

Comparative study between nalbuphine and ondansetron in prevention of intrathecal morphine-induced pruritus in women undergoing cesarean section

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Abstract

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Background:

Intrathecal morphine provides effective postoperative analgesia, but their use is associated with numerous side effects, including pruritus, nausea, vomiting, urinary retention, and respiratory depression. Pruritus is the most common side effect with a reported incidence of 58–85%.

Objectives:

This prospective, randomized, and double-blinded study was performed for women scheduled for cesarean delivery using spinal anesthesia to compare nalbuphine and ondansetron in the prevention of intrathecal morphine-induced pruritus.

Patients and Methods:

Ninety women after spinal anesthesia with hyperbaric bupivacaine and intrathecal morphine patients randomly divided into three groups. Women in placebo group (*P* group) received 4 ml of normal saline intravenous (IV) injection, nalbuphine group (*N* group) received 4 ml of a 4 mg nalbuphine IV injection, and ondansetron 4 group (*O* group) received 4 ml of a 4 mg ondansetron IV injection, immediately after delivery of the baby. Studied women observed in postanesthesia care unit for 4 h. The primary outcome measures success of the treatment, defined as a pruritus score 1 (no pruritus) or 2 (mild pruritus - no treatment required) at 20 min after treatment.

Results:

Although, there was no significant difference between the three studied groups regarding; score 1 pruritus, while, score 2 pruritus (mild pruritus - no treatment requested) was significantly high in *N* and *O* groups compared to placebo group. Pruritus score 1 (no pruritus) plus pruritus score 2 were significantly high in *N* and *O* groups compared to placebo group (20 cases, 20 cases, 5 cases; respectively, $P = 0.008$). In addition; score 3 pruritus (moderate - treatment requested) was significantly less in *N* and *O* groups

compared to placebo group.

Conclusion:

Nalbuphine and ondansetron were found to be more effective than placebo for prevention of intrathecal morphine-induced pruritus in women undergoing cesarean delivery and nalbuphine is preferred than ondansetron because it is not excreted in the breast milk.

Keywords: Cesarean section, morphine, nalbuphine, ondansetron, pruritus

INTRODUCTION

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Intrathecal morphine provides effective postoperative analgesia, but their use is associated with numerous side effects, including pruritus, nausea, vomiting, urinary retention, and respiratory depression.[1,2,3]

Pruritus is the most common side effect with a reported incidence of 58–85%.[2,4,5] It is a subjective unpleasant and irritating sensation that provokes an urge to scratch which is usually localized.[1]

The exact mechanism of intrathecal morphine-induced pruritus is unclear. More than one mechanism may be responsible for the development of this unpleasant symptom.[6]

Pruritus prevention and treatment remains a strong challenge for all anesthesiologists. Many drugs have used to prevent or to treat this side effect. Naloxone can effectively treat the pruritus even in severe cases, but it may do so at the expense of the analgesic effect.[7]

Other drugs as antihistamines, 5-hydroxytryptamine 3 (5-HT₃) (serotonin) receptor antagonists, opioid antagonists, opioid agonist-antagonists, propofol, and nonsteroidal anti-inflammatory drugs have been used.[8,9,10,11]

Nalbuphine is an opioid agonist-antagonist and its analgesic and possible antipruritic effects are mediated via actions on the μ - and κ -receptors.[4]

Many studies have noted the efficacy of intravenous (IV) nalbuphine in treating opioid-induced pruritus without reversal of analgesia or other significant side effects.[12,13]

Ondansetron, a selective serotonin type 3 receptor antagonist,[3] commonly used for nausea and vomiting in patients undergoing cancer chemotherapy and morphine-induced itching.

Several studies have shown that ondansetron is effective in treating pruritus of various causes; including intrathecal morphine-induced pruritus.[14,15,16]

PATIENTS AND METHODS

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This prospective, randomized, and double-blinded study was performed from March 2014 to March 2015, at Ahmadi Hospital, Kuwait Oil Company, Kuwait. After approval of the Institute Ethical Committee and after written consent from all studied women. American Society of Anesthesiologists physical status I or II nonbreast feeding women scheduled for cesarean delivery using spinal anesthesia with intrathecal morphine recruited for this study. Women who had known allergy to ondansetron, morphine, or bupivacaine and those with a preexisting pruritus due to pregnancy or a coexisting skin disorders or any other pruritogenic systemic diseases excluded from this study.

