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Efficacy of liposomal bupivacaine *vs.* traditional anaesthetic infiltration for pain management in total hip arthroplasty: a systematic review and meta-analysis

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Abstract. – In this review, we assess the effectiveness of liposomal bupivacaine against the traditional bupivacaine infiltration in the postoperative management of total hip arthroplasty (THA). Various databases including PubMed Central, Medline, Scopus, Embase, Google Scholar, Cochrane library and ScienceDirect (inception date till August 2020) were searched. The quality of published trials was assessed using Cochrane risk of bias tool, and a random-effects model was used for meta-analysis. We report pooled Risk ratios (RR) or pooled Standardized Mean difference (SMD) with 95% confidence intervals (CIs). We analyzed a total of 13 studies with 62,582 participants. The majority of the studies were retrospective with lower bias risks. Liposomal bupivacaine was significantly associated with the reduction in opioid requirement at 48 hours (SMD = -0.25; 95% CI: -0.40 to -0.09; *p*=0.002) and length of hospital stay (SMD = -0.25; 95% CI: -0.43 to -0.07, *p*=0.006) following THA compared with the control group. However, there was no statistically significant difference between the effect of liposomal bupivacaine and other agents for pain score (24 and 48 hours), opioid requirement at 24 hours and incidence of nausea. Liposomal bupivacaine has selective benefits in terms of opioid consumption and length of hospital stay against the traditional bupivacaine among the patients undergoing THA.

Key Words:
Liposomal bupivacaine, Meta-analysis, Pain, Total hip arthroplasty.

Introduction

Total hip arthroplasty (THA) is a highly efficacious operative procedure for the patients having end-stage degenerative diseases of the hip joint[1,2]. It has been reported that more than 300,000 THAs were performed every year in the United States[3]. With the increase in number of surgeries, there is also a possibility of escalated burden of inappropriate postoperative management of pain associated with these surgeries. At present, no gold standard method available for the effective management of pain following the THA[4].

Postoperative multimodal analgesia for THA has shown to enhance patient satisfaction, reduce THA-associated adverse reactions and shorten postoperative hospital[5,6]. The local infiltration has been effective for management of postoperative pain in total knee arthroplasty patients[7]. Local infiltration is an easier procedure compared to the peripheral nerve block that does not weaken the lower limbs muscular strength[8]. However, the use of these traditional local anesthetic infiltrations can be limited by their shorter-lasting effect[9,10].

Liposomal bupivacaine formulation (EXPAREL) is a prolonged-release medication, usually indicated usually for the single-dose administration into surgical site for producing postoperative analgesia[11,12]. Liposomal bupivacaine alleviates significantly alleviates pain and improves the quality of outcomes in the postoperative THA management[3]. However, other reports have shown that the efficacy of liposomal bupivacaine in pain control is similar to traditional method and also increases the total cost of surgery for the THA patients[13]. The differences between the results in these studies may be explained by the limited sample sizes. The main goal of the current systematic review and meta-analysis is to investigate the effect of liposomal bupivacaine against the traditional bupivacaine infiltration in the postoperative management of THA.

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Materials and Methods

Inclusion Criteria

Included studies

Only prospective and retrospective studies, parallel-arm individual randomized, quasi randomized or cluster-randomized controlled trials (RCTs) were selected for the current review. We included full text or abstract publications, while excluded unpublished studies or data.

Study participants

Only studies carried out among patients who have undergone THA were included.

Type of intervention

We included the studies comparing the efficacy of liposomal bupivacaine with the traditional anaesthetic infiltration

Type of outcome measure

Studies disclosing the following outcome measures in both arms were included: pain score (24 and 48 hours post surgery), opioid medication requirement (24 and 48 hours post surgery), and adverse events (nausea).

Search Strategy

Comprehensive electronic search was performed in the following databases and search engines: Medline, Embase, PubMed Central, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, ScienceDirect, Google Scholar, ClinicalTrials.gov, and WHO International Clinical Trials Registry Platform (ICTRP). The MeSH and free-text terms used for the search were: "Bupivacaine", "Liposomal Bupivacaine" "Traditional Anesthetic Infiltration", "Pain", "Adverse Reaction", "Opioid", "Total Hip Arthroplasty" and "Randomized Controlled Trial" in various combinations. Time restriction for the search was from inception of the database till August 2020 and language was restricted to English. We have checked the list of references from the retrieved or selected articles and searched for the articles matching the eligibility criteria of our study.

