Tropical Journal of Pharmaceutical Research January 2022; 21 (1): 193-199
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i1.28

Original Research Article

Effect of bupivacaine combined with fentanyl for simultaneous spinal-epidural anesthesia on hemodynamics, and maternal and infant outcomes in patients undergoing cesarean section

Shuai Li[1-3], Xiao Dai[2-4], Ying Wang[5], Lei Shen[6], Nannan Hao[1-3]*

[1]Department of Anesthesiology, Xuzhou Central Hospital, Xuzhou, Jiangsu, [2]The Affiliated Xuzhou Central Hospital of Nanjing University of Chinese Medicine, [3]Xuzhou Clinical School of Xuzhou Medical University, [4]Operating Theatre, Xuzhou Central Hospital, Xuzhou, Jiangsu, [5]Department of Anesthesiology, The Affiliated Yanda Hospital of Heibei Medical University, Langfang, Hebei, [6]Department of Anesthesiology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu, China

For correspondence:* ***Email:* *paperworkdan@163.com;* ***Tel:*** *+86-018168778159*

Sent for review: 9 August 2021 *Revised accepted: 14 December 2021*

Abstract

Purpose: *To compare the effects of bupivacaine combined with fentanyl vs. bupivacaine alone in cesarean patients undergoing combined spinal-epidural anesthesia (CSE).*
Methods: *This was a randomized controlled study that included 84 healthy women with singleton foetuses who were scheduled for cesarean delivery at Xuzhou Central hospital. They were divided into fentanyl combined with bupivacaine group (group A, n = 42) and bupivacaine alone group (Group B, n = 42). The primary outcome was hemodynamic changes in patients undergoing cesarean section while the secondary outcomes were neonatal Apgar score, incidence of intraoperative and postoperative adverse reactions and time to onset, and duration of anesthesia.*
Results: *One hour after the surgery started, blood pressure was significantly lower in group A than in group B. Upon skin incision and one hour after commencement, the group A showed decreased heart rate compared with group B. Intraoperative pain level was significantly lower in group B than in group A. Compared with group A, group B has shorter motor block time, and duration of motor block was significantly longer in group B than in group A.*
Conclusion: *Bupivacaine combined with fentanyl improves maternal hemodynamic stability during cesarean section, resulting in faster onset of anesthesia and prolonged motor block, but with no difference from bupivacaine alone in terms of intraoperative and intraoperative adverse reactions, neonatal cardiopulmonary and circulatory function.*

Keywords: *Bupivacaine, Fentanyl, Cesarean section, Spinal-epidural anesthesia*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

With the increasing demand for comfort measures in childbirth and the lifting of birth control restrictions in China, cesarean delivery has become increasingly popular [1,2]. Cesarean delivery is a priority in pregnant women with contraindications for natural delivery, abdominal

disorders, scar pregnancy, and advanced age [3]. Due to the unique physiological state of mother, anesthetic management during cesarean delivery must be rapid in onset, complete analgesia, and good muscle relaxation, as well as ensuring stable maternal and fetal vital signs [4]. The effects of anesthesia not only affect out of bed activities in the early stage and breastfeeding, but are also associated with postoperative complications such as thromboembolism and may even be the cause of chronic pain [4].

It is generally accepted that caesarean delivery under general anesthesia tends to cause birth asphyxia. Therefore, general anesthesia is rarely performed in women requiring cesarean delivery. The combined spinal–epidural technique (CSE) has become increasingly popular in recent years, which was associated with high satisfaction among both surgeons and patients [5]. Despite precautions, hypotension remains a dangerous side effect of C-sections. Reduced dose of local anesthetic drugs has a beneficial effect on hemodynamic stability, and one study found effect of intrathecal bupivacaine on maternal arterial blood pressure showed a dose-dependent manner. However, lower dose of bupivacaine leads to increased pain level during surgery [6]. The addition of opioids to low-dose bupivacaine improves the quality of anesthesia while reducing the incidence of hypotension.

Therefore, the aim of this study was to compare the effects of bupivacaine combined with fentanyl in cesarean delivery with bupivacaine alone during C-section.

