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"Comparison of Pre-Treatment with ondansetron Versus Tramadol For Reduction of Pain on Injection of Propofol – A Prospective, Randomized Study"

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Abstract
Background: *Propofol, most frequently used intravenous anaesthetic, is used for induction, maintenance of anaesthesia and for sedation in patients scheduled for routine elective surgical procedure. A unique action of propofol is its antiemetic effect, which remain present at concentration less than producing sedation. Pain on injection of propofol still remains a considerable concern for the anaesthesiologist. A number of techniques has been tried to minimize propofol-induced pain with variable results. There are some hypotheses that intravenous administration of ondansetron might decrease propofol injection induced pain. Moreover, some studies have shown that pretreating the vein with i.v. tramadol has proved to be effective in preventing propofol injection pain in adults. In the present prospective randomized study, we compared pretreatment with ondansetron versus tramadol for prevention of propofol injection pain.*
Materials and Methods: *A total of 60 patients were taken up in the study in the age group of 18 to 60 years of either sex, ASA grade I/II, scheduled for routine elective surgical procedure under general anesthesia with endotracheal intubation. The patients enrolled were divided randomly into three groups of 20 patients each. Group I received 2 ml of ondansetron intravenous (2 mg/ml). Group II received 2 ml of 50 mg tramadol intravenous in saline. Group III received 2 ml of 0.9% normal saline intravenous. The patients were asked to report their pain according to the scale provided to them in the form of none, mild, moderate, and severe (verbal rating scale). Statistical testing was conducted with the statistical package for the social science (SPSS) for Windows. For all statistical tests, $p<0.05$ was taken to indicate a significant difference.*
Results: *Mean age of patients in Group I was 37.6 years, in Group II was 40.75 years and in Group III was 40.45 years. All mean ages were comparable. Also, patients of both the sexes were equally distributed in three groups. As per McCririck and Hunter scale, no pain was reported by 75%, 85% and 20% patients in i.v. ondansetron, i.v. tramadol and i.v. normal saline groups respectively. Mild pain was reported by 25%, 15% and 45% patients in i.v. ondansetron, i.v. tramadol and i.v. normal saline groups respectively. No patients in i.v. ondansetron and i.v. tramadol drug groups reported moderate or severe pain, whereas 15% and 20% respectively reported moderate and severe pain in i.v. normal saline group. Statistically significant difference is observed when i.v. ondansetron drug group is compared with i.v. normal saline group ($p=0.001$), as well as when i.v. tramadol drug group is compared with i.v. normal saline group ($p=0.000$).*
Conclusion: *Intravenous ondansetron is equally effective and can be used alternatively to injection tramadol for relief of pain due to propofol injection without any significant side effects.*
Keywords: *ondansetron, tramadol, propofol*.

I. Introduction

Propofol is a common intravenous anesthetic agent used for induction and maintenance of general anesthesia since 1977. It is the drug of choice for millions of patients every year because of its rapid onset and short duration of action, easy titration, and favourable profile for side effects (1). Although propofol has these positive characteristics, it has some unwanted effects like injection pain which impairs patient comfort (2). The pain may cause hand withdrawal and dislodging of the venous cannula (3). In the absence of treatment regimens, 28 to 90% of adult patients experience moderate to severe pain when propofol is injected into peripheral vein (4). Nature of the vascular pain is expressed by the patients as aching, burning and crushing. It is due to phenol group present in propofol. Phenol group is irritating to skin, mucous membrane and venous intima. The mechanism of pain is attributed to the activation of the kinin-kallikrein system that releases bradykinin, causing vasodilatation and hyperpermeability, thereby increasing contact between the aqueous phase propofol and the free nerve endings (5).

Although investigators did not find clear and definite pathway or mechanism for pain induce by propofol, they designed different interventions in the trial studies for the assessment of the role of some other drugs to alleviate pain of intravenous propofol injection (6). Studies have reported that ondansetron has been

routinely administered as premedication to prevent postoperative nausea and vomiting in patients scheduled for general anaesthesia. Some investigators demonstrated that ondansetron, a specific 5-HT antagonist, blocks Na channels in rat brain neurons. They also found that ondansetron is 15 times more potent than lidocaine in causing numbness when injected under the skin (7). There are some hypotheses that intravenous administration of ondansetron might decrease propofol injection induced pain. However, there is relatively little published data about the efficacy of ondansetron on the propofol induced pain (8,9).

