Original Research Article

Prevention of immediate and delayed pain on propofol injection: A comparative study of pretreatment with lignocaine and ondansetrone, India

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Abstract

Introduction: Pain on propofol injection (POPI) is a common problem and can be very distressing to the patient. POPI could be immediate as well as delayed after 10–20s. Many studies have shown the efficacy of Lignocaine in reducing this pain. Ondansetrone is found to have 15 times more potent local anesthetic property compared to Lignocaine. In this study we have compared the efficacy of Ondansetrone and Lignocaine pretreatment in reducing pain on propofol injection. during induction of anaesthesia. **Aims:** To compare the efficacy of the pretreatment with Ondansetrone with that of Lignocaine in reducing the pain injection of propofol during induction of anaesthesia. **Materials and methods**: A randomized control study was conducted on ninety adult patients aged between 20-60 yrs belonging ASA 1 and ASA 2 grade scheduled for various elective surgeries. Patients were assigned to one of the three groups: Group 1 to receive 5ml of 0.9% saline, Group 2 to receive 50 mgs of Lignocaine diluted in 5 ml, Group 3 to receive 4 mgs of Ondensetrone diluted in 5ml. The injections were given on the dorsum of the hand using 20G cannula. Tourniquet applied above the level cannula was released after one minute and then calculated dose of propofol was injected at a rate of two ml every five seconds. During injections patients were asked about the pain or discomfort at the site of injection and their behavioural signs were assessed using Mc Cririck and Hunter scale. **Results:** Lignocaine and Ondansetrone significantly reduced the incidence and severity of pain on propofol injection more than placebo ($p < 0.01$-S). The efficacy of Ondensetrone in alleviating the pain on injection of Propofol was statistically comparable to that of Lignocaine. **Conclusion**: Intravenous Ondansetrone pretreatment may be used to reduce the incidence of immediate and delayed pain on injection of propofol.

Keywords: Pain, Propofol, Lignocaine, Ondansetrone.

Introduction

International association for study of pain (IASP)[1] defines pain as "an unpleasant emotional experience, actual or potential tissue damage, or described in terms of such damage".

Propofol has been widely used as an induction agent providing a smooth induction and rapid recovery. However, it often causes pain or discomfort on injection. Pain on propofol injection (POPI) is a common problem and can be very distressing to the patient. This has a high incidence of pain on injection when compared to other intravenous agents[2]. POPI could be immediate as well as delayed after 10–20s[2]. The incidence of pain on injection varies between 28% and 90%[2] in adults. Propofol induced pain ranked seventh among the 33 low morbidity clinical outcomes by expert anesthesiologists, when both clinical importance and frequency were considered[3]. Propofol has a high incidence of pain on injection when compared to other intravenous agents[2].

Several methods have been tried for the relief of pain on injection with varying degree of success. The methods which have been tried so far include, site of injection, decreasing the speed of injection, use of local anaesthetic, different temperatures, opiates, metoclopramide, ketamine, granisetrone[4-10].

The use of lignocaine to prevent pain on propofol injection is the most extensively studied technique and is the most common method used in clinical practice[6]. Many studies have shown the use of lignocaine to be effective. But the failure rate was between 13% and 32%. Ondansetron is a SHTs antagonist, commonly used for the prevention of post operative nausea and vomiting. It has got local anesthetic properties and is found to have 15 times more potent local anesthetic property compared to lignocaine[11].

With this background, we conducted a controlled study to determine the efficacy of ondansetrone and lignocaine pretreatment in reducing pain on propofol injection during induction of anaesthesia.

Aim s and objectives

To compare the efficacy of Ondansetrone pretreatment with Lignocaine pretreatment in reducing the immediate and delayed pain on injection of propofol.

Materials and methods

A prospective controlled study was undertaken at Karnataka Institute of Medical Sciences, Hubli during the year 2006-2007. The study design was approved by the institutional ethics committee.

