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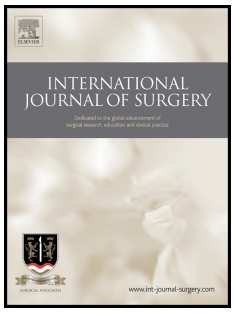

Comparison of peri-articular liposomal bupivacaine and standard bupivacaine for postsurgical analgesia in total knee arthroplasty: a systematic review and meta-analysis

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PII: S1743-9191(17)30134-6

DOI: 10.1016/j.ijsu.2017.02.011

Reference: IJSU 3550

To appear in: *International Journal of Surgery*

Received Date: 24 October 2016

Revised Date: 27 December 2016

Accepted Date: 8 February 2017

Please cite this article as: Wang X, Xiao L, Wang Z, Zhao G, Ma J, Comparison of peri-articular liposomal bupivacaine and standard bupivacaine for postsurgical analgesia in total knee arthroplasty: a systematic review and meta-analysis, *International Journal of Surgery* (2017), doi: 10.1016/j.ijsu.2017.02.011.

Comparison of liposomal bupivacaine and standard bupivacaine for postsurgical analgesia in total knee arthroplasty: a systematic review and meta-analysis

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Comparison of peri-articular liposomal bupivacaine and standard bupivacaine for postsurgical analgesia in total knee arthroplasty: a systematic review and meta-analysis

Abstract

Objective: This meta-analysis aimed to compare the efficacy and safety of intraoperative peri-articular liposomal bupivacaine and standard bupivacaine in patients undergoing total knee arthroplasty.

Methods: A systematic search was performed in Medline (1966 – 2016.9), PubMed (1966 – 2016.9), Embase (1980 – 2016.9), ScienceDirect (1985 – 2016.9) and the Cochrane Library. Only high-quality studies were selected. Meta-analysis was performed using Stata 11.0 software.

Results: Three randomized controlled trials (RCTs) and two non-randomized controlled trials (Non-RCTs), including 1214 patients met the inclusion criteria. The present meta-analysis indicated that there were significant differences between groups in terms of visual analogue scale (VAS) score at 24 h (SMD = -0.241, 95% CI: -0.374 to -0.108, P =0.000), VAS score at 48 h (SMD = -0.124, 95% CI: -0.256 to 0.009, P =0.0068), morphine equivalent consumption on POD 1 (SMD = -0.275, 95% CI: -0.398 to -0.153, P =0.000) and incidence of nausea (RD = 0.038, 95% CI: 0.001 to 0.074, P=0.042) and vomiting (RD = 0.38, 95% CI: 0.003 to 0.072, P =0.032).

Conclusion: Compared to standard bupivacaine, intraoperative peri-articular liposomal bupivacaine infiltration promotes superior pain relief and less morphine consumption after total knee arthroplasty. In addition, there were fewer side effects associated with liposomal bupivacaine infiltration.

Key words: liposomal bupivacaine, standard bupivacaine, total knee arthroplasty, pain control, meta-analysis

1. Introduction

Total knee arthroplasty (TKA) is a popular surgical procedure for treating end-stage osteoarthritis of the knee joint. It has been estimated that more than 700,000 of these procedures are performed in the United States annually [1]. However, TKA usually results in moderate to severe postoperative pain. Inadequate pain management is associated with delayed recovery, poor functional outcome and higher medical costs [2-4]. Moreover, additional opioids are required, which may cause adverse effects such as nausea, vomiting, respiratory depression and urinary retention [5, 6]. Postoperative pain control remains an interesting topic for surgeons. Many strategies have been used to control pain, including femoral nerve block, local infiltration, epidural morphine and adductor canal block [7, 8]. The optimal analgesia method remains controversial. Local infiltration analgesia has been considered the most common method due to its effectiveness and safety.

Bupivacaine, a local anaesthetic, is frequently used in TKA. However, even when multimodal analgesia is performed, the efficiency of bupivacaine is still limited due to the short duration of analgesia. Liposomal bupivacaine (LB) is a long-acting, local anaesthetic that is administered via single-dose infiltration to produce postsurgical analgesia. Bupivacaine is encapsulated into multivesicular liposomes, resulting in a slow and controlled release. To extend its analgesic effects, LB uses DepoFoam® as its mechanism of delivery; thus, bupivacaine can be released over 72 h [9]. Previously published studies have shown that LB infiltration can relieve postoperative pain and reduce morphine consumption [10, 11] Marcet assessed the effect of an opioid-sparing multimodal analgesia regimen with liposomal bupivacaine and compared these findings with the effects of standard of care on postsurgical opioid use They found that a liposome bupivacaine-based multimodal analgesic regimen resulted in statistically significant and clinically meaningful reductions in opioid consumption (mean, 20 mg versus 112 mg, $P<0.01$). Gorfine indicated that bupivacaine extended-release demonstrated a statistically significant reduction in

pain through 72 hours (141.8 vs 202.5, P < 0.0001), and it decreased opioid requirements (22.3 mg and 29.1 mg, P<0.0006) and improved patient satisfaction compared with placebo after haemorrhoidectomy.

However, some studies have reported that LB did not show analgesic effects that were superior to traditional local anaesthetics. Thus, we performed a systematic review and meta-analysis to compare the efficiency and safety of intraoperative peri-articular liposomal bupivacaine infiltration with that of standard bupivacaine for pain control in total knee arthroplasty.

2. Methods

2.1 Search strategy

We systematically searched electronic databases including Embase (1980 – 2016.9), MEDLINE (1966 – 2016.9), PubMed (1966 – 2016.9), ScienceDirect (1985 – 2016.9) , Web of Science (1950 – 2016.9) and the Cochrane Library for potentially relevant articles. Grey academic studies were also identified from the references of the identified studies. There was no language restriction. The following terms were used as key words in combination with the Boolean operators AND or OR: “Total knee replacement OR arthroplasty”, “Liposomal bupivacaine”, ‘‘bupivacaine’’ and “pain control’’. The retrieval process is presented in Fig 1.

2.2 Inclusion and exclusion criteria

Studies were considered eligible if they met the following criteria: 1) Published clinical randomized controlled trials (RCTs) or non- randomized controlled trials (non-RCTs); 2) Patients undergoing TKA surgery, where the experimental group received intraoperative peri-articular liposomal bupivacaine infiltration for postoperative analgesia and the control group received traditional bupivacaine infiltration; and 3) Surgical outcomes, including postoperative pain scores, morphine equivalent consumption, length of stay, and drug-related adverse effects, such as nausea and vomiting were reported. Studies were excluded from the meta-analysis if they had incomplete data or were case reports or review articles.

