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Prevention of Propofol Injection Pain: A Comparison between Ondansetron, Dexamethasone and Lidocaine

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Abstract

Introduction: Propofol (2,6 di-isopropyl phenol) is widely used agent for induction of anaesthesia, although the pain during its injection remains a concern for all anaesthesiologists. The incidence of Propofol injection pain (PIP) varies between 28% to 90% in adults. Despite several interventions and pretreatment with drugs to alleviate pain, the failure rate is 13-32%. The aim of this study was to find the most efficacious method of alleviating PIP by combining intervention of venous occlusion along with Lignocaine, Dexamethasone or Ondansetron pretreatment. *Methods:* This is a double blinded randomized prospective clinical study on adult patients between the age group of 18-59 years scheduled for elective general surgical procedures. 150 patients were randomly allocated through computer generated table into three groups scheduled to receive 2ml of Lignocaine (20mg), Ondansetron (4mg) or Dexamethasone (6mg). Drugs were administered after tourniquet application inflated to 40mm Hg and occlusion was released after 30 seconds and then 0.5mg/kg of propofol was administered at the rate of 0.5ml / sec. The blinded investigator evaluated the pain score using the four point scale at 15 second interval. Statistical analysis was made by SPSS version 16. *Results:* The incidence and intensity of pain in patients receiving Lidocaine and Dexamethasone were significantly lower than those receiving Ondansetron ($p<0.001$). *Conclusion:* Pretreatment with intravenous Dexamethasone and Lidocaine along with venous occlusion for 30 seconds was found to be equally effective in reducing Propofol injection pain. Both these drugs were found to be superior to Ondansetron in achieving this goal.

Keywords: Propofol; Ondansetron; Dexamethasone; Lidocaine; Pain; Injection.

Introduction

Propofol is the most popular intravenous anesthetic agent. But the concern to all anaesthesiologists is the pain on its bolus dose injection. The incidence of Propofol injection pain (PIP) varies between 28% to 90% in adults if a vein on dorsum of hand is used [1]. A number of pharmacological and non-pharmacological approaches have been tried but have failed to find its remedy with just one intervention in all patients.

Individually Dexamethasone, Ondansetron and Lidocaine have been used as pre-treatment to alleviate PIP [2,3,4]. Due to paucity of data comparing these drugs and identifying the best among these three drugs along with venous occlusion to reduce the incidence of PIP, we did this study.

Materials and Methods

After obtaining Ethical committee clearance, all consenting patients who were posted to undergo elective surgical procedures under general anesthesia at St Johns Medical College hospital from October 2017 to January 2018 were enrolled for the study. A

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double blinded randomized prospective clinical study was done in adult patients between the age group of 18-59 yrs. 150 patients belonging to American society of Anesthesiologists (ASA) Physical Status I and II class were randomly allocated through computer generated table into three groups scheduled to receive study drug in a 2ml syringe. Group 1 received pretreatment with Ondansetron (4mg diluted to 2ml), Group 2 received pretreatment with Lignocaine (20 mg of 2% solution diluted to 2ml) and Group 3 received Dexamethasone (6mg diluted to 2ml). A written informed consent was taken from the patients for participation in the study. Patients having problems in communication, requiring rapid sequence induction and history of allergic response to either propofol or 5HT 3 antagonists, patients on medications with pain modifying drugs, with small caliber veins, pregnant or lactating patients were excluded from this study. As per standard practice, all patients were thoroughly examined clinically and pre anesthetic checkup was done. Airway was assessed using modified Mallampati classification. Patient were instructed to be NPO (nil per oral) pre-operatively for 6 hours. They were pre-medicated with Tab Alprazolam 0.5mg and Tab Ranitidine 150mg night before surgery. On arrival to operation theatre, baseline vital parameters-Blood pressure, heart rate (EKG) and oxygen saturation (SpO2) were recorded. A 20G intravenous access was secured on the largest vein on the dorsum of the non-dominant hand and lactated Ringer's solution was infused.

