A comparative study of three concentrations of intravenous nalbuphine combined with hydromorphone for post-cesarean delivery analgesia

Chun-Yun Huang, Shu-Xi Li, Mei-Juan Yang, Li-Li Xu, Xin-Zhong Chen

Department of Anesthesia, Women's Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310006, China.

Abstract

Background: Nalbuphine has been suggested to be used for post-cesarean section (CS) intravenous analgesia. However, ideal concentration of nalbuphine for such analgesia remains unclear. The present study was conducted to explore an ideal concentration of nalbuphine for post-CS intravenous analgesia by evaluating the analgesic effects and side-effects of three different concentrations of nalbuphine combined with hydromorphone for post-CS intravenous analgesia in healthy parturients.

Methods: One-hundred-and-fourteen parturients undergoing elective CS were randomly allocated to one of three groups (38 subjects per group) according to an Excel-generated random number sheet to receive hydromorphone 0.05 mg/mL + nalbuphine 0.5 mg/mL (group LN), hydromorphone 0.05 mg/mL + nalbuphine 0.7 mg/mL (group MN), and hydromorphone 0.05 mg/mL + nalbuphine 0.9 mg/mL (group HN) using patient-controlled analgesia (PCA) pump. Visual analog scale (VAS) for pain, PCA bolus demands, cumulative PCA dose, satisfaction score, Ramsay score, and side-effects such as urinary retention were recorded.

Results: The number of PCA bolus demands and cumulative PCA dose during the first 48 h after CS were significantly higher in group LN (21 ± 16 bolus, 129 ± 25 mL) than those in group MN (15 ± 10 bolus, 120 ± 16 mL) (both $P < 0.05$) and group HN (13 ± 9 bolus, 117 ± 13 mL) (both $P < 0.01$), but no difference was found between group HN and group MN (both $P > 0.05$). VAS scores were significantly lower in group HN than those in group MN and group LN for uterine cramping pain at rest and after breast-feeding within 12 h after CS (all $P < 0.01$) and VAS scores were significantly higher in group LN than those in group MN and group HN when oxytocin was intravenously infused within 3 days after CS (all $P < 0.05$), whereas VAS scores were not statistically different among groups for incisional pain (all $P > 0.05$). Ramsay sedation scale score in group HN was significantly higher than that in group MN at 8 and 12 h after CS (all $P < 0.01$) and group LN at 4, 8, 12, 24 h after CS (all $P < 0.05$).

Conclusions: Hydromorphone 0.05 mg/mL + nalbuphine 0.7 mg/mL for intravenous PCA could effectively improve the incisional pain and uterine cramping pain management and improve comfort in patients after CS.

Trial registration number: ChiCTR1800015014, http://www.chictr.org.cn/ Chinese Clinical Trial Registry.

Keywords: Hydromorphone; Nalbuphine; Cesarean section; Post-operative analgesia; Patient-controlled intravenous analgesia

Introduction

Cesarean section (CS) is usually accompanied by severe post-operative pain, which mainly consists of somatic pain (incisional pain) and visceral pain caused by uterine muscle contraction (uterine cramping pain).[1] Clinically, oxytocin is often used during and after CS to promote uterine contraction and reduce post-partum hemorrhage, which increases the intensity of post-operative uterine cramping pain.[2,3] Severe post-operative pain could result in delayed breastfeeding[4,5] and a series of complications such as post-partum depression, immune system disorder, and venous thromboembolism.[6-8] Studies have shown that effective post-operative analgesia can reduce the stress response, accelerate post-operative immune system recovery, and promote wound healing.[9] Hydromorphone, widely used in the clinical practice, is a potent and semi-synthetic μ-opioid receptor agonist and has valuable advantages of rapid onset and robust analgesic efficacy on somatic pain with no ceiling effect.[10-12] However, it does not work very well for visceral pain.[13,14] Studies have shown that the combination of μ-opioid receptor agonists and mixed agonist-antagonist opioids can relieve both somatic and visceral pain with decrease in side-effects such as nausea, vomiting, itching, urinary retention, and respiratory depression.[15-18] Nalbuphine is a synthetic opioid agonist-antagonist analgesic, which appears to be an agonist in κ-opioid receptors (KORs) and an antagonist in μ-opioid receptors. It has a strong analgesic effect on

