Review Article

Efficacy of low dose bupivacaine with intrathecal fentanyl for cesarean section on maternal hemodynamic: Systemic review and meta-analysis

ABSTRACT

Hypotension during spinal Anesthesia is the most common complication with maternal and neonatal morbidity and mortality. Low dose bupivacaine with intrathecal fentanyl is recommended as strategy to prevent spinal Anesthesia induced hypotension and related complications. The aim of this systemic review is to evaluate the efficacy of low dose bupivacaine with Intrathecal fentanyl on the improvement of maternal and neonatal outcomes compared to conventional dose bupivacaine among mothers who undergone cesarean section. We conducted a systemic search of the electronic databases of Pubmed, Medline, LILACS and others with PICO strategy for randomized controlled clinical trials comparing low dose bupivacaine with fentanyl and conventional dose bupivacaine for cesarean section. Joanna Briggs Institute (JBI) standardized data extraction form was used for data extraction and finally entered into Review Manager for data synthesis. Ten Randomized trials (552) were included in this review. Incidence of hypotension was less likely in mothers who received low dose bupivacaine with Fentanyl as compared to those with conventional dose of bupivacaine alone (RR = 0.43, 95% confidence interval (CI) 0.12-0.47, ten trials, 552 participants). The review revealed that Low dose bupivacaine combined with intrathecal Fentanyl decrease incidence of hypotension.

Key words: Bupivacaine; cesarean section; hypotension; spinal Anesthesia

Introduction

Spinal anesthesia is the most common techniques of regional anesthesia for cesarean section with minimal maternal and neonatal complications as compared to general anesthesia which is associated with difficult airway and risk of aspiration.[1-4] However, hypotension during spinal anesthesia for cesarean section is the most common complication associated with nausea and vomiting, altered mental status and risk of aspiration.[1,4-9]

Incidence of hypotension during spinal anesthesia for cesarean section varies in different studies based on the definition of hypotension which ranges from 55-100 percent.[5,10,11] Recent systemic review on definition of hypotension showed that systolic blood pressure less than 94 mmHg or systolic blood pressure less than 24% of the baseline is the accepted value.[10]

Bupivacaine is the most commonly used local anesthetics in spinal anesthesia for cesarean section. The dose of bupivacaine for spinal anesthesia in non-obstetric patient is 13-15 mg where as it is about 12.5 mg for pregnant mothers to avoid high and extensive block due to physiologic and mechanical effects of

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pregnancy. Even with standard doses of bupivacaine (12.5 mg) for pregnant lady, there are evidences of severe hypotension and related maternal and neonatal complications.[3,12-14]

Different adjuvant like Opioids and non-Opioids have been tried to improve intraoperative anesthesia, and to prolong postoperative analgesic duration. Fentanyl, a lipophilic opioid, has rapid onset of action after intrathecal administration.[2,3,5,8,12,15] After intrathecal administration, fentanyl diffuses into epidural space and subsequently into the plasma, suggesting that it acts not only through spinal opioid receptors but also systemically. Delayed respiratory depression is less likely associated with fentanyl, as it does not reach to 4th ventricle in sufficient concentrations.[9,16]

Though high dose of bupivacaine provides sensory and motor block, it is also associated with high incidence of hypotension and poor neonatal outcomes.[16-19] On the other hand, low dose bupivacaine (<8 mg) is associated with inadequate anesthesia despite low incidence of hypotension.[17-19] Low dose bupivacaine with fentanyl provides adequate anesthesia with stable maternal hemodynamic and neonatal outcomes. However, there are discrepancies on the efficacy of low dose bupivacaine with fentanyl.[17,18] Therefore, we conducted this systemic review and meta-analysis to assess the efficacy of low dose bupivacaine with intrathecal fentanyl on maternal and neonatal outcomes.

Objective and Research Question

Objective

The objectives of this systemic review and meta-analysis is to assess the efficacy of low dose bupivacaine with intrathecal fentanyl for cesarean section on maternal hemodynamic as compared with that of conventional doses of bupivacaine.

Research question

Does low dose bupivacaine with intrathecal fentanyl prevent spinal induced hypotension and associated complications as compared with that of conventional dose of bupivacaine in mothers who are undergoing cesarean section?

Methods

Types of studies

We considered randomized controlled trials comparing low dose bupivacaine with intrathecal fentanyl and conventional dose bupivacaine for cesarean section.

Types of participants

All parturient scheduled for cesarean section.

Types of Intervention

Intervention

Parturient mothers receiving intrathecal fentanyl with low dose bupivacaine.

Control

Parturient mothers receiving spinal anesthesia with conventional dose bupivacaine

Outcomes

The primary outcome interest was incidence of hypotension. The secondary outcomes were onset of sensory block, duration of block, block failure, nausea and vomiting, and neonatal outcomes.

Criteria for selection of clinical trials

The inclusion criteria of this search articles include the following:

1. Randomized controlled trial received low dose bupivacaine with intrathecal fentanyl for cesarean section
2. Control group received conventional dose bupivacaine
3. Articles comparing hypotension as primary outcomes
4. Articles with full text available.

The exclusion criteria of the search articles include the following:

1. Studies comparing ASA III and above parturient
2. Observational studies
3. Cross sectional studies
4. Cross over and Quasi-expermental studies.

Searching strategy

Databases were searched for randomized clinical trials comparing intrathecal fentanyl and low bupivacaine without date and language restriction as shown below with medical subject heading (MeSH) terms of parturient, hemodynamic stability, pain, nausea and vomiting, and spinal anesthesia were searched as follows:

1. Cesarean section
2. Intrathecal fentanyl
3. Low dose bupivacaine
4. Spinal hypotension
5. Analgesia
6. #1 and #2 and #3 and #4 or #5
7. Clinical trial
8. #6 and #7
9. Randomized control
10. #8 and #9.

Data extraction

Different databases were explored to identify controlled clinical trials comparing fentanyl co-administered with

low dose bupivacaine and conventional bupivacaine dose for spinal anesthesia in cesarean section. Full reports of all controlled clinical trials were searched without date and language restriction. There have been 14 controlled trails collected for eligibility assessment and eleven trials were incorporated for extraction of outcomes. Two review authors independently assess the eligibility of studies with customized checklist that was adopted from Joana Briggs Institute [Table 1], and disagreement was fixed by consensus. Characteristics of Included studies [Table 2], and the reason for exclusion of studies was described in detail [Table 3]. The study selection process was summarized using PRISMA chart [Figure 1].