After limb elevation for 15 sec, venous drainage was occluded by placing a tourniquet inflated to 40 mm Hg. The study drug consisting of 2ml of Lignocaine (20mg), Ondansetron (4mg) or Dexamethasone (6mg) stored at room temperature was administered by a consultant anesthesiologist who was blinded to the drug. Tourniquet was deflated after 30 seconds and then 0.5mg/kg of Propofol (Neorof 1% from Neon laboratories) was administered at the rate of 0.5ml/sec. The intensity of pain was assessed by a second anesthesiologist who was unaware of the group to which the patient had been allocated. Although visual analogue scale (VAS) is the reference standard for measuring acute pain, it has practical limitation in its use, particularly in this setting because the pain in this study was measured just before patient lost consciousness, so we decided to use verbal rating scale which is relatively easy to use and simple to respond compared to VAS. Assessment included standard questions asked to the patient about the comfort of the injection, verbal response and behavioral signs (such as facial grimacing, arm withdrawal or tears from the eyes). Pain was graded using a four point scale which is called the Mc Crirrick and Hunter pain intensity scale.

Mc Crirrick and Hunter pain intensity scale

Pain Score	Degree of Pain	Response
0	None	Negative response to pain
1	Mild	pain reported only in response to questioning without any behavioral signs
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 or tears.

Later anesthesia was induced with intravenous Fentanyl 2µg/kg and Propofol 2mg/kg. Tracheal intubation was facilitated with Injection Atracurium and anesthesia was maintained with Isoflurane. Hemodynamic parameters were monitored. In the post-operative period, the trachea was extubated and patients were assessed for pain, swelling or allergic reaction at the site of injection by a blinded anesthesiologist.

Statistical Analysis

Considering previous studies, the incidence of PIP was assumed as 80% and 50% reduction was considered significant. Based on the alpha value of 0.05 and a power value of 80%, our study required at least 41 patients per group. Assuming drop-outs, the sample size was increased to 50 per group. Continuous data are reported as mean±standard deviation. Categorical data were analyzed using Chi-square test. Since measurements for pain are in scores, non- parametric methods were used for analysis. Kruskal-Walli's ANOVA was used for multiple group comparisons followed by Mann-Whithey U test for group wise comparison. A $p < 0.05$ or less was considered for statistical significance. SPSS version 16 software was used for analysis.

Results

There were no significant difference in demographic characteristics between the three groups (Table 1). No incidence of pain or discomfort was reported during the injection of pre-treatment solution in any group. The overall incidence of pain was 22% in lidocaine group, 66% in Ondansetron group and 34% in Dexamethasone group as shown in figure 1. The average pain scores expressed as Mean±SD pain score in Group 1 was 0.9±0.8, Group 2 was 0.2±0.4 and Group 3 was 0.3±0.5 as depicted in Table 2. The incidence of pain was significantly less ($p < 0.001$) in patients receiving lidocaine and dexamethasone than those receiving Ondansetron (Table 3).

Moderate to severe pain was seen in 66% of study population in Ondansetron group compared to 22% in lidocaine group and 34% in dexamethasone group which was statistically significant ($p<0.001$). The difference in moderate to severe pain between lidocaine and dexamethasone groups was not statistically significant as shown in Table 3 ($p = 0.18$).

Table 1: Subjects information

		Gr 1 Ondansetron	Gr 2 Lignocaine	Gr 3 Dexamethasone	Significance
No. of cases		50	50	50	-
Age (Yrs)	Mean ± SD	39.8 ± 12.0	40.4 ± 12.4	37.9 ± 11.9	ANOVA, F = 0.62,
	Range	19 - 59	18 - 59	22 - 59	P =0.54,NS
Sex	M	26	31	25	$X^2 = 1.67$,
	F	24	19	25	P=0.43, NS

Demographic data of the patients in all the three groups. Gr-Group, No-Number, yrs-Years, SD- Standard Deviation, NS-No Significance