Women with inadequate spinal anesthesia necessitating conversion to general anesthesia also excluded.

No premedication given and all women hydrated with 500–1000 ml of normal saline solution before administration of spinal anesthesia. The subarachnoid block performed with patients in the left lateral position at either L3-4 or L4-5 interspace level, per our standard practice, with a 25-or 27-gauge Quincke spinal needle (Becton, Dickinson and Company, New Jersey, USA).

Once free flow of clear cerebrospinal fluid had demonstrated, 2.2 ml of 0.5% hyperbaric bupivacaine and 0.2 ml (0.2 mg) of preservative-free morphine, mixed in the same syringe, injected. Studied women then immediately placed in the supine position with left uterine displacement and supplemental oxygen delivered using facemask at 5 L/min.

After a satisfactory spinal block verified by loss of sensation to cold or pinprick, caesarean delivery performed.

Studied women randomly divided into three groups. Women in placebo group (*P* group) received 4 ml of normal saline IV injection, nalbuphine group (*N* group) received 4 ml of a 4-mg nalbuphine (Nubain; Dupont Pharma, Manati, Puerto Rico) IV injection, and ondansetron 4 group (*O* group) received 4 ml of a 4 mg ondansetron (Zofran; Glaxo Wellcome, Greenford, UK) IV injection, immediately after delivery of the baby. The block randomization sequence selected according to a random number table that wrote on a paper enclosed in a sealed envelope. Randomly, allocated coded syringes prepared by a nurse anesthetist not involved in the study and drugs administered in a double-blinded fashion.

In the postanesthesia care unit (PACU), vital signs recorded every 20 min for 4 h. Data collected by a single investigator. Women observed for scratching and its location. The degree of pruritus was evaluated at 20 min intervals by asking about the presence and severity of pruritus and whether treatment was desired (1 no pruritus, 2 mild pruritus - treatment not requested, 3 moderate pruritus - treatment requested, and 4 severe pruritus - treatment requested). Pruritus scores, arterial blood pressure, heart rate, and oxygen saturation recorded every 20 min intervals.

Verbal numeric pain score (0 no pain to 10 worst imaginable pain) and 4-point sedation score (1 fully awake, 2 somnolent - responds to voice, 3 somnolent - responds to tactile stimulation, and 4 asleep - responds to pain). Also, 4-point rating scale for nausea and vomiting (1 no nausea nor vomiting, 2 queasy, 3 severe nausea, and 4 vomiting) and a 4-point rating scale for shivering (1 no shivering, 2 mild shivering - treatment not necessary, 3 moderate shivering - treatment desirable, and 4 severe shivering - treatment desirable) recorded. The primary outcome measures success of the treatment, defined as a pruritus score 1 (no pruritus) or 2 (mild pruritus - no treatment required) at 20 min after treatment. Studied women evaluated every 20 min for 4 h postoperative to determine the duration of the antipruritic response. In absence of positive response (pruritus score of 3 or 4), result was considered as a treatment failure and those whose pruritus scores continued to be 3 or more were rescued with IV naloxone divided doses (10–20 µg).

Tramadol 0.5 mg/kg was prescribed for shivering when needed, also tramadol 1 mg/kg was administered for pain control (if pain score is more than 5 or on patient's request).

After each drug administration, arterial blood pressure, heart rate, respiratory rate, oxygen saturation, dizziness, extrapyramidal effects, mood changes, presence of hallucination, other adverse effects and the onset of pruritus recorded. Demographic and surgical characteristics of studied women also recorded. The study ended after 4 h of postoperative observation and after shift of the participants to the ward.

