

## Review Article

# Local anaesthetic wound infiltration used for caesarean section pain relief: a meta-analysis

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**Abstract:** Purpose: Local anaesthetic wound infiltration techniques were reported to reduce opiate requirements and pain scores in women undergoing caesarean section (CS). However, the results were conflicting. The primary aim of this meta-analysis was to assess whether local analgesia could reduce pain intensity when injected via wound catheters. Methods: A search of randomized clinical trials (RCTs) evaluating local analgesia in caesarean surgery in PubMed, EMBASE and the Cochrane database was performed. Cumulative morphine consumption and pain scores at rest at different time point after surgery were extracted and synthesized using random or fixed model for meta-analysis. Subgroup analysis was performed according to incision type and administration regimen. Results: Nine RCTs with a total of 512 patients were included. Cumulative morphine consumption was lower in LA group compared with placebo group in the first 12 h (SMD = -0.736, 95% CI (-1.105, -0.368)), 24 h (SMD = -0.378, 95% CI (-0.624, -0.132)) and 48 h after surgery (SMD = -0.913, 95% CI (-1.683 to -0.143)). Lower morphine consumption was observed in the first 6 h after surgery but the reduction failed to meet the common level of significance. Pain scores was significantly reduced at 12 h but not 6 h after surgery in the LA group compared with placebo group. At 24 h and 48 h after surgery, the pain score was lower but the difference did not meet the common level of significance. Lower rate of post-operative nausea was observed in the LA group. Conclusions: Local anaesthetic wound infiltration can reduce morphine requirements and the rate of patients suffer nausea but not pain scores after caesarean section. Further procedure-specific RCTs were encouraged to confirm the efficacy of local anaesthetic wound infiltration techniques.

**Keywords:** Local anaesthetic wound infiltration, caesarean section, meta-analysis

## Introduction

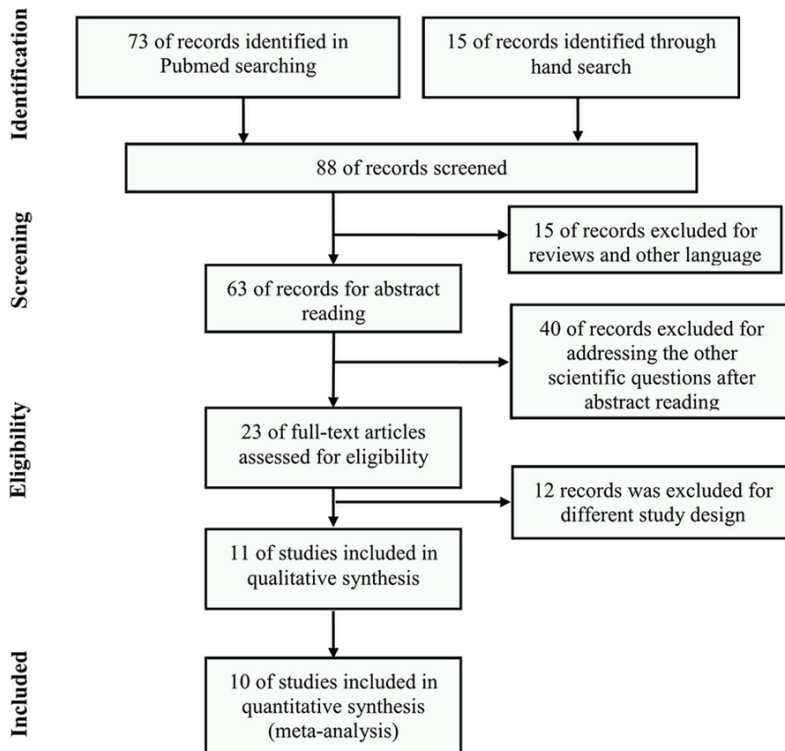
Caesarean section is the most widely performed obstetric procedure [1]. Postoperative pain is one of the greatest concerns during and after caesarean delivery [2]. Caesarean section commonly induces moderate to severe pain lasting 48 hours after surgery, and poor pain control in the post-operative period can lead to the failure to take care of the newborn soon after delivery, chronic pain syndromes and poor quality of life [3].

Currently, opioids are commonly used for relief of postoperative pain after caesarean section, either by intrathecal administration prior to section or postoperative parenteral administration [4]. But the usage of opioids are associated

with many undesirable side effects such as drowsiness, nausea and vomiting [5]. Thereafter, there are needs for alternative analgesic drugs to reduce the amount of opioids [6]. Local anesthetics (LA) are injected via catheters placed in surgical wounds for post-operative analgesia to provide analgesia by both single shot and continuous infiltration.

However, the use of local anaesthetic wound infiltration for alleviating post-operative pain has been studied in past decades with conflicting reports and scholars hold distinctly different views towards this issue [7, 8]. Two major endpoints to assess the efficacy of LA wound infiltration are the decrease of opioids use and pain score relief. Some studies indicated that wound infusion with LA for post-caesarean section

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**Figure 1.** A flow diagram of the studies identified and included is shown. RCT, randomized-controlled trial.

analgesia was effective in reducing opioid consumption [9-11]. On the contrary there are also studies with similar design demonstrated no significant reduction in opioid requirements [12]. However, most published studies indicated there was not a significant improvement in reduced pain scores [13].

