REVIEW

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Efficacy of Liposomal Bupivacaine in Arthroscopic Rotator Cuff Repair: a Systematic Review and Meta-Analysis of Randomized Controlled Trials

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SUMMARY

Objective. To conduct the first-ever meta-analysis of all randomized controlled trials (RCTs) that scrutinized the analgesic efficacy of liposomal bupivacaine (LB, intervention) *versus* nonliposomal local anesthetic agents (NLAAs, control) during arthroscopic rotator cuff repair (ARCR).

Methods. Five databases were screened from inception until 09-April-2022. Subgroup analyses according to the postoperative day (POD, POD 0-7) were conducted. The data were summarized as weighted mean difference (WMD) with 95% confidence interval (CI) under the random-effects model.

Results. Seven RCTs comprising 442 patients were included. Three, three, and one RCT(s) were judged to have an overall "low", "high", and "unclear" risk of bias, respectively. Regarding overall VAS pain score, there was no significant difference between both groups (WMD = -0.56, 95% CI [-1.16, 0.04], p = 0.07). Subgroup analyses showed significantly reduced postoperative VAS pain scores in favor of the LB group on POD 1/2; however, these reductions were not clinically meaningful. Also, LB correlated with a significant reduction in overall postoperative opioid consumption (WMD = -7.72 MME, 95% CI [-11.48, -3.97], p < 0.001). Subgroup analyses showed a significantly reduced postoperative opioid consumption in favor of the LB group on POD 1/2/3; however, these reductions were not clinically meaningful.

Conclusions. Among patients undergoing ARCR, this systematic review and meta-analysis of RCTs showed that LB did not correlate with clinically meaningful reductions in postoperative VAS pain scores and overall opioid consumption. Future large-sized and well-designed RCTs are needed to consolidate the presented evidence.

KEY WORDS

Liposomal bupivacaine; interscalene brachial plexus block; rotator cuff repair; pain; opioids.

INTRODUCTION

Rotator cuff tear is a common orthopedic problem that can occur secondary to trauma or natural degeneration (1). From a procedural point of view, arthroscopic rotator cuff repair (ARCR) is rapidly evolving as the standard of care with satisfactory clinical outcomes (1, 2). Nevertheless, uncontrolled postoperative pain continues to be a major complaint following ARCR, and is linked to an array of unfavorable aftermaths, such as patient displeasure, extended hospitalization, frequent hospital visits, postoperative complications, and most importantly severe discomfort warranting narcotic consumption and dependence (3-5).

A multimodal approach is endorsed to offer optimal pain control following shoulder surgeries (5, 6). Within these lines, regional analgesia with interscalene brachial plexus block (IBPB) is highly encouraged and frequently utilized by operating orthopedic surgeons (7, 8). Nevertheless, single-shot IBPB with long-acting local anesthetic - for example, ropivacaine and bupivacaine - does not extend pain relief beyond 24 hours postoperatively (9-11), resulting in early moderate-to-severe rebound pain (12). Thus, there is a growing necessity to identify an optimal local anesthetic that yields selective sensory blockade, offers longer postoperative analgesia, and reduces opioid intake after ARCR.

Liposomal bupivacaine (LB), also commercially known as Exparel, is approved by the United States (US) Food and Drug Administration (FDA) for single-shot intraoperative infiltration and IBPB to provide postsurgical local and regional analgesia, respectively, in adults (13). Contrary to the conventional bupivacaine, LB is characteristically manufactured to offer prolonged pain control up to 72 hours, by slowing the release of bupivacaine over time from the liposomes (14). Several randomized controlled trials (RCTs) examined the toxicity and clinical benefits of LB among patients undergoing ARCR; nevertheless, the results were limited by small sample size, variable method of LB administration, and contradictory results (15-21). Additionally, there exists no meta-analysis thus far that is carried out to compile the evidence on the clinical efficacy of LB compared with nonliposomal local anesthetic agents after ARCR.

Hence, the aim of this research is to accomplish the first-ever systematic review and meta-analysis on the clinical efficacy - specifically postoperative analgesia and opioid consumption - of LB *versus* nonliposomal local anesthetic agents among patients undergoing ARCR. The proposed hypothesis is that administration of LB will be correlated with better analgesic benefits compared with nonliposomal local anesthetic agents among patients undergoing ARCR.

MATERIALS AND METHODS

Search protocol

We conducted this systematic review and meta-analysis in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (22). Additionally, we followed the steps highlighted in the Cochrane Handbook for Systematic Reviews of Interventions (23). This research comprised previously published studies; thus, ethical approval was not required.