Justification and statistical analysis

Using data from previous studies and Epi Info[®] version 6.0, a sample size of 90 women was needed to produce a significant difference. Statistical analysis was done using SPSS (Statistical Package for Social Sciences); computer software version 18 (SPSS Inc., Chicago, IL, USA). Mean and standard deviation were used to represent numerical variables, while, number and percentage were used to represent categorical variables. Student's *t*-test was used for analysis of quantitative data, Chi-square (χ^2) test for analysis of qualitative data. $P < 0.05$ was considered significant.

RESULTS

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Ninety-four women enrolled in the study. Four patients excluded due to failure of spinal anesthesia. There

was no statistical significant difference between studied groups regarding; demographic data, operative time, and onset of pruritus Tables [1](#) and [2](#).

Regarding pruritus score in PACU, there was 2 women with no pruritus, 3 mild, 24 moderate, and 1 with severe pruritus in P group, while 7 women with no pruritus, 13 mild, 9 moderate, and one with severe pruritus in N group. In addition, 6 women with no pruritus, 14 mild, 8 moderate, and two with severe pruritus in O group [[Table 3](#)].

Although, there was no significant difference between the three studied groups regarding score 1 pruritus, while, score 2 pruritus (mild pruritus - no treatment requested) was significantly high in N and O groups compared to placebo group.

Pruritus score 1 (no pruritus) plus pruritus score 2 (mild pruritus - no treatment required) were significantly high in N and O groups compared to placebo group (20 cases, 20 cases, 5 cases; respectively, $P = 0.008$). In addition; score 3 pruritus (moderate - treatment requested) was significantly less in N and O groups compared to placebo group [[Table 3](#)].

Severe pruritus was similar with no significant difference between the three studied groups [[Table 3](#)].

The distribution of pruritus was mainly in the trunk, back, neck, and around the nose and eyes. Most of women with moderate pruritus in the three studied groups treated (when they asked for) successfully with IV 10–20 μg naloxone.

Nausea/vomiting, sedation, shivering, and pain scores at the PACU were similar in all studied groups. With no significant difference [[Table 4](#)].

DISCUSSION

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Neuraxial opioid analgesia is one of the significant breakthroughs in pain management, and spinal morphine is one of the most frequently used methods of analgesia after cesarean delivery and other surgical procedures.

This study demonstrated an incidence of pruritus of 90%, which was high and consistent with other studies.[[9,11,14,17](#)]

Pregnant women seem to be more susceptible to pruritus after neuraxial opioid administration than other populations.[[3,6,18](#)]

A recent systemic review revealed that the mean incidence of pruritus is 83% in postpartum patients and 69% in nonpregnant patients including males and females.[[19](#)] Possible explanations are increased cephalic spread of spinally administered drug[[17](#)] and interaction of estrogen with the opioid receptors has been suggested.[[20](#)]

Studied women kept for 4 h in the PACU, because pruritus onset usually occurs within a few hours of intrathecal morphine injection.[[21](#)]

The onset of pruritus in this study ranged from 30 to 180 min, which is also consistent with other previous studies.[[22](#)]

The mechanism of intrathecal opioid-induced pruritus not fully understood. It is probably not related to histamine release, because antihistamines are ineffective in the therapy of pruritus caused by spinal morphine.[[13](#)]

One hypothesis stated that pruritus is likely due to cephalad migration of neuraxial opioids to the medulla where the “itch center” is thought to be located and where they interact with the trigeminal nucleus.[[23,24](#)]

Another theory stated that the pain pathway and pruritus are transmitted by the same small unmyelinated sensory nerve fibers (C fibers).[[25](#)]

The most commonly cited theory that pruritus mediated by μ -opioid receptors, which are responsible for pain modulation and some side effects, especially pruritus and nausea or vomiting.

