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ORIGINAL RESEARCH ARTICLE

PRETREATMENT WITH ONDANSETRON IN PREVENTION OF PAIN ON PROPOFOL INJECTION

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Key words: Ondansetron; Pain; Propofol.

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ABSTRACT

Background: Pain on intravenous injection of propofol is seen in almost 70% of patients without any pretreatments. This study was conducted to evaluate the effect of ondansetron in reducing the occurrence of pain on intravenous injection of propofol.

Methods: Two hundred and thirty-two patients aged between 18- 60 years of either sex belonging to ASA status I and II, scheduled for laparoscopic cholecystectomy under general anesthesia at Chitwan Medical College, Bharatpur, Nepal, from from September 1, 2020 to March 31, 2021 were recruited in this study. They were assigned randomly into two groups with 116 participants in each, where Group 1 received 2 ml (4 mg) of ondansetron and Group 2 received 2 ml of 0.9% saline (placebo) intravenously as the pretreatment solution prior to injection of propofol for induction of general anesthesia. The overall incidence of pain in the saline group was 84.5% compared to 48.3% in the ondansetron group (P < 0.001).

Result: Pain was of mild intensity in most patients who belonged to the ondansetron group (33.6%) whereas it was of moderate intensity in most participants of the saline group (54.3%). Few patients in the study group experienced severe pain (0.9%) as compared to the placebo group (9.5%) with P < 0.001.

Conclusion: Therefore, it was concluded that pretreatment with ondansetron may be a useful intervention in reducing the incidence of pain on intravenous propofol administration without any adverse effects in significant number of patients.

Keywords: Ondansetron; Pain; Propofol.

INTRODUCTION

Propofol is one the most commonly used intravenous (IV) anesthetic for induction and maintenance of general anesthesia (GA). It is favored for its rapid onset, short duration and a good recovery. Pain on propofol injection (POPI) has been seen in about 70% of the patients, without any pretreatment and was rated as the 7th most unwanted outcome of clinical anesthesia.[1] Many methods have been described to alleviate POPI, including the use of local anaesthetics.[2] Ondansetron, a 5-HT_3 antagonist, is commonly used prophylactic measure to reduce postoperative nausea and vomiting (PONV). Ye and colleagues reported that ondansetron blocks sodium channels in rat brain neurons. They also demonstrated that ondansetron was 15 times more potent than lidocaine as a local anaesthetic when injected under the skin.[3]

The effect of pretreatment with ondansetron for reducing POPI has been found to be comparable with lidocaine and magnesium sulphate.[4] However, there is relatively a few published data on the efficacy of ondansetron on POPI in our country. In our hospital, ondansetron has been routinely used for prevention of PONV for all cases scheduled for elective laparoscopic cholecystectomy but not for POPI. This study was therefore conducted with the aim to evaluate the effectiveness of ondansetron for POPI in our setting.

METHODS

This was a comparative observational study conducted at Chitwan Medical College, Bharatpur, Nepal from September 1, 2020 to March 31, 2021. After approval from the institutional ethical committee, 232 patients aged between 18- 60 years of either sex belonging to ASA status I and II, scheduled for elective laparoscopic cholecystectomy under general anesthesia were enrolled in the study. Exclusion criteria were patients who refuse to participate in the study, with known allergy to study drugs, who cannot communicate or speak, and patients with autonomic or peripheral neuropathy. Participants were randomized based on computer generated randomization list into two groups of 116 participants each. Patients in Group 1 were administered 2 ml (4 mg) of IV Ondansetron and those in Group 2 with 2 ml of 0.9% saline (placebo) intravenously, as the pretreatment solution prior to induction of general anesthesia

with propofol.

The day prior to the conduct of anesthesia while in surgery, a detailed preoperative history was obtained and physical examination done for each patient fulfilling the selection criteria. Related information including risk and benefits regarding the study was given to the participants and their attendants and written consent was obtained from all the participants. Patients were kept nil per oral for 8 hours prior to surgery.

