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Original Article

Adequate Anesthesia and More Effective Analgesia by Adjusted Doses of Bupivacaine during Cesarean Section: A Randomized Double-blind Clinical Trial

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Abstract

Background: Several adjuvants, added to local anesthetics, were suggested to induce an ideal regional block with high-quality analgesia. The purpose of this study was to evaluate the particular blocking properties of low-dose bupivacaine in combination with meperidine and fentanyl in spinal anesthesia during Cesarean sections.

Methods: A randomized, double-blind clinical trial was conducted at Hafez Hospital affiliated with Shiraz University of Medical Sciences (Shiraz, Iran) from February 2015 to February 2016. A total of 120 pregnant women, who underwent spinal anesthesia during elective Cesarean section were enrolled in the study. Based on block-wise randomization, the patients were randomly assigned to three groups, namely "B" group received 2 mL bupivacaine 0.5% (10 mg), "BM" group received 8 mg bupivacaine and 10 mg meperidine, and "BF" group received 8 mg bupivacaine and 15 µg fentanyl intrathecally. The block onset, the duration of analgesia, and the time of discharge from the post-anesthesia care unit (PACU) were all assessed. Data were analyzed using SPSS software version 21, and $P<0.05$ were considered statistically significant.

Results: The mean duration of motor blocks in the B group (150 min) were significantly higher than the BM (102 min) and BF (105 min) groups ($P<0.0001$). In both the BM and BF groups, the duration of sensory and motor blocks was the same. The length of stay in the PACU was significantly longer in the B group ($P<0.001$) than the BM and BF groups. When meperidine or fentanyl was added to bupivacaine, the duration of the analgesia lengthened ($P<0.001$).

Conclusion: Intrathecal low-dose spinal anesthesia induced by bupivacaine (8 mg) in combination with meperidine and/or fentanyl for Cesarean section increased maternal hemodynamic stability, while ensuring effective anesthetic conditions, extending effective analgesia, and reducing the length of stay in PACU.

Trial Registration Number: IRCT2015013119470N14.

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Keywords ● Bupivacaine ● Anesthesia, spinal ● Local anesthesia ● Meperidine ● Fentanyl ● Cesarean section

What's Known

- Some research suggests that reducing the spinal dose of bupivacaine can result in high-quality anesthesia with fewer hemodynamic side effects.

What's New

- For Cesarean section, intrathecal low-dose spinal anesthesia induced by bupivacaine (8 mg) in combination with meperidine and/or fentanyl increased maternal hemodynamic stability, while also ensuring safe anesthetic conditions, extending safe analgesia, and minimizing the length of stay in a post-anesthesia care unit (PACU).

Introduction

Regional anesthesia techniques, particularly spinal anesthesia, are known as appropriate and safe methods of providing Cesarean section anesthesia. A recent alternative for anesthetizing women in Cesarean section deliveries is the combined spinal epidural (CSE) procedure. The standard dose of bupivacaine, as a primary local anesthetic, was gradually decreased to 8-12.5 mg.[1] Although lower doses of bupivacaine may be accompanied with a lower incidence of complications such as hypotension, bradycardia, nausea, and vomiting and an improved maternal cardiac index (CI),[1] it may also be associated with the incidence of inadequate anesthesia.[2-4]

Sufentanil, fentanyl,[5] clonidine,[6] morphine,[7] and meperidine[8] are some of the adjuvants that can be combined with low-dose intrathecal bupivacaine in local anesthesia to enhance the quality of anesthesia, lengthen the duration of sensory block, and reduce the incidence of hemodynamic instability.

Among numerous opioids used in spinal anesthesia, meperidine has considerable local anesthetic properties. It has a long duration of action and provides satisfactory postoperative analgesia. Additionally, no reports of neurological impairment as a result of intrathecal meperidine were documented.[9] However, to the best of our knowledge, previous studies did not investigate effective analgesia and reduced length of stay, which are important issues in Cesarean section. The main focus of this study was to assess the specific blocking characteristics and adverse effects of low-dose bupivacaine (8 mg) in combination with a low dose of meperidine (10 mg) and fentanyl (15 µg) in spinal anesthesia during Cesarean section procedures.