Ninety inpatients aged between 20-60 years of either gender, belonging to ASA grade I and II scheduled for elective general surgical, gynaecological and orthopedic procedures were selected randomly after obtaining the informed consent. They were allotted randomly into one of the three groups equally: Group A, Group B and Group C. All the patients were evaluated on the previous day of surgery. Patients belonging to ASA grade I and II between 20-60 years of either gender were included. Exclusion criteria was: Patient refusal, patients with history of previous allergy to propofol and

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Lignocaine, patients with history of seizures, patients allergic to egg, patents with difficult airway, patients with history of chronic pain syndrome and who are on analgesics, pregnant and lactating women, patients with lipid metabolism disorder. Hemoglobin, Urine examination, Blood sugar, Blood urea, Serum Creatinine and Serum Electrolytes (if required), Electrocardiogram and Chest x-ray (if required) were done preoperatively. All patients were given diazepam 10 mg and Ranitidine 150mg orally on previous night and no pre medication on the day of surgery.

Pre induction monitoring
All patients were monitored with pulse oximetry, non invasive blood pressure and ECG. Further monitors were used depending upon the nature of surgery.

Details of the study
Patients were randomly allotted to one of the three groups. Group A: 5 ml of 0.9% saline, Group B: 50 mg of Lignocaine diluted to 5ml, Group C: 4 mg ondansetrone diluted to 5 ml.

All patients were cannulated with 20G cannula on the dorsum of the non dominating hand, without using Lignocaine or EMLA cream. No analgesics or intravenous fluid was started before induction.

Procedure
Depending upon the group of the patient, pretreatment solutions were prepared and kept in a 5ml syringe. An arm tourniquet was applied and inflated to 50 mmHg. The 5ml of pretreatment solution was administered over 20 seconds. After one minute tourniquet was released, then calculated dose of propofol (2.5mg/kg) at room temperature was administered at the rate of 2ml for every 5 seconds.

Assessment of pain
During the injection, patients were asked about the presence of pain or discomfort at the site of injection at every 5 seconds till the patients are unconscious. The verbal response and the behavioral signs, such as facial grimacing, arm withdrawal or tears were noted. Patients were looked for any adverse effects. Level of pain was assessed in accordance with the scale advocated by Mc Crirrick and Hunter.

Pain score

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

Induction and maintenance
Induction of anesthesia was continued with the remaining calculated dose of propofol. After the induction, the choice of anesthetic technique and drugs were left to the discretion of the attending anaesthesiologist.

Statistics
Statistical analysis of all the quantitative data was done by "student's t-test" (e.g.: age, pain score, heart rate, systolic blood pressure, diastolic blood pressure). Statistical analysis of all the qualitative data was done by using the 'Chi-((X^2) square test (e.g.: gender).
P value was calculated and interpreted as:
P value <0.05 statistically 'significant'(SIG).
P value <0.01 statistically 'highly significant'HS)
P value <0.001 statistically 'very highly significant'(VHS).
P value >0.05 statistically 'not significant'(NS).

Observation and results
Ninety patients belonging to the American Society of Anesthesiology physical status I and II were categorized into three groups and received the pretreatment solution. After one minute induction of general anaesthesia with propofol 2.5mg/kg was administered.
Group A: received 5 ml of 0.9% saline
Group B: received 50 mg of Lignocaine diluted to 5ml.
Group C: received 4 mg ondansetrone diluted to 5 ml.

Table 1: **Age Incidence in Different Groups (Data are mean ± standard deviation)**

Group	Mean	Standard deviation
Group A	38.93	10.092
Group B	39.93	10.748
Group C	36.93	10.799