Literature search

We searched five major databases (PubMed, Scopus, Web of Science, Embase, and Cochrane Library of Clinical Trials) from inception till April 9, 2022. We employed the following query search in all databases: (liposomal bupivacaine OR Exparel) AND (arthroscopic) AND (rotator cuff) AND (randomized OR randomised OR randomly). There was no language restriction during database search. Two investigators conducted the literature search independently and conflicts were resolved by consensus among the two investigators.

Inclusion and exclusion criteria

We included all studies that met the following evidence-based PICOS criteria: 1) Patients: patients undergoing ARCR, 2) Intervention: LB in the form of IBPB or local infiltration, 3) Comparator: nonliposomal local anesthetic agents, 4) Outcomes: postoperative pain scores and opioid consumption, and 5) Study design: RCTs. We excluded non-randomized studies, conference abstracts, reviews, animal studies, and articles with orthopedic patients undergoing shoulder surgeries other than ARCR (for example, total shoulder arthroplasties).

Screening and study selection

We considered three steps in determining the eligibility of the retrieved citations for inclusion in the meta-analysis. First, we removed the duplicated citations retrieved from the database search. Second, we inspected the titles and abstracts for first-look eligibility and omitted the irrelevant ones. Third, we carried out full-text screening of the remaining eligible citations for final inclusion in the meta-analysis. Moreover, we scrutinized the reference lists of all eligible articles and recent systematic reviews for potential inclusion of additional pertinent studies. Two investigators screened the results independently and conflicts were rectified by consultation with a third investigator.

Data extraction

We abstracted relevant data from the eligible studies using a previously formatted data extraction sheet. With regard to

baseline characteristics of the included studies, we extracted data pertaining to first author's name, publication year, country of publication, mean age of participants, gender of participants, study groups, sample size of study groups, and details of experimental/control groups in terms of analgesic technique, drug, and dose. With respect to efficacy endpoints, we extracted data pertaining to postoperative pain scores and opioid consumption at postoperative day (POD) 0-7. Postoperative pain scores were evaluated according to the 10-cm visual analogue scale (VAS) in which "0" corresponded to no pain at all and "10" corresponded to the worst possible pain imaginable. Postoperative opioid consumption was reported as oral morphine milligram equivalents (MME). Three investigators (in groups of two) independently participated in data collection and conflicts were rectified by consensus and consultation with a fifth investigator.

Risk of bias assessment

We appraised the risk of bias of included RCTs in accordance to the Cochrane risk of bias assessment instrument (24). This instrument gauges the following domains: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective outcome reporting, and 7) other potential sources of bias. We graded each domain as unclear, low, or high risk. Two investigators completed the risk of bias assessment independently and conflicts were rectified by consensus and consultation with a third investigator.

Data analysis

We used the Review Manager Software version 5.4.0. for meta-analysis computations. We analyzed continuous data using the Inverse Variance method and pooled them as weighted mean difference (WMD) with 95% confidence intervals (CI). We defined between-study heterogeneity in accordance to the chi-square $p < 0.1$ and I-square test (I^2) > 50% (25). We used the random-effects models for analysis data. As the number of included studies was small (less than n = 10 per outcome), we did not assess for publication bias using funnel plots, as the results would be unreliable (26). We used the WebPlotDigitizer software (www.automeris.io/WebPlotDigitizer/) to extract data from figures when written numerical values were not provided in the full-texts. Three studies reported median and interquartile ranges (or minimum-maximum values) and we computed the desired means and standard deviations, as previously described by Wan *et al.* (27) and endorsed in the Cochrane Handbook for Systematic Reviews of Interventions (23).

RESULTS

Search results and summary of included studies

Literature search generated a total of 56 studies after omission of duplicated ones. After title and abstract screening, 41 studies were excluded and the remaining 15 studies progressed to full-text screening for eligibility. Finally, a total of seven (n = 7) studies met the inclusion criteria and were included in the qualitative and quantitative synthesis (15-21) (**figure 1**). This meta-analysis included 442 patients; 224 and 218 patients were assigned to LB and control group, respectively. All studies originated in United Stated of America and included only patients who underwent ARCR. With regard to the method of LB administration, four studies administrated LB in the form of an IBPB (15, 17, 19, 21). Two studies administered LB in the form of intraoperative local infiltration in addition to preoperative IBPB with plain bupivacaine/ropivacaine (16). One study administered LB in the form of periarticular injection (18, 20). The dose of LB ranged from 88 mg to 266 mg, and two studies did not report the dose (16, 19) (**table I**).