Patients and Methods

This randomized double-blinded prospective study was conducted on pregnant women who were candidates for elective Cesarean section admitted to Hafez Hospital (Shiraz, Iran) from February 2015 to February 2016. Written informed consent was obtained from all the participants. The study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (code: cp-p-9365-6925). This clinical trial was registered in the Iranian Registry of Clinical Trials (IRCT2015013119470N14, 09/02/2015). The study included parturients with American Society of Anesthesiologists (ASA) physical status I and II and uncomplicated term pregnancy with singleton fetuses. The exclusion criteria included gestational hypertension, contraindications to regional anesthesia, a positive history of cardiovascular or liver disease, renal failure, seizure or other neurologic disorders, allergic reaction to the study agents, Hb<8 mg/dL, three or more prior Cesarean sections, a history of drug abuse, and patients who were unable to communicate or refused to participate.

For any possible intervention, pieces of resuscitation equipment such as oxygen supply, tracheal tubes of the proper sizes, laryngoscopes with long and short blades, vasopressors, antihistamines, and anticonvulsants were prepared.

The sample size was calculated using the comparison of two means formula according to a previous study on the onset time of complete motor block (meperidine=6.24±0.66 and fentanyl=6.67±0.64).[10] The number of required patients was obtained at 37 in each group for a power of 80%, a significance level of 5%, and a dropout rate of 10%. Thus, a total of 120 pregnant women, who underwent spinal anesthesia during elective Cesarean section were enrolled in the study. Patients were randomly assigned to each group using block-wise randomization in a block size of six. The block list was extracted from www.sealedenvelope.com.

All the participants were randomly allocated into three groups of similar size (n=40), namely the “B” group, the “BM” group, and the “BF” group. Each group received the following treatments: The B group received 2 mL of bupivacaine 0.5% (10 mg). The BM group received 8 mg bupivacaine and 10 mg meperidine, and the BF group received 8 mg bupivacaine and 15 µg fentanyl.

In this study, the following criteria were used to compare the recovery profiles after spinal anesthesia with bupivacaine and meperidine or fentanyl as adjuvants to bupivacaine: 1. times of initiation of sensory and motor blocks, 2. duration of sensory and motor blocks, 3. duration of effective analgesia, 4. the length of stay in a post-anesthesia care unit (PACU), and 5. adverse outcomes for mothers and neonates.

The technician preparing the solutions for the study was blinded to the study design. Electrocardiography (ECG), heart rate (HR), non-invasive blood pressure (NIBP), and pulse oximetry were all applied as standard monitoring techniques. After prepping the incision site, spinal anesthesia was administered in a sitting position using a Quincke needle through L4-L5 or L5-S1 intervertebral spaces. An anesthetist, who was blinded to the study design, recorded the level of sensory block by using the Pinprick test.[11]

The time between intrathecal injection and a loss of sensation at T6 (initiation of the sensory

block), and the time interval between intrathecal injection and two dermatomes sensory regression (duration of the sensory block) were recorded. Sensory and motor blockade onset and regression were assessed every 10 min after the spinal block, using a modified Bromage score of 0-3 (0: no motor block, 1: unable to raise extended legs but able to move knees and feet, 2: unable to raise extended legs and move knees but able to move feet, 3: complete motor block of the lower limbs).[12]

The parturient estimated her pain intensity using a visual pain score (VPS) ranging from 0 (pain-free) up to 10 (unbearable pain). VPS was recorded in the recovery room and also every time someone experienced pain after that. The termination of analgesia was defined as the moment at which VPS was greater than four. The mean length of stay in PACU was compared in all study groups. Systolic blood pressure (SBP) and heart rate were both measured and recorded. Hypotension, defined as a drop in SBP >30% of the baseline value, and bradycardia, defined as heart rate <50 beats/min, were treated with intravenous ephedrine (5 mg) and atropine (0.6 mg), respectively. Neonatal Apgar scores and umbilical venous blood PH were also recorded.

