J Anesth (2012) 26:752–757
DOI 10.1007/s00540-012-1421-7

ORIGINAL ARTICLE

Intravenous butorphanol administration reduces intrathecal morphine-induced pruritus after cesarean delivery: a randomized, double-blind, placebo-controlled study

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Received: 7 April 2011 / Accepted: 18 May 2012 / Published online: 7 June 2012

Abstract
Purpose Pruritus associated with intrathecal opioid administration is a common side effect. There is evidence that κ-opioid receptor agonists have antipruritic activity. Butorphanol has agonist actions at both κ-opioid and μ-opioid receptors. This study was designed to evaluate the antipruritic efficacy of butorphanol after intrathecal morphine administration in the setting of a randomized, double-blind study of parturients undergoing cesarean section.
Methods Ninety-one women who received combined spinal–epidural anesthesia with 1.2 ml 0.5 % isobaric bupivacaine and 0.1 mg preservative-free morphine were included in this study. After delivery of the baby, the parturients were randomly allocated to two groups: butorphanol group ($n = 46$) and physiological saline group ($n = 45$). In the butorphanol group, parturients received an intravenous loading dose of 1 mg butorphanol followed by infusion of 0.2 mg/h butorphanol. The physiological saline group received an infusion of the same volume of physiological saline. The presence of pruritus, visual analog scores for pain, sedation scores, and adverse effects were recorded 1, 2, 4, 6, 8, 10, 12, and 24 h after intrathecal morphine administration.
Results The incidence of pruritus at 24 h was significantly more frequent in the physiological saline group than in the butorphanol group (48.9 vs. 13.0 %, $P < 0.001$). The severity of pruritus was significantly greater in the saline group than in the butorphanol group 2, 4, 6, 8 and 10 h after intrathecal morphine injection ($P = 0.004$, 0.001, 0.002, and 0.003, respectively). The visual analog scale scores at 24 h were significantly lower in the butorphanol group than in physiological saline group ($P < 0.001$). The Ramsay sedation score in the butorphanol group was significantly higher than that in the physiological saline group after 1, 2, 4, 6, 8, 10, 12, and 24 h ($P < 0.05$). There were no significant differences between the two groups in nausea/vomiting and other adverse effects.
Conclusion Administration of intravenous butorphanol after delivery of the baby can reduce pruritus that has been induced by intrathecal morphine administration in cesarean delivery with combined spinal–epidural anesthesia.

Keywords Pruritus · Intrathecal opioid administration · κ-Opioid receptor

Introduction

Intraspinal administration of opioids is one the most effective analgesic methods in many surgical procedures. However, intrathecal opioid injections are often accompanied by many troublesome adverse reactions, e.g., nausea, vomiting, and pruritus [1, 2]. Pruritus has been reported in 30–100 % of patients [3]. Currently, the neurobiological pathway underlying opioid-related pruritus remains uncertain. Intrathecal opioid-induced pruritus has been treated with 5-HT3 receptor antagonists, opioid receptor antagonists, a mixture of opioid receptor agonists and antagonists, antihistamines, propofol, droperidol, and nonsteroidal anti-inflammatory drugs [4]. Butorphanol is a synthetic opioid

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with partial agonist action at both μ-opioid and κ-opioid receptors [5]. WHO guidelines suggest using butorphanol as an adjunctive preanesthetic or analgesic for postoperative pain relief [6]. Other advantages of butorphanol include few side effects, very low addiction potential, and low toxicity [7]. In a rhesus monkey study, butorphanol was shown to be effective at attenuating intrathecal morphine-induced pruritus without reducing morphine's analgesic effect [8]. More importantly, several clinical studies have shown that epidural administration of butorphanol can alleviate morphine-induced pruritus [9–11]. These findings support use of butorphanol as a potential antipruritic. Thus, we conducted this prospective, randomized, double-blind, placebo-controlled trial to evaluate the effect of intravenous butorphanol on intrathecal morphine-related pruritus after cesarean section. Our research hypothesis was that, compared with a saline control, intravenous infusion of butorphanol would reduce the incidence of pruritus at 24 h.