Data Collection and Analysis

Selection of studies

Primary and secondary authors performed the literature search independently. Title and abstracts of the studies identified during their primary screening were further screened. Full-text articles that are relevant to our study objectives were then retrieved. Secondary screening of the full text articles was then independently carried out by the primary and secondary authors, and studies matching the eligibility criteria of our study were selected. Any disagreements were resolved during the selection procedure through consensus and consultation with the third author. We used the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist to report our findings[14].

Data extraction and management

Study data from the final included studies were extracted by the primary author, and included: general information (retrieval date, first author, year of publication); methodology details (study design and settings, study participants); participants selection details, (number of participants in each arm in total, inclusion/exclusion criteria, outcome measures at baseline and endline); reported interventions (intervention groups, comparison groups, duration of study follow up); study outcomes (primary and secondary outcomes reported, time of outcome assessment and other details essential for study quality assessment. Secondary author entered the data into the statistical software Review Manager (RevMan). Third author subsequently ensured correct data entry.

Risk of bias assessment in included studies

Risk of bias was independently assessed by primary and secondary authors for random sequence generation, allocation concealment, blinding (participants and outcome assessment), incomplete outcome data and selective reporting using the Cochrane risk of bias tool[15].Risk of bias was graded as low, high (information is inadequate) and unclear (missing information).

For non-RCTs, we used Cochrane risk of bias tool[15] to assess the risk of bias under the following domains: participants' selection criteria, confounding variables, intervention assessment, blinding (outcome), incomplete outcome data and selective outcome reporting.

Statistical Analysis

Continuous outcomes such as pain score and opioid requirement (at 24 and 48 hours) were expressed as the standardized mean difference (SMD), 95% Confidence interval (CI). It was calculated by using the mean and standard deviation reported at follow up or end line. Categorical out-

comes such as incidence of nausea were reported as pooled relative risk (RR) with 95% CI that was calculated using RevMan software to estimate the pooled effect size. Random effects model with inverse variance method was used for all studies[15].

Heterogeneity between studies was measured using chi square test and I^2 statistics, with $I^2 < 25\%$ considered mild, 25-75% moderate and $I^2 > 75\%$ substantial heterogeneity[15]. Results were graphically represented by forest plot. Publication bias was assessed using funnel plot.

Results

Selection of Studies

Systematic search was performed to identify the studies that compare liposomal bupivacaine with the traditional anesthetic infiltration for the management of patients with THA. In total, 674 citations were identified, during the primary screening of title and abstract (Figure 1). 79 relevant articles were retrieved and subjected to secondary screening by reviewing their full-text versions for the inclusion criteria. A total of 13 studies with 62,582 participants that satisfied the inclusion criteria were selected[3,13,16-26].

Characteristics of Included Studies

Characteristics of the selected studies are listed in Table I. All the studies were conducted in the United States except Chen et al[19] (conducted in Taiwan). Two selected studies were RCTs and 11 were retrospective studies. Out of 62,582 participants, 9,397 participants comprised the liposomal bupivacaine group and 53,185 participants comprised the control group. Sample sizes of both arms varied from 14 to 54,604. Sample size in the intervention group varied from 9 to 5,267 and from 5 to 49,337 in the control group. Follow-up period of the studies ranged from a minimum of 2 days to a maximum of 12 months. Study participants ranged in age from 52 to 72.3 years in the intervention group and 54 to 73 years in the control group. Out of 13 included, 6 reported on pain score after 24 hours of surgery, 6 studies on pain score after 48 hours, 8 studies on opioid requirement after 24 hours, 8 studies on opioid requirement after 48 hours, 11 studies on length of hospital stay and 4 studies on incidence of nausea.

