Original Article

Comparative study between intravenous ramosetron and dexamethasone as pre-treatment to attenuate pain during intravenous propofol injection

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ABSTRACT

Background: Propofol as an induction agent has disadvantage of pain on intravenous injection (IV). **Objective**: The aim of this study was to compare the efficacy of ramosetron and dexamethasone as a pretreatment drug for attenuation of pain due to propofol injection. **Methods**: This randomized comparative study was conducted at a tertiary care hospital in Eastern India, over a period of one year (March 2016-February 2017). Total 90 American Society of Anesthesiologists (ASA) grade I and II patients were randomly assigned into three groups (30 in each). Group R received 2 ml (0.3mg) of ramosetron, Group D received 2 ml (0.1mg/kg) of dexamethasone, and Group N received 2 ml of 0.9% normal saline. Venous drainage was occluded by using a tourniquet in mid-forearm before injecting the pre-treatment solution and released after 1 min and then 2 ml of propofol was injected over 5 sec. Patients were observed and questioned 15 sec later, if they had pain in the arm or discomfort during drug injection. The pain was scored on a four-point scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain. Pearson's Chi Square test/Fisher's Exact Test and Mann-Whitney U test/Kruskal Wallis Test were used to analyze the results. **Results**: The overall incidence of pain was 90% in the saline group, 17% in the ramosetron group and 10% in the dexamethasone group. The intensity of pain was significantly less in patients receiving ramosetron and dexamethasone than those receiving saline ($P < 0.05$). Haemodynamic parameters like heart rate (HR) and mean blood pressure (MBP) were recorded at different points of time. No significant inter group differences in MBP and HR were noted at any point of time. **Conclusion**: Pre-treatment with intravenous ramosetron and dexamethasone both lead to relief of pain on injection of IV propofol without any significant difference between their effects**.**

Key words: *Injection, Pain, Propofol, Ramosetron, Dexamethasone.*

Propofol is a common intravenous (IV) anaesthetic drug used for induction and maintenance during general anaesthesia with rapid onset and short duration of action [1]. With the decrease in morbid adverse events after surgery, patient satisfaction with perioperative care is assuming more importance [2]. Pain on injection of anaesthetic is an important source of patient dissatisfaction and is a recognized adverse effect of propofol. Among 33 low-morbidity clinical outcomes, considering clinical importance and frequency, pain during injection of propofol was ranked as the seventh most important problem of current clinical anaesthesiology by a panel of anaesthesiologists from academic and community practices, thus deserving high priority for improvement. In addition, the hyperdynamic cardiovascular response to the pain can precipitate adverse events in high- risk patients with history of coronary artery disease and/or abnormal heart rhythm [3]. The reported incidence of pain on injection of propofol varies between 28% and 90% in adult when injection given through small vein. Propofol, an alkyl phenol compound, is virtually insoluble in aqueous solution. Therefore it is formulated as emulsion containing 1% (weight /vol) propofol, 10% soya bean oil, 2.25% glycerol & 1.2% purified egg phosphatid [4]. Propofol

evokes pain on intravenous injection though its pH and osmolality are close to those of blood. Various interventions, both non pharmacological and pharmacological, have been tried to attenuate pain during intravenous injection of propofol. Non pharmacological strategies that have been employed include injection in a larger vein, injection in a fast running IV fluid, cooling propofol to 4 °C [5], diluting with 10% intralipid, injecting cold saline at 4 °C before propofol [5], different infusion rates, venous occlusion, different needle sizes, different injection sites and microfiltration [6]. In the pharmacological class of interventions, several classes of drugs like alpha2 agonists- dexmedetomidine [7], antiemetics- metoclopramide [8], barbiturates, cholinesterase inhibitors [9], kallikrein inhibitors, N-methyl-D-aspartate (NMDA) receptor antagonists ketamine [7], magnesium sulphate [10], nitroglycerin [11], Non-steroidal anti-inflammatory drugs (NSAIDS) [12], opioids- tramadol [13], remifentanyl [14], steroids- dexamethasone [15], hydrocortisone [16], methylprednisolone [17], and local anesthesthetics- lidocaine [13], have been tried.

