ORIGINAL ARTICLE

Optimal Dose of Granisetron in Reducing the Incidence and Severity of Pruritus Post Intrathecal Morphine for Caesarean Delivery

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ABSTRACT

INTRODUCTION: Pruritus is one of the common side effects observed after intrathecal morphine (ITM), especially among parturient. Granisetron, a 5-HT_3 antagonist, has been shown to reduce this side effect. This study compared the incidence and severity of pruritus using two different doses of granisetron in parturient undergoing Caesarean delivery with ITM. **MATERIAL AND METHODS**: In this equivalence randomised controlled trial, 120 parturient with a singleton uncomplicated pregnancy undergoing Caesarean delivery who received spinal anaesthesia with ITM 0.1 mg were recruited. After delivery, the parturient were randomised to receive either intravenous granisetron 1 mg (Group 1) or 3 mg (Group 2). The incidence and severity of pruritus were assessed within 24 hours at different intervals and were graded. **RESULTS**: At baseline, patients' demographic and clinical characteristics were comparable between the two groups. The incidence for pruritus in Group 1 and 2 was 63.3% and 65.0%, respectively (P= 0.849). The difference in the severity of pruritus at different intervals and the need for rescue treatment and patient satisfaction between the two groups were not statistically significant. **CONCLUSION**: IV granisetron 1 mg is as effective as 3 mg when given as prophylaxis in reducing the incidence and severity of ITM-induced pruritus among parturient undergoing Caesarean delivery.

INTRODUCTION

Intrathecal morphine (ITM) is one of the most effective and commonly used opioids for Caesarean delivery, with few reported unwanted side effects such as pruritus.[1-3] Nonetheless, the incidence of ITM-induced pruritus among parturient is high, ranging from 60% to 100% and is believed to be related to the interaction between the oestrogen and opioid receptors.[1,4] The average onset time of the pruritus is around 90 to 180 minutes which peaks at 4 hours and rapidly declines after 12 hours of ITM administration.[5-8]

In clinical practice, the prevention and treatment of ITM-induced pruritus remains a problem due to its uncertain and complex mechanisms. To date, the exact mechanism of ITM-induced pruritus is still unclear. One of the postulated mechanisms includes modulating the 5-hydroxytryptamine subtype 3 (5-HT_3) or serotonergic pathway. The superficial layers of the dorsal horn and the nucleus of the spinal tract of the trigeminal nerve in the medulla are rich with 5-HT_3 and μ receptors. The spinal trigeminal nucleus acts as an integrative centre for sensory input from the face and this area is known as the "itch centre". The cephalic spread of ITM and activation of 5-HT_3 receptors may contribute to ITM-induced pruritus.[1,9] There is a strong link between pain and pruritus as both are transmitted by the same sensory neurones, C-fibers.[1,2,9] Activation of μ receptors by ITM is accountable for its analgesic effect as well as its unwanted side effects, including pruritus.[10,11]

Several pharmacological therapies have been tried and shown efficacy in reducing the incidence and severity of ITM-induced pruritus. Prophylactic administration of 5-HT_3 receptor antagonists with intravenous (IV) ondansetron and granisetron have significantly reduced the incidence of ITM-induced pruritus, its severity and the need for rescue treatment. [5,6,8,12-16] Given that granisetron has a longer duration of action of up to 24 hours, granisetron 3 mg has been shown to be superior to IV ondansetron 8 mg for reducing severity of pruritus after ITM.[14] However, a lower dose of granisetron 1 mg also showed its antipruritic effect when fentanyl 25 μg was given intrathecally.[16] This study compared the incidence and severity, the need for rescue treatment and patient satisfaction in ITM-induced pruritus using two different doses of IV granisetron 1mg and 3 mg among parturient undergoing Caesarean delivery.

MATERIALS AND METHODS

This trial was approved by the Research Committee of the Department of Anaesthesiology and Intensive Care, Universiti Kebangsaan Malaysia Medical Centre (UKMMC) and the institution's Medical Research and Ethics Committee with the approval code of FF-2019-121. The inclusion criteria for this study were adult parturient aged between 18-45 years old with singleton, term and uncomplicated pregnancies who were scheduled for elective Caesarean delivery under spinal anaesthesia. Patients with American Society of Anesthesiologists (ASA) class III or above, prolonged QT interval, asthma, known allergy to granisetron, pre-existing pruritogenic systemic disease, pregnancy-induced pruritus, and a coexisting skin disorder were excluded from this study. Written informed consents were obtained from consented patients who fulfilled the study criteria.