2.3 Selection criteria

Two reviewers independently reviewed the abstracts of the potential studies. After an initial

decision, the full text of the studies that potentially met the inclusion criteria were reviewed before a final decision was made. A senior reviewer was consulted in cases of disagreement.

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2.4 Data extraction

Two reviewers independently extracted the relevant data from the included studies. When incomplete data were encountered, the corresponding author was consulted. The following data were extracted: first author names, publication year, study design, comparable baseline, anaesthesia methods, dosage and type of anaesthetic drug and intervening procedures. Outcome parameters included postoperative pain scores at different periods; cumulative morphine equivalent consumption; length of stay; and drug-related adverse effects, such as nausea and vomiting. Other relevant data were also extracted from individual studies.

2.5 Quality assessment

The quality assessment of the included studies was performed independently by two reviewers. The modified Jadad score which was based on the Cochrane Handbook for Systematic Reviews of Interventions was used for the assessment of the RCTs. Studies with scores greater than four points were considered to be high-quality. We created a "risk of bias'' table that included the following key points: random sequence generation, allocation concealment, blinding, incomplete outcome data, free of selective reporting and other bias. The Methodological Index for Non-Randomized Studies (MINORS) scale, which assigns scores ranging from 0 to 24, was used to assess non-RCTs. Consensus was reached through discussion.

2.6 Data analysis and statistical methods

All calculations were completed in Stata 11.0 (The Cochrane Collaboration, Oxford, United Kingdom). Each outcome parameter was expressed using forest plots. Statistical heterogeneity was assessed based on the value of P and I^2 using a standard chi-square test. When $I^2 > 50\%$, $P<0.1$ was considered to indicate significant heterogeneity. A random-effects model was used in the meta-analysis. Otherwise, a fixed-effect model was utilized. If possible, a sensitivity analysis was performed to explore the origins of the heterogeneity. The results of any test with dichotomous outcomes were expressed as a risk difference (RD) with a 95% confidence interval (CI). For continuous outcomes, the mean difference (MD) or standard mean difference (SMD)

with a 95% confidence interval (CI) was used in the assessment.

3. Results

3.1 Search result

A total of 210 studies were preliminarily reviewed. By reading the title and abstracts, 205 reports were excluded from the current meta-analysis based on the inclusion criteria. No grey references were obtained. Finally, 3 RCTs [12-14] and 2 non-RCTs [15, 16] that had been published between 2012 and 2016 were enrolled in the present meta-analysis; the studies included 481 patients in the liposomal bupivacaine groups and 733 patients in the traditional bupivacaine groups.

3.2 Risk of bias assessment

Demographic characteristics and details about the included studies are summarized in Table 1. The modified Jadad score, which was based on the Cochrane Handbook for Systematic Reviews of Interventions was used for the assessment of RCTs (Table 2). All RCTs provided clear inclusion and exclusion criteria and suggested a methodology of randomization, and two [15-17] of them described randomization algorithm was generated from a computer. All of the studies [10, 17] stated that allocation concealment was achieved by sealed envelope. Double blinding was performed in all RCTs [16, 17]. Only one of the studies attempted to blind the assessors [10, 16, 17]. All RCTs reported complete outcome data. None of the studies performed intent–to-treatment analysis, and thus a potential risk of type Ⅱ statistical errors exists. Each risk of bias item is presented as the percentage across all included studies, which indicates the proportion of different levels of risk of bias for each item (Table 3). The MINORS scale was used to assess non-RCTs by assigning scores ranging from 0 to 24 (Table 4).

3.3 Study characteristics

The sample sizes of the included studies ranged from 59 to 597. All of the studies compared the efficiency and safety of intraoperative peri-articular liposomal bupivacaine infiltration with that of traditional bupivacaine for pain control in TKA. Experimental groups received LB

infiltration, while control groups received traditional bupivacaine. Three studies applied spinal anaesthesia and the remaining studies used general anaesthesia. All studies reported that preoperative oral medication was used for pain prevention, and the patient-controlled analgesia technique was performed for concomitant pain management. All of the studies reported the outcomes for at least 95 % of the patients. The follow-up period ranged from 3 to 6 weeks.

3.4 Outcomes of the meta-analysis

3.4.1 VAS score at 24 h

Four articles [12-14, 16] reported the outcomes of the VAS score at 24 h following TKA. There was no significant heterogeneity among the studies ($\chi2 = 7.69$, df = 3, $I^2 = 61\%$, P = 0.053), and thus a fixed-effects model was used. The pooled results demonstrated that the VAS score at 24 h in the control groups was significantly higher than that in the experimental groups (SMD = -0.241, 95% CI: -0.374 to -0.108, P = 0.000; Fig 2).

3.4.2 VAS score at 48 h

Four studies [12-14, 16] reported the outcomes of the VAS score at 48 h following TKA. There was no significant heterogeneity among the studies ($\chi2 = 1.62$, df = 3, $I^2 = 0\%$, P = 0.655), and thus a fixed-effects model was used. The pooled results demonstrated that there was a significant difference between groups regarding the VAS score at 48 h. (SMD = -0.124, 95% CI: -0.256 to 0.009, P = 0.0068; Fig 3).

3.4.3 VAS score at 72 h

Four studies [12-14, 16] reported the outcomes of the VAS score at 72 h following TKA. There was no significant heterogeneity among these studies ($\chi2 = 5.18$, df = 3, $I^2 = 42.1\%$, P = 0.159), and thus a fixed-effects model was used. The pooled results demonstrated that there was no significant difference between groups regarding the VAS score at 72 h (SMD = 0.007, 95% CI: -0.125 to 0.139, P =0.918; Fig 4).

3.4.4 Morphine equivalent consumption at POD 1

Morphine equivalent consumption at POD 1 was reported in four studies [12, 14-16]. No significant heterogeneity among these studies was observed, and thus a fixed-effects model was applied ($\chi 2$ = 1.21, df = 3, I2 = 0%, P =0. 751). The pooled results indicated that morphine equivalent consumption at POD 1 was significantly higher in the standard bupivacaine groups (SMD = -0.275, 95% CI: -0.398 to -0.153, P =0.000; Fig 5).

3.4.5 Morphine equivalent consumption at POD 2

Morphine equivalent consumption at POD 2 was provided in four studies [12, 14-16]. No significant heterogeneity among these studies was observed, and thus a fixed-effects model was used ($\chi 2$ = 4.07, df =3, I^2 =26.3%, P = 0.254). There was no significant difference between the two groups in terms of morphine equivalent consumption at POD 2 (SMD =0.059, 95% CI: -0.063 to 0.181, P=0.347; Fig 6).