Methods of the review

The corresponding author had chosen appropriate trials from those identified by the search strategy and retrieved the full articles, and duplicate publications from the same data set were only used once. The two authors independently assessed the methodological quality of the included trials using tools that were adapted from Cochrane Handbook for systemic reviews and Jadad scale [Table 4], which incorporates generation of allocation sequence, allocation concealment, blinding and loss to follow up. For all trials, each quality component apart from blinding was classed as adequate, inadequate or unclear. For loss to follow up, inclusion of 90% of participants was considered adequate. Blinding was assessed using the following criteria: blinding of participants, blinding of Health care providers and blinding of outcome assessment. Blinding was assessed as open or single blind. Disagreements between authors were resolved by discussion.

Data analysis

The data were analyzed using Review Manager (RevMan 5.3, Cochrane Collaboration) and comprehensive meta-analysis (CMA). Statistical combination of data from two or more separate trials in a meta-analysis was decided based on the evaluation of the clinical and methodological heterogeneity. The inconsistency throughout trials was quantified with the I^2 statistic proposed by Higgins and colleagues, assuming a value more than 50% as a substantial heterogeneity and subgroup analysis were conducted to see the source of heterogeneity. We conducted logarithmic transformation of the risk ratio (RR) effect estimates and its standard errors by construction of Begg's funnel plots, and assessment of the degree of symmetry with Egger's test to explore publication bias. The summary effect measure were risk ratio (RR) and odd ratio for dichotomous variables and mean Difference and standard deviation for continuous variables along with their

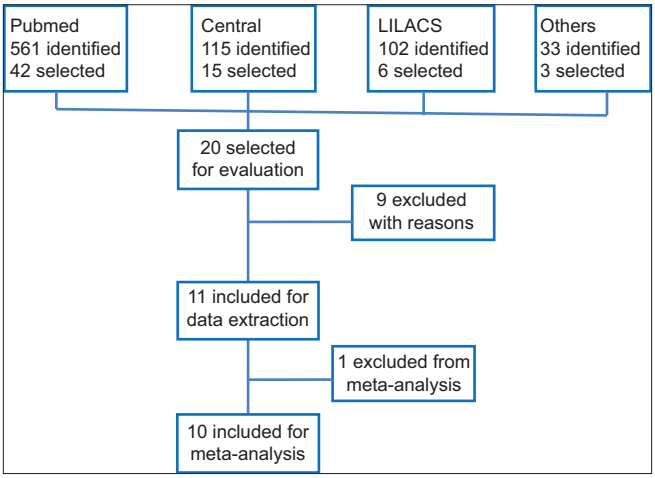

Figure 1: PRISMA flow diagram

Table 1: Study Eligibility Assessment Tool

S. No.	Parameters	Assessment			Comment
		Yes	Unclear	No	
	Type of study design				
1	Is the study described as randomized? (Excluding cross over and Quasi-experiment)				
	Types of participants				
2	Were participants diagnosed as patients with disease of interest?				
3	Were inclusion and exclusion criteria described?				
4	Was the ethical review described?				
5	Were participants of the prespecified age? Yes, if ages are mixed as < and > but not only one				
	Interventions				
6	Were comparison groups treated with prespecified intervention in one group and control intervention in other group?				
	Outcomes				
7	Did the study report prespecified outcomes?				
8	Was the full article accessible or available?				
9	Was appropriate statistical used?				

FINAL DECISION: Any parameter with 'NO' value will be excluded. Adapted from Cochrane-Handbook of systemic Reviews, 201

Table 2: Description of included studies

Study	Sample size	Comparison	Spinal technique	Analgesic/vasopressor/ supplementation	Efficacy criteria
Bruce and colleague	32	IB 0.5% 5 mg B + 15 mg F; 10 mg B alone	Sitting position	Ephedrine was provided for	Pain assessment; sensory block T4,5
Gajbhare and colleague	60	HB 0.5% 8 mg + 20 mg F ; HB 10 mg B	Left lateral with UD	Mephenteramine was provided	Pain assessment; sensory block T5
Gandam and colleagues	50	HB 0.5% 7.5 mg B + 25 mg F; 10 mg B alone	Not available	N/a	Pain assessment; sensory block T6
Gauchan and colleagues	70	HB 0.5% 10 mg B + 20 mg F; 12 mg B alone	Sitting position	N/a	Pain assessment; sensory block T4
Manowarul and colleagues	90	HB 0.5% 8.5 mg B + 25 mg F; HB 0.5% 8.5 mg + 75 mg cl; HB 0.5% 10 mg B + placebo	Sitting position	More ephedrine required for B group alone	Pain assessment; sensory block T4
Mohammed and colleagues	60	HB 0.5% 7.5 mg B + 25 mg F; 10 mg B alone	LLD with UD	N/a	Pain assessment; sensory block T8
Nasir and colleagues	60	HB 0.5% 8 mg B + 25 mg F; 12.5 mg B alone	Sitting position	Ephedrine was used	Pain assessment; sensory block T4
Selima and colleagues	40	HB 0.5% 4 mg B + 25 mg F; 10 mg B alone	Sitting position	Ephedrine dose was higher in B, fentanyl	Pain assessment; sensory block T6
Sheikh and colleagues	50	HB 0.5% 10 mg B + 12.5 mg F; 10 mg B with placebo	Sitting position	N/a	Pain assessment; sensory block T5
Seyedhejazi and colleagues	40	HB 0.5% 8 mg B + 25 mg F; 12 mg B alone	Sitting position	Ephedrine was used	Pain assessment; sensory block T4-5

HB: Hyperbaric; IB: Isobaric Bupivacaine; B: Bupivacaine; F: Fentanyl; RLD: Right Lateral Decupitus; LLD: Left Lateral Decupitus; UD: Uterine Displacement; N/a: Not Available

Table 3: Descriptions of excluded studies

Study	Publication Year	Sample size	Reason for exclusion
Ahmed and colleagues	2012	172	Comparison was bupivacaine with fentanyl for the each groups
Atanas and colleagues	2009	60	Comparison was bupivacaine with fentanyl for the each groups
Canaan and colleagues	2012	40	Comparison was bupivacaine and levobupivacaine with fentanyl for each group
Kajal and colleagues	2013	24	Comparison was bupivacaine with fentanyl for the each groups
Maqsood and colleagues	2017	90	Low and high bupivacaine dose without Adjuvant
Mhamed and colleagues	2010	80	Comparison was bupivacaine with fentanyl and morphine
Moshir and colleagues	2017	60	Low and high bupivacaine dose without Adjuvant
Sachi and colleagues	2015	60	Comparison was for orthopedic elderly patients
Subisa and colleagues	2012	80	Comparison was bupivacaine and levobupivacaine with fentanyl for each group
Vankateswara and colleagues	2015	120	Comparison three groups with low dose bupivacaine and fentanyl for each