METHODS

Subjects

After ethics committee approval and written informed consent was signed, 84 healthy patients with singleton fetuses, scheduled to undergo cesarean delivery, were randomized.

Inclusion criteria

1. singleton, full-term pregnancy lasting 37 - 42 weeks; 2. Pregnant woman aged over 21 years; 3. No history of diabetes or hypertension before pregnancy and normal blood pressure during pregnancy, The American Society of Anesthesiologists (ASA) classification: 1-2; 4. Expected to receive cesarean delivery; 5. signed consent to participate in this study. Exclusion criteria: 1. women who were unable to undergo CSE; 2. women who were allergic to bupivacaine or fentanyl; 3. women with coagulation disorders; 4. women with grade 3 or higher cardiac insufficiency, liver and kidney dysfunction; 5. women with severe pregnancy complications; 6. women who had been diagnosed with intrauterine fetal growth retardation, congenital anomalies and placenta previa.

The 84 women who met the inclusion criteria were divided into bupivacaine alone group (group A) and fentanyl combined bupivacaine group (group B) through randomization, with 42 cases in each group.

Ethical approval

Ethical approval for the human studies was obtained from the ethics committee of Xuzhou Central Hospital for the human studies (approval no. 2020PS33K) and followed the guidelines of Declaration of Helsinki for medical research involving human subjects [7].

Treatments

Intravenous antibiotics and oxytocin were administrated with two separate catheters after delivery of the fetus. Both were injected with 1500 ml of Hartmann's solution preheated to 37°C through the intravenous catheter within 20 min prior to anesthesia. All women lay in right lateral position. After routine disinfection, L2-L3 or L3-L4 intervertebral space was selected as the puncture point which was punctured via intravenous cannulation. The needle was withdrawn after breaking through the dura mater. The position of the spinal needle was confirmed by aspiration of cerebrospinal fluid, followed by injection of drugs.

The bupivacaine alone group was infused with 5 mg bupivacaine (Shanghai Hefeng Pharmaceutical Co. Ltd, Shanghai, China). Group B was administered with 30 ug fentanyl (Shanghai Harvest Pharmaceutical Co. Ltd, Shanghai, China) + 5 mg bupivacaine. The level of motor block was determined with a swab and the procedure was started when the L4 level was reached. Oxygen was administered through a mask at a flow rate of 4 l/min. The hemodynamic indicators, including blood pressure, heart rate, and electrocardiogram were monitored. In the event of blood pressure falling below 20% of the pre-anaesthetic level or systolic blood pressure falling below 100 mmHg, 5 mg intravenous ephedrine was immediately administered and repeated if necessary. After the operation, the mother was transferred to the ward and instructed to lie flat with the pillow removed for 8 h. Follow-up was performed for 3 days.

Assessment of haemodynamics

Maternal mean arterial pressure (MAP), heart rate (HR) while the mother was quiet in the ward (T0), before anesthetic administration (T1), 2 min after administration (T2), upon skin incision (T3), 1 h after beginning of surgery (T4), and at the end of cesarean delivery (T5) were recorded.

Evaluation of anesthetic effect

The postoperative maternal pain (evaluated using visual analogue scale) are recorded for each group: a score of 0 to 10 indicated pain levels ranging from completely painless to unbearably severe pain. The time to onset of sensory block (the onset of a sensation of heat, tingling, or numbness in the lower extremities); the time to onset of motor block (the onset to a sensation of heavy leg lifting), and the duration of motor block were recorded. The level of intraoperative muscle relaxation was evaluated with reference to abdominal muscle contractility and fatigue: Grade I, complete relaxation of the abdominal muscle, smooth operation of opening and closing the abdomen; Grade II, slightly tense abdominal muscle, mild restriction of opening and closing the abdomen; Grade III, severe tension of the abdominal muscle, hindering surgical operation.

Assessment of outcomes

Maternal adverse reactions

Within 2 days from the completion of surgery, the general events reported by puerpera and their families in each group were recorded, including dragging pain, respiratory depression, chills, nausea and vomiting. The evaluation criteria for chills were the presence of facial and neck convulsions, or the facial and systemic muscle tremors. In terms of neurological complications, postoperative headache, lumbar radiculopathy and cauda equina syndrome were recorded.

