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Comparison of Pretreatment Effect of Ondansetron and Low Dose Lignocaine in Reducing Propofol Induced Pain on Injection: A Prospective Randomized Study

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Abstract

Background: Propofol is a commonly used intravenous induction agent but it is associated with intense pain on injection in majority of patients.Various methods have been studied to reduce the propofol induced pain. Lignocaine, a local anesthetic agent and Ondansetron, a $5HT_3$ receptor antagonist,both have been shown to effectively reduce the pain due to propofol injection. So aim of our study was to compare the efficacy of low dose lignocaine (0.1 mg/kg) and ondansetron (0.1 mg/kg) pretreatment to reduce the propofol induced pain on injection. *Methods:* The present study was conducted at our institute included one hundred adult patients of either sex, aged 18-60 years, with American Society of Anesthesiologists (ASA) grade 1 and 2 scheduled for various elective surgeries under general anesthesia. All the patients were randomly allocated into two groups of 50 patients each; Group L (Lignocaine group) received lignocaine (2%, preservative free) 0.1 mg/kg and Group O (Ondansetron group) received ondansetron 0.1 mg/kg (both diluted up to 5ml in normal saline) as pretreatment before induction of general anesthesia using propofol 1%, 2 mg/kg. A tourniquet was applied on the same upper arm with a pressure of around 70 mm Hg for venous occlusion to about 20 seconds. After giving the pretreatment drug, the tourniquet was released, propofol was administered thereafter and the patients were assessed for level of pain intensity using the scale advocated by McCririck and Hunter. *Results:* The incidence of propofol induced pain in Group L and Group O were 46% and 40% respectively.(P>0.05) In Group L, out of 23 patients, 6 patients recalled pain whereas in Group O, 13 patients recalled pain out of 20 patients, but both incidence and recall of pain were found to be statistically insignificant between two groups. (P>0.05) 24% patients in Group L and 16% patients in Group O had experienced post operative nausea and vomiting (PONV) which was also statistically insignificant (P>0.05). The various hemodynamic parameters remained stable. *Conclusion:* Although we had used lignocaine at its lower dose (0.1 mg/kg) as pretreatment but both lignocaine and ondansetron were found to be equally effective in reducing propofol induced pain on injection.

Keywords: Ondansetron; Lignocaine; Propofol; Pain; Injection.

Introduction

Propofol is a commonly used intravenous induction agent during general anesthesia. Propofol is a preferred drug for induction of anesthesia as it has rapid onset and short duration of action along with rapid recovery and a favorable side effect profile. However, an unacceptable side effect of the use of propofol for induction is its association with pain on injection in about 28 to 90% of patients which may produce intense agitation and interferes with smooth induction of anesthesia [1-3]. The pain associated with propofol injection may be extremely sharp, aching or burning in nature especially when given in small veins of dorsum of hand or forearm and many patients recall it as most painful procedure during induction of anesthesia [4].

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Various strategies have been adopted to reduce the incidence of pain during propofol injection including injection of propofol into a larger vein, mixing lignocaine with propofol, cooling or warming propofol, diluting the solution or pretreatment with other drugs like lignocaine, metoclopramide, magnesium sulphate, ondansetron, dexmedetomidine or opioids but all had variable results and none of the above strategies proved to be superior to other [5-8].

Lignocaine, an amide local anesthetic agent has been used since a long time in anesthetic practice and is well documented to reduce the incidence and severity of propofol induced pain on injection during induction of general anesthesia. The intravenous lignocaine is used in its preservative free form for this purpose [9,10].

Ondansetron, a $5HT_3$ receptor antagonist is commonly used to prevent post operative nausea and vomiting, however, it has some local anesthetic property also and has been shown to effectively reduce the pain due to propofol injection. Ondansetron is found to be 15 times more potent in producing numbness when injected under skin, as compared to lignocaine [11,12].

So with above hypothesis we conducted a prospective randomized study to compare the efficacy of low dose lignocaine (0.1 mg/kg) and ondansetron (0.1 mg/kg) pretreatment to reduce the propofol induced pain on injection in patients scheduled for various elective surgeries under general anesthesia.

