \\ 4.44 \\ 3.57 \\ 5.6 \\ 0.03; (z = 0.0, 0.3; (z = 0.0, 0.0) \\ 0.03; (z = 0.0, 0.0; (z = 0.0, 0.0) \\ 0.04, (z = 0.0, 0.0) \\ 0.0$	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = 2 0.16 1.84 1.43 1.43 1.44 1.43 1.43 1.44 1.43 Chi ² = 2 Chi ² =	Total 25 58 58 58 104 38 283 231 12.07, 0.67) 514 58 112.07, 0.45) = 0.40 Total 51 58 104 213 P = 07 54 35 90 54 35 90 51 51 51 51 52 35 90 54 359 90 54 359 90	$\begin{array}{c} \text{Mean} \\ 4.1 \\ 4.8 \\ 3.13 \\ 3.3 \\ 3.13 \\ f = 4 (f \\ 4.96 \\ 5.25 \\ 3.51 \\ 4.57 \\ 3.59 \\ 5.25 \\ df = 5 \\ df = 1 \\ \hline \\ \text{Mean} \\ 4.1 \\ 2.57 \\ 3.9 \\ 79); l^2 = \\ 4.29 \\ 4 \\ 4.24 \\ y^{-1} \\ 2.57 \\ 3.9 \\ 79); l^2 = \\ 4.29 \\ 4 \\ 4.1 \\ 3.9 \\ 3.9 \\ 79); l^2 = \\ 4.29 \\ 4 \\ 4.24 \\ y^{-1} \\ 4 \\ 4.24 \\ y^{-1} \\ 4 \\ 4 \\ 4 \\ 4 \\ 4 \\ 3 \\ y^{-1} \\ 4 \\ 4 \\ 4 \\ 4 \\ 3 \\ y^{-1} \\ 4 \\ 4 \\ 4 \\ 3 \\ y^{-1} \\ 4 \\ 4 \\ 4 \\ 4 \\ 4 \\ y^{-1} \\ y^$	$\begin{array}{c} \text{TPAI} \\ \text{SD} \\ 2.5 \\ 2.1 \\ 1.87 \\ P = 0.3 \\ 0.16 \\ 1.94 \\ 1.43 \\ 0.48 \\ 1.3 \\ (P = 0. \\ 0.48 \\ 1.62 \\ 3.16 \\ 1.62 \\ 3.16 \\ 0.18 \\ 1.62 \\ 3.16 \\ 0.06 \\ 0.18 \\ 0.68 \\ 0.18 \\ 0.18 \\ 0.06 \\ 0.$	Total 35 53 59 96 59 70; 1² = 51 18 35 49 5228 006); 1² 530 .066); 1² 530 .066); 1² Total 47 59 202 51 35 86	Weight 2.0% 4.9% 5.7% 3.6% 2.2% 1.85% 6% 33.8% 2.2% 1.85% 81.5% 6% 100.0% 6 Weight 0.9% 1.0% 0.6% 1.0% 96.4% 97.4%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.20 [-0.92, 1.50] -0.20 [-0.20, 0.16] 0.31 [-0.70, 0.44] -0.02 [-0.20, 0.16] 0.35 [-0.42, 1.12] -0.05 [-0.26, 0.12] -0.05 [-0.26, 0.12] -0.07 [-0.26, 0.12] -0.19 [-0.88, 0.50] 0.13 [-0.54] 0.00 [-0.42, 0.42] 0.00 [-0.42, 0.42] 0.00 [-0.42, 0.42] 0.00 [-0.42, 0.42]	Mean Difference IV, Random, 95% CI
Study or Subgroup 1.3.1 bupivacaine 2012 Brannett 2015 Schroer 2012 Brannett 2015 Schroer 2017 Alijanipour 2017 Smith 2018 Zlornicki Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect: 2018 Danoff 2016 Schwarzkopf 2016 Schwarzkopf 2016 Snyder 2018 Danoff 2018 Suarez Subtotal (95% CI) Heterogeneity: Tau ² Test for overall effect: Test for subgroup diff Study or Subgroup 1.4.1 bupivacaine 2015 Schroer 2017 Alianipour 2017 Smith Subtotal (95% CI) Heterogeneity: Chi ² Test for overall effect: Test for overall effect: 1.4.2 Cocktail 2016 Collis 2016 Schroer 2017 Alianipour 2017 Smith Subtotal (95% CI) Heterogeneity: Chi ² Test for overall effect 1.4.2 Cocktail 2016 Collis 2016 Snyder Subtotal (95% CI) Heterogeneity: Chi ² Test for overall effect 1.4.2 Cocktail 2016 Collis 2016 Snyder Subtotal (95% CI) Heterogeneity: