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Liposomal bupivacaine versus interscalene nerve block for pain control after shoulder arthroplasty
A meta-analysis

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Abstract

Background: Postoperative pain control after total shoulder arthroplasty (TSA) can be challenging. Liposomal bupivacaine and interscalene nerve block are 2 common pain control protocol for TSA patients. However, whether liposomal bupivacaine was superior than interscalene nerve block was unknown. This meta-analysis aimed to illustrate the efficacy liposomal bupivacaine versus interscalene nerve block for pain control in patients undergoing TSA.

Methods: In May 2017, a systematic computer-based search was conducted in PubMed, EMBASE, Web of Science, Cochrane Database of Systematic Reviews, and Google database. Data on patients prepared for TSA in studies that compared liposomal bupivacaine versus interscalene nerve block were retrieved. The endpoints were the visual analogue scale (VAS) at 4 hours, 8 hours, 12 hours, 24 hours, and 2 weeks, total morphine consumption at 24 hours, and the length of hospital stay. Software of Stata 12.0 was used for pooling the final outcomes.

Results: Five clinical studies with 573 patients (liposomal bupivacaine group = 239, interscalene nerve block group = 334) were ultimately included in the meta-analysis. There was no significant difference between the VAS at 4 hours, 8 hours, and 2 weeks between liposomal bupivacaine group and interscalene nerve block group ($P > .05$). Compared with interscalene nerve block group, liposomal bupivacaine was associated with a reduction of VAS score at 12 hours, 24 hours by appropriately 3.31 points and 6.42 points respectively on a 100-point VAS. Furthermore, liposomal bupivacaine was associated with a significantly reduction of the length of hospital stay by appropriately by 0.16 days compared with interscalene nerve block group.

Conclusion: Current meta-analysis indicates that compared with interscalene nerve block, liposomal bupivacaine had comparative effectiveness on reducing both pain scores and the length of hospital stay. However, studies with more patients and better-designed methods are needed to establish the optimal regimen and the safety of liposomal bupivacaine in TSA patients.

Abbreviations: CI = confidence interval, RCT = randomized controlled trial, TSA = total shoulder arthroplasty, VAS = visual analogue scale, WMD = weighted mean differences.

Keywords: interscalene nerve block, liposomal bupivacaine, meta-analysis, total shoulder arthroplasty

1. Introduction

The annual number of total shoulder arthroplasty (TSA) is rising with the growing elderly population and development of new technologies such as reverse shoulder arthroplasty.[1] In the year of 2011, there were 53,000 shoulder arthroplasties performed annually in United States.[2] Traditional postoperative pain control has centered on the use of parenteral narcotics in the hospital, which have well-known side effects of respiratory depression, somnolence, and inconsistent pain relief.[3,4] Efficacy pain control after surgery may improve pain control and decreased the length of stay. A common method of pain control after shoulder surgery involves regional anesthesia with the use of an interscalene nerve block. Local infiltration anesthesia has shown various benefits, the agents used in the analgesic cocktail have a short duration of action, after which patients can experience increased pain. Liposomal bupivacaine has been approved by the U.S. Food and Drug Administration for administration into the surgical site, with proven safety in both animal and human studies.[5] This suspension is created using a lipid-based delivery system that encapsulates the drug in multivesicular liposomal particles that then release the drug over a 72-hour time period.[6] Although, there were several randomized controlled trials (RCTs) comparing liposomal bupivacaine and interscalene nerve block for pain control in TSA; however, the results were controversial.[7,8] Hannan et al[7] reported that liposomal bupivacaine was associated with less pain, less opioid consumption, and shorter hospital stays after TSA compared with interscalene nerve block. However, Namdari et al[8] reported that liposomal bupivacaine require greater intraoperative narcotics compared with patients treated with

interscalene nerve block. In addition to the above disputes, it should be noted that the sample size of these studies was limited (ranging from 48 to 98 patients), which may affect the accuracy of relevant conclusions. The purpose of this meta-analysis was to evaluate whether liposomal bupivacaine was superior than interscalene nerve block in reducing pain scores, total morphine consumption, and length of hospital stay.

2. Materials and methods

This systematic review was reported according to the preferred reporting items for systematic reviews and meta-analyses guidelines.[9]

2.1. Search strategies

The following databases: PubMed (1950–May 2017), EMBASE (1974–May 2017), Web of Science (1950–May 2017), and Cochrane Library (May 2017 Issue 5) were searched. The Mesh terms and key words used in the search were as follows: ([(interscalene nerve block) AND liposomal bupivacaine]) AND ([([(TSR) OR TSA] OR total shoulder replacement) OR total shoulder arthroplasty] OR "Arthroplasty, Replacement, Shoulder" [Mesh]). The reference lists of related reviews and meta-analysis were searched for any omitted studies. There was no language or region restriction. We picked the most recent study when multiple studies were published. Meta-analysis was collect relevant data from published papers, and thus no ethics committee approval was need for this meta-analysis.

