Research Article

Use of Intravenous Butorphanol for Intrathecal Morphine-induced Pruritus after Cesarean Section: A Randomized, Placebo Controlled Study

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ABSTRACT

Pruritus is a troublesome side-effect of neuraxial (epidural and intrathecal) opioids. Sometimes it may be more unpleasant than pain itself. The prevention and treatment still remains a challenge. A variety of medications with different mechanisms of action have been used for the prevention and treatment of opioid-induced pruritus, with mixed results. This study was designed to evaluate the antipruritic efficacy of butorphanol after intrathecal morphine administration in the setting of a randomized, double-blind placebo controlled study of parturients undergoing cesarean section.

Keywords: Pruritus, neuraxial opioids, butorphanol, intrathecal.

INTRODUCTION

Neuraxial opioids are one of the most frequently used methods of analgesia after cesarean delivery and other surgical procedure. The beneficial effect is to augment and prolong intraoperative and postoperative analgesia. A wide range of side effects has been reported, out of which one is pruritus.[1] It is a subjective unpleasant and irritating sensation that provokes an urge to scratch and the symptoms usually localized to facial areas, innervated by the trigeminal nerve.[2] The spinal nucleus of the trigeminal nerve is rich in opioid receptors and is continuous with the substantia gelatinosa and Lissauer tract at C3-C4.[3] The ophthalmic division of the spinal sensory nucleus of the trigeminal nerve is most inferior; thus, supporting the observation that the pruritus following neuraxial opioid administration is typically in the nose and upper part of the face.[3] The incidence of pruritus is 83% in postpartum patients as compared to 69% in others[4-7]. This increased incidence may be due to an interaction of estrogen with opioid receptors[4,5]. Many mechanisms have been postulated, currently the exact mechanism of morphine-induced pruritus is unclear but no single mechanism can explain all instances. 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 placebo controlled study of parturients undergoing cesarean section.

MATERIALS AND METHODS

In this double-blind, randomized and placebo controlled study, 100 women of ASA I–II scheduled for cesarean section using spinal anesthesia were recruited. Nine patients were excluded 4 patients because of inadequate anesthesia & 5 patients because of incomplete data collection.

Exclusion criteria includes: pre-eclampsia, eclampsia, systemic diseases, pre-existing chronic pruritus, nausea, and known allergy to the medication.

After approval by the hospital ethics committee informed consent was obtained from each patient**.**

Patients were randomly allocated into two groups by sealed envelope technique.

GROUPA: Normal Saline group (Control group) [1 ml of normal saline] [n=45]

GROUP B: Butorphanol group (Study group) [1ml of 1mg butorphanol] [n=46]

Standard monitors were connected. Spinal anesthesia was administered with 10mg 0.5% hyperbaric bupivacaine and Morphine 125 μg in the left lateral position by using 25-gauge quinckes spinal needle.

The patients were then placed in the supine position and wedge given under the right hip. Oxygen (5L/min) was given by venturi mask.

The intravenous infusion rate was adjusted according to blood pressure. Ephedrine was used to maintain the blood pressure within 30 % of the baseline.

The conventional cesarean section procedure was performed after the block was deemed to be adequate (block level at T4).

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 sedation

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 post operatively.

Pruritus severity was assessed by use of a verbal rating scale as, 0 = no itch, 1 = minor itch, 2 = moderate itch, 3 = severe itch.

Sedation level was assessed by use of the Ramsay sedation scale. Pain scores were recorded by use of VAS between 0 and 10, 0 = no pain and 10 = unbearable pain. Other adverse effects including postoperative nausea, vomiting, vertigo, dizziness, shivering and respiratory depression were recorded. Nausea and vomiting were treated with intravenous ondansetron(4mg). Severe pain was treated with inj Tramadol. 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 software SPSS 20.0. Reduction of pruritus incidence by 30% was considered clinically significant. 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 were analyzed by ANOVA. Nonparametric data 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

The two groups were comparable for general characteristics and physical parameters. 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 10hr (Table 1-6).

Table 1

	Group-A (n=45)	Group-B (n=46)
Age (in yrs)	27.2 ± 3.6	27.9 ± 5.1
Height (in cm)	160.9 ± 2.9	160.6 ± 4.2
Weight (in kgs)	72.1 ± 9.8	70.1 ± 10.7
Gestational AGE(in weeks)	38.8 ± 1.2	38.4 ± 1.5
Duration of Surgery (in mins)	35.8 ± 9.9	33.2 ± 10.0

Table 2: Assessment of Severity of Pruritus (Group A (Saline)

	1hr	2hr	4hr	6hr	8hr	10hr	12hr	24hr
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%)
Mod 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

Table 2: Group B (Butorphanol)

	1hr	2hr	4hr	6hr	8hr	10hr	12hr	24hr
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%)
Mod 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

Table 3: Vas Score

	1hr	2hr	4hr	6hr	8hr	10hr	12hr	24hr
Group-A (Saline)	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
Group-B (Butorphanol)	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	2.3 ± 0.6

Ramsay sedation score at 4 hr was significantly higher in the butorphanol group than in the normal saline group but patient were easy to wake up, suggesting they were not too deeply sedated.

Table 4: Ramsay sedation score

	1hr	2hr	4hr	6hr	8hr	10hr	12hr	24hr
Group-A (Saline)	2.1 ± 0.3	2.1 ± 0.3	2.1 ± 0.2	2.3 ± 0.4	2.1 ± 0.3	1.9 ± 0.4	1.9 ± 0.4	1.9 ± 0.4
Group-B (Butorphanol)	2.4 ± 0.5	2.4 ± 0.5	2.3 ± 0.4	2.1 ± 0.3	2.2 ± 0.4	2.1 ± 0.3	2.0 ± 0.3	1.9 ± 0.4

Table 5: Rescue Analgesia Requirement

	1hr (%)	2hr (%)	4hr (%)	6hr (%)	8hr (%)	10hr (%)	12hr (%)	24hr (%)
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)
Mod 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

Table 6

	1hr	2hr	4hr	6hr	8hr	10hr	12hr	24hr
Group-A (Saline)	nil	nil	20	nil	nil	Nil	Nil	nil
Group-B (Butorphanol)	nil	nil	5	nil	nil	nil	nil	nil

There were no statistically significant differences in postoperative nausea, vomiting, vertigo, dizziness, or chills between the two groups. No arrhythmia or respiration depression was observed.

DISCUSSION

The exact mechanism of neuraxial opioid-induced pruritus is unclear.

Many mechanisms have been postulated, but no single mechanism can explain all instances. Experiments in animals and the clinical response to μ opioid receptor antagonists in humans suggest a central μ opioid receptor mediated mechanism as the primary cause for Opiod induced pruritus.

Naloxone, a μ-receptor antagonist, can prevent intrathecal 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. Butorphanol has both agonist antagonist at μ receptor so it does affect the analgesic effect of opiod.

Togashi found that κ and δ agonist can inhibit antihistamine-sensitive and insensitive pruritus and intrathecal opiod induced pruritus in monkeys. Butorphanol has also κ agonist action, so it is a superior than other drugs for treatment of opiod induced pruritus. Our results also show that a bolus dose of butorphanol successfully reduced the incidence of pruritus from 49 to 13 %.

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, the neurotransmitters glutamate and GABA or NMDA receptors all of which have important effects in inducing pruritus. There are some limitations to our study as mentioned bellow.

- First, pruritus is a subjective symptom.
- Second, we did not study the dose 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.

CONCLUSION

Therefore, butorphanol is a potentially effective treatment of intrathecal morphine-induced pruritus in cesarean section.

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