Observational Study

Medicine

OPEN

Analgesic effect of butorphanol tartrate combined with hydromorphone on patients with cesarean section

A prospective cohort study

Ying Zhang, Doctor[a], Shixuan Xie, Bachelor[a], Guanglei Zhang, Doctor[b], Xun Gong, Doctor[a,*]

Abstract

To evaluate the analgesic effect of butorphanol tartrate combined with hydromorphone on the patients with cesarean section, we conducted a prospective cohort study. A total of 90 patients were given patient-controlled intravenous analgesia (PCIA) with hydromorphone for 24 hours after the cesarean section. After stopping PCIA, they were divided into 2 groups randomly. The cases treated with butorphanol tartrate intravenous drip were evaluated as the butorphanol group (n = 45) and the cases treated with saline were evaluated as the control group (n = 45). We compared the vital signs, analgesic effect, adverse reactions, the bladder and gastrointestinal function recovery, and neonatal jaundice between the 2 groups. The visual analog score in butorphanol group was significantly lower than that of control group at 3 and 4 hours after stopping PCIA ($P < .05$), but there was no significant difference in visual analog score at 6 and 12 hours after stopping PCIA. The first time of getting out of bed and urination in butorphanol group was significantly later than that in control group while there was no significant difference in the first anal ventilation and the neonatal jaundice index between the 2 groups. We should pay attention to the pain of patients with cesarean section after stopping PCIA. The combination of butorphanol tartrate and hydromorphone play a good effect to relieve the pain while nursing care should be strengthened to urge patients to take early activities to reduce the occurrence of urinary retention.

Abbreviations: PCIA = patient controlled intravenous analgesia, VAS = visual analog score.

Keywords: analgesia, butorphanol tartrate, cesarean section, hydromorphone, visual analog score (VAS)

1. Introduction

Postpartum pain is a clinical reality that affects 6.1% to 11.5% of women after cesarean section and affects their recovery.[1] Effective postoperative analgesia can prevent most complications such as depression caused by lack of sleep, long-term chronic pain, and prolonged hospitalization[2,3] and in the meantime achieve the goals of unrestricted maternal daily activities, minimal maternal and neonatal side effects, rapid recovery, and early discharge home.

Opioids are recommended and are the most widely used drugs for analgesia after cesarean section.[4] Morphine is the most widely used opioid for post cesarean analgesia.[5] while they are associated with many adverse effects that may prevent patient recovery after surgery. Furthermore, the opioid crisis has reached an unprecedented magnitude worldwide and opioid misuse among obstetric patients are extremely concerning.[6] Clinicians try to use a multimodal analgesic regimen with nonopioid agents. Researchers have explored alternative analgesic options and the use of intrathecal hydromorphone is growing. Sharpe reported that the pain assessment scores did not differ between intrathecal hydromorphone and intrathecal morphine with movement at 24 hours or at any time point,[5] they both provided high patient satisfaction rates, and there was no significant difference in adverse effects of nausea and pruritus between groups.[7] The PCIA containing hydromorphone usually be stopped after using 24 hours in China. In fact, the patients with cesarean section still had different degrees of the wound pain and uterine cramping pain after stopping hydromorphone.

Butorphanol tartrate is a new synthetic opioid and it has a strong affinity for μ and κ receptors.[8,9] Some published studies have reported that it can alleviate the uterine contraction pain in the second stage of labor.[9] *In this paper, we used butorphanol for the patients with cesarean section after stopping* hydromorphone *to evaluate their analgesic effect, vital signs, postoperative rehabilitation and adverse reactions so as to guide clinical application.*

The work was supported by Natural Science Foundation of Xinjiang Uygur Autonomous Region, China (NO.2021D01F20).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available. Readers can obtain all data by contacting the corresponding author.

[a] Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China, [b] Department of Anesthesiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China.