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Correspondence to: Dr. Xin-Zhong Chen, Department of Anesthesia, Women's Hospital, Zhejiang University School of Medicine, No. 1 Xueshi Road, Hangzhou, Zhejiang 310006, China
E-Mail: chenxinz@zju.edu.cn

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women,[19,20] with a significant effect on visceral pain.[21-23] Nalbuphine can also reduce side-effects such as nausea, vomiting, and itching caused by activation of μ-opioid receptor.[15] Both the analgesic efficacy and respiration depression of nalbuphine have a ceiling effect.[24] Nalbuphine can also achieve a stable analgesic effect by continuous intravenous (IV) infusion.[25] The analgesic effects and side-effects of combinations of hydromorphone and nalbuphine for IV analgesia after CS are not clear. The main purpose of this study was to compare the quality of pain relief and the adverse effects of three different concentrations of IV nalbuphine co-administered with IV hydromorphone and to determine an appropriate concentration of nalbuphine when combined with a fixed concentration of hydromorphone for patient-controlled post-CS IV analgesia in the healthy parturients receiving epidural analgesia.

Methods

Ethical approval

This prospective, randomized, double-blind study was conducted in accordance with the principles of the *Declaration of Helsinki* and national regulations. This study has been approved by the Medical Ethics Committee of Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China (No. 20150105), and registered at Chinese Clinical Trial Registry (https://www.chictr.org.cn) (No. ChiCTR1800015014). Written informed consent was obtained from all participants included in the study.

Study population

The study was performed at the Department of Anesthesia, Women's Hospital, Zhejiang University School of Medicine, between June 2017 and August 2018. One-hundred-and-fifteen parturients (aged 25–35 years), with the American Society of Anesthesiologist (ASA) physical status II, scheduled to undergo elective CS with epidural anesthesia were recruited in the study. The inclusion criteria were as follows: singleton pregnancy, gestational age >37 weeks, duration of surgery <2 h, body mass index (BMI) between 19 and 29 kg/m^2, and requirement for IV patient-controlled analgesia (PCA). The exclusion criteria were as follows: (1) allergic to any drugs used in the present study; (2) history of chronic pain; (3) long-term use of opioid analgesic or nonsteroidal anti-inflammatory drugs for the treatment of chronic pain; (4) pregnancy complicated by hypertension, diabetes mellitus, cardiac disease, or renal disease; (5) with pre-eclampsia or placenta previa; (6) with endocrine system disease or mental illness; (7) in addition to CS, other operations were also completed simultaneously, such as oophorocystectomy, myomectomy, etc; and (8) intraoperative blood loss greater than 500 mL.

Sample size calculation

Sample size was calculated with the one-way analysis of variance (ANOVA) power analysis using PASS® (version 11.0.7, NCSS, LLC, Kaysville, UT, USA). Calculations were based on the results of early preliminary data that showed that the PCA bolus demand numbers were 20, 15, and 10 in the corresponding groups receiving nalbuphine 0.5, 0.7, and 0.9 mg/mL, respectively, co-administered with hydromorphone 0.05 mg/mL for patient-controlled IV analgesia (PCIA) for post-CS analgesia. We determined that a sample size of 81 patients in total (27 patients per group) would have 90% power to detect a difference among groups and a significance level of 0.05. Allowing for possible dropouts, the sample size was increased to 114 patients.

Study design

Patients were allocated randomly into one of the three groups according to the concentration of nalbuphine. Group LN: hydromorphone 0.05 mg/mL + nalbuphine 0.5 mg/mL; Group MN: hydromorphone 0.05 mg/mL + nalbuphine 0.7 mg/mL; and Group HN: hydromorphone 0.05 mg/mL + nalbuphine 0.9 mg/mL. The PCA pump was set at a basal infusion rate of 2 mL/h, a loading dose of 2 mL, a 2-mL bolus, and a lockout interval of 10 min. The 1 h maximum dose limit was 14 mL, and each PCA pump had a capacity of 150 mL, which was maintained for 48 h. If the medicine was not enough, the pharmacist added it in time. The patients were familiarized with evaluating the visual analog scale (VAS) and using the PCA pump. Randomization was performed using Excel-generated random number codes. The entire randomization sequence was generated before the enrollment of the first participant. Group allocation codes were placed in sealed, opaque envelopes, which were opened at the time of randomization.