On the day of the surgery, in the operation theatre, peripheral venous access was secured at the dorsum of the non-dependent hand with 18 gauze IV cannula and ringer's lactate infusion was started. Intraoperative fluid calculation was done as per Holliday-Segar method. Routine monitors for measuring vital parameters (heart rate, electrocardiogram, blood pressure, peripheral oxygen saturation and end tidal carbon dioxide) according to the ASA standards were attached to the patients and baseline blood pressure, heart rate, oxygen saturation values were recorded. After administration of 2 mg of IV midazolam for sedation, each patient of group 1 received 2 ml (4 mg) of ondansetron and those of group 2 received 2 ml of 0.9% saline while the venous drainage was occluded manually at mid arm by an assistant. The occlusion was released after 1 minute, followed by anesthetic induction with IV propofol 2 mg/kg, administered slowly over a running drip. No analgesics were given before propofol administration. The level of pain was assessed by a second, independent anesthesiologist who was unaware of the group to which the patient had been allocated. The patients were asked a standard question about the comfort of the injection; the verbal response and behavioral signs, such as facial grimacing, arm withdrawal, or tears, were noted. A score of 0-3, which corresponded to no pain or mild, moderate, and severe pain, was recorded (Table 1). Adverse effects, if any, were noted. Then analgesia was provided with IV Fentanyl and endotracheal intubation was facilitated with IV rocuronium. Anesthesia was maintained with isoflurane, vecuronium and oxygen + air. Other complications during extubation as well as in recovery room were noted.

Table 1: Assessment of pain[5]

Pain score	Degree of pain	Response
0	None	Negative response to questioning.
1	Mild	Pain reported in response to questioning only without any behavioural signs
2	Moderate	Pain reported in response to questioning and accompanied by a behavioural sign or pain reported spontaneously without questioning
3	Severe	Strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears

RESULTS

A total of 232 patients were enrolled in the study. Group 1: Ondansetron group (n = 116) and Group 2: 0.9% saline (n = 116). The baseline characteristics were comparable between the two study groups with no statistically significant difference (P > 0.05) (Table 2).

Table 2: Comparison of baseline characteristics of the study participants between the two intervention groups

Variables	Group 1 (n = 116)	Group 2 (n = 116)	p-value
Age (years)	40.8 ± 11.5	42.2 ± 11.6	0.35
Gender			
Male	26 (22.4)	22 (19.0)	0.52
Female	90 (77.6)	94 (81.0)	
Weight (kg)	63.7 ± 7.7	64.4 ± 7.8	0.45
Height (cm)	156.6 ± 4.4	155.6 ± 4.6	0.95
ASA status			
I	110 (94.8 %)	111 (95.7 %)	0.60
II	6 (5.2 %)	5 (4.3 %)	
Surgery duration (min)	86.1 ± 17.5	88.2 ± 16.7	0.46

Table 3: Comparison of pain scores and complications between the two intervention groups

Variable	Group 1 (n = 116)	Group 2 (n = 116)	P-value
Pain score			
0	60 (51.7)	18 (15.52)	<0.001
1	39 (33.6)	24 (20.7)	
2	16 (13.8)	63 (54.3)	
3	1 (0.9)	11(9.4)	
Complication			
1. Hiccup	3 (2.6)	2 (1.7)	0.54
2. Nausea/ Vomiting	1 (0.9)	1 (0.9)	0.39

The overall incidence of POPI was among 98 patients (84.5 %) in the placebo group compared to 56 patients (48.3%) in the ondansetron group (P < 0.001). Pain was of mild intensity in most patients in ondansetron group (33.6%) whereas it was of moderate intensity in most participants in saline group (54.3%). Fewer patients in the study group experienced severe pain (0.9%) as compared to the placebo group (9.5%) with P < 0.001. None of the patient in either group experienced pain or

discomfort during the injection of the pretreatment solution. Complications like hiccup (2.6% Vs 1.7%; P = 0.54) nausea and vomiting in recovery room (0.9% Vs 0.9%; P = 0.39) were observed in both the ondansetron group and saline group respectively (Table 3).

All the patients in ondansetron group complaint of significantly less Pain as suggested in Figure 1.

