

# Ondansetron and Metoclopramide Can Prevent Intrathecal Sufentanil-Induced Pruritus

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**Background:** We have compared the effectiveness of metoclopramide and ondansetron in the prevention of pruritus caused by intrathecal injection of sufentanil in parturients undergoing elective caesarean section under spinal anesthesia.

**Methods:** 123 parturients ASA I & II divided in to 3 groups with random allocation software, with 41 parturient in each group. Spinal anesthesia was performed with 2 ml of bupivacaine 0.5% plus 2.5 microgram sufentanil.

The first group received 4mg of ondansetron, the second group 10mg of metoclopramide and the third group placebo, immediately after clamping of the umbilical cord. During surgery and postoperative period, the parturients were assessed for hemodynamic changes, pruritus, nausea and vomiting and shivering.

**Results:** There were significant differences in the incidence of pruritus among three groups. The incidence of moderate pruritus was significantly higher in control group (47.5%) in comparison with ondansetron (15.8%) and metoclopramide (10%) groups. Severe pruritus was significantly higher in the control group (15%). The incidence of shivering was significantly lower in metoclopramide group (37.5% in comparison with 89.5% and 72.5% in the ondansetron and control groups). Moreover, the incidence of nausea and vomiting was significantly higher in placebo group.

**Conclusion:** Ondansetron and metoclopramide can effectively prevent and reduce the severity and the incidence of intrathecal sufentanil induced pruritus. Both drugs can reduce the incidence of nausea and vomiting. Metoclopramide also reduces shivering in this study.

**Keywords:** ondansetron; metoclopramide; spinal anesthesia; pruritus

Spinal anesthesia is commonly used in many obstetrical and gynecological procedures such as, cerclage, tubectomy, curettage and most commonly used in caesarean section, because of its practicality and rapid onset of action [1].

Hyperbaric solutions are mostly used in this method since, they have a more rapid onset duration, Marcaine 0.5 % being the most commonly used. This drug usually produces sensory, motor and somatic block in about 9-10 minutes of intrathecal injection [1-3]. Using additives such as clonidine, morphine, fentanyl and sufentanil creates a more rapid block with more superior block quality [4-5].

Short-acting lipophilic opioids like fentanyl and sufentanil cause intraoperative anesthesia and analgesia [6-7]. Morphine can provide post-operative analgesia as well [6-7]. On the other hand, intrathecal opioid administration can cause some complications which if not treated, can be

unpleasant for patients.

Three of the most common side effects include urinary retention, pruritus, nausea and vomiting, which occur in 60-100% of patients [4-6]. Pruritus is the most common side effect which occurs mostly in the mid-facial, nasal and upper chest areas [1].

Pruritus can be irritating to the mother which can impede bonding between the mother and the new born especially during the first hours after childbirth.

On the other hand, pruritus is more common in parturient women than the general population [8].  $\mu$ -receptor antagonists can be used for the definite treatment of pruritus but can attenuate intrathecal analgesic properties [9].

As a result, using an effective medication to prevent pruritus can be beneficial in pregnant women.

The probable pathophysiological mechanisms of pruritus are the activation of opioid  $\mu$  receptors in the spinal cord and brain, D2 dopaminergic receptors, 5- Hydroxytryptamine type 3 (5-HT<sub>3</sub>) serotonergic receptors, prostaglandins, glycine and Gamma-Amino butyric Acid (GABA) receptors [9]. As a result, medications such as, corticosteroids and antihistamines frequently used in clinical practice to treat pruritus, have no effect in the treatment of pruritus caused by intrathecal opioid injection [10]. On the other hand, ondansetron which is a selective and potent 5-Hydroxytryptamine (5-HT) blocker can be used to treat pruritus caused by activation of central 5-HT<sub>3</sub> receptors [11-

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12].

Metoclopramide has an anti-dopaminergic effect, which can be used to treat pruritus caused by dopaminergic receptor stimulation [13].

Although the anti-pruritic effects of these drugs after intrathecal opioid injection have been studied, no study has previously compared the effects of these medications especially in parturient women.

The objective of the present study is to compare the effects of ondansetron and metoclopramide in prevention of pruritus due to intrathecal sufentanil with each other and with a control group.

## Methods

This study was a randomized double blind clinical trial conducted on 123 parturient women divided into three groups with Random Allocation Software, with 41 patients in each group.

After obtaining institutional approval and written consent from patients the study was initiated. Inclusion criteria were: parturient who were classified as American Society of Anesthesiologists (ASA) physical status I or II with no contraindication of regional anesthesia, no previous allergies to ondansetron or metoclopramide, no previous history of pruritic diseases, no complaints of pruritus prior to surgery or pregnancy. Patients placed under general anesthesia (GA) due to insufficient spinal analgesia, were also excluded from the study.