Statistical Analysis

All the data were analyzed using the SPSS software, version 21 (IBM Statistics, Chicago, USA). Data were expressed as mean±SD, median (interquartile range), or numbers and percentages. Continuous variables were analyzed using analysis of variance (ANOVA). The Kruskal-Wallis test, which uses nonparametric *post hoc* for pairwise comparison, was also used to analyze the data. For categorical variables, the comparison was assessed using the Chi square test or Fisher's exact test. $P<0.05$ was considered statistically significant.

Results

One hundred and twenty pregnant women who underwent spinal anesthesia for a Cesarean section were assigned randomly to one of the three experimental groups of the study, namely the B group received 2 mL of bupivacaine 0.5% (10 mg), the BM group received 8 mg bupivacaine and 10 mg meperidine, and the BF group received 8 mg bupivacaine and 15 µg fentanyl (figure 1).

The demographic characteristics, hemodynamic parameters of the baseline heart rate, and SBP of all the participants are presented in table 1. It also displays the demographic

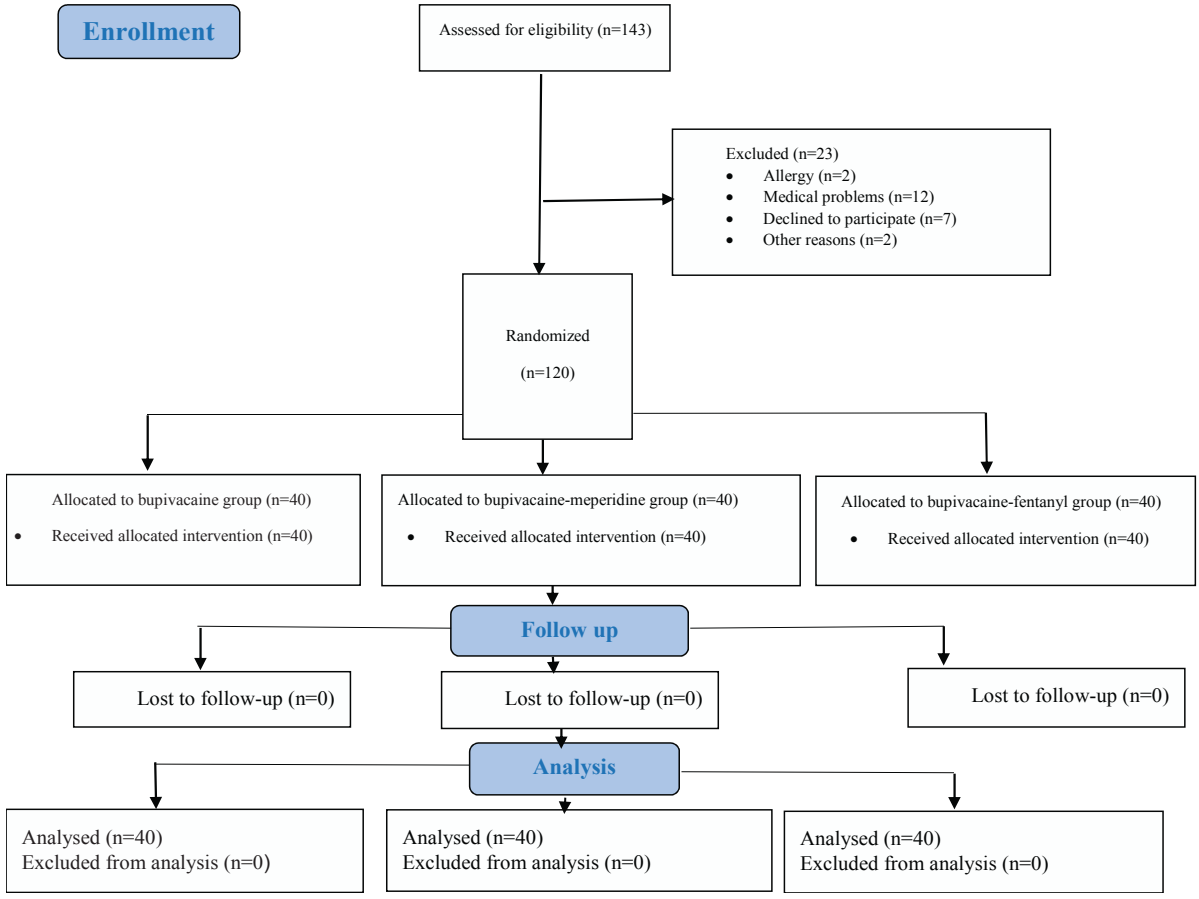

Figure 1: The CONSORT flow diagram of the study shows the inclusion and random allocation of the participants.

Table 1: Demographic and surgical characteristics of the patients

Variables	Groups			P value
	B (n=40) mean±SD	BM (n=40) mean±SD	BF (n=40) mean±SD	
Age (year)	27.1±4.4	27.6±3.7	27.8±4.4	0.71
Weight (Kg)	79.4±1.2	79.7±1.1	79.7±8	0.97
Systolic Blood Pressure Base (mm Hg)	126.56±2.05	127.66±1.61	123.6±2.64	0.44
Heart Rate Base (beats/min)	97.2±2.9	94±2.1	98.3±2.8	0.53

n: Number of patients; B: Bupivacaine group; BM: Bupivacaine+Meperidine group; BF: Bupivacaine+Fentanyl group; ANOVA was used. P<0.05 was considered statistically significant.