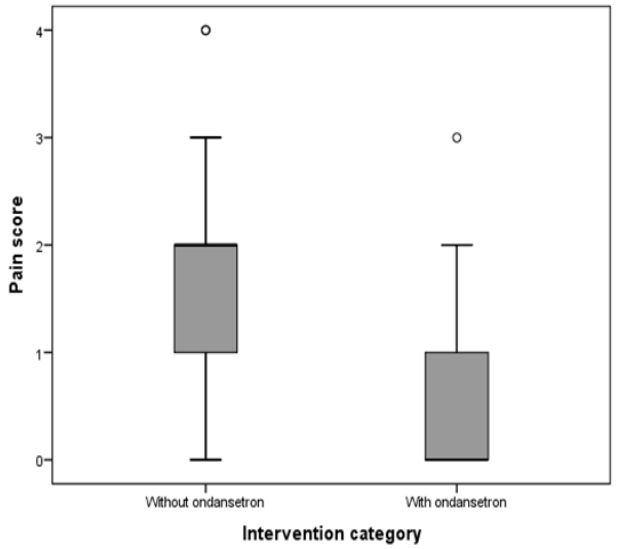

Figure 1: Box plot showing comparison of pain scores between the two intervention groups

DISCUSSION

In recent years quality assurance has been of great value for improving patient satisfaction. Pain on propofol injection can be very distressing and was reported by the patients as the 7^{h} most unwanted outcome of clinical anesthesia. Therefore, it needs to be addressed for standard anesthetic practice.[1] Several studies have shown the underlying mechanism of propofol-induced pain. The possible mechanism may be that propofol can activate the kallikrein–kinin system and release bradykinin, resulting in venous dilation and increased permeability, thereby increasing contacts between propofol aqueous phase and free nerve endings, causing POPI.[6]

Ondansetron, when administered intrathecally, ondansetron reduces the nociceptive responses of dorsal horn neurons in animals.[7] Ye et al. concluded that ondansetron is approximately 15 times more potent as local anesthetic than lidocaine in rats, and postulates this property contributes to its antiemetic action. Ondansetron exhibits agonist activity at the opioid [micro sign] receptors in humans.[3] Ondansetron through its multifaceted actions as a Na channel blocker, a 5-HT$_3$ receptor antagonist, and opioid agonist, it can potentially be used to alleviate pain.

In this study, we found that IV ondansetron was effective in reducing POPI with statistical significance (P < 0. 001). Most patients in the study group complained of POPI that was mild in nature in contrast to the participants in the placebo group, where maximal patients had moderate intensity pain. As for severe POPI, Ondensetron group recorded only a few cases compared to the 0.9 % saline group with statistical significance (P < 0.001).

In a systematic review and meta-analysis performed by Jalota L and colleagues, incidence of POPI was reported as 60% in patients without any pretreatment.[8] Manandhar S, Manandhar K. demonstrated that, POPI was found significantly higher in the placebo group compared to the ondansetron group (62.5% vs 35.4%). Similar to our finding, most patients in their study who belonged to ondansetron group had a mild dregree of POPI, whereas, a significant number of patients in the placebo group experienced pain of higher intensities.[9]

Study done by Ambesh SP and colleagues, showed that, the overall incidence of pain in the saline group was 55%, compared to 25% in the ondansetron group (P < 0.05). Fewer patients in the ondansetron group experienced severe pain compared to the saline group (7.5% vs 32.5%; P < 0.05) in their study thereby affirming our findings [7]. Pain is a subjective sensation and slight variation on pain scales in our study may be been noted due to variation in pain tolerance capacity of each individual.
In a meta-analysis, the effect of pretreatment with ondansetron for reducing POPI has been found to be comparable with lidocaine and magnesium sulphate.[4] Abdelnaser MA, Alfadel AA. in their study showed that incidence and severity of POPI was significantly in higher in the control group when compared to the group of patients receiving pretreatment with IV lidocaine or ondansetron, with ondansetron exhibiting superior effects than lidocaine for this purpose.[10]

CONCLUSION

In conclusion, OND pretreatment provides a simple and safe method of reducing the incidence of pain on injection of propofol with the added advantage of preventing PONV.

CONFLICT OF INTEREST: None

FINANCIAL DISCLOSURE: None

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