COMPARISON OF THE EFFECT OF DEXMEDETOMIDINE PRETREATMENT, LIDOCAINE PRETREATMENT AND PLACEBO ON PAIN ON INJECTION OF PROPOFOL: A RANDOMISED CONTROL TRIAL

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ABSTRACT

Aims and objectives: This study was designed to compare and evaluate efficacy of lignocaine, dexmedetomidine & placebo in preventing pain due to propofol injection.Methods: 90 adults were assigned into three groups. With aim of keeping the drug in the vein, forearm was squeezed with tourniquet upto70mmHg.Group 1 (n=30) received 0.25 µg kg-1 of dexmedetomidine, group 2 (n=30) 0.5 mg/kg of lignocaine diluted in 5ml of NS & group 3(n=30) 5ml of NS followed by an injection of propofol from same vein after releasing the occlusion. Pain assessment was made immediately after propofol injection using Mc Crirrik & Hunter Scale.Result: The number of patients who suffered from any degree of pain was low in group 1 & 2. Discussion: Lidocaine and Dexmedetomidine significantly reduced the incidence and severity of propofol injection pain more than placebo ($P < 0.001$). The efficacy of Dexmedetomidine in alleviating the pain on injection of propofol is no different from lidocaine.Conclusion: Dexmedetomidine pre treatment may be used to reduce the incidence of pain on injection of propofol, with added advantage of sparing effect on the requirement of analgesics and sedatives, better hemodyanmics profile and anti-shivering action.

Keywords:
Propofol, dexmedetomidine, lignocaine

No: of Figures:2 **No: of Tables: 04** **No: of Reference:27**

INTRODUCTION

Propofol has become the most popular intravenous agent. Propofol is a short acting, intravenously administered hypnotic agenda. It is associated with pleasant sleep, rapid recovery and little postoperative nausea and minimal hemodynamics changes intraoperatively. Due to anaphylactic reactions propofol was reformulated as an emulsion of a soya oil/propofol mixture in water. The currently available preparation is 1% propofol, 10% soybean oil, and 1.2% purified egg phospholipid as an emulsifier, with 2.25% of glycerol as a tonicity-adjusting agent, and sodium hydroxide to adjust the pH. Following concerns regarding microbial growth in the emulsion, disodium edetate (0.005%) was added as a retardant of bacterial growth. This formulation has a pH of 7 and appears as a slightly viscous, milky white substance.

Propofol belongs to group of phenol that can irritate the skin, mucous membrane and venous intima. **Scott et al** [1] speculated that the injection pain is caused by activation of the kallikrein-kinin system either by propofol or the lipid solvent, thereby generating kinins, probably bradykinin. Bradykinin, by producing local vasodilation and hyper permeability, may increase the contact between the aqueous phase propofol and the free nerve ending resulting in pain on injection **[24].** This pain has a 10-20 sec delayed onset. But immediate pain may be caused by direct irritation of afferent nerve endings within the veins, thus the use of an adjuvant medication before propofol to reduce the pain of injection has become a common practice. In our study, pain was assessed just after the propofol injection thus immediate pain was assessed.Despite many positive attributes and one of the most commonly used intravenous induction agent , about three out of five patients experience severe or excruciating pain. The most common problem with the administration of i.v. propofol is the pain at the injection site. On an average 70% of the patients report pain on injection.

There are many factors which appear to affect the incidence of pain on propofol injection. These are size of the vein, speed of the injection, propofol concentration in the aqueous phase. Several methods have been used to reduce this pain; Diluting the propofol solution, injection of propofol in large vein [1], adding lidocaine, pre-treatment with ephedrine, ketamine, metoclopramide, etc. [2],[3] All have been tried with many different results. Despite these recommendations, the technique failed to gain widespread popularity, possibly because of the time needed to apply the tourniquet. As a result, the pain associated with injection of propofol remains a challenge and more than 100 new studies have explored additional and alternative strategies. These include novel propofol emulsions, 34 modified emulsions, and microemulsion formulations, 5-7 as well as diverse drugs and their combinations However, despite various methods to reduce propofol injection pain, the effective methods have not been identified.

