

## Original Article

# The comparative study of intravenous Ondansetron and sub-hypnotic Propofol dose in control and treatment of intrathecal Sufentanil-induced pruritus in elective caesarean surgery

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Received: January 2015  
Accepted: March 2015

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## ABSTRACT

**Objective:** Pruritus is a common and disturbing side effect of neuraxial opioids after cesarean section. The purpose of this study was to compare the efficacy of intravenous ondansetron and sub-hypnotic dose of propofol in control and treatment of intrathecal sufentanil induced pruritus in cesarean surgery.

**Methods:** Totally, 90 parturient with American Society of Anesthesiology physical status grade I-II, undergoing spinal anesthesia with 2.5 µg sufentanil and 10 mg bupivacaine 0.5% were enrolled to this randomized, prospective, double-blind study. The women were randomly assigned to two groups who received 8 mg ondansetron or 10 mg propofol to treat pruritus grade  $\geq 3$ . The patient was evaluated after 5 min and in the lack of successful treatment, the doses of two drugs repeated and if the pruritus is on-going, the exact treatment with naloxone was done.

**Findings:** The incidence of pruritus was 69.3%. Both groups were well-matched. The peak time pruritus was 30–75 min after injection. The percentage of individuals consumed naloxone were 6.8% and 15.9% in ondansetron and propofol groups, respectively ( $P = 0.18$ ). The mean score of satisfaction (according to visual analog scale criteria) was  $9.09 \pm 1.1$  in ondansetron group and  $9.3 \pm 1.07$  in the propofol group ( $P = 0.39$ ).

**Conclusion:** Ondansetron and sub-hypnotic dose of propofol are both safe and well-tolerated. Due to their same efficacy in the treatment of intrathecal sufentanil-induced pruritus, they can be widely used in clinical practice.

**Keywords:** Caesarean surgery; intrathecal opioid; Ondansetron; Propofol; pruritus

## INTRODUCTION

Single shot spinal anesthesia is widely used for most surgical operations especially in obstetric such as hysterectomy, tubal ligation after vaginal delivery, cesarean and cortege etc.; however, in general, cesarean is considered as the most common indication for spinal anesthesia in pregnant women.<sup>[1]</sup> In this technique, usually hyperbaric drugs

are used due to rapid onset of anesthesia effect; marcaine 0.5% is the mostly used drug.<sup>[1,2]</sup> This drug leads to sensation, kinetic, and somatic block after 9–10 min and its effect is more desired and the block effect time is rapid by adding some additives such as clonidine, morphine, fentanyl, and sufentanil.<sup>[3]</sup> Intrathecal opioids are used in cesarean and painless delivery due to analgesia effect. Short effect lipid-soluble opioids such as fentanyl and sufentanil lead to anesthesia and painless during operation and morphine can create postsurgery painless; however, administration of intrathecal opioids have some effects that in case of lack of treatment can be unpleasant for patient. Its three prevalent effects are urinary retention, pruritus, nausea, and vomiting. Pruritus happens in 60–100% of cases<sup>[6-9]</sup> and is the most prevalent effect of intrathecal opioids<sup>[4-6]</sup> and

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DOI: 10.4103/2279-042X.155751

usually it happens in the middle part of face and nose and above breast.

Various drugs have been recommended for control of pruritus and have been investigated in various studies. Naloxone is the most effective treatment for pruritus even in severe cases, but it can reverse the analgesic effect of opioid.<sup>[5]</sup> Hence, treatment with most effective drugs with no effect on the analgesic effect is more practical and safe to use.