Infantile adverse reactions

The Apgar test was performed on the newborn at 1 minute after birth by a doctor. According to the performances of breathing effort, heart rate, muscle tone, reflexes and skin color, the Apgar score was provided. Apgar score usually ranges from 7 to 10, with 4 to 6 implying mild asphyxia and below 4 indicating the need for immediate resuscitation.

Statistical analysis

Statistical analyses were performed using the Statistic Package for Social Science (SPSS) version 24.0 package (SPSS Inc, Chicago IL, USA). Continuous variables are expressed as mean and standard deviation (mean ± SD). Plots were made using GraphPad Prism8 (La Jolla, CA, USA). Qualitative variables are reported as frequencies or percentages. Quantitative variables were evaluated using the *t*-test, while qualitative variables were evaluated using by chi-square test. $P < 0.05$ was considered statistically significant.

RESULTS

Patient profile

Eighty-four women were included in the study, with 42 in each group. There were no significant differences in demographic variables such as age, weight, and week of gestation, between two groups (Table 1).

Hemodynamics

Mean arterial pressure and heart rate at basal level, measured in the ward, did not differ significantly between two groups. Prior to anesthesia, elevated arterial pressure and accelerated heart rate were observed in two groups, presumably related to patient tension. After anesthesia there was a decrease in blood pressure in both groups, and at the 1-h after beginning of surgery, blood pressure in group A was significantly lower than that in group B (Figure 1). Heart rate in group A was significantly lower than that in group B upon skin incision and 1-h after beginning of surgery (Table 2 and Figure 2).

Table 1: Demographics and characteristics of patients

Variable	Group A (n=42)	Group B (n=42)	*P*-value
Age (years)	26.67±3.46	26.83±3,64	0.83
BMI (kg/m^2)	27.00±2.07	27.12±1.60	0.77
Gestational age (weeks)	39.09±0.45	39.09±0.53	0.54
Primipara/multipara	30/12	27/15	0.48
Mean ASA score	1.29±0.46	1.48±0.51	0.07

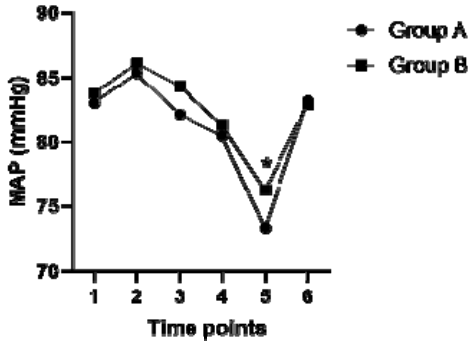

Figure 1: Comparison of MAP between the 2 groups. * *P* < 0.05. Group A = bupivacaine group: Group B = bupivacaine combined with fentanyl group. MAP, mean arterial pressure

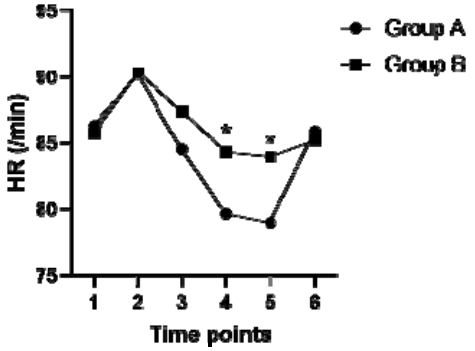

Figure 2: Comparison of HR between the two groups. **P* < 0.05; Group A: Bupivacaine group; Group B: Bupivacaine combined with fentanyl group; HR – heart rates

Anesthesia effect

According to VAS, intraoperative maternal pain was significantly lower in group B than in group A. Therefore, the pain relief by combined drugs was better than that of one drug alone. There was no significant difference between two groups in the time to onset of sensory block, but the time to onset of motor block was significantly shorter in group B than in group A, and the duration of motor block was significantly longer in group B than in group A. Based on the abdominal muscle relaxation score, all patients in group B met the surgical requirements of anesthesia, and more people in group A scored grade II or III than in group B (Table 3).