Methods

In this randomized, double-blind and controlled study, 100 ASA (American Society of Anesthesiologists) I–II women scheduled for cesarean section using combined spinal–epidural anesthesia were recruited. The exclusion criteria included pre-eclampsia, eclampsia, systemic diseases, pre-existing pruritus, nausea, and known allergy to the medication. The study was approved by the hospital ethics committee. Informed consent was obtained from each patient.

By use of a computer-generated sequence of random numbers and a sealed envelope technique, the patients were allocated to two groups: a butorphanol group (butorphanol injection) and a normal saline group (normal saline injection). The patients in the butorphanol group were given butorphanol (1 mg/mL) intravenously (Lianyungang Hengrui Pharmaceutical Company, China) followed by continuous intravenous injection of butorphanol (0.2 mg/2 mL/h) for 24 h, by use of an infusion pump (Kagoshima AMI Institute, Japan). The patients in the normal saline group were given normal saline (1 mL) intravenously, followed by continuous intravenous injection of normal saline (2 mL/h) for 24 h. The study was double-blind for all the researchers, physicians who collected data, nurses, and staff who prepared the medications. Every syringe was filled with the same amount of either butorphanol or normal saline from the same type of ampoule.

Electrocardiography, oxygen saturation, and noninvasive blood pressure were monitored during the cesarean section. Combined spinal and epidural anesthesia were administered in the left lateral position by use of a 17-gauge epidural needle and a 25-gauge spinal needle. After successful lumbar puncture, subarachnoid administration of 6 mg isobaric bupivacaine (0.5 %, 1.2 mL) and 0.1 mg morphine (0.1 mL) was given, followed by insertion of a 19-gauge epidural catheter.

The patients were then placed in the supine position, elevated under the right hip and tilted to the left. Oxygen (2–4 L/min) was given by nasal catheter. The intravenous infusion rate was adjusted according to blood pressure. Ephedrine was used to maintain the blood pressure within 70 % of the baseline or to keep the systolic blood pressure above 100 mmHg. The conventional cesarean section procedure was performed after the block was deemed to be adequate (block level at T6 or higher). The study drug was given intravenously after delivery of the newborn and umbilical cord clamping. The main evaluation criterion was incidence of pruritus within 24 h. Other criteria included Ramsay score, visual analog scale (VAS) pain score, and other adverse effects and complications.

The level of pruritus, sedation, pain score, and other adverse effects were evaluated 1, 2, 4, 6, 8, 12, and 24 h after post-intrathecal morphine administration. Pruritus severity was assessed by use of a verbal rating scale: 0 = no itch, 1 = minor itch, 2 = moderate itch, 3 = severe itch [12]. Sedation level was assessed by use of the Ramsay scale [13]. Pain scores were recorded by use of VAS between 0 and 10, with 0 = no pain and 10 = unbearable pain [14].

Other adverse effects and complications after intrathecal morphine administration included postoperative nausea, vomiting, vertigo, dizziness, shivering and respiratory depression. These effects were all recorded, and it was explained to the patients that these symptoms were treatable. Nausea and vomiting were treated with intravenous ondansetron (4 mg). Severe pain was treated with paracetamol suppository. Severe pruritus was treated with 10 mg oral loratadine tablets. The adverse effects were only treated at the request of the patient.

Statistical analysis

Statistical analysis was performed by use of the statistical software SPSS 13.0. Reduction of pruritus incidence by 30 % was considered clinically significant. The sample size was estimated with the requirement of Type I and II errors <0.05 and <0.2, respectively. In the pilot study, the incidence of pruritus in the control group was 45 %. Therefore, each group had to include at least 45 patients for the requirement of 30 % reduction of pruritus incidence. Continuous data are represented as mean $\pm$ standard deviation. The data were analyzed by ANOVA. Nonparametric data are represented as number and percentage. They were analyzed by use of a chi-squared test and Fisher's exact probability test. A P value ≤ 0.05 was considered statistically significant.

Results

One hundred pregnant women were recruited in this study. Nine patients were excluded from the study: 3 patients because of inadequate anesthesia, 2 patients because of incomplete data collection, and 4 patients for using non-steroidal anti-inflammatory drugs to treat postoperative pain. Therefore, data from 46 patients in the butorphanol group and 45 patients in the normal saline group were included in the study (Fig. 1).