Table 4: Risk of Bias within studies

Study	Sequence generation	Allocation concealment	Blinding	Incomplete Outcome data	Selective Outcome reporting	Free of other bias	Jadad scale		
							randomization	Blinding	Withdrawal
Bruce and colleague	C	A	C	A	A	A	2	0	0
Gajbhare and colleague	A	A	C	A	A	A	2	0	0
Gandam and colleagues	C	C	A	A	A	A	2	2	0
Gauchan and colleagues	C	A	A	A	A	A	2	2	0
Manowarul and colleagues	C	C	C	A	A	A	1	1	0
Mohammed and colleagues	C	C	A	A	A	A	2	2	0
Nasir and colleagues	C	C	C	A	A	A	2	2	0
Selima and colleagues	A	C	A	A	A	A	2	2	0
Sheikh and colleagues	C	C	C	A	A	A	1	1	0
Seyedhejazi and colleagues	A	A	A	A	A	A	2	2	0

A: low risk; B: High risk; C: uncertain/unclear risk of bias. Jadad scale: 2- double; 1-single; 0-no blind at all or withdrawal

corresponding 95% confidence intervals (CI). This systematic review was carried out using the methods established by the Cochrane Handbook for Systematic Reviews of Interventions and we followed the recommendations and checklist items from the PRISMA Statement for Reporting Systematic Reviews and Meta-analysis [Table 5].

Table 5: Prisma statement checklist

Section/topic	Number	Checklist item	Page
		TITLE	
Title	1	Efficacy of low dose Bupivacaine with Intrathecal fentanyl for cesarean section on maternal hemodynamic: systemic Review and Meta-analysis	1
		ABSTRACT	
Structured summary	2	Background: Hypotension during spinal anesthesia is the most common complication which is associated with maternal and neonatal morbidity and mortality. Objective: The aim of this systemic review is to compare low dose bupivacaine with intrathecal fentanyl and conventional dose bupivacaine for ASA I and II term pregnant mother for elective cesarean section. Methods: We conducted a systemic search of the electronic databases of Pubmed, Medline, LILACS and others with PICO strategy for randomized controlled clinical trials comparing low dose bupivacaine with fentanyl and conventional dose bupivacaine for cesarean section. Eligibility assessment was performed independently by the two review authors using a customized form, while discrepancies were resolved by consensus. The Data from individual randomized clinical trial were extracted and entered Review Manager for synthesis. Results: Incidence of hypotension was less likely in mothers who received low dose bupivacaine with fentanyl as compared to those with conventional dose of bupivacaine alone (RR=0.43, 95% confidence interval (CI) 0.12-0.47, ten trials, 552 participants). Conclusion: The review revealed that low dose bupivacaine combined with intrathecal fentanyl decrease incidence of hypotension and associated complications despite Pruritus which is self-limiting without significant morbidity	2
		INTRODUCTION	
Rationale	3	High dose bupivacaine provides sensory and motor block but associated with high incidence of hypotension and maternal and poor neonatal outcomes. On the other hand, low dose bupivacaine (<8 mg) is associated with inadequate anesthesia despite low incidence of hypotension. Low dose bupivacaine with fentanyl provides adequate anesthesia with stable maternal hemodynamic and neonatal outcomes. However, there are discrepancies on efficacy of low dose bupivacaine and fentanyl. Therefore, we conducted this systemic review and meta-analysis to assess efficacy of low dose bupivacaine with intrathecal fentanyl	3
Objectives	4	The aim of this systemic review is to compare low dose bupivacaine with intrathecal fentanyl and conventional dose bupivacaine for ASA I and II term pregnant mother for elective caesarean section	4
		METHODS	
Protocol and registration	5	Protocols of individual trials were checked	5
Eligibility criteria	6	Term ASA I and II pregnant women scheduled for elective caesarean section and followed for 24 hrs perioperatively	5
Information sources	7	The electronic databases of Pubmed, Medline, LILACS and others with PICO strategy for randomized controlled clinical trials comparing low dose bupivacaine with fentanyl and conventional dose bupivacaine for cesarean section were searched without date and language restriction	6
Search	8	The electronic databases of Pubmed, Medline, LILACS and others with PICO strategy for randomized controlled clinical trials comparing low dose Bupivacaine with fentanyl and conventional dose bupivacaine for cesarean section were searched without date and language restriction as shown below with medical subject heading (MeSH) terms of parturient, hemodynamic stability, pain, nausea and vomiting, spinal anesthesia were searched as follows: Cesarean section Intrathecal fentanyl Low dose bupivacaine Spinal hypotension Analgesia #1 and #2 and #3 and #4 or #5 Clinical trial #6 and #7 Randomized control #8 and #9.	5
Study selection	9	The author has chosen appropriate trials from those identified by the search strategy and retrieved the full articles and duplicate publications from the same data set were only used once. The two authors autonomously evaluated each article for inclusion in the review using the information described in the section criteria for considering studies for this review. The two authors independently assessed the methodological quality of the included trials which were measured by Generation of allocation sequence, allocation concealment, blinding and loss to follow up. For all trials, each quality component apart from blinding was classed as adequate, inadequate or unclear. For loss to follow up, inclusion of 90% of participants was considered adequate. Blinding was assessed using the following criteria: blinding of participants, blinding of health care providers and blinding of outcome assessment.	7

Contd...

Table 5: Contd...