The analgesic solution for the PCA pump was prepared by a pharmacist who knew the patient grouping during the CS. The PCA pump was connected to the patient by an attending anesthesiologist. The anesthesiologist decided the time to start the PCA pump when the patient could lift both her lower limbs after CS. Both the pharmacist and the attending anesthesiologist were not involved in the data collection of the study.

Patient characteristics and anesthesia

All patients strictly fasted for 8 h before surgery. S/5 Anesthesia Monitor (GE Healthcare, Helsinki, Finland) was used to monitor electrocardiography, heart rate, blood pressure, and oxygen saturation. All patients were administered 500 mL of hydroxyethyl starch solution before anesthesia administration. Epidural anesthesia was achieved in the left lateral decubitus position at the L_{2-3} vertebral interspace with 1.75% carbonated lidocaine mixed with 1:600,000 epinephrine. After no backflow of blood or cerebrospinal fluid was found in the negative aspiration test, 5 mL of the local anesthetic was injected into the epidural space and observed at least for 5 min. If there were no symptoms of central nervous system toxicity and high spinal blockade, a 7-mL local anesthetic solution was injected again. An epidural catheter was threaded into epidural space and a 5-mL local anesthetic solution was administered through the catheter. The patient was then placed in a left lateral tilt position (at 15°). The surgery began when the T6 level of sensory blockade was achieved and the patient felt no pain. Tropisetron was administered

to each patient about 15 min before the completion of the surgery and the epidural catheter removed after the completion of surgery. The PCA pump started when the patient was able to lift both of her lower limbs evaluated by the attending anesthesiologist. Twenty units of oxytocin were infused IV once a day for the first 3 days to promote uterine contractions (4 h post-partum, 10:30 on the second day, and 10:30 on the third day). Patients were taught to use the PCA pump carefully for post-operative pain in case it affected the sleep quality or in case of VAS $\geq$ 4 (VAS: 0, no pain; 1–3, mild pain; 4–6, moderate pain; 7–9, severe pain; 10, worst pain imaginable).

Definition and outcome assessments

Patients' VAS for pain, number of PCA bolus demands, the ratio of number of PCA bolus delivered and PCA bolus demands (delivery/demand ratio), cumulative PCA dose at 48 h, and patient satisfaction (1, very unsatisfactory; 2, unsatisfactory; 3, neutral; 4, satisfactory; 5, very satisfactory)[26] were recorded during the first 48 h after surgery. The observer taught the patient how to distinguish the incisional pain from uterine cramping pain (incisional pain mainly comes from the sharp pain of the incision area, and uterine cramping pain was mainly caused by paroxysmal uterine spasm), then assessed VAS of incisional pain at rest (VAS-I-R), VAS of incisional pain on mobilization (VAS-I-M) such as coughing, getting out of bed and walking, VAS of uterine cramping pain at rest (VAS-U-R), VAS of uterine cramping pain after breast-feeding (VAS-U-F), and VAS of uterine cramping pain when oxytocin was intravenously infused (VAS-U-O), and measured PCA demands, PCA injected, cumulative PCA dose at 48 h, Ramsay sedation scale (RSS) scores, the occurrence of side-effects such as hypoxemia (peripheral oxygen saturation [SpO_2] < 90%), urinary retention, nausea, vomiting, the time to first flatus and satisfaction rate in 48 h post-operatively. RSS score was applied to assess the patient's sedation level: 1, anxious, agitated, or restless; 2, cooperative, oriented, and tranquil; 3, responds to command; 4, brisk response to a light glabellar tap or loud auditory stimulus; 5, sluggish response to a light glabellar tap or loud auditory stimulus; 6, no response to the stimuli.[26] Naloxone would be administered if respiratory depression occurred, 5 mg tropisetron was administered if nausea or vomiting occurred and a urinary catheter was reinserted in case of any urinary retention.