Quality of Methodology

Risk of bias assessment is summarized in Tables IIA and IIB. All the included RCTs had low risk of bias in selection bias domains (random sequence generation and allocation concealment) and attrition bias domain such as incomplete outcome data. Majority of the studies had low risk of bias related to blinding (participants) and outcome assessment and selective reporting of outcome. All the included non-randomized studies had high risk of bias related to selection of participants, and five out of 11 studies had high risk of bias for confounding. All the studies had low risk of bias regarding intervention measurement and incomplete outcome data. However, the risk of

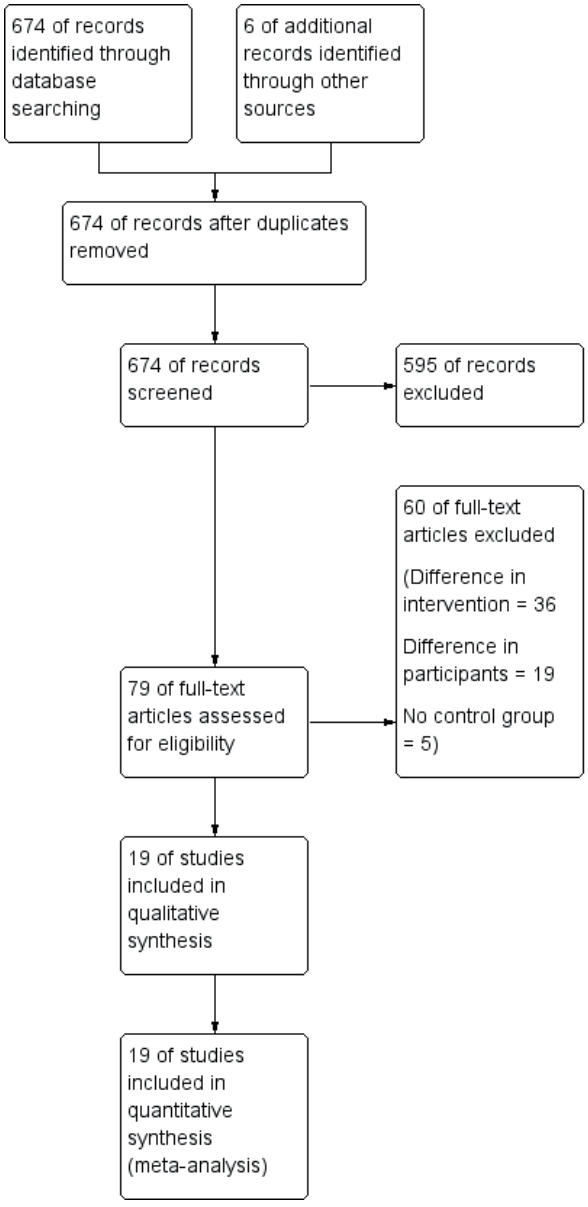

Figure 1. PRISMA flow chart showing the selection of studies for the current review (n=13).

Table I. Characteristics of the included studies, N=13.

S.No	Author and year	Country	Study Design	Sample size in Liposomal Bupivacaine group	Sample size in the control group	Dosage of Liposomal Bupivacaine	Follow up	Mean age of participants (Liposomal Bupivacaine group)	Mean age of participants in control group
	Asche 2017	United States	Retrospective	64	66	266 mg	2 days	67	71
	Asche 2019	United States	Retrospective	3576	3524	NA	3 months	72.3	73
	Beachler 2017	United States	Retrospective	29	40	NA	12 months	57.2	57
	Bradford 2019	United States	Retrospective	24	24	NA	5 days	60.7	60.5
	Chen 2010	Taiwan	Randomized controlled trial	45	46	NA	3 months	52	54
	Cherian 2016	United States	Retrospective	5267	49337	266 mg	Unclear	64.2	64.7
	Domb 2014	United States	Retrospective	27	30	266 mg	12 months	55.5	55.8
	Jacob 2017	United States	Retrospective	68	45	266 mg	3 days	62	62
	Perets 2017	United States	Randomized controlled trial	50	57	266 mg	2 months	61.9	62.4
	Rainville 2019	United States	Retrospective	70	103	NA	3 months	NA	NA
	Van Wagner 2018	United States	Retrospective	85	85	NA	3 days	66.4	64.2
	Yu 2016	United States	Retrospective	93	93	266 mg	Unclear	62.9	62.7
	Zamora 2019	United States	Retrospective	9	5	266 mg	Unclear	66	64

NA – Not Available

Table IIA. Risk of bias assessment for randomized studies, N=2.

S.No	Study	Random sequence generation	Allocation concealment	Blinding of the participants, outcome assessment	Incomplete outcome data	Selective reporting of outcome	Other risk of bias
1.	Chen 2010	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
2.	Perets 2017	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk

Table IIB. Risk of bias assessment for non-randomized studies, N=11.