Section/topic	Number	Checklist item	Page
		METHODS	
Data collection process	10	Data extraction was done by two authors. Trials that had similar methods of reporting outcomes (mean, proportion, etc.) were taken for meta-analysis data extraction. For trials that did not report the outcomes, the authors were contacted through email.	7
Data items	11	No special data items to be described and defined as it has been described in methodology.	
Risk of bias in individual studies	12	Risk of bias was assessed with independently as described in #9	7
Summary measures	13	The main summary measures were relative risk, odd ratio, and mean difference	7
Synthesis of results	14	Synthesis of results was carried out with review manager. Heterogeneity of results between studies were quantified with I squared where I2 50% is taken as a substantial heterogeneity and source of heterogeneity were assessed with subgroup analysis and regression analysis.	7
Section/topic	**#**	**Checklist item**	**Page**
Risk of bias across studies	15	We tried to assess publication bias with funnel plot and we did not see that much publication bias as shown with Egger's test	7
Additional analyses	16	Subgroup analysis was done to find out source of heterogeneity (dose of bupivacaine (<8 and >8 mg), baricity, and patient position during injection)	11
		RESULTS	
Study selection	17	There were about 811 randomized trials identified from different databases as described in methodology section. There were about 20 trials that were selected for evaluation after successive screening. About 10 trials with 552 participants were included for final analysis and the rest were excluded with reasons	8
Study characteristics	18	Population sizes ranged from 32 to 90. Power analysis was mentioned in two studies and the variables considered for calculations were ephedrine requirements and duration of analgesia. The included clinical trials were published from 2000 up to 2017. The mean age of the patients included ranged from 24 to 37 year where as the mean weight reported was between 58 and 62 kg The majority of trials reported an appropriate method of randomization (1-3, 5-9).	8
Risk of bias within studies	19	It has been mentioned on Table 3	
Results of individual studies	20	It has been mentioned on the figures	
Synthesis of results	21	Incidence of hypotension was less likely in mothers who received low dose bupivacaine with fentanyl as compared to those with conventional dose of bupivacaine alone (RR/OR=0.43, 95% confidence interval (CI) 0.12-0.47, ten trials, 552 participants). Incidence of Pruritus was thirteen times more likely in low dose bupivacaine with fentanyl (OR/RR=12.60, 95% confidence interval CI) 3.56 to 44.61, 5 trials, 290 participants)	11
Risk of bias across studies	22	Risk of bias was tried to be addressed with funnel plot but we did not present the graph	
Additional analysis	23	Table 10 was about subgroup analysis	
		DISCUSSION	
Summary of evidence	24	Low dose bupivacaine combined with fentanyl provides adequate analgesia without compromising maternal neonatal outcomes which in turn brings about cost effective patient care with high patient satisfaction and early discharge from the hospital.	12
Limitations	25	Data combing for pooled analysis was difficult as there was dissimilarity in reporting of some outcome variables	12
Conclusions	26	The finding of the pooled analysis was in consistent with the majority of included studies but the cut point for low dose bupivacaine is variable which varies from 4 mg to 10 mg.	13
		FUNDING	
Funding	27	Authors own resources	

Qualitative Data Synthesis

Description of included studies

There were about 811 randomized trials identified from different databases as described in methodology section [Figure 1]. There were about 20 trials that were selected for evaluation after successive screening. About 10 trials with 552 participants were included for final analysis, and the rest were excluded with reasons [Table 3]. Population sizes ranged from 32–90. Power analysis was mentioned in two studies and the variables considered for calculations were ephedrine requirements, and duration of analgesia.

The study included clinical trials that were published from 2000 up to 2017. The mean age of the patients included and ranged from 24–37 years whereas the mean weight reported was between 58 and 62 kg. The majority of trials reported an appropriate method of randomization.[1-3,5-8,20] There was a large variety of working hypotheses and primary outcomes. In 7 reports, the principal aim of the study was to test whether improved analgesia with fewer adverse effects could be achieved with the combination of a small dose of an opioid with a reduced dose of local anesthesia.[2,3,5-8,20] The local anesthetic used was bupivacaine with dose range from 7–13.5 mg and added fentanyl dose that was 10–25 μg.

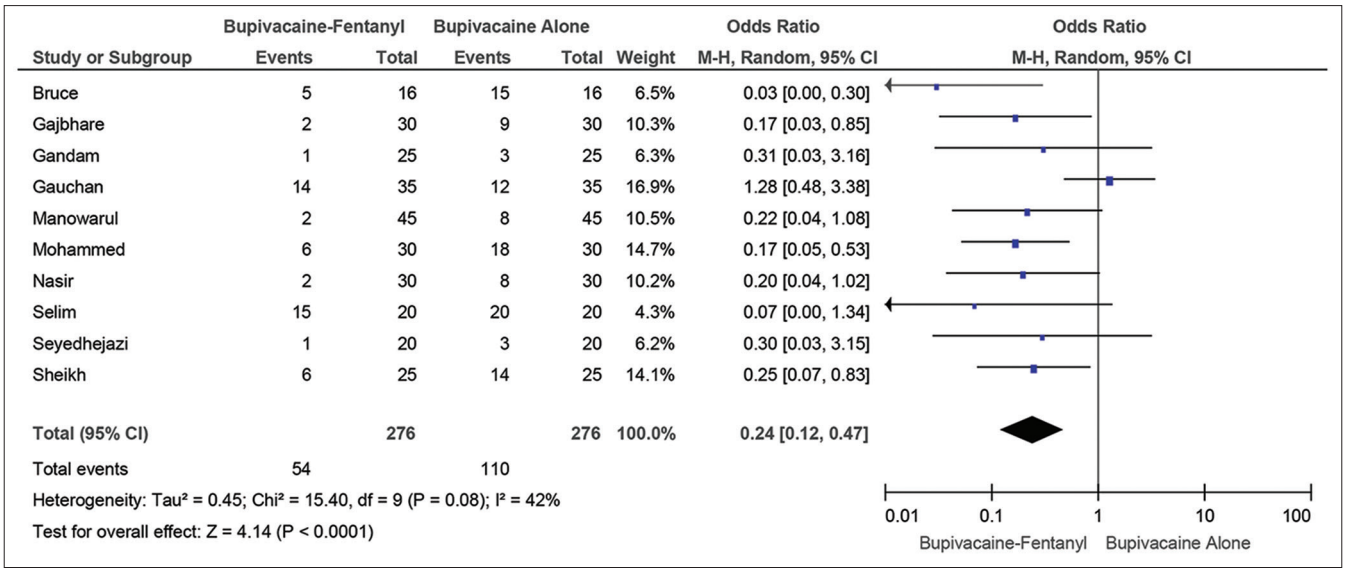

Figure 2: Forest plot for incidence of hypotension low dose bupivacaine-fentanyl vs bupivacaine alone: individual trials and meta-analysis. Events: the total numbers with the events. Total: the total number of participants in intervention and control. Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. M–H, Mantel–Haenszel methods