Patients were randomly assigned into two groups using computer-generated randomisation numbers of 1 to 120 with an equal allocation of 60 in each group. Group 1 received IV granisetron 1 mg while Group 2 received IV granisetron 3 mg. All drugs were diluted to 5 ml with normal saline and numbered according to the allocation number generated, which appeared identical as clear solution in 5 ml syringes. The allocation number and drugs were prepared by the researcher alone (who was not blinded) and were handed to the anaesthetist-in-charge of the patient in the operating theatre. The anaesthetists who administered the medication and who collected the data postoperatively were blinded. The study drug used was IV granisetron 3 mg ampoule (Kytril® 3mg/3ml Roche).

All patients were given prophylaxis for gastric acid aspiration preoperatively. Adequate IV access and standard monitoring were established before anaesthesia. Each patient was started on 500 ml of Hartmann's solution prior to administration of spinal anaesthesia, performed under aseptic technique at the level of L3/L4 or L4/L5 interspace with a 27G Pencan® needle. Hyperbaric bupivacaine 0.5% ranging between 1.5 to 2.1 ml (taking into consideration the patients' height) with preservative-free fentanyl 15 mcg and morphine 0.1 mg mixed in the same syringe was administered into the intrathecal space. Once the sensory block of up to T4 level was achieved, the surgery was allowed to commence. Rescue doses of phenylephrine or ephedrine was given to maintain the systolic blood pressure of more than 90 mmHg and heart rate of more than 50 beats per minute when necessary.

Once the baby was delivered and the umbilical cord clamped, the study drug was administered intravenously after a slow bolus of IV oxytocin five units. At the end of the surgery, all patients were given suppository diclofenac 1 mg/kg with oral celecoxib 200 mg twice daily in the ward.

Patients were evaluated for pruritus at 0, 0.5, 1, 4, 8 ,12 and 24 hours, where 0 hour was immediately after the spinal anaesthesia was administered. The severity of pruritus was adopted from the pruritus grading system by Firas et al.[17] (Appendix 1). Patients with moderate to severe pruritus were treated with IV chlorpheniramine 10 mg and IV metoclopramide 10 mg, respectively. After 24 hours, the patients were asked to rate their satisfaction towards pruritus management on a three-point scale as satisfied, neutral or not satisfied.

Sample size estimation was calculated using two population proportions for the equivalence formula.[18]

Prior data by Charuluxananan et al indicated that the proportion of no pruritus score in the ondansetron 4 mg group was 0.13 and ondansetron 8 mg group was 0.12.[6] With the margin of equivalence is 0.20, a minimum sample size of 52 participants per group was able to reject the null hypothesis with probability (power) 0.8. The type I error probability associated with this null hypothesis test was 0.05. With an additional 15% dropout rate, the sample size was 60 participants per group.

Data were analysed using IBM SPSS Statistics version 22. For continuous data which were normally distributed, the independent Student's t-test was used for analysis and presented as mean±SD. For categorical data, the occurrence of pruritus was initially categorised into yes or no, which was further sub-grouped into none, mild, moderate and severe and were analysed using Fisher's exact test or Pearson's chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 120 patients were recruited in this study. There was no withdrawals or dropouts. Patients' demographics and clinical characteristics were comparable between the two groups, as shown in Table 1.

Table I: Demographic and clinical characteristics

	Group 1 (n= 60)	Group 2 (n=60)	*P* value
Age (years)	33.9 ± 4.23	33.9 ± 4.28	0.949[a]
Weight (kg)	72.1 ± 11.15	73.7 ± 11.27	0.442 [a]
Height (cm)	155.7 ± 6.64	156.1 ± 5.89	0.706 [a]
BMI (kg/m^2)	29.6 ± 3.89	30.3 ± 4.59	0.401[a]
Gestation age (weeks)	38.0 ± 0.78	38.0 ± 0.91	0.914[a]
Gravida			
1	10 (16.7)	13 (21.7)	0.596[b]
2	7 (11.7)	14 (23.3)	
3	20 (33.3)	17 (28.3)	
4	13 (21.7)	10 (16.7)	
5	4 (6.7)	2 (3.3)	
>5	6 (10)	4 (6.7)	

BMI: Body Mass Index.
[a] Independent Student's t-test
[b] Fisher's exact test

The incidence of pruritus was comparable in both Groups 1 and 2 with 63.3% and 65.0%, respectively (p=0.849). The proportion difference of pruritus between the two groups was 1.7% (margin of equivalence 2.3%).