S.No	Study	Selection of participants	Confounding variable	Intervention measurement	Blinding of the outcome assessment	Incomplete outcome data	Selective reporting of outcome
1.	Asche 2017	High risk	High risk	Low risk	Unclear risk	Low risk	Unclear risk
2.	Asche 2019	High risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk
3.	Beachler 2017	High risk	High risk	Low risk	Unclear risk	Low risk	Unclear risk
4.	Bradford 2019	High risk	High risk	Low risk	Unclear risk	Low risk	Unclear risk
5.	Cherian 2016	High risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk
6.	Domb 2014	High risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk
7.	Jacob 2017	High risk	High risk	Low risk	Unclear risk	Low risk	Unclear risk
8.	Rainville 2019	High risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk
9.	Van Wagner 2018	High risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk
10.	Yu 2016	High risk	High risk	Low risk	Unclear risk	Low risk	Unclear risk
11.	Zamora 2019	High risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk

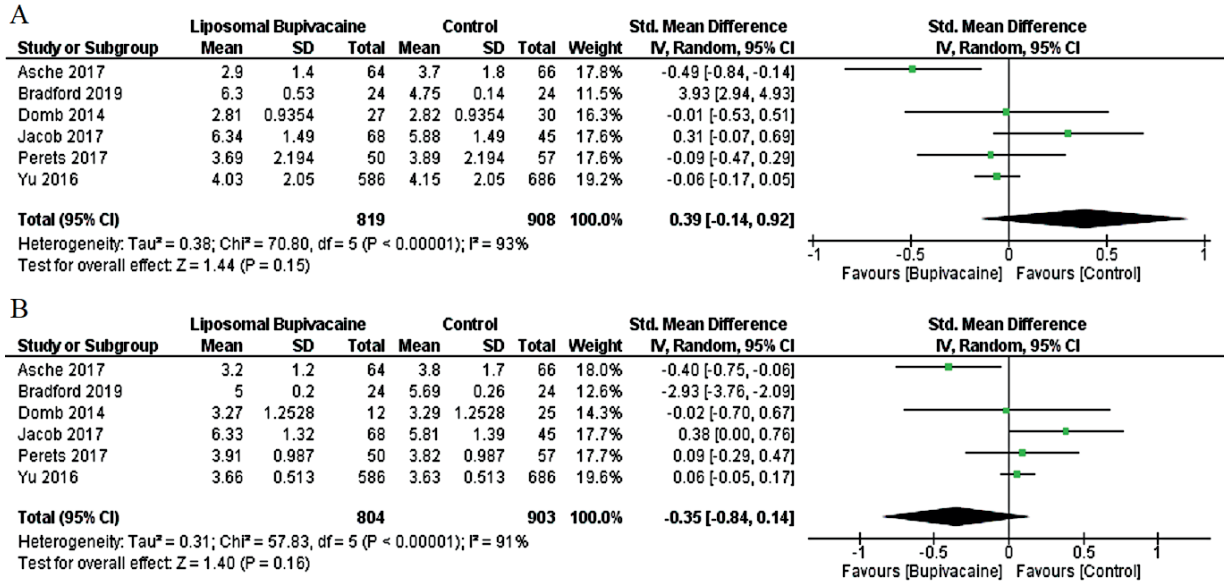

Figure 2. Forest plot showing the difference in pain score **A**) 24 hours following THA between liposomal bupivacaine and control groups (n=6); **B**) 48 hours following THA between liposomal bupivacaine and control groups (n=6).

bias for blinding of outcome assessment remained unclear

Efficacy of Liposomal Bupivacaine Against the Traditional Anesthetic Infiltration

Table III shows the effect of liposomal bupivacaine against the control group on pain score, opioid requirement, length of hospital stay and incidences of nausea.

Pain Score at 24 Hours Following THA

In total, 6 studies evaluated pain score at 24 hours following the THA. We found that the use of liposomal bupivacaine was not associated with the significant reduction of pain score at 24 hours compared to the control group (SMD = 0.39; 95% CI: -0.14 to 0.92, p=0.15) (Figure 2A). We found a statistically significant heterogeneity in the studies reporting pain scores at 24 hours (x^2=70.80, df=5, I^2=93%, p<0.001).