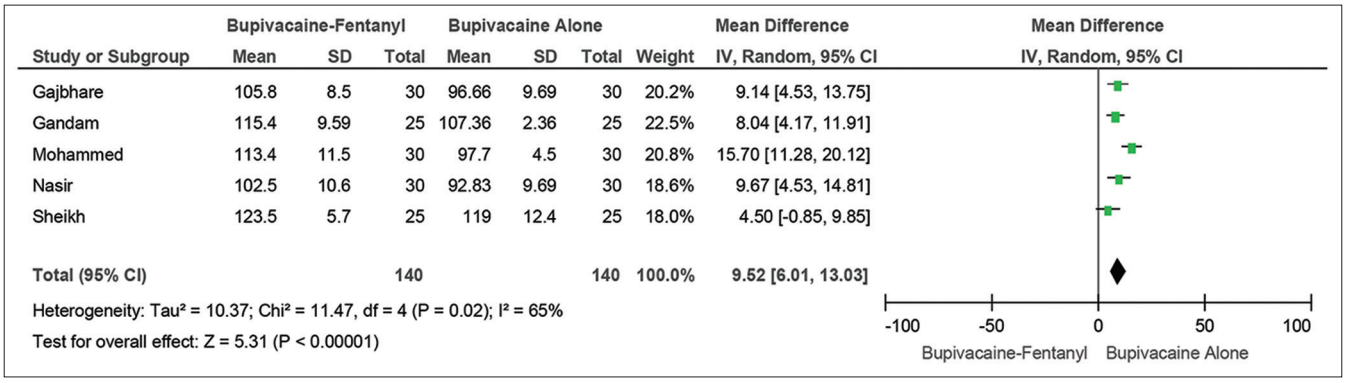

Figure 3: Forest plot for mean intraoperative systolic blood pressure comparing low dose bupivacaine-fentanyl vs bupivacaine alone: individual trials and meta-analysis total: the total number of participants in intervention (BF) and control (B). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR: Inverse Variance

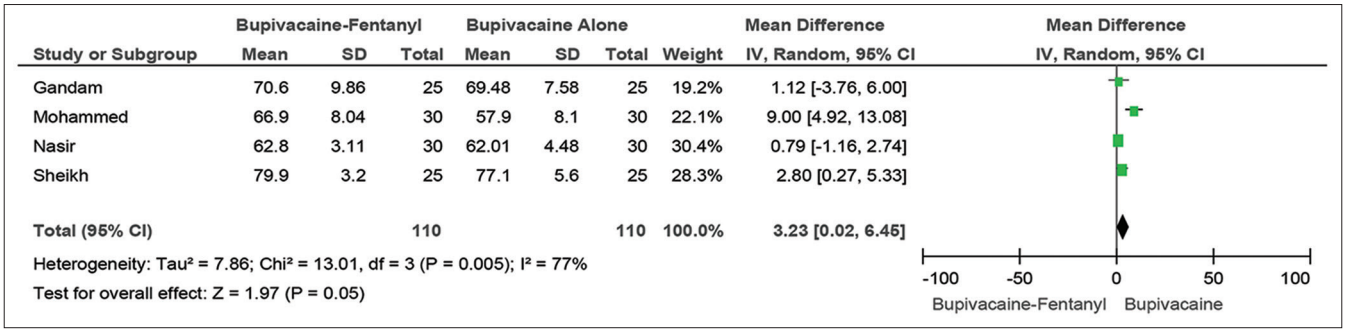

Figure 4: Forest plot for mean intraoperative diastolic blood pressure comparing low dose bupivacaine-fentanyl vs bupivacaine alone: individual trials and meta-analysis total: the total number of participants in intervention (BF) and control (B). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR: Inverse Variance

Ringer's lactate solution was most commonly used for preloading, in the range of 500–1500 ml. Hypotension was managed with ephedrine as a sole drug in five studies[1,5-7,9] and mephentermine was used in one study.[3] Bradycardia (defined as a heart rate <45–50 min/min) was managed with IV atropine in three studies.[3,8,20]

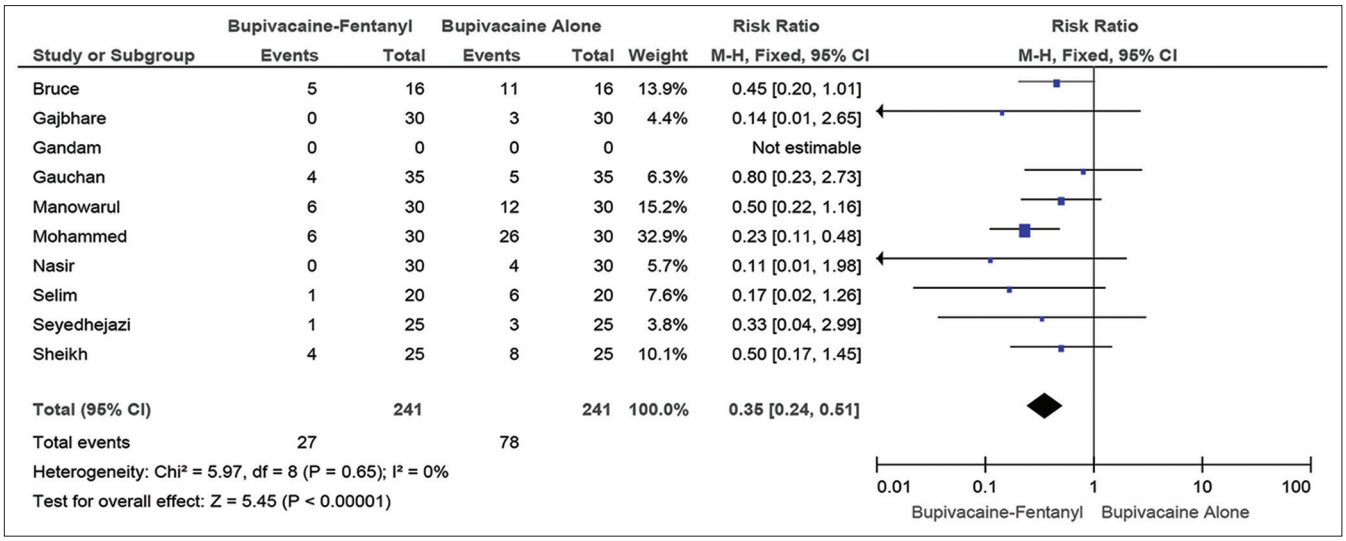

Figure 5: Forest plot for incidence of nausea/vomiting comparing low dose bupivacaine-fentanyl vs bupivacaine alone: individual trials and meta-analysis. Events, the total numbers with the events total: the total number of participants in intervention (SA) and control (GA). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. M–H, Mantel–Haenszel methods