A previous meta-analysis summarized the results of 3 studies in applying LA infiltration to patients underwent Gynecological surgeries [14], but the result was still gauge. As more articles published, we intended to test the efficacy of LA infiltration in patients underwent CS by comparing the cumulative opioid consumption and the pain score from 4 h to 48 h after surgery.

### Methods

#### Publication search

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search was carried out including the following databases: PubMed, EMBASE

and the Cochrane database covering the period from 1966 to November 2014. The search strategy included the following key words: "postoperative pain" OR "postoperative analgesia", "local anesthetics", "continuous" OR "infusion" OR "perfusion," OR "irrigation" OR "instillation", "Caesarean section", "Caesarean delivery". A manual search of the reference lists from selected articles was also carried out to further increase the number of publications with relevant data.

#### Criteria for inclusion and exclusion

The inclusion criteria were (a) randomized, controlled trials; (b) continuous infiltration by catheters or intermittent injections or continuous infusions with LA and postoperative pain after caesarean delivery. (c) sufficient published data for estimating, and (e) article was either in English or Chinese.

Exclusion criteria were studies that (a) did not have a control group; (b) single injection of a LA through a wound catheter; (c) comparing LA with other means of analgesia (for example, epidural analgesia); (d) without a proper control group (an active substance or a combination of drugs); (e) intra- or extra-pleural catheters, mediastinal catheters, intra-abdominal catheters for drug. Reviews and repeated literatures were excluded.

In the searching period, 73 records were included in the Pubmed and Embase. And 15 articles were found through hand search of the citations of included articles. Sixty-six articles remained after removal of repeated literatures and article in other languages. We screened the remaining 66 articles and found that 40 of these studies focused on other means of drug delivery. In the remaining 23 studies for qualitative analysis, 12 articles were of a different study designs and excluded thereafter. One article failed to be eligible for quantitative syn-

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**Table 1.** Characteristics of eligible studies

No.	First Author	Cases	OQS	Sites of placement	Method of injection	Intervention	NRS Score	Morphine consumption	LA drug
1	Trotter TN, et al. 1991	14+14	5	Over the fascia	Single injection	0.5% bupivacaine; Saline	NA	Lower consumption at 12 h and 24 h	Morphine
2	Fredman B, et al. 2000	25+25	5	Over the fascia	Intermittent	0.2% ropivacaine; Sterile water	Lower pain at 3, 4 and 5 h	Lower consumption during 0-6 h	Morphine
3	Givens VA, et al. 2002	20+16	5	Over the fascia	Continuous; Bolus 25 ml	0.25% bupivacaine; Saline	No difference	Lower consumption during 0-48 h	Morphine
4	Lavand'homme PM, et al. 2007	30+30	5	Over the fascia	Intermittent	0.2% ropivacaine; Saline	Lower pain 12 h	Lower consumption	Morphine
5	Mecklem DW, et al. 1995	35+35	5	Below the fascia; Beneath the rectus sheath	Intermittent	0.25% bupivacaine; Saline	Lower pain 18-24 h	Lower consumption during 0-4 h and 18-24 h	Morphine
6	Zohar, et al. 2006	30+30	5	Over the fascia	Intermittent	0.25% bupivacaine; Saline (+i.v. diclofenac)	No difference	Higher consumption	Morphine
7	Anthony AB, et al. 2008	50+50	5	All layers of abdominal wall and the peritoneum	Single injection	0.75% ropivacaine; Saline	Lower pain during 15 min-24 h	Lower consumption during 1-24 h	Pethidine
8	Kainu JP, et al. 2012	22+20	5	Below the fascia	Intermittent; Bolus 20 ml	0.375% ropivacaine; Saline	No difference	Lower consumption 6, 9, 12 h	Oxycodone
9	Pavy T, et al. 2012	20+20	5	Over the fascia	Single injection	0.5% bupivacaine; Saline	No difference	NA	codeine phosphate +paracetamol
10	Reinikainen M, et al. 2014	33+34	5	Over the fascia	Continuous; Bolus 10 ml	0.75% ropivacaine; Saline	No difference	Lower consumption at first 6 h; but not 6-48 h.	Oxycodone

**Table 2.** Main Results of meta-analysis of cumulative morphine consumption and pain score

No.	Outcome	Time Span/Time epoch	No. of studies	No. of patients	Model	Test of association		Test of heterogeneity		
						SMD (95% CI)	P-value	chi-squared	P-value	I <sup>2</sup>
1	Morphine consumption	0-6 hours	3	177	Random	-0.816 (-1.779, 0.148)	0.097	18.44	<0.001	89.2%
2	Morphine consumption	0-12 hours	3	124	Fixed	-0.613 (-0.977, -0.249)	0.001	3.41	0.182	41.4%
3	Morphine consumption	0-24 hours	5	265	Random	-0.487 (-0.735, -0.240)	0.000	11.85	0.018	66.2%
4	Morphine consumption	0-48 hours	5	275	Random	-0.913 (-1.683, -0.143)	0.020	35.31	<0.001	88.7%
5	Pain Score	4 h	4	237	Random	0.255 (-0.503, 1.013)	0.510	23.12	<0.001	87.0%
6	Pain Score	12 h	4	191	Random	-0.647 (-1.263, -0.031)	0.039	12.29	0.006	75.6%
7	Pain Score	24 h	7	370	Fixed	-0.139 (-0.344, 0.066)	0.185	6.68	0.351	10.2%
8	Pain Score	48 h	6	273	Random	-0.092 (-0.332, 0.148)	0.453	9.89	0.079	49.4%

thesis because of insufficient data for meta-analysis. The final meta-analysis included 512 cases in 9 studies (**Figure 1**).