Since one of the reasons for pruritus is activation of central receptor of 5-hydroxytryptamine receptor type 3 (5-HT<sub>3</sub>). Ondansetron that is selective and strong controller of 5-HT<sub>3</sub> receptor can be effective in removing pruritus. Although the reason of pruritus due to intrathecal opioids is unknown, it seems that it is independent of release of histamine.<sup>[10]</sup> Some researchers have concluded that pruritus is due to disturbance of the sensational receptors due to dispersion of opioids in cerebrospinal fluid and effect on the nucleus of trigeminal or sub-nucleus caudalis.<sup>[11,12]</sup>

Neural pathways of pruritus interfere with pain pathways. Thus, when the pain is controlled, pruritus also would disappear. Serotonergic system plays some modification role in neuron network. Spinal cord dorsal horn and the trigeminal nerve of spinal cord are controlled by 5-HT<sub>3</sub>. On the other hand, it is proved that intrathecal morphine leads to pruritus by activation of 5-HT<sub>3</sub> receptors through the mechanism independent on opioids receptors. Thus, by prescription of antagonist of 5-HT<sub>3</sub> receptor, it is possible to control pruritus.<sup>[13]</sup> In addition, propofol leads to depression of anterior and posterior spinal cord in animal studies. Thus, it seems that propofol applies its anti-pruritus effect through depression of anterior and posterior spinal cord.<sup>[14]</sup>

George *et al.*,<sup>[15]</sup> have considered the use of antagonists of receptor 5-HT<sub>3</sub> as prophylactic in control of pruritus and this has been proved in Ben-David *et al.*,<sup>[16]</sup> studies. In Ben-David *et al.*,<sup>[16]</sup> the therapeutic effect of 4 mg and 8 mg ondansetron in control of pruritus due to intrathecal opioids has been proved.<sup>[17]</sup> On the other hand, Borgeat *et al.*,<sup>[14,18]</sup> explained that sub-hypnotic propofol dose is effective in control and treatment of pruritus due to intrathecal opioids; however, there is no study comparing the effect of these two drugs, that is, ondansetron (antagonist of 5-HT<sub>3</sub> receptor) and propofol. Thus, we conducted this prospective, double-blind, randomized study to compare the effect of these two drugs on pruritus in pregnant women under elective cesarean surgery with spinal anesthesia with intrathecal sufentanil.

## METHODS

This randomized, double-blind trial study was approved by an Institutional Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran. This study has been done from 2012 to 2013 in Shahid Beheshti Medical Training Center in Isfahan.

The inclusion criteria were pregnant women candidate for elective cesarean under spinal anesthesia, with American Society of Anesthesiology (ASA) physical status grade I-II, lack of experience of any previous disease that is manifested by pruritus, and lack of complain of pruritus before operation. Furthermore, it was decided that in case of showing any allergy to drugs and any change in anesthesia technique, the patient would be excluded from the study.

The required sample size of this study was considered as 45 individuals in each group by the use of sample size estimation formula for comparison the ratio considering the reliability level of 95%, test power of 80%, prevalence of pruritus after injection of intrathecal opioids that was considered 0.5 due to lack of any similar local study. Furthermore, the least significant difference between two methods was considered as 20%.

Without any premedication, all parturients were hydrated with 500 ml ringer lactate solution before spinal anesthesia. Spinal anesthesia was induced with 2 cc marcaine 0.5% and 2.5 µg sufentanil in the same syringe. The systolic, diastolic, mean blood pressure, and heart rate were investigated and registered before spinal anesthesia and in 5, 10, 15, 30, 45, and 60 minutes after spinal performance and then every 15 minutes until discharge from the recovery unit.

Patients were evaluated for scratching and its severity. The severity of pruritus was divided into 4 degrees (without pruritus, and mild, moderate, and severe pruritus), whereas 3 and 4 were treated.

The incidence of pruritus was evaluated by the anesthesiologist every 15 min until discharging from recovery unit. The ondansetron group was treated by 8 mg ondansetron, and the propofol group was treated by 10 mg propofol, and if the itching was not disappeared, two doses of the drug repeated again. If we had no responding to the above drugs, it was defined as unsuccessful treatment and divided doses of naloxone (40 µg) was administered.

In cases of any side effect after injection of the drug, the required actions were taken and registered. Furthermore, in case of hypotension <20% of base limit after spinal anesthesia, 5 mg ephedrine was injected and in case of bradycardia <25% of base limit after performing spinal anesthesia, 0.5 mg atropine was injected.

Data were analyzed by SPSS version 20 (SPSS Inc., Chicago, IL, USA). Severity of pruritus was analyzed with Mann–Whitney test and the frequency distribution with Chi-square test.