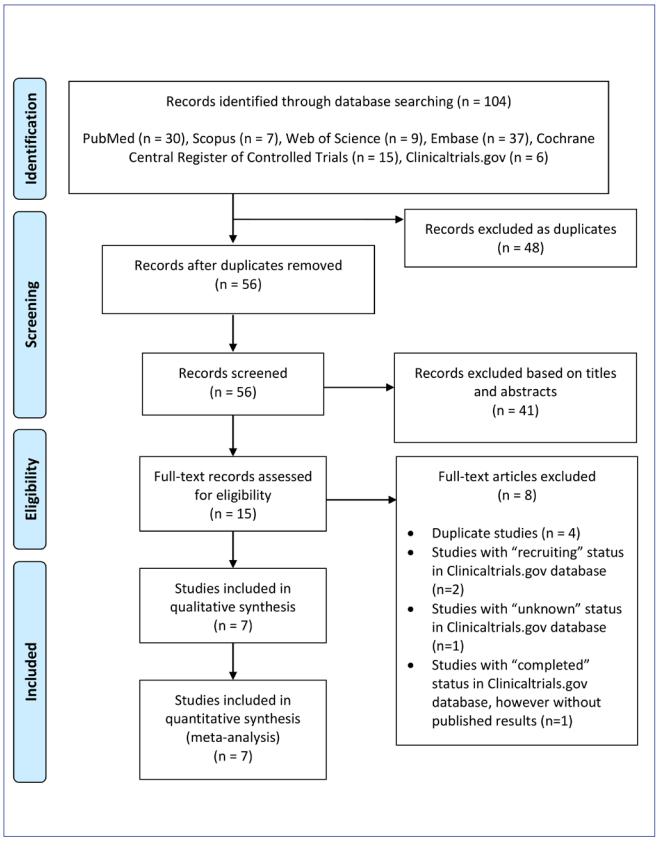

Figure 1. The PRISMA flowchart for literature search.

Table I. The baseline characteristics of the included studies.

Author	Year	Country	NCT identifier	Groups	n	Age in yr, mean (SD)	Gender (M/F), n	Details of intervention
Verdecchia	2020	USA	NCT03149887	Experimental	27	58.2 (7.2)	15/12	IBPB with bupivacaine/ropivacaine 0.5% (15-20 mL), in addition to intraoperative local infiltration with LB 266 mg diluted in 40 mL of saline to a total of 60 mL
				Control	27	56.2 (7.8)	15/12	IBPB with bupivacaine 0.5% (15-20 ml), in addition to intraoperative local infiltration of 60 mL of normal saline
Sethi	2019	USA	NCT03692546	Experimental	25	56.2	13/12	IBPB with bupivacaine 0.5% (20 mL) and 4 mg dexamethasone, in addition to intraoperative local infiltration with LB (20 mL; dose not reported) diluted in 40 mL of saline and injected into a triangular field block, 10 mL bolus into the suprascapular notch, and 3 mL injections into the muscle
				Control	25	59	14/11	IBPB with bupivacaine 0.5% (20 mL) and dexamethasone 4 mg
Baessler	2020	USA	NCT03822182	Experimental	26	57.5 (8.8)	12/14	IBPB with bupivacaine 0.5% (15 mL), LB 133 mg (10 mL), dexamethasone 4 mg, and normal saline 5 mL
				Control	26	59.1 (9)	15/11	IBPB with bupivacaine 0.5% (30 mL) and dexamethasone 4 mg
Shariat	2018	USA	NCT01977352	Experimental	20	55.1 (9.55)	9/11	IBPB with LB 88 mg (20 mL)
				Control	19	54.69 (9.45)	7/12	IBPB with bupivacaine 0.25% (20 mL)
Mandava	2020	USA	NCT03728946	Experimental	50	61.9	24/26	IBPB with LB (10 mL; dose not reported) and bupivacaine 0.5% (15 mL), in addition to intravenous dexamethasone 10 mg
				Control	50	58.3	27/23	IBPB with bupivacaine 0.5% (25 mL), in addition to intravenous dexamethasone 10 mg
Hillesheim	2021	USA	NR	Experimental	41	57.56 (7.97)	22/19	Periarticular injection of 20 mL of 1.3% LB (266 mg) mixed with 40 mL of 0.25% plain bupivacaine.
				Control	36	54.17 (8.63)	25/11	IBPB with 30 mL of 0.5% bupivacaine plus epinephrine and/or dexamethasone as per discretion of the treating anesthesiologist.
Flaherty	2022	USA	NCT03587584	Experimental	35	59.2 (11)	24/11	IBPB with 10 mL 0.5% bupivacaine plus 10 ml of 133 mg LB.
				Control	35	57.6 (8.8)	22/13	IBPB with 20 mL of 0.5% bupivacaine