Maternal and infant outcomes

A few women in both groups experienced adverse effects such as stretch reflex, chills, nausea and vomiting, but no more serious adverse reactions such as respiratory depression were observed in either group. Neurological complications such as postoperative headache, lumbar radiculopathy and cauda equina syndrome occurred less in group B than in group A within 2 days after surgery, but there was no statistical difference between two groups (Table 4). There were no respiratory or circulatory disturbances in the neonates of both groups after birth. There was no significant difference in Apgar scores at 1 and 5 minutes after birth (Table 5).

Table 2: Hemodynamic variables of patients during operations

Time-point	MAP (mmHg)		*P*-value	HR (times/min)		*P*-value
	Group A	*Group B*		*Group A*	*Group B*	
T0	82.98±1.24	83.72±1.53	0.98	86.33±1.34	85.73±1.62	0.89
T1	85.34±1.46	86.13±1.57	0.95	90.21±1.82	90.35±1.62	0.97
T2	82.09±1.22	84.35±1.86	0.68	84.52±1.54	87.43±1.62	0.43
T3	80.48±1.58	81.27±1.32	0.74	79.65±1.72	84.33±1.56	0.02
T4	73.3±0.98	76.3±1.57	0.02	78.98±1.87	83.97±1.23	0.01
T5	83.17±1.21	82.93±1.42	0.78	85.92±1.73	85.21±1.65	0.93

Table 3: Anesthetic effect

Variable		Group A	Group B	*P*-value
Sensory block onset time (seconds)		42.82±16.27	40.68±9.02	0.46
Motor block onset time (minutes)		7.61±1.14	5.88±0.86	<0.01
Motor block duration time (minutes)		121±20.54	161±23.79	<0.01
Visual analogue scale		5.04±0.40	2.95±0.27	<0.01
Muscle relaxation score	I	36	39	*0.44*
	II	5	3	
	III	1	0	

Table 4: Adverse reactions during and after the operations

Group	Dragging pain	Respiratory depression	Nausea and vomiting	Shiver	Neurological complications
A	2	0	3	2	4
B	3	0	3	1	1
p	0.65		1	0.56	0.17

Table 5: The Apgar scores for infants

Group	Apgar score	
	1 min after birth	***5 min after birth***
A	8.47±0.73	9.49±0.47
B	8.69±0.65	9.51±0.46
p	0.16	0.91

DISCUSSION

Cesarean delivery is one of most common surgical procedures [1,2]. Although cesarean delivery could reduce the risk of birth injuries such as asphyxia, shoulder dystocia, and fractures, which are associated with moderate-to-severe intraoperative pain [8]. The effect of anesthesia not only affects early mobility and breastfeeding, but is also associated with postoperative complications such as thromboembolism and may even induce chronic pain [3]. The present study found that bupivacaine combined with fentanyl improved hemodynamic stability during cesarean section, resulting in faster onset of anesthesia, longer duration of motor block (compared to bupivacaine alone), and showed no difference from bupivacaine alone in terms of intraoperative and intraoperative adverse reactions, neonatal cardiopulmonary and circulatory function.

Local anesthesia is more commonly used than general anesthesia for cesarean delivery [9]. It allows the mother to remain awake and actively participate in the delivery of the baby, avoiding fatal risks of general anesthesia [10]. Spinal anesthesia and epidural anesthesia have respect advantages: the former is simple to perform and provides reliable anesthetic blockade through small doses of anesthetics, while the latter provides stronger analgesic effects and postoperative analgesia [11]. Both have their own shortcomings: spinal anesthesia has been associated with higher incidence of severe hypotension, post-dural puncture headache, and poor control of sensory levels; epidural anesthesia demands higher dose, which is time consuming, and has a high incidence of inadequate block [12]. Combined lumbar and epidural anesthesia has gained popularity is that it combines the reliability of spinal anesthesia with the flexibility of epidural anesthesia during cesarean delivery [13]. However, evidence from clinical studies on effects of combined lumbar and epidural anesthesia is still insufficient [5].