Materials and Methods

After obtaining approval from institutional ethical committee and a written informed consent from the patients, this prospective randomized comparative study was conducted at our institute which included one hundred adult patients of either sex, aged 18-60 years, with American Society of Anesthesiologists (ASA) grade 1 and 2 scheduled for various elective surgeries under general anesthesia. The patients with ASA grade 3 and above, patients undergoing emergency surgeries, patients with known systemic disease, pregnant females, patients allergic to study drugs and patients with difficulty in communication were excluded from our study.

All the patients were randomly allocated into two groups of 50 patients each using computer generated table of random numbers and allocation concealment was done using sequentially numbered closed opaque sealed envelope technique. Group L (Lignocaine group) received lignocaine (2%, preservative free) 0.1 mg/kg and Group O (Ondansetron group) received ondansetron 0.1 mg/kg (both diluted up to 5ml in normal saline) as pretreatment before induction of general anesthesia using propofol 1%, 2 mg/kg. The study drugs were prepared by the anesthesiologist who was not directly involved in the study.

All the patients had undergone a thorough pre-anesthetic evaluation prior to day of surgery including complete history, general and systemic examination along with relevant investigations. The patients were kept nil per oral 6-8 hours before surgery and were given alprazolam 0.5 mg and ranitidine 150 mg orally the night before surgery. On arrival of the patient to operating room, standard monitors were attached and baseline vital parameters were recorded including arterial oxygen saturation (SpO_2),non invasive blood pressure (NIBP), electrocardiogram (ECG) and capnography ($EtCO_2$). A 20 G intravenous (IV) cannula was secured on the dorsum of left hand and lactated ringer solution was started. A pneumatic tourniquet was applied on the same upper arm with a pressure of around 70 mm Hg to occlude the venous drainage for about 20 seconds.

The pretreatment drugs either lignocaine (0.1 mg/kg) or ondansetron (0.1 mg/kg) was given thereafter through the secured intravenous line. After injecting the pretreatment drugs, the tourniquet was released and initially one-fourth of the total dose of propofol was administerd over 10 seconds.The patients were assessed for level of pain intensity just after injecting one fourth dose of propofol and then every 10-15 seconds till the patient had received the total calculated dose (2 mg/kg) of propofol and achieved adequate induction. After the induction, succinylcholine 2 mg/kg was given for endotracheal intubation and anesthesia was maintained with oxygen, nitrous oxide, isoflurane and vecuronium.

All the patients were already been explained about the scale to be used for assessment of propofol induced pain on injection advocated by McCririck and Hunter [13,14] before hand, which evaluated the severity of pain according to four point scale:

None (0) – No response to questioning;

Mild (1) – Pain reported in response to questioning only without any behavioural signs;

Moderate (2) – Pain reported in response to questioning and accompanied by behavioural signs or pain reported spontaneously without questioning;

Severe (3) – Strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears. Postoperatively, in recovery room all the

patients were asked for recall for pain if there was pain during propofol injection and incidence of pain was graded as no recall or recall of pain present.

The various hemodynamic parameters including heart rate (HR), systolic blood pressure (SBP), diastolic pressure pressure (DBP) and SpO_2 were recorded before induction, during induction, and thereafter at intervals of 2 min, 5 min,10 min intraoperatively and then at completion of the surgery. The side effect profile including post operative nausea and vomiting (PONV) was also observed postoperatively.

Statistical Analysis

Based on previous studies, a sample size of 50 patients in each group was calculated assuming the 80% incidence of propofol induced pain on injection and considering the 50% reduction in pain to be clinically significant with alpha error of 0.05 and 80% power (simultaneously assumed all drop out rates). All the data were represented as Mean ± S.D. and number (%). The results of comparison of both continuous and categorical data were analyzed using various statistical tools including Student's t-test and chi-square test or fisher's exact test. Statistical analysis was done using Statistical Packages for the Social Sciences (SPSS; Windows ver. 16.0, SPSS Inc., Chicago, IL,USA). A p value of <0.05 was considered to be clinically significant.

Results

The patients in both the groups were comparable with respect to their demographic datas including age, sex, weight and ASA grade, P>0.05 (Table 1).

While comparing pain during propofol injection in both groups, it was found that 54% of patients in Group L and 60% of patients in Group O had experienced no pain.The incidence of mild pain was 34% and 24% in Group L and Group O respectively. 10% of patients in both the groups had moderate pain whereas 2% of patients in Group L and 6% of patients in Group O had severe pain which was found to be statistically insignificant, P>0.05 (Table 2).