F: female; IBPB: interscalene brachial plexus block; LB: liposomal bupivacaine; M: male; NCT: national clinical trial; S: sample size; SD: standard deviation; USA: United States of America; Yr: year

Risk of bias assessment of the included studies

Overall, three studies had overall low risk of bias for all domains (15, 18, 21). One study by Shariat *et al.* (17) had accessible results on clinicaltrials.gov, but was not published in full-text in a peer-reviewed journal. As no adequate details were available for this study (17), we judged the selection, performance, and detection bias domains as unclear risk. One study by Mandava *et al.* (19) assigned case-control status to enrolled patients using odd/even numbers of the last digit of the patient's medical record number; hence, we judged the selection and performance bias domains as high risk, due to improper randomization, allocation, and blinding of investigators. One study by Hillesheim *et al.* (20) was conducted as nonblinded, and we judged the performance bias domain as high risk. One study by Sethi *et al.* (16) randomized patients according to coin tossing with foreseeable assignment of the alternating participant; hence, we judged the allocation bias domain as high risk. The risk of bias summary is depicted in **figure 2**.

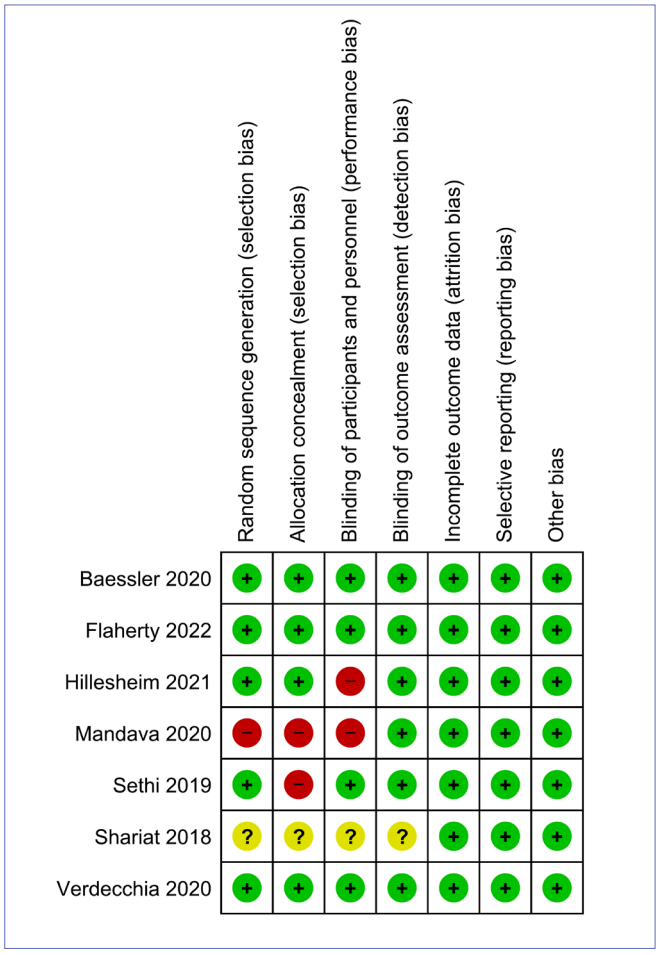

Figure 2. Risk of bias summary of the included studies.

Meta-analysis of the postoperative VAS pain scores

Using the random-effects model, the overall effect estimate revealed no significant difference between both groups (WMD = -0.56, 95% CI [-1.16, 0.04], p = 0.07). The pooled analysis was heterogeneous (I^2 = 94%, p < 0.001) (**figure 3**). Using the random-effects model, subgroup analyses according to the POD showed significantly reduced postoperative VAS pain scores in favor of the LB group *versus* control group on POD 1 (WMD = -1.34, 95% CI [-2.1, -0.59], p < 0.001) and POD 2 (WMD = -0.93, 95% CI [-1.3, -0.56], p < 0.001). However, there were no statistically significant differences between both groups on POD 0 (WMD = 0.24, 95% CI [-1.67, 2.16], p = 0.80), POD 3 (WMD = -0.54, 95% CI [-1.15, 0.07], p = 0.08), POD 4 (WMD = -0.22, 95% CI [-0.75, 0.30], p = 0.4), POD 5 (WMD = -0.18, 95% CI [-0.80, 0.44], p = 0.57), and POD 7 (WMD = -1.19, 95% CI [-0.84, 0.46], p = 0.56) (**figure 3**).

