INTRAVENOUS ONDANSETRON VERSUS INTRAVENOUS NALBUPHINE IN REDUCING INTRATHECAL FENTANYL INDUCED PRURITUS DURING CESAREAN DELIVERY : A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: This prospective, randomized, double-blinded study wasundertaken to compare the effectiveness and side effects of intravenous Ondansetron and Nalbuphine in the reduction of intrathecal Fentanyl-induced pruritus in obstetric patients of Chittagong Medical College Hospital. **Materials and methods :** This study was done in CMCH during the period August 2012 to January 2014. One hundred and thirty women of ASA status I or II undergone caesarean section by spinal anesthesia using Inj. Bupivacaine 10 mg and Inj. Fentanyl 15 µgm was randomly allocated in two groups, by simple random method. The patients received Nalbuphine 4mg or Ondansetron 8mg as intravenous injection in respective of groups, immediately after the baby was delivered and umbilical cord was clamped. Onset of pruritus, the degree of pruritus, four-point rating score for nausea and vomiting were assessed and recorded as per case record form and preserved for analysis. All statistical analysis was performed using SPSS® software package version SPSS-16 (SPSS, Chicago, Illinois, USA) for windows XP. p-value was considered statistically significant when it was less than 0.05($p \leq 0.05$). **Results :** Intravenous Ondansetron was more effective in reducing the incidence of fentanyl-induced pruritus than Nalbuphine. Pruritus was mild and relatively short duration in most patients. Patients remained hemodynamically stable after using both Ondansetron and Nalbuphine. **Conclusion:** Ondansetron is more effective and cheaper than Nalbuphine in reducing the intrathecal Fentanyl induced pruritus during cesarean delivery and safely used as an alternative to expensive drug Inj. Naloxone.

Key words
Pruritus; Itching; Opioids; Labor; Cesarean; Ondansetron.

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Introduction

The use of neuraxial opioids getting popularity over the last few years. Addition of intrathecal Fentanyl with local anesthetic solution to enhance the quality of subarachnoid block is widely practiced. But their use is associated with a frequent incidence of troublesome side effects such as pruritus, nausea, and vomiting[1-3]. Although pruritus is not life-threatening, it can be a source of discomfort for many patients. The incidence of pruritus has been reported 60% to 100 %in obstetric population[4]. The reason for the higher incidence may be due to an interaction between estrogen and opioid receptors[4-6].

Mechanism of pruritus after the neuraxial administrationof opioids is not fully understood. Opioid receptors arelocated both supraspinally and at the spinal cord level.Spinal opioids activate the opioid receptors in thesubstantia gelatinosa of the spinal cords dorsal horn[6]. These receptors may be involved in pruritus, nausea or vomiting. This would explain the antipruritic effect of Nalbuphine or Naloxone, because both of them are antagoniststo opioid receptor[7]. Although the exact mechanisms of opioid induced pruritus are not fully understood, a possible mechanism was described by Waxler et al who stated that, itching could be a result of neuraxial opioids acting on central serotonin receptors[7]. Opioids and the serotoninergic system interact closely in the CNS.

Ondansetron, a specific 5-hydroxytryptamine-3($5HT_3$) receptor antagonist, has an antipruritic effect[8-10].The role of Ondansetron in nociception has also been reported[11]. In severe pruritus, Naloxone is very effective, but sometimes the analgesic effect is antagonized[12-14]. Nalbuphine, Propofol, and Ondansetron have been used effectively for treating pruritus associated with neuraxial opioids in surgical patients[15-16]. Charuluxananan et alobserved that Nalbuphine is more effective than Propofol for the treatment of intrathecalmorphine-induced pruritus in obstetric patients[17]. Yeh et al reported that prophylactic intravenous Ondansetron greatly reduced the incidence of intrathecalmorphine-induced pruritus in patients undergoing cesarean delivery[18].

Naloxone can control pruritus effectively, but it is costly & not readily available in our clinical setting. On the other hand, Nalbuphine and Ondansetron are comparatively cheaper than Naloxone and easily available in our clinical setting. So, as a cost effective and easily available drug Inj. Nalbuphine or Inj. Ondansetron can be used for prevention of intrathecal Fentanyl-induced pruritus in patients undergoing cesarean delivery.