Before induction of spinal anesthesia, all patients received an infusion of 500 ml of Ringer's Lactate solution and subsequently placed under spinal anesthesia using a 25-gauge Quincke spinal needle at the L3-L4 or L4-L5 levels through a midline approach. After free flow of CSF 2 ml of Marcaine 0.5% plus 2.5 µg of preservative free sufentanil were administered.

Afterwards, all parturient were immediately positioned supine with a proper wedge under right hip to alleviate aortocaval compression.

With proper noninvasive monitoring of all women, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MAP), heart rate and arterial O<sub>2</sub> saturation (SpO<sub>2</sub>) were measured prior to spinal anesthesia and also at 5, 10, 15, 30, 45, 60 minutes after spinal anesthesia and every 15 minutes thereafter until discharge from the recovery ward (post anesthesia care unit).

Any complications that occurred after receiving the medications were recorded. If hypotension occurred as BP decreasing by 20% of baseline BP or bradycardia occurred as 25% lowering of HR, 5 mg of ephedrine and 0.5 mg atropine were administered to patients, respectively to stabilize the patients.

The first group received 4mg of ondansetron, the second group 10 mg of metoclopramide and the third group placebo, immediately after clamping of the umbilical cord.

To determine the level of sensory block, the pin-prick test was used, which was performed with a 24gauge blunted needle bilaterally along the mid-clavicular line at 2-min intervals for the first 15 min after the injection.

An anesthetist nurse prepared the solutions, and the anesthesiologist who performed the intrathecal injection was not involved in the study. An independent nurse blinded to used drugs for each parturient, made all assessments. The severity of pruritus was divided into:

- 1- No pruritus,
  - 2- Mild pruritus (bearable)
  - 3- Moderate pruritus
  - 4- Severe (intense) pruritus
- Grades 3 and 4 required treatment.

The presence and the severity of pruritus were recorded every 15 minutes during the surgery and recovery periods by an anesthesiologist or nurse blinded to the study. The absence of response to the above mentioned medications (presence of pruritus as grade 3 or 4) was considered as unsuccessful treatment and the opioid effects were reversed using 0.2mg of naloxone. The patients were discharged from the recovery ward after diminished neuroaxial block (bromage scale no: 1) [the Bromage scale (0, no block; 1, impaired hip flexion; 2, impaired hip and knee movement; and 3, impaired hip, knee and ankle movement)] and the absence of nausea and vomiting and hemodynamic stabilization.

Sample size was calculated using this equation:

$$N = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{(d)^2} = \frac{(1.96 + 0.84)^2}{(0.25)^2} \times 2 \times 0.2 \times 0.8 = 41$$

Which Z 1-α is confidence limits, Z1-β is power.

Data was collected and subsequently analyzed using SPSS software version 20 (SPSS Inc., Chicago, IL, USA) and Chi-square and analysis of variance methods. The Kruskal-Wallis one-way analysis of variance and Mann-Whitney tests were used to compare continuous variables and the Pearson's χ<sup>2</sup>-test was used to compare categorical variables between the treatment groups.

## Results

There were no significant differences between the three groups regarding age, pregnancy age, gravity and demographic variables (Table 1), surgery duration (mean 57±0.02 min), recovery duration (1.21±0.03 hour), ASA values (ASA 1 and 2, 62.2% and 37.8% respectively, in the ondansetron receiving group, ASA 1 and 2, 70% and 30% respectively, in the metoclopramide receiving group and ASA 1 and 2, 71.8% and 28.2% respectively, in the control group, p value = 0.643).

Furthermore, the level of maximal sensory block using the pin prick method showed no significant difference in the three groups. The incidence of spinal block at the T4 level were 48.6% and 45% in the ondansetron and metoclopramide receiving groups, respectively. Spinal block occurred at the T5 level in 42.5% patients in the control group (Figure 1).

Patient satisfaction using the VAS method was not statistically different among the three groups (p>0.05) (Table 2).

There were also no significant differences in mean of systolic, diastolic and mean blood pressure (MAP) in the three groups, before spinal anesthesia and at 5, 10, 30, 45 or 60 minutes after spinal anesthesia. However, there was a significant difference in mean systolic BP during time of entry into the recovery unit among the groups in which, the mean systolic BP was significantly higher in the control group (115.2 mmHg) compared to the ondansetron receiving group (106.6 mmHg) (Figure 2). In addition, there was a significant difference in the mean diastolic BP after 30 minutes in the recovery unit between the groups, where the

main diastolic BP was significantly higher in the control group (70.5 mmHg) compared to the group that received ondansetron (61.8 mmHg) (Figure 3). There was also a significant difference in the mean BP among the groups. The mean blood pressure was higher after 30 minutes in the recovery unit in the control group (85.9 mmHg) compared to the ondansetron receiving group (76.7 mmHg) (Figure 4).