Meta-analysis of the postoperative opioid consumption

Using the random-effects model, the overall effect estimate revealed a significantly reduced postoperative opioid consumption in favor of the LB group *versus* control group (WMD = -7.72 MME, 95% CI [-11.48, -3.97], p < 0.001). The pooled analysis was heterogeneous (I^2 = 88%, p < 0.001) (**figure 4**). Using the random-effects model, subgroup analyses according to the POD showed significantly reduced postoperative opioid consumption in favor of the LB group *versus* control group on POD 1 (WMD = -11.48 MME, 95% CI [-18.57, -4.4], p < 0.001), POD 2 (WMD = -9.25 MME, 95% CI [-13.92, -4.59], p < 0.001), and POD 3 (WMD = -9.36 MME, 95% CI [-16.81, -1.92], p = 0.01). However, there were no statistically significant differences between both groups on POD 0 (WMD = 0.59 MME, 95% CI [-15.65, 16.83], p = 0.94), POD 4 (WMD = -7.67, 95% CI [-19.96, 4.61], p = 0.22), POD 5 (WMD = -7.84 MME, 95% CI [-22.69, 7], p = 0.3), and POD 7 (WMD = -0.09 MME, 95% CI [-4.72, 4.55], p = 0.97) (**figure 4**).

DISCUSSION

Summary of findings

This systematic review and meta-analysis aimed to summarize the clinical efficacy of LB compared with nonliposomal local anesthetic agents among orthopedic patients undergoing ARCR. We included seven relevant RCTs comprising 442 patients; 244 and 218 patients were assigned to LB and control group, respectively. Overall, from a statistical point of view, our findings showed that LB significantly reduced