3.4.6 Morphine equivalent consumption at POD 3

Morphine equivalent consumption at POD 3 was reported in four studies [12, 14-16]. There was no significant heterogeneity among the pooled data, and thus a fixed-effects model was used ($\chi 2$ = 4.81, df = 3, I^2 =37.6%, P = 0.186). There was no significance between the two groups in terms of morphine equivalent consumption at POD 3. (SMD = -0.08, 95% CI: -0.202 to 0.042, P=0.197; Fig 7).

3.4.7 Occurrence of nausea and vomiting at POD 1

The occurrence of nausea and vomiting was reported in five studies [12-16]. No significant heterogeneity among these studies was observed, and thus a fixed-effects model was used (nausea: $\chi 2$ = 3.48, df = 4, I^2 =0%, P = 0.481; vomiting: $\chi 2$ = 5.36, df = 4, I^2 =25.3%, P = 0.253). There was a significant difference between the two groups in terms of the incidence of nausea (RD = 0.038, 95% CI: 0.001 to 0.074, P=0.042; Fig 8) and vomiting (RD = 0.38, 95% CI: 0.003 to 0.072, P =0.032; Fig 8) at POD 1.

3.4.8 Occurrence of pruritus at POD 1

Postoperative pruritus was reported in five studies [12-16]. No significant heterogeneity among the studies was observed, and thus a fixed-effects model was used ($\chi 2 = 1.16$, df = 4, I^2 =0%, P = 0.885). There was no significant difference between the two groups in terms of the incidence of pruritus (RD = 0.023, 95% CI: -0.010 to 0.056, P=0.174; Fig 9).

4. Discussion

To the best of knowledge, this is the first systemic review and meta-analysis from published clinical trials to compare the effectiveness and safety of peri-articular liposomal bupivacaine infiltration with that of traditional bupivacaine for pain control in total knee arthroplasty. The most important finding of the present meta-analysis was that peri-articular liposomal bupivacaine infiltration could significantly decrease pain scores within 48h and reduce morphine equivalent consumption on the first day after TKA. Furthermore, there was a decreased risk of nausea and vomiting in the liposomal bupivacaine groups.

With the ageing population, the occurrence of knee osteoarthritis is increasing, and TKA is a popular treatment. However, pain control following TKA can be very challenging. Optimal analgesia may shorten hospital stays and result in decreased risks of deep vein thrombosis (DVT) and pulmonary embolism (PE). Furthermore, early rehabilitation exercise contributes to a satisfied sufficient functional recovery. Postoperative pain control is an interesting topic in orthopaedic surgery. Multiple perioperative pain management strategies have been implemented following TKA, including femoral nerve block, spinal analgesia, and periarticular or intra-articular injection of anaesthetics.

Periarticular administration has been performed for more than 10 years and was first introduced by Bianconi [17]. Since then, it has been widely used specifically in lower limb surgery for its ease of injection and lack of motor block [18, 19]. A single injection of bupivacaine, ropivacaine or a mixture is commonly used. However, traditional local anaesthetics have been criticized for their short-term analgesia and additional morphine consumption. Although bupivacaine is considered one of the longest-acting anaesthetics, a longer duration of analgesia is needed particularly for elderly individuals.

Liposomal bupivacaine, a long-acting local anaesthetic, has attracted great attention due to

its high efficiency and safety. It was approved by the US Food and Drug Administration for local injection into surgical sites. Several studies have shown sufficient measured outcomes following TKA. Barrington [20] reported that peri-articular liposomal bupivacaine infiltration results in postoperative pain control that is superior to that of femoral nerve block in TKA. Despite its promising potential, the difference in analgesic efficacy between liposomal bupivacaine and traditional bupivacaine remains controversial. Schroer showed that liposomal bupivacaine did not provide improved pain relief or lower narcotic use compared to standard bupivacaine. However, Alijanipour [12] reported that periarticular injection of liposomal bupivacaine did not result in a statistically significant improvement of pain scores. The present meta-analysis indicated that peri-articular liposomal bupivacaine infiltration had an analgesic effect that was superior to that of standard bupivacaine on PODs 1-2 after TKA. Theoretically, peri-articular LB should decrease the VAS at PODs 1-3. However, there is a discrepancy. The potential reasons for this discrepancy are as follows: VAS would be reduced starting on the first day following TKA. On POD 3, both groups showed a decrease to a lower baseline, although we detected a tendency toward reduced VAS in POD 3 in the LB groups. However, there was no significant difference. Indeed, the LB analgesia still took effect. Furthermore, the various doses of LB and the small number of included studies also affected the results. Thus, long-term studies with high-quality RCTs are needed.

Patients who undergo TKA usually suffer from moderate to severe postoperative pain. Additional opioids, including oral and patient-controlled analgesia (PCA) administration were applied as concomitant pain control. Opioid consumption is considered an objective method to measure pain. Several studies have reported that peri-articular liposomal bupivacaine infiltration is associated with a reduction in opioid consumption, resulting in fewer adverse effects, such as nausea, vomiting, respiratory depression and pruritus [9, 21, 22]. In addition to the side effects described above, drug dependence is also an important issue that should be considered. Minimizing opioid consumption would potentially achieve a better physical outcome [23]. The present meta-analysis indicated that there was decreased morphine equivalent consumption in the LB groups compared to controls on POD 1. However, no significant difference was found between the groups in terms of morphine equivalent consumption on POD 2 and 3.

Postoperative pain that results in additional morphine consumption would lead to being bedridden long, which would increase the risk of rehabilitation delay and the occurrence of

thrombotic events. Multiple factors would affect the length of stay following total knee arthroplasty; for instance, body mass index, age, American Society of Anaesthesiologists status and postoperative complications [22] . In the present meta-analysis, no statistical significance in the length of hospital stay between the treatment groups was identified.

Nausea and vomiting are common side effects that are frequently associated with oral or intravenous morphine. Sufficient anaesthetic techniques can reduce opioid consumption and subsequently decrease the risk of complications. The present meta-analysis indicated that compared to standard bupivacaine, peri-articular liposomal bupivacaine infiltration could significantly reduce the occurrence of nausea and vomiting on POD 1. Only five studies were included in our meta-analysis, and thus we did not perform investigation on dose-dependence. Large sample sizes from quality RCTs are needed to confirm the safety of peri-articular liposomal bupivacaine infiltration.