Regarding the mean heart rate among the three groups, no significant difference was found, before spinal anesthesia and at 5, 10, 30, 45 or 60 minutes after spinal anesthesia. However, the mean heart rate was significantly higher in the group receiving metoclopramide (87.6 BPM) compared to the other two groups (p =0.038) (Figure 5).

There was a significant difference in the incidence of pruritus among the three groups (Figure 6). The incidence of moderate pruritus was significantly higher in the control group (47.5%) compared to the ondansetron (15.8%) and

metoclopramide receiving (10%) groups. Severe pruritus was significantly higher in the control group (15%) compared to the other two groups (5.3% and 2.5% in the ondansetron and metoclopramide receiving groups respectively). In addition, the incidence of cases without pruritus was significantly higher in the group receiving ondansetron (60.5%) compared to the other two groups (52.2% and 30% in the metoclopramide and placebo receiving groups respectively), which also showed a significantly higher incidence of required naloxane in the placebo group (62.5%) compared to the other two groups (21.10% and 12.5% in the ondansetron and metoclopramide receiving groups respectively). The mean severity of pruritus was statistically higher in the placebo group (2.3) compared to the ondansetron (1.16) and metoclopramide (1.18) receiving groups.

**Table 1- distribution of demographic variables among the three groups.**

Variable	Ondansetron group	Metoclopramide group	Control group	P value
Age(year)	30.00±5.41	30.30±6.26	30.80±5.14	0.817
Gravity	2.05±0.90	2.20±0.85	2.18±0.98	0.750
Pregnancy age(week)	38.16±1.08	37.85±1.39	38.13±1.02	0.440
Weight(kg)	81.32±13.83	78.82±16.25	80.20±15.28	0.768
Height(cm)	162.79±7.29	160.88±6.02	160.92±6.68	0.361
BMI(kg/m <sup>2</sup> )	30.60±4.15	30.53±5.99	30.61±5.15	0.998

Data expressed as mean±SD.  
P value<0.05 was statistically significant.

**Table 2- Patient satisfaction among the three groups.**

Variable	Ondansetron group	Metoclopramide group	Control group	P value
Patient satisfaction	9.06±1.07	8.92±1.04	8.90±0.99	0.779

Data was expressed as mean±SD  
P value< 0.05 was statistically significant.