In Group L, out of 23 patients who had pain during propofol injection, only 6 patients recalled pain whereas in Group O, 13 patients recalled pain out of 20 patients, but was found to be statistically insignificant, P>0.05 (Table 3).

76% patients in Group L and 84% patients in Group O had no PONV while 24% in Group L and 16% in Group O had experienced PONV which was also insignificant statistically,P>0.05 (Table 4).

Table 1: Demographic data

Patient Characteristics	Group L (n = 50)	Group O (n = 50)	P Value
Age (yr.)	35.91 ± 12.81	37.21 ± 10.21	
Sex (M/F)	19 (38%) / 31 (62%)	20 (40%)/30 (60%)	
Weight (Kg)	47.8 ± 6.60	46.6 ± 3.64	> 0.05
ASA Grade (1/2)	29 (58%) / 21 (42%)	31(62%) / 19 (38%)	

*Data are represented as Mean ± SD and number(n) /percentage (%)
** P>0.05; not significant, Group L- Lignocaine, Group O- Ondansetron

Table 2: Pain scores (McCririck Hunter scale) in two groups

Pain Score	Group L (n = 50)	Group O (n = 50)	P Value
No Pain	27 (54%)	30 (60%)	> 0.05
Pain	23 (46%)	20 (40%)	
Mild Pain (1)	17 (34%)	12 (24%)	
Moderate pain (2)	5 (10%)	5 (10%)	
Severe pain (3)	1 (2%)	3 (6%)	

*Data are represented as number (percentage)
** P>0.05; not significant, Group L- Lignocaine, Group O- Ondansetron

Table 3: Recall of pain in two groups

Pain Recall	Group L (n = 50)	Group O (n = 50)	P Value
No (Absent)	44 (88%)	37 (74%)	>0.05
Yes (Present)	6 (12%)	13 (26%)	

*Data are represented as number (percentage)
**P >0.05; not significant, Group L- Lignocaine, Group O- Ondansetron

Table 4: Side effects (PONV) in two groups

PONV	Group L (n = 50)	Group O (n = 50)	P Value
No	38 (76%)	42 (84%)	> 0.05
Yes	12 (24%)	8 (16%)	

*Data are represented as number (percentage)
**P>0.05, not significant, Group L- Lignocaine, Group O- Ondansetron