Statistical analysis

SPSS software version 21.0 (IBM Corp, Armonk, NY, USA) was used for statistical analysis, and the figures were created by GraphPad Prism version 7 (GraphPad Software Inc., San Diego, CA, USA). Categorical variables were reported as absolute numbers and frequencies (%), and continuous variables were reported as mean $\pm$ standard deviation for normally distributed data and median (Q_1, Q_3) for non-normally distributed data. One-way ANOVA was used to analyze pain scores, RSS scores, PCA demands, cumulative PCA dose, and satisfaction scores. Tukey's test was used for *post hoc* testing. The incidences of side effects were compared using the Pearson's Chi-squared test with Bonferroni correction. $P < 0.05$ indicated a significant difference.

Results

Basic information

Out of 115 patients assessed for the study, one patient was excluded due to a change in her surgical protocol. The remaining 114 patients were enrolled after randomization [Figure 1]. Two patients withdrew consent in group HN. A total of 112 patients, 38 patients in group LN, 38 patients in group MN, and 36 patients in group HN, were included in the final analysis. There was no statistically significant difference in the demographic and obstetric characteristics among the groups [Table 1].

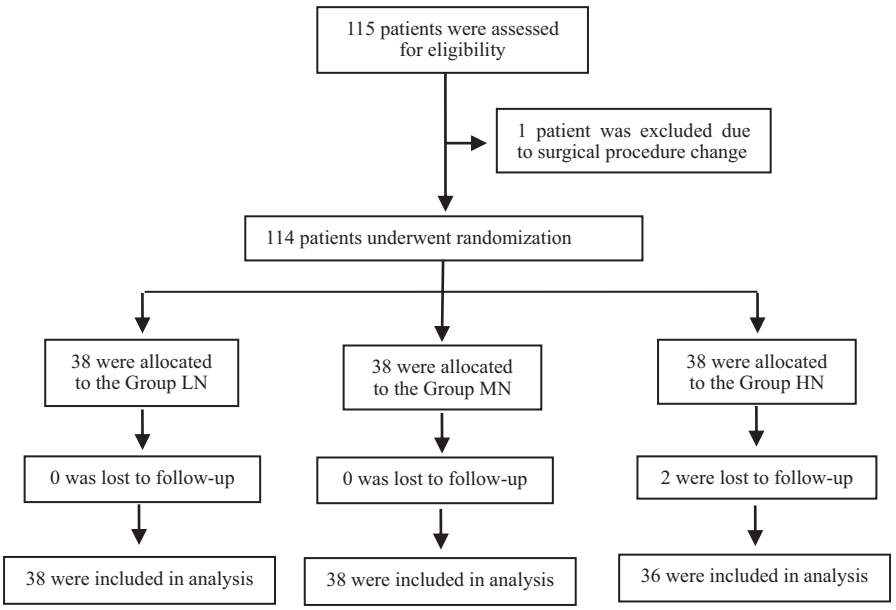

Figure 1: Flow chart for patient enrollment, randomization, and analysis. Group LN: Hydromorphone 0.05 mg/mL + nalbuphine 0.5 mg/mL; Group MN: Hydromorphone 0.05 mg/mL + nalbuphine 0.7 mg/mL; Group HN: Hydromorphone 0.05 mg/mL + nalbuphine 0.9 mg/mL.

Table 1: Baseline characteristics of patients receiving three concentrations of intravenous nalbuphine combined with hydromorphone for post-cesarean delivery analgesia ($N = 112$).

Items	Group LN ($n = 38$)	Group MN ($n = 38$)	Group HN ($n = 36$)	F	P
Age, years	31.4 ± 2.7	30.2 ± 3.8	30.1 ± 2.9	1.952	0.147
BMI, kg/m^2	25.6 ± 2.7	26.7 ± 1.8	26.3 ± 1.2	2.916	0.058
Duration of surgery, h	1.20 ± 0.18	1.26 ± 0.18	1.23 ± 0.18	1.056	0.352
Gestational period, weeks	38.5 ± 0.9	38.7 ± 0.9	38.6 ± 0.9	0.469	0.627

Data are presented as mean ± standard deviation. Group LN: Hydromorphone 0.05 mg/mL + nalbuphine 0.5 mg/mL; Group MN: Hydromorphone 0.05 mg/mL + nalbuphine 0.7 mg/mL; Group HN: Hydromorphone 0.05 mg/mL + nalbuphine 0.9 mg/mL; BMI: Body mass index.