** Correspondence: Xun Gong, Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China (e-mail: gongxun4019@163.com).*

How to cite this article: Zhang Y, Xie S, Zhang G, Gong X. Analgesic effect of butorphanol tartrate combined with hydromorphone on patients with cesarean section: A prospective cohort study. Medicine 2022;101:48(e31901).

Received: 16 May 2022 / Received in final form: 27 October 2022 / Accepted: 27 October 2022

http://dx.doi.org/10.1097/MD.0000000000031901

2. Methods

The study protocol was approved by the Institutional Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. The study was registered on Clinical trial.gov (ID: NCT04490980). This manuscript adheres to the consolidated standards of prospective cohort study guidelines.

A total of 90 Chinese patients were included according to established inclusive and exclusive criteria from Jan 8, 2021 to Mar 31, 2022. The inclusive criteria were as follows: singleton full-term pregnancy; American Society of anesthesiologists grades I and II; meeting the indications of cesarean section. The exclusive criteria were as follows: severe organ dysfunction; internal and surgical diseases; long-term use of antipsychotics and opioids; allergy to the anesthetic drugs involved in this study. All included patients signed informed consent documents.

All the patients took routine preoperative preparation and indwelling catheter before operation. Epidural anesthesia was used for cesarean section in all patients. They were given patient controlled intravenous analgesia (PCIA) with 10 mg hydromorphone and 5% saline 100 mL for 24 hours after cesarean section and the infusion was 2 mL/hour. Then the PCIA was removed, and the patients were divided into 2 groups randomly: 45 patients were given butorphanol tartrate 0.5 mg+5% saline 500 mL intravenous drip. The patients' infusion rate is 1.5 mL/minute. another 45 patients were only given saline intravenous drip in the control group with the same infusion rate of 1.5 mL/minute.

The visual analog score (VAS) was used to evaluate the pain degree at 0, 1, 2, 3, 4, 6, and 12 hours after stopping PCIA, the higher the score, the more severe the pain. We recorded the vital signs before and after using butorphanol tartrate, the VAS, the discomfort, and the recovery of gastrointestinal and bladder function of all included patients. And the neonatal jaundice index at 24, 48, and 72 hours after birth were also recorded.

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL). The measurement data in $\bar{X} \pm SEM$ was analyzed using Student's *t* test. Chi-squared test was used for the counting data. *P* value < .05 was considered statistically significant.

3. Results

Obstetric and demographic variables of the 2 groups are summarized in Table 1. There was no statistical difference in body mass index, average age, gestational weeks, and vital signs between the 2 groups. And no significant difference was found in the birth weight and Apgar score between the 2 groups ($P > .05$).

The patients complained that the abdominal incision pain was relieved after 24 hours of hydromorphone use and the pain mainly came from uterine contraction pain. In the control group, VAS increased after PCIA was stopped, especially the pain increased sharply in the first 3 hours, then the pain level remained at a high level after reaching the peak. While in butorphanol group, the VAS increased slowly, especially from the 2nd hour to 4th hour, which was significantly lower than that of the control group ($P < .05$). There was no significant difference in VAS score between the 2 groups at 6h and 12h after stopping PCIA ($P > .05$, Table 2, Figure 1).

There were 11 patients who complained of discomfort in the butorphanol tartrate group: 5 patients had mild nausea and disappeared 3 hours later, and 6 patients had drowsiness, without vomiting, shivering, and headache. There were 12 patients complained of discomfort in control group: 2 patients had a headache, 6 patients had nausea, 2 patients had drowsiness, and 2 patients had both drowsiness sleepy and shivering. There was no significant difference in the adverse effects between the 2 groups.

The first time of getting out of bed and urination in butorphanol group were delayed compared with control group and the differences were statistically significant (Table 3). There were no statistical differences in the first time of anal ventilation between the 2 groups (Table 3).