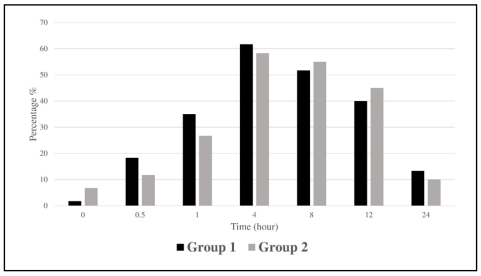

Figure 1: Incidence of pruritus over 24hrs

Over the first 24hrs of observation, the incidence of pruritus was found to peak at 4 hours post ITM in patients from both groups, as shown in Figure 1.

The severity of pruritus score throughout the 24-hr period between groups was not significant. The majority of our patients from both groups, experienced mild pruritus. None, however, complained of severe pruritus, as shown in Table II.

Table II: Pruritus score at different time intervals within first 24 hours

	Group 1 (n= 60)	Group 2 (n=60)	*P* value
T0			
None	59 (98.3)	56 (93.3)	0.364[a]
Mild	1 (1.7)	4 (6.7)	
Moderate	0 (0)	0 (0)	
Severe	0 (0)	0 (0)	
T0.5			
None	49 (81.7)	53 (88.3)	0.306[b]
Mild	11 (18.3)	7 (11.7)	
Moderate	0 (0)	0 (0)	
Severe	0 (0)	0 (0)	
T1			
None	39 (65)	44 (73.3)	0.429[a]
Mild	20 (33.3)	16 (26.7)	
Moderate	1 (1.7)	0 (0)	
Severe	0 (0)	0 (0)	
T4			
None	23 (38.3)	25 (41.7)	0.266[a]
Mild	30 (50)	33 (55)	
Moderate	7 (11.7)	2 (3.3)	
Severe	0 (0)	0 (0)	
T8			
None	29 (48.3)	27 (45)	0.722[a]
Mild	29 (48.3)	29 (48.3)	
Moderate	2 (3.3)	4 (6.7)	
Severe	0 (0)	0 (0)	
T12			
None	36 (60)	33 (55)	0.780[a]
Mild	23 (38.3)	25 (41.7)	
Moderate	1 (1.7)	2 (3.3)	
Severe	0 (0)	0 (0)	
T24			
None	52 (86.7)	54 (90)	0.570[b]
Mild	8 (13.3)	6 (10)	
Moderate	0 (0)	0 (0)	
Severe	0 (0)	0 (0)	

T0: time immediately after the spinal anaesthesia with intrathecal morphine was administered
T0.5, T1, T4, T8, T12 and T24 hours denotes time interval at 30 mins, 1hr, 4hrs, 8hrs,12hrs and 24hours after administration of ITM.
Data expressed in frequency (percentage).
[a]: Fisher's exact test
[b]: Pearson's chi-square test

A small number of patients who experienced moderate pruritus requiring treatment were similar in both groups, with six patients from Group 1 and three patients from Group 2 (p=0.491). In addition, patients' satisfaction towards overall treatment was high for both groups, 95.0% for Group 1 and 98.3% for Group 2 (p=0.619) (Table III).

Table III: Rescue treatment for pruritus and patient satisfaction

	Group 1 (n=60)	Group 2 (n=60)	*P* value
Rescue treatment for pruritus			
Yes	6 (10)	3 (5)	0.491[a]
Satisfaction			
Satisfied	57 (95)	59 (98.3)	0.619[a]
Neutral	3 (5)	1 (1.7)	
Not Satisfied	0 (0)	0 (0)	

Data are expressed in frequency (percentage).