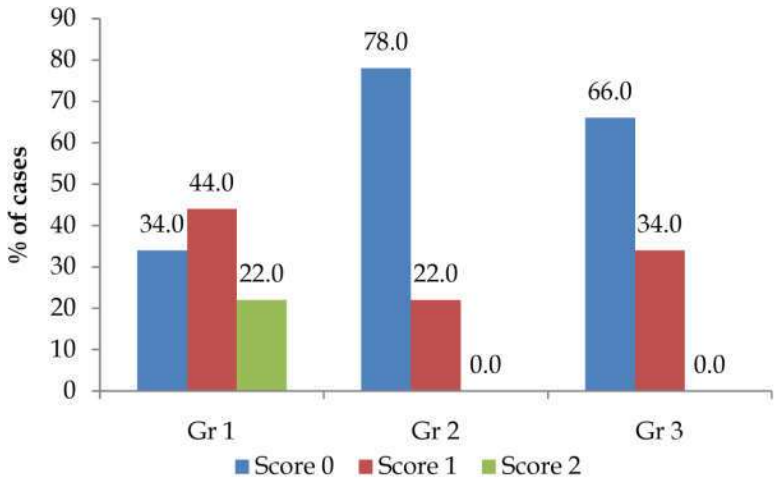

Fig. 1: Percentage distribution of cases in three groups with corresponding pain score
Group 1- Ondansetron, Group 2-Lidocaine, Group 3- Dexamethasone

Table 2: Comparison of Pain scores

Groups	Pain score Mean ± SD	Median	Range
Gr 1	0.9 ± 0.8	1	0 - 2
Gr 2	0.2 ± 0.4	0	0 - 1
Gr 3	0.3 ± 0.5	0	0 - 1

Kruskal-Walli's ANOVA, $\chi^2 = 26.92$, $p < 0.001$, HS

Group wise comparison of the pain scores.
Group 1- Ondansetron, Group 2-Lidocaine, Group 3- Dexamethasone
Gr-Group, SD-Standard Deviation, HS- High Significance.

Table 3: Groupwise comparisons*

Groups compared	P value	Significance
1 v/s 2	< 0.001	HS
1 v/s 3	< 0.001	HS
2 v/s 3	0.18	NS

Mann-Whitney's Test
Intergroup comparison. Group 1- Ondansetron, Group 2-Lidocaine, Group 3- Dexamethasone
HS-High significance, NS-No Significance.

Discussion

Patient satisfaction in perioperative care setting is assuming more importance in recent years. With the development and improvement of surgical and anesthetic techniques, critical incidents like cardiac arrest or death during peri-operative period have been obviously minimized. Thus more attempts have been made to address minor but potentially distressing clinical anesthetic problems such as pain, post-operative nausea and vomiting (PONV) to further improve the quality of anesthetic care. PIP is one such intriguing problem and the quality of pain is described as extremely sharp, aching or burning. The incidence of pain with intravenous Propofol varies between 28% to 90% in adults [1] if a vein on dorsum of hand is used. Most patients remember it as one of the unpleasant encounters with anaesthetists. It has been arranged as the seventh most important problem in current practise of clinical anaesthesia by American society of Anaesthesiologist [5].

Many factors appears to affect the incidence of pain, which includes site of injection, size of the vein, varying speed of injection and carrier fluid, buffering effect of blood, temperature of propofol and concomitant use of drugs such as local anaesthetic, antiemetics, ketamine, magnesium and opioids [6,7]. Despite several interventions and pretreatment with drugs, the failure rate is 13-32% [8]. Considering the extensive use of propofol in clinical practice, the pain frequently reported on induction of anesthesia cannot be neglected.

Propofol belongs to group of sterically hindered phenol that can irritate the skin, mucous membrane and venous intima. PIP can be immediate or delayed. The immediate pain could be the results of a direct irritant effect, but the Kallikrein-kinin cascade is probably the cause of delayed pain [9]. Peripheral veins are innervated with polymodal nociceptors, which mediate the pain response to the injection of certain anesthetic agents like Propofol. Scott et al speculated that the pain on injection is caused by activation of Kallikrein-kinin system either by Propofol or the lipid solvent, there by generating kinins probably bradykinin [10].

Bradykinin, by producing local vasodilatation and hyperpermiability, may increase the contact between the aqueous phase Propofol and the free nerve ending involving myelinated Aδ fibres [11], resulting in pain of injection. This pain has latency of 10-20 seconds in onset.