### *Assessment of quality*

Included reports were read and scored independently by two authors using the Oxford quality score, a three-item, quality scale score from 1 to 5 to assess the adequacy of randomization and blinding [15]. Discrepancies in the scoring were resolved by discussion.

### *Data extraction*

Data were independently abstracted by two investigators using a standard protocol and data-collection form in accordance to the criteria stated above and checked by the others. The following information of included studies was extracted using a standardized data collection protocol (**Tables 1** and **2**): the first author, year of publication, number of cases and controls in the trials, sites of the catheters placed, method of injection, intervention, numeric rating score (NRS) or visual analogue score (VAS), main result of the studies. Data were extracted to the closest single decimal place in the graph, when it was presented in the form of a histogram. When reports present data as median and range, the mean was approximated by the median while the SD was calculated as: maximum-minimum/4. Similarly, when data were presented as inter-quartile range (IQR), SD was calculated as IQR (range)/2.

### *Statistical analysis*

Homogeneity was tested using Cochran's Q-test to determine if there was statistically significant heterogeneity across studies. Cochran's Q-statistic follows a distribution with  $(k-1)$  degrees of freedom, where  $k$  is the number of studies. We applied tests of heterogeneity between trials, if appropriate, using the  $I^2$  statistic.  $I^2$  is equivalent to the quantity of Cochran's Q minus its degrees of freedom divided by Cochran's Q, or  $I^2 = (Q-df)/Q$ . The value of  $I^2$  ranges between 0% and 100%, where 0% indicates no observed heterogeneity and larger values indicate increasing heterogeneity [16]. In the event of significant heterogeneity, we used a random-effects meta-analysis as an overall summary if appropriate. Sensitivity analysis was performed to assess the stability of the results by excluding each and every study at

each time. Publication bias was assessed by Begg's funnel plot and Egger's test [17];  $P < 0.05$  was considered statistically significant. All statistical tests for this meta-analysis were performed with STATA (version 11.0; Stata Corporation, College Station, TX).

## **Results**

### *Study characteristics*

All potentially eligible studies investigating the effectiveness of LA in CS were screened and characteristics of eligible studies were summarized in **Table 1**. A total of 512 patients from nine RCT, of which 259 received local anesthetics, were enrolled in this study. The sites of placement of the catheter were at the incision, at the subfascial layer or at all layers of the abdominal wall and the peritoneum, which was further categorized to two groups: over the fascia and below the fascia. Three studies used multiple injection (continuous and intermittent) of anesthetics and the others used single injection. Two types of interventions, bupivacaine or ropivacaine, were used in the LA group. Quality assessment indicated that all of included studies were of high quality with a Jadad score of 5.