P value=0.536 not significant

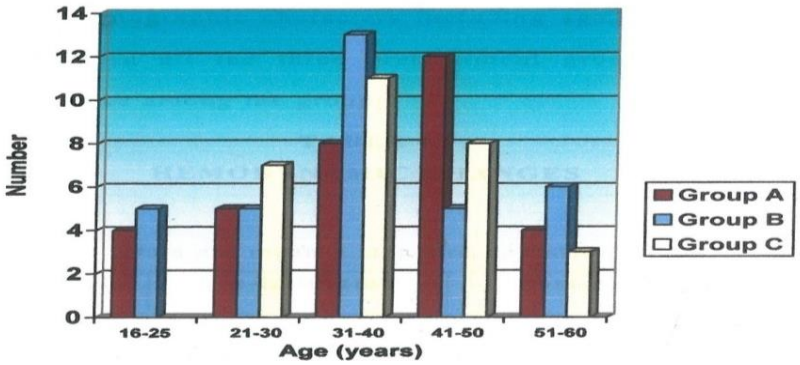

Fig 1: Age Distribution

Table 2: **Gender (Data In Numbers)**

Group	A	B	C	TOTAL
M	18	20	20	58
F	12	10	10	32
TOTAL	30	30	30	90

P = 0.824 Not significant

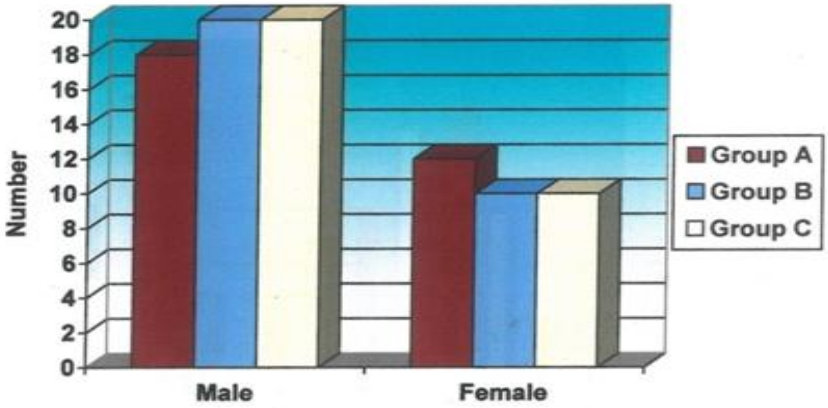

Fig 2: Gender Distribution

Table 3: Weight (Data are mean ± standard deviation)

Group	Mean	Standard deviation
A	61.83	10.235
B	65.16	12.169
C	64.93	10.976

P value=0.437 Not significant

Table 4: Hemodynamic Changes Pulse (Data are mean ± standard deviation)

Group	Pre-induction	Post-induction
A	75.2718.333	73.83±7.777
B	78.17±8.302	77.13±8.701
C	75.80±8.727	75.37±8.381

P=0.521 Not significant

Table 5: **Blood Pressure (Systolic, in mmHg) (Data are mean ± standard deviation)**

Group	Pre-induction	Post-induction
A	124.00±9.006	105.90±9.622
B	126.47±11.076	106.2719.766
C	125.6719.144	106.3019.774

P = 0.529 not significant.

Table 6: **Blood Pressure (Diastolic, in mmHg) (Data are mean ± standard deviation)**

Group	Pre-induction	Post-induction
A	75.77+6.714	62.6715.927
B	77.6717.774	63.3316.397
C	77.5316.882	63.6014.530

P' = 0.521 Not significant

Table 7: **Incidence of Pain On Propofol Injection (data are in numbers and percentages)**

	Group A	Group B	Group C	Total
No pain	5(16.7%)	24 (80%)	17 (56.7%)	46 (51.1%)
Pain	25 (83.3%)	6 (20%)	13 (43.3%)	54 (49.9%)
Total	30 (100%)	30 (100%)	30 (100%)	90 (100%)

P<0.005 significant

Table 8: Pain Relief

	X^2	P value	Inference
Group A Vs B	21.624	<0.0001	Very highly significant
Group A Vs C	9.284	0.0032	Highly significant
Group B Vs C	3.954	0.138	Not significant