2.2. Inclusion criteria and study selection

Patients: adult human subjects (age > 18 years) prepared for shoulder arthroplasty (TSA, reverse shoulder arthroplasty); Intervention: use liposomal bupivacaine as an intervention group; Comparison: administration interscalene nerve block as a comparison group; Outcomes: visual analogue scale (VAS) at 4 hours, 8 hours, 12 hours, 24 hours, and 2 week, total morphine consumption at 24 hours, and the length of hospital stay; Study design: RCTs and non-RCTs. Two independent reviewers screened the title and abstracts of the identified studies after removing the duplicates of the search results. Any disagreements about the inclusion or exclusion of a study were solved by discussion or consultation with an expert. The reliability of the study selection was determined by Cohen kappa test, and the acceptable threshold value was set at 0.61.[10,11]

2.3. Data abstraction and quality assessment

A specific extraction was conducted to collect the following data from the included trials: patients' general characteristics, country, the intervention group and comparison group, study design, outcomes, and follow-up duration. Outcomes such as VAS at 4 hours, 8 hours, 12 hours, 24 hours, and 2 week, total morphine consumption at 24 hours, and the length of hospital stay were abstracted and recorded in a sheet. Postoperative pain intensity was measured by a 100-point VAS. When the numerical rating scale was reported, it was converted to a VAS. Additionally, a 10-point VAS was converted to a 100-point VAS.[12] Data in other forms (ie, median, interquartile range, and mean±95% confidence interval [CI]) were converted to the mean±standard deviation according to the Cochrane Handbook.[13] If the data were not reported numerically, we extracted these data using "GetData Graph Digitizer" software from the published figures. All the data were extracted by 2 independent reviewers, and disagreements were resolved by discussion. The methodological quality of all included trials was independently assessed by 2 reviewers on the basis of the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (http://www.cochrane-handbook.org/).

2.4. Outcome measures and statistical analysis

Continuous outcomes (VAS at 4 hours, 8 hours, 12 hours, 24 hours, and 2 week, total morphine consumption at 24 hours, and the length of hospital stay) were expressed as the weighted mean differences (WMD) and respective 95% CI. Statistical significance was set at $P < .05$ to summarize the findings across the trials. The meta-analysis was calculated by Stata software, version 12.0 (Stata Corp., College Station, TX). Statistical heterogeneity was tested using the chi-squared test and I^2 statistic. When there was no statistical evidence of heterogeneity ($I^2 < 50\%$, $P > .1$), a fixed-effects model was adopted; otherwise, a random-effect model was chosen. Publication bias was tested using funnel plots. Since the number of the included studies was less than 10, thus, publication bias was not necessary to perform.

3. Results

3.1. Search results

In the initial research, a total of 316 papers were identified from the electronic databases (PubMed = 121, Embase = 98, Web of Science = 75, and Cochrane Library = 22). The number of articles after duplicates had been removed by Endnote X7 software was 255. After screened the abstracts and title of these 255 studies, 243 papers were excluded because they were irrelevant or did not meet the criteria. Finally, a total of 5 studies with 573 patients were available for meta-analysis (liposomal bupivacaine group = 239, interscalene nerve block group = 334).[7,8,14–16] The general characteristic of the included studies can be obtained in Table 1. Among the 5 studies, there were non-RCTs[7,14,16] and 2 were RCTs.[8,15] The sample size ranged from 21 to 165. All of the included studies use 266 mg liposomal bupivacaine as intervention group. All of the studies use ultrasound for interscalene nerve block and only study[15] use nerve stimulators. The follow-up duration ranged from 1 day to 12 weeks (Fig. 1).

3.2. Quality assessment

The risk of bias summary and risk of bias graph can be seen in Figs. 2 and 3, respectively. Two studies were with low risk of bias of the random sequence generation, allocation concealment, blinding to participants and personnel, blinding to the outcome assessment, reporting bias, and other bias. However, the rest 3 studies were all with high risk of bias.

3.3. Results of meta-analysis
3.3.1. VAS at 4 hours.
There was no statistical heterogeneity between included studies ($I^2 = 0.0\%$, $P = .321$), and fixed-effect model was used to perform the meta-analysis. Postoperative VAS scores at 4 hours were reported in 2 studies, and the pooled results indicated that there was no significant difference between the liposomal bupivacaine and interscalene nerve block in terms of VAS scores at 4 hours (WMD = −0.69, 95% CI −4.28, 2.90, $P = .706$, Fig. 4).