There are some limitations to the current meta-analysis that should be noted. (1) Only five studies were included in the present meta-analysis; although all of these studies were recently published, the sample size was relatively small; (2) Functional outcome is an important parameter; due to the insufficiency of relevant data, we failed to perform a meta-analysis of functional outcomes. (3) Doses of anaesthetics were varied, and the concomitant pain management regimes differed from each other, which may affect the results of the meta-analysis; (4) The duration of follow-up was relatively short, which led to an underestimation of complications. (5) Publication bias in present meta-analysis may affect the results. (6) We only assessed the efficiency and safety of LIA in TKA; multimodal methods of analgesia, including LIA with adrenalin and NSAIDs or LIA combined femoral nerve block should be taken into consideration in subsequent studies to explore the optimal analgesia regime.

Despite the limitations above, this is the first meta-analysis of recently published studies to compare the effectiveness and safety of intraoperative peri-articular liposomal bupivacaine infiltration with that of traditional bupivacaine for pain control in total knee arthroplasty. Higher quality RCTs are needed to explore the functional outcome of the knees and other adverse effects.

5. Conclusion

Compared to standard bupivacaine, intraoperative peri-articular liposomal bupivacaine infiltration promotes superior pain relief and less morphine consumption after total knee arthroplasty. In addition, there were fewer side effects associated with liposomal bupivacaine infiltration.

Conflicts of interest

The authors declare that they have no competing interests.

Authors' contributions

XW and ZYW conceived of the design of the study. LX GHZ performed and collected the data and contributed to the design of the study. JBM finished the manuscript. All authors read and approved the final manuscript.

Acknowledgments

None

Figure length

Reference

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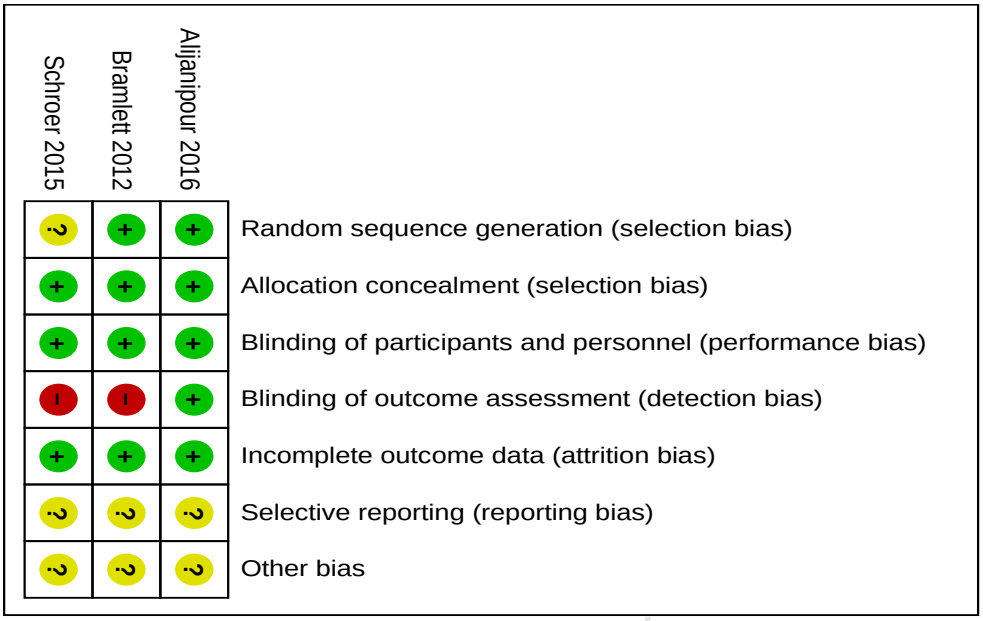
Studies	Cases (LB/TB)	Mean age (LB/TB)	Female patient (LB/TB)	Anesthesia	Drug dose of LB	Drug dose of TB	Concomitant Pain Management	Outcome Neutral	Outcome Beneficial
Bramlett 2012 [13]	25/34	61.1/62.2	12/23	general anesthesia	20ml(266mg) LB	60ml (150mg) TB HCl	IV ketorolac 30mg, ketoprofen 100 mg, or diclofenac 75 mg	VSA 48-72	VAS 24
Schroer 2015 [14]	58/53	67/68.6	34/32	spinal anesthesia	20ml (266mg) LB mixed 30ml(75mg) TB	60ml (150mg) TB	400 mg celecoxib, 20 mg oxycontin, and a 6 mg scopolamine patch topically	VAS 24	VSA 48-72 MC POD 1-3
Kenes 2015 [15]	67/262	68/67.4	47/203	general anesthesia	20ml (266mg) LB	5% TB in 400ml, 4 mL/hr	Morphine equivalents	MC POD 2-3	MC POD 1
Alijanipour 2016 [12]	59/59	64.3/64.9	30/32	spinal anesthesia	20ml (266mg) LB with 40 mL of sterile normal saline and 0.5 mL epinephrine	20ml (50 mg) TB	975mg oral acetaminophen,400mg celecoxib, and 75mg pregabalin	MC POD3	VSA 24-72 MC POD 1-2
Sporer 2016 [16]	272/325	63.4/65	168/202	spinal anesthesia	20ml (266mg) LB	30 ml 0.25% TB combined femoral nerve block	Celecoxib, Oxycodone, and transdermal scopolamine.	VSA 72 MC POD 2-3	VSA 24-48 MC POD 1

Table 1 Trials characteristics

LB: liposomal bupivacaine, TB: traditional bupivacaine, IV: intravenous, VAS: visual analogue scale, MC: morphing consumption