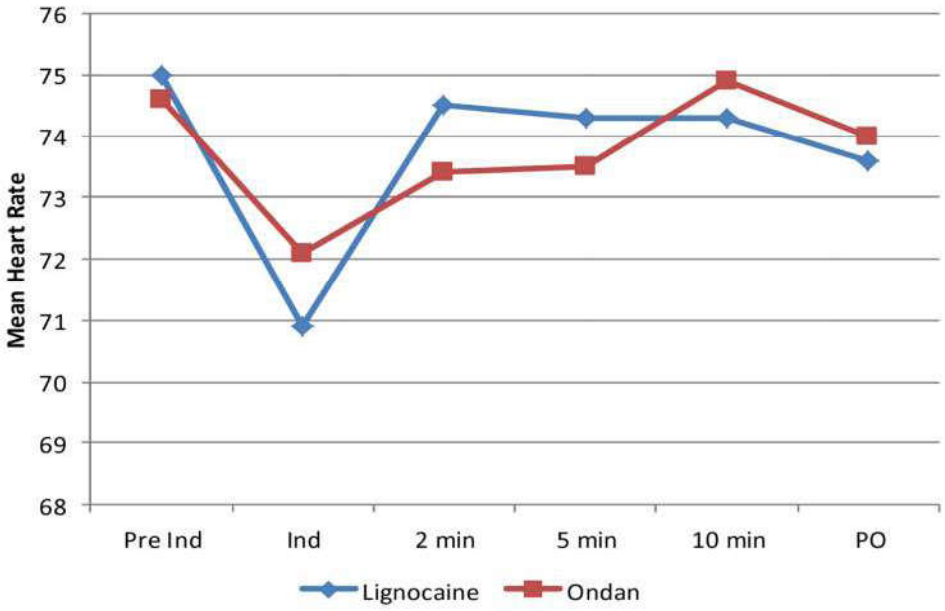

Fig. 1: Comparison of mean HR between two groups

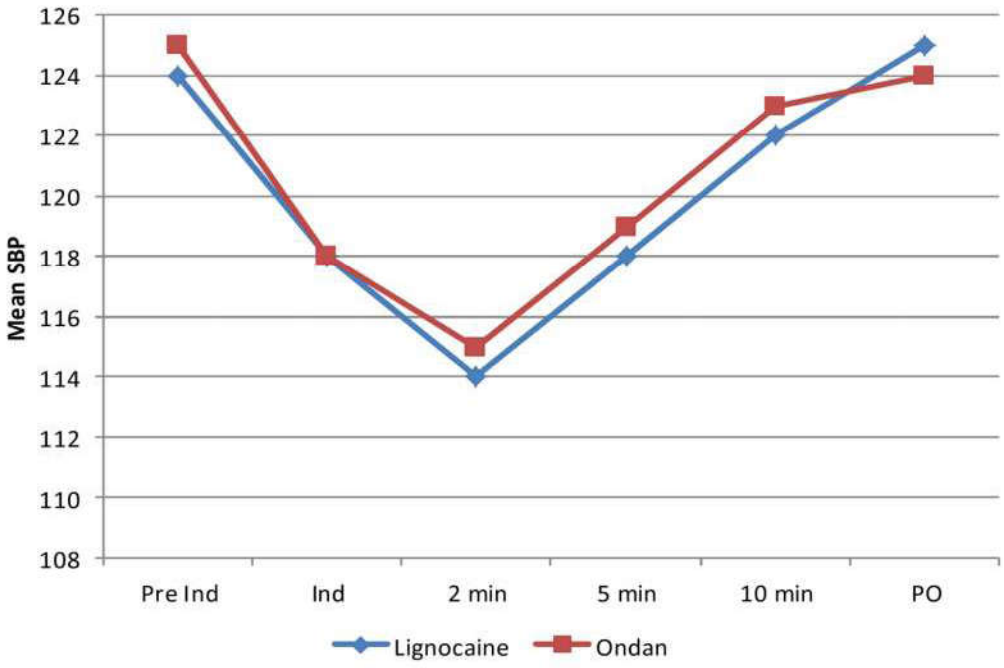

Fig. 2: Comparison of mean SBP between two groups

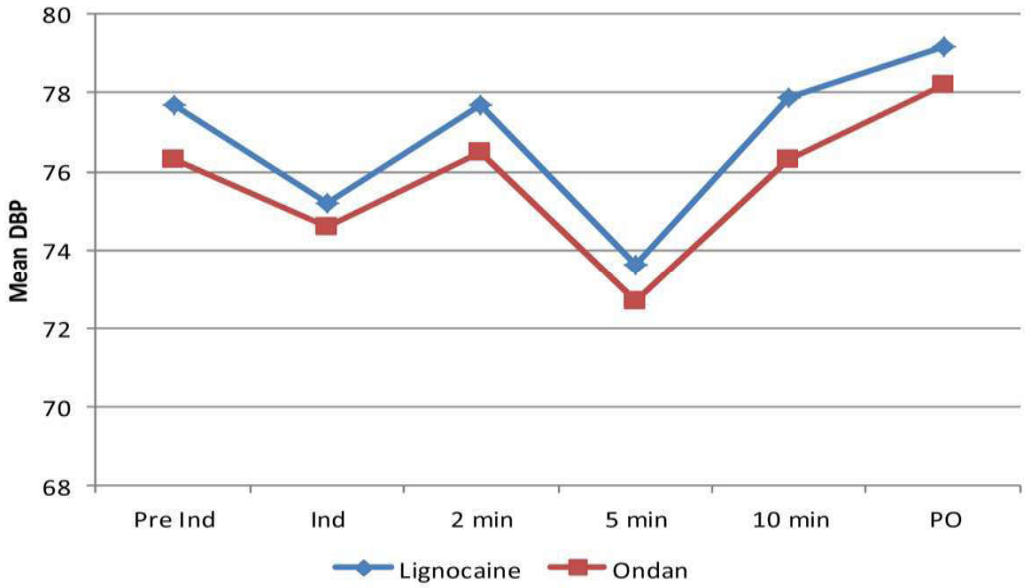

Fig. 3: Comparison of mean DBP between two groups

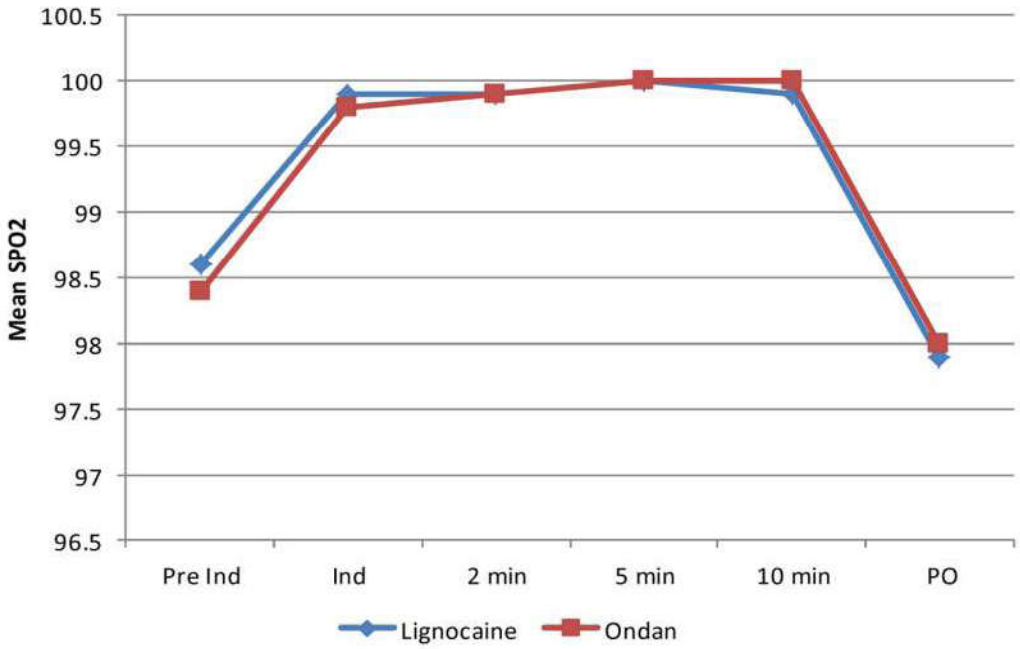

Fig. 4: Comparison of mean SpO_2 between two groups

The various hemodynamic parameters were compared at different time intervals including HR, SBP, DBP and SpO_2 before induction, during induction, at 2 min, 5 min, 10 min and postoperatively after completion of surgery and no significant changes were observed at any time interval,P>0.05. (Figure 1-4).

Discussion

Propofol has got popularity as an induction agent for general anesthesia especially in day care surgeries and for sedation in intensive care units. It provides excellent sedation, amnesia, anxiolysis along with added advantages of having antiemetic action and

suppression of airway reflexes during laryngoscopy and tracheal intubation. However, it is associated with various side effects including myoclonus, apnea, hypotension and pain on injection.The pain on injection due to propofol had been extensively studied so various studies were conducted to search for the most effective method or an ideal agent for reducing propofol induced pain on injection but none of them was found to be ideal with variable results [15,16].