Table 1

The general characteristic of the included studies.

| Study | Country | Intervention group | | Comparison group | | Ultrasound | Nerve stimulators | Outcomes | Study | Follow-up |
		No of patients	Drugs and dose	No of patients	Drugs					
Weller 2017	USA	58	20 mL (266 mg) of liposomal 0.5% bupivacaine, 10 cc of 0.5% bupivacaine with epinephrine, 2 mg of morphine, and 30 mg of ketorolac into the deltoid	165	20 mL of 0.5% bupivacaine with 1:200,000 epinephrine	Yes	No	4, 5, 6, 7	RCS	12 wk
Okoroha 2016	USA	26	20 mL of LB (266 mg) mixed in 20 mL of sterile saline	31	A single dose of 40 mL of 0.5% ropivacaine	Yes	Yes	1, 2, 3, 4, 6, 7	RCT	3 d
Namdari 2017	USA	78	20 mL of LB (266 mg) mixed in 20 mL of sterile saline	78	30 mL of 0.5% ropivacaine	Yes	No	2, 3, 4, 6, 7	RCT	1 d
Hannan 2016	USA	37	20 mL of LB (266 mg) mixed in 40 mL of sterile saline	21	30 mL of 5% ropivacaine (5 mg/mL)	Yes	No	1, 2, 4, 5, 6, 7	RCS	10 d
Srikumaran 2016	USA	40	20 mL of LB (266 mg) mixed in 40 mL of sterile saline	39	30 mL of 5% ropivacaine (5 mg/mL)	Yes	No	3, 4, 5	RCS	2 wk

1, VAS at 4 h; 2, VAS at 8 h; 3, VAS at 12 h; 4, VAS at 24 h; 5, VAS at 2 wk; 6, total morphine consumption at 24 h; 7, length of hospital stay. RCT = randomized controlled trial, RCS = retrospective controlled study, VAS = visual analogue scale.

3.3.2. VAS at 8 hours. There was large statistical heterogeneity between included studies ($I^2 = 91.4\%$, $P = .000$), and random-effect model was used to perform the meta-analysis. Postoperative VAS scores at 8 hours were reported in 3 studies, and the pooled results indicated that there was no significant difference between the liposomal bupivacaine and interscalene nerve block in terms of VAS scores at 8 hours (WMD = 3.75, 95% CI −12.63, 20.14, $P = 0.654$, Fig. 5).
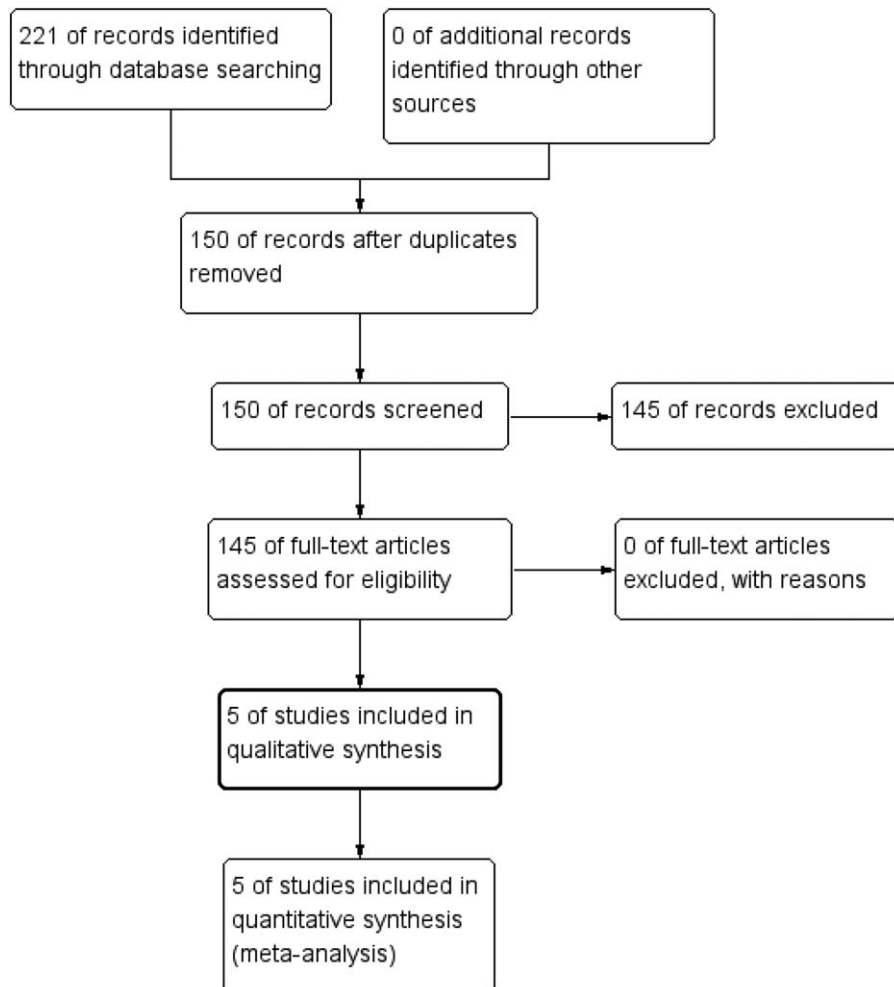