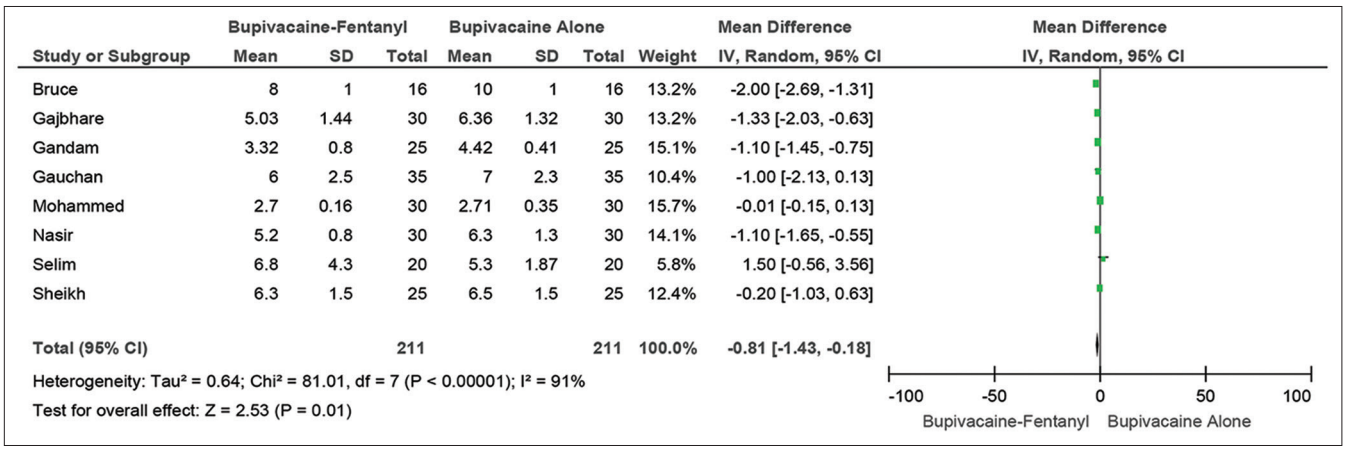

Figure 6: Forest plot for time to sensory block comparing low dose bupivacaine-fentanyl vs bupivacaine alone: individual trials and meta-analysis. Total: the total number of participants in intervention (BF) and control (B). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR: Inverse Variance

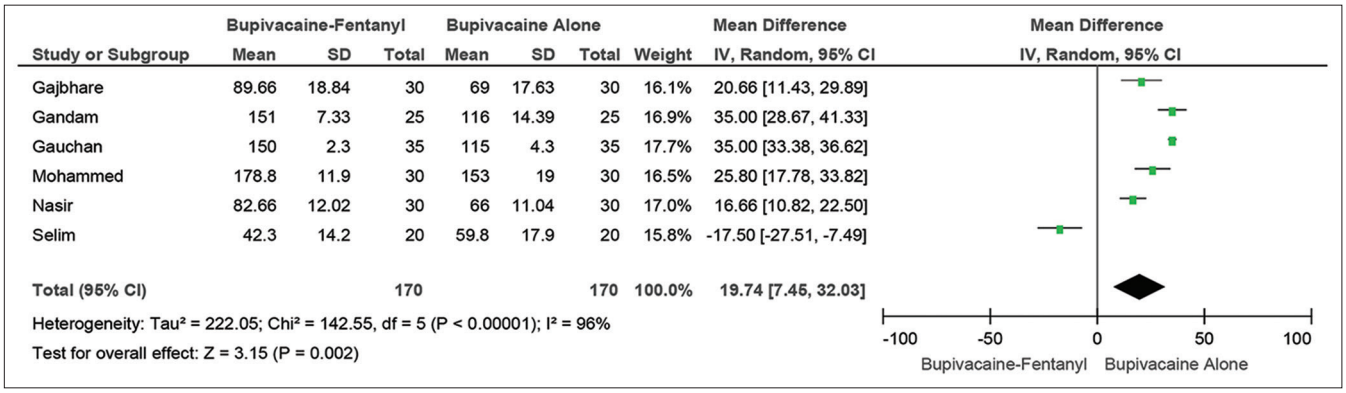

Figure 7: Forest plot for time to two segment regression comparing low dose bupivacaine-fentanyl vs bupivacaine alone: individual trials and meta-analysis. Total: the total number of participants in intervention (BF) and control (B). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR: Inverse Variance

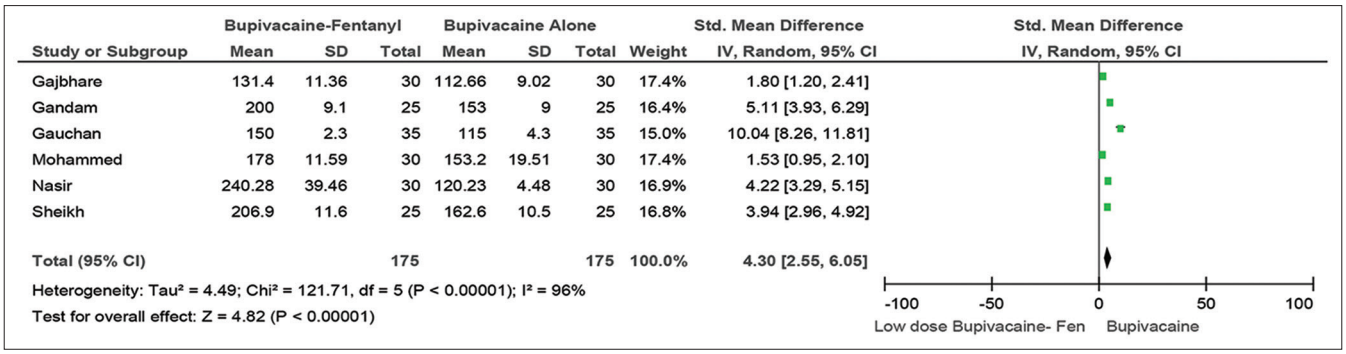

Figure 8: Forest plot for complete sensory recovery comparing low dose bupivacaine-fentanyl vs bupivacaine alone: individual trials and meta-analysis total: the total number of participants in intervention (BF) and control (B). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR: Inverse Variance

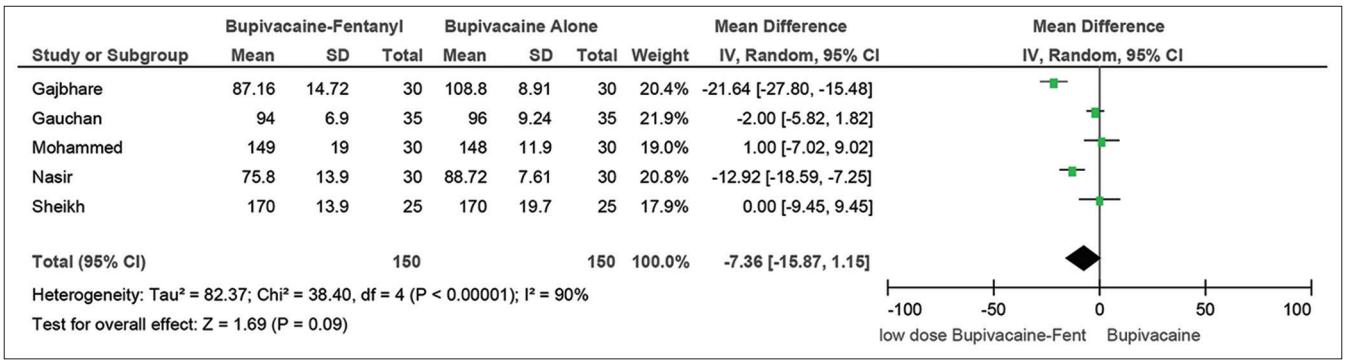

Figure 9: Forest plot for complete motor recovery comparing low dose bupivacaine-fentanyl vs bupivacaine alone: individual trials and meta-analysis total: the total number of participants in intervention (BF) and control (B). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR: Inverse Variance