Several methods for prevention of pain have been tried with varying degree of success, with lidocaine pretreatment being the most commonly used [12,13]. Analgesic effects of lignocaine may occur because of local anesthetic effect or an inhibitory effect on the enzymatic cascade which leads to release of kinins. However literature reports the failure rate between 13-23% [14]. Also it is reported that addition of lidocaine may destabilize the emulsion formulation of Propofol with a potential risk of causing pulmonary fat embolism along with risk of bacterial contamination or anaphylaxis [16]. Hence, the search for a drug which can alleviate PIP completely is a need for all anesthesiologists.

There are fewer studies on the use of pretreatment with steroid based drug and anti-emetics like Ondansetron for amelioration of PIP, hence, we performed this study. We combined the use of pre-treatment of drugs along with interventions like venous occlusion using a tourniquet raised to 40 mmHg [16]. Since the incidence of PIP being as high as 80% it was deemed unethical to inject this drug with saline as pretreatment, hence we decided to compare the efficacy of commonly used antiemetics drugs like Ondansetron and Dexamethasone with Lidocaine which is the most commonly used pretreatment to alleviate PIP.

In this study, we found the overall incidence of moderate to severe pain was 66% in Ondansetron group (Group 1) whereas in the Lignocaine group (Group 2) and Dexamethasone group (Group 3), patients experienced only moderate pain with the incidence being 22% and 34% respectively. No patients in either group experienced severe pain.

Ondansetron, a specific (5HT3) 5-hydroxytryptamine receptor antagonist, is a routinely used anti-emetic drug which is demonstrated to provide relief from PIP [17]. Its action is proposed to be multifaceted as a Na channel blocker and (mu) μ opioid agonist. Thus Ondansetron pretreatment may be used to reduce the incidence of PIP with an added advantage of prevention of PONV. Previous studies have demonstrated Ondansetron to be 15 times more potent than lignocaine [18] and also they have found it to be as effective as Tramadol [19].

Similar to the study done by Sumalatha et al, We found that Ondansetron was less effective when compared to Lidocaine [4] and Dexamethasone with an incidence of moderate to severe pain being about 66%. When compared to Lignocaine and Dexamethasone, patients in the Ondansetron group experienced more pain which was statistically significant ($p<0.001$).

Dexamethasone is a commonly used glucocorticoid, which is proven to minimize post-operative pain and nausea/vomiting without any increase in infection or altered hyperglycemic response in the postoperative period [3]. It is demonstrated the dexamethasone reduces the nitric oxide production associated with PIP. Although both these drugs are individually found to relive propofol injection pain, there are no studies comparing the effects of pretreatment of these drugs with Lignocaine. In a study done previously they found the incidence of PIP after Dexamethasone pretreatment was 31% with moderate to severe pain noted in 17.14% [20].

We found the incidence of moderate pain to be 34% which is similar to previous study done by Singh et al. Also we found that Dexamethasone was as effective as Lignocaine in alleviating PIP. The pain scores comparison in Lignocaine was 0.2±0.4 with a Median of 0 and that of Dexamethasone was 0.3±0.5 with a Median of 0. Group wise comparisons of these two groups were found to be statistically insignificant.

Pretreatment with Dexamethasone 6mg and Lidocaine 40mg along with venous occlusion was associated with significant reduction of Propofol injection pain when compared to Ondansetron 4mg. These drugs are routinely used and are cost effective, thus seems to be the most pragmatic option for preventing PIP. This effective and convenient method allows the clinician to use routinely available drugs and avoids delay in busy operating room schedules. In our study pretreatment was administered 30 seconds prior to the administration of Propofol which may be a short contact time. We believe that with higher contact time of about 60 seconds, the incidence of PIP can be reduced further [12,21].

Thus this technique is useful in elective surgery with an added advantage of prevention of post-operative nausea and vomiting.

Conclusion

A multimodal approach, combining intervention like venous occlusion and pretreatment with drugs should be routinely used to eliminate Propofol injection pain. The analgesic efficacy of Ondansetron is less effective in preventing PIP in comparison to Lidocaine and Dexamethasone. Dexamethasone given as a pretreatment before Propofol is as effective as Lignocaine in preventing PIP along with an added advantage of preventing post-operative nausea and vomiting.

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