Recently, 5-hydroxytryptamine-3 (5-HT3) antagonists such as ondansetron, granisetron, ramosetron and palonosetron which are used as antiemetics, have been shown to effectively alleviate propofol-induced pain individually [13,18-21]. Corticosteroids are systemic anti-inflammatory agents [22], systemic analgesics and are known to block nociceptive C fibres when applied locally [23]. Dexamethasone has been shown to reduce propofol injection pain [7,23]. Despite some of the strategies showing promising results, none of the above-mentioned methods has been fully effective in attenuating the pain due to propofol injection and the research for the ideal agent or intervention, that would make anesthesia administration with propofol a pleasing experience, continues. In our practice, ramosetron and dexamethasone both are routinely used as premedication to prevent post-operative nausea and vomiting (PONV) in patients following general anesthesia.

Ramosetron is a serotonin 5HT3 receptor antagonist and demonstrates superior efficacy and longer duration to ondansetron because of a slower rate of dissociation from the target receptor and higher binding affinity [24]. Since there is no data available regarding the effectiveness of ramosetron compared to dexamethasone presently, we decided to study the efficacy of ramosetron as pretreatment to attenuate the pain of propofol injection and to compare the results with IV pretreatment with dexamethasone and placebo.

METHODS

This randomized comparative study was conducted at a tertiary care hospital in Eastern India over a period of one year (March 2016-February 2017). We included 90 patients belonging to American Society of Anesthesiologists (ASA) physical status (PS) I and II, of either sex, aged 18–60 years, weighing between 40 and 80 kg, scheduled for various elective general and uro surgical procedures under general anesthesia. The patients were explained about the procedure during the pre-anesthetic visit. Exclusion criteria for the study were patient's refusal, h/o allergy to propofol or 5HT3 receptor antagonist or corticosteroid, patients with known cardiac disorders, other systemic disorders of lungs and liver, pregnant patients, patients for emergency procedures, BMI>30kg/m2, ASA grades III-IV patients, patients with difficulty in communication and patients who had received analgesic drug within 12 hours prior to surgery. After obtaining Institutional ethical committee approval and informed written consent from patients, eligible patients were randomly allocated using computer generated -randomized test to one of three equal (30 in each group) groups: the two study groups (R and D) and the control group (N).

Patients were kept NPO for 8 hours and no analgesic was given 12 hours prior to surgery. On the day of surgery, after confirming patient's identity and NPO status, patients were shifted to the operating room and connected to multiparameter monitor. Non-invasive blood pressure (NIBP), ECG, heart rate (HR), SPO2 and end tidal carbon dioxide, was monitored throughout the surgery. A 20G cannula was inserted into a vein on the dorsum of nondominant hand of the patient. One bottle of crystalloid solution was infused. Mean arterial blood pressure and HR were recorded for statistical comparison among the three groups at baseline, after pretreatment, after injecting full dose of propofol. Patients in Group-R (n=30) , Group-D (n=30) and Group-N (n=30) received 2 ml (0.3mg) of ramosetron, 2ml (0.1mg/kg) of dexamethasone and 2ml 0.9% normal saline respectively over a period of 5 seconds through intravenous route.

All the drugs were prepared at the room temperature and the anaesthesiologist was unaware of its content. Venous drainage was occluded by using a tourniquet in mid-forearm before injection of pre-treatment solution

injection and maintained for 60 seconds. After the release of the tourniquet, initially a 2ml bolus of propofol was injected over 5 seconds. After 15 seconds of this injection, any complain of pain or discomfort by the patient, was elicited followed by giving rest of the induction dose. A researcher, who was unaware of group assignment, assessed the pain according to the verbal rating scale: 0 = none (negative response to questioning), 1=mild pain (pain reported only in response to questioning without any behavioural signs), 2=moderate pain (pain reported in response to questioning and accompanied by a behavioural sign or pain reported spontaneously without questioning), 3= severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears). After propofol injection, and pain assessment, fentanyl 2 microgram/kg and atracrium 0.5 mg/kg were given. Intubation was done 3min after atracrium administration; Anesthesia was maintained by a mixture of nitrous oxide and oxygen supplemented with desflorane. Muscle relaxation was maintained by increments of atracrium. At the end of surgery reversal was done by giving injection neostigmine 0.04 mg/kg and glycopyrolate injection 0.01mg/kg through intravenous route. The data including HR, mean blood pressure (MBP) and pain during propofol injection were collected by a blinded observer and was analyzed statistically.