Chi ² Test for overall effect Test for overall effe	$\begin{tabular}{lllllllllllllllllllllllllllllllllll$	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = $2(P = 0 - 1)^{2}$ 0.16 1.84 1.43 1.45 1.43 1.45 1.45 1.47 1.5 1.7 1.7 2.05 1.7 1.7 2.05 1.7 1.7 2.05 1.7 1.7 2.05 1.7 1.7 2.05 1.7 1.7 2.05 1.7 1.7 2.05 1.7 1.7 2.05 1.7 1.7 2.05 1.7 1.7 2.05 1.7 1.7 2.05 1.7 1.7 2.05 1.7 1.7 1.7 2.05 1.7 1.7 1.7 1.7 2.05 1.7 1.7 1.7 1.7 1.7 1.7 1.7 1.7	Total 25 58 58 58 58 104 38 243 203 231 112.07, 0.67) 514 51 58 107.71, 0.45) = 0.400 Total 51 58 104 213 P = 0.7.0 6.090 S1 58 90 90, P = 0.051 54 359	$\begin{array}{c} \text{Mean} \\ 4.1 \\ 4.8 \\ 3.13 \\ 3.3 \\ 3.13 \\ f = 4 (f \\ 4.96 \\ 5.25 \\ 5.25 \\ 3.51 \\ 4.57 \\ 3.59 \\ 3.51 \\ 4.57 \\ 3.59 \\ 3.51 \\ 4.57 \\ 3.9 \\ 79); l^2 = \\ 4.29 \\ 4 \\ 4.29 \\ 4 \\ 4.29 \\ 4 \\ 34); l^2 = \end{array}$	$\begin{array}{c} \text{TPAI} \\ \text{SD} \\ 2.5 \\ 2.1 \\ 1.87 \\ 2 = 0.3 \\ 0.16 \\ 1.94 \\ 1.84 \\ 1.87 \\ 0.16 \\ 1.94 \\ 1.94 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.62 \\ 3.16 \\ 0.06 \\ 1.83 \\ 1.83 \\ 0.618 \\ 1.83 \\ 1.83 \\ 0.618 \\ 1.83$	Total 35 53 59 96 59 96 59 50 51 18 35 49 52 228 302 228 303); $l^2 =$ 530 0.060; l^2 530 70; $l^2 =$ 530 70; $l^2 =$ 530; $l^2 =$ 530 70; $l^2 =$ 530;	Weight 2.0% 4.9% 5.7% 3.6% 2.3% 5.7% 8.6% 33.8% 2.3% 5.7% 81.5% 6% 100.0% 0% 0% 0% 0% 0.6%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.32 [-1.04, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.20 [-0.22, 1.50] 0.02 [-0.20, 0.16] 0.03 [-0.70, 0.44] -0.02 [-0.20, 0.16] 0.05 [-0.26, 0.12] -0.05 [-0.26, 0.12] Mean Difference IV, Fixed, 95% CI -0.19 [-0.88, 0.50] 0.13 [-0.54, 0.80] 0.09 [-0.76, 0.94] 0.00 [-0.42, 0.42] 0.07 [0.00, 0.14] 0.07 [0.00, 0.14]	Mean Difference IV, Random, 95% CI
Study or Subgroup	$\begin{array}{c} \textbf{Mean} \\ 3.2 \\ 4.4 \\ 2.81 \\ 3.38 \\ 3.9 \\ 0.01; (2 \\ z = 0.2 \\ 0.03; (2 \\ z = 0.2 \\ 0.04; (2 \\ z = 1.2 \\ 0.04, (2 \\ z = 1.2 \\ 0.$	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = - 2.(P = - 0.16 1.84 1.48 1.7 1.7 1.7 2.05 2.97 1.7 1.7 2.05 2.97 1.7 1.7 2.05 2.97 1.7 1.98 1.88 0.82 1.98	Total 25 58 58 58 58 104 38 283 241 2035 47 2035 231 112.07, 0.67) 514 17.71, 0.45) = 0.400 Total 51 58 104 213 P = 0.2 60.99 90 91 92 94 954 954 90,000 544 355 302	$\begin{array}{c} \text{Mean} \\ 4.1 \\ 4.8 \\ 3.13 \\ 3.3 \\ 3.13 \\ f = 4 (f \\ 4.96 \\ 5.25 \\ 5.5 \\ 5.5 \\ 5.5 \\ 5.5 \\ df = 1 \\ df = 10 \\ df = 10 \\ df = 11 \\ 2.57 \\ 3.9 \\ 79); 1^2 = \\ 4.29 \\ 4.29 \\ 4$	$\begin{array}{c} \text{TPAI} \\ \text{SD} \\ 2.5 \\ 