PCA pump data and patient satisfaction

The number of PCA bolus demands ($F = 5.078$, $P = 0.008$) and total cumulative PCA dose ($F = 4.107$, $P = 0.019$) within 48 h after CS were statistically different among the three groups, and were significantly higher in group LN than those in group MN ($P = 0.031$ and $P = 0.047$, respectively) and group HN ($P = 0.003$ and $P = 0.007$, respectively), whereas no significant difference was found between group MN and group HN ($P = 0.370$ and $P = 0.380$, respectively). The ratio of PCA delivered/PCA demands was also statistically different among groups ($F = 6.428$, $P = 0.002$), and was significantly lower in group LN than that in group MN ($P = 0.010$) and group HN ($P = 0.001$), whereas no significant difference was found between group MN and group HN ($P = 0.490$). Satisfaction rating on pain management at 48 h in group MN was significantly higher than that in group LN ($P < 0.001$) and HN ($P = 0.002$), but there was no significant difference between group LN and HN ($P = 0.109$) [Table 2].

VAS of incisional pain and uterine cramping pain

There was no significant difference in VAS-I-M and VAS-I-R scores among three groups within 48 h after the surgery (all $P > 0.05$) [Table 3].

During the first 12 h (at 4, 8, and 12 h) post-CS, VAS-U-R scores and VAS-U-F scores were statistically different among groups (all $P < 0.05$). VAS-U-R scores and VAS-U-F scores were significantly higher in group LN than those in group HN and group MN (all $P < 0.05$), whereas no statistical difference was found between group HN and group MN ($P > 0.05$). In addition, there was no significant difference in VAS-U-R scores and VAS-U-F scores at 24 and 48 h post-CS [Table 4].

Table 2: PCA pump data and satisfaction scores among patients receiving three concentrations of intravenous nalbuphine combined with hydromorphone for post-cesarean delivery analgesia ($N = 112$).

Items	Group LN ($n = 38$)	Group MN ($n = 38$)	Group HN ($n = 36$)	F	P
PCA bolus demands, n	21 ± 16	15 ± 10*	13 ± 9†	5.078	0.008
PCA delivery/demand ratio	0.75 ± 0.11	0.81 ± 0.22*	0.83 ± 0.11†	6.428	0.002
Cumulative PCA dose within 48 h, mL	129 ± 25	120 ± 16*	117 ± 13†	4.107	0.019
Satisfaction score	3.9 ± 0.7	4.6 ± 0.7‡,§	4.4 ± 0.7	9.849	<0.001

Data are presented as mean ± standard deviation. $^{*}P < 0.05$, compared with group LN. $^{\dagger}P < 0.01$, compared with group LN. $^{\ddagger}P < 0.001$, compared with group LN. $^{\S}P < 0.01$, compared with group HN. PCA: Patient-controlled analgesia; Group LN: hydromorphone 0.05 mg/mL + nalbuphine 0.5 mg/mL; Group MN: hydromorphone 0.05 mg/mL + nalbuphine 0.7 mg/mL; Group HN: hydromorphone 0.05 mg/mL + nalbuphine 0.9 mg/mL.

Table 3: VAS scores of incisional pain in patients receiving three concentrations of intravenous nalbuphine combined with hydromorphone for post-cesarean delivery analgesia ($N = 112$).

	VAS-I-R					VAS-I-M				
Time after surgery, h	Group LN ($n = 38$)	Group MN ($n = 38$)	Group HN ($n = 36$)	F	P	Group LN ($n = 38$)	Group MN ($n = 38$)	Group HN ($n = 36$)	F	P
4	1.4 ± 0.5	1.5 ± 0.6	1.5 ± 0.8	0.333	0.718	3.7 ± 0.5	3.8 ± 0.4	3.7 ± 0.5	1.015	0.366
8	1.3 ± 0.6	1.3 ± 0.7	1.4 ± 0.8	0.213	0.809	3.7 ± 0.5	3.7 ± 0.5	3.6 ± 0.5	0.195	0.823
12	0.9 ± 0.6	1.0 ± 0.7	1.2 ± 0.7	2.079	0.130	3.5 ± 0.6	3.6 ± 0.6	3.6 ± 0.7	0.300	0.741
24	0.4 ± 0.5	0.6 ± 0.5	0.7 ± 0.8	1.665	0.194	3.2 ± 0.5	3.3 ± 0.6	3.1 ± 0.8	0.847	0.432
48	0.2 ± 0.4	0.1 ± 0.3	0.3 ± 0.5	1.601	0.206	2.9 ± 0.4	2.8 ± 0.4	2.9 ± 0.8	1.039	0.357