Tramadol is a centrally-acting drug, which is effective in the treatment of moderate to severe pain. In addition to its systemic effect, the local anesthetic effect of tramadol has been shown in both clinically and laboratory studies (10). According to this action, pretreating the vein with i.v. tramadol has proved to be effective in preventing propofol injection pain in adults, the incidence of tramadol treated patients was 23% vs 69% in the control group (11). In the present prospective, randomized study, we compared pretreatment with ondansetron versus tramadol for prevention of propofol injection pain.

II. Materials And Methods

The present prospective, randomized study was conducted in the Postgraduate Department of Anaesthesiology and Intensive Care, Government Medical College and Associated Hospitals, Jammu. After obtaining approval from hospital ethics committee, a total of 60 patients, ASA grade I/II were taken up in the study in the age group of 18 to 60 years of either sex scheduled for routine elective surgical procedure under general anesthesia with endotracheal intubation.

Patients excluded were those who had difficulty in communication, had history of adverse effects to propofol, study drugs, patients who required rapid sequence induction, having difficulty in venous access, presence of hepatic or renal dysfunction, patients with cardiac failure, rhythm abnormalities, patients with seizure disorder, history of drug abuse, uncontrolled hypertension, morbidly obese patients, pregnant and lactating women, and patients who received any kind of analgesic or sedative in the 24 hour prior to surgery Informed written consent was taken from each patient fulfilling inclusive criteria. Pre-anaesthetic check-up was done a day before surgery including a detailed history, a thorough physical and systemic examination and relevant demographic characteristics and baseline haemodynamic parameters were recorded.

Routine investigations included haemoglobin, bleeding/clotting time, platelet count, routine urine test, electrocardiogram, serum urea, serum creatinine, serum electrolytes, blood sugar and radiograph chest. No premedication other than the study drug was administered to the patients. The patients were fasted for 8 hours preoperatively. In the operating room, monitors including non-invasive arterial pressure, electrocardiography, and pulse oximetry were applied. A 20 gauge i.v. cannula was secured in the vein on the dorsum of the non-dominant hand. Depending upon the drug used for premedication, patients were randomly allocated to three groups (Group I, Group II or Group III) using computer generated table with random numbers.

The study drug kept at room temperature was divided into equal volumes of 2 ml with addition of normal saline. The patients enrolled were divided randomly into three groups of 20 patients each. Group I received 2 ml of ondansetron intravenous (2 mg/ml). Group II received 2 ml of 50 mg tramadol intravenous in saline. Group III received 2 ml of 0.9% normal saline intravenous. The patients were asked to report their pain according to the scale provided to them in the form of none, mild, moderate, and severe (verbal rating scale) (12).

A 20 G intravenous cannula was placed in a vein on the dorsum of the hand. All drugs were administered in a dedicated intravenous line connected to this cannula. Another cannula was placed in a vein of the other hand for infusion of i.v fluids. The mid arm of the side on which cannula was placed on the dorsum of hand was manually occluded by an assistant. The study drugs were randomly handed for injection to the anaesthetist before injecting the study drugs. The study drug was then injected and maintained in the vein for 1 minute. After 1 minute, the manual occlusion was removed and followed immediately by i.v injection of propofol 2 ml over 4 seconds. 15 seconds later, the patient were asked by a blinded investigator to rate immediately any sensation of pain during injection of propofol. The patients were asked standard questions regarding the comfort of the injection and were continuously observed for vocal response, facial grimacing, arm withdrawal, or tears suggesting severe pain. The data for each case were noted down on a proforma prepared specially for the study and it was subjected to statistical analysis.

After the assessment of pain, induction of anesthesia was completed with the remaining dose of propofol, and tracheal intubation was facilitated with the injection of succinylcholine. Anesthesia was maintained with injection of vecuronium, oxygen, nitrous oxide (66%) and isoflurane on intermittent positive pressure ventilation. Statistical testing was conducted with the statistical package for the social science (SPSS) for Windows. Demographic data was presented as mean ± standard deviation and compared utilising Student's *t*-test. Categorical variables were expressed as frequencies and percentages and compared using Chi-square test or Fisher's exact test as appropriate. For all statistical tests, $p<0.05$ was taken to indicate a significant difference.