2.1 \\ 1.87 \\ 2 = 0.3 \\ 0.16 \\ 1.94 \\ 1.84 \\ 1.87 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.62 \\ 3.16 \\ 0.08 \\ 1.83 \\ 1.83 \\ 0.48 \\ 1.83 \\ $	Total 35 53 59 96 59 96 59 50 50 50 51 18 35 228 302 77; $1^2 = -$ 51 18 35 228 303; $1^2 = -$ 530 (0.06); $1^2 = -$ 530 (0.06); $1^2 = -$ 530 228 530 228 530 202 51 51 51 51 51 51 51 51 51 51	Weight 2.0% 4.9% 5.7% 3.6% 2.3% 5.7% 8.5% 6% 33.8% 2.3% 5.7% 81.5% 6% 100.0% Weight 0.9% 1.0% 0.9% 1.0% 96.4% 1.0% 97.4%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.20 [-0.22, 1.50] 0.02 [-0.20, 0.16] -0.22 [-0.20, 0.16] -0.25 [-0.26, 0.12] -0.05 [-0.26, 0.12] -0.05 [-0.26, 0.12] -0.07 [-0.26, 0.12] -0.07 [-0.26, 0.12] 0.09 [-0.76, 0.94] 0.00 [-0.64, 0.60] 0.00 [-0.66, 0.66] 0.07 [0.00, 0.14] 0.07 [-0.00, 0.14]	Mean Difference IV, Random, 95% CI
Study or Subgroup	$\begin{array}{c} \textbf{Mean} \\ 3.2 \\ 4.4 \\ 2.81 \\ 3.38 \\ 3.9 \\ 0.01; (2 \\ z = 0.) \\ 5.02 \\ 2.5, 54 \\ 2.4 \\ 2.4 \\ 3.57 \\ 5.6 \\ 0.03; (2 \\ z = 0.) \\ 0.04; (2 \\ z = 1.) \\ 0.04, (2 \\ z = 1.) \\ 0.04, (2 \\ z = 1.) \\ 0.04, (2 \\ z = 1.) \\ 0.01, (2 \\ z = 1.) \\ 0.$	LB SD 2.5 2.1 2.08 3.08 3.55 Chi ² = - 2(P =	Total 25 58 58 58 58 58 58 58 58 283 231 12.07, 0.67) 514 58 104 17.71, 0.45) = 0.40 Total 51 58 104 213 P = 0.5 60.99 54 35 36 9P = 0.6 9P = 0.7 54 352 9P = 0.0 302 P = 0.0 302	$\begin{array}{c} \text{Mean} \\ 4.1 \\ 4.8 \\ 3.13 \\ 3.3 \\ 3.13 \\ f = 4 (f \\ 4.96 \\ 5.25 \\ 5.25 \\ 5.25 \\ 6f = 10 \\ df = 10 \\ df = 10 \\ df = 11 \\ 2.57 \\ 3.9 \\ 7.9 \\ 1.25 \\ 7.9 \\ 3.9 \\ 1.25 \\ 7.9 \\ 1.25 \\ 7.9 \\ 1.25 \\$	$\begin{array}{c} \text{TPAI} \\ \text{SD} \\ 2.5 \\ 2.1 \\ 1.87 \\ 2 = 0.3 \\ 0.16 \\ 1.94 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.3 \\ 0.48 \\ 1.62 \\ 3.16 \\ 0.08 \\ 1.83 \\ 1.83 \\ 0\% \\ 0.18 \\ 1.83 \\ 0\% \\ 0\% \\ 0 \\ 0\% \\ 0\% \\ 0\% \\ 0\% \\ 0\%$	Total 35 53 59 96 59 302 77: 1² = 51 18 35 49 500; 1² = 530 .006); 1² = 530 .006); 1² = .53), 1² Total 47 59 96 202 51 35 202 51 35 86 288	Weight 2.0% 4.9% 5.7% 5.7% 8.5% 2.3% 5.7% 8.15% 6% 33.8% 2.3% 5.7% 81.5% 6% 91.0% 9.1% 9% 100.0%	Mean Difference IV, Random, 95% CI -0.90 [-2.18, 0.38] -0.32 [-1.04, 0.38] -0.32 [-1.04, 0.40] 0.08 [-0.85, 1.01] 0.77 [-0.46, 2.00] -0.20 [-0.62, 0.22] 0.06 [-0.00, 0.12] 0.20 [-0.22, 1.50] 0.02 [-0.20, 0.22] 0.03 [-0.42, 1.22] -0.05 [-0.42, 0.40] -0.35 [-0.42, 0.40] -0.35 [-0.42, 0.12] -0.07 [-0.26, 0.12] Mean Difference IV, Fixed, 95% CI -0.19 [-0.88, 0.50] 0.09 [-0.76, 0.94] 0.00 [-0.66, 0.66] 0.07 [0.00, 0.14] 0.07 [-0.00, 0.14]	Mean Difference IV, Random, 95% CI