Values are expressed as mean ± standard deviation. VAS: Visual analog scale; VAS-I-R: Visual analog scale of incisional pain at rest; VAS-I-M: Visual analog scale of incisional pain on mobilization; Group LN: Hydromorphone 0.05 mg/mL + nalbuphine 0.5 mg/mL; Group MN: Hydromorphone 0.05 mg/mL + nalbuphine 0.7 mg/mL; Group HN: Hydromorphone 0.05 mg/mL + nalbuphine 0.9 mg/mL.

In the first 3 days post-CS, VAS-U-O scores were statistically different among groups (all $P < 0.05$). VAS-U-O scores were significantly higher in group LN than those in group MN and group HN (all $P < 0.05$), but no statistical difference was found between group MN and group HN (all $P > 0.05$) [Table 5].

Side effects

During the first 24 h post-CS, the RSS scores were statistically different among groups (all $P < 0.05$), and RSS scores were significantly higher in group HN than those in group LN at 4, 8, 12, and 24 h post-CS (all $P < 0.05$) and group MN at 8 and 12 h post-CS (all $P < 0.01$), but no statistical difference was found between group MN and group LN (all $P > 0.05$) [Table 6]. The time to first flatus and the occurrence of urinary retention were significantly higher in group HN than those in group MN and group LN (all $P < 0.05$), whereas no difference was found between group LN and group MN (all $P > 0.05$). There were no significant differences in 5-min Apgar scores and incidence of vomiting among three groups (all $P > 0.05$) [Table 7].

Discussion

Post-operative pain after CS mainly consists of incisional pain (somatic pain) and uterine cramping pain (visceral

Table 4: VAS-U-R and VAS-U-F scores in patients receiving three concentrations of intravenous nalbuphine combined with hydromorphone for post-cesarean delivery analgesia ($N = 112$).

Time after surgery, h	VAS-U-R					VAS-U-F				
	Group LN ($n = 38$)	Group MN ($n = 38$)	Group HN ($n = 36$)	F	P	Group LN ($n = 38$)	Group MN ($n = 38$)	Group HN ($n = 36$)	F	P
4	3.0 ± 0.8	2.0 ± 0.8*	1.9 ± 0.9*	18.588	<0.001	3.4 ± 0.8	3.0 ± 0.8†	2.9 ± 0.8*	4.628	0.012
8	2.6 ± 0.9	2.1 ± 0.6*	1.9 ± 0.6*	8.529	<0.001	3.3 ± 0.8	2.7 ± 0.4*	2.6 ± 0.8*	10.964	<0.001
12	2.2 ± 1.0	1.9 ± 0.9†	1.6 ± 0.8*	5.099	0.008	2.9 ± 0.8	2.5 ± 0.8†	2.2 ± 1.0*	7.249	0.001
24	1.5 ± 0.8	1.5 ± 0.8	1.4 ± 0.8	0.169	0.845	2.2 ± 0.7	2.0 ± 0.7	1.9 ± 0.8	2.180	0.118
48	1.0 ± 0.8	0.9 ± 0.6	0.8 ± 0.5	0.438	0.647	1.5 ± 0.6	1.3 ± 0.5	1.2 ± 0.8	1.878	0.158

Values are expressed as mean ± standard deviation. * $P < 0.01$, compared with group LN. † $P < 0.05$, compared with group LN. VAS-U-R: Visual analog scale of uterine cramping pain at rest; VAS-U-F: Visual analog scale of uterine cramping pain after breast-feeding; Group LN: Hydromorphone 0.05 mg/mL + nalbuphine 0.5 mg/mL; Group MN: Hydromorphone 0.05 mg/mL + nalbuphine 0.7 mg/mL; Group HN: Hydromorphone 0.05 mg/mL + nalbuphine 0.9 mg/mL.