Table 2 Methodological quality of the randomized controlled trials



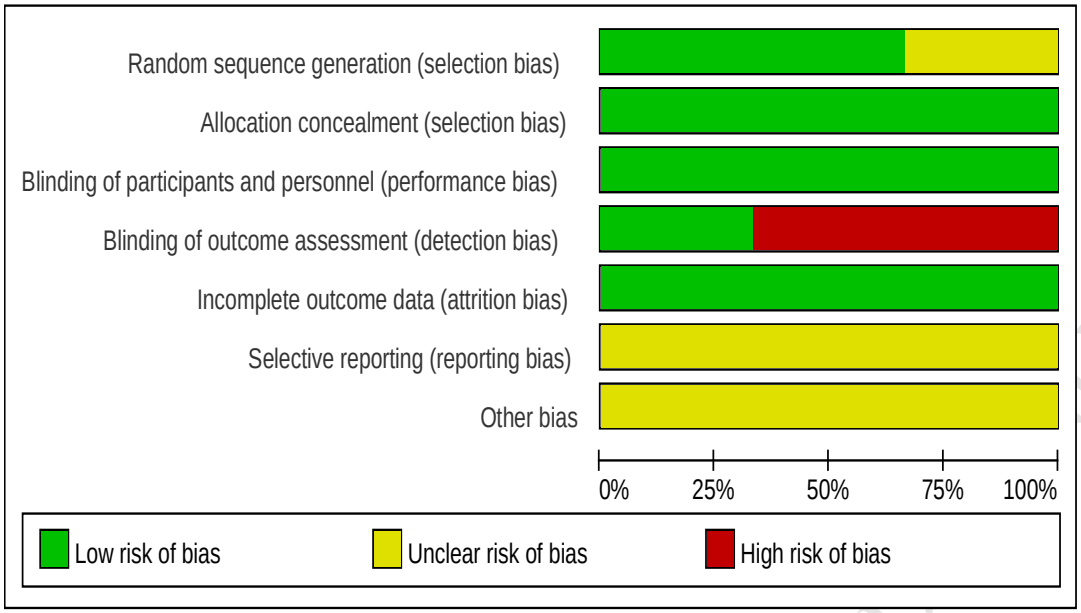


Table 3. Risk of bias

Quality assessment for non-randomized trials	Kenes 2015	Sporer 2016
A clearly stated aim	2	2
Inclusion of consecutive patients	2	2
Prospective data collection	2	2
Endpoints appropriate to the aim of the study	2	2
Unbiased assessment of the study endpoint	0	0
A follow-up period appropriate to the aims of study	2	2
Less than 5 % loss to follow-up	2	2
Prospective calculation of the sample size	0	2
An adequate control group	2	2
Contemporary groups	0	1
Baseline equivalence of groups	2	2
Adequate statistical analyses	2	2
Total score	18	21