Therefore, we have undertaken a prospective, randomized, double-blinded study to compare the effectiveness and side effects of intravenous Ondansetron and Nalbuphine in the reduction of intrathecal Fentanyl-induced pruritus in obstetric patients of Chittagong Medical College Hospital.

According to Charuluxananan S et al, 4 mg of Nalbuphine and 8 mg of Ondansetron are effective in the treatment of intrathecal morphine-induced pruritus[5,8,19,9]. Gulhas et al also used 8 mg dose of Ondansetron in this context[20]. So in our study we used Inj. Nalbuphine 4 mg and Inj. Ondansetron 8 mg to compare the effectiveness of pruritus control.

After the approval of study protocol by the institutional ethical committee and written, informed consent was obtained from each patient. This prospective, double-blinded randomized controlled trial was performed at the Obstetric O.T. of Chittagong Medical College Hospital, a 1330 bed hospital.

Materials and methods

Term pregnant women who undergoing cesarean delivery under spinal anaesthesia in obstetrics units of Chittagong Medical College Hospital with ASA (American Society of Anesthesiologists) physical status I and II and age between 18-40 yrs. were included in the study. Known hypersensitivity to Inj. Bupivacaine/ Fentanyl/ Nalbuphine or Ondansetron and history of systemic disease with pruritus (Example: Obstructive jaundice etc.) and patient with pruritus during pregnancy were excluded from the study. Simple random sampling by envelope type lottery method done. A total of 130 patients who gave written consent and who met the mentioned enrollment criteria were consecutively included in the study. The co-worker divided the pts randomly by lottery method in 2 groups and equal 2 types of 130 cards were prepared named A & B. Each patient was asked to pick a card blindly and included in the group written in the card and co-worker noted it down in a record book.

Group-A will receive Inj. Nalbuphine (4 mg/10ml) and Group-B will receive Inj. Ondansetron (8 mg/10ml). The demographic variables were age, weight and gravidity. The pre-operative variables were mean blood pressure, Heart rate and SpO_2. The per-operative variables were Mean Blood Pressure (MBP) Heart rate, SpO_2, Pruritus score, Nausea & vomiting score. The patients received Nalbuphine 4mg or Ondansetron 8mg as intravenous injection in respective of group immediately after the baby was delivered and umbilical cord was clamped. All the test drugs were from same batch. Drugs were prepared by a co-worker who was not involved in the study. At the per-operative and post-operative period, vital signs were recorded by the researcher himself. Onset of pruritus, the degree of pruritus, four-point rating score for nausea and vomiting were assessed and recorded as per case record form and preserved for analysis.

All statistical analysis was performed using SPSS® (Statistical Package for Social Sciences) software package version SPSS-16 (SPSS, Chicago, Illinois, USA) for windows XP. p-Value was considered statistically significant when it was less than 0.05($p \leq 0.05$).

Results

Table I : Preoperative & per-operative hemodynamic comparison of two groups

	Drug type	N	Mean	Std. Deviation	Std. Error Mean
Pulse pre	Group A	65	89.2154	7.53843	.93503
	Group B	65	90.3385	7.76063	.96259
Pulse per	Group A	65	90.9803	12.19305	1.51236
	Group B	65	93.0518	4.93456	.61206
MBP pre	Group A	65	94.2923	12.29421	1.52491
	Group B	65	95.5385	12.73538	1.57963
MBP per	Group A	65	91.4968	14.02627	1.73974
	Group B	65	97.8325	6.20188	.76925
SpO2 pre	Group A	65	97.7538	.93593	.11609
	Group B	65	97.7077	.94742	.11751
SpO2 per	Group A	65	97.7174	.78393	.09723
	Group B	65	97.6882	.67990	.08433

Group A= Inj. Nalbuphine, Group B= Inj. Ondansetron

Table II: Pruritus score comparison between two groups

Group	Pruritus Score (0-10)				Total
	0	1	2	3	
A	39	2	20	4	65
B	48	2	13	2	65
Count	87	4	33	6	130

Group A= Inj. Nalbuphine, Group B= Inj. Ondansetron.