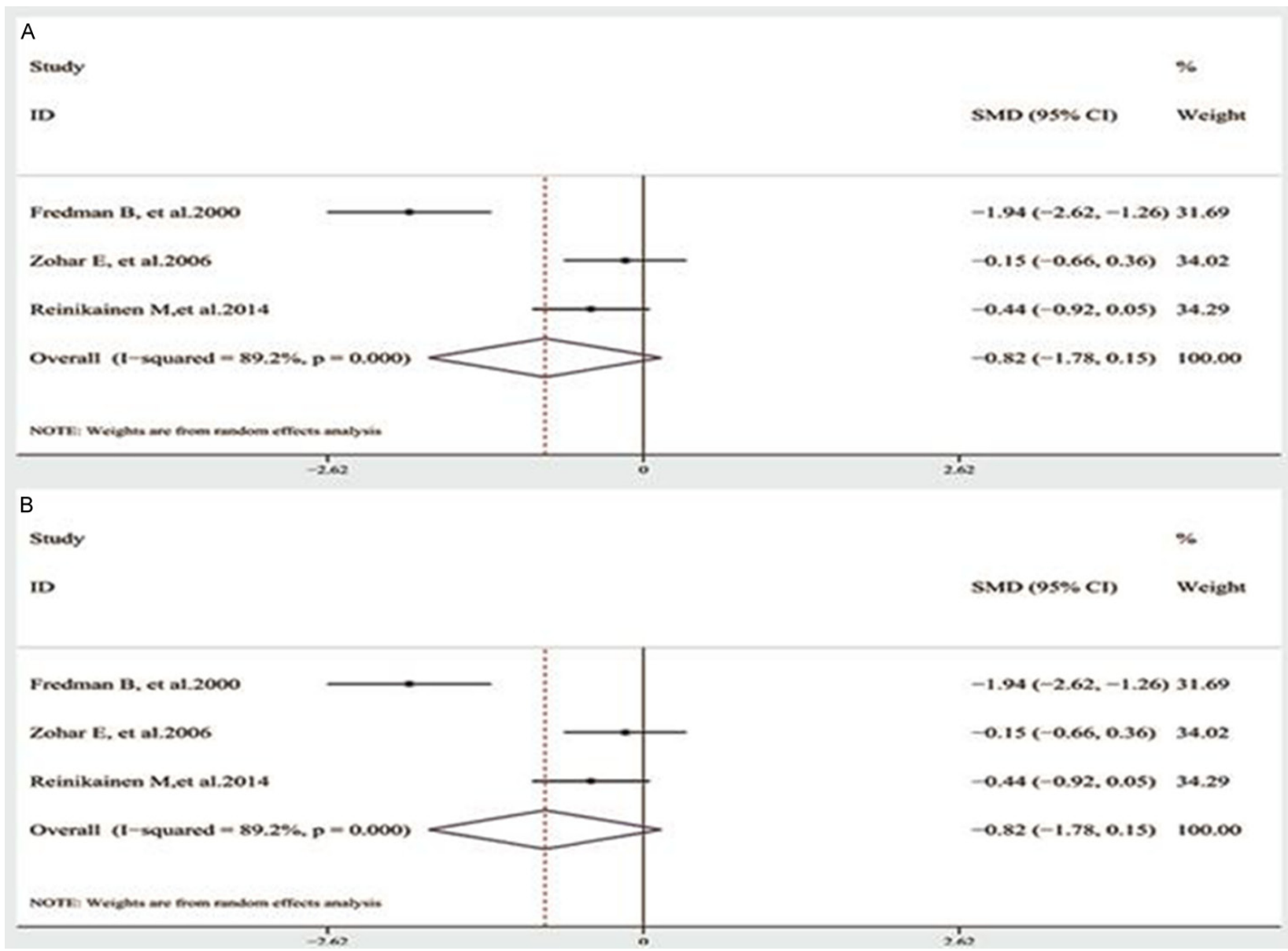
### *Test of homogeneity*

There was significant heterogeneity across the studies of the cumulative morphine consumption in the first 6 h and first 48 h and pain score at 4 h and 12 h after surgery. So a random-effects model was utilized to analyze these data and the stability of the pooled results was further explored in the sensitivity test in presence of substantial heterogeneity. For other meta-analysis, the fixed-effect model was implied and the results of random-effects model have been compared as a type of sensitivity test.

