Nalbuphine vs. chlorpheniramine in reducing intrathecal opioid-induced pruritus in parturients undergoing lower-segment caesarean section

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ABSTRACT

Background: Pruritus is a common complication of intrathecal opioids and numerous medications have been used to prevent or treat this complication. However, the efficacy of these medications vary. The choice of medications also depends on the availability and the cost. We performed a randomised double-blind study to evaluate whether nalbuphine is as effective as chlorpheniramine, a medication that is commonly used for treating pruritus for the treatment of intrathecal opioid-induced pruritus in parturients undergoing lower-segment caesarean section. **Materials and Methods:** Two hundred and thirty four parturients with American Society of Anaesthesiologists (ASA) physical status I or II who had intrathecal opioid-induced pruritus were assigned to receive either intravenous nalbuphine (4 mg eight-hourly) or intravenous chlorpheniramine (5 mg eight-hourly) for a period of 24 hours. Pruritus was assessed using a qualitative scale at pre-treatment, six, nine, 12 and 24 hours post-treatment. **Results:** The occurrence of intrathecal opioid-induced pruritus was significantly reduced in parturients treated with intravenous nalbuphine as compared to intravenous chlorpheniramine at all intervals studied. **Conclusion:** In conclusion, nalbuphine is more effective than chlorpheniramine in reducing intrathecal opioid-induced pruritus for parturients undergoing lower-segment caesarean section.

Keywords: Anaesthesia, anti-histamine, intrathecal opioids, pregnancy, pruritus

INTRODUCTION

Intrathecal opioids have been used for a variety of surgical operations as they provide effective pain relief in the acute post-operative period. However, a broad side effect profile limits their use. This includes pruritus, sedation, hypotension, postoperative nausea and vomiting as well as delayed

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depression. The main deterrent is the delayed respiratory depression. [1-3]

Pruritus is one of the most common complaints with the use of intrathecal opioids. [3-5] Unfortunately, it has not received as much attention as delayed respiratory depression and is often neglected. Post-operatively, pain control may be excellently managed, but often patients have to endure pruritus that can range from mild to severe as treatment provided for pruritus is often inadequate. [6, 7] Aggressive treatment of post-operative pruritus could enhance patient satisfaction.

In our centre, we routinely use chlorpheniramine (intravenous [IV] or oral) as it is readily available, costs less and has fewer sedative effects. This is despite chlorpheniramine having been shown to have a variable degree of success in the treatment of intrathecal opioid induced pruritus (OIP). The initial assumption was that OIP was due to histamine release. [2, 5, 7] Other antihistamines also used in the management of intrathecal OIP are diphenhydramine and promethazine. [2, 5, 7] Nalbuphine is a semi-synthetic narcotic agonist-antagonist analgesic of the phenantherene series. It has been used to treat pruritus associated with neuroaxial opioids in surgical and obstetric patients but the results have been inconsistent. [8-10]

The objective of this study was to determine whether IV nalbuphine is more effective than IV chlorpheniramine in reducing intrathecal OIP for parturients undergoing lower -segment caesarean section (LSCS) in a predominantly Malay population.

MATERIALS AND METHODS

This was a prospective randomised, double–blind study with involvement of multiple operators. After obtaining institutional ethics committee approval and written informed consent, 234 parturients who developed pruritus postoperatively were recruited. Those included were American Society of Anaesthesiologists (ASA) I or II patients between the ages of 18–45 years undergoing LSCS under spinal anaesthesia. The exclusion criteria were patients with contraindications or known allergy to the study medications or drugs used in the study format, those with a body weight > 100 kg and patients with coexisting skin disorders or other pruritogenic systemic diseases (eg. eczema and psoriasis).

In the operating room, an 18G IV line was established and 0.9% normal saline infused. Standard monitoring was applied: electrocardiogram, non-invasive blood pressure, pulse oximeter and respiratory rate were continuously monitored. All patients were hydrated with 500 to 1000 mls of 0.9% normal saline before the administration of spinal anaesthesia. The block was performed under aseptic technique with the patient in a sitting position either at lumbar (L) interspace L3-4 or L4-5 using a 25 or 27 gauge Pencan spinal needle. A cocktail of 0.5 ml (25mcg) of fentanyl, 1.8-2.0 ml (9-10 mg) of 0.5% hyperbaric bupivacaine and 0.1 ml (0.2 mg) of morphine were mixed in the same syringe and injected once a free flow of clear cerebrospinal fluid had been demonstrated.

Patients were only recruited into the study when they showed positive signs and symptoms of pruritus; either in the operating theatre or while being monitored postopera–

tively in the recovery room. However, all patients received their first treatment dose while they were in the recovery room. The patients were randomised into two groups by computer generated randomised numbers. Group A received IV chlorpheniramine 5mg eight-hourly and Group B received IV nalbuphine 4mg eight-hourly. The presence of pruritus was recorded at pre-treatment and six, nine, 12 and 24 hours post-treatment with study medications. Pre-treatment was designated as 'Time 0' which was taken at the recovery room and before the study drug was given.