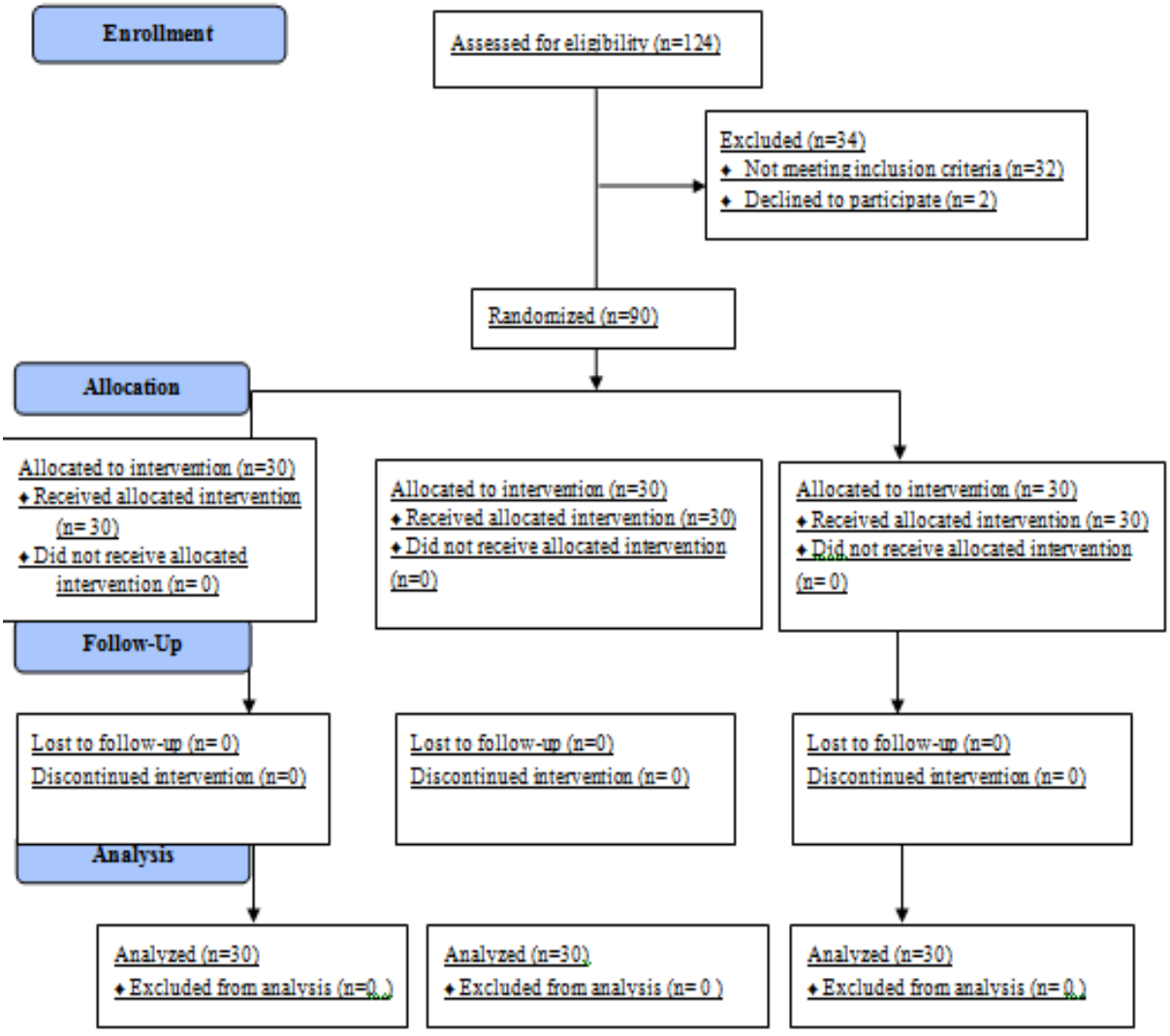

Figure 1- CONSORT diagram showing division of patients at every stage of trial

Based on the review of the literatures [11,23], 30 patients were calculated as the minimum size for each group assuming an α-value of 0.05 and a power value of 80%. The statistical software SPSS version 20 was used for the analysis. Categorical variables were expressed as number of patients and percentage of patients and