Fig. 5 Forest plot of the VAS during postoperative day. From top to bottom are POD 0, POD1, POD2 and POD3

	LB						9	itd. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2016 Jain	98.9	41.6	63	100.1	42.2	62	28.0%	-0.03 [-0.38, 0.32]	_
2016 Schwarzkopf	116.62	44.97	20	113.02	50	18	8.5%	0.07 [-0.56, 0.71]	
2016 Snyder	6.89	6.56	35	8.73	7.48	35	15.6%	-0.26 [-0.73, 0.21]	
2017 Alijanipour	32.78	36.8	59	42.96	25.49	55	25.2%	-0.32 [-0.69, 0.05]	
2018 Suarez	51.51	48.14	52	30.03	48.14	52	22.7%	0.44 [0.05, 0.83]	
Total (95% CI)			229			222	100.0%	-0.02 [-0.21, 0.16]	•
Heterogeneity: Chi ² =	8.99, df	= 4 (P =	= 0.06)	$I^2 = 56\%$	6				
Test for overall effect:	Z = 0.22	P = 0	.82)						Favours LB Favours TPAI



		LB			TPAI Std. Mean Difference			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2016 Schwarzkopf	83.38	50	20	112.47	50	18	27.1%	-0.57 [-1.22, 0.08]	
2016 Snyder	6.89	5.79	35	13.11	13.3	35	34.0%	-0.60 [-1.08, -0.12]	_
2017 Alijanipour	20.68	30.43	59	17.5	30.43	55	38.9%	0.10 [-0.26, 0.47]	
Total (95% CI)			114			108	100.0%	-0.32 [-0.83, 0.19]	
Heterogeneity: Tau ² = Test for overall effect	= 0.14; C :: Z = 1.2	hi ² = 6 3 (P = 0	.49, df).22)	= 2 (P =	0.04); I	² = 69%	6		-1 -0.5 0 0.5 1 Favours LB Favours TPAI

Fig. 6 Forest plot of morphine consumption equivalents. From top to bottom are postoperative 0–24 h, 24–48 h and 48–72 h

Secondary outcome

Consumption of morphine equivalents

Morphine consumption was divided into three time periods: postoperative 0–24 h, 24–48 h, and 48–72 h (Fig. 6). Morphine consumption during 0–24 h.

A meta-analysis of five studies [26–29, 33] with 451 patients revealed no significant difference between the two groups (p = 0.82).

Morphine consumption during 24–48 h.

A meta-analysis of four studies [27–29, 33] with 326 patients revealed that morphine consumption in the LB group was less than in the TPAI group (p = 0.04).

Morphine consumption during 48–72 h.

A meta-analysis of three studies [27-29] with 222 patients indicated no significant difference, although morphine consumption appeared to be lower in the LB group than in the control group (p = 0.22).