Table 5: VAS-U-O scores in patients receiving three concentrations of intravenous nalbuphine combined with hydromorphone for post-cesarean delivery analgesia ($N = 112$).

Time after surgery, day	VAS-U-O				
	Group LN ($n = 38$)	Group MN ($n = 38$)	Group HN ($n = 36$)	F	P
1	4.8 ± 0.9	3.5 ± 0.9*	3.3 ± 0.7*	34.727	<0.001
2	3.6 ± 0.9	3.0 ± 0.8*	2.7 ± 0.7*	12.867	<0.001
3	2.5 ± 1.0	2.0 ± 1.0†	1.8 ± 0.9*	5.609	0.005

Values are expressed as mean ± standard deviation. * $P < 0.01$, compared with group LN. † $P < 0.05$, compared with group LN. VAS-U-O: Visual analog scale of uterine cramping pain when oxytocin was intravenously infused; Group LN: Hydromorphone 0.05 mg/mL + nalbuphine 0.5 mg/mL; Group MN: Hydromorphone 0.05 mg/mL + nalbuphine 0.7 mg/mL; Group HN: Hydromorphone 0.05 mg/mL + nalbuphine 0.9 mg/mL.

Table 6: Ramsay sedation scale (RSS) score within 48 h after surgery in patients receiving three concentrations of intravenous nalbuphine combined with hydromorphone for post-cesarean delivery analgesia ($N = 112$).

Time after surgery, h	RSS scores				
	Group LN ($n = 38$)	Group MN ($n = 38$)	Group HN ($n = 36$)	F	P
4	2.03 ± 0.16	2.16 ± 0.37	2.22 ± 0.42*	3.304	0.040
8	2.08 ± 0.27	2.18 ± 0.39	2.56 ± 0.50†,‡	14.444	<0.001
12	2.08 ± 0.27	2.13 ± 0.34	2.42 ± 0.50†,‡	8.324	<0.001
24	2.05 ± 0.23	2.11 ± 0.31	2.25 ± 0.44*	3.421	0.036
48	2.00 ± 0.00	2.00 ± 0.00	2.06 ± 0.23	2.175	0.118

Values are expressed as mean ± standard deviation. * $P < 0.05$, compared with group LN. † $P < 0.01$, compared with group LN. ‡ $P < 0.01$, compared with group MN. Group LN: Hydromorphone 0.05 mg/mL + nalbuphine 0.5 mg/mL; Group MN: Hydromorphone 0.05 mg/mL + nalbuphine 0.7 mg/mL; Group HN: Hydromorphone 0.05 mg/mL + nalbuphine 0.9 mg/mL.

Table 7: Side effects in patients receiving three concentrations of intravenous nalbuphine combined with hydromorphone for post-cesarean delivery analgesia ($N = 112$).

Items	Group LN ($n = 38$)	Group MN ($n = 38$)	Group HN ($n = 36$)	Statistics	P
Time to first flatus, h	43 ± 8	40 ± 14	48 ± 6[*,†]	$F = 6.363$	0.002
Incidence of urinary retention, %	2 (5.3)	2 (5.3)	4 (11.1)[†,‡]	$x^2 = 4.107$	0.019
5-min Apgar score ≤9, *n*	0	0	0	–	1.000
Incidence of vomiting, *n*	1 (2.6)	0	2 (5.6)	$x^2 = 2.189$	0.335

Values are expressed as mean ± standard deviation or *n* (%). [*] $P < 0.05$, compared with group LN. [†] $P < 0.01$, compared with group MN. [‡] $P < 0.01$, compared with group LN. Group LN: Hydromorphone 0.05 mg/mL + nalbuphine 0.5 mg/mL; Group MN: Hydromorphone 0.05 mg/mL + nalbuphine 0.7 mg/mL; Group HN: Hydromorphone 0.05 mg/mL + nalbuphine 0.9 mg/mL; –: Not applicable.

pain). Ideal post-CS analgesia requires the elimination of both visceral pain and somatic pain. However, doctors usually pay more attention to somatic pain than visceral pain in clinical practice. Visceral pain is associated with a variety of neurotransmitters, channels, and receptors, suggesting that a single analgesic is unlikely to provide excellent attenuation of the visceral pain and that a combination of analgesics could provide better efficacy.[14,27] In this study, we applied hydromorphone (for somatic pain) in combination with nalbuphine (for visceral pain), a KOR agonist, for relieving the post-operative pain using IV-PCA in patients undergoing CS. The primary aim of the present study was to determine an ideal concentration of IV nalbuphine, co-administered with hydromorphone at a fixed concentration for post-CS analgesia by PCA in healthy patients.