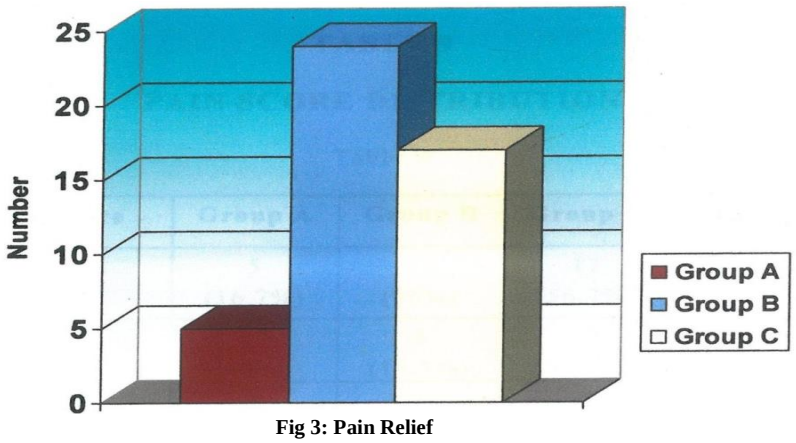

Fig 3: Pain Relief

Table 9: Pain Score Distribution

Pain score	Group A	Group B	Group C	Total
0	5 (16.7%)	24 (80%)	17 (56.7%)	46 (53.3%)
1	12 (40%)	4 (13.3%)	10 (33.3%)	26 (28.9%)
2	8 (26.7%)	2 (6.7%)	2 (6.7%)	12 (13.3%)
3	5 (16.7%)	0 (0%)	1 (3.3%)	6 (6.7%)
Total	30 (100%)	30 (100%)	30 (100%)	90 (100%)

(Data are in numbers and percentages)

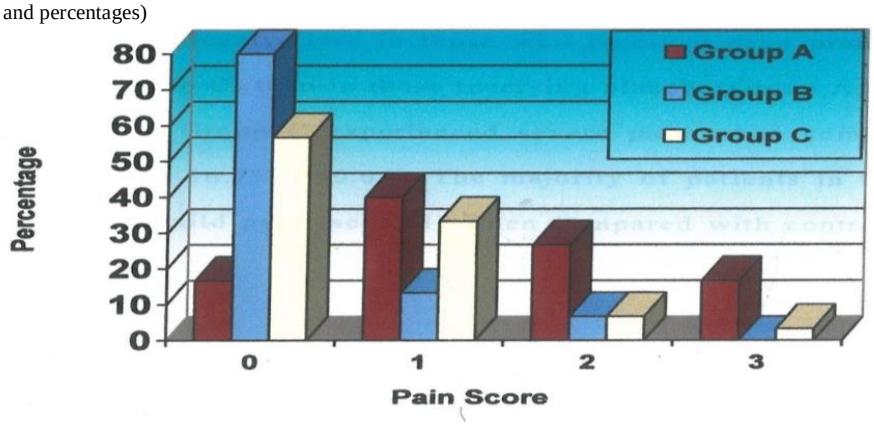

Fig 4: Pain Score Distribution

Table 10: Side Effects (data are in numbers and percentages)

Side effects	Group A	Group B	Group C	Total
Nil	24 (80%)	27(90%)	25(82.5%)	76(83.6%)
Head ache	1(3.3%)	0(3.3%)	1(3.3%)	2(2.2%)
Dizziness	1(3.3%)	0	2 (6.6%)	3(3.3%)
Sedation	1(3.3%)	0	1(3.3%)	2(2.2%)
Rashes	2(6.6%)	1(3.3%)	0	2(2.2%)
Myoclonus	1(3.3%)	2(6.6%)	1(3.3%)	4(4.4%)
Total	30(100%)	30(100%)	30(100%)	90(100%)

P = 0.439 Nothing significant.

Demographic data

The age distribution in all the groups was similar and was not Statistically significant (Table 1, Fig. 1).

The gender distribution in all the groups was comparable and was not statistically significant (Table 2, Fig 2). The mean weight in all the groups was comparable and statistically insignificant.

Patient's demographic characters including age, gender and weight were comparable in all the three pretreatment groups. There was no

statistical difference among the groups (Table 3). The change in pulse rate after induction was similar in all pretreatment groups and there was no statistical difference (Table 4).
All the pretreatment/ test drugs affected the systolic blood pressure to a similar extent and were not statistically significant (Table 5).
The change in post induction diastolic blood pressure was comparable in all three groups (Table 6).
Incidence of pain in group A (Placebo) was 83.3% compared to group B (lignocaine) and group C (ondansetrone) which were 20% and 43.3% respectively (Table 7,8). Nearly 80% of patients given lignocaine and 65% of patients given ondansetrone did not have pain on injection of propofol. This contrasted with the 83% incidence of pain in the placebo group given normal saline. Statistical analysis was done using Chi square test. Statistical analysis showed that the incidence of pain in group A was significant ($p<0.01$), than the other two groups. The inter group comparison between lignocaine and ondansetrone showed that both reduced pain on protocol injection but the incidence of pain relief in lignocaine was better than ondansetrone group. Statistical analysis showed that the incidence of pain relief between Lignocaine and ondansetrone was not significant (Fig.3).