The initial preparations of propofol produced more pain so it was reformulated to decrease the intensity of pain during injection but it was found that several other factors might be responsible for causation of pain [15]. Scott et al found that the intensity of pain was lesser when larger veins like antecubital veins were used for propofol injection and considered to be an important factor while administering propofol as the drug injected into larger veins have no contact with sensitive wall of veins [1]. However, we preferred to choose a larger vein on dorsum of hand to elicit the propofol induced pain on injection as chosing the antecubital veins as the site of injection might be uncomfortable along with increased tendency of venous occlusion. In previous studies, the incidence of pain on propofol injection was significantly reduced from 46% to 23% when it was given at around 4 degree centigrade because the cold temperature might cause relative inactivation of kinin cascade which is thought to be responsible for causation of pain [13]. However, in our study, the drug was kept at room temperature before administering to the patient.

Although various drugs have been studied for reducing the intensity of propofol induced pain on injection, the lignocaine was the most commonly used drug as pretreatment before propofol injection [17]. Subsequently the various doses of lignocaine were studied and variable results were found with different doses used. Gehan G et al showed in their study that lignocaine at a dose of 0.1 mg/kg had significantly reduced the incidence of pain but no significant improvement was noted with further incremental doses [16]. The dose of lignocaine used in our study was 0.1 mg/kg which is similar to one of the doses used in above study and was found to be effective in alleviating the propofol induced pain on injection.