[a]: Fisher's exact test

DISCUSSION

The overall incidence of pruritus in our study for both Group 1 and Group 2 was much lower with 63.3% and 65.0% respectively, compared to other series, which was reported to be between 80% to 95%. This may be attributed to the lower dose of ITM used in our study, which was 0.1 mg, compared to higher doses used in previous studies of 0.15 mg and 0.2 mg as it is known that the pruritic side effects from ITM is dose-dependent and that granisetron has a longer duration of action compared to ondansetron.[6,8,14] However, Koju et al. reported the lowest incidence of pruritus involving only 16% of his patients who received IV ondansetron 4 mg despite having received 0.2 mg ITM.[15] This could be due to the timing of the ondansetron, which was administered 30 minutes before ITM in his cohort of patients. Despite early administration of 5-HT_3 receptor antagonists prior to ITM, the side effects of pruritus could not be abolished completely. This is not surprising as the exact mechanism of pruritus remain unclear.[1,9] Majority of the studies chose to administer 5-HT_3 receptor antagonists immediately after the baby was delivered, presumably to avoid unwanted side effects of the drug on the newborn as it crosses the placenta.[5-8,14]

Majority of our patients in both groups experienced the highest incidence of pruritus (61.7% and 58.3% respectively) as well as severity of pruritus at four hours post ITM which subsequently subsided over time (Figure 1) which was consistent to the findings of Siddik-Sayyid et al.[7] Morphine, when given intrathecally, activates the opioid receptors located at the supraspinal and spinal cord level in the central nervous system (CNS). Due to its hydrophilic nature, morphine has a slower onset and maintains its concentration in the cerebrospinal fluid for a longer duration which prolongs its analgesic effect as well as unwanted side effects. The concentration of morphine decreases along with pruritus, being one of its side effects, over time.[10] This may explain why the occurrence of pruritus in our cohort of patients peaked at four hours after administration and exerted a prolonged effect in a small percentage of patients even after 24 hours which was similar to the findings by Siddik-Sayyid et al ad Tan et al.[7,14]

When comparing the proportion of patients who required rescue treatment for pruritus in those who received granisetron 3 mg in our study with the findings of Tan et al., the requirement for such treatment was much lower in our patients (5% vs 20% respectively).[14] This may be attributed to the lower doses of ITM used in our study. IV chlorpheniramine 10 mg was used as our rescue treatment despite the fact that ITM-induced pruritus was not related to histamine release. The benefits of administering chlorpheniramine not only provides sedation to the patients but also aids in interrupting the itch-scratch cycle.[10] Other available drugs such as naloxone and propofol have also been proven to be effective in treating pruritus; however, these are not suitable to be used in the wards as it requires monitoring and administration by trained personnel.[9,10]

The use of non-steroidal anti-inflammatory drugs (NSAIDs) as a supplement of analgesia post-Caesarean delivery is common in practice. All our patients received suppository diclofenac at the end of the surgery and oral celecoxib postoperatively. NSAIDs is believed to have some antipruritic effect as they inhibit cyclooxygenases and reduce the formation of prostaglandins. The release of prostaglandins potentiates pruritus, and this further enhances the transmission of C-fibers to the central nervous system, which may be accountable for lower incidence and severity of pruritus in our study.[1,9]

The main limitation of this study is that the sample size was small, and data of patients were from a single centre. In addition, while timing and administration of the study drug was standardised in all patients, the assessment of pruritus in the postoperative period over 24 hr may be quite subjective and was performed by multiple medical personnel at various time intervals. Future studies involving multiple centres with a larger cohort of patients may be required to confirm our findings further and also to include the benefits of granisetron as an anti-emetic agent.

CONCLUSION

IV granisetron 1mg is as effective as 3 mg when given as prophylaxis in reducing the incidence, severity and the need for rescue treatment in ITM-induced pruritus among parturient undergoing Caesarean deliveries.

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APPENDIX 1

Modified Pruritus Grading System score (based on Firas et al, 2012)

Criteria		Score
Distribution	Solitary site	1
	Multiple sites	2
	Generalised	3
Frequency	Episodic	1
	Frequent	3
	Continuous	5
Severity	Rubbing	1
	Scratching	1
	Localised excoriations	3
	Generalised excoriations	5
Sleep disturbance	Rare	0
	Occasional	2
	Frequent	4
	Totally restless	6

The grading is calculated as the sum of the individual scores as:
None: 0 score
Mild grade: if total score is between 1 and 5
Moderate grade: if total score is between 6 and 11
Severe grade: if total score is between 12 and 19

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