## RESULTS

Totally, 90 patients under cesarean surgery were enrolled into the study [Figure 1]. Two patients were excluded due to inadequate spinal anesthesia necessitating induction of general anesthesia. In Table 1, mean and standard deviation of demographic and general specification of patients in two groups have been shown. According to *t*-test, mean age, weight, body mass index, duration of operation, and recovery duration in two groups had not significant difference; however, pregnancy age in two groups was different ( $P = 0.002$ ). Furthermore, according to Chi-square test, frequency distribution of gravity and ASA in two groups was not different ( $P > 0.05$ ).

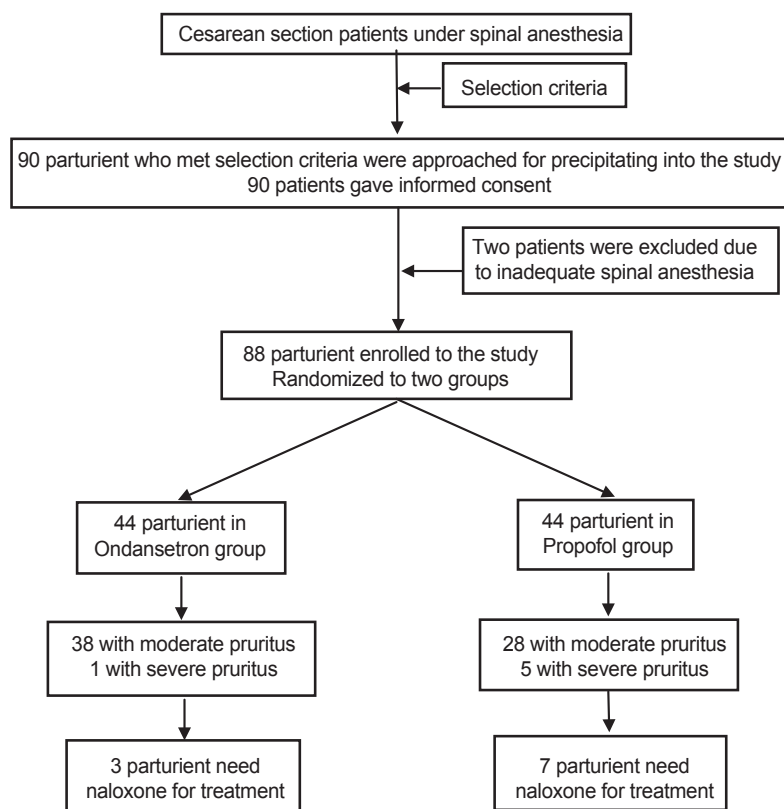
Mean hemodynamic parameters from the time before anesthesia until the end of stay in recovery unit have been shown in Figures 2-7. Variance analysis test with repetition of observations on the mentioned variables showed that variation of none of the mentioned parameters had not significant difference in two study groups ( $P > 0.05$ ).

Table 2 includes the frequency distribution of pruritus from the anesthesia until 135 minutes in two groups receiving ondansetron and propofol. During the study, 32 members from ondansetron group and 29 members of propofol group suffered from degrees of pruritus (72.7% against 65.9%); and according to Chi-square test, the frequency distribution of pruritus incidence in two groups had not significant difference ( $P = 0.49$ ). Performing Mann–Whitney test on the mentioned

**Table 1: Distribution of demographic data and general variables in two groups**

Variable	Ondansetron	Propofol	<i>P</i>
Age (year)	5.6±30.3	4.8±28.9	0.22
BMI (kg/m <sup>2</sup> )	4.5±30.6	4.9±29.4	0.22
Gestational age (week)	1.2±38.2	2.8±36.8	0.002
Gravity			0.99
1	15(34.1)	15(34.1)	
2	19(43.2)	19(43.2)	
3	8(18.2)	7(15.2)	
4 and more	2(4.5)	3(6.9)	
ASA physical status grade			0.57
I	37(86)	34(79.1)	
II	6(14)	9(20.9)	
Surgery duration (min)	15.8±60	14.5±57.5	0.44
Recovery duration (min)	17.8±55.9	16.2±55.8	0.98