The severity of pruritus was graded using a qualitative scale and was given a score of: 0 (no pruritus after treatment), 1 (mild), 2 (moderate) and 3 (severe). Intractable pruritus was considered as failure of the study drug in treating OIP and for these patients, IV naloxone 0.1 mg boluses were given (titrated to effect) as a rescue treatment. These patients were recorded but were not continued as subjects in the study.

At the end of operations, all patients received suppository sodium diclofenac 100 mg. In the ward, they also received a combination of oral sodium diclofenac 50 mg eight-hourly and paracetamol 1 gm six-hourly for pain relief.

Statistical analysis

Statistical analysis was done using the Student's t test, Chi-square test and the Mann-Whitney test where appropriate. A *p*-value of <0.05 was considered statistically significant.

RESULTS

A total of 234 patients were recruited in this study. Out of this, 34 patients were excluded from the statistical analysis due to protocol violation (different combinations of drugs used intrathecally, different drug medications or dosages used for treatment of pruritus or pain relief and incomplete charting of pruritus). There were no differences between the patient groups (Table 1).

The occurrence of pruritus before and after receiving treatment is summarised in Table 2. The occurrence of pruritus during the pre-treatment period was not statistically different between the two groups. In the post-treatment period, pruritus occurred in fewer

Table 1: Comparisons of the demographics of patients and control group.

Demographic	Group A (n=100)	Group B (n=100)	P value
Age (years)			
18-25	23	24	0.926 for trend
26-23	60	61	
36-45	17	15	
Race			
Malay	69	65	0.740 for trend
Chinese	7	5	
Indian	10	14	
Others	14	16	
Height (cm)	155.7 ± 6.9	155.9 ± 6.9	0.834
Weight (kg)	71.8 ± 9.7	71.4 ± 11.1	0.786
Body Mass Index (BMI kg/m^2)	29.7 ± 3.7	29.3 ± 4.4	0.487

Table 2: Pruritus in patients before and after receiving treatment.

Pruritus	Group A (n=100)	Group B (n=100)	P value
Pre-treatment			
None	87	83	0.554 for trend
Mild	11	16	
Moderate	2	1	
Severe	2	0	
6 hours post-treatment			
None	28	47	0.001 for trend
Mild	69	46	
Moderate	1	7	
Severe	2	0	
9 hours post-treatment			
None	34	65	0.0001 for trend
Mild	61	32	
Moderate	5	3	
Severe	0	0	
12 hours post-treatment			
None	45	60	0.046 for trend
Mild	54	38	
Moderate	1	2	
Severe	0	0	
24 hours post-treatment			
None	66	90	0.001 for trend
Mild	34	10	
Moderate	0	0	
Severe	0	0	

patients in Group B at six, nine, 12 and 24 hours and these were statistically significant.

DISCUSSION

Pruritus is an unpleasant sensation that elicits the desire or reflex to scratch.[4, 6] It can be a localised or generalised sensation on the skin, mucous membranes or conjunctivae. [4] It can cause major distress, increase patient dissatisfaction, prolong hospital stay, increase overall treatment cost and use of personnel resources.

The mechanisms of pruritus are complex and not completely understood. Many theories and hypotheses have been proposed to explain the complex interactions. Understanding the different mechanisms involved will be helpful in the management of pruritus. The incidence of OIP varies as quoted by different authors. It ranges from 20 to 100% by Ganesh and 60 to 90% by Charuluxananan *et al*. [6, 9, 10] OIP appears to be a centrally mediated process via opioid receptors, and the medullary dorsal horns may be important sites of action in producing pruritus. [11, 12] The opioid induced pruritus is mainly confined to the face and trunk. This is partly explained by the high concentration of opioid receptors in the spinal nucleus of the trigeminal nerve innervating facial areas, particularly at the ophthalmic division. [6, 7] The severity depends on the dose, type of opioid agent and concentration used. [6, 7]

The incidence of pruritus after intrathecal fentanyl is between 67 and 100% and after intrathecal morphine between 62 and 82%. [8] Therefore, when administered together in neuraxial anaesthesia, the inci–

dence is higher. Patients at higher risk for developing OIP include obstetric patients, patients with chronic liver, renal or skin disease and use of systemic or regional opioids. It is uncertain if age and gender have any major impact. [6, 7] Pregnant women are more at risk due to the hormonal interactions as well as the presence of intrahepatic cholestasis which can occur during pregnancy. [4, 6]