Fig. 7 Forest plot of nausea and vomiting incidence

Incidence of nausea and vomiting

A meta-analysis of six studies [15, 19, 23, 24, 28, 36] with 566 participants revealed no significant difference (p = 0.23), although the incidence of nausea and vomiting appeared to be lower in the LB group than in the control group (Fig. 7).

Length of hospital stay

A meta-analysis of eight studies [19, 24–26, 30, 31, 33, 36] with 928 participants found that the LB group had

a longer hospital stay than the control group, but there was no significant difference between the two groups (p = 0.17) (Fig. 8).

Quality of evidence

The quality of each outcome was evaluated using the GRADE system. Most of the outcome qualities were moderate (Table 2).



Fig. 8 Forest plot of length of hospital stay

-)	5	/				
Outcomes	No. of included studies	No. of	patients	(S)MD or RR (95%CI)	Heterogeneity	Quality of
		LB	TPAI			evidence (GRADE)
VAS at POD0 (Bupivacaine)	[23, 31]	129	131	- 0.28 [- 1.16, 0.60]	I2=60%, P=0.11	Moderate ²
VAS at POD0 (Cocktail)	[27, 28, 32]	78	76	- 0.02 [- 0.51, 0.47]	I2=51%, P=0.13	Low ^{1,2}
VAS at POD1 (Bupivacaine)	[23, 24, 26, 29, 31, 34]	346	345	— 0.15 [— 0.73, 0.43]	I2=60%, P=0.03	Low ^{1,5}
VAS at POD1 (Cocktail)	[25, 27, 28, 30, 32, 33]	231	228	- 0.04 [- 0.32, 0.24]	I2=20%, P=0.28	Moderate ¹
VAS at POD2 (Bupivacaine)	[23, 24, 29, 31, 34]	283	302	- 0.20 [- 0.62, 0.22]	I2=6%, P=0.37	Moderate ¹
VAS at POD2 (Cocktail)	[25, 27, 28, 30, 32, 33]	231	228	- 0.05 [- 0.26, 0.17]	I2=59%, P=0.03	Low ^{1,5}
VAS at POD3 (Bupivacaine)	[24, 29, 31]	213	202	0.00 [- 0.42, 0.42]	12=0%, P=0.79	High
VAS at POD3 (Cocktail)	[25, 28]	89	86	0.07 [0.00, 0.14]	12=0%, P=0.84	Moderate ¹
Opioid consumption at 24 h	[26–29, 33]	229	222	- 0.02 [- 0.21, 0.16]	12=56%, P=0.06	Moderate ¹
Opioid consumption at 48 h	[27–29, 33]	166	160	- 0.22 [- 0.44, - 0.01]	I2=46%, P=0.14	Moderate ¹
Opioid consumption at 72 h	[27–29]	114	108	- 0.32 [- 0.83, 0.19]	I2=69%, P=0.04	Moderate ¹
Nausea and vomiting	[15, 19, 23, 24, 28, 36]	284	282	0.79 [0.53, 1.16]	I2=54%, P=0.05	High
Length of hospital stay	[19, 24–26, 30, 31, 33, 36]	474	454	0.07 [- 0.03, 0.17]	12 = 29%, P = 0.20	Moderate ¹

Table 2 Quality of each outcome of TKA using GRADE system

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Very low quality: We are very uncertain about the estimate

¹ Risk of bias

² Inconsistency

³ Indirectness

⁴ Imprecision

⁵ Publication bias

Discussion

The findings of this meta-analysis provided moderatequality evidence that the LB group had lower morphine consumption equivalent in the second 24 h than the TPAI group. However, the overall postoperative pain scores, morphine consumption equivalents in the first and the third 24 h, the incidence rate of nausea and vomiting, and the length of hospital stay did not differ significantly between the LB and TPAI groups for patients who underwent TKA.

The liposomal bupivacaine was hardly enough to completely blind the surgeon who administered the drugs because it has a cloudy liquid appearance and is more viscous than the conventional pain cocktail, which also contains bupivacaine or ropivacaine [30]. Smith et al. consequently instructed the surgeon to leave the operation room while trained medical assistants administered the drugs [31]. Snyder et al. transferred the LB to a sterile syringe covered in an opaque bandage [28]. Most studies [19, 24–29, 33, 34, 36] simply excluded the surgeon from any outcome assessment or data analysis; however, this approach could not eliminate the performance bias.

