Retrospective Study

Effects on newborns of applying bupivacaine combined with different doses of fentanyl for cesarean section

Yun Wang, Wen-Xun Liu, Xiao-Hong Zhou, Min Yang, Xin Liu, Yuan Zhang, Ke-Rong Hai, Qing-Shan Ye

Abstract

BACKGROUND
The choice of anesthesia for cesarean section is very important.

AIM
To compare the effects of applying bupivacaine combined with different doses of fentanyl on newborns after cesarean section.

METHODS
We randomly divided one hundred and twenty patients undergoing cesarean section into the following 4 groups: group B (bupivacaine group), group BF10 (bupivacaine combined with 10 µg fentanyl), group BF30 (bupivacaine combined with 30 µg fentanyl) and group BF50 (bupivacaine combined with 50 µg fentanyl). The heart rate, mean arterial pressure, block plane fixation time and sensory block time were recorded. Umbralical artery blood was then collected immediately after delivery for blood gas analysis and qualitative detection of fentanyl. Additionally, data on the neonatal 1-min and 5-min Apgar scores, results of umbilical artery blood gas analysis and qualitative detection of fentanyl in umbilical artery blood were recorded.

RESULTS
Although the mean arterial pressure decreased in all four groups at 3 min after anesthesia, the percentage of the decrease was less than 20% of the baseline. In addition, there were no significant differences in the 1-min or 5-min Apgar scores or the umbilical artery blood gas analysis among the four groups ($P > 0.05$).
INTRODUCTION

In older parturients, parturients with difficulties and other parturients who cannot give birth vaginally, the demand for cesarean section[1, 2] has increased, and the vaginal delivery rate has decreased in recent years. However, the choice of anesthesia for cesarean section is very important. It is necessary for anesthesiologists to carefully consider this in order to select reasonable anesthetic methods and appropriate anesthetic drugs.

Spinal anesthesia[3, 4] is a common method of anesthesia for cesarean section. In fact, many studies have shown that opioids plus local anesthetics can have many benefits, such as prolonging the time of intraoperative and postoperative analgesia[5], effectively inhibiting the traction reaction caused by surgery[6] and allowing more stable hemodynamics[7]. Fentanyl[8] is a commonly used opioid drug and is administered by intrathecal injection. However, reports on whether fentanyl enters the blood and affects the safety of newborns are rare.

Thus, this study aimed to qualitatively detect the concentration of fentanyl in umbilical artery blood using an ELISA kit[9] to examine the effects of bupivacaine combined with different doses of fentanyl on newborns delivered by cesarean section.

MATERIALS AND METHODS

Materials
This study was approved by the Medical Ethics Committee of our hospital (Ethical approval Number: 063) and all patients signed an informed consent form.

One hundred and twenty cases of singleton full-term cesarean section were selected, whose characteristics were as follows: ASA grade: II, age: 25-35 years old, weight: 70-90 kg, no obstetrical-related complications (such as hypertensive disorder complicating pregnancy, pregnancy complicated with diabetes, maternal congenital heart disease, placental abruption, fetal distress, placenta previa, etc.), no known fetal developmental abnormalities and malformations, no infectious diseases such as syphilis, hepatitis B and HIV, and no contraindications to lumbar anesthesia.

Methods
Grouping: The patients were randomly divided into 4 groups: bupivacaine (B) group (0.75% bupivacaine 2 mL + cerebrospinal fluid total 3 mL); BF10 group: (0.75% bupivacaine 2 mL + fentanyl 10 μg + cerebrospinal fluid total 3 mL); BF30 group: bupivacaine combined with fentanyl 30 μg group (0.75% bupivacaine 2 mL + fentanyl 30 μg group) 0.75% bupivacaine 2 mL + fentanyl...
30 μg + cerebrospinal fluid total 3 mL); Group BF30: bupivacaine combined with fentanyl 30 μg group (0.75% bupivacaine 2 mL + fentanyl 30 μg + cerebrospinal fluid total 3 mL). BF50 group: bupivacaine combined with fentanyl 50 μg group (0.75% bupivacaine 2 mL + fentanyl 50 μg total 3 mL).