Results

Primary outcomes

Incidence of hypotension

All the included trials reported the presence or absence of maternal arterial hypotension. Various criteria were used to define hypotension in included studies. Some studies recorded hypotension as systolic blood pressure (SBP) decreased by 20-30% or <90–95 mmHg and others defined hypotension when systolic blood pressure decreased by 20-30% from baseline. Incidence of hypotension was reported in all included studies.[1-3,5-9,12,20] Assessment of reduction in mean systolic and diastolic blood pressure was reported in five studies.[1-3,5,12]

Nausea/vomiting

Incidence was reported either separately as nausea, vomiting in two trials[1,3] or combined nausea/vomiting in seven studies.[5-9,12,20]

Analgesia

Time to sensory onset was reported in eight studies,[1-3,6-8,12,20] whereas complete sensory regression was mentioned in six studies.[1-3,7,8,20]

Four trials reported the duration of postoperative analgesia, which defined as the time from the end of surgery until the first request for rescue analgesia.[1-3,20]

Failed block and conversion to general anesthesia occurred in only one study and supplemental fentanyl required in bupivacaine-fentanyl group.[6] There were no reported events of conversion to general anesthesia for bupivacaine group in any of the study.

Secondary outcomes

Sedation

Sedation was assessed with objective score based on Ramsay sedation scale in one of the study[9] and in the other study using categories (alert, drowsy, dozes-rouses spontaneously, dozes-arousable, and not arousable as an outcome.[6]

Shivering

Shivering was reported in five studies.[1,3,7,9,12] There was not much statistically significant differences.

Urinary retention

One study reported the risk of postoperative urinary retention. None of the patients complained urinary retention in both groups.[12]

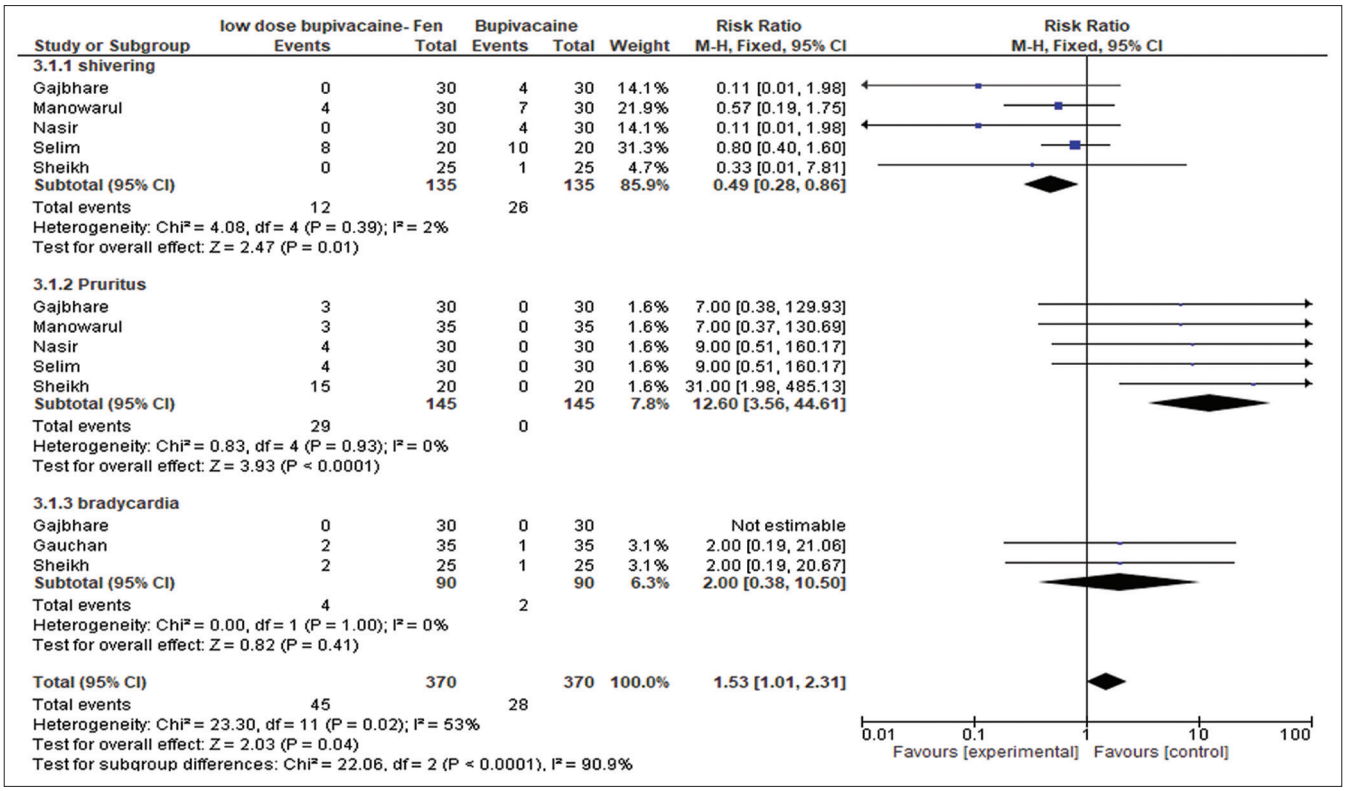

Figure 10: Forest plot for Incidence of adverse effects comparing low dose bupivacaine-fentanyl vs bupivacaine alone: individual trials and meta-analysis. Events, the total numbers with the events total: the total number of participants in intervention (SA) and control (GA). Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. M–H, Mantel–Haenszel methods

Pruritus

Pruritus was reported in five studies.[1,3,7,9,12]

Maternal Bradycardia

Maternal Bradycardia was reported in three studies.[3,8,12] But there was no significant difference between the groups.