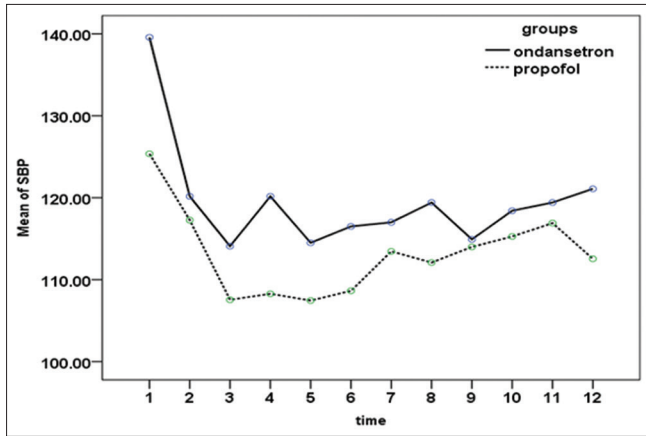
BMI=Body Mass Index, ASA=American Society of Anesthesiology. Data presented as Mean ± SD, or Number(%), where applicable.



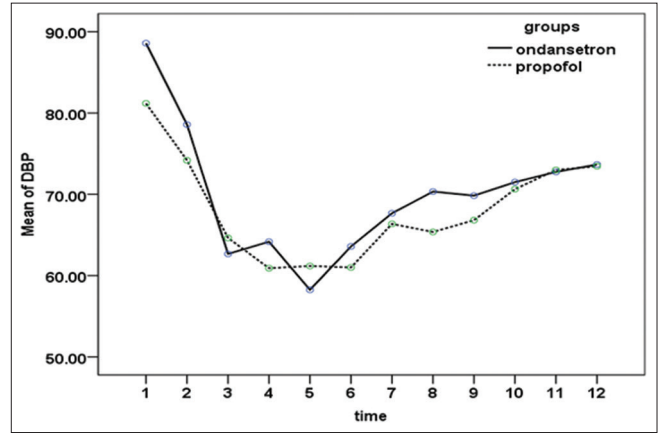
**Figure 1: CONSORT diagram of the study**

data showed that mean pruritus during the study had no significant difference in two groups ( $P = 0.44$ ) [Figure 7].

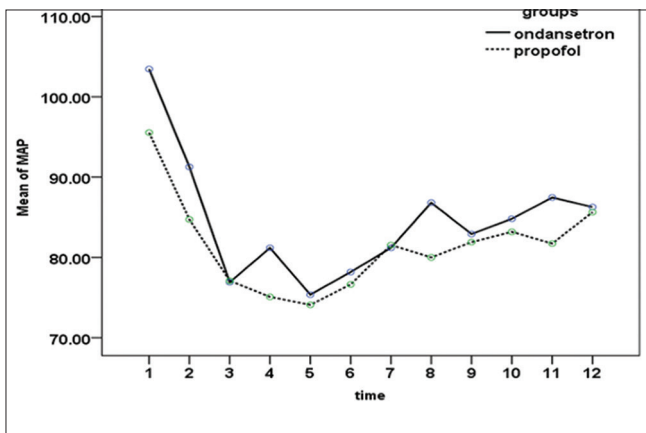
The incidence of nausea and vomiting in ondansetron and propofol groups were 39.4% ( $n = 16$ ) and 21.5% ( $n = 9$ ), respectively. Only 9.1% ( $n = 4$ ) and