Table 4 Methodological quality of the non-randomized controlled trials

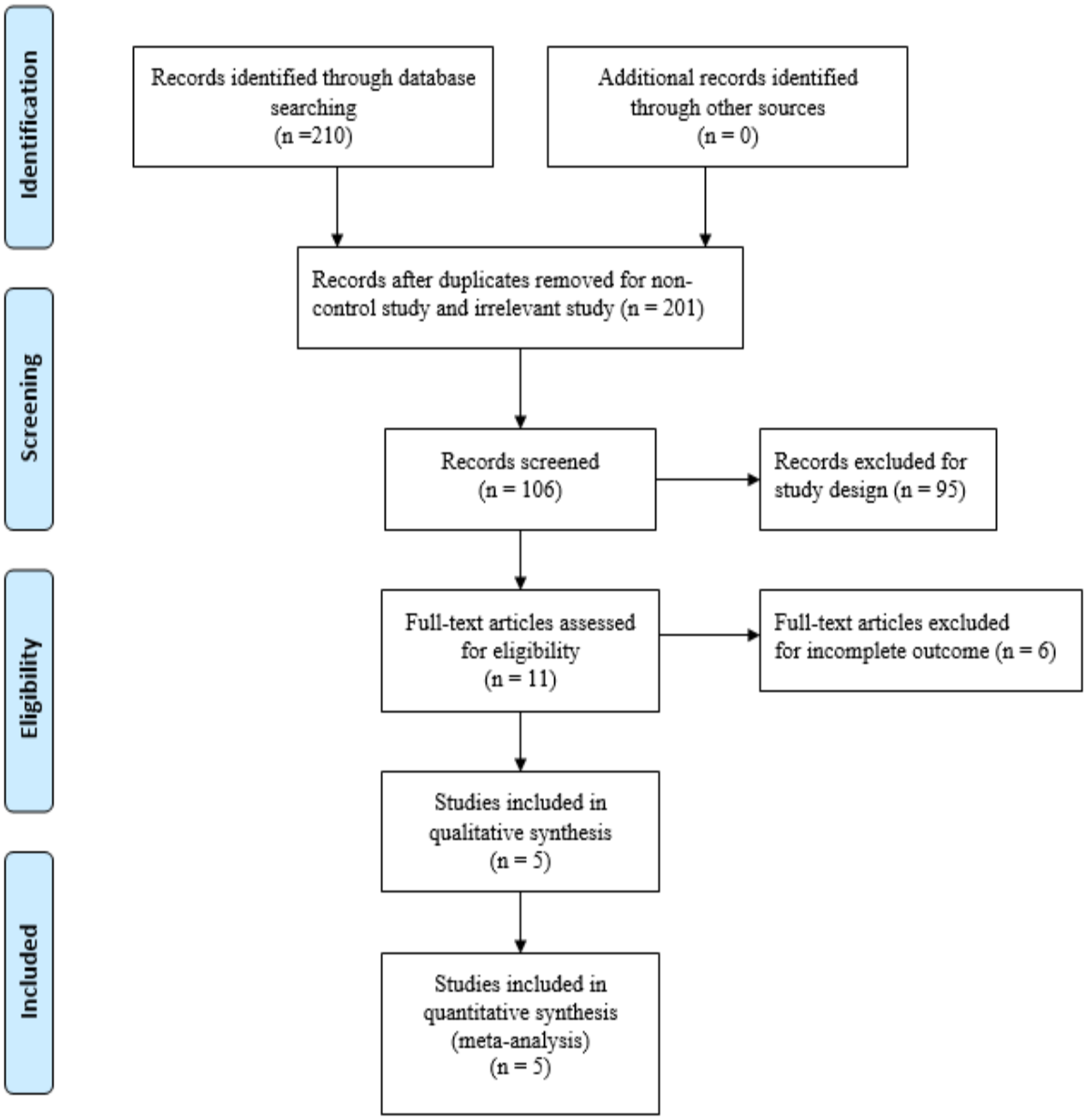


Fig. 1 Search results and the selection procedure

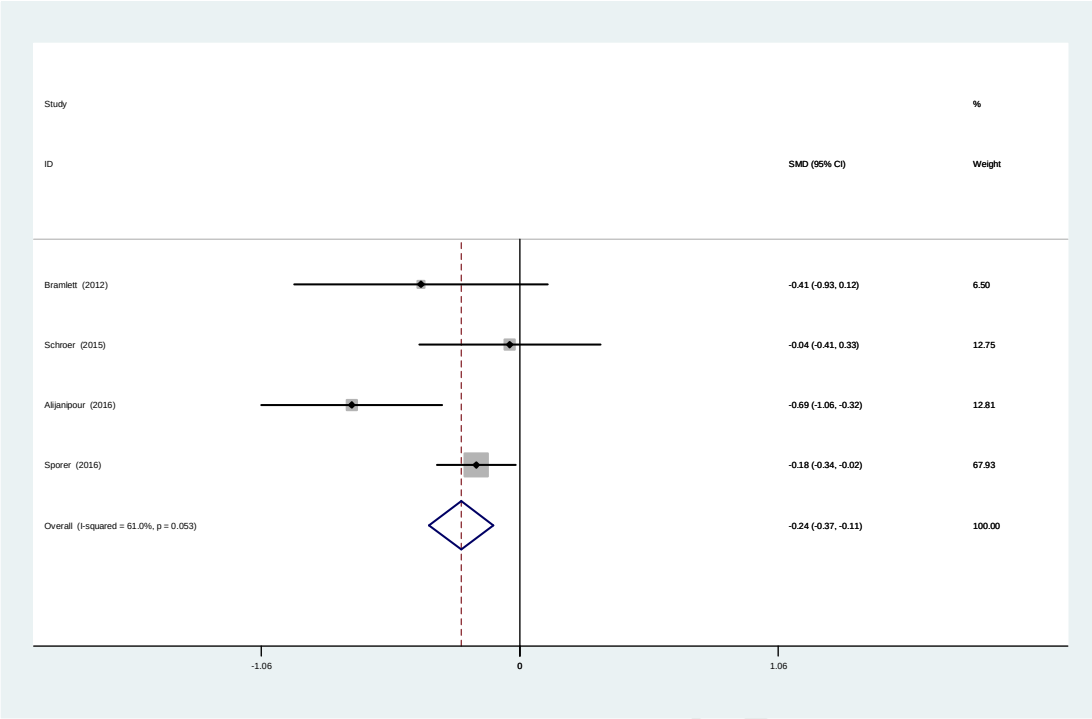


Fig. 2 Forest plot diagram showing postoperative pain scores at 24 hours following TKA

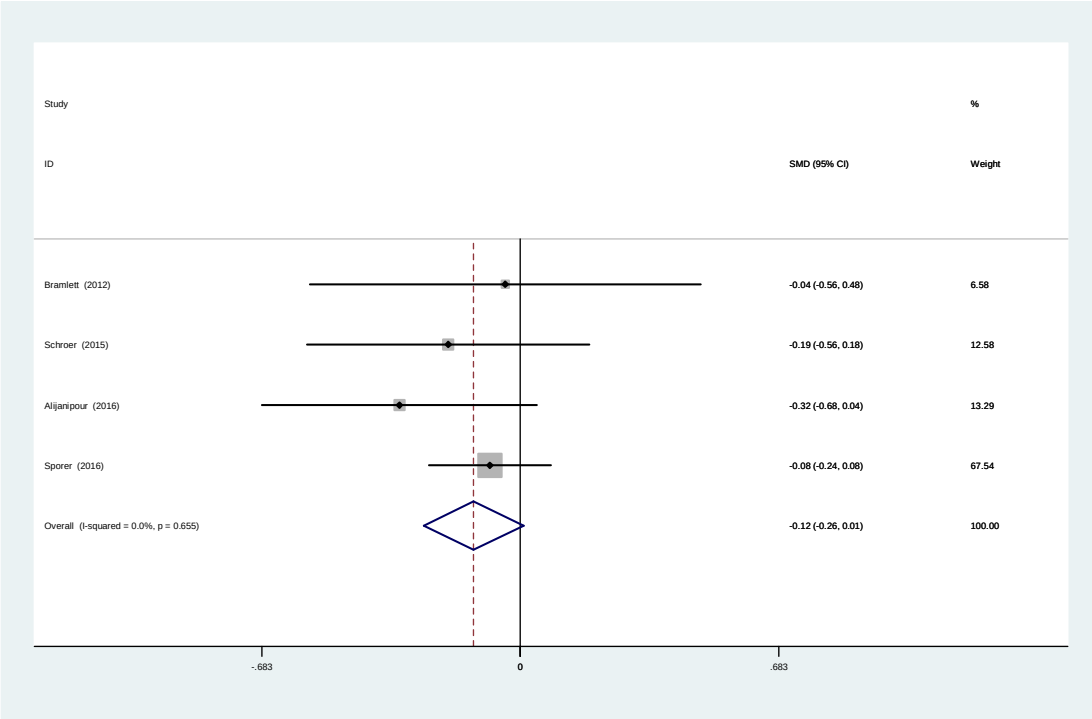


Fig. 3 Forest plot diagram showing postoperative pain scores at 48 hours following TKA

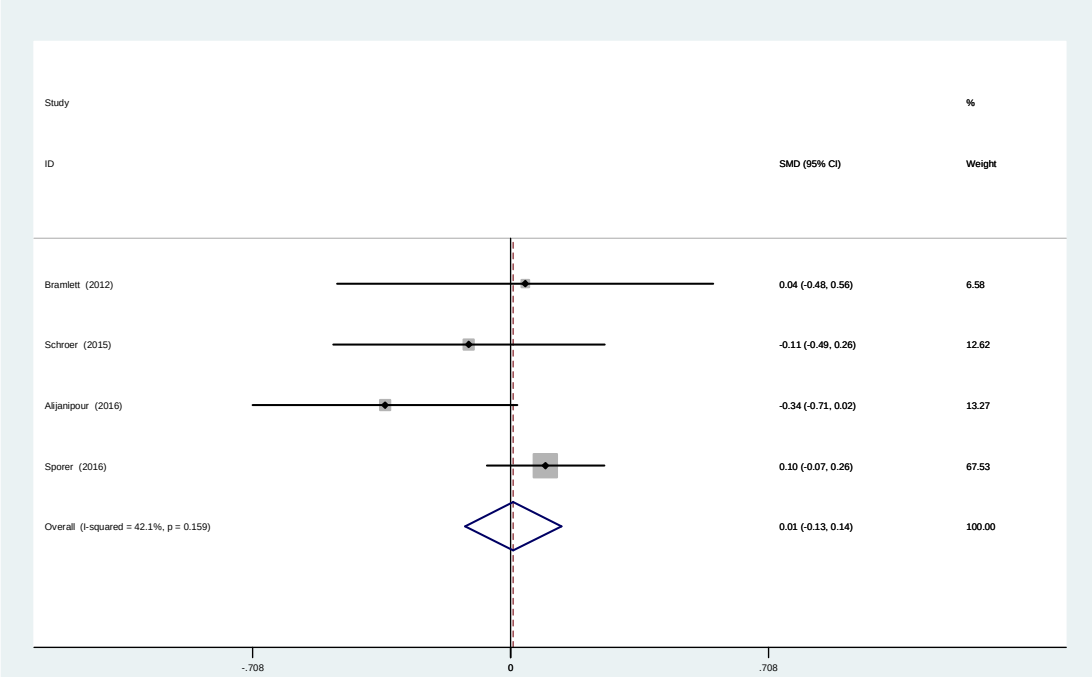


Fig. 4 Forest plot diagram showing postoperative pain scores at 72 hours following TKA