The general characteristics of the two groups were not statistically different (Table 1). Intrathecal morphine-induced pruritus in both groups was expressed as scratching of the face. The incidence of pruritus was 13 % (6/46) in the butorphanol group and 48.9 % (22/45) in the normal saline group. There was a significant difference between the two groups ($P < 0.001$). The level of pruritus was significantly different between the two groups after 2, 4, 6, 8, and 10 h ($P = 0.004$, 0.001, 0.002, 0.003 and 0.007) (Table 2).

Good analgesic effect was achieved at 12 h in both groups, with similar VAS scores. The VAS score at 24 h was significantly lower in the butorphanol group than in the normal saline group ($P < 0.001$; Table 3). The Ramsay sedation score at 24 h was significantly higher in the butorphanol group than in the normal saline group ($P < 0.05$; Table 4). Although there was more sedative effect in the butorphanol group, patients in that group were easy to wake up, suggesting they were not too deeply sedated. There were no statistically significant differences in postoperative nausea, vomiting, vertigo, dizziness, or chills between the two groups (Table 5). No arrhythmia or respiration depression was observed.

Discussion

In this prospective, randomized, double-blind trial we compared the antipruritic effect of butorphanol and normal saline for patients undergoing cesarean section. Our results show that a bolus dose followed by 24-h infusion of butorphanol successfully reduced the incidence of pruritus from 49 to 13 %.

Pruritus is more likely to occur in pregnant women, for whom the incidence is between 60 and 100 % and is dose-

Table 1 Patient characteristics

	Butorphanol group ($n = 46$)	Physiological saline group ($n = 45$)	P
Age (years)	27.2 ± 3.6	27.9 ± 5.1	0.417
Weight (kg)	72.1 ± 9.8	70.1 ± 10.7	0.383
Height (cm)	160.9 ± 2.9	160.6 ± 4.2	0.743
Gestational age (weeks)	38.8 ± 1.2	38.4 ± 1.5	0.130
Duration of surgery (min)	35.8 ± 9.9	33.2 ± 10.0	0.227
Number of patients with pruritus	6	22	<0.001

Values are expressed by mean ± SD (standard deviation)

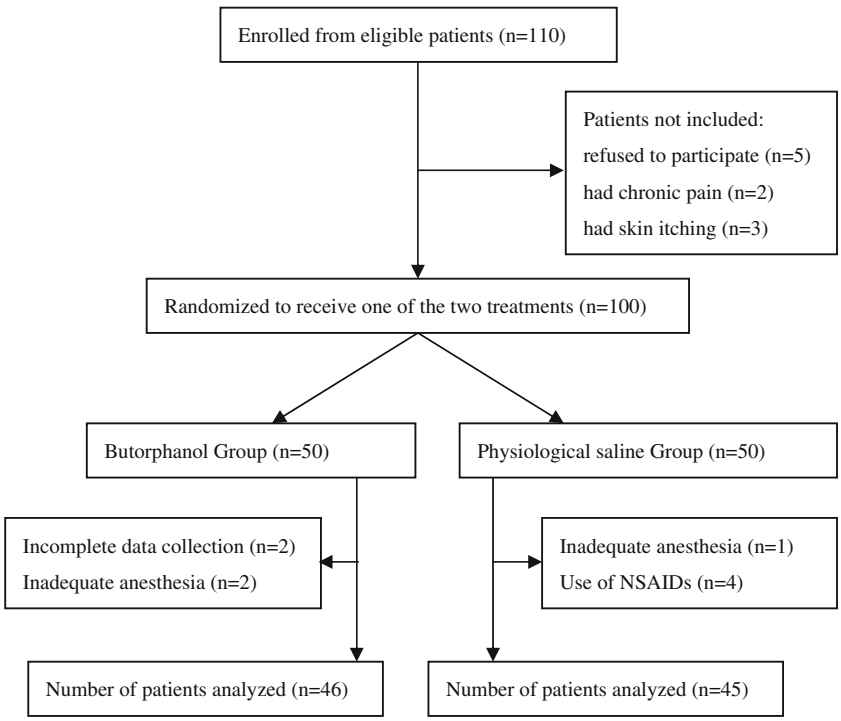

Fig. 1 CONSORT flow chart of study

Table 2 Assessment of severity of pruritus 1, 2, 4, 6, 8, 10, 12, and 24 h after intrathecal morphine administration