Analysis of pain score

Analysis of pain score (Table 9), revealed that 16.7% of patients in Group A had no pain (score 0), 40% had mild pain (score 1), 8% had moderate pain (score 2) and 5% had severe pain (score 3).
In Group B, 84% of the patients had no pain (score 0), 13.3% had mild pain (score 1), 6.7% had moderate pain (score 2) and none had severe pain (score 3).
In Group C, 56.7% of patients had no pain (score 0), 33.3% had mild pain (score 1), 6.7% had moderate pain (score 2) and 1 had severe pain (score 3).
Inter group comparison of pain score revealed that, the intensity of the pain was significantly less in those who received drug pretreatment (Group B and Group C) than in those receiving placebo (Group A;$P<0.05$). Fewer patients in Group C experienced severe pain when compared to Group A (3.3% vs. 16.7% $P<0.05$). The majority of patients in Group .B and Group C had mild pain (score 1) when compared with control group (Group C) (Table 9, Fig. 4).
Statistical analysis showed that the there were no significant adverse effects between the groups (Table 10).

Discussion

Propofol causes pain at injection site during induction. Incidence of pain varies from 28 - 90% in adults which limits the use of propofol[2]. The immediate pain is due to irritation of vein endothelium whereas delayed pain is due to the release of mediators such a kininogen from kinin cascade. Pain on Propofol Injection (POPI) has also been described as angialgia by some meaning that the pain is due to vascular involvement. POPI is immediate as well as delayed after 10–20s[2].
A large number of trials have identified several factors contributing to a high incidence of pain with propofol, and several strategies have evolved to minimize both the incidence and severity of pain.
Lignocaine the popular local anaesthetic, either premixed or as pretreatment is the most common and proven method to reduce the pain of propofol injection used in clinical practice[6]. In a quantitative systemic review on prevention of pain on injection of propofol Picard and Martin[12] concluded that, for best prevention of pain on injection with propofol, lidocaine 0.5mg/kg should be given with rubber tourniquet before the propofol injection.
Ondansetron, a 5 HT3 antagonist is another agent which has been tried in alleviating the pain on injection of propofol because of its local anaesthetic property, supplemented by its proven anti emetic activity[11].
In a comparative study Memis and associates[13] observed tramadol and ondansetrone equally effective in preventing pain on propofol injection and favoured ondansetrone for the added benefit of prevention of postoperative nausea and vomiting in this group.
In our institute, we commonly use propofol as induction agent for various surgeries under general anaesthesia and we decided to conduct a prospective controlled study to compare the efficacy of ondansetrone in reducing the pain on injection of propofol to that of lignocaine.
This study was conducted on ninety patients belonging to American Society of Anaesthesiologists physical status I and II posted for various surgeries under general anaesthesia at Karnataka Institute of Medical Sciences Hubli.
Selected patients were categorized into three groups. Each group received different pretreatments to reduce the pain on injection of propofol.
Patients in group A received 5 ml of 0.9% normal saline pretreatment with tourniquet before the injection of propofol. We used this group as control group. In the study groups, group B received 50 mg of Lignocaine diluted to 5ml as pretreatment and patients in group C received ondansetrone 4mg diluted to 5ml as pretreatment.
The demographic profile was similar in all the three groups. There was no statistical difference of age, gender and weight between groups (Table 1, 2 and 3).