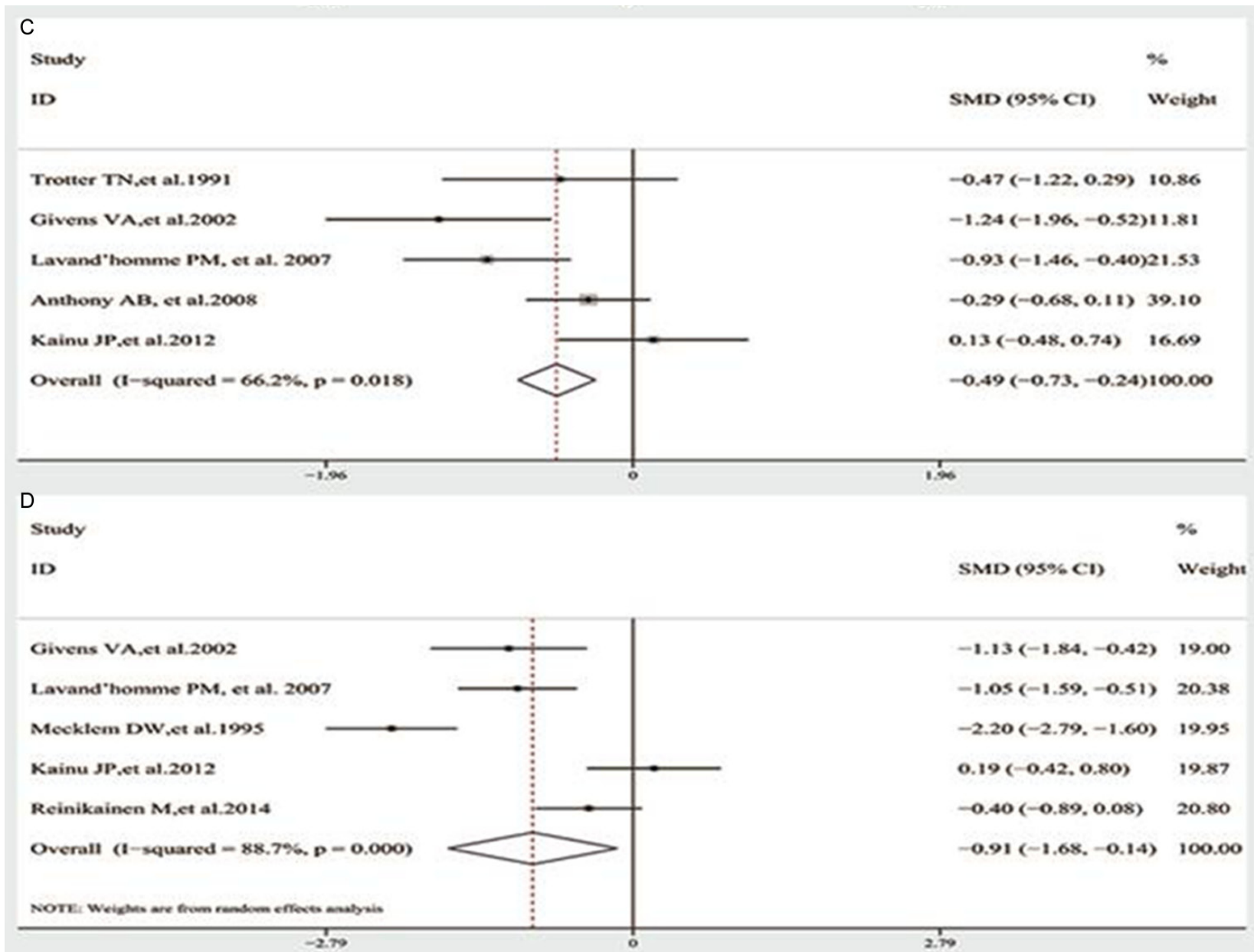
### *Cumulative morphine consumption*

All of the 9 trials included in the meta-analysis presented data on morphine consumption at different time epochs. Results of morphine consumption for first 12 h, 24 h and 48 h were pooled from 3 studies (124 cases), and 3 studies (265 cases) and 5 studies (275 cases). Cumulative morphine consumption was lower in LA group compared with placebo group in the first 12 h (SMD = -0.736, 95% CI (-1.105, -0.368)), 24 h (SMD = -0.378, 95% CI (-0.624,

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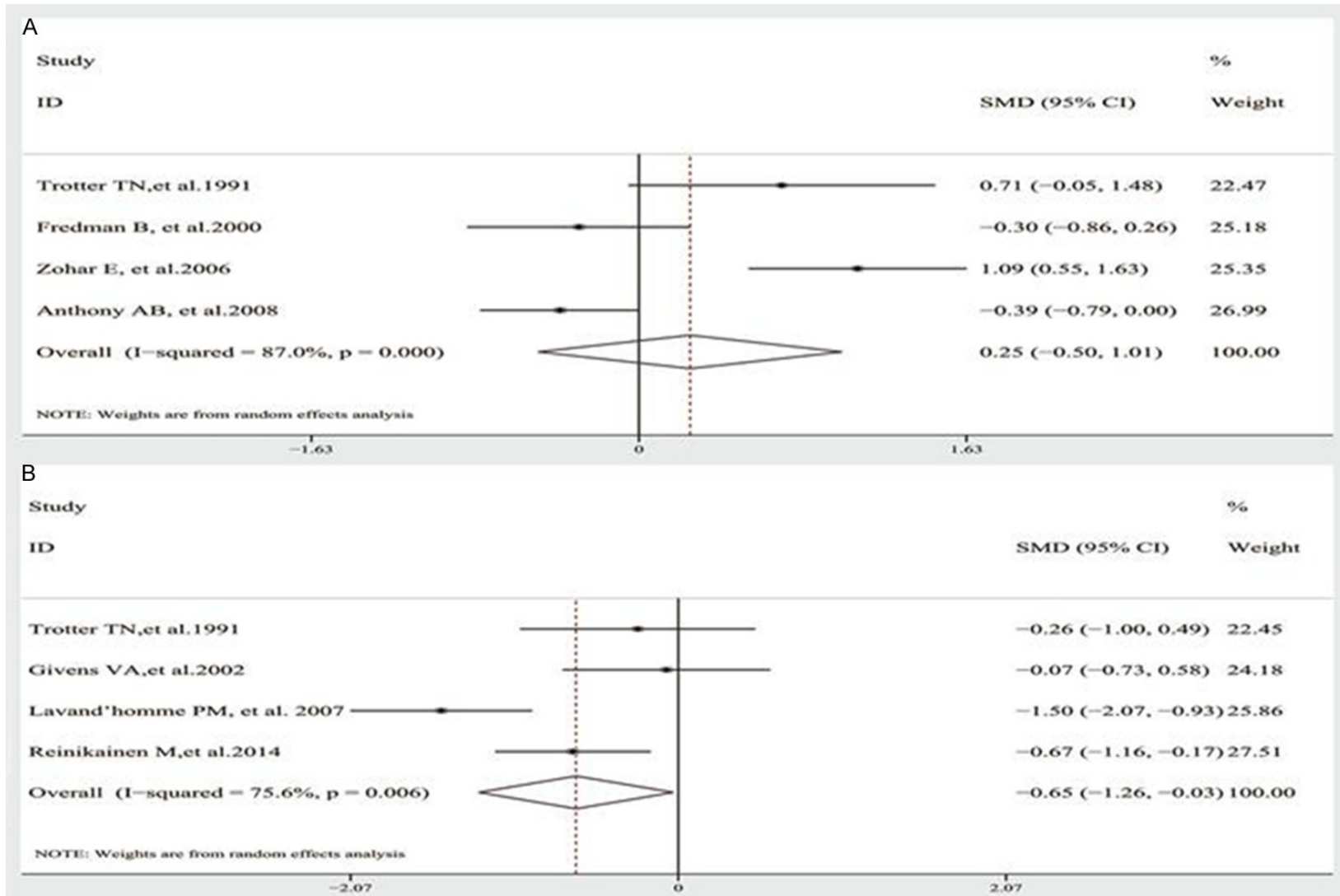