	1 h	2 h*	4 h†	6 h‡	8 h△	10 h▲	12 h	24 h
Butorphanol group ($n = 46$)								
No pruritus	42 (91.3 %)	42 (91.3 %)	42 (91.3 %)	42 (91.3 %)	43 (93.5 %)	45 (97.8 %)	45 (97.8 %)	45 (97.8 %)
Mild pruritus	2 (4.3 %)	2 (4.3 %)	2 (4.3 %)	4 (8.7 %)	3 (6.5 %)	1 (2.2 %)	1 (2.2 %)	1 (2.2 %)
Moderate pruritus	2 (4.3 %)	2 (4.3 %)	2 (4.3 %)	0	0	0	0	0
Severe pruritus	0	0	0	0	0	0	0	0
Physiological saline group ($n = 45$)								
No pruritus	42 (93.3 %)	30 (66.7 %)	28 (62.2 %)	29 (64.4 %)	31 (68.9 %)	36 (80.0 %)	39 (86.7 %)	43 (95.6 %)
Mild pruritus	1 (2.2 %)	5 (11.1 %)	7 (15.6 %)	9 (20.0 %)	12 (26.7 %)	8 (17.8 %)	6 (13.3 %)	2 (4.4 %)
Moderate pruritus	2 (4.4 %)	10 (22.2 %)	10 (22.2 %)	7 (15.6 %)	2 (4.4 %)	1 (2.2 %)	0	0
Severe pruritus	0	0	0	0	0	0	0	0

Categorical variables are presented as count (and percentage)

*$P = 0.004$, †$P = 0.001$, ‡$P = 0.002$, △$P = 0.003$, ▲$P = 0.007$ compared by χ^2 tests

Table 3 Pain VAS scores

	1 h	2 h	4 h	6 h	8 h	10 h	12 h	24 h
Butorphanol group ($n = 46$)	2.1 ± 0.6	2.1 ± 0.6	2.2 ± 0.6	2.3 ± 0.5	2.3 ± 0.5	2.3 ± 0.6	2.3 ± 0.6	1.9 ± 0.6*
Physiological saline group ($n = 45$)	2.2 ± 0.6	2.3 ± 0.6	2.5 ± 0.5	2.4 ± 0.6	2.6 ± 0.7	2.5 ± 0.6	2.5 ± 0.6	2.8 ± 0.6

Values are expressed by mean ± SD (standard deviation)

*$P < 0.001$ versus physiological saline group

Table 4 Ramsay sedation scores

	1 h	2 h	4 h	6 h	8 h	10 h	12 h	24 h
Butorphanol group ($n = 46$)	2.4 ± 0.5*	2.4 ± 0.5*	2.3 ± 0.4*	2.3 ± 0.4*	2.2 ± 0.4*	2.3 ± 0.4*	2.2 ± 0.4*	2.2 ± 0.4*
Physiological saline group ($n = 45$)	2.1 ± 0.3	2.1 ± 0.3	2.1 ± 0.2	2.1 ± 0.3	2.0 ± 0.4	2.0 ± 0.3	2.0 ± 0.3	1.9 ± 0.4

Values are expressed by mean ± SD (standard deviation)

*$P < 0.05$ versus physiological saline group

Table 5 Adverse events

	Butorphanol group ($n = 46$), n (%)	Physiological saline group ($n = 45$), n (%)	P
Dizziness	3 (6.5)	0	0.242
Nausea	5 (10.9)	3 (6.7)	0.714
Vomiting	0	1 (2.2)	0.495
Blurred vision	0	1 (2.2)	0.495

dependent [15–18]. In our observations, the incidence of pruritus was 49 % in the normal saline group after intrathecal morphine (0.1 mg) administration, with the peak 4–6 h after intrathecal injection, which is similar to previous findings: Lockington et al. reported that the incidence of pruritus with cesarean section after intrathecal morphine administration was 48 % [19].