compared across the groups using Pearson's chi square test for independence of attributes/Fisher's exact tests, as appropriate. Continuous variables were expressed as mean ± standard deviation and compared across the groups using Mann-whitney U test/Kruskalwallis test as appropriate. An alpha level of 5% had been taken that if any p value was < 0.05 it had been considered as significant.

RESULTS

In total, 124 patients were screened for the study and 90 patients were randomised into three groups. The flow of the patients enrolled was represented in the CONSORT-flow diagram (Figure 1). There was no significant difference in the demographic characteristics in all the three groups (Table 1 and 2). No patients in any group experienced pain and discomfort during the injection of pretreatment solution. The incidence of pain during IV injection of propofol in various groups is shown in Table 3.

The incidence of pain on injection of propofol in the saline (N) group was 90% (27/30), as compared to 17% (5/30) in ramosetron (R) group and 10% (3/30) in dexamethasone (D) group. The incidence of pain was significantly less (P < 0.05) in patients receiving drugs for pre-treatment than those receiving saline. Mild pain was observed in 3 (10%) and 2 (6%) patients in Groups R and D, respectively, as compared to 10 (33%) patients in N group. Moderate pain was observed in 2 (6%) and 1 (3%) patients in Groups R and D respectively as compared to 12 (40%) patients in N group. None of the study groups' patients felt any severe pain as compared to control group (17%). Significant difference in mean pain score were observed between group R and N (P < 0.001) and group D and N (P < 0.001), but not between R and D (Table 4). Regarding haemodynamic parameters, no significant inter group differences in HR and MBP were noted at any point of time (Table 5).

Table 1 - Comparison of Age and Body weight among three groups

Parameters	Group R (n=30)	Group D (n=30)	Group N (n=30)	P Value			
	Mean±SD	Mean±SD	Mean±SD	Over all	R vs D	R vs N	D vs N
Age (years)	42.7±1.64	43±1.55	42.33±1.67	0.272	0.494	0.366	0.107
Weight (kg)	60.4±7.16	61.97±6.47	60.43±5.2	0.455	0.542	0.835	0.124

Table 2 - Comparison of Sex among three groups

Sex	Groups, n (%)			Total	P Value			
	Group R (n=30)	Group D (n=30)	Group N(n=30)		Over all	R vs D	R vs N	D vs N
Female	8 (26.67)	10 (33.33)	9 (30)	27 (30)	0.957	0.779	0.774	0.781
Male	22 (73.33)	20 (66.67)	21(70)	63 (70)				
Total	30(100)	30(100)	30(100)	90(100)				

Table 3 - Incidence and intensity of pain following Propofol injection

Pain experienced	Group R	Group D	Group N	P Value
No pain (>05[#])	25 (83)	27 (90)	3 (10)	< 0.05*
Pain	5 (17)	3 (10)	27(90)	< 0.05*
Mild Pain (>05[#])	3 (10)	2 (6)	10 (33)	<0.05*
Moderate pain	2 (6)	1 (3)	12 (40)	<0.05*
Severe Pain	0	0	5 (16)	<0.05*

Data is expressed as number of patients (%). *P -value between Group N and Group R & D. [#]P -value between Group R and D

Table 4 - Comparison of mean pain score (VAS) among three groups

Pain score (VAS)			P Value			
Group R	Group D	Group N				
Mean±SD	Mean±SD	Mean±SD	Over all	R vs D	R vs N	D vs N
0.2±0.48	0.1±0.31	1.67±0.88	≤0.001	0.430	≤0.001	≤0.001