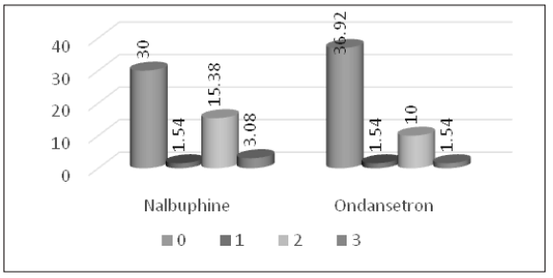

Fig 1 : Comparison between Nalbuphine & Ondansection

Table III : Difference in onset of pruritus between two groups

Onset of pruritus	N	Mean	Std. Deviation	Std. Error
Group-A	65	11.6769	22.97356	2.84952
Group-B	65	10.6154	21.33270	2.64600
Total	130	11.1462	22.08866	1.93730

Group-A=Inj. Nalbuphine; Group – B= Inj. Ondansetron, Time expressed in minute.

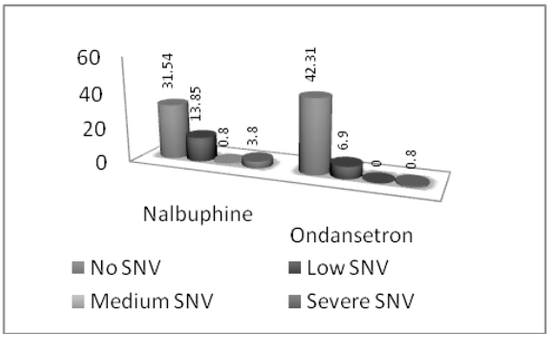

Fig 2 : Severity of Nausea and Vomiting (SNV) of the patients in two groups

Table IV : Pre-operative & per-operative hemodynamic comparison of two groups

Variables	Drug type	N	Mean	Std. deviation	Std. Error Mean
Pulse Pre	A	65	89.2154	7.53843	.93503
	B	65	90.3385	7.76063	.96259
Pulse Per	A	65	90.9803	12.19305	1.51236
	B	65	93.0518	4.93456	.61206
MBP Pre	A	65	94.2923	12.29421	1.52491
	B	65	95.5385	12.73538	1.57963
MBP Per	A	65	91.4968	14.02627	1.73974
	B	65	97.8325	6.20188	.76925
SpO_2 Pre	A	65	97.7077	.94742	.11751
	B	65	97.7538	.93593	.11609
SpO_2 per	A	65	97.6882	.67990	.08433
	B	65	97.7174	.78393	.09723

Group A= Inj. Nalbuphine, Group B= Inj. Ondansetron

Table V : ANOVA test of Significance of pre-operative variables

Variable	Test used	Calculated Value	DF	Sig. Value	Comments
Pulse	T-test	0.837	128	0.404	Test is not significant
MBP	T-test	0.568	128	0.571	Test is not significant
SpO_2	T-test	0.279	128	0.780	Test is not significant

$p<0.05$ (Calculated by t- test)

Table VI : ANOVA test of Significance of per-operative variables

Variable (Case per)	Test used	Calculated Value	DF	Sig. Value	Comments
Pulse	T-test	1.270	128	0.206	Test is not significant
MBP	T-test	3.33	128	0.101	Test is not significant
SpO_2	T-test	0.227	128	0.821	Test is not significant

$p< 0.05$ (Calculated by t- test)

One hundred and thirty women of ASA status I or II undergoing caesarean section by spinal anesthesia using Inj. Bupivacaine (10 mg) and Inj. Fentanyl (15 µgm) was randomly allocated in two groups, by simple random method. No patients were withdrawn from the study. The prescribed variables and hemodynamic parameters were recorded in the case record form. The findings of data analysis are documented below.

Demographic Data Table of Two Groups

In our study, mean age of patients in group-B was 25.98 yrs. and group-A 26.23 yrs. Mean weight was 60.90 kg in group-B and 61.61 kg in Group-A. Mean gravidity of the patients was almost similar. All these parameters were statistically insignificant between the two groups. So, demographic data of two groups were comparable.

Independent Sample T-test for Nalbuphine & Ondansetron.

The variables Pulse, MBP & SpO_2 have no effect on Drug group.

Table II showing that the Group-B is highly related with no pruritus (Approx. 74%) or antipruritic affect in the cesarean delivery than the Group-A (Approx. 60% no pruritus).