III. Results

Patients were randomly distributed in three groups of 20 patients each. Mean age of patients in Group I (i.v. ondansetron) was 37.6 years, in Group II (i.v.tramadol) 40.75 years and in Group III (i.v. normal saline) was 40.45 years. There as equal number of male and female patients in Group I, while in Group II and Group III respectively female patients (60%) slightly dominated male patients. The mean weight in all the three groups was comparable. In Group I it was 78.33 kg, in Group II 82.13 kg and in Group III it was 80.70 kg. American Society of Anesthesiologists (ASA) patient acuity classification I dominated in all the three drug groups with 75%, 70% and 70% in Group I, Group II and Group III respectively. Mean baseline vital characteristics like heart rate, peripheral oxygen saturation and noninvasive blood pressure of the patients in all the three groups were comparable (Table 1).

Table 1. Mean Baseline Heart Rate, Peripheral Oxygen Saturation And Noninvasive Blood Pressure Of The Patients In The Three Groups

Variable	Group I (n=20) (i.v. Ondansetron) Mean ± Standard deviation	Group II (n=20) (i.v. Tramadol) Mean ± Standard deviation	Group III (n=20) (i.v. Normal Saline) Mean ± Standard deviation
Mean heart rate (beats/minute)	75.75 ± 7.58	76.95 ± 6.61	75.4 ± 7.65
Mean SpO_2 (%)	98.4 ± 0.88	98.2 ± 0.83	98.25 ± 0.91
Mean SBP (mmHg)	121.35 ± 10.68	123.6 ± 10.65	122.1 ± 11.41
Mean DBP (mmHg)	74.9 ± 5.25	74.8 ± 6.66	73.3 ± 5.95

Most of the elective surgeries undertaken in all the three groups are those of laproscopic cholecystectomy, followed by percutaneous nephrolithotomy. Other surgeries undertaken were septoplasty, transurethral resection of bladder tumor, functional ensocopic sinus surgery, laproscopic hysterectomy and tonsillectomy. As per McCririck and Hunter scale, no pain was reported by 75%, 85% and 20% patients in Group I, Group II and Group III respectively. Mild pain was reported by 25%, 15% and 45% patients in Group I, Group II and Group III respectively. No patients in Group I and in Group II reported moderate or severe pain, whereas 15% and 20% respectively reported moderate and severe pain in Group III (Table 2).

Table 2. Distribution of the patients according to degree of propofol induced pain in three groups

Degree of pain	Group I (n=20) (i.v. Ondansetron) No. (%)	Group II (n=20) (i.v. Tramadol) No. (%)	Group III (n=20) (i.v. Normal Saline) No. (%)
None (0)	15 (75.00)	17 (85.00)	4 (20.00)
Mild (1)	5 (25.00)	3 (15.00)	9 (45.00)
Moderate (2)	0	0	3 (15.00)
Severe (3)	0	0	4 (20.00)
Total	**20 (100.00)**	**20 (100.00)**	**20 (100.00)**

On comparing results of incidence of propofol induced pain, no significant difference was seen when i.v. ondansetron drug group (Group I) was compared with i.v. tramadol drug group (Group II). However, statistically significant difference was observed when i.v. ondansetron drug group is compared with i.v. normal saline group (Group III) (p=0.001), as well as when i.v. tramadol drug group was compared with i.v. normal saline group (0.000) (Table 3). This shows that pain intensity was significantly less in patients receiving ondansetron and tramadol drugs for pretreatment than those receiving normal saline, while the efficacy of ondansetron in alleviating the incidence and severity of propofol induced pain was no different from tramadol.