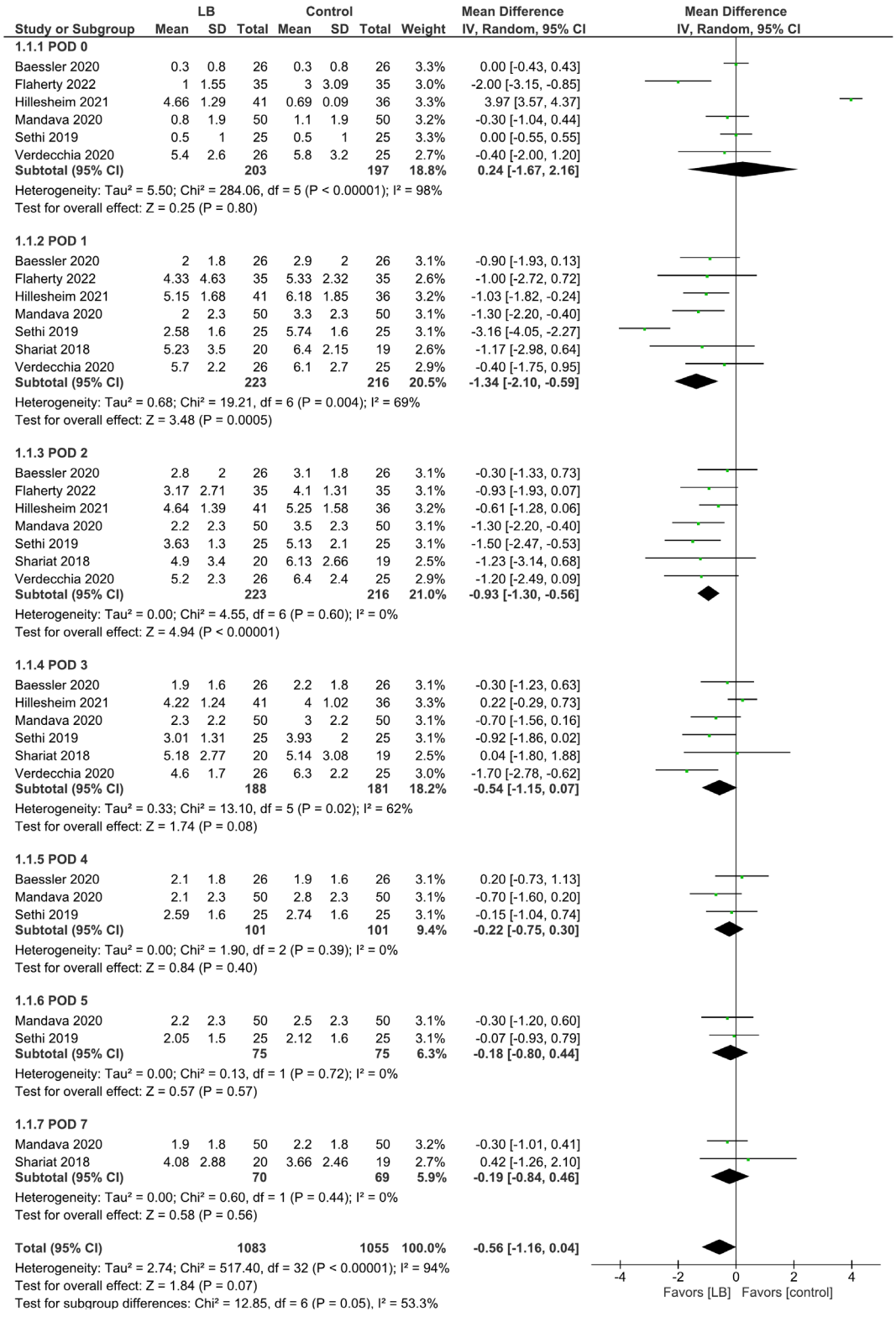

Figure 3. Meta-analysis of the VAS postoperative pain scores between LB and control groups.

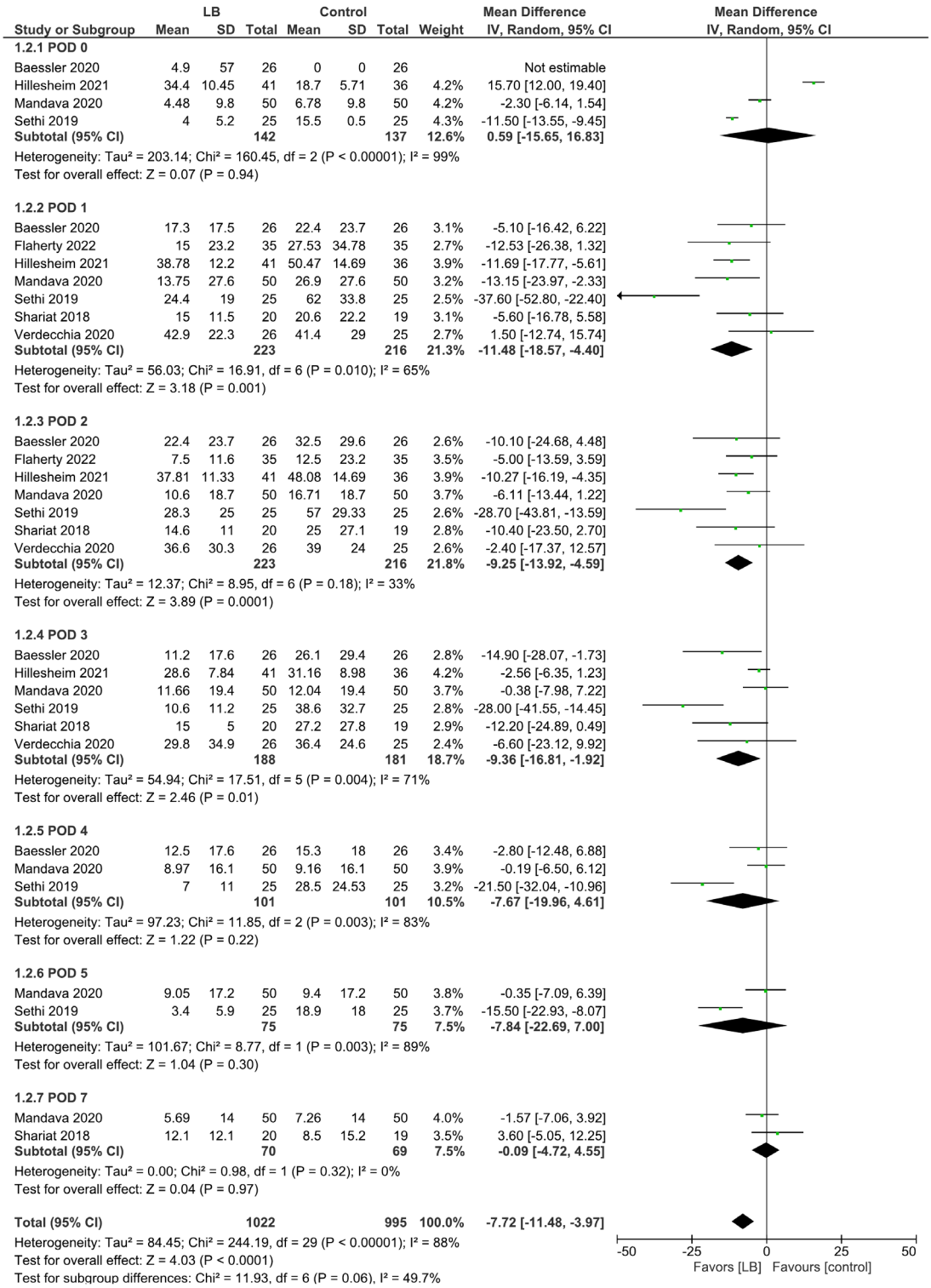

Figure 4. Meta-analysis of the postoperative opioid consumption between LB and control groups.

postoperative VAS pain scores and opioid consumption during the early POD time points.