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**Figure 2.** A Forrest plot of morphine consumption in patients undergoing caesarean section procedures at 6 h (A), 12 h (B), 24 h (C) and 48 h (D) post-operatively is shown.



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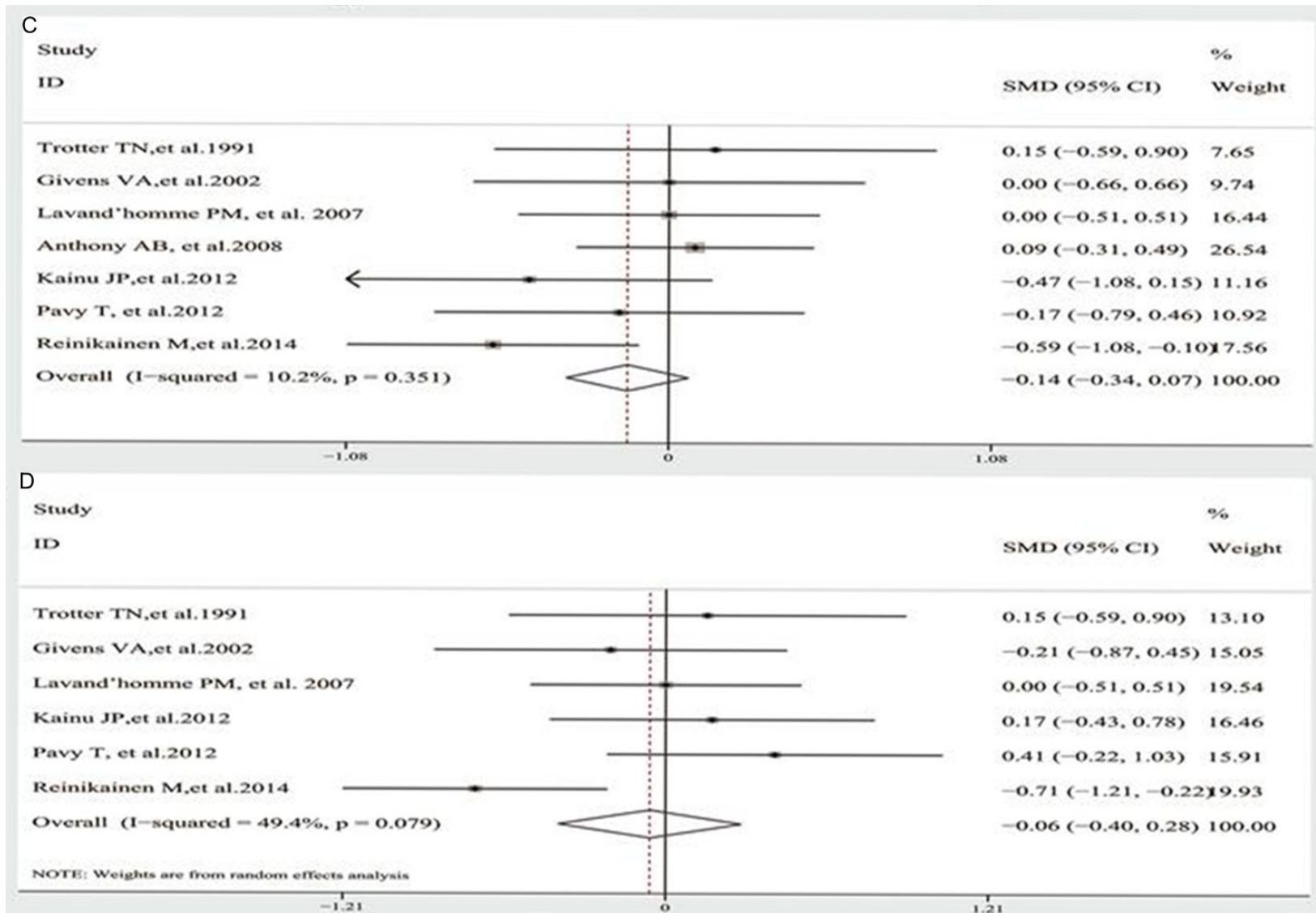
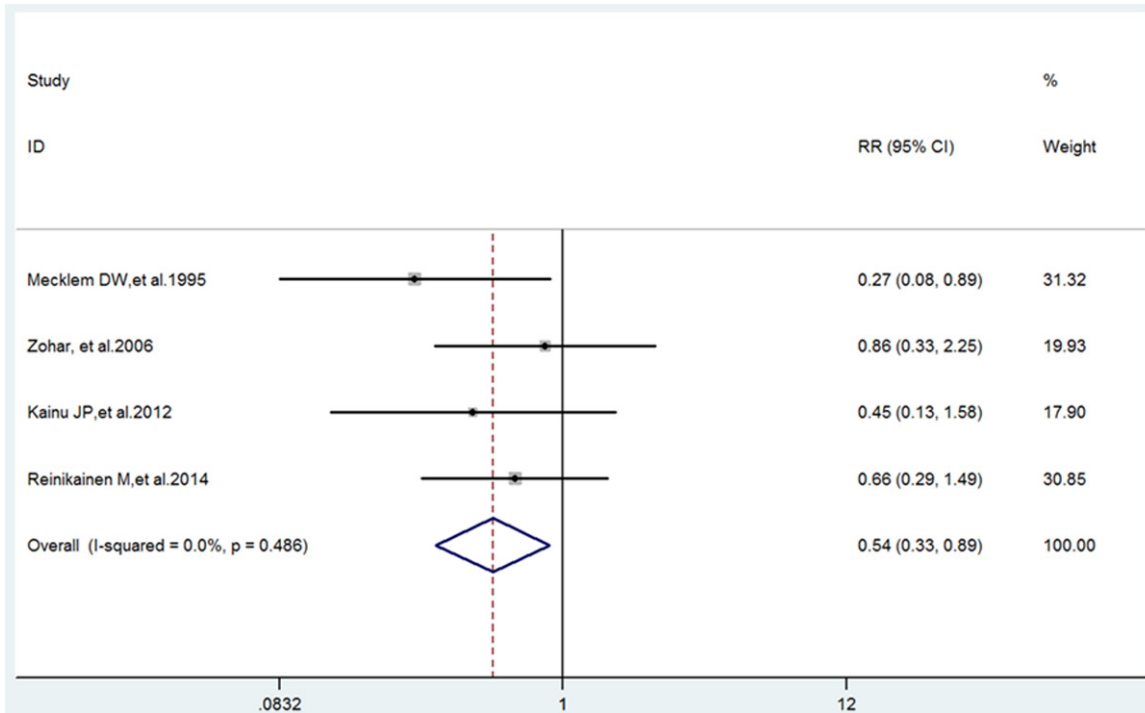