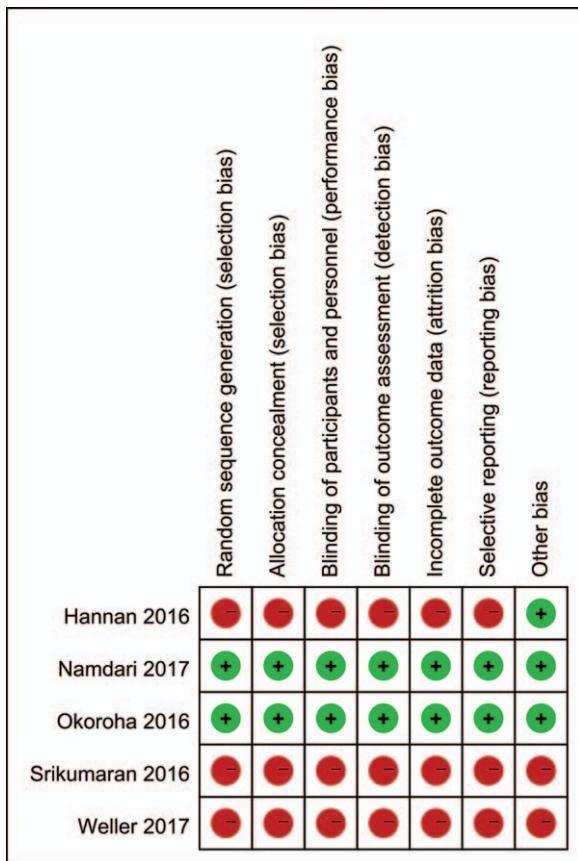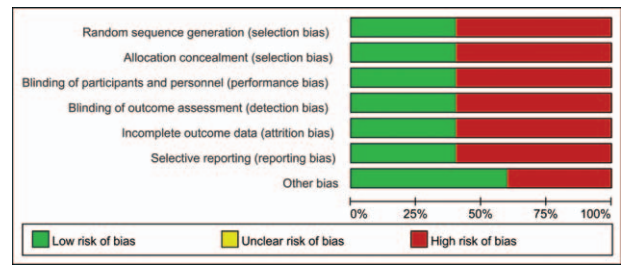Figure 1. Flowchart of study search and inclusion criteria.

Figure 2. Risk of bias summary of included randomized controlled trials. +, no bias; –, bias; and ?, bias unknown.

Figure 3. The risk of bias graph.

of VAS scores at 12 hours (WMD=−3.31, 95% CI −6.54, −0.08, P=.045, Fig. 6).

3.3.4. VAS at 24 hours. There was moderate statistical heterogeneity between included studies ($I^2=54.9\%$, $P=.064$), and random-effect model was used to perform the meta-analysis. Postoperative VAS scores at 24 hours were reported in 3 studies, results showed that liposomal bupivacaine was associated with a reduction of VAS scores at 24 hours than interscalene nerve block (WMD=−6.42, 95% CI −10.90, −1.94, P=.005, Fig. 7).

3.3.5. VAS at 2 week. There was large statistical heterogeneity between included studies ($I^2=92.0\%$, $P=.000$), and random-effect model was used to perform the meta-analysis. Postoperative VAS scores at 2 week were reported in 3 studies, and the pooled results showed that liposomal bupivacaine has comparable pain control at 2 week compared with interscalene nerve block (WMD=−13.68, 95% CI −31.02, 3.66, P=.122, Fig. 8).

3.3.6. Total morphine consumption at 24 hours. There was high statistical heterogeneity between included studies ($I^2=91.1\%$, $P=.000$) in terms of total morphine consumption at 24 hours, and random-effect model was used to perform the meta-analysis. Total morphine consumption at 24 hours were reported in 4 studies, and final results revealed that there was no significant difference between liposomal bupivacaine and interscalene nerve
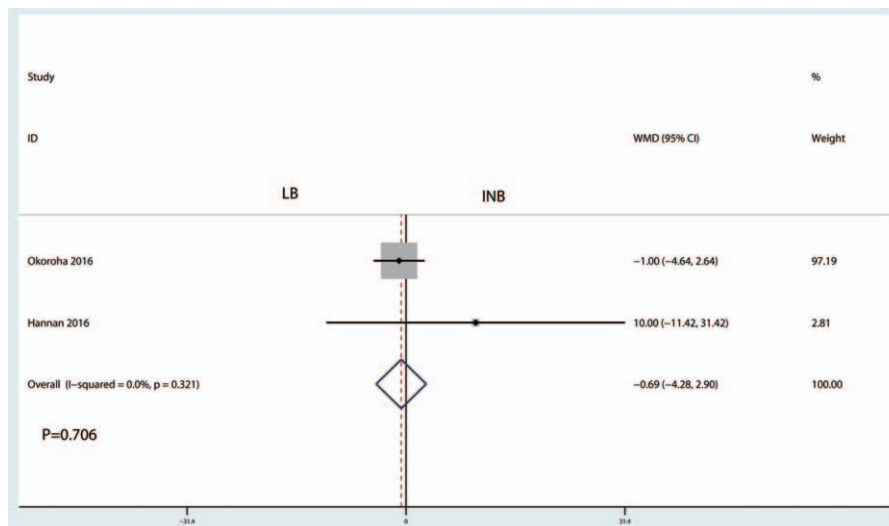
3.3.3. VAS at 12 hours. There was no statistical heterogeneity between included studies ($I^2=0.0\%$, $P=0.908$), and fixed-effect model was used to perform the meta-analysis. Postoperative VAS scores at 12 hours were reported in three studies, and the pooled results indicated that there was no significant difference between the liposomal bupivacaine and interscalene nerve block in terms