**Anesthesia procedure:** Electrocardiograph (ECG), heart rate, blood pressure and pulse oxygen saturation were monitored regularly in all parturients. Venous access on one side of the upper limb was achieved and 500 mL of warm compound sodium chloride was infused at a speed of 30 mL/min. The routine preparation of first aid drugs phenoxyphrine (40 μg/mL) and atropine 0.5 mg was conducted. All patients were placed in the left recumbent position, the L3-4 intervertebral space was punctured using a 25G lumbar anesthesia needle, and local anesthesia with lidocaine 2 mL was administered. When two breakthroughs were felt, colorless transparent cerebrospinal fluid which flowed smoothly was seen after the core of the needle was removed, and the drug solution was injected at the speed of 0.2 mL/s. Finally, patients were asked to turn over and lie flat after anesthesia, the operating bed was tilted 15 degrees to the left, and the patient inhaled oxygen by mask. ECG, heart rate, blood pressure and pulse oxygen saturation were continuously monitored.

**Main observation indices**
The heart rate and mean arterial pressure were recorded every 3 min.

The fixed time of block plane and the maintenance time of sensory block were recorded.

Apgar scores in 1 min and 5 min in newborns were recorded.

The surgical assistant collected 1 mL umbilical artery blood using a blood gas needle for analysis and the results were recorded immediately after delivery of the fetus.

Umbilical artery blood (3 mL) was collected using a heparinized aseptic syringe and injected into vacuum collection vessels. The upper serum was collected and stored in a -80°C refrigerator and the concentration of fentanyl was determined after high-speed centrifugation.

**Statistical analysis**
The data from each group were analyzed using SPSS19.0 statistical software. The measurement data were expressed as mean ± SD. The t test was used for comparisons between groups, the χ² test for comparisons of counting data and Fisher’s exact probability method was used to compare rates. P values < 0.05 were considered statistically significant.

**RESULTS**
There were no significant differences in age, height, weight, gestational age, ASA grade and basal mean arterial pressure (MAP) between the groups (Table 1). The results of related indices of anesthesia and surgery in the four groups were as follows: Although MAP decreased 3 min after anesthesia, the percentage of decrease in the basic value was less than 20%. In addition, there were no significant differences in the time from the completion of anesthesia to fetal delivery and the duration of surgery in each group (P > 0.05). Furthermore, there was a significant difference in the recovery time of sensory block among the four groups (P < 0.05) (Table 2).

Neonatal Apgar scores and umbilical artery blood gas analysis among the four groups were not significantly different (P > 0.05) (Table 3).

The qualitative test results for fentanyl in umbilical artery blood in the four groups were negative according to the standard analysis of the test results of the Fentanyl Group ELISA Kit (NEOGEN, United States) (Table 4).

**Fentanyl group ELISA Kit criteria**
Positive results: the absorbance was less than or equal to the standard specified by the laboratory, and positive results were quantitatively detected by gas chromatography or mass spectrometry.

Negative results: the absorbance was greater than the standard specified by the laboratory.
## Table 1 Comparison of general data in the four groups of patients (n = 30, mean ± SD)

|               | B         | BF<sub>10</sub> | BF<sub>30</sub> | BF<sub>50</sub> |
|---------------|-----------|-----------------|-----------------|-----------------|
| Age (yr)      | 28.9 ± 4.3| 29.1 ± 3.0      | 28.0 ± 2.8      | 28.3 ± 2.4      |
| Weight (kg)   | 75.1 ± 3.9| 74.1 ± 6.6      | 73.6 ± 3.8      | 74.1 ± 4.4      |
| Height (cm)   | 163.7 ± 4.2| 162.2 ± 3.7    | 163.3 ± 2.7     | 162.8 ± 2.5     |
| Gestational age (wk) | 38.4 ± 1.3 | 38.4 ± 1.3   | 38.6 ± 0.8      | 38.7 ± 0.9      |
| ASA grade (I/II)  | 22/8      | 23/7           | 22/8            | 23/7            |
| MAP (mmHg)    | 91.6 ± 7.3| 90.0 ± 7.1      | 93.0 ± 9.6      | 89.7 ± 7.1      |
| Heart rate    | 89.0 ± 15.2| 89.8 ± 14.1    | 92.8 ± 20.3     | 93.5 ± 10.4     |

Group B (bupivacaine group), BF10 group (bupivacaine combined with 10 μg fentanyl), BF30 group (bupivacaine combined with 30 μg fentanyl), BF50 group (bupivacaine combined with 50 μg fentanyl). MAP: Mean arterial pressure.