Figure 3. A Forrest plot of pain score in patients undergoing caesarean section procedures at 4 h (A), 12 h (B), 24 h (C) and 48 h (D) post-operatively is shown.



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**Figure 4.** A Forrest plot of nausea in patients after caesarean section procedures is shown.

-0.132)) and 48 h after surgery (SMD = -0.913, 95% CI (-1.683 to -0.143)) (**Table 2**). The result of morphine consumption in the first 6 hours after surgery was lower in the LA group than in placebo group in the meta-analysis consisting of 3 studies with a marginal significance ( $P = 0.097$ ) (**Figure 2**).

### Pain score

All included studies reported the comparison of pain score between the two groups. The pooled pain scores were based on 237, 191, 330 and 233 patients from 4, 4, 6 and 5 studies, at 4 h, 12 h, 24 h and 48 h after surgery, respectively. No significant reduction in pain score was observed in most of these studies. For instance, there is only one study indicated alleviation of pain intensity at 4 h, 24 h and 48 h after surgery. Aggregated data showed pain intensity was only significantly lower in LA group than placebo group at 12 h after surgery (SMD = -0.647, 95% CI (-1.263, -0.031)). There was no statistically significant reduction in pain at any other time epochs between the two groups (**Figure 3**).

### Stratified analyses

Following criteria were used for stratification analysis: the layer of catheter placement and

the type of local anesthetics used, the method of local anesthetics injection given to the patients.

When stratified by the layer of catheter placement, the morphine consumption of 24 h and 48 h after surgery was pooled. In studies with the catheter placed over and below the fascia, morphine consumption was still lower in LA group than in placebo group in the first 24 h and 48 h. The pain score at 24 h after surgery was still controversial in patients with catheter placed over the fascia at 24 h and 48 h ( $P = 0.184$  and  $0.290$ , respectively). There were only 1 and 2 studies with catheters placed below the fascia at 24 h and 48 h, respectively, and the stratified analysis was not performed.

For morphine consumption in the first 24 h, 3 studies used multiple injection and 2 studies used single injection indicated a similar result as in the overall assessment. For pain alleviation at 24 h and 48 h, only the group of patients received multiple injections indicated a benefit of LA infiltration over the placebo at 24 h. Results of other sub-group were in accordance with the overall results.

Four studies used bupivacaine and the rest used ropivacaineas intervention. Stratified

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analysis was performed in morphine consumption in the first 24 h and 48 h, and pain score at 24 h and 48 h after surgery. All of these stratified analysis by the type of LA drugs revealed similar result to that of the overall analysis.

### *Side effects*

Side effects in the LA group and control group were assessed. The rate of patients with nausea and vomiting were assessed in several included studies [9, 12, 18, 19]. However, only the rate of patients with nausea was adequate for meta-analysis. The pooled result was summarized in **Figure 4**. Less patients in LA group suffers from nausea compared with placebo group (RR = 0.54, 95% CI (0.33, 0.89)) (**Figure 4**).