Our meta-analysis revealed that the overall postoperative VAS pain score was not statistically significantly lower in favor of the LB group (WMD = -0.56, 95% CI [-1.16, 0.04], p = 0.07). Moreover, this difference was not clinically meaningful. For patients with rotator cuff injury, the minimal clinically important difference (MCID) in postoperative VAS pain score that is perceived as beneficial by patients is 1.4 (28). Only VAS pain scores on POD 1 (and nearly POD 2) attained this MCID in favor of the LB group. Thus, overall, our results suggest that administration of LB does not appear to offer clinically meaningful reduction in postoperative VAS pain scores when compared with nonliposomal local anesthetic agents. The most statistically and clinically significant reductions in postoperative VAS pain scores were attained in the study by Sethi *et al.* (16). This could be partially ascribed to the combined utility of IBPB with bupivacaine in addition to intraoperative local infiltration with LB targeting the suprascapular notch. The triangular field block technique used by Sethi *et al.* (16) has been previously delineated in early 1940s by Wertheim and Rovenstine (29). This technique advantageously numbs the branches of the suprascapular nerve, which supplies up to two-thirds (70%) of the sensory input to the glenohumeral joint, including the supraspinatus and infraspinatus muscles. According to this anatomical foundation, this technique has been advocated to provide adequate pain control, including equivalent analgesic effects to IBPB (30) during shoulder surgery (16). A recent RCT by Sayed *et al.* showed that the addition of suprascapular nerve block to intraarticular injection of steroids or hyaluronic acid resulted in enhanced analgesic effects among patients with adhesive capsulitis of the shoulder (31).

Narcotic medications are habitually administered, often in high quantities, to orthopedic patients undergoing ARCR (3) and this may possibly result in undesired chronic opioid dependence (32, 33). Therefore, pharmacological means to lessen pain burden on ARCR patients and decrease their opioid consumption and related toxicities would be clinically relevant. Our meta-analysis showed that LB significantly culminated in favorable opioid-sparing effects when compared with nonliposomal local anesthetic agents. Largely, LB reduced opioid consumption by 1-2 tablets of oxycodone 5 mg (7.5-15 MMEs) and this reduction in opioid ingestion does not seem to be clinically important and beneficial. In patients receiving IBPB with LB, Mandava *et al.* (19) reported significantly higher proportion of patients with opioid-free analgesics when compared with patients receiving IBPB with plain bupivacaine (44% *vs* 15%, p = 0.03). By POD 5, Sethi *et al.* (16) reported a similar trend in favor of the LB group compared with the control group (80% *vs* 12%, p < 0.001). Additionally, it must be noted that preoperative patient education on appropriate use of postoperative narcotics can further substantially decrease narcotic intake and dependence by patients following ARCR when compared with uneducated patients (34).

Clinical implications

ARCR procedures are often associated with painful perceptions in the postoperative period (35) and control of this pain is central to accelerate rehabilitation (7). Indeed, optimal postoperative analgesia is favorably linked to decreased postsurgical capsule retractions, adhesions, and intraarticular fibrous tissue depositions (7), all of which are aftermaths that may collectively result in undesired shoulder stiffness postoperatively (36).

A multimodal approach is endorsed to offer optimal pain control following total shoulder arthroplasties and ARCR procedures (5, 6). While single-shot IBPB with ropivacaine/bupivacaine provides adequate regional analgesia, however, its pain-free duration is disadvantageously restricted to less than 24 hours postoperatively (9-11). This phenomenon often culminates in the occurrence of early moderate-to-severe rebound pain (12) that necessities a sharp and excessive intake of opioids to control the intolerable perception of discomfort (3-5). Several mechanisms have been proposed to prolong the analgesic duration, such as the utility of adjuvant dexamethasone (37) and continuous indwelling catheter-based IBPB (38, 39). A recent meta-analysis of 33 RCTs revealed that perineural dexamethasone could only prolong IBPB by an average of 6-8 hours, extending the average total analgesic interval to a rough maximum of 30-32 hours only (40). On the other hand, although continuous indwelling catheter-based IBPB is effective, it has several drawbacks that limit its wider application, such as device-related infection, malfunction, and displacement, in addition to time-consuming and resource-intensive disadvantages (41, 42). Therefore, there is a pressing need to identify longer-acting and easy to administer analgesic agents that can produce sustained analgesia with smoother transition to the rebound pain after ARCR.