**Figure 1- Incidence of spinal block in the three groups.**

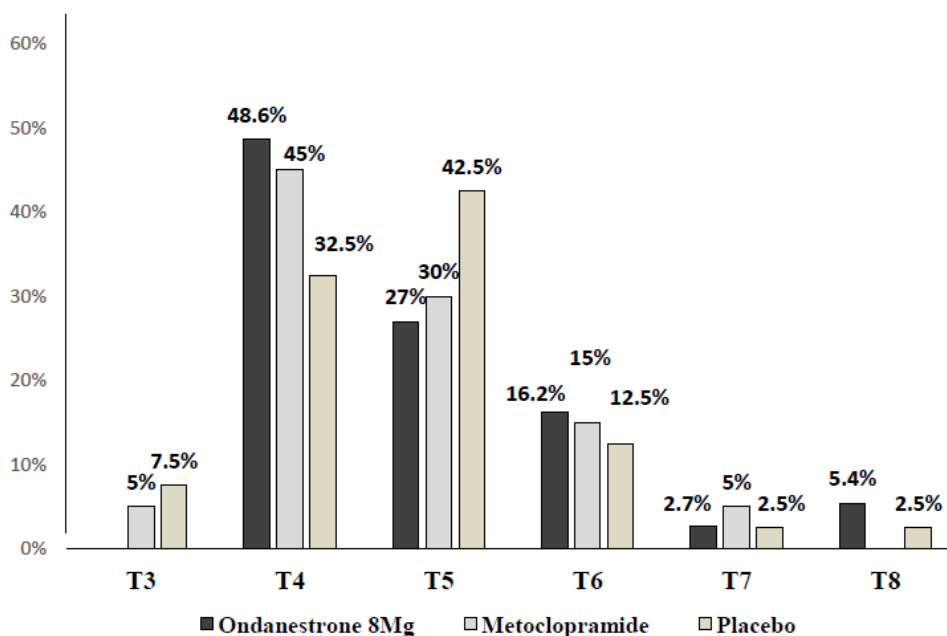


Figure 2- Linear graph on changes of mean of systolic blood pressure