Fig 1 shows that the Group-B (Inj. Ondansetron) is highly related with no pruritus (Approx. 74%) or antipruritic affect in the cesarean delivery than the(Inj. Nalbuphine) Group-A (Approx. 60% no pruritus) within group. Moreover the overall 67% (30% Nalbuphine &37% Ondansetron) have no pruritus effect on the cesarean delivery for both drugs.

Fig 2 shows that the Group-B is highly related with no SNV (Approx. 85%) effect in the cesarean delivery than the Group-A (Approx. 63% no SNV). Moreover the bar diagrams showing, the overall 74% (32% Group-A & 42% Group-B) had no SNV effect during cesarean delivery.

Independent Sample T-test of Group-A & Group-B for Pulse, MBP & SpO_2.

The variables Pulse, MBP & SpO_2 have no effect on Drug group.

Table IV showing the group statistics. Mean Pulse, Mean Blood Pressure and Mean SpO_2 are higher in Group-B (Drug Ondansetron) than Group-A (Drug Nalbuphine).

Discussion

Opioids are effective drugs for relieving acute and chronic pain. Using them in Sub-Arachnoid Block (SAB) increase duration and strength of analgesia[21]. Pruritus is the one of the most common side effect associated with spinal or epidural opioid. Exact mechanism of Fentanyl induced pruritus is not clearly known. It is possible that other mechanisms, independent of serotonin and µ receptors might be involved in the pathogenesis of Fentanyl induced pruritus. Pregnant women has the highest sensitivity to intrathecal opioid which could be due to reaction between estrogens and opioid receptors[4,22]. The present study was a prospective double blind randomized clinical trial, carried out with the objectives to compare the efficacy between Nalbuphine and Ondansetron, given intravenously for the prevention of intrathecal Fentanyl-induced pruritus during cesarean delivery and observed their complications. In our study, mean age of patients in group-B was 25.98 yrs. and group-A 26.23 yrs. Mean weight was 60.90 kg in group-B and 61.61 kg in Group-A. Mean gravidity of the patient was almost similar. All these parameters were statistically insignificant between the two groups. So, demographic data of two groups were comparable. The incidence of pruritus after intrathecal Fentanyl was reported 60-100% in pregnant women[4,23]. The pruritus score was graded (0-10) beyond score 3 was moderate to severe pruritus. In our study none of the patient in any group had moderate to severe pruritus. The difference in Pruritus score between the two groups