Table 2: Spinal block characteristics, the duration of analgesia, and time in different groups of patients

Variable	B (n=40)	BM (n=40)	BF (n=40)	P value*
Time of initiation of sensory block (sec)	45 (40-54)	65 (50-90)	70 (60-90)	<0.001
Time to reach highest sensory block (sec)	60 (51-750)	90 (70-120)	90 (80-120)	<0.001
Duration of sensory block (min)	150 (130-164)	102.5 (91-115)	105 (95-124)	<0.001
Time of initiation of motor block (sec)	60 (50-74)	100 (70-120)	95 (81-120)	<0.001
Duration of motor block (min)	137 (120-150)	90 (85-105)	95 (85-110)	<0.001
Duration of effective analgesia (min)	132 (107-167)	360 (289-596)	305 (182-386)	<0.001
Time of discharge from PACU (min)	145 (130-160)	100 (90-110)	105 (90-120)	<0.001

n: Number of patients; B: Bupivacaine group; BM: Bupivacaine+Meperidine group; BF: Bupivacaine+Fentanyl group; *Differences between B vs BM and BF groups. No statically differences were between BM and BF groups. Kruskal-Wallis test was used. P<0.05 was considered statistically significant.

Table 3: The highest sensory block and the degrees of sensory block after 120 minutes

Variables	Thoracic number	B (n=40)	BM (n=40)	BF (n=40)	P value
Highest sensory block	T4	14 (35)	12 (30)	9 (22.5)	0.58
	T5	8 (20)	13 (32.5)	12 (30)	
	T6	18 (45)	15 (37.5)	19 (47.5)	
Sensory block after 120 minutes	T9	33 (82.5)	8 (20)	10 (25)	<0.001*
	T≥10	7 (17.5)	32 (80)	30 (75)	

n: The number of patients; B: Bupivacaine group; BM: Bupivacaine+Meperidine group; BF: Bupivacaine+Fentanyl group; *Differences between BM and BF vs B groups. Chi squared test was used. P<0.05 was considered statistically significant.

comparison of all the studied groups (table 1). In terms of patient demographic characteristics such as age, weight, and hemodynamic parameters, there was no significant difference between the study groups.