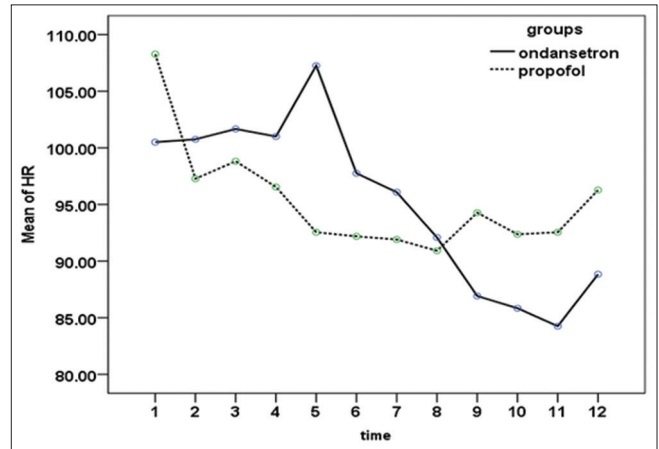
**Figure 2:** Mean systole blood pressure (mmHg) from pre-surgery to the end of recovery ( $P = 0.07$ )



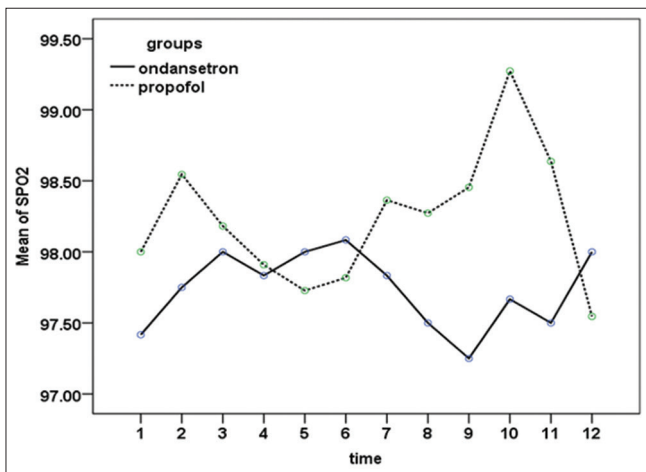
**Figure 3:** Mean diastole blood pressure (mmHg) from pre-surgery to the end of recovery ( $P = 0.52$ )



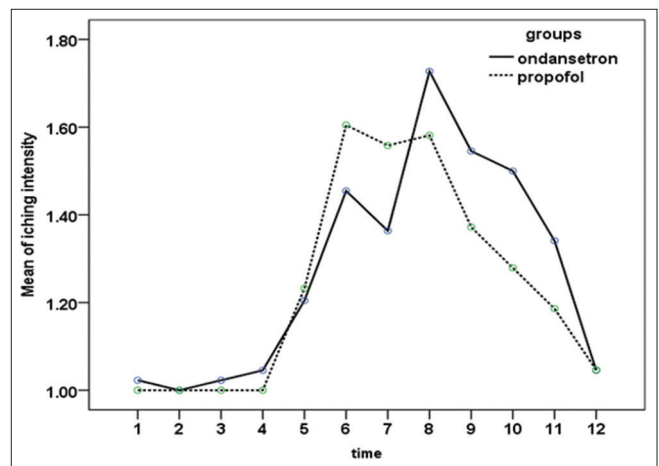
**Figure 4:** Mean arterial pressure (mmHg) from pre-surgery to the end of recovery ( $P = 0.26$ )