All neonates started breast feeding as early as possible after birth. In the control group, one newborn was transferred to neonatology department due to the increase of jaundice index measured at 24 hours after birth, and the jaundice index of the other 44 newborns at 24, 48, and 72 hours were, respectively, 3.06 ± 0.22, 7.07 ± 0.22 and 8.76 ± 0.28. 3 newborns were transferred to neonatology department due to the increase of jaundice index measured at 24 hours after birth in butorphanol group and the jaundice index of the other 42 neonates was 3.48 ± 0.21, 6.47 ± 0.22 and 9.09 ± 0.24 at 24, 48, and 72 hours after birth, respectively. There were no statistical differences in jaundice index between the 2 groups at 24, 48, and 72 hours after birth ($P > .05$). The neonatal defecations in 2 groups were normal.

All patients were discharged on the fourth day after delivery and took reexamination at 42 days postpartum in clinics. All included patients complained no obvious abnormality and *the* lasting time of *lochia was about 4-6 weeks*. The jaundice index and defecation of the newborns were normal.

4. Discussion

Cesarean delivery rates are increasing worldwide. Effective postoperative pain is a key priority after cesarean section. The analgesic effect after cesarean section directly affects the postpartum rehabilitation.[10] Postoperative pain management in women

Table 1

The major obstetric characteristics and neonatal outcomes in 2 groups.

	Age (year)	Gestation (wk)	Neonate weight (g)	Apgar score (1 min)	Body mass index
Butorphanol group (n = 45)	31.91 ± 0.66	38.33 ± 0.11	3162 ± 49.47	8.56 ± 0.07	22.96 ± 0.23
Control group (n = 45)	30.51 ± 0.57	38.67 ± 0.12	3310 ± 63.25	8.67 ± 0.07	23.21 ± 0.24

Table 2

The visual analog score at 0, 1, 2, 3, 4, 6, 12 h after stopping patient-controlled intravenous analgesia in 2 groups.

	0 h	1 h	2h	3h	4h	6h	12h
Butorphanol group	1.58 ± 0.09	1.73 ± 0.08	2.13 ± 0.09	2.27 ± 0.07	2.38 ± 0.08	2.78 ± 0.11	3.09 ± 0.14
Control group	1.40 ± 0.08	1.78 ± 0.77	2.06 ± 0.09	2.98 ± 0.14	3.02 ± 0.13	3.07 ± 0.11	3.11 ± 0.15

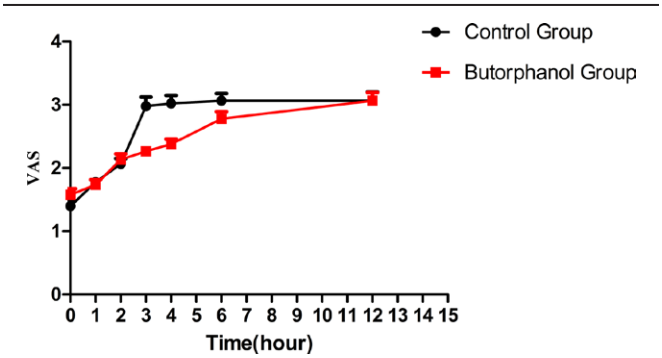

Figure 1. The VAS at 0, 1, 2, 3, 4, 6, 12 h after stopping PCIA in 2 groups.

after cesarean section is unique because pregnant women do not need preoperative analgesia. Hydromorphone is a reasonable alternative to morphine for postcesarean delivery analgesia.[11] A published study reported that hydromorphone can provide a similar superior analgesic effect as morphine.[5] The ratio of intrathecal morphine to intrathecal hydromorphone for effective post cesarean analgesia is 2:1 and the analgesic effect of intrathecal hydromorphone appears to extend at least 12 h and may extend up to 24 h after cesarean section.[7,12] With the dosing used in our study, the pain of patients increased sharply in the first 3 hours after stopping hydromorphone and maintained at a high level after reaching the peak, then the pain did not increase. The patients with cesarean section do need analgesia after using hydromorphone 24 hours, which are in accordance with previous studies.[13]