Figure 4. Forest plots of the included studies comparing the visual analogue scale (VAS) at 4 hours.
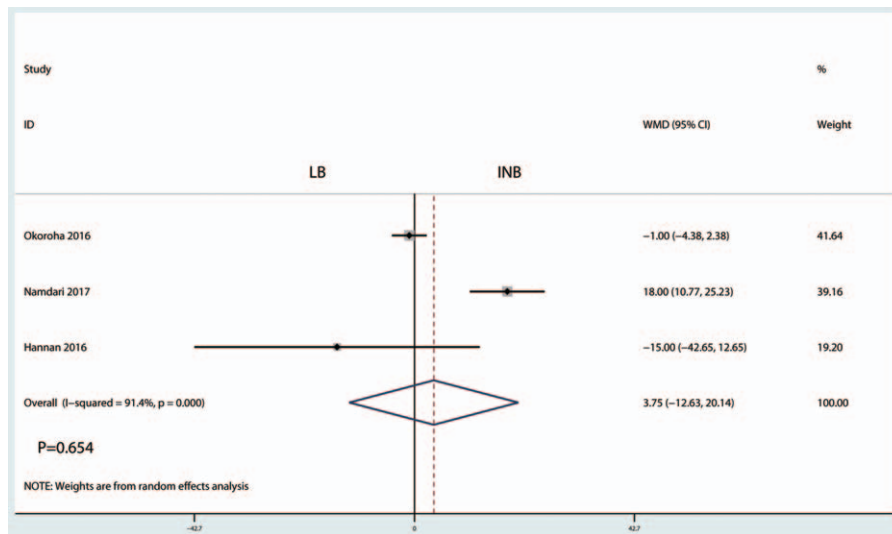
Figure 5. Forest plots of the included studies comparing the visual analogue scale (VAS) at 8 hours.

block in terms of the total morphine consumption at 24 hours (WMD = 8.60, 95% CI −5.64, 22.84, P = .236, Fig. 9).

3.3.7. Length of hospital stay. There was no statistical heterogeneity between included studies (I^2 = 0.0%, P = .576), and fixed-effect model was used to perform the meta-analysis. Postoperative VAS scores with rest at 12 hours were reported in 4 studies, and the pooled results indicated that preoperative administration of pregabalin can decrease VAS score with rest at 12 hours (WMD = −0.16, 95% CI −0.29, −0.03, P = .014, Fig. 10).

3.4. Sensitivity analysis

The sensitivity analysis results of VAS at 8 hours, 2 week and total morphine consumption at 24 hours can be seen in Fig. 11, Fig. 12,

and Fig. 13, respectively. Final results indicated that none of the included study affects the final results.

4. Discussion

As far as we know, this the first meta-analysis that comparing liposomal bupivacaine and interscalene nerve block for pain control after shoulder arthroplasty. Pooled results indicated that liposomal bupivacaine shows similar pain control at 4 and 8 hours when compared with interscalene nerve block. Liposomal bupivacaine was associated with a reduction of pain scores at 12 and 24 hours when compared with interscalene nerve block. The liposomal bupivacaine was associated with a reduction of the length of hospital stay. There was no significant difference between the liposomal bupivacaine and interscalene nerve block in terms of the total morphine consumption at 24 hours. A total
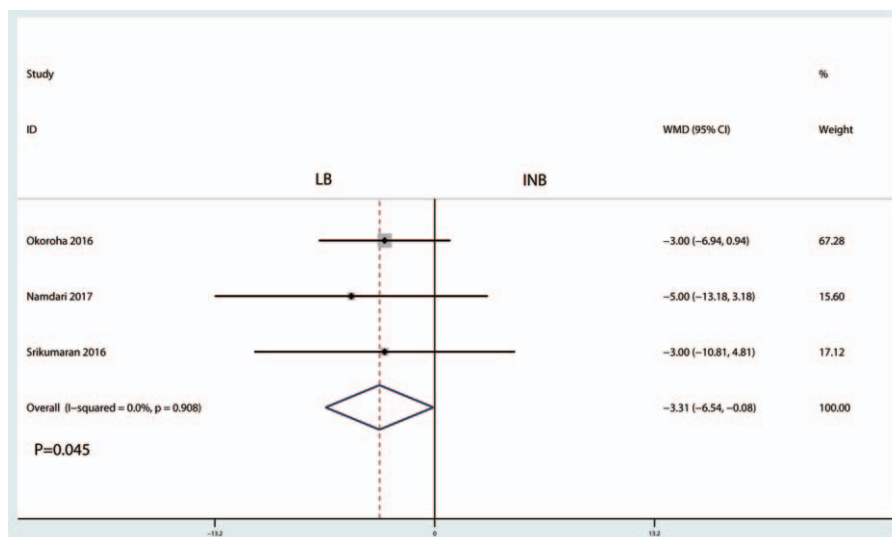