The present study showed that an increase of nalbuphine concentration resulted in a increase in the ratio of PCA delivered/PCA demands and a decrease in the total number of PCA demands and the cumulative PCA dose during the first 48 h after CS, indicating a better analgesic efficacy with a higher nalbuphine dose. The VAS scores of incisional pain at both rest and during movement were comparable among three groups, suggesting the concentration of 0.05 mg/mL hydromorphone was enough for attenuating post-operative incisional (somatic) pain. Oxytocin was released increasingly in response to stimulation of the nipples from breastfeeding, which led to exacerbated uterine contractions.[4] The difference in uterine cramping pain among the three groups was particularly evident after breastfeeding and oxytocin infusion. The uterine cramping pain scores in the middle (nalbuphine 0.7 mg/mL) and high-concentration (nalbuphine 0.9 mg/mL) groups were significantly lower than those in the low-concentration group (nalbuphine 0.5 mg/mL). Also, the satisfaction score in the low-concentration group was significantly lower than that in the mid- and high-concentration group. Our results indicated that the concentration of nalbuphine 0.7 and 0.9 mg/mL had a better analgesic effect in terms of uterine cramping pain.

The low fat-solubility of nalbuphine determined that the level of nalbuphine in milk only with an estimated relative infant dose of 0.59%[28]; the fat solubility of hydromorphone is between morphine and fentanyl derivatives, and the suckling infants only receive approximately 0.67% of the maternal hydromorphone dosage.[29] The Apgar scores of the newborns were ten points after 5 min of breastfeeding in both of the groups, therefore breastfeeding was not contraindicated. Four patients (11.1%) showed urinary retention in the high-concentration group in comparison to two patients (5.3%) each in the mid- and the low-concentration groups, suggesting that nalbuphine probably has a mild effect on urinary muscle contraction. The use of opioids could lead to intestinal motor depression, but compared with other opioids, nalbuphine has a slight effect on gastrointestinal motility.[23,30] However, surgical stress response and post-operative pain could increase the secretion of catecholamines in patients, thereby inhibiting the recovery of gastrointestinal motor function. Therefore, the time to first flatus in the low- and high-concentration groups was longer than that in the mid-concentration group. One patient (2.6%) experienced vomiting in the low-concentration group, whereas vomiting was seen in two patients (5.6%) in the high-concentration group, but none of the patients experienced any hypotension, hypoxemia, respiratory depression, pruritus, or dizziness. RSS scores (sedation levels) in the high-concentration group were significantly higher than those in the mid-concentration group at 8 and 12 h, although the level of sedation remained within a safe range. Prolonged sedation could lead to lower levels of energy in the mother and delay in communication between the mother and her newborn, and subsequently delay the initiation of lactation. To limit major and minor side-effects, the use of low-dose IV drugs has been advocated. While the side effect profile (the incidence of urinary retention and vomiting) appears better with the mid-concentration group, and considering the time to first flatus and RSS scores were lower in mid-concentration group than those in high-concentration group, we chose to use mid-concentration nalbuphine (0.7 mg/mL) for the visceral pain control post-operatively.

There are some limitations in this study. Further research is needed to evaluate the difference of the initiation time of lactation and the plasma levels of prolactin among three groups. Although some patients experienced vomiting, there was no significant difference among three groups. Therefore, further investigation with larger samples is required in the future.

In summary, the present study showed a similar incisional pain reduction in all three groups, probably because of the same hydromorphone dose used. Furthermore, patients

with the highest concentration of nalbuphine reported lowest uterine cramping pain scores but showed the highest RSS. These findings suggest that a combination of hydromorphone 0.05 mg/mL and nalbuphine 0.7 mg/mL could be recommended as a suitable analgesia protocol for post-CS analgesia.

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Conflicts of interest

None.

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