## Table 2 Comparison of the results of related indices of anesthesia and surgery in the four groups of patients (n = 30, mean ± SD)

|               | B         | BF<sub>10</sub> | BF<sub>30</sub> | BF<sub>50</sub> |
|---------------|-----------|-----------------|-----------------|-----------------|
| 3 min MAP decreased after anesthesia (as a percentage of the basal value) % | 11.5 | 10.9 | 7.6 | 8.6 |
| The time of sensory block reaching T6 (min) | 4.13 ± 0.74 | 3.23 ± 0.48 | 3.24 ± 0.40 | 3.22 ± 0.56 |
| The time when movement was completely blocked (min) | 9.85 ± 1.34 | 8.10 ± 1.15 | 7.70 ± 0.92 | 7.80 ± 1.24 |
| Time from completion of anesthesia to cesarean section (min) | 13.75 ± 1.20 | 13.60 ± 1.44 | 13.96 ± 1.48 | 13.72 ± 1.31 |
| Duration of operation (min) | 59.40 ± 7.33 | 60.75 ± 4.56 | 59.28 ± 4.22 | 61.30 ± 6.36 |
| Sensory block recovery time (min) | 254.95 ± 23.32 | 301.10 ± 18.75 | 322.75 ± 22.21 | 373.15 ± 20.74 |

Group B (bupivacaine group), BF10 group (bupivacaine combined with 10 μg fentanyl), BF30 group (bupivacaine combined with 30 μg fentanyl), BF50 group (bupivacaine combined with 50 μg fentanyl). MAP: Mean arterial pressure.

## Table 3 Neonatal umbilical artery blood gas analysis and Apgar score (n = 30, mean ± SD)

|               | B         | BF<sub>10</sub> | BF<sub>30</sub> | BF<sub>50</sub> |
|---------------|-----------|-----------------|-----------------|-----------------|
| pH            | 7.34 ± 0.04 | 7.32 ± 0.07     | 7.33 ± 0.06     | 7.34 ± 0.04     |
| PO<sub>2</sub> (mmHg) | 42.3 ± 3.8 | 43.4 ± 6.0      | 42.6 ± 3.6      | 42.8 ± 5.6      |
| PCO<sub>2</sub> (mmHg) | 31.1 ± 1.7 | 30.8 ± 2.0      | 30.9 ± 1.9      | 30.2 ± 1.8      |
| BE (mEq/L)    | -3.1 ± 0.5 | -3.2 ± 0.8      | -3.3 ± 0.5      | -3.1 ± 0.9      |
| Lac (mmol/L)  | 1.68 ± 0.33 | 1.68 ± 0.2      | 1.67 ± 0.25     | 1.68 ± 0.19     |
| 1 min Apgar score ≤ 7(N) | 0 | 0 | 0 | 0 |
| 5 min Apgar score ≤ 7(N) | 0 | 0 | 0 | 0 |

Group B (bupivacaine group), BF10 group (bupivacaine combined with 10ug fentanyl), BF30 group (bupivacaine combined with 30 μg fentanyl), BF50 group (bupivacaine combined with 50 μg fentanyl).

## DISCUSSION

As an opioid analgesic, fentanyl is suitable for sedation and labor pain before, during and after anesthesia[10]. Although animal reproduction studies have suggested that fentanyl has toxic side effects on the fetus, no corresponding human experiments have been carried out[11]. In fact, fentanyl can pass through the placenta and may affect the fetal heart rate during delivery, but it has little effect on respiratory and nervous system function in perinatal newborns[12]. In addition, many studies have shown that
opioids combined with local anesthetics can prolong the time of analgesia and maintain the stability of vital signs, which is of extraordinary importance for ensuring a normal cesarean section in pregnant women and for reducing postoperative complications. Consequently, the benefits of spinal anesthesia combined with fentanyl may outweigh the potential hazards.

The results of this study showed that bupivacaine combined with fentanyl spinal anesthesia provided a good anesthetic effect during cesarean section and that the duration of sensory block was prolonged with increasing fentanyl concentration. In addition, blood pressure in the four groups decreased 3 min after anesthesia, but the decrease was 20% lower than the baseline. Consistent with the research results of many scholars\(^\text{[13-17]}\), the hemodynamics were stable, and no neonatal adverse events were observed.