Incidence of Pain

In our study pain was assessed using the scale used by Mc'Crirrick and Hunter. The incidence of pain in control group (group A) was 83.3% which is comparable to the wide range of incidence observed in other studies (28-90%)[6].
In group B (who received lignocaine 50 mg pretreatment), the incidence of pain reduced to 20% which is statistically significant. ($p<0.005$)(Table 7, Fig 3).
Various other studies have shown similar decrease in the incidence of pain by using lignocaine pretreatment[6].
Johnson RA et al[15] studied the effect of lignocaine pretreatment in a dose of 20 mg and 40 mg on pain produced by intravenous injection of propofol. Pain reduced significantly in both the groups but more in the group in which dose of 40 mg was used. They found incidence of 18% pain in patients who received 40mg lignocaine pretreatment. Our finding correlates with their finding.
Scott RP et al[4] in a multi centric evaluation found that lignocaine 10mg used either as a pretreatment or mixed with propofol reduced the incidence of pain from 28.5% to 8.8% but they did not differentiate between the methods.
In the present study, in group C (ondansetrone 4 mg pretreatment), the incidence of pain was 43.3% compared to 83.3% in the control group (group A) ($p<0.005$) (Table 7, Fig 3). This decrease in incidence is statistically significant and comparable to other studies.
Ambesh et al[14] in their study on ondansetrone pretreatment to alleviate pain on propofol injection found the overall incidence of pain in placebo group was 55% compared to 25% in ondansetrone group. **Incidence of Pain Relief**
Only 16.7% of patients in control group (group A) had no pain, which indicates low incidence of pain relief in control group where only normal saline pretreatment was used.
In group B where patients were pretreated with lignocaine 50 mg, the pain relief was in 80% of patients which was clinically and statistically significant. In quantitative systemic review on prevention of pain on injection of propofol, Picard and Martin[12] found overall 50-70% pain relief in studies where lignocaine pretreatment was used. They also suggested that, for the best prevention of pain on injection of propofol, lidocaine 0.5 mg/kg should be given with tourniquet before the injection of propofol.
In patients who received ondansetrone 4mg as pretreatment (group C), pain relief was found in 56.7%, which is statistically significant (Table 8, Fig 3).
The amount of pain relief in our study is comparable to the study done by Ambesh et al[14]. In their study they observed 65% of pain relief in the group who received ondansetrone as pretreatment.

Memis D et al[13] in their study compared the ondansetrone and tramadol in reducing the pain on injection of propofol. They found 60% incidence of pain relief in patients who received ondansetrone as pretreatment.When we compared the pain relief between the study groups and the control, we found that there is statistically significant decrease in the incidence of pain when either lignocaine (group B) or ondansetrone (group C) pretreatment was used. The pain relief was clinically more in the group B, where lignocaine pretreatment was used compared to the group C where ondansetrone pretreatment was used. But this clinical observation was not statistically significant ($p = 0.138$). (Table 8, Fig 3). **Severity of Pain**

In our study analysis of severity of pain was done by using a scale used by McCrick and Hunter. The same scale was applied by most of the studies on prevention of pain on injection of propofol.

We observed that 16.7% patients in control group (group A), experienced severe pain (score 3) compared to 0% and 3.3% in Lignocaine (group B) and ondansetrone (group C) respectively. The incidence of severe pain is significantly reduced in group B and C. (Table 9, Fig 4).Similar reduction in the incidence of severe pain (score 3) was found in other studies when Lignocaine was used as pretreatment. Memis D et al[13] in their study found only 6% of patients in the ondansetrone group had severe pain which is comparable with our observation.The incidence of mild to moderate pain 43.3% in control group and reduced to 20% and 30% in Lignocaine (group B) and ondansetrone group (group C) respectively. On comparison between ondansetrone and lignocaine, we observed that ondansetrone was less efficacious than Lignocaine in reducing the incidence of pain, but the patients who experienced the pain in ondansetrone group had mild to moderate degree of pain. Thus we found that ondansetrone is able to reduce the severity of pain. (Table 9, Fig 4).A similar study was conducted by Ambesh P et al[14] in which they compared the efficacy of ondansetrone 4mg (as 2mg/mL solution) pretreatment with placebo (2ml of normal saline). The results of their study showed that the overall incidence of pain in the saline group was 55%, compared with 25% in the ondansetrone group ($P < 0.05$). Fewer patients in the ondansetrone group experienced severe pain (7.5% vs. 32.5%; $P < 0.05$). The number of patients who experienced mild to moderate pain was 22.5% and 17.5% in the saline and ondansetrone groups respectively. The change in pulse rate and fall in blood pressure among the study and study groups had similar trend and there was no statistical difference. All the patients were followed up for presence of any side effects of the drugs used in the study like, head ache, dizziness, sedation, rashes and myoclonus. Side effects were minimal in all the groups and were clinically insignificant. (Table 10).

Conclusion

Intravenous Ondansetrone pretreatment is less efficacious in preventing the occurrence of pain on injection of propofol both immediate and delayed when compared to intravenous Lignocaine. However, it does decreases the severity of pain and can be a possible alternative with added advantage of prevention of post operative nausea and vomiting associated with general anaesthesia.

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