The dose range for LB was 106–532 mg. Hu et al.'s [37] comparison of various doses of LB revealed a quantitative similarity in the plasma concentration versus time profiles as well as a lower incidence of adverse events in the group of LB \leq 226 mg than in the group of LB \geq 226 mg. Most of the RCTs used LB in a dose of 266 mg, which is the maximum FDA-approved dose, in a single 20 mL vial. Its widespread use may be attributed to a sufficient plasma concentration and fewer adverse events.

The pharmacokinetics of LB were also demonstrated by Hu et al. [37], with the first peak occurring within an hour after injection and the second peak 12–36 h later. The present study found a similar VAS score and morphine consumption between the LB and TPAI groups in POD 0 and POD 1. The morphine rescue dose was lower in the LB group up until POD 2, but the incidence of nausea and vomiting was not significantly lower. There was no significant difference in VAS score and morphine consumption between the two groups after POD 3. Overall, LB did not significantly improve the VAS score when compared to TPAI.

A total of six studies [15, 19, 23, 24, 28, 36] evaluated the incidence of nausea and vomiting. There was no significant difference in the incidence of nausea and vomiting, although the consumption of morphine equivalents in the LB group was less than in the TPAI group during the postoperative 24–48-h period. This may be attributed to no significant difference in morphine consumption and an insufficient number of included studies.

A total of eight studies [19, 24–26, 30, 31, 33, 36] reported the length of hospital stay. Several factors

influence the duration of hospital stay after TKA, including age, sex, and preoperative hemoglobin. Postoperative pain and functional recovery are also critical factors. The lack of a significant difference in VAS score may implicate that the processes of rehabilitation and functional recovery were similar for both groups, regardless of LB or TPAI usage. There is currently no conclusive evidence that LB can shorten the length of hospital stay.

Several RCTs compared the cost of LB with that of standard periarticular injection. Collis et al. [25] reported that the total cost of LB injection was \$285 US, which was more than seven times the cost of the modified Ranawat suspension (Ropivacaine, epinephrine, ketorolac, clonidine) (\$40 US). Hyland et al. [19] reported that the cost of LB, which was approximately \$300.66 US per patient in 2019, was more than 17 times that of the PAI (approximately \$16.83 US). The nonsignificant outcome differences found in this study seems not support for the use of LB. However, there may be variations in the cost of LB in different countries/regions. We consider that LB may become more competitive if its cost is cheap enough.

The pain-relieving effect of periarticular multimodal drug injection (PMDI) has been widely reported [7-12]. However, it is challenging to interpret the results of studies that combined local anesthetics with epinephrine, nonsteroidal anti-inflammatory drugs (NSAIDs), and morphine. Some studies used standard bupivacaine injection as the control group, whereas others used ropivacaine or cocktail agents. Despite this, the present study divided the population into two groups on the basis of whether standard bupivacaine or a cocktail was used as the control. The components in either the bupivacaine or cocktail subgroup remain inconsistent. For instance, some studies combined epinephrine, whereas others did not. The risk of bias could not be eliminated even after the subgroups were classified. Despite the possible bias, the current clinical situation was more consistent with the different PAI components. The most optimal components are still inconclusive. There are increasing studies exploring the specific effect of single agents in the PMDI. A comparison with LB will provide more valid results if the most acceptable agents are confirmed.

Strengths and limitations

Only RCTs were included in the present meta-analysis, and of similar studies, to the best of our knowledge, this study analyzed the most RCTs. Most of the RCTs explained their randomization method, and all of them blinded the participants and outcomes assessors. The present study not only followed the PRISMA guidelines but also used the GRADE system to evaluate the evidence level of each outcome. More and newer data were included than in previous meta-analyses to obtain more compelling results.

There are several limitations in the present study. First, there were multiple TPAI components, and differences of the components were observed in most of the RCTs, contributing to the risk of bias when comparing them to each other. Second, different RCTs used different time units. For example, some studies used POD 1, POD 2, and POD 3. In some other studies, the time units were the first 24 h, second 24 h, at 24 h, or at 48 h. There might be some bias introduced by combining these different time units. Third, this study contains only a small number of RCTs. Although 16 RCTs were identified, not every study provided the outcomes expected. For instance, only five RCTs provided the VAS score on the operation day. Additionally, because the majority of RCTs had fewer than 50 participants, it was challenging to determine the incidence rate of nausea and vomiting, which may be better observed in a large study population. Fourth, various anesthesia methods were adopted in these RCTs, with spinal anesthesia being the most common choice. However, spinal anesthesia may also have an effect on postoperative pain, and this issue was not addressed in our study. Finally, all of the RCTs were conducted in the USA. Therefore, it is difficult to generalize the results to other countries or races.