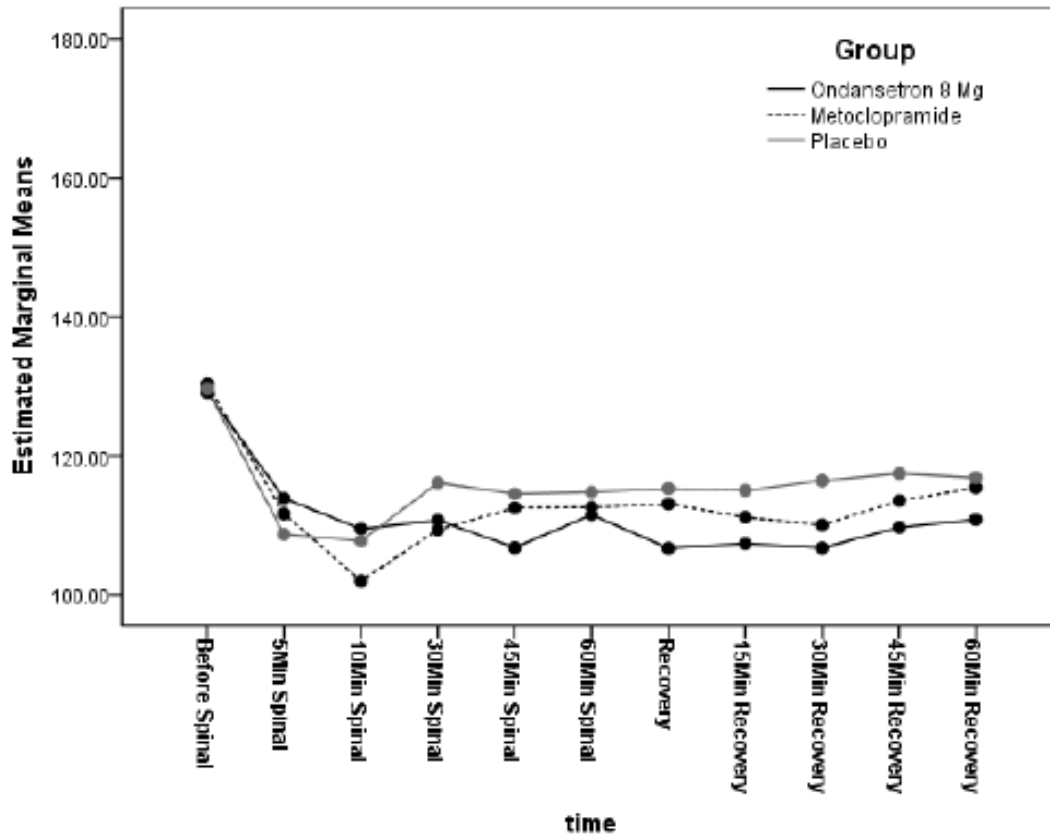


Figure 3- Linear graph on changes of mean of diastolic blood pressure

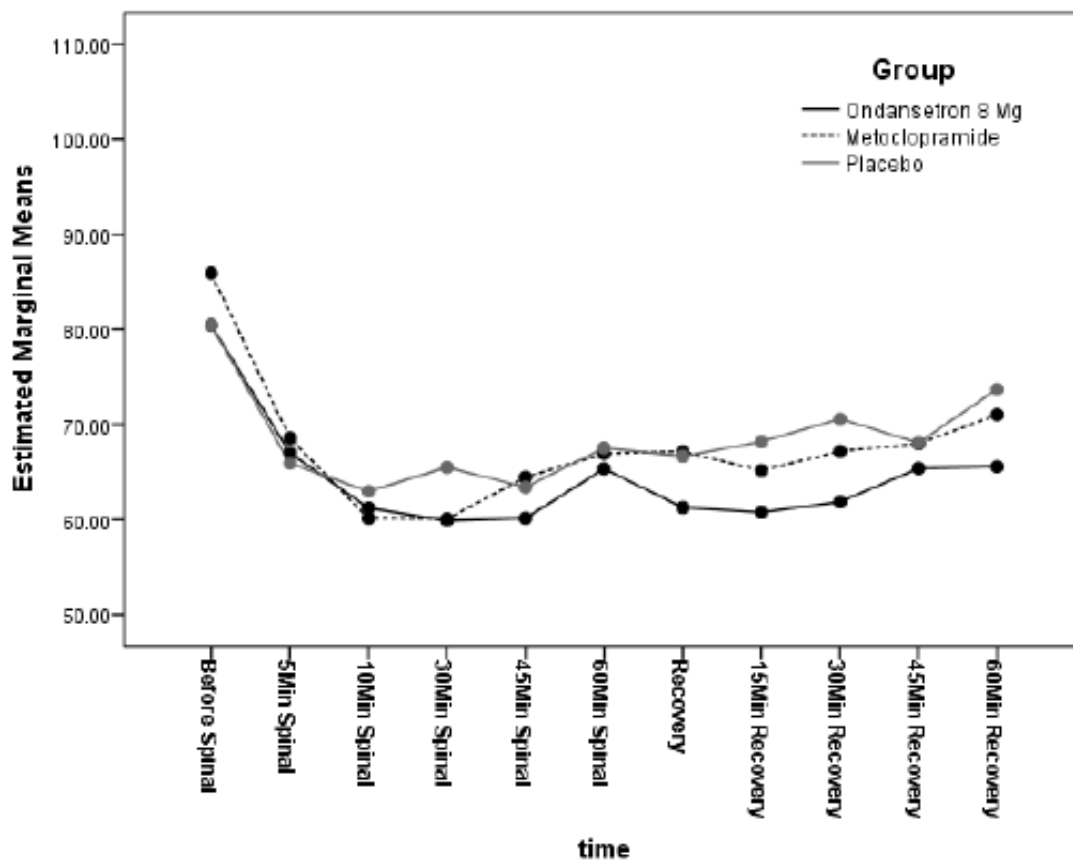