Figure 6. Forest plots of the included studies comparing the visual analogue scale (VAS) at 12 hours.
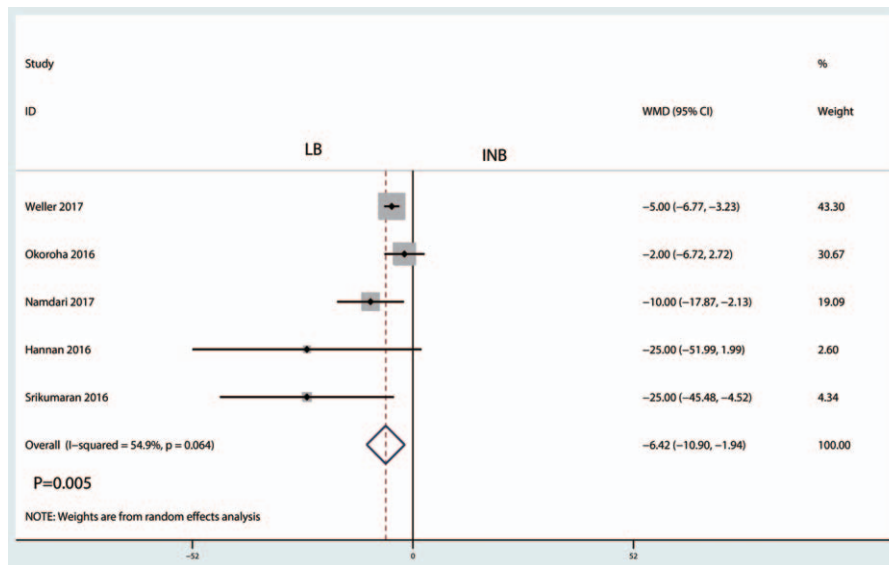
Figure 7. Forest plots of the included studies comparing the visual analogue scale (VAS) at 24 hours.

of 5 studies were finally included in this meta-analysis. Two RCTs were with high quality and presented with low risk of bias. Three non-RCTs were with low quality. The preferred reporting items for systematic reviews and meta-analyses guidelines and Cochrane Handbook were applied to assess the quality of the results published in all included studies to ensure that the results of our meta-analysis were reliable and veritable. Another strength of current meta-analysis was that the comprehensively search from the electronic databases (PubMed, EMBASE, Web of Science, and Cochrane Library).

Adequate pain management protocols after TSA enables quicker functional recovery and reduces postoperative complications and treatment costs. Postsurgical pain can be significant and usually require the use of opioid analgesics. However, opioids are associated with significant adverse effects, including respiratory depression, which often drive the use of multimodal

therapy with nonopioid analgesics, including local and regional analgesia techniques. However, the use of older local anesthetics provides a limited duration of analgesia. Liposomal bupivacaine is a safe and effective analgesic for pain relief with the support of the local infiltration technique. The present meta-analysis was conducted to determine whether administration liposomal bupivacaine provided comparative, and possibly additional long-acting, benefits as did the interscalene nerve block used in TSA patients in the perioperative period.

Current meta-analysis indicated that interscalene nerve block has similar pain control when compared with liposomal bupivacaine at 8 hours after TSA. And liposomal bupivacaine was superior than interscalene nerve block in terms of the VAS at 12 and 24 hours after TSA. The benefits of interscalene brachial plexus blockade in shoulder surgical procedures have been reported. Abdallah et al[17] reported that interscalene brachial
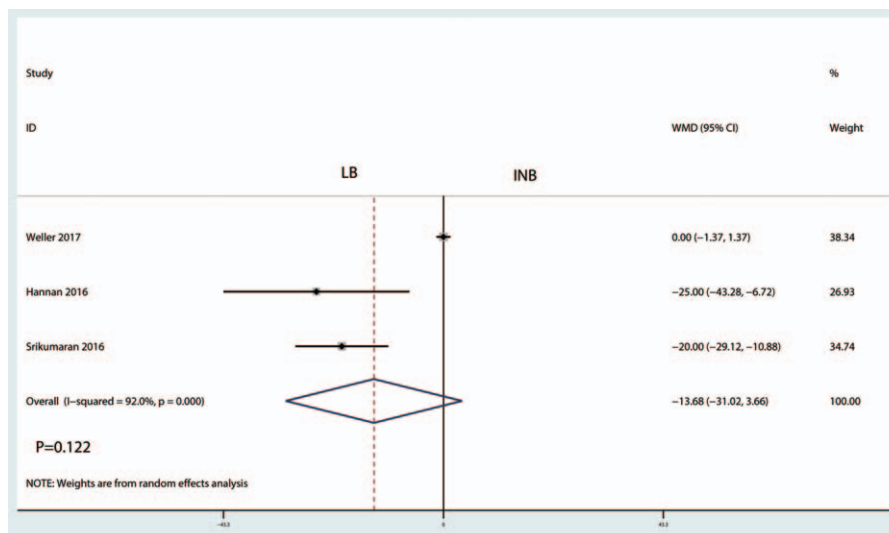