Implications for practice and research

Analyses of functional recovery, range of motion of the joints, or other complications besides nausea and vomiting were not performed due to the limited availability of data. These are valuable outcomes in addition to the VAS score. Future studies may consider analyzing more postoperative parameters.

Conclusion

Morphine consumption equivalents were lower in the LB group in postoperative 24–48 h. LB administration during TKA is not superior to TPAI in terms of postoperative VAS, nausea and vomiting incidence, and length of hospital stay. Studies with larger sample size are needed to validate our findings.

Acknowledgements

We thank Wallace Academic Editing for helping us editing the manuscript.

Author contributions

J-JC, J-SW, and C-HL designed the work. J-JC and Y-CW reviewed articles and carried out the analysis. All authors contributed to interpretation of the findings. J-JC wrote the first draft of the manuscript. Y-CW, J-SW, and C-HL reviewed the manuscript and made critical revisions. All authors reviewed and approved the final version of the manuscript.

Funding

Each author certifies that there are no funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article related to the author or any immediate family members.

Availability of data and materials

All data generated or analyzed during this study are included in published articles.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 25 January 2023 Accepted: 9 March 2023 Published online: 16 March 2023

References

- Kurtz S, et al. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am. 2007;89(4):780–5.
- Ranawat AS, Ranawat CS. Pain management and accelerated rehabilitation for total hip and total knee arthroplasty. J Arthroplasty. 2007;22(7 Suppl 3):12–5.
- Correll DJ, Vlassakov KV, Kissin I. No evidence of real progress in treatment of acute pain, 1993–2012: scientometric analysis. J Pain Res. 2014;7:199–210.
- Kerr DR, Kohan L. Local infiltration analgesia: a technique for the control of acute postoperative pain following knee and hip surgery: a case study of 325 patients. Acta Orthop. 2008;79(2):174–83.
- Peters CL, Shirley B, Erickson J. The effect of a new multimodal perioperative anesthetic regimen on postoperative pain, side effects, rehabilitation, and length of hospital stay after total joint arthroplasty. J Arthroplasty. 2006;21(6 Suppl 2):132–8.
- Parvataneni HK, et al. Controlling pain after total hip and knee arthroplasty using a multimodal protocol with local periarticular injections: a prospective randomized study. J Arthroplasty. 2007;22(6 Suppl 2):33–8.
- Busch CA, et al. Efficacy of periarticular multimodal drug injection in total knee arthroplasty. A randomized trial. J Bone Joint Surg Am. 2006;88(5):959–63.
- Vendittoli PA, et al. A multimodal analgesia protocol for total knee arthroplasty. A randomized, controlled study. J Bone Joint Surg Am. 2006;88(2):282–9.
- Koh IJ, et al. Additional pain relieving effect of intraoperative periarticular injections after simultaneous bilateral TKA: a randomized, controlled study. Knee Surg Sports Traumatol Arthrosc. 2010;18(7):916–22.
- Joo JH, et al. Is intra-articular multimodal drug injection effective in pain management after total knee arthroplasty? A randomized, doubleblinded, prospective study. J Arthroplasty. 2011;26(7):1095–9.
- Fu P, et al. Efficacy of intra-articular cocktail analgesic injection in total knee arthroplasty: a randomized controlled trial. Knee. 2009;16(4):280–4.
- 12. Koh IJ, et al. Does periarticular injection have additional pain relieving effects during contemporary multimodal pain control protocols for TKA? A randomised, controlled study. Knee. 2012;19(4):253–9.
- Dasta J, et al. Bupivacaine liposome injectable suspension compared with bupivacaine HCl for the reduction of opioid burden in the postsurgical setting. Curr Med Res Opin. 2012;28(10):1609–15.
- 14. Vyas KS, et al. Systematic review of liposomal bupivacaine (Exparel) for postoperative analgesia. Plast Reconstr Surg. 2016;138(4):748e–56e.
- Mont MA, et al. Local infiltration analgesia with liposomal bupivacaine improves pain scores and reduces opioid use after total knee arthroplasty: results of a randomized controlled trial. J Arthroplasty. 2018;33(1):90–6.