Table 5 - Comparison of Heart Rate & Mean blood pressure among three groups

Parameters	Group R	Group D	Group N	P Value			
	Mean±SD	Mean±SD	Mean±SD	Over all	R vs D	R vs N	D vs N
Base Line HR	83.43±9.1	82.43±7.61	83.2±6.97	0.693	0.434	0.532	0.732
HR: After Pretreatment	79.1±9.35	82.2±7.44	80.87±7.28	0.412	0.229	0.458	0.403
HR: After Injecting Full dose Of propofol	90.63±8.3	93.1±5.7	93.23±6.51	0.513	0.368	0.288	0.801
Baseline MBP	96.18±5.26	98.07±5.34	96.23±5.59	0.393	0.219	0.923	0.257
MBP: After Pretreatment	94.58±5.29	94.44±5.11	96.51±5.37	0.277	0.882	0.115	0.245
MBP: After injecting full dose of propofol	82.12±4.95	83.77±4.26	83.29±5.04	0.309	0.166	0.242	0.615

HR: Heart Rate (in beats/ minute); MBP: Mean Blood Pressure (in mm-Hg)

DISCUSSION

Propofol is the drug of choice for induction of anaesthesia in millions of patients every year because of its rapid onset and short duration of action, easy titration, and favourable profile for side effects [1].Considering the extensive use of propofol in clinical practice, the pain frequently reported on induction of anaesthesia cannot be neglected. Chemically, propofol belongs to the group of sterically hindered phenols. It is no wonder that during intravenous injection propofol like any other phenol will be irritating the skin, mucous membrane and venous intima [6]. As the underlying mechanism of pain is not fully understood, a number of hypotheses have been put forward to explain the propofol induced pain. The immediate vascular pain on propofol injection is attributed to a direct irritant effect of the drug by stimulation of venous nociceptive receptors or free nerve endings involving myelinated Aδ fibres .The delayed pain of injection has a latency of 10–20 s mediated by activation of kallikrein–kinin system [12].

The most important finding of this study was the reduction in the number of patients who reported moderate or severe pain following propofol administration, when pretreated with ramosetron and dexamethasone compared to saline. 5-HT3 receptor antagonists have been widely used as anti- emetics. Ondansetron, a 5-HT3 receptor antagonist, blocked the sodium channel in an animal study, and had a 15-fold-higher local anesthetic efficacy than lidocaine. In addition, as 5-HT3 receptor antagonists act as agonists by combining with the μ receptor, and as peripheral 5-HT3 receptors are involved in the nociceptive pathway, the 5-HT3 receptor antagonist results in an analgesic effect. Descending monoaminergic pathways from brainstem are known to able to influence nociceptive signaling in the dorsal horn of the spinal cord. Such descending influences are both facilitatory and inhibitory in nature. Suzuki and colleagues [25] showed that the descending influences are predominantly facilitatory, and act via spinal 5-HT3 receptors (expressed on nerve terminals of small diameter afferents), revealing a role for selective 5-HT3 receptor antagonists like ondansetron and granisetron in relieving pain.

Ramosetron is a tetrahydro-benzimidazole derivative structurally independent of previously developed drugs such as ondansetron, granisetron and tropisetron. Ramosetron is more potent and has longer lasting effects because of a slower rate of dissociation from the target receptor and higher binding affinity[24]. Ramosetron has been used during anaesthesia induction or before the end of surgery to prevent nausea and vomiting after surgery or anti-cancer treatment [26,27]. The present study showed incidence of propofol injection pain was 17% (5/30) in ramosetron (R) group as compared to in the saline (N) group was 90% (27/30). Only 3 (10%) patients in D group and 2 (6%) patients in R group complained of mild and moderate pain respectively in comparison to the control group N (33% and 40%).