Figure 4- Linear graph on changes of mean of mean arterial pressure

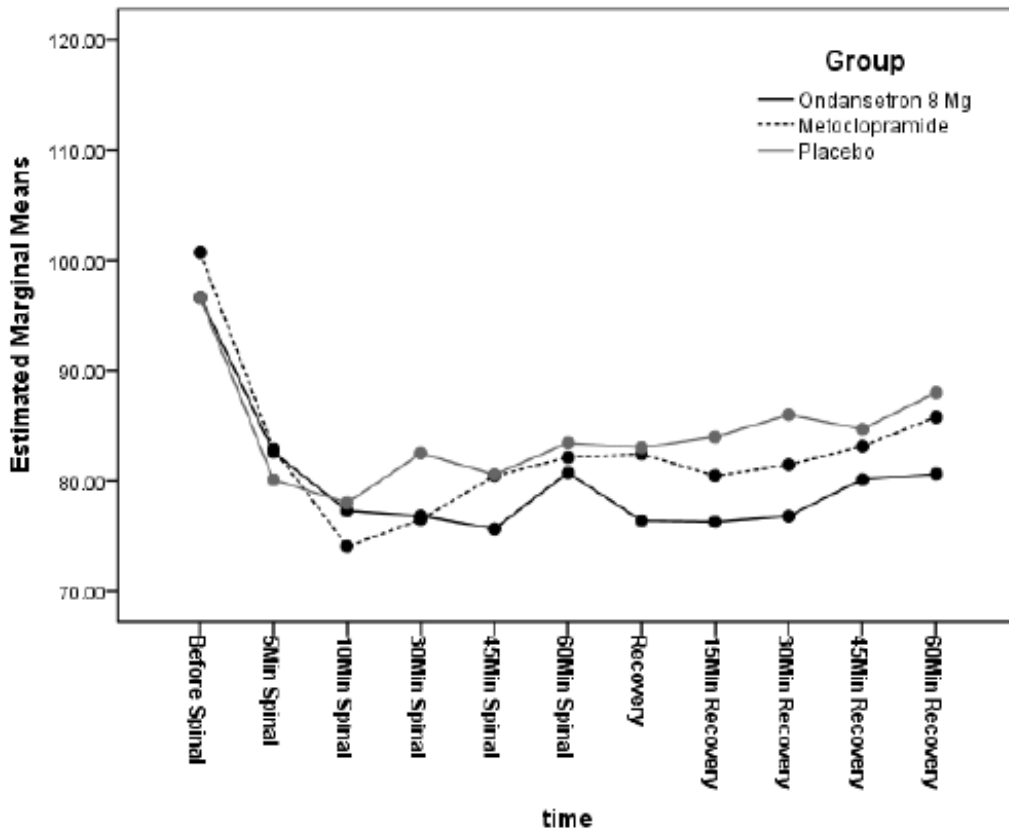
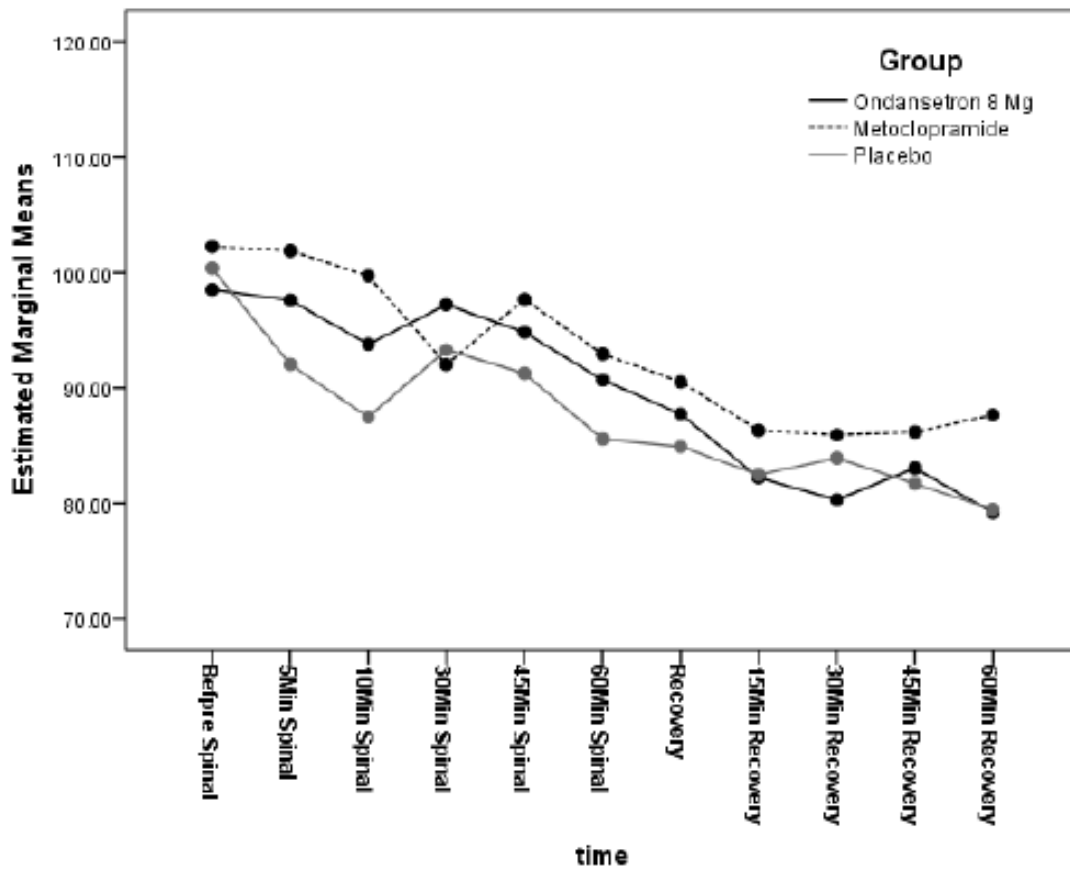
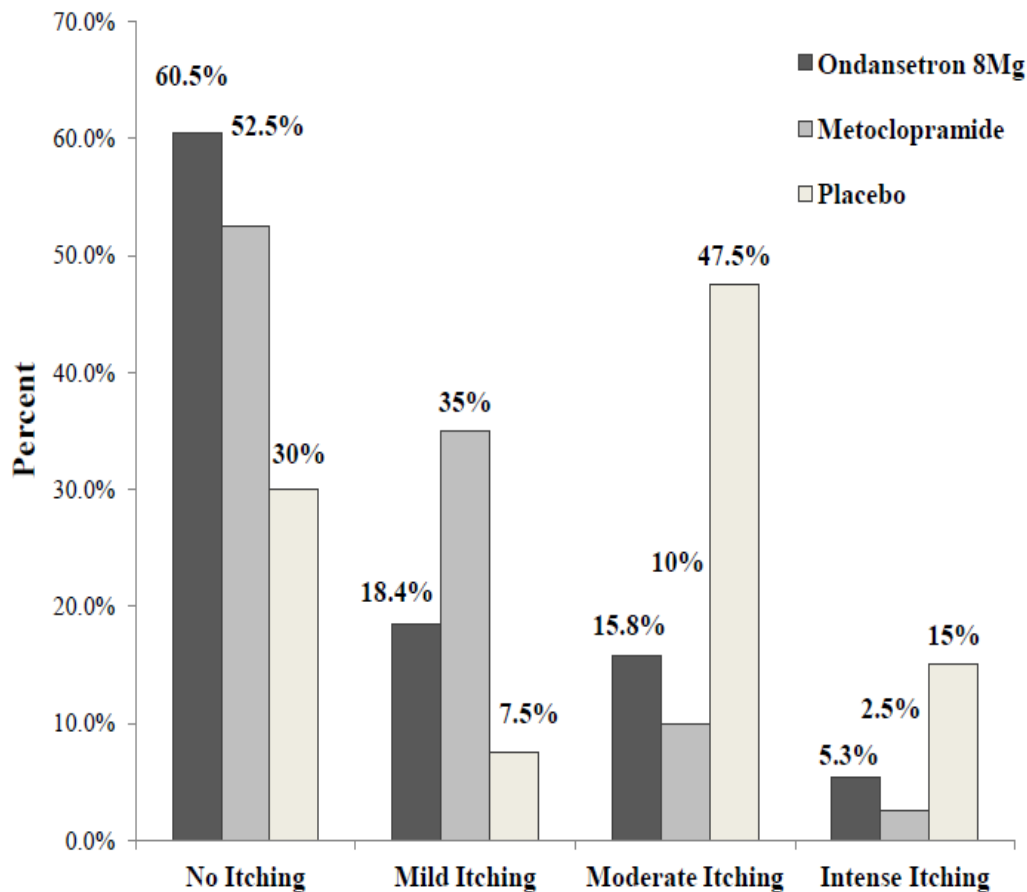