The postoperative pain of cesarean section comes from uterine contraction pain besides abdominal incision pain. Uterine contraction pain is distinct from abdominal incision pain in both pharmacological responses to analgesic agents and pathophysiological mechanism, and thus making postoperative pain of cesarean section different from other postoperative pains.[14] Published guidelines recommend that oxytocin should be routinely used to strengthen uterine contraction after cesarean section to reduce the incidence of postpartum hemorrhage[15] and sometimes the oxytocin use maintained 48 hours after cesarean section in China for prevention of uterine atony. The abdominal incision pain is often relieved 24 hours after operation while the uterine contraction pain still plagues the puerpera. Uterine contraction pain is one of the most serious visceral pains. The range of uterine contraction pain was diffuse, and its location was not accurate. Therefore, the uterine contraction pain may be one of the main reasons for incomplete analgesia with hydromorphone after cesarean section.

In this paper, we chose butorphanol for further analgesia after the use of hydromorphone and the subsequent uterine contraction pain was significantly reduced. Butorphanol can relieve visceral pain in a dose-dependent manner.[16,17] Uterine contraction pain is a kind of visceral pain. Visceral pain is transmitted both through the spinal cord thalamic tract and the intrinsic tract in the gray matter of the spinal cord.[18] The opioids often exert analgesic effects on pain stimuli in the spinal cord dorsal horn through μ, δ, and κ receptors, which are the 3 major classes of opioid receptors.[19] The management of visceral pain is mainly realized by activating the peripheral κ opioid receptor.[18] As a new synthetic opioid, Butorphanol tartrate has a strong affinity for κ receptors but no obvious effect on δ receptor. Perhaps this is why butorphanol can inhibit uterine contraction pain. Butorphanol is used in combination with or alone for postoperative analgesia and can be used for labor analgesia. A large number of clinical studies have confirmed that butorphanol used in the second stage of labor has better safety than other opioid receptor agonists, and almost does not cause neonatal respiratory depression.[9] In this study, compared with the control group, the VAS of butorphanol group was significantly reduced, especially at the 2nd, 3rd, and 4th hours, indicating significant relief of pain. The pain did not increase until the 6th hour. Limited data indicate that butorphanol is excreted into breastmilk in small amounts.[20]In this study, the newborns have a good prognosis.

However, since butorphanol causes drowsiness, it will delay and reduce the postoperative activity time. Related to these reasons, the urination time in butorphanol group were delayed compared with control group. It suggests that we should strengthen the management of the patients using butorphanol after operation, such as urging patients to get out of bed early, encouraging early urination, to reduce the risk of urinary retention and thrombosis. Moreover, the analgesic effect of butorphanol was gradually decreased after using 6 hours. Whether the drug should be continued needs to be further studied.

There are some limitations in this paper. Limited sample size may lead to bias in the research results, we still need further studies with large samples. Secondly, no concentration gradient of hydromorphone and butorphanol was set in this study, which we need to find the drug combination with the best analgesic effect and the lowest side effects.

In conclusion, the patients with cesarean section still need analgesia after using PCIA pump with hydromorphone for 24 hours. Butorphanol tartrate is effective for patients to relieve pain without significant adverse effects on women and the neonatal outcome. Therefore, the combination of butorphanol tartrate and hydromorphone for postcesarean analgesia is safe and effective for clinical use.

Acknowledgments

We thank all participants in this study. The authors declared that they have no conflicts of interest to this work.

Author contributions

Conceptualization: Xun Gong, Ying Zhang.
Data curation: Shi-xuan Xie, Ying Zhang.
Supervision: Guang-lei Zhang, Xun Gong.
Writing—original draft: Ying Zhang, Xun Gong.
Writing—review and editing: Guang-lei Zhang, Xun Gong.

Table 3

The gastrointestinal and bladder recovery in 2 groups.