Figure 8. Forest plots of the included studies comparing the visual analogue scale (VAS) at 2 week.
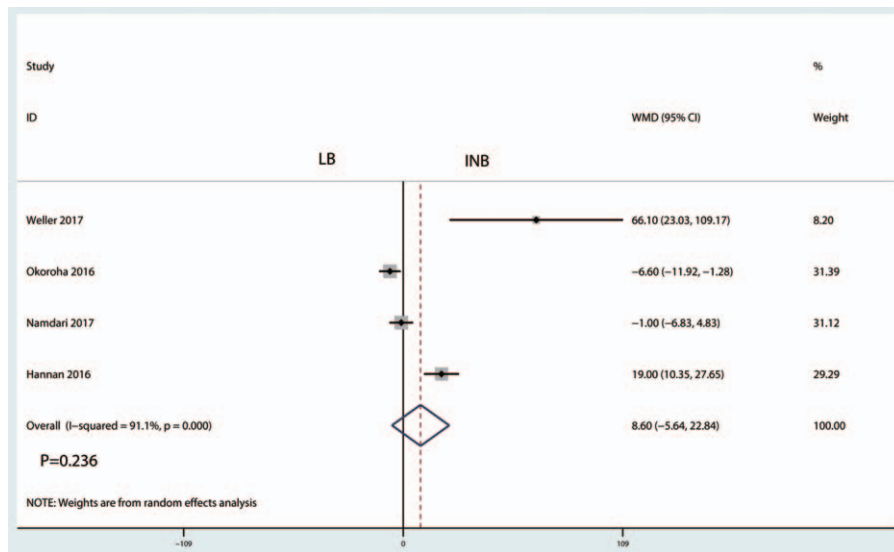
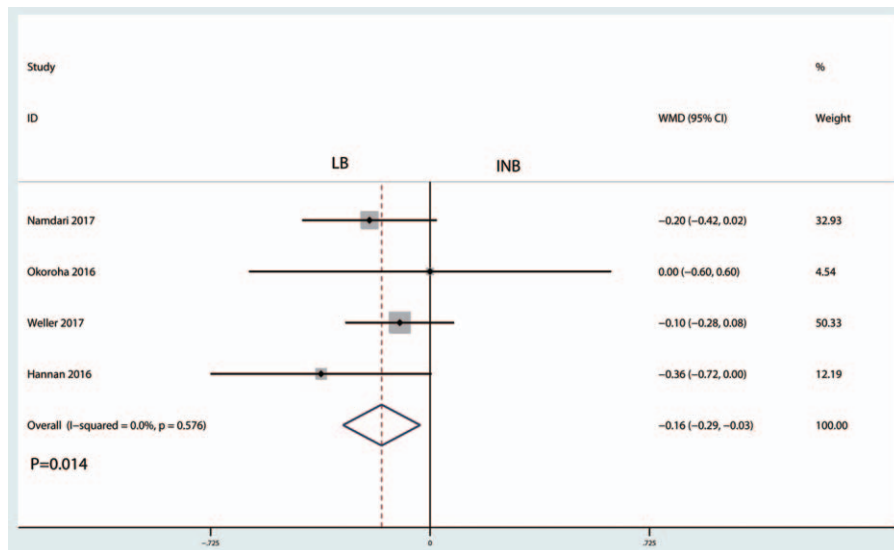**Figure 9.** Forest plots of the included studies comparing the total morphine consumption at 24 hours.

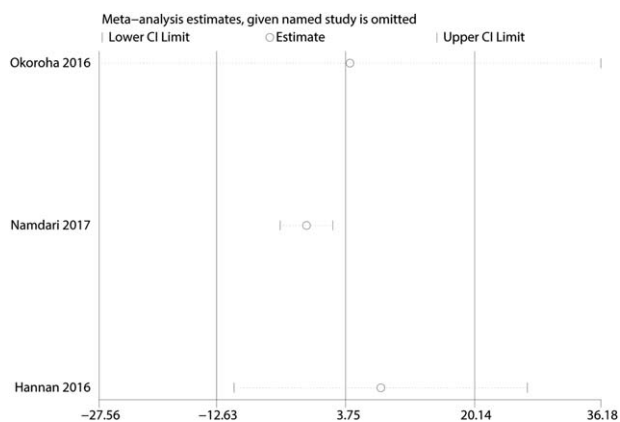**Figure 10.** Forest plots of the included studies comparing the length of hospital stay.