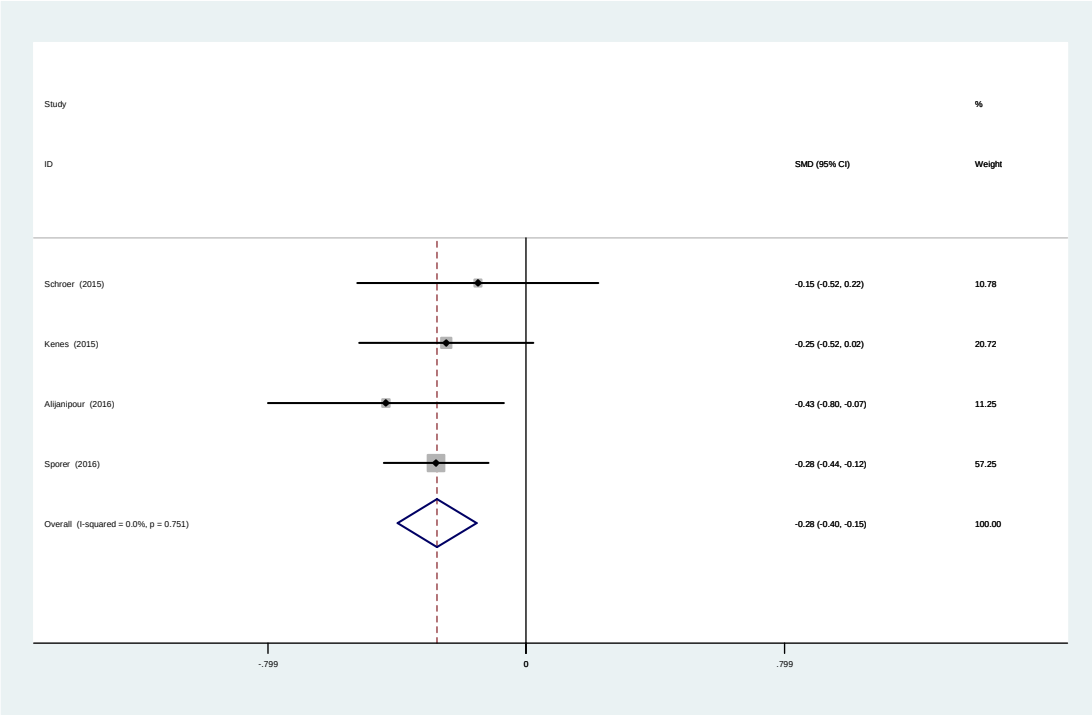


Fig. 5 Forest plot diagram showing morphine equivalent consumption at POD 1

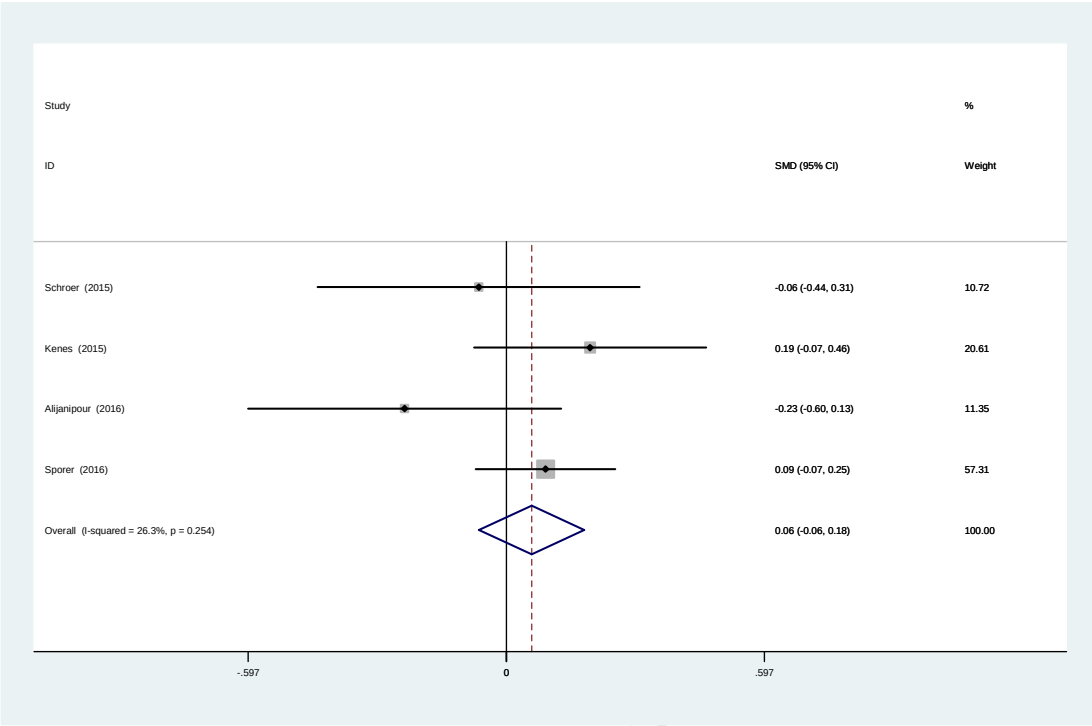


Fig. 6 Forest plot diagram showing morphine equivalent consumption at POD 2

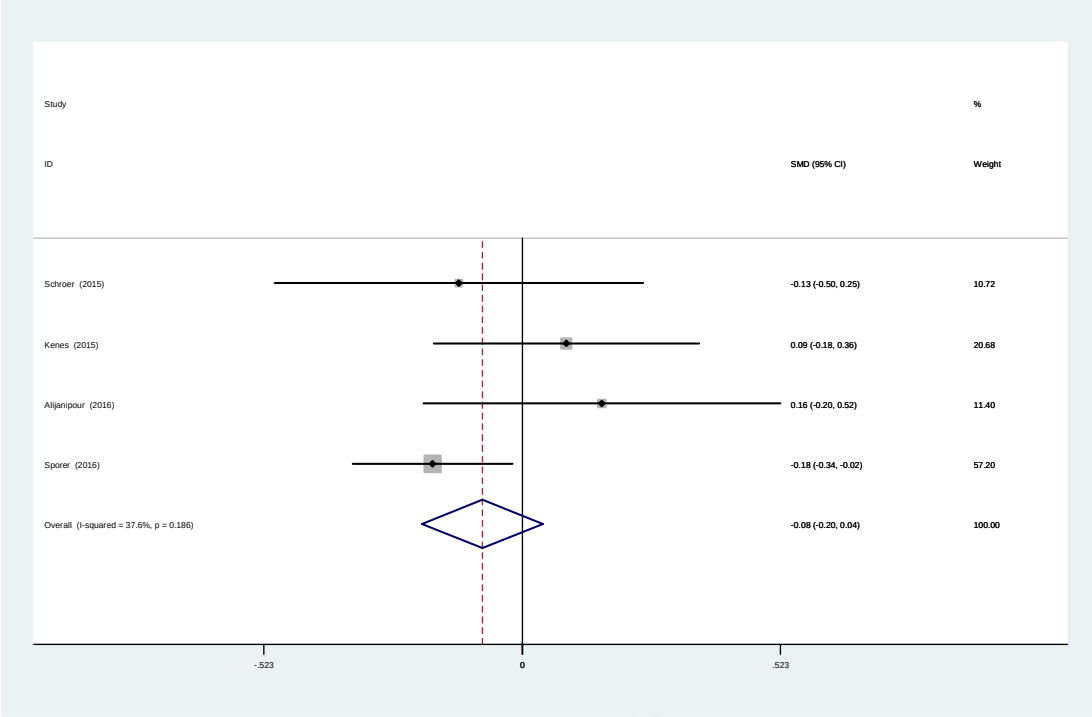


Fig. 7 Forest plot diagram showing morphine equivalent consumption at POD 3

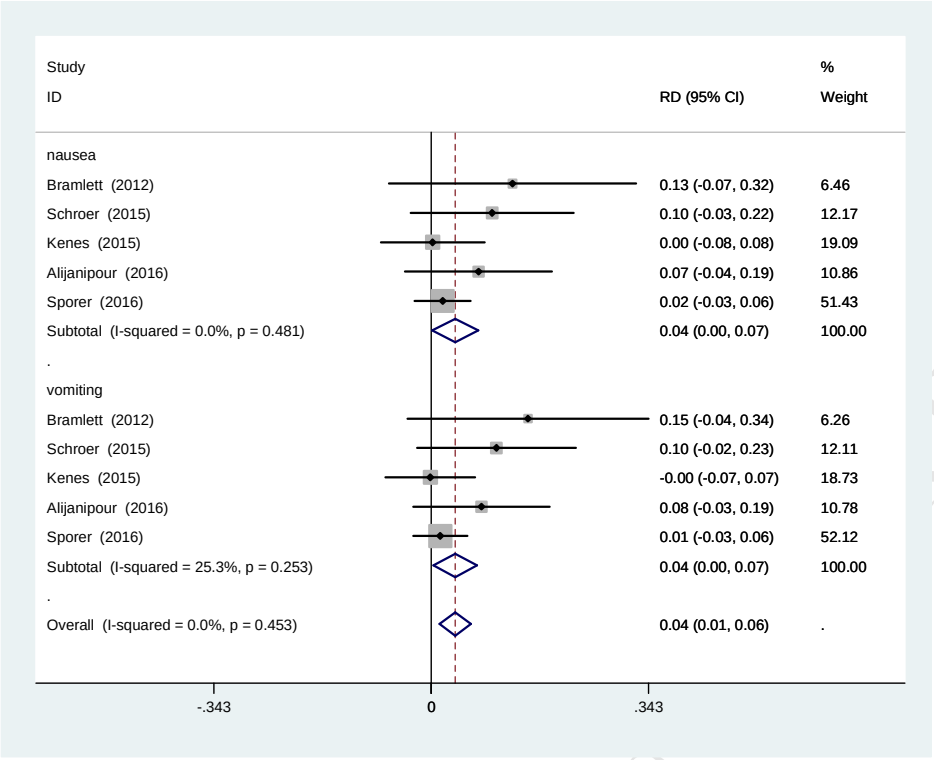


Fig. 8 Forest plot diagram showing incidence of nausea and vomiting at POD 1