Since the discovery of opioid receptors in the brain and spinal cord, intrathecal injection of opioids was recognized as an effective method of analgesia [14]. Hydrophilic morphine causes some of their analgesic effects through spinal selectivity due to its slow clearance from the spinal cord. However, hydrophilicity also leads to slow penetration as well as slow onset of analgesia, prolonged duration of metabolism in the cerebrospinal fluid and the risk of delayed respiratory depression due to possible diffusion to the medulla oblongata. In contrast, lipophilic opioids such as fentanyl, have a good clinical profile with rapid onset of action, longer duration, and less risk of delayed respiratory depression. Therefore, fentanyl is a better choice for use in combination with bupivacaine. However, there is no consensus on the dose of opioids.

Previous studies have proposed that intrathecal fentanyl as a supplement to bupivacaine should be administered at a dose of 10 g to achieve intraoperative pain relief and 12.5 ug to achieve prolonged postoperative analgesia [15]. For higher doses, studies have shown that the duration of postoperative analgesia increases with increasing doses of fentanyl. However, time to regain motor and sensory are not prolonged. This is contrary to the ceiling effect proposed by some evidence [16]. It has been suggested that 20 – 30μg of fentanyl should be administered intrathecally as a supplement to bupivacaine anesthesia [17]. In this study, 30 ug of fentanyl produced effective analgesia.

Common adverse reactions in cesarean delivery include stretch reflex, chills, nausea and vomiting. These adverse reactions not only increase intraoperative maternal discomfort but, more importantly, increase oxygen consumption, which can cause hemodynamic instability and, in severe cases, life-threatening organ dysfunction

or cardiac arrhythmias. Although fentanyl combined with local anesthetics provides additional analgesia, it also increases the risk of urinary retention, pruritus, excessive shock, or respiratory depression [18]. Therefore, it is vital to use as small dose of fentanyl as possible when combining bupivacaine and fentanyl, and to closely monitor maternal signs and symptoms associated with epidural analgesia.

Opioids are commonly believed to cause nausea, but in fact, intrathecal administration modalities can prevent intraoperative nausea and vomiting [19]. Several studies have shown that fentanyl combined with local anesthetics significantly reduces the incidence of perioperative nausea and vomiting and reduces the consumption of antiemetic medication during cesarean delivery [20]. The incidence of nausea and vomiting was similar in both groups in this study.

Previous studies have suggested that the combination of sufentanil reduces the incidence of shivering and visceral pain after spinal anesthesia, which may be related to the blockage of visceral neurotransmission by sufentanil [21]. However, the number of adverse reactions in our study was similar to that of bupivacaine alone, differing significantly from the results of previous studies. The difference between studies may be attributed to some influencing factors such as duration of fasting and the straining of the peritoneum during suturing. Therefore, studies with larger samples are still needed to address these differences. In terms of duration of anesthesia, our findings are consistent with previous studies confirming that opioids such as fentanyl or sufentanil combined with bupivacaine for cesarean anesthesia prolongs the duration of analgesia and motor block.

Limitations of the study

This study has some shortcomings, including the lack of quantitative criteria for indicators such as nausea, and the short observation period of the trial and small sample sizes.

CONCLUSION

Bupivacaine combined with fentanyl improves maternal hemodynamic stability during cesarean section, with faster onset of anesthesia and prolonged motor block, but is not different from bupivacaine alone in terms of intraoperative and intraoperative adverse reactions, neonatal cardiopulmonary and circulatory function. Therefore, this anesthetic approach has definite advantages over the use of fentanyl alone.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