**Figure 5:** Mean heart rate (beats/min) from pre-surgery to the end of recovery ( $P = 0.99$ )



**Figure 6:** Mean SpO<sub>2</sub> (%) from pre-surgery to the end of recovery ( $P = 0.20$ )



**Figure 7:** Mean pruritus intensity from pre-surgery to the end of recovery ( $P = 0.44$ )

**Table 2: Frequency distribution of pruritus (severity) in two studied groups**

Time period	Group	Pruritus severity				P
		No	Low	Mild	Severe	
Before analgesia	Ondansetron	43 (97.7)	1 (2.3)	0 (0)	0 (0)	0.99
	Propofol	44 (100)	0 (0)	0 (0)	0 (0)	
After analgesia	Ondansetron	44 (100)	0 (0)	0 (0)	0 (0)	0.99
	Propofol	44 (100)	0 (0)	0 (0)	0 (0)	
5 <sup>th</sup> min	Ondansetron	43 (97.7)	1 (2.3)	0 (0)	0 (0)	0.99
	Propofol	44 (100)	0 (0)	0 (0)	0 (0)	
10 <sup>th</sup> min	Ondansetron	42 (95.5)	2 (4.5)	0 (0)	0 (0)	0.49
	Propofol	44 (100)	0 (0)	0 (0)	0 (0)	
15 <sup>th</sup> min	Ondansetron	38 (86.4)	3 (6.8)	3 (6.8)	0 (0)	0.53
	Propofol	36 (81.8)	6 (13.6)	2 (4.5)	0 (0)	
30 <sup>th</sup> min	Ondansetron	30 (68.2)	8 (18.2)	6 (13.6)	0 (0)	0.45
	Propofol	28 (63.6)	6 (13.6)	8 (18.2)	2 (4.5)	
45 <sup>th</sup> min	Ondansetron	31 (70.5)	10 (22.7)	3 (6.8)	0	0.48
	Propofol	27 (61.4)	11 (25)	4 (9.1)	2 (4.5)	
60 <sup>th</sup> min	Ondansetron	24 (54.5)	9 (20.5)	10 (22.7)	1 (2.3)	0.75
	Propofol	27 (61.4)	10 (22.7)	6 (13.6)	1 (2.3)	
75 <sup>th</sup> min	Ondansetron	26 (59.1)	12 (27.3)	6 (13.6)	0 (0)	0.45
	Propofol	31 (70.5)	10 (22.7)	3 (6.8)	0 (0)	
90 <sup>th</sup> min	Ondansetron	28 (63.6)	10 (22.7)	6 (13.6)	0 (0)	0.25
	Propofol	35 (79.7)	6 (13.6)	3 (6.8)	0 (0)	
105 <sup>th</sup> min	Ondansetron	33 (75)	7 (15.9)	4 (9.1)	0 (0)	0.35
	Propofol	37 (84.1)	6 (13.6)	1 (2.3)	0 (0)	
120 <sup>th</sup> min	Ondansetron	42 (95.5)	2 (4.5)	0 (0)	0 (0)	0.22
	Propofol	43 (97.7)	0 (0)	1 (2.3)	0 (0)	

Data presented as number (%) of patients

2.3% ( $n = 9$ ) in ondansetron and propofol group were suffered with 2 times vomiting. According to Fisher test, the incidence of vomiting had not significant difference in two groups ( $P = 0.19$ ).

In this study, 28 (63.6%) in ondansetron and 29 (65.9%) in propofol group received ephedrine due to hypotension and according to Chi-square, no significant difference was observed between two groups ( $P = 0.82$ ). The mean  $\pm$  SD dose of consumed ephedrine in ondansetron and propofol group was  $5.8 \pm 0.97$  and  $6.14 \pm 0.89$  mg, respectively; and according to  $t$ -test, no significant difference was observed between two groups ( $P = 0.8$ ).

In ondansetron and propofol group, 7 (15.9%) and 9 (20.5%) individuals who had bradycardia received atropine and according to Chi-square, the difference between two groups was not significant ( $P = 0.58$ ). The dizziness was the other adverse effect had been observed [Table 3].

In ondansetron group, 38 of 44 patients (86.3%) and in the propofol group, 28 patients (63.3%) had moderate pruritus after 30 min of induction of spinal anesthesia. Only 1 (2.2%) and 5 (11.3%) of ondansetron and propofol group had severe pruritus after 45 min of spinal anesthesia ( $P > 0.05$ ).

**Table 3: Frequency distribution of adverse effects**

Adverse effects	Groups		P
	Ondansetron	Propofol	
Hypotension	28 (63.6)	29 (65.9)	0.82
Bradycardia	7 (15.9)	9 (20.5)	0.58
Nausea and vomiting	16 (39.4)	9 (21.5)	0.19
Dizziness	11 (25)	16 (36.4)	0.86

Data presented as number (%) of patients

Three patients (6.8%) in ondansetron group against 7 parturient (15.9%) in propofol group were suffered with pruritus whereas the administration of naloxone was necessary; while according to the mentioned test, the difference between two groups was not significant ( $P = 0.18$ ).