The application of opioids in the spinal canal can enhance the degree of sensory block but cannot enhance the sympathetic block\(^\text{[18]}\). It has been found that fentanyl can act directly on opioid receptors in the spinal cord and on the thalamus, hypothalamus, reticular system and neurons by directly acting on opioid receptors in the spinal cord and absorbing blood through the paraspinal venous plexus\(^\text{[19]}\). In theory, fentanyl is slowly absorbed into the blood through the subarachnoid venous plexus following subarachnoid injection. In addition, the dosage of fentanyl in the subarachnoid space is lower, the circulation of cerebrospinal fluid is slow, and the blood concentration of the drug can be ignored. Moreover, coupled with hemodilution after absorption and the decomposition of fentanyl by the maternal liver and placental barrier, the amount of fentanyl entering the fetus is small and thus has little effect on newborns. To some extent, umbilical artery blood gas and lactic acid are the best indices of neonatal oxygenation and acid-base status\(^\text{[20]}\). In our study, the concentration of fentanyl in umbilical artery blood was qualitatively detected by ELISA, and the results of the four groups were all negative. The Apgar scores of the newborns at 1 min and 5 min were all above 7, and there was no difference in the results of umbilical artery blood gas analysis between the four groups. The fact that the time from completion of spinal anesthesia to delivery in this study was within 15 min may account for this difference. Consequently, we believe that we will have a more comprehensive understanding of the mechanism of fentanyl between the mother and fetus by including different times from spinal anesthesia administration to delivery and a larger sample size. However, this requires further study. Future multi-center studies are needed to confirm these findings.

### CONCLUSION

In general, the anesthetic effect of bupivacaine combined with different doses of fentanyl in cesarean section was satisfactory. In addition, the qualitative detection of fentanyl concentration in umbilical artery blood following the administration of 10 µg, 30 µg and 50 µg fentanyl, were negative, which suggested the safety of fentanyl in newborns.
ARTICLE HIGHLIGHTS

Research background
The choice of anesthesia for cesarean section is very important. It is necessary for anesthesiologists to carefully consider this in order to select reasonable anesthetic methods and appropriate anesthetic drugs.

Research motivation
Reports on whether fentanyl enters the blood and affects the safety of newborns are rare.

Research objectives
Examine the effects of bupivacaine combined with different doses of fentanyl on newborns delivered by cesarean section.

Research methods
One hundred and twenty patients undergoing cesarean section were randomly divided into the following 4 groups: group B (bupivacaine group), group BF10 (bupivacaine combined with 10 µg fentanyl), group BF30 (bupivacaine combined with 30 µg fentanyl) and group BF50 (bupivacaine combined with 50 µg fentanyl).

Research results
There were no significant differences in the 1-min or 5-min Apgar scores or the umbilical artery blood gas analysis among the four groups ($P > 0.05$).

Research conclusions
Bupivacaine combined with fentanyl spinal anesthesia is effective in cesarean section.

Research perspectives
Different anesthetics will have different effects on newborns during cesarean section. Safer intravenous anesthetics should be investigated.

REFERENCES

1. Sung S, Mahdy H. Cesarean Section. 2020. Treasure Island (FL)
2. McQuivey RW, Block JE. Vacuum-assisted cesarean section. *Int J Womens Health* 2017; 9: 151-155 [PMID: 28331371 DOI: 10.2147/IJWH.S129814]
3. Martin-Flores M. Epidural and Spinal Anesthesia. *Vet Clin North Am Small Anim Pract* 2019; 49: 1095-1108 [PMID: 31402542 DOI: 10.1016/j.cvsm.2019.07.007]
4. Veličković I, Pujic B, Baysinger CL. Continuous Spinal Anesthesia for Obstetric Anesthesia and Analgesia. *Front Med (Lausanne)* 2017; 4: 133 [PMID: 28861414 DOI: 10.3389/fmed.2017.00133]
5. Farzi F, Mirmansouri A, Naderi Nabi B, Atkar Roushan Z, Ghazanfar Tehran S, Nematoollahi Sani M, Makhlooghi Azad S, Nemati M. Comparing the Effect of Adding Fentanyl, Sufentanil, and Placebo with Intrathecal Bupivacaine on Duration of Analgesia and Complications of Spinal Anesthesia in Patients Undergoing Cesarean Section. *Anesth Pain Med* 2017; 7: e12738 [PMID: 29696107 DOI: 10.5812/aapm.12738]
6. Asehnoune K, Larousse E, Tadié JM, Minville V, Droupy S, Benhamou D. Small-dose bupivacaine-sufentanil prevents cardiac output modifications after spinal anesthesia. *Anesth Analg* 2005; 101: 1512-1515 [PMID: 16244022 DOI: 10.1213/01.ANE.0000180996.91358.CC]
7. Kariya N, Tashiro C. [Spinal anesthesia for cesarean section—safe and effective anesthetic management]. *Masui* 2010; 59: 311-318 [PMID: 20229749]
8. Armenian P, Vo KT, Barr-Walker J, Lynch KL. Fentanyl, fentanyl analogs and novel synthetic opioids: A comprehensive review. *Neuropharmacology* 2018; 134: 121-132 [PMID: 29042317 DOI: 10.1016/j.neuropharm.2017.10.016]
9. Saito E, Doi H, Kuribara K, Kato K, Abrutani K, Shoji M, Naka Y, Koerner T, Poepping B, Boison J. The Validation of the Wheat Gluten ELISA Kit. *J AOAC Int* 2019; 102: 1162-1173 [PMID: 30808436 DOI: 10.5740/jaoacint.19-0005]
10. Raleigh MD, Baruffaldi F, Peterson SJ, Le Naour M, Harmon TM, Vigliaturo JR, Pentel PR, Pravetoni M. A Fentanyl Vaccine Alters Fentanyl Distribution and Protects against Fentanyl-Induced Effects in Mice and Rats. *J Pharmacol Exp Ther* 2019; 368: 282-291 [PMID: 30409833 DOI: 10.1124/jpet.118.253674]
11. Dai Z, Abate MA, Smith GS, Kramer JC, Mock AR. Fentanyl and fentanyl-analog involvement in drug-related deaths. *Drug Alcohol Depend* 2019; 196: 1-8 [PMID: 30658219 DOI: ]
Wang Y et al. Bupivacaine combined with fentanyl for cesarean section