Figure 5 - Linear graph on changes of mean of heart rate.



**Figure 6- incidence of pruritus in the three groups.**



Shivering was one of the most prevalent side effects that occurred among all groups (Table 3). The incidence of shivering was significantly lower in the group receiving metoclopramide (37.5% compared to 89.5% and 72.5% in the ondansetron receiving and control groups, respectively).

Moreover, the incidence of nausea and vomiting was also significantly different in the groups (Table 4), where the incidence of this side effect was severely higher in the placebo group (22 %) compared to the ondansetron and metoclopramide groups (6% and 8% respectively).

The mean dosage (amount) of required ephedrine and atropine showed no statistical difference between the three

groups, while the mean dosage (amount) of required naloxone and metoclopramide were significantly higher ( $p < 0.05$ ) in the control group compared to the ondansetron and metoclopramide receiving groups (Table 5).

The frequency of atropine and ephedrine usage displayed no significant difference in the three groups, although, the frequency of usage of these two drugs was higher in the metoclopramide and ondansetron receiving groups. Furthermore, the frequency of metoclopramide and naloxane administration was significantly higher in the control group ( $p < 0.05$ ) (Figure 7)

**Table 3- Incidence of shivering among the three groups.**

p-value	Total	Shivering		Group
		Yes	No	
0.001*	38	34	4	Ondansetron 8 mg
	100.0%	89.5%	10.5%	
	40	15	25	Metoclopramide
	100.0%	37.5%	62.5%	Placebo
	40	29	11	
	100.0%	72.5%	27.5%	
	118	78	40	Total
	100%	66.1%	33.9%	

Data expressed as n (%)  
 P value < 0.05 was statistically significant

**Table 4- Incidence of nausea and vomiting among the three groups.**

p-value	Total	Nausea and Vomiting		Group
		Yes	No	
0.001*	38	6	32	Ondansetron 8 mg
	100.0%	15.8%	84.2%	
	40	8	32	Metoclopramide
	100.0%	20.0%	80.0%	
	40	22	18	Placebo
	100.0%	55.0%	45.0%	
	118	36	82	Total
	100%	30.5%	69.5%	

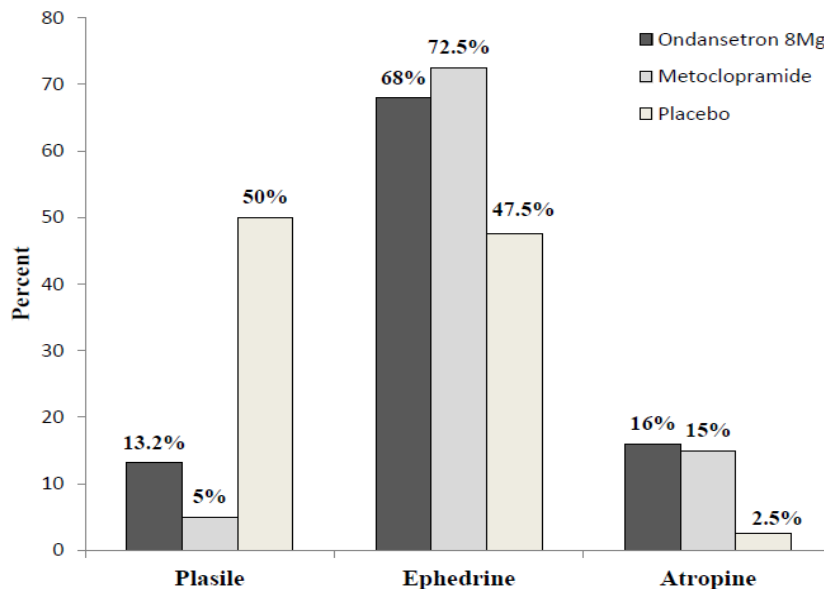
Data expressed as n (%)  
P value < 0.05 was statistically significant