Pain Score at 48 Hours Following THA

In total, 6 studies evaluated pain score at 48 hours following the THA. Liposomal bupivacaine had no significant effect on pain reduction score at 48 hours as compared with the control group (SMD = -0.35; 95% CI: -0.84 to 0.14; p=0.16) (Figure 2B). We found a statistically significant heterogeneity in the studies reporting pain scores at 48 hours (x^2=57.83, df=5, I^2=91%, p<0.001).

Opioid Requirement at 24 Hours Following THA

A total of 8 studies evaluated opioid requirement at 24 hours following the THA. We found

Table III. Effect of liposomal bupivacaine against the control group with respect to pain score, opioid requirement, length of hospital stay and incidence of nausea.

Outcome	Number of studies pooled	Pooled ES# SMD (95% CI)	I^2	Figure
Pain score (at 24 hours)	6	-0.39 (-0.14 to 0.92)	93%	Figure 2A
Pain score (at 48 hours)	6	-0.35 (-0.84 to 0.14)	91%	Figure 2B
Opioid requirement (at 24 hours)	8	-0.23 (-0.54 to 0.07)	91%	Figure 3A
Opioid requirement (at 48 hours)	8	-0.25 (-0.40 to -0.09)	68%	Figure 3B
Length of hospital stay	11	-0.25 (-0.43 to -0.07)	95%	Figure 4
Incidence of nausea	4	RR = 1.26 (95%CI: 0.72-2.21)	22%	Figure 5

ES – Effect size; SMD – Standardized Mean Difference; RR – Relative risk; CI – Confidence Interval.

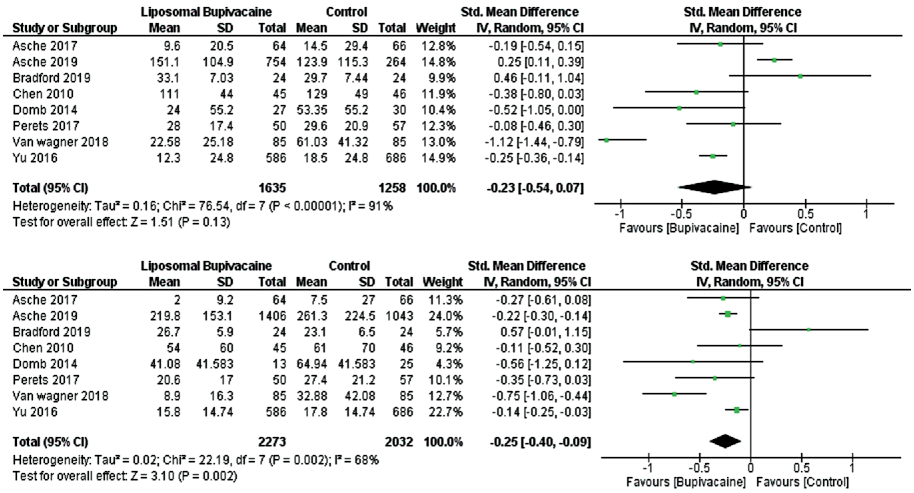

Figure 3. Forest plot showing the difference in opioid requirement **A**) 24 hours following THA between liposomal bupivacaine and control groups (n=8); **B**) 48 hours following THA between liposomal bupivacaine and control groups (n=8).

that the use of liposomal bupivacaine was not associated with the significant reduction in opioid requirement at 24 hours following THA compared with the control group (SMD = -0.23; 95% CI: -0.54 to 0.07); p=0.13) (Figure 3A). We found a statistically significant heterogeneity in the studies reporting the opioid requirement at 24 hours (x^2=76.54, df=7, I^2=91%, p<0.001).

Opioid Requirement at 48 Hours Following THA

In total, 8 studies evaluated opioid requirements at 48 hours following the THA. We found that liposomal bupivacaine use coincided with the significant reduction in opioid requirement at 48 hours following THA compared with the control group (SMD = -0.25; 95% CI: -0.40 to -0.09; p=0.002) (Figure 3B). We found a statistically significant heterogeneity in the studies reporting the opioid requirement at 24 hours (x^2=22.19, df=7, I^2=68%, p=0.002).