This would explain the antipruritic effect of nalbuphine or naloxone, because both of them are specific antagonists.[26]

Naloxone's reversibility of opioid-induced pruritus supports the existence of an opioid receptor mediated central mechanism.[27]

However, the use of naloxone for the treatment of pruritus is limited to low doses, because high doses of naloxone may reverse the analgesic effect of opioids. Specifically, the 5-HT₃ receptor has implicated and this stimulated interest in investigating the potential for the 5-HT₃ receptor antagonists to reduce the incidence of intrathecal morphine complication. One study investigated the use of ondansetron for the treatment of established pruritus and reported that it was more effective than placebo.[11]

Although, Chiravanich *et al.*, concluded in their randomized controlled trial that a preoperative gabapentin 600 mg did not significantly reduces the postoperative intrathecal morphine-induced pruritus.[28,29]

Bonnet *et al.*,[19] who published a quantitative systematic review of the efficacy of 5-HT₃ receptor antagonists for the prophylaxis of neuraxial opioids (morphine, fentanyl, and sufentanil) induced pruritus in patients undergoing a wide variety of surgical procedure and labor. They concluded that 5-HT₃ receptor antagonists were effective in reducing the incidence of pruritus, also recently Koju *et al.*, concluded that prophylactic administration of ondansetron to parturient receiving intrathecal morphine for postoperative analgesia provides a significant reduction of intrathecal morphine-induced pruritus and nausea and vomiting.[30]

Previous report conducted by George *et al.*, for the prophylaxis against neuraxial opioid-induced pruritus and they concluded that the incidence of pruritus was reduced with 5-HT₃ receptor antagonists.[31]

In addition, Borgeat and Stirnemann[10] reported that ondansetron was effective for the treatment of spinal or epidural morphine-induced pruritus in a randomized, double-blinded study of 100 patients.

Yeh *et al.*[3] and Charuluxananan *et al.*,[14] demonstrated that prophylactic ondansetron reduced the frequency of subarachnoid morphine-related pruritus in patients undergoing cesarean delivery. These conflicting results may attributed to the different doses of subarachnoid morphine administered, different scales and definitions used, as well as different periods for assessment.[32] Unlike nalbuphine, ondansetron is lipophilic and may excreted in breast milk, but there are no reports defining the concentration of this drug in breast milk. Therefore, ondansetron not currently recommended for routine use in breastfeeding mothers, which may limit its use in patients undergoing cesarean delivery until further data are available.[33] Use of nalbuphine would be associated with a somewhat larger cost of care, which balanced by increased patient satisfaction due to decrease incidence of pruritus.

Many studies also showed that κ -receptor agonists inhibit neuraxial opioid-induced pruritus.[34]

Nalbuphine is a mixed opioid κ -agonist and μ -antagonist. This would explain its antipruritic effect via action on the μ - and κ -receptors. In previous studies, IV nalbuphine (2–3 mg) was proven optimal in the treatment of intrathecal morphine-induced pruritus after cesarean section without increased pain scores or other side effects.[8,35]

On the other hand, doses of 4 mg of nalbuphine and 4 mg of ondansetron were chosen because these doses had proven successful in the treatment of intrathecal morphine-induced pruritus.[8,11,22]

Yeh *et al.*, revealed that 4 mg of nalbuphine and 4 mg of ondansetron were more successful in preventing intrathecal morphine-induced pruritus than placebo.[3] Nausea and vomiting are also common after neuraxial opioids. Nausea usually occurs within 4 h of injection and vomiting occurs soon thereafter.[36]

During their 4 h stay at the PACU, there was no significant difference among studied groups in the

incidence of nausea or vomiting. The sedation score and pain score were similar in the three studied groups.

Larger studies are required to investigate the use of the 5-HT₃ receptor antagonists for prevention of pruritus, intraoperative and postoperative nausea, and vomiting in the obstetric population.

CONCLUSION

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Nalbuphine and Ondansetron were found to be more effective than placebo for prevention of intrathecal morphine-induced pruritus in women undergoing cesarean delivery, in spite of Nalbuphine is preferred than Ondansetron because it is not excreted in the breast milk. However, neither drug was effective in all patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest

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Figures and Tables

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Table 1

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Demographic data of studied women

Table 2

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Operative time and onset of pruritus in studied groups

Table 3

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Pruritus score in postanesthesia care unit

Table 4

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Recorded side effects in studied groups

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