LB is an FDA-approved agent to provide postsurgical local (infiltration) and regional (peripheral nerve block) analgesia in adults (13). The physiochemical make up of LB allows the free bupivacaine to be slowly released over time, resulting in a hypothetically prolonged analgesic interval up to three days (14).

Comparison with previous meta-analyses

In the field of orthopedic surgery, LB has been used widely and several meta-analyses have explored its clinical utili-

ty. In patients undergoing total hip arthroplasty, Zhou *et al.* (43) conducted a meta-analysis comprising 13 studies (two RCTs and 11 retrospective studies) and concluded no clinical superiority of periarticular infiltration of LB over conventional local anesthetics with regard to various postoperative analgesic outcomes. Similarly, for patients undergoing total knee arthroplasty, Hussain *et al.* (44) conducted a meta-analysis comprising 17 RCTs and concluded no advantages of periarticular infiltration of LB over conventional local anesthetics with regard to postoperative opioid consumption and pain scores. Additionally, for patients undergoing total knee arthroplasty, Yayac *et al.* (45) conducted a meta-analysis of 15 studies (two RCTs and 13 retrospective observational studies) and concluded no tangible benefit of periarticular infiltration of LB over femoral nerve block with regard to postoperative opioid consumption and pain scores. Lastly, for patients undergoing orthopedic surgeries in general, Abildgaard *et al.* (46) conducted a meta-analysis comprising 27 RCTs and concluded no superior advantage of LB over nonliposomal anesthetic agents in terms of better pain relief and reduced opioid use. The lack of LB superiority was inclusive of both periarticular infiltration and peripheral nerve block when compared with the respective control nonliposomal anesthetic agents (46).

With regard to shoulder surgeries, among patients undergoing total shoulder arthroplasty, Sun *et al.* (47) conducted a meta-analysis comprising seven studies (four RCTs and three retrospective controlled studies) and concluded comparable benefits (in terms of pain control, opioid-sparring, and length of hospitalization) between LB-based infiltration *versus* IBPB. To date, five RCTs reliably and specifically evaluated the clinical utility of LB among patients undergoing ARCR. However, no meta-analysis up till now has been carried out to comprehensively summarize the evidence on the clinical benefit of LB among patients undergoing ARCR, and this is the novel driving force behind accomplishing our research.

Safety of LB was not extensively elaborated on by the meta-analyzed studies. Nevertheless, overall, LB appeared to be safe with comparable toxicological profile to the control group (16-18, 21).

Strengths and limitations

Our research has several strengths. Most substantially, this is the first systematic review and meta-analysis to amass evidence on the clinical utility of LB among patients undergoing ARCR. We conducted an up-to-date search and included only relevant RCTs to summarize high quality evidence. Additionally, we performed subgroup analyses according to the postoperative days (POD 0 to POD 7) for VAS pain scores and opioid consumption. That being said, our study is not without limitations. A key limitation includes the relative small number of meta-analyzed RCTs and their corresponding small sample size. Moreover, the perception of postoperative pain was subjectively self-reported and hence it could be liable to recall bias and underestimation/overestimation. Additionally, the included studies varied with regard to the method of LB administration (IBPB only *versus* IBPB plus intraoperative local infiltration) which could have influenced the summary results. Some VAS scores were underpowered as the overall effect sizes were pooled from only two studies.

Future research directions

Future research directions comprise figuring out the optimal dose and administration method of LB among patients undergoing ARCR. Additional prospective research enterprises include the potential synergetic 3-step combination of IBPB, suprascapular nerve block, and intraoperative local infiltration with LB *versus* plain bupivacaine.

CONCLUSIONS

Among patients undergoing ARCR, this systematic review and meta-analysis of RCTs showed that LB did not correlate with clinically meaningful reductions in postoperative VAS pain scores and overall opioid consumption. Future large-sized and well-designed RCTs are needed to consolidate the presented evidence.

FUNDINGS

None

DATA AVAILABILITY

All the data are available in the manuscript and derived from cited published studies.

CONTRIBUTIONS

SIA: conceptualization, design, literature review, data collection and analysis, draft. MFA, MYA, MAA, ASA: literature review, data collection, draft. MMA, SMA: study supervision, data validation, manuscript revision. All authors read and approved the final draft of the manuscript.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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