Length of Hospital Stay

Eleven studies evaluated length of hospital stay following the THA. We found that liposomal bupivacaine was associated with significant reduction in length of hospital stay (SMD = -0.25; 95% CI: -0.43 to -0.07, p=0.006 versus control group) (Figure 4). We found a statistically significant heterogeneity in the studies reporting length of hospital stay following THA (x^2=214.42, df=10, I^2=95%, p<0.001). We found a possibility of publication bias indicated by the asymmetrical funnel plot **(Supplementary Figure 1)**.

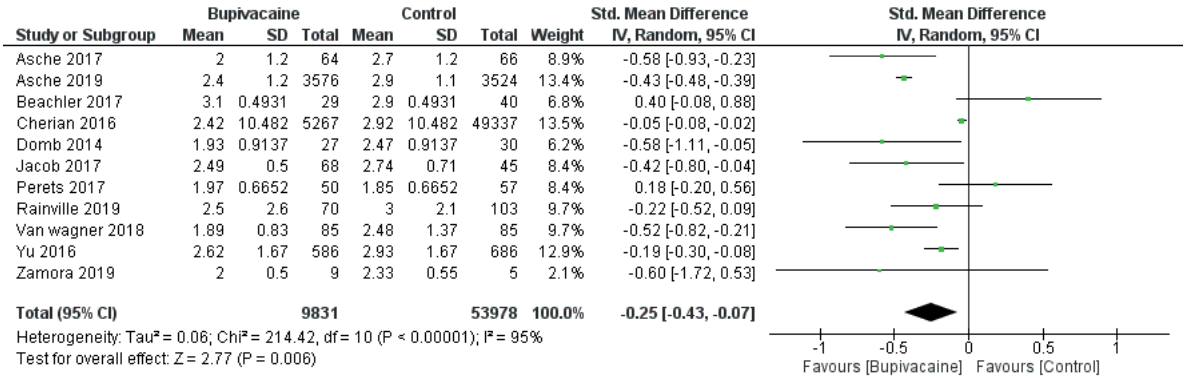

Figure 4. Forest plot showing the difference in length of hospital stay following THA between liposomal bupivacaine and control groups (n=11).

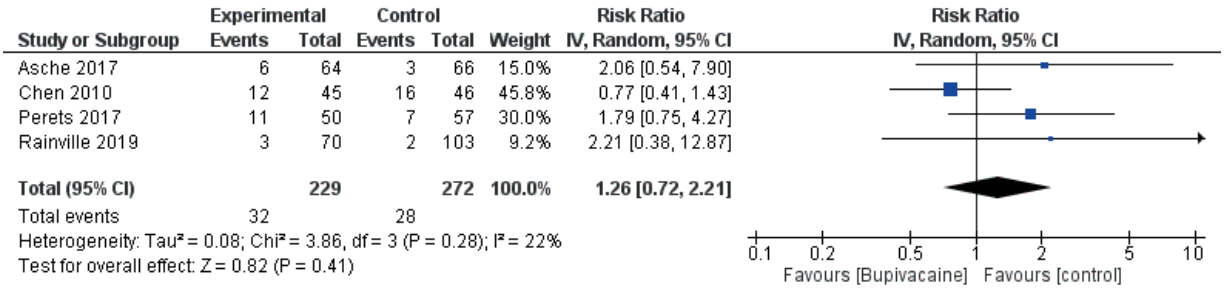

Figure 5. Forest plot showing the difference in incidence of nausea following THA between liposomal bupivacaine and control groups (n=4).

Incidence of Nausea

In total, 4 studies evaluated incidence of nausea following the THA. We did not detect statistically significant relation between liposomal bupivacaine administration and the reduction in incidence of nausea compared with the control group (RR = 1.26; 95% CI: 0.72-2.21; p=0.41) (Figure 5), with no significant heterogeneity between the studies (x^2=3.86, df=3, I^2=22%, p=0.28).

Discussion

THA is one of the most widely performed orthopedic procedures for end-stage osteoarthritis due to degenerative disease. Despite its benefits, THA is still accompanied by significant postoperative adverse events such as pain and nausea. Local infiltration analgesia, a mixture of long acting local anaesthetic agents in combination with non-steroid anti-inflammatory drugs, adrenaline, opioids, and/or steroids, is commonly used for pain management post-THA. One such agents is the liposomal bupivacaine, a long-lasting anesthetic consisting of lipid-based multivesicular particles. Previous reviews have showed mixed data on the efficacy of liposomal bupivacaine for pain and adverse effects management following THA[27,28]. The main goal of this review was to estimate the efficacy of liposomal bupivacaine in reducing the pain, length of hospital stay, opioid requirement and adverse reactions.