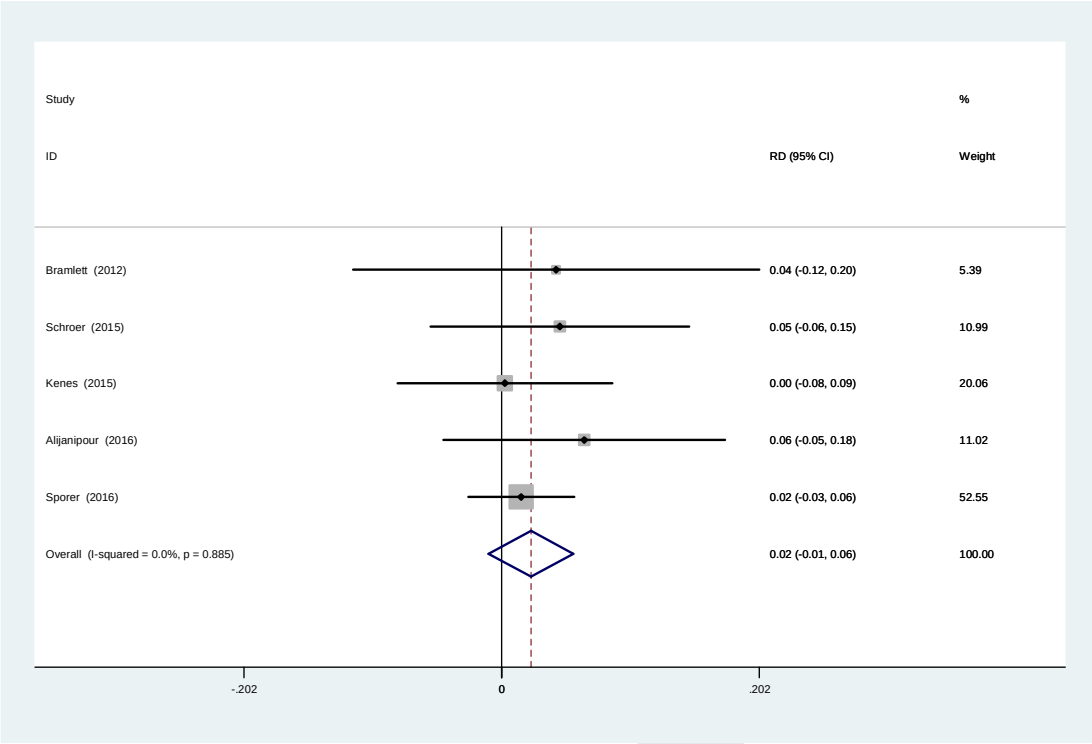


Fig. 9 Forest plot diagram showing incidence of pruritus at POD 1

1. To investigate the efficacy and safety between liposomal bupivacaine and standard bupivacaine in patients undergoing total knee arthroplasty.

2. Only high quality studies were selected.

3. Liposomal bupivacaine infiltration provides superior pain relief and less morphine consumption compared standard bupivacaine in total knee arthroplasty.