was statistically significant. In our study, Group-B (Ondansetron), 73.8 % (Within the group) of patients had no pruritus. The incidence of pruritus increases with higher dose of Fentanyl[24]. As studies used 25µgm Fentanyl intrathecally in non-pregnant women that might be the reason for the slight higher incidence of pruritus than our study. They classified the degree of pruritus as 0-No pruritus, 1- mild pruritus, 2- moderate pruritus, and 3- severe pruritus. Pruritus score was ≤1 in most patients of that studies and similarly in our study it varied from 1-3 (Mild pruritus) in both groups. In Manal Abdalla M Zaglol study, comparison was made between intravenous Ondansetron and Nalbuphine for reduction of subarachnoid Fentanyl induced pruritus in patients undergoing elective cesarean delivery[25]. In our study, the incidence of pruritus in Group-A (Nalbuphine) was 40% and in Group-B (Ondansetron) was 26.2%.However the incidence of pruritus in Group-A coincided with above study, but the result of Group-B (Ondansetron) was much lower in our study. Pruritus effect probably depended on intrathecal opioid dose[25]. In our study, all the patients received same dose of Fentanyl (15 µgm) and Ondansetron was found to be more efficacious in reducing pruritus than Manal Abdalla M Zaglol study[26]. The difference might be due to lower dose of intrathecal Fentanyl used in our study. We only compared efficacy between Nalbuphine and Ondansetron. Inclusion of a placebo arm would have been interesting. Ondansetron was more effective as antipruritic agent than Nalbuphine (p-value < 0.05). It was also compatible with Charuluxananan et al results which revealed that Nalbuphine (4mg) and Ondansetron (4mg and 8mg) were more effective than placebo for the prevention of intrathecal morphine (0.2mg) induced pruritus after cesarean delivery[19]. The degree of pruritus, whether treatment was requested or not, were graded like Manal Abdalla M Zaglol study[26]. Their success rate for Nalbuphine was 20% and in our study, it was 60% within the group. The difference in success rate of Nalbuphine might be due to use of different opioid intrathecally. None of the patients had severe pruritus and this result was agreed with our study. Mean onset of pruritus in Group-B was 10.61 min and in Group-A it was 11.67 min which showed insignificant difference between the two groups (p-value > 0.05). So the difference in mean onset of pruritus might be due to chance and it was similar to previous studies done by Charuluxananan et al, Borgeat A, Stirnemann H. and Shah MK, et al[19,8,27]. Nausea and vomiting are also common after neuraxial opioids. Ondansetron also significantly decreased the incidence of nausea and vomiting more than Nalbuphine in our study. Other studies reported various results of Ondansetron effects on SNV. Similarly, some authors reported reduction of SNV with prophylactic IV Ondansetron after cesarean delivery[25]. In studies by Siddik-Sayyid et al and Bonnet M. et al observed the significant reduction of SNV in patients with IV Ondansetron receiving intrathecal opioid[28,5]. These results were agreed with our study. Similar result was also noted in S. Saeed Jahan bakhsh et al study[29]. In contrast with our study, [Manal Abdalla M Zaglol study and Charuluxananan S, et al demonstrated no significant difference among the groups, in four rating score for nausea and vomiting[26,19]. So, further studies are needed using different doses of Ondansetron in large sample to evaluate this difference. We observed positive correlation between pruritus score and SNV in group-B but not in group-A. So Ondansetron was more efficacious than Nalbuphine in reducing pruritus and SNV (p>0.05) in cesarean delivery. Our results were coincided with Bonnet M., Marret, E. et al who observed the same result using IV Ondansetron[5]. In contrast, perioperative mean pulse rate changes at different times were almost similar between two groups (p>0.05). Similarly mean blood pressure changes at different times and mean $Sp0_2$ almost consistent between two groups and no significant (p>0.05) difference were found. Previous studies did not show any changes in hemodynamic variables, done by Pirat, A. et al , Bonnet et al , Toomey et al (2006) and Waxler et al[25,5,6,7]. Naloxone is the specific µ receptor antagonist which was kept as rescue antipruritic drug in our study. None of our patient required Inj. Naloxone because, pruritus scores in our study was within 0-3. In our clinical setup Inj. Naloxone is more expensive than Inj. Nalbuphine & Inj. Ondansetron and it is not easily available. Among the three drugs Inj. Ondansetron found to be least expensive and readily available in the operation theatre. The routine prophylactic use of Ondansetron during cesarean delivery would be associated with a little higher cost of care, but it might be balanced by increased patient satisfaction as a result of decreased incidence of pruritus and SNV.

Limitation and Recommendations of the Study

There was no control group in our study. Site of pruritus should have been included in the study as a variable.Patient's satisfaction was not documented. Peroperative hypotension due to regional anaesthesia might cause nausea and vomiting but it was not correlated in our study. Study population was limited and confined to only in Obstetrics units of CMCH. Further study should be conducted with large sample size in other surgical specialties like orthopedics, general surgery to generalize drug effects. Patient's follow- up should be continued for longer time in post-operative period to evaluate pruritus score. Multicenter study and Meta-analysis are needed for validate the study result.

Conclusion

In this prospective double-blinded randomized control study, main comparison was done on control of pruritus by prophylactic use of Inj. Nalbuphine and Inj. Ondansetron. In our study Inj. Ondansetron was more effective than Inj. Nalbuphine in reducing the intrathecal Fentanyl induced pruritus during cesarean delivery. The drug used in group B (Inj. Ondansetron) was cheaper than group-A (Inj. Nalbuphine) and Inj. Naloxone.

In our study, hemodynamic stability was observed better in group-B than group-A though it was not statistically significant. So, in the perspective of our present study, on the basis of cross tabulation and Chi-square test, we can conclude that Ondansetron is more effective and cheaper than Nalbuphine in reducing the intrathecal Fentanyl induced pruritus during cesarean delivery and safely used as an alternative to expensive drug Inj. Naloxone.

Disclosure

All the authors declared no competing interest.

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