10.1016/j.drugalcdep.2018.12.004

12. Abdulk Hadi B, Sbeitan SM, Shakya AK. Fentanyl vs fentanyl-dexmedetomidine in lumbar foraminotomy surgery. Ther Clin Risk Manag 2019; 15: 885-890 [PMID: 31406463 DOI: 10.2147/TCRM.S195109]

13. Lanni SM, Tillinghurst J, Silver HM. Hemodynamic changes and baroreflex gain in the supine hypotensive syndrome. Am J Obstet Gynecol 2002; 187: 1636-1641 [PMID: 12501076 DOI: 10.1067/mob.2002.127304]

14. Jain K, Grover VK, Mahajan R, Batra YK. Effect of varying doses of fentanyl with low dose spinal bupivacaine for caesarean delivery in patients with pregnancy-induced hypertension. Int J Obstet Anesth 2004; 13: 215-220 [PMID: 15477049 DOI: 10.1016/j.ihoa.2004.04.006]

15. Sun S, Wang J, Bao N, Chen Y. Comparison of dexmedetomidine and fentanyl as local anesthetic adjuvants in spinal anesthesia: a systematic review and meta-analysis of randomized controlled trials. Drug Des Devel Ther 2017; 11: 3413-3424 [PMID: 29238167 DOI: 10.2147/DDDT.S146092]

16. Koltka K, Uludag E, Senturk M, Yavru A, Karadeniz M, Sengul T, Ozyclcin S. Comparison of equipotent doses of ropivacaine-fentanyl and bupivacaine-fentanyl in spinal anaesthesia for lower abdominal surgery. Anaesth Intensive Care 2009; 37: 923-928 [PMID: 20014598 DOI: 10.1177/0310057X0903700606]

17. Palanisamy A, Mitani AA, Tsen LC. General anesthesia for cesarean delivery at a tertiary care hospital from 2000 to 2005: a retrospective analysis and 10-year update. Int J Obstet Anesth 2011; 20: 10-16 [PMID: 21036594 DOI: 10.1016/j.ihoa.2010.07.002]

18. Oohata M, Aoki Y, Miyata M, Mizobe H, Suzuki KS. Japanese traditional herbal medicine reduces use of pregabalin and opioids for pain in patients with lumbar spinal canal stenosis: a retrospective cohort study. JAC Clin Rep 2017; 3: 60 [PMID: 29457103 DOI: 10.1186/s40981-017-0130-5]

19. Malvasi A, Tinelli A, Stark M, Pontrelli G, Brizzi A, Wetzel RG, Behamoud O. Low-dose sequential combined spinal-epidural anaesthesia in elective Stark caesarean section: a preliminary cohort study. Eur Rev Med Pharmacol Sci 2016; 14: 215-221 [PMID: 20391961]

20. Choi DH, Ahn HJ, Kim MH. Bupivacaine-sparing effect of fentanyl in spinal anesthesia for cesarean delivery. Reg Anesth Pain Med 2000; 25: 240-245 [PMID: 10834777 DOI: 10.1016/s1098-7339(00)90005-1]