**Table 5- Required dosage (amount) of naloxone, metoclopramide, ephedrine and atropine in the three groups.**

Variable	Ondansetron group	Metoclopramide group	Control group	P value
Naloxone	0.04±0.08	0.03±0.07	0.13±0.10	0.001
Plasil	0.13±0.34	0.05±0.22	0.50±0.51	0.001
Ephedrine	5.66±4.38	5.75±4.17	4.50±5.41	0.418
Atropine	0.8±0.18	0.8±0.18	0.1±0.08	0.107

Data was expressed as mean±SD  
P value < 0.05 was statistically significant

**Figure 7- Frequency of metoclopramide, ephedrine and atropine use in the three groups.**



## Discussion

This study compared the effectiveness of metoclopramide and ondansetron in the prevention of pruritus, nausea, and vomiting and shivering caused by intrathecal injection of sufentanil in parturient undergoing elective caesarean section under spinal anesthesia. Treatment and prevention of intrathecal opioid pruritus is still a challenge among anesthesiologists as in Kumar review article [14] mentioned in detailed. Previous studies [12-17] have examined the effectiveness of metoclopramide and ondansetron in the prevention of opioid-induced pruritus after intrathecal injection, but there have been no studies that have compared the effectiveness of these two medications to each other, as was done in our study.

Studies conducted previously have demonstrated that

pruritus was prevalent in 60 to 100% of patients undergoing spinal anesthesia using intrathecal opioids [4-6,14], which is compatible to our study. The prevalence of pruritus was 47.8% in the metoclopramide group and also 39.5% in ondansetron group which were significantly lower than the control group (70%), which is indicative of the effectiveness of metoclopramide and ondansetron in this study. This is in contrast to previous studies that stated metoclopramide to be ineffective in reducing opioid induced pruritus after intrathecal injection [14].

In our study ondansetron and metoclopramide reduced the severity of pruritus in this study which is in agreement with previous studies that indicated that ondansetron reduced the severity of pruritus and need for rescue medication [12-13, 15-16]. Metoclopramide was not effective in reducing pruritus in previous studies [14,18].



Shivering was also a common side effect which occurred; overall in 66.1% of patients [1,3]. Shivering was decreased significantly by using metoclopramide prophylactically (37.5%) compared to using prophylactic ondansetron (89.5%) and control group (72.5%). It needs further study to find its effectiveness and mechanism.

Our study showed that nausea and vomiting were also decreased by using metoclopramide and ondansetron as preventive medications. This is also in accordance with previous studies conducted which showed that ondansetron decreased nausea and vomiting after intrathecal opioid injection [12,14-16].

The required dosage and frequency of naloxone and metoclopramide injection used as rescue medications, were also decreased by using metoclopramide and ondansetron in this study which was also demonstrated in previous studies. On the other hand, the required dosage of ephedrine and atropine were not different in any of the patients who received either metoclopramide or ondansetron.

In conclusion, metoclopramide and ondansetron reduced the severity of pruritus and the incidence of shivering and nausea and vomiting in our study and they also reduced the required dose of rescue medication including naloxone and pasilil in our patients but they did not have an effect on the required doses of atropine or ephedrine.

There were a few limitations in our study; for example, since metoclopramide was used in our study, this drug could not be used as aspiration prophylaxis. In addition, a number of patients were excluded from the study due to the extended duration of surgery or unsatisfactory levels of spinal block, thus being placed under general anesthesia.

It is recommended that in future studies, a higher number of patients and various doses of intrathecal opioids should be used and the effectiveness of more medications evaluated.

## Conclusion

Ondansetron and metoclopramide can effectively prevent and reduce the severity and the incidence of intrathecal sufentanil induced pruritus. Both drugs can reduce the incidence of nausea and vomiting. Metoclopramide also reduce shivering under spinal anesthesia in this study.

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Sciences, Isfahan, Iran) and all patients gave written, informed consent.

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