Because high doses of morphine do not increase analgesic effect, but instead cause more adverse effects, 0.1 mg morphine is the most commonly recommended dose [20]. Pruritus caused by medication or systemic disease is complicated and its mechanism is not known [21]. Systematic reviews have shown serotonin receptor antagonists to be an effective treatment of intraspinal opioid-induced pruritus and postoperative nausea and vomiting [22]. It is generally believed that pruritus induced by intraspinal, intraventricular, or intrathecal administration of opioids is mediated by the μ receptor because of the rich expression of opioid receptors in the central nervous system [21]. Naloxone, a μ-receptor antagonist, can prevent intrathecal and epidural opioid-induced pruritus. The effects of naloxone support the theoretical mechanism of central opioid receptor-mediated pruritus. However, naloxone application to treat pruritus was limited to low doses because high does of naloxone can reverse the analgesic effect of opioids [19]. Togashi et al. [23] found that TRK-820 can inhibit antihistamine-sensitive and insensitive pruritus via the κ receptor, and κ receptor agonists can also inhibit

subcutaneous and intrathecal-induced pruritus in monkeys [24], cholestasis-induced pruritus in rodents [25], and uremia-induced pruritus in humans [26]. More importantly, pentazocine (a κ receptor agonist and partial μ receptor agonist) 15 mg has been shown to be superior to ondansetron 4 mg for treatment of intrathecal morphine-induced pruritus [27].

In this clinical study, we observed the effect of butorphanol in the treatment of intrathecal morphine-induced pruritus. The incidence of pruritus was reduced to 13 % in the butorphanol group. These findings support the potential antipruritus effect of the κ receptor, which might be activated by butorphanol to reduce pruritus [28]. However, butorphanol cannot completely prevent pruritus. In this study ten percent of patients still had pruritus after treatment. This result might be because of inappropriate dose and timing of drug delivery, or it might be because butorphanol cannot affect other neurotransmitters that induce pruritus, for example prostaglandins [29], the neurotransmitters glutamate and GABA [1] or NMDA receptors [30], all of which have important effects in inducing pruritus.

Butorphanol reduced the incidence of pruritus. It also enhanced sedation depth, especially in combination with midazolam. The sedative effect of butorphanol is because of its activation of central κ receptors [31]. Therefore, butorphanol has been used in perioperative sedation. In the follow-up, all the patients cooperated well with us and remained calm, maintained stable respiration and a good cough reflex, and were easy to wake, indicating they were not too deeply sedated.

In our observations, VAS scores were similar in the two groups after 12 h, both indicating good analgesic effectiveness. However, the VAS score after 24 h was significantly lower in the butorphanol group than in the normal saline group, possibly because of the limited analgesic effect of a single intrathecal injection of morphine. Butorphanol has both analgesic and sedative effects. Therefore, addition of continuous intravenous injection of butorphanol to intrathecal morphine administration resulted in better postoperative analgesic effect and less sedative effect than use of morphine alone. In addition to inducing pruritus, intrathecal morphine injections also induce nausea and vomiting by activating serotonin receptors in the emetic chemoreceptor trigger zone [32]. However, there were no differences in nausea and vomiting between two groups. Very few patients requested antiemetics. There were also no differences in other postoperative side effects, for example vertigo, dizziness and chills, between two groups. No arrhythmia or respiration depression was observed.

There are some limitations to our study. First, pruritus is a subjective symptom. Second, we did not study the dose-dependence of butorphanol in the treatment of pruritus; therefore, we did not optimize the dose. Third, because butorphanol can pass through the placental barrier, we did not compare the effects of butorphanol when using preoperative or preintrathecal injection. Further study will focus on optimization of dose and timing in drug delivery.

In summary, continuous intravenous injection of butorphanol can significantly reduce the incidence of induced by intrathecal morphine injection, attenuating pruritus severity with enhanced analgesic effect and moderate sedative effect. Therefore, butorphanol is a potentially effective treatment of intrathecal morphine-induced pruritus in cesarean section.

Conflict of interest The authors have no commercial, proprietary, or financial interest in the products or companies described in this article.

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