In all, we selected 13 studies with 62,582 participants for our meta-analysis, with most of the studies taking place in the United States. Only two studies were RCTs and the rest were retrospective studies. The majority of the included studies had overall low risk of bias. We found significant heterogeneity for all the outcomes in our review except incidence of nausea, hence a random effects model was used.

Liposomal bupivacaine showed significant effect on reducing the opioid medication requirement after 48 hours of THA and length of hospital stay following the surgery compared to traditional anesthetic infiltration. The opioid consumption is one of the important indicators for evaluation of post-THA analgesic effect. Although several analgesic methods were used to manage postoperative pain, the vast majority of them were not effective enough for satisfactory pain management. Liposomal bupivacaine is frequently used as an agent of choice to manage postoperative pain, as it provides an extended release into the peripheral tissues, and guarantees the progressive and sustained pain relief last as long as 3 days after a single infiltration[29,30]. However, we did not find any significant effect 24 hours following the surgery. The effect of liposomal bupivacaine became significant only 48 hours post THA. This might be due to the fact that the liposomal bupivacaine is released from liposomes slowly, limiting the concentration of the free agent at the site of surgery during the early postoperative period[31].

We did not find conclusive evidence that liposomal bupivacaine was beneficial for other assessed outcomes, especially pain score and nausea. This shows that the liposomal bupivacaine has selective benefits compared to the traditional anesthetic infiltration among patients undergoing THA. This finding is in agreement with previous reviews that reported selective benefits for the outcomes such as opioid requirement, length of hospital stay and incidence of nausea. However, there were mixed reports in terms of pain scores following surgery[27,28].

The major strength of our study is a broad search strategy that allowed us to gather all the relevant publications, and overall extensive literature search. Our research further contributes to the existing evidence on comparison of the liposomal bupivacaine with the traditional anesthetic

infiltration for the post-operative management of THA. Though similar reviews were conducted on this topic, we have added a greater number of studies and outcomes in our investigation.

Our study has certain limitations. Different perioperative pain management protocols have been used in all the included studies, contributing to the heterogeneity. Limitations of the included studies did not allow us to do subgroup analysis and meta-regression to assess other possible sources of heterogeneity. Most of the studies have used a dosage of 266 mg liposomal bupivacaine. However, there is no evidence that this dose is optimal for the full effect of the drug. We found a possibility of publication bias in our study. Since we only included papers comparing the effect of liposomal bupivacaine with the traditional bupivacaine, it is plausible that unpublished papers might influence the findings. Over half of the included studies were retrospective. It is possible that our results may be influenced by the potential participant's selection bias. Finally, the generalizability of our findings is limited, since the majority of the selected studies were performed in the United States.

The strengths of our work lie in the large number of studies analyzed in this review. Our analysis presents a comprehensive evidence on the efficacy of liposomal bupivacaine for THA which shall be able to guide clinicians involved in the direct management of these patients. Pooled analyses of pain scores, opioid consumption were carried out for different time periods to better elucidate the efficacy of liposomal bupivacaine for objective, as well as subjective outcomes. An important factor in selecting liposomal bupivacaine over traditional bupivacaine is the cost of the drug[11]. Based on current evidence on THA patients, routine use of liposomal bupivacaine cannot be recommended owing to limited benefits offered by the drug. Our study also has implications for future research. Data on the effectiveness and the optimal dose of traditional and liposomal bupivacaine are still inconsistent. Our work contributes to better understanding of the most optimal ways to manage postoperative THA patients by providing a reliable pooled estimate for the efficiency of anesthetics. However, since there have been no studies to check the optimal dose of liposomal bupivacaine, more RCTs or prospective studies with larger sample size are needed to strengthen the evidence for recommendations on how to best manage the THA patients postoperatively.

To summarize, liposomal bupivacaine has selective benefits in terms of opioid consumption and length of hospital stay against the traditional bupivacaine among the patients undergoing THA. However, RCTs or prospective investigation with larger numbers of participants are required to fully assess the effectiveness, optimal dose and postoperative management.

Author Contributions

SZ and ZW conceived and designed the study, SZ and BL collected data and performed data analysis. SZ wrote the draft of this manuscript. ZW edited the manuscript.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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