The mean score of satisfaction with treatment (according to visual analog scale criteria) in ondansetron group was  $9.09 \pm 1.1$  and in propofol group, it was  $9.3 \pm 1.07$  while the difference between two groups was not significant ( $P = 0.39$ ).

## DISCUSSION

Neuroaxial opioids especially sufentanil due to its property in improving the quality of block and

analgesia after cesarean delivery can be used safely in parturient practice. Unfortunately, naloxone as the most effective treatment for this disturbed symptom can remove the analgesic effect of intrathecal opioids.<sup>[5,6,8]</sup>

This study demonstrated the incidence of pruritus 69.3% with peak time of 30–75 min after spinal anesthesia that consistent with other studies.<sup>[17-20]</sup> They showed the incidence of pruritus with intrathecal sufentanil was 45–95% intraoperative and in the postoperative period; however, no significant difference was observed generally between two groups. Although other studies<sup>[3,15,17]</sup> indicate the effect of ondansetron in the prevention of pruritus, in our study, ondansetron had treating effect the same as propofol. In Ronald's study, the positive effect of ondansetron and in Borgeat's *et al.*, study, the positive effect of propofol in treatment of pruritus has been supported.<sup>[15,18]</sup> Thus, concerning the obtained results, it can be concluded that both ondansetron and propofol had a similar effect in the treatment of pruritus in patients under intrathecal sufentanil. In the clinical condition, both of these drugs are safe and well-tolerated.

In Beilin *et al.*, study,<sup>[19]</sup> they showed that sub-hypnotic dose of propofol do not relieve the intrathecal opioids induced pruritus, but we investigated that it had the same efficacy in treatment of pruritus with ondansetron as the other investigations.<sup>[3,14]</sup>

There were several limitations in this study design and conclusions. First, pruritus is a subjective symptom, so the sensation of severity can be different between individuals. Second, we have not studied the dose-response of antipruritic activity of two drugs to determine the optimal dose. Third, our results can only be applied to postpartum women.

Moreover, the incidence of pruritus in parturient likely depends on factors such as high dose of sufentanil and lower dose of ondansetron and propofol in patients. Since the incidence of pruritus during operation and after it, is a disturbing symptom for patients, it is required to carry out wider studies with higher sample size and different doses of ondansetron proportionate to the sufentanil to be used. Furthermore, the probability of combined use of ondansetron and propofol and the effect of their synergy should be investigated.

In conclusion, intravenous ondansetron and propofol are both effective in the treatment of moderate to severe pruritus-induced intrathecal sufentanil in obstetric patients. Side effects after treatment are too mild that are negligible. Therefore, instead of naloxone, in clinical practice especially for parturient undergone cesarean delivery, propofol and ondansetron can use for pruritus due to intrathecal sufentanil.

## ACKNOWLEDGMENTS

The authors wish to sincerely thank the support of all the colleagues in Baheshti Hospital Medical Center affiliated to Isfahan University of Medical Sciences in Isfahan, Iran. Furthermore, our special thanks go to the patients, who wholeheartedly and actively assisted us to carry out this research. This prospective randomized observational study was approved by the Ethics Committee of our university, (Isfahan University of Medical Sciences) and all patients gave written, informed consent.

## AUTHORS' CONTRIBUTION

Dr. Hirmanpour has selected the title, cooperated in preparing proposal and collected the samples and written the manuscript. Dr. Safavi has cooperated in preparing proposal and help to submit the manuscript. Dr. Honarmand supervised the statistical analysis and suggested the references. Dr. Zavarani Hosseini who has got this project for his Doctor of medicine. Search the references and write the proposal and supervised the process of collecting data (patients informed consent,...). Mrs. Sepehrian was cooperated in collected the patients data and blinding the samples, help to preparing the manuscript.

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**How to cite this article:** Hirmanpour A, Safavi M, Honarmand A, Hosseini AZ, Sepehrian M. The comparative study of intravenous Ondansetron and sub-hypnotic Propofol dose in control and treatment of intrathecal Sufentanil-induced pruritus in elective caesarean surgery. *J Res Pharm Pract* 2015;4:57-63.

**Source of Support:** Nil, **Conflict of Interest:** None declared.