Ondansetron is routinely used as a premedication for prevention of PONV at a dose of 0.1 mg/kg. Ye JH et al showed that ondansetron is more potent than lignocaine as local anesthetic. Similarly ondansetron has the property of blocking sodium channels along with $5HT_3$ receptor antagonist activity. It also has μ opioid agonist action which when combined with above properties proved to be useful in reducing the intensity of pain due to propofol injection [18]. Picard P et al found that pretreatment with lignocaine using tourniquet was the most effective method to reduce pain and similarly other drugs like ondansetron, opioids, metoclopramide were studied [19]. However, different methods were studied for pretreatment to be given either before propofol or with tourniquet or drug mixed with propofol. In our study,we have used tourniquet pressure of 70 mm Hg which was maintained for about 20 seconds duration during pretreatment and released prior to propofol injection. Similar method was adopted by Lee P et al [9] in their study too.

In our study,we have used four point verbal categorical scoring system advocated by McCririck and Hunter for assessment of propofol induced pain as it is simple and easily understood by the patients and the same scale had also been used in some previous studies too [5-8]. Other methods for assessment of pain i.e., Visual analog scale (VAS) might not be feasible due to rapid change in state of consciousness during induction of anesthesia which may result into false interpretation. Both ondansetron (0.1 mg/kg) and lignocaine (0.1 mg/kg) have significantly reduced the pain on propofol injection but no statistically significant difference was found between the two groups. 54% patients in lignocaine group and 60% patients in ondansetron group had experienced no pain. Ambesh SP et al found in their study that ondansetron had decreased pain in almost 50% of patients [11]. Similarly Kang WJ et al showed that about 60% of patients had no pain after pretreatment with ondansetron [20]. Similar results were also found in studies done by Sunny A et al[21] and Mohammadi et al [8] using almost similar doses of ondansetron. Zahedi H et al concluded that pain intensity was significantly lesser in patients who received pretreatment as ondansetron when compared to tramadol [22].

As far as lignocaine pretreatment is concerned none of the previous authors had studied the effect of such a low dose of lignocaine (0.1 mg/kg) to reduce propofol induced pain on injection in their studies other than Gehan et al. In a recent study by Singh HS et al, pretreatment with lignocaine (0.5 mg/kg) was found to be more effective when compared to dexmedetomidine in alleviating propofol injection pain [7]. Sumalatha GS et al also concluded that pretreatment with ramosetron 0.3 mg is equally effective as 2% lignocaine (0.5 mg/kg) [5]. Similar results were demonstrated by Singh D et al [6]. Gehan et al [16] reported that lignocaine at a dose of 0.1 mg/

kg significantly reduced propofol injection pain as 84% of patients had experienced no pain during the procedure. In our study the same dose of lignocaine was found to significantly reduce the pain but the effect was not as pronounced as the previous study.

Although the previous studies has shown significantly lesser incidence of pain on propofol injection when they had used lignocaine at higher doses i.e.,20 to 50 mg with or without venous occlusion [5-8, 23-25]. In our study,we have used lignocaine at a dose of 0.1 mg/kg which was lowest among all previous studies and was found to be equally effective when compared with ondansetron in reducing propofol induced pain. We have also reduced the venous occlusion time to only 20 seconds which might have given better results with such a low dose of lignocaine in decreasing propofol injection pain. One study showed that lignocaine (20 mg) had reduced both the incidence and severity of injection pain (32% had pain) during induction as well as recall of pain [25].

In our study, both lignocaine and ondansetron did not produce significant hemodynamic changes during induction.The patients in ondansetron group had an added advantage of having lower incidence of PONV.

Conclusion

Ondansetron (0.1 mg/kg) was found to be equally effective as lignocaine (0.1 mg/kg) to reduce the pain on propofol injection. Although we have used the lower dose of lignocaine in our study but it was found to has significant effect in reducing propofol induced pain on injection even at its lower dose.The ondansetron group had an added advantage of having lesser incidence of PONV. The incidence of postoperative pain recall was higher in ondansetron group but the patients in both groups remained hemodynamically stable perioperatively. So we concluded that ondansetron can be used as an effective alternative to lignocaine for propofol induced pain but even lignocaine can be used effectively at its lower dose (0.1 mg/kg).

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