### *Publication bias*

Begg's funnel plot and Egger's test were performed to assess the publication bias of the currently available literature. The shapes of all eight funnel plots in the comparison of the LA group and placebo group appeared symmetrical. The Egger's test revealed there was not a strong publication bias in all of the eight analyses ( $P = 0.202, 0.565, 0.577, 0.880$  for morphine consumption in the first 6 h, 12 h, 24 h, 48 h and  $P = 0.349, 0.553, 0.900, 0.333$  for pain score at 4 h, 12 h, 24 h, 48 h after surgery).

### **Discussion**

Overall, our meta-analysis indicated that the continuous instillation of bupivacaine or ropivacaine in the surgical wound after CS resulted in lower morphine consumption at most time epoch after surgery but a greater pain reduction only at a few time epochs compared with that in placebo group. Although the comparison of LA and control group was performed in the meta-analysis performed in 2011 by Gupta A, et al., [14] there were very limited reports that could provide sufficient data for quantitative analysis at a limited time epoch. Only two studies were enrolled for the estimation of pain and the cumulative morphine consumption. In this meta-analysis, we conducted the comparison of pain relieve and cumulative morphine consumption in the LA group and placebo group at four time epoch. The enrollment of newly published studies enabled us to perform analysis for different time epochs and stratified analy-

sis. The result of our meta-analysis encouraged the use of LA wound infiltration or instillation through catheters in patients undergoing CS for lowering morphine consumptions but not related with benefits in pain relief after surgery. Reduced morphine consumption was observed in the first 12 h, 24 h and 48 h after surgery but not in the first 6h after surgery. The result of the 6 h indicated that LA infiltration is beneficial than placebo but the benefit failed to reach the common level of significance ( $P = 0.097$ ), indicating the potential of LA infiltration in reducing morphine consumption in very early stage after surgery.

Our study indicated a disparity between the result of pain score and morphine consumption. Although the improvement of pain score relief was not statistically significant, lower morphine consumption was observed in the LA group than the control group. We suggest that the evaluation of pain score was of a subjective nature and the differences on pains score is hard to be revealed in a limited sample size in each study. However, the reduced morphine consumption would serve well as an important indicator to judge if there is a substantial benefit of LA treatment.

Significantly less patients suffer from nausea in the LA group than control group, which may be the direct result of a lower consumption of morphine consumption. As side effects like nausea is essential to quality of life of the recipient [20], the use of LA infiltration would therefore significantly improve the quality of life in patients undergoing CS.

However, previous studies indicated conflicting results on this issue. For instance, the meta-analysis by Gupta, et al. [14] indicated that there was not a substantial benefit of using LA in patients underwent CS, although a number of included studies illustrated a benefit in morphine consumption and improved pain score. Moiniche S, et al. [7] listed several reasons that why they considered the locally use of anesthetics at the incision was of little clinical use in patients after surgery. They suggested that the assessment of pain using VAS pain score itself was of limited clinical use and they argue there was huge heterogeneity in the way that these studies were performed such as the surgical procedure, the modes of local anesthetic administration and different catheter place-

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ment. On this base, they were against quantitative estimate of different analysis. Nevertheless, such views were rejected by Rawal N et al. [8] who values the comparisons of data currently available. They believed it was still too early to shut the doors for estimating the benefit of using LA in patients after surgeries. Currently, the wound catheter infusion technique was recommended in some guidelines and the PROSPECT recommendation advocated the use of LA infiltration in patients underwent laparoscopic cholecystectomy, open colon surgeries and a couple of abdominal surgeries.

In the view of Rawal N et al. [21], the comparison of pain relief and morphine consumption should be based on a group of studies with similar study design. In this meta-analysis, we performed stratified analysis according to main influential factors in study design. However, the results of stratified analysis by location of the catheter or the modes of the LA administration were not significantly different from the overall analysis.

Therefore, attempts to reduce the postoperative pain after a CS by using a continuous infusion of local anesthetic has been proved to be reasonable on the basis of evidence currently available. However, some cautions should be taken in interpreting the results. First, the heterogeneity among involved studies may have distorted this meta-analysis. For instance, there was a strong heterogeneity in the study design. Future studies should consider different situations in the study design or, in one of the most effective ways, to perform analysis in a similar way with the previous studies and in accordance to the clinical working pattern. Secondly, there are still very limited studies in our article and results of stratification should be adopted in caution due to an even more limited case number. Our opinions are in accordance with that of Rawal N et al. [8, 21], that more high-quality studies should be performed and heterogeneity among these studies may be reduced in the initiation of study design to yield more evidence. In the future, head-to-head comparison with alternative analgesic techniques should be initiated to identify the most cost-effective modality for different procedures.

### Conclusion

In conclusion, this meta-analysis evaluated the efficacy of LA in CS in 512 patients from 9

RCTs. Local anaesthetic wound infiltration in Caesarean section was associated with significant lower morphine consumption, lower rate of nausea but not with lower pain scores comparable to the placebo group based on a group of heterogeneous studies.

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### Disclosure of conflict of interest

None.

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