- Ellimoottil C, Vijan S, Flanigan RC. A primer on clinical trial design. Urol Oncol. 2015;33(3):116–21.
- Yayac M, et al. The efficacy of liposomal bupivacaine over traditional local anesthetics in periarticular infiltration and regional anesthesia during total knee arthroplasty: a systematic review and meta-analysis. J Arthroplasty. 2019;34(9):2166–83.
- Liu Y, et al. The efficacy of liposomal bupivacaine compared with traditional peri-articular injection for pain control following total knee arthroplasty: an updated meta-analysis of randomized controlled trials. BMC Musculoskelet Disord. 2019;20(1):306.
- Hyland SJ, et al. Liposomal bupivacaine versus standard periarticular injection in total knee arthroplasty with regional anesthesia: a prospective randomized controlled trial. J Arthroplasty. 2019;34(3):488–94.
- Page MJ, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372: n71.
- Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). 2022.
- Atkins D, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490.
- Bramlett K, et al. A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam bupivacaine, an extendedrelease liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty. Knee. 2012;19(5):530–6.
- Schroer WC, et al. Does extended-release liposomal bupivacaine better control pain than bupivacaine after total knee arthroplasty (TKA)? A prospective, randomized clinical trial. J Arthroplasty. 2015;30(9 Suppl):64–7.
- Collis PN, et al. Periarticular injection after total knee arthroplasty using liposomal bupivacaine vs a modified ranawat suspension: a prospective, randomized study. J Arthroplasty. 2016;31(3):633–6.
- Jain RK, et al. The AAHKS clinical research award: liposomal bupivacaine and periarticular injection are not superior to single-shot intra-articular injection for pain control in total knee arthroplasty. J Arthroplasty. 2016;31(9 Suppl):22–5.
- Schwarzkopf R, et al. Is there a benefit for liposomal bupivacaine compared to a traditional periarticular injection in total knee arthroplasty patients with a history of chronic opioid use? J Arthroplasty. 2016;31(8):1702–5.
- Snyder MA, et al. Improving total knee arthroplasty perioperative pain management using a periarticular injection with bupivacaine liposomal suspension. Arthroplast Today. 2016;2(1):37–42.
- Alijanipour P, et al. Periarticular injection of liposomal bupivacaine offers no benefit over standard bupivacaine in total knee arthroplasty: a prospective, randomized, controlled trial. J Arthroplasty. 2017;32(2):628–34.
- DeClaire JH, et al. Effectiveness of bupivacaine liposome injectable suspension for postoperative pain control in total knee arthroplasty: a prospective, randomized, double blind, controlled trial. J Arthroplasty. 2017;32(9s):S268-s271.
- Smith EB, et al. Periarticular liposomal bupivacaine injection versus intra-articular bupivacaine infusion catheter for analgesia after total knee arthroplasty: a double-blinded, randomized controlled trial. J Bone Joint Surg Am. 2017;99(16):1337–44.
- Danoff JR, et al. Periarticular ropivacaine cocktail is equivalent to liposomal bupivacaine cocktail in bilateral total knee arthroplasty. J Arthroplasty. 2018;33(8):2455–9.
- Suarez JC, et al. Effectiveness of novel adjuncts in pain management following total knee arthroplasty: a randomized clinical trial. J Arthroplasty. 2018;33(7s):5136-s141.
- Zlotnicki JP, et al. Liposomal bupivacaine vs plain bupivacaine in periarticular injection for control of pain and early motion in total knee arthroplasty: a randomized, prospective study. J Arthroplasty. 2018;33(8):2460–4.
- 35. Dysart SH, et al. Local infiltration analgesia with liposomal bupivacaine improves early outcomes after total knee arthroplasty: 24-hour data from the PILLAR study. J Arthroplasty. 2019;34(5):882-886.e1.
- Schumer G, et al. Liposomal bupivacaine utilization in total knee replacement does not decrease length of hospital stay. J Knee Surg. 2019;32(9):934–9.
- Hu D, et al. Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. Clin Drug Investig. 2013;33(2):109–15.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