The pathogenesis of OIP involve several mechanisms. Involvement of the μ opioid receptors is the dominant pathway for OIP. [4, 6] It is claimed that the primary cause for OIP is a central μ opioid receptor-mediated mechanism which takes place in the brain and spinal cord. The central mechanism may be related to rostral spread within the spinal cord and its action on the medullary dorsal horn and trigeminal nerve nucleus in the medulla as well as at the dorsal horn of the spinal cord. [11, 12] Other suggested mechanisms involve dopamine D_2 receptors, serotonin 5-HT_3 receptors, the prostaglandin system, gamma amino-butyric acid (GABA) receptors and glycine receptors. [6-8] Numerous medications have been used to prevent or treat OIP in the surgical setting. The efficacy of each medication with its own regime varies with different degree of success. Such medications include mixed opioid agonist-antagonists, serotonin 5 -HT3 receptor antagonists, propofol, non-steroidal anti-inflammatory drugs (NSAIDs), dopamine-2 (D2) receptor antagonists and antihistamines. [6-8]

The role of histamine in the pathogenesis of OIP is probably minimal. [6-9] Some have argued that histamine release does not take place following administration of neuraxial opioids. [8, 13, 14] Therefore, it is unlikely to be a major component of OIP. Despite this, chlorpheniramine is still widely used for the treatment of OIP because it is widely available and cheap. The only advantage of using antihistamine is through its sedative property. The sedative effects may allow the patient to rest or sleep which may also interrupt the itch-scratch cycle without actually relieving the pruritus. [3, 8]

Studies using μ opioid receptor antagonists have supported the primary mechanism of OIP. Drugs with mixed agonist-antagonist properties such as nalbuphine (μ-antagonist, κ- and δ-agonists) is promising. Activation of κ- and δ- opioid receptors does not cause pruritus. [13, 14]

Charuluxananan *et al*. compared the efficacy of IV nalbuphine 3 mg and IV propofol 20 mg for treating intrathecal morphine-induced pruritus after LSCS. [9] The treatment success rate was higher in the nalbuphine group than in the propofol group (83% vs. 61%; $p < 0.001$). Charuluxananan *et al*. also compared the prophylactic efficacy of IV nalbuphine 4 mg, ondansetron 4 mg, ondansetron 8 mg and normal saline (as placebo) for the prevention of intrathecal morphine induced pruritus after LSCS. [10] The success rate for nalbuphine, ondansetron and placebo groups were 20%, 13%, 12% and 6% respectively ($p<0.001$). They concluded that both nalbuphine and ondansetron were more effective than placebo for the prevention of intrathecal morphine-induced pruritus after LSCS.

In our study, we showed that nalbuphine was more effective compared to chlorpheniramine. Nalbuphine was more successful

in reducing intrathecal OIP and this was evident up to 24 hours of treatment. This study's finding concurs with the studies reported by Charuluxananan *et al*. [9-10] There–fore, the use of chlorpheniramine in treating intrathecal OIP should be re-evaluated. Despite this, it may still be difficult to change the current practice of using chlorpheniramine in OIP treatment because of the limited availability and cost of nalbuphine. Emergence of evidence showing potential of more readily available agents such as serotonin antagonists (5HT3-antagonists) and gabapentin may impact on decision-making in terms of which agents to use in the future. [15-17]

In our study, we only compared nalbuphine and chlorpheniramine. Inclusion of a placebo arm would have been interesting. However, it would not have been considered ethical not to provide treatment. Despite knowing that chlorpheniramine is inferior for the treatment of OIP, it is still currently drug of choice in our local setting in mild to moderate OIP. Use of diclofenac may have confounded our result. Although, diclofenac can cause pruritus, it has also been reported that NSAIDs may be effective in reducing OIP. [19] However, in our case, all the patients were given diclofenac and this would have reduced any confounding effects.

In conclusion, nalbuphine is IV more effective than IV chlorpheniramine in reducing intrathecal OIP for parturients undergoing LSCS.

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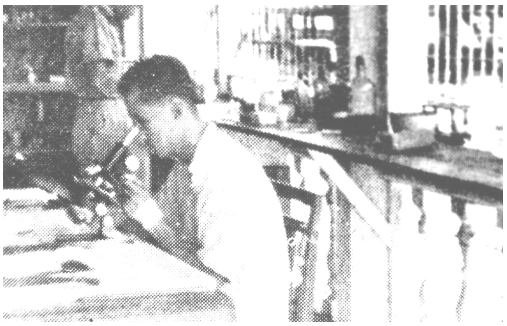
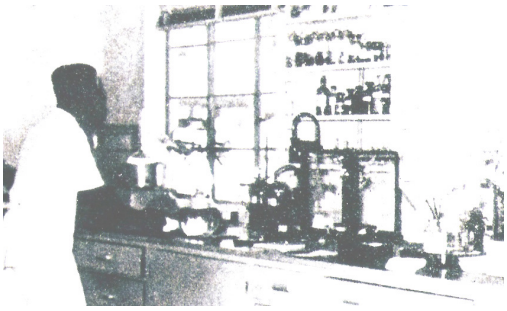


A laboratory technician examining a specimen under the microscope in the laboratory of the temporary hospital (*Healthcare in Brunei Darusalam: Temporary hospitals after the Second World War. Brunei Int Med J. 2012: 8 (3):115*) after the Second World War.



Another part of the laboratory of the temporary hospital after the Second World War.