Patient satisfaction

Participants were asked to grade their level of overall satisfaction with the anesthesia quality using scores or categories as that of excellent, good, average, or poor based on incidence of side effect.[6,7]

Quantitative data analysis

Spinal anesthesia is compared with low dose bupivacaine combined with fentanyl and conventional dose of bupivacaine for cesarean section. About 10 randomized trials were included in the meta-analysis for data extraction.

In the pooled analysis, incidence of hypotension was higher in mothers who received conventional dose of bupivacaine alone as that compared to those with low dose bupivacaine with fentanyl (RR = 0.43, 95% confidence interval (CI) 0.12-0.47, 8 trials, 532 participants) [Figure 2].

There were about five studies that reported the mean intraoperative systolic blood pressure and the result of meta-analysis showed relative stable systolic blood pressure in low dose bupivacaine combined with intrathecal fentanyl when compared with conventional bupivacaine alone (MD = 9.52, (95% confidence interval (CI) 6.01 to 13.03, 5 trials, 280 participants) [Figure 3].

From the pooled analysis of four results showed that mean intraoperative diastolic blood pressure was found to be better in mothers who received spinal anesthesia with low dose bupivacaine with fentanyl as compared to that of the conventional bupivacaine dose (MD = 3.23, 95% confidence interval (CI) 0.02 to 6.45, 4 trials, 220 participants) [Figure 4].

Nausea and vomiting was very common in patient with conventional bupivacaine dose as compared to that of low dose bupivacaine combined with intrathecal fentanyl as shown with pooled results of meta-analysis (RR = 0.35, confidence interval (CI) 0.24 to 0.51, 9 trials, 482 participants) [Figure 5].[20]

Adequacy of sensory and motor block was reported in majority of included studies. Peak sensory block was faster in low dose bupivacaine with fentanyl as compared to conventional dose bupivacaine (MD = −0.8, (95% confidence

Interval (CI) -1.43 to 0.18, 8 trials, 222 participants). However, complete motor block (bromage scale >3) was faster in conventional dose bupivacaine as compared to low dose bupivacaine with fentanyl (MD = 0.07, 95% confidence interval (CI) 0.01 to 0.04, 5 trials, 300 participants) [Figures 6 and 7].

Complete sensory recovery was prolonged in low dose bupivacaine with fentanyl as compared to bupivacaine alone (MD = 4.3, 95% confidence interval (CI) 2.55 to 6.05, 6 trials, 350 participants), whereas complete motor recovery was shorter in low dose bupivacaine with fentanyl when compared with bupivacaine alone (MD = 0.07, 95% confidence interval CI), 5 trials, 300 participants) [Figures 8 and 9].

From the secondary outcomes, incidence of Pruritus was 13 times more likely in low dose bupivacaine with fentanyl (OR = 12.60, 95% confidence interval CI) 3.56 to 44.61, 5 trials, 290 participants whereas the risk of shivering was higher in bupivacaine alone (OR = 0.43, 95% confidence interval (CI) 0.28 to 0.86, 5 trials, 270 participants. There was no significant difference between the group regarding Bradycardia (OR = 2.07, 95% confidence interval 0.36 to 11.79, 3 trials, 180 participants) [Figure 10].

Discussion

This review was conducted to explore the efficacy of low dose bupivacaine combined with intrathecal fentanyl as the conventional bupivacaine dose is associated with hemodynamic instability despite its adequate analgesia and anesthesia for cesarean section.

Maternal and neonatal mortality was not reported in included randomized trials and this might witness the relative safety of low dose bupivacaine combined with intrathecal fentanyl for cesarean section.

The review has shown that incidence of hypotension is less likely in mothers with low dose bupivacaine with intrathecal fentanyl. This finding is consistent with another meta-analysis that conducted with low dose bupivacaine and conventional doses of bupivacaine for cesarean section.

The mean intraoperative systolic blood pressure was relatively stable in low dose bupivacaine with fentanyl unlike the mean diastolic blood pressure which did not show any significant difference in pooled analysis of four randomized trials.

The pooled analysis of the included randomized clinical trials showed that incidence of intraoperative nausea and vomiting was lower in low dose bupivacaine combined with intrathecal fentanyl when compared with that of conventional dose of bupivacaine alone.

The finding of this review is consistent with included individual trials and another meta-analysis conducted somewhere else. This might be due to fewer episodes of hypotension incidents in low dose bupivacaine with fentanyl as a result of relatively less tense sympathetic blockade in which parasympathetic vagal dominance in gastrointestinal tract is balanced unlike with high bupivacaine dose where vagal dominance is pronounced.

The pooled analysis of included trials showed fast sensory onset and prolonged complete sensory recovery in low dose bupivacaine with fentanyl. This finding is inconsistent with some of included trials and one meta-analysis where there was inadequate sensory block and additional analgesic supplementations that were required. This might be the variation in definition of low dose bupivacaine and fentanyl in different included studies which ranges from 4-8 mg and 10-25 μg respectively.

Motor onset was slower in low dose bupivacaine with fentanyl whereas complete motor regression was faster in low dose bupivacaine with Bupivacaine as compared to that of conventional dose alone.

In included trials reporting neonatal outcomes it did not show any significant difference between the groups but qualitative data extraction was not done due to dissimilarities in method of reporting outcomes.

From the adverse events, incidence of Pruritus was 15 times more likely in low dose bupivacaine with fentanyl whereas incidence of shivering was more common in Bupivacaine dose alone compared with low dose bupivacaine with fentanyl.

Comparison with other systemic reviews

As of our information, there is no systemic review conducted with low dose bupivacaine with intrathecal fentanyl and conventional bupivacaine alone. However, there is one systemic review and meta-analysis comparing low dose and conventional dose of bupivacaine irrespective of intrathecal fentanyl. They incorporated studies comparing low dose and conventional dose with or without intrathecal adjuvant besides fentanyl with which comparison with our systemic review and meta-analysis is inappropriate.

Conclusion and clinical applicability

This systemic review and meta-analysis shows low dose bupivacaine combined with intrathecal fentanyl improves

maternal hemodynamic parameters without significant difference in adequacy of analgesia and anesthesia. Many institutions in Ethiopia did not use low dose bupivacaine and intrathecal fentanyl despite having the advantages of stable hemodynamic and adequate anesthesia. However, further randomized clinical trials are required to set out the standard low dose bupivacaine to be used with fentanyl as there is variation in defining how low is low. Overall, intrathecal fentanyl in spinal anesthesia prevents complications associated with profound sympathetic blockade.

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Conflicts of interest
There are no conflicts of interest.

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