Table 2 indicates the block onset and duration of the intrathecal agents, the duration of analgesia, and the time of discharge from PACU in each group. The onset of sensory blockade was significantly shorter in the B Group (45 sec) than the BM and BF groups (65 and 70 sec, respectively). The sensory block took a different amount of time to reach the T6 segment as the highest sensory level. The B group attained the T6 sensory block in a shorter time than the BM and BF groups (P<0.001). In comparison to the BM and BF groups, the duration of sensory and motor blocks was also significantly longer in the B group (P<0.001). The duration of effective analgesia in the BM (360 min) and BF (305 min) groups were significantly longer than the B group (132 min). Patients in the B group stayed in the PACU for a statistically longer time than those in BM and BF groups (145 min vs 100 and 105 min, respectively).

The T6 level was prevalent in 45% of the cases with the highest level of sensory block, with no significant difference between the groups. The sensory block level at 120 min following the spinal anesthesia was significantly different between groups, in the way that the level of sensory block in the B group was in T9 for 82.5% of the patients and ≥T10 for 75%-80% of the patients in the BM and BF groups, respectively (table 3).

Table 4 summarizes the adverse events in all the studied groups. Hypotension (P=0.002) and bradycardia (P=0.013) were significantly less prevalent in the BF and BM groups than in the B group, and about 58% of hypotension cases were in group B. There were no statistical differences in the incidence of nausea, vomiting,

Table 4: Maternal adverse outcomes

Event	B (n=40)	BM (n=40)	BF (n=40)	P value
Hypotension	19 (47.5)	8 (20)	6 (15)	0.002[a]
Bradycardia	10 (25)	3 (7.5)	2 (5)	0.013[b]
Nausea	5 (12.5)	9 (22.5)	5 (12.5)	0.060
Vomiting	1 (2.5)	5 (12.5)	2 (5)	0.270
Pruritus	0 (0)	6 (15)	0 (0)	0.003[c]
Shivering	5 (12.5)	2 (5)	2 (5)	0.500

n: The number of patients; B: Bupivacaine group; BM: Bupivacaine+Meperidine group; BF: Bupivacaine+Fentanyl group; a: Differences between BM and BF groups vs B group. b: Differences between BM and BF groups vs B group. c: Differences between BM vs B and F groups. Chi squared test was used. P<0.05 was considered statistically significant.

Table 5: Apgar scores and umbilical artery gas analysis

Variable	B (n=40) mean±SD	BD (n=40) mean±SD	BM (n=40) mean±SD	P value
APGAR (1 min)	8.27±0.72	8.25±0.74	8.22±0.73	0.95
APGAR (5 min)	9.82±0.38	9.80±0.4	9.82±0.38	0.94
PH	7.26±0.02	7.26±0.02	7.26±0.09	>0.99

n: The number of patients; B: Bupivacaine group; BM: Bupivacaine+Meperidine group; BF: Bupivacaine+Fentanyl group; The statistical test was ANOVA. P<0.05 was considered statistically significant.

and shivering among the three groups. Apgar scores (at 1 and 5 min) and umbilical artery PH were within normal ranges in all the studied groups, with no significant differences between groups (table 5).

Discussion

The findings of the present study indicated that intrathecal low-dose spinal anesthesia ensured effective anesthetic conditions, prolonged safe analgesia, and reduced the length of stay in PACU, while also increasing maternal hemodynamic stability.

The time to onset of sensory and motor block is shorter with bupivacaine, and this group achieved the maximum sensory block level in the shortest time. According to the findings, the mean times for sensory and motor regression among subjects who received meperidine or fentanyl in combination with 8 mg bupivacaine were significantly shorter (P<0.0001) than for bupivacaine. This implies that the duration of sensory and motor blocks was longer in the bupivacaine group.