Open Access

REFERENCES

1. *Wood S, Tang S. Changes in the Frequency of Cesarean Delivery in Nulliparous Women in Labor in a Canadian Population, 1992-2018. Obstet Gynecol 2021; 137(2): 263-270.*
2. *Sakai-Bizmark R, Ross MG, Estevez D, Bedel L, Marr EH, Tsugawa Y. Evaluation of Hospital Cesarean Delivery-Related Profits and Rates in the United States. JAMA Netw Open 2021; 4(3): e212235.*
3. *Gregory KD, Jackson S, Korst L, Fridman M. Cesarean versus vaginal delivery: whose risks? Whose benefits? Am J Perinatol 2012; 29(1): 7-18.*
4. *Lim G, Facco FL, Nathan N, Waters JH, Wong CA, Eltzschig HK. A Review of the Impact of Obstetric Anesthesia on Maternal and Neonatal Outcomes. Anesthesiology 2018; 129(1): 192-215.*
5. *Klimek M, Rossaint R, van de Velde M, Heesen M. Combined spinal-epidural vs. spinal anaesthesia for caesarean section: meta-analysis and trial-sequential analysis. Anaesthesia 2018; 73(7): 875-888.*
6. *Fan SZ, Susetio L, Wang YP, Cheng YJ, Liu CC. Low dose of intrathecal hyperbaric bupivacaine combined with epidural lidocaine for cesarean section--a balance block technique. Anesth Analg 1994; 78(3): 474-477.*
7. *Mandal J, Acharya S, Parija SC. Ethics in human research. Trop Parasitol 2011; 1(1): 2-3.*
8. *Hankins GD, Clark SM, Munn MB. Cesarean section on request at 39 weeks: impact on shoulder dystocia, fetal trauma, neonatal encephalopathy, and intrauterine fetal demise. Semin Perinatol 2006; 30(5): 276-287.*

9. Ikeda T, Kato A, Bougaki M, Araki Y, Ohata T, Kawashima S, Imai Y, Ninagawa J, Oba K, Chang K, et al. A retrospective review of 10-year trends in general anesthesia for cesarean delivery at a university hospital: the impact of a newly launched team on obstetric anesthesia practice. Bmc Health Serv Res 2020; 20(1): 421.
10. Afolabi BB, Lesi FE. Regional versus general anaesthesia for caesarean section. Cochrane Database Syst Rev 2012; 10: D4350.
11. Carrie LE, O'Sullivan G. Subarachnoid bupivacaine 0.5% for caesarean section. Eur J Anaesthesiol 1984; 1(3): 275-283.
12. Rukewe A, Adebayo OK, Fatiregun AA. Failed Obstetric Spinal Anesthesia in a Nigerian Teaching Hospital: Incidence and Risk Factors. Anesth Analg 2015; 121(5): 1301-1305.
13. Guasch E, Brogly N, Gilsanz F. Combined spinal epidural for labour analgesia and caesarean section: indications and recommendations. Curr Opin Anaesthesiol 2020; 33(3): 284-290.
14. Nanji JA, Carvalho B. Pain management during labor and vaginal birth. Best Pract Res Clin Obstet Gynaecol 2020; 67: 100-112.
15. Chu CC, Shu SS, Lin SM, Chu NW, Leu YK, Tsai SK, Lee TY. The effect of intrathecal bupivacaine with combined fentanyl in cesarean section. Acta Anaesthesiol Sin 1995; 33(3): 149-154.
16. Hunt CO, Naulty JS, Bader AM, Hauch MA, Vartikar JV, Datta S, Hertwig LM, Ostheimer GW. Perioperative analgesia with subarachnoid fentanyl-bupivacaine for cesarean delivery. Anesthesiology 1989; 71(4): 535-540.
17. Hamber EA, Viscomi CM. Intrathecal lipophilic opioids as adjuncts to surgical spinal anesthesia. Reg Anesth Pain Med 1999; 24(3): 255-263.
18. Youssef N, Orlov D, Alie T, Chong M, Cheng J, Thabane L, Paul J. What epidural opioid results in the best analgesia outcomes and fewest side effects after surgery? a meta-analysis of randomized controlled trials. Anesth Analg 2014; 119(4): 965-977.
19. Palmer CM, Cork RC, Hays R, Van Maren G, Alves D. The dose-response relation of intrathecal fentanyl for labor analgesia. Anesthesiology 1998; 88(2): 355-361.
20. Dahlgren G, Hultstrand C, Jakobsson J, Norman M, Eriksson EW, Martin H. Intrathecal sufentanil, fentanyl, or placebo added to bupivacaine for cesarean section. Anesth Analg 1997; 85(6): 1288-1293.
21. de Figueiredo LG. Incidence of shivering after cesarean section under spinal anesthesia with or without intrathecal sufentanil: a randomized study. Rev Bras Anestesiol 2012; 62(5): 676-684.