	Getting out of bed	Urination	Anal ventilation
Butorphanol group	27.98 ± 0.67	28.27 ± 0.97	25.82 ± 1.12
Control group	24.00 ± 0.33	25.33 ± 0.45	22.98 ± 1.19
P	<.05	<.05	>.05

References

[1] Lavand'homme P. Postpartum chronic pain. Minerva Anestesiol. 2019;85:320–4.

[2] Kangha J, Hye Park M, Kyung Kim D. Prediction of postoperative pain and opioid consumption using intraoperative surgical pleth index after surgical incision: an observational study. J Pain Res. 2020;13:2815–24.

[3] Gerbershagen HJ, Aduckathil S, van Wijck AJ, et al. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology. 2013;118:934–44.

[4] White LD, Hodsdon A, An GH, et al. Induction opioids for caesarean section under general anaesthesia: a systematic review and meta-analysis of randomised controlled trials. Int J Obstet Anesth. 2019;40:4–13.

[5] Sharpe EE, Molitor RJ, Arendt KW, et al. Intrathecal morphine versus intrathecal hydromorphone for analgesia after cesarean delivery: a randomized clinical trial. Anesthesiology. 2020;132:1382–91.

[6] Landau R. Post-cesarean delivery pain. Management of the opioid-dependent patient before, during and after cesarean delivery. Int J Obstet Anesth. 2019;39:105–16.

[7] Sviggum HP, Arendt KW, Jacob AK, et al. Intrathecal hydromorphone and morphine for postcesarean delivery analgesia: determination of the ED90 using a sequential allocation biased-coin method. Anesth Analg. 2016;123:690–7.

[8] Shah B, Gupta R, Sarkar S, et al. Injection Butorphanol dependence: a case report. Asian J Psychiatr. 2018;35:45–6.

[9] Yadav J, Regmi MC, Basnet P, et al. Butorphanol in labour analgesia. JNMA J Nepal Med Assoc. 2018;56:940–4.

[10] Guasch E, Brogly N, Gilsanz F. Combined spinal epidural for labour analgesia and caesarean section: indications and recommendations. Curr Opin Anaesthesiol. 2020;33:284–90.

[11] Huang CY, Li SX, Yang MJ, et al. A comparative study of three concentrations of intravenous nalbuphine combined with hydromorphone for post-cesarean delivery analgesia. Chin Med J (Engl). 2020;133:523–9.

[12] Rauch E. Intrathecal hydromorphone for postoperative analgesia after cesarean delivery: a retrospective study. AANA J. 2012;80:S25–32.

[13] Conway SM, Puttick D, Russell S, et al. Females are less sensitive than males to the motivational-and dopamine-suppressing effects of kappa opioid receptor activation. Neuropharmacology. 2019;146:231–41.

[14] Cai Q, Gong HL, Fan MB, et al. The analgesic effect of tramadol combined with butorphanol on uterine cramping pain after repeat caesarean section: a randomized, controlled, double-blind study. J Anesth. 2020;34:825–33.

[15] Muñoz M, Stensballe J, Ducloy-Bouthors AS, et al. Patient blood management in obstetrics: prevention and treatment of postpartum haemorrhage. A NATA consensus statement. Blood Transfus. 2019;17:112–36.

[16] Fu HM, Zhong CC, Fu Y, et al. Perioperative analgesic effects of preemptive ultrasound-guided rectus sheath block combined with butorphanol or sufentanil for single-incision laparoscopic cholecystectomy: a prospective, randomized, clinical trial. J Pain Res. 2020;25:1193–200.

[17] Houghton KJ, Rech RH, Sawyer DC, et al. Dose-response of intravenous butorphanol to increase visceral nociceptive threshold in dogs. Proc Soc Exp Biol Med. 1991;197:290–6.

[18] Davis MP. Drug management of visceral pain: concepts from basic research. Pain Res Treat. 2012;2012:265605.

[19] Michael C. Toward an effective peripheral visceral analgesic: responding to the national opioid crisis. Am J Physiol Gastrointest Liver Physiol. 2018;314:637–46.

[20] Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD). Butorphanol: National Library of Medicine (US); 2006.