Several studies were conducted to investigate the effect of adding different dosages of fentanyl and meperidine to 10 mg of bupivacaine.[13, 14] In addition, there is some evidence that suggests reducing the spinal dose of bupivacaine can generate effective anesthesia with fewer hemodynamic side effects.[15] However, these studies did not investigate effective analgesia and shorter length of stay, which are crucial factors in Cesarean section procedures. To the best of our knowledge, this is the first study that evaluated the effect of intrathecal meperidine or fentanyl on a spinal block using low-dose bupivacaine.

In a study, Frances Conway and others evaluated three equal groups of patients who received meperidine at different doses: 0.8 mg/ Kg, 0.4 mg/ Kg plus 1.5 mL of 0.5% heavy bupivacaine, or 3 mL of heavy bupivacaine 0.5%. They reported that meperidine caused a slower onset of sensory and motor block than bupivacaine.[16]

In this study, we observed that the duration of effective analgesia was significantly longer in BM and BF groups than in the B group (P<0.001), and the latter group had a statistically longer length of stay in the PACU than the other two groups. Meperidine and fentanyl bind to different opioid receptors on the cell surface, stimulate the exchange of GTP for GDP on the G-protein complex, and trigger intracellular mechanisms that eventually lead to cell hyperpolarization and nerve activity inhibition.[17] Bupivacaine appears to exert its analgesic effects by binding to the prostaglandin E2 receptors, which inhibits prostaglandins production, reducing fever, inflammation, and hyperalgesia.[18]

In a study by Yu and colleagues, meperidine was applied as an adjuvant to hyperbaric bupivacaine in a Cesarean section. They found that the duration of effective analgesia in the meperidine group was longer than the bupivacaine group.[13] In another study, Wojciech Weigl and others found that adding 25 µg of intrathecal fentanyl to local anesthetics was

effective for intraoperative analgesia and decreased opioid consumption after Cesarian section without increasing maternal or neonatal adverse effects.[19]

In this study, itching complications were observed in 6 (15%) patients of the BM group. It means that the administration of meperidine with bupivacaine increased the feeling of itching, whereas bupivacaine alone or in combination with fentanyl had no similar effect. Chun and others compared their side effects and found that itching complication was more prevalent in the meperidine group than in the saline group (16% vs. 0%).[20]

Hypotension and bradycardia were found to be significantly less frequent in BM and BF groups than in the B group. The incidence of hypotension during Cesarean section with conventional local anesthetic doses can be as high as 70–80%.[21, 22] Studies that compared the combined epidural with low-dose spinal anesthesia found a decreased incidence of hemodynamic instability, including hypotension, bradycardia, nausea, and vomiting.[23-26]

Lowering the bupivacaine dose also appears to result in less nausea and less use of vasopressor.[27, 28] Reduced intrathecal bupivacaine doses in combination with various opiates decreased the incidence of hemodynamic instability and enhanced anesthesia quality.[28-31]

In line with previous findings,[32, 33] the findings of the present study revealed that there were no signs of neonatal adverse effects, as indicated by Apgar scores between 8 and 10 at 1 and 5 min, respectively.

Conclusion

Although lower bupivacaine doses might be associated with a lower incidence of complications and an improved maternal cardiac index, they might not provide adequate anesthesia for surgery. According to the findings of the present study, intrathecal low-dose spinal anesthesia induced by bupivacaine (8 mg) in combination with meperidine or fentanyl for Cesarean section increased maternal hemodynamic stability, while also ensuring effective anesthetic conditions, extending effective analgesia, and reducing the length of stay in the PACU.

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Authors' Contribution

Z.F: Study conception, data collection, writing of the proposal, and writing and editing the final version of the manuscript; V.N: Study conception, writing the proposal and the manuscript, and revising the final article; A.A: Data collection, data analysis, proposal preparation and writing the draft of the manuscript; S.A: Data analysis, writing the draft of the manuscript, and editing and revising the final version of the manuscript; N.A: Study design, data collection, data analysis, and writing the draft of the manuscript; M.B.KH: Study conception, proposal design, writing the draft of the manuscript, and revising the final manuscript; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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