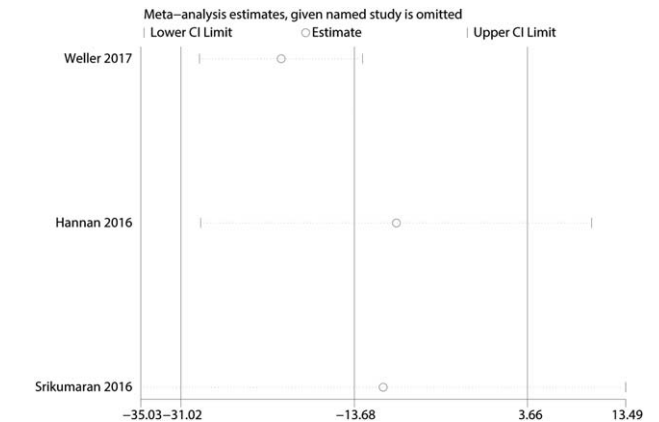**Figure 11.** Sensitivity analysis of the visual analogue scale (VAS) at 8 hours.

Figure 12. Sensitivity analysis of the visual analogue scale (VAS) at 2 week.
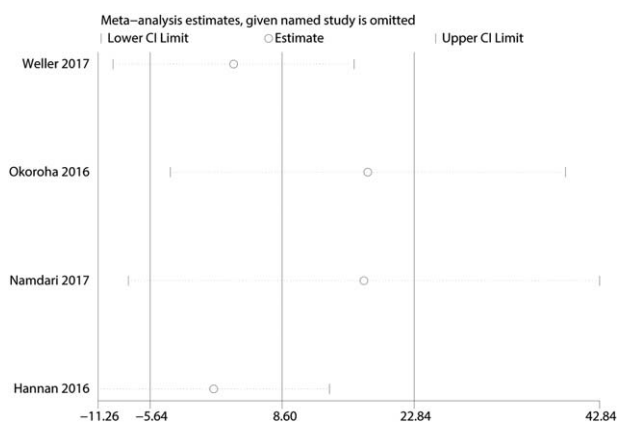
Figure 13. Sensitivity analysis of the total morphine consumption.

plexus blockade can provide effective analgesia up 8 hours, with no demonstrable benefits thereafter after TSA. These differences in pain values are consistent with the known pharmacokinetics of liposomal bupivacaine.[18] Liposome bupivacaine injectable has been shown in previous studies to be safe for local soft-tissue infiltration at the time of the surgical procedure (including total knee arthroplasty and total hip arthroplasty).[19–22] Theoretically speaking, a reduction of VAS scores will lead to the decrease of total morphine consumption. Current meta-analysis indicated that there was no significant difference between the total morphine consumption at 24 hours.

Another major finding was that liposomal bupivacaine was associated with a reduction of the length of hospital stay by appropriately by 0.16 days. Wu et al[23] reported that liposomal bupivacaine was associated with a reduction of the length of hospital stay by appropriately by 0.08 days than traditional bupivacaine in total knee arthroplasty patients. When compared with femoral nerve block, liposomal bupivacaine was associated with a reduction of the length of hospital stay by 0.43 days in total knee arthroplasty patients.[19]

Interscalene nerve block also requires additional time and resources in the perioperative period, including an anesthesiologist with specialized training, assistants, and ultrasonography or nerve stimulation equipment contraindicated in patients taking blood thinners. Current meta-analysis included 5 clinical trials and all of these included studies use ultrasonography and one study uses nerve stimulation equipment. Thus, local infiltration anesthesia with liposomal bupivacaine will decrease the additional time of these devices. Another concern was the costs of liposomal bupivacaine. Weller et al[14] revealed that the average cost for the liposomal bupivacaine was $289.04, and for interscalene nerve block, including equipment and anesthesia fees, was $1559.42. Thus, liposomal bupivacaine was associated with a less costs than interscalene nerve block.

There were a number of limitations in our meta-analysis:

(1) Only 2 RCTs and 3 non-RCTs with small samples, ranging from 21 to 165 patients per group, were included in our meta-analysis.
(2) The follow-up period was relatively short, and thus the relevant complications may underestimated.
(3) Only 5 relevant studies were included in our meta-analysis; funnel plot was not performed and publication bias is unknown.

(4) There was large heterogeneity between the outcomes (VAS at 8 hours, VAS at 2 week, and total morphine at 24 hours) and should be interpreted with caution.

5. Conclusion

Current meta-analysis indicated that compared with interscalene nerve block, liposomal bupivacaine had comparative effectiveness on reducing acute pain intensity and the length of hospital stay. However, well-designed studies with large sample patients are needed to identify the optimal regimen and the safety of liposomal bupivacaine in TSA patients.

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