The result was consistent with the study done by Basappa G and colleagues [28] who studied the effect of lignocaine, ondansetron and ramosetron on attenuation of propofol injection induced pain. The study concluded that pre- treatment with IV ramosetron 0.3mg is equally effective as 0.5mg/kg of 2% lignocaine in preventing

propofol induced pain and both were better than ondansetron. Singh D et al [18] compared the incidence of pain induced by propofol injection in patients pre-treated with ramosetron with those pre-treated with lidocaine, concluded that pre-treatment with ramosetron 0.3mg and lidocaine 40mg are equally effective in preventing pain from propofol injection, which is consistent with the results of present study. Lee HY et al [29] investigated the effect of ramosetron on pain induced by microemulsion propofol injection on 200 ASA I and II patients undergoing general anesthesia. They found that incidence of pain was 96%, 76%, 60% and 38% in patients receiving normal saline, lidocaine 20mg, ramosetron 0.3mg and lidocaine 20mg plus ramosetron 0.3mg, respectively ($p<0.008$). The study concluded that pretreatment with ramosetron 0.3mg with or without lidocaine 20mg with a tourniquet on the forearm 30 seconds before the injection of microemulsion propofol is more effective than lidocaine 20mg or normal saline in preventing pain from a microemulsion propofol injection.

In the current study, it was found that 27 patients (90%) in D group had no pain. In contrast, the number of patients without pain in N group was 3(10%). There was significant decrease in moderate and severe pain in group D (1% and nil in each) compared with normal saline group (40% and 16%, respectively). A previous study found that 31% of patients felt pain ($P < 0.01$) after dexamethasone pre-treatment and moderate to severe pain was noticed in 17.14% [30]. Another study comparing lignocaine, pethidine and dexamethasone as pre-treatment found that 48% of the patients with dexamethasone pre-treatment had no pain [31]. The combination of lignocaine 20 mg and dexamethasone 6 mg with venous occlusion for 1 min was more effective than lignocaine 20 mg (34.3%) or dexamethasone 6 mg (37.1%) alone for pain control during propofol injection [23]. Dexamethasone given at higher analgesic doses reduces pain associated with the injection of propofol [3]. These results showed an effective reduction in the incidence and severity of propofol injection pain after pre-treatment with dexamethasone which was similar to our study. Patel M, et al also concluded in their study that pretreatment with iv lignocaine 0.5mg/kg, ondansetron 0.1mg/kg, dexamethasone 0.1mg/kg in preventing pain from propofol injection were better than cold propofol per se [32].

Propofol has been shown to release nitric oxide (NO) from vessels in animals and humans, and the release of nitric oxide has been linked to the generation of pain in the veins in human. In addition, NO from the vascular endothelium binds to guanyl cyclase this catalyzes the conversion of guanosine triphosphate to guanosine monophosphate, which facilitates PGE2-induced hyperalgesia. It has been found that pain following intravenous injection of bradykinin and hyperosmolar solutions can be blocked by pretreatment with NO synthase (NOS) inhibitor, suggesting that an intact NOS pathway is needed to elicit vascular nociception. The effects of corticosteroids such as dexamethasone on NO production have been previously demonstrated. In addition, the efficacy of steroids to alter nitric oxide release has also been demonstrated in several disease conditions [33,34] .Therefore, the choice of dexamethasone to minimize propofol-induced vascular pain was not only based on its wide clinical utilization but also due to its biological basis.

In the current study, though we found that ramosetron and dexamethasone significantly reduced the occurrence and severity of pain due to propofol injection in comparison to placebo, we could not find any significant difference in mean pain score between these two drugs ($P < 0.430$). No significant inter group differences in MBP and HR were noted at any point of time. The present study proved that intravenous ramosetron besides its antiemetic action can effectively attenuate the pain on injecting IV propofol equally as dexamethasone. However, the choice of agent should, therefore, be individualized with due consideration to the cost-effectiveness and benefit to the patient. There were few limitations to this study; the outcome of this study may not be applicable in emergency induction. This technique is useful in elective surgery and adult participants.

A limitation of all studies evaluating propofol injection pain is the use of a subhypnotic dose of propofol so that reliable pain assessments reporting can be obtained. Finally, our study was underpowered to detect the difference in the incidence of moderate to severe pain between ramosetron and dexamethasone.

CONCLUSION

The analgesic efficacy of ramosetron given as pre-treatment with propofol is as effective as dexamethasone in preventing propofol-induced pain and both have an added advantage of preventing PONV.

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