Table 3. Intergroup comparison of i.v. ondansetron (Group I), i.v. tramadol (Group II) and i.v. normal saline (Group III) according to propofol induced pain

Comparison	No Pain No.	Incidence of Pain No.	Statistical inference (Fisher's test)
Group I versus Group II	15 versus 17	5 versus 3	p=0.69*
Group I versus Group III	15 versus 4	5 versus 16	p=0.001**
Group II versus Group III	17 versus 4	3 versus 16	p=0.000**

*Not significant; **Significant

IV. Discussion

Several methods for prevention of pain on propofol injection have been tried. These include: using large antecubital vein to inject propofol, varying the speed of propofol injection, use of aspirin and other non

steroidal anti-inflammatory drugs, the use of local anesthetics, dilution of propofol, opioids, metoclopramide, thiopentone, ketamine and aspiration of blood into the propofol syringe. The methods have been tried, with varying success, to reduce the incidence and severity of propofol injection pain (13). Nakane and Iwama suggested that the pain produced by propofol injection is due to activation of plasma kallikreinkinin system by lipid solvent, and this result in formation of bradykinin. It modifies vessel, and permeability is increased, which causes more drug to come in contact with free nerve endings (14).

Yull *et al.* demonstrated that pain on injection of propofol may be related to release of local kininogens and that the nonsteroidal anti-inflammatory drugs (*e.g.* ketorolac) may have a role in reducing that pain (15). In the present study, 60 patients were equally distributed (n=20) in Group I (i.v. ondansetron 2 mg/ml), Group II (i.v. 50 mg tramadol 2 ml) and Group III (0.9% normal saline 2 ml) according to their age and weight. A higher number of female patients in the study were due to the fact that most of the operations performed were cholecystectomy, as cholelithiasis has a female preponderance. All pretreatment drugs were preceded by manual occlusion of vein for 1 minute. Propofol in a very subanesthetic dose was administered after release of venous occlusion and then pain was assessed with a four point scale.

In our study, it was found that both ondansetron and tramadol drugs significantly reduced the pain on propofol injection compared to the normal saline group. Ondansetron was found to be almost as effective as tramadol in reducing propofol induced pain. Ambesh *et al.* conducted a randomized, controlled, double-blinded design to study the effect of ondansetron pretreatment on the pain produced by the i.v. injection of propofol. They found that pain was reduced significantly in the ondansetron group ($p<0.05$). In our study, we also found that ondansetron was quite effective in reducing propofol induced pain ($p=0.001$) (16). Wong and Cheong studied the role of tramadol in reducing pain on propofol injection. They found that there was a significant reduction in the incidence of pain associated with propofol administration in patients pretreated with lignocaine and tramadol ($p<0.05$). In our study, we found that tramadol was also very effective in reducing propofol induced pain ($p=0.000$) (17).

In our study, there was no case of moderate or severe pain in either ondansetron or tramadol groups. On comparing results of incidence of propofol injection pain, no significant difference ($p>0.05$) was seen when i.v. ondansetron drug group was compared with i.v. tramadol drug group. Memis *et al.* compared the efficacy of tramadol and ondansetron in minimizing the pain due to injection of propofol in 100 patients. They concluded that tramadol and ondansetron are equally effective in preventing pain from propofol injection (9). Our results are also consistent with their study ($p>0.05$). Both the study drugs significantly reduced the pain on propofol injection compared to the normal saline group. Tramadol was slightly more effective than ondansetron in reducing the incidence of pain on propofol injection. Ondansetron has the ability to block sodium channels. Peripheral 5-HT3 receptors involve nociceptive pathways (7). Ondansetron binds to the opioid μ receptors in humans and exhibits agonist activity (18). As a result of its multifaceted actions as a Na channel blocker, a 5-HT3 receptor antagonist, and μ-opioid agonist, ondansetron may potentially be used to alleviate pain produced by a drug similar to propofol. Ondansetron is mostly used at the time of induction of anesthesia for the prevention of post operative nausea and vomiting (PONV) (19).

Tramadol, is a centrally acting weak μ-receptor agonist, inhibits noradrenaline re-uptake as well as promotes seratonin release and can be used to treat moderate and severe pain (20). In addition to its systemic effect, the local anesthetic effect of tramadol on peripheral nerves has been shown in both clinically and laboratory studies (21). More complete data have produced the effect of tramadol on the release of monoaminergic neurotransmitters in the central nervous system and its agonist action at peripheral and central opioid receptors. It has been confirmed in humans that the analgesic effect of tramadol is apportioned between the opioid and monoaminergic components (22).

V. Conclusion

Intravenous ondansetron is equally effective and can be used for relief of pain due to propofol injection without any significant side effects. Also, ondansetron can be used alternatively to injection tramadol as seen in the present study.

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