Dexmedetomidine is a newly introduced alpha adrenergic agonist. They have a sparing effect on the requirement of analgesics and sedatives, better hemodynamic profile and anti-shivering action [6]. Local anesthetic action of dexmedetimidine has not been completely understood till date despite, many studies comparing its efficacy in prevention of propofol injection pain has been done. Dalle C et al (2001) [14] elucidated that clonidine, by increasing the threshold for initiating the action potential, induces a slowing or block of conduction and that this mechanism is the origin of the clonidine-induced anti-nociception. Finally, this study suggested a novel role for inwardly rectifying hyperpolarization activated conductance's in peripherally mediated antinociception. Since clonidine and dexmedetomidine both are selective alha2 adrenergic agonists, we postulated that dexmedetomidine might also decrease pain on injection. **Shirasaka T et al [8] in 2007** showed that activation of a G protein-coupled inwardly rectifying K+ current and suppression of Ih contribute to dexmedetomidine-induced inhibition of rat hypothalamic paraventricular nucleus neurons. **Oda A et al [9] in 2007** showed that dexmedetomidine has an inhibitory action on AP conduction, because dexmedetomidine depresses voltage-gated Na+-channel currents.

Despite the frequent studies have been done in this field, there are many contradictory and controversial results, showing the need for more studies to investigate the problem. We designed this double-blind, placebo-controlled study to compare the efficacy of dexmedetomidine with lidocaine in reducing the pain of both propofol injection during anesthesia induction.

Material and methods

A prospective randomized study was conducted at Indira Gandhi Institute of Medical Sciences, Patna conducted between march 2012-nov 2013 on patient (n=90) posted for elective surgical procedures in different surgical departments. the study was approved by Institutional Ethics Committee on 08/02/2012 (memo no: GIMS/2012/19). Written informed consent was taken from all the patients keeping the personal details disclosed.

Participants

A total of 90 patients of ASA I & II, aged between 18-70 yrs of either sex requiring general anesthesia were divided into three groups (30 each)

Patients requiring concomitant analgesic or sedative medication, rapid sequence induction, anticipated difficulty venous access, difficulty in communication or known sensitivity to lignocaine or dexmedetomidine or presence of infection on the dorsum of hand where excluded from the study.

The patients visited a day prior to surgery and were subjected to detailed clinical history and complete general physical examination. Investigations were performed as per the protocol of the hospital.

Patients were given oral diazepam 5mg a night before surgery. On arrival in

operation theatre monitors were attached and baseline heart rate, blood pressure, and spo2, ECG were recorded. Before induction of anesthesia, the patients were told that they would be receiving IV anesthesia that might cause pain in forearm and were instructed to inform the investigator about the amount of pain they experienced by verbal response and behavioral signs. 20 Gaze intravenous cannula was placed on dorsum of the non-dominant hand and infusion of acetated Ringer's lactate started. After the patient understood the instruction, the IV infusion was stopped, and the arm with the IV line was elevated for 15 sec for gravity drainage of venous blood. A pneumatic tourniquet was placed on same upper arm with pressure inflated to 70 mmHg to produce a venous occlusion [10].

Patients was randomly allocated to one of the 3 groups

Group A- 5ml of normal saline.
Group B- Group Lignocaine (n=55)—0.5 mg/kg diluted in 5ml of NS.
Group C- Group Dexmedetomidine (n =55)—0.25 microgram/kg in 5ml of NS.

The study drugs at room temperature was injected over 5 secs and the patient was asked if they felt any pain. Tourniquet was left inflated for 2 minutes [4]. After release of the tourniquet 25% induction dose of propofol at room temperature was administered over 10 secs. The occurrence and severity of pain was accessed as per [McCrirrik & Hunter Scale] [11]

Degree of pain ***Response:***
None [0] No response to questioning Mild [1] Pain reported in response to questioning only without any behavioral signs Moderate [2] Pain reported in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning Severe [3] Strong vocal response or response accompanied by. At the same time the changes in pulse, BP, SpO2, etc. was also monitored. Anesthetic induction was continued with propofol after administering fentanyl 2-3 mg/kg body weight intravenously. Tracheal intubation and balanced general anesthesia followed as per standard protocol.

Patients will be followed up in recovery room and asked for recall, if there was pain during injection of propofol in recovery room and incidence of pain was graded as:

0 – No recall of pain
1 – recall of pain

Data collection and Randomization:
Keeping alpha error of 0.05, power of 0.85, 26 patients were required in each group. Keeping in mind natural drop outs 30 patients in each group was taken. Each and every subject who fulfills the eligibility criteria for this study was assigned a sequence number in increasing trend starting from 01. Then random selection of patients by lottery system and preparation

of drug was done by one of the colleagues to maintain the blindness of the study. My colleague helped me in randomly allocating patients to one of the groups and prepared the study drug accordingly. He handed over the prepared drug to me with unique code of identification on it. I completed all the observations and recordings of the cases without knowing the group of the patient. Only after completion of the study, I came to know the group of the patient with the

Statistical Analysis

The data was entered into the computer through Epilog Version 3.3.2 to create a database of the study and was analyzed using SPSS version 15.0 to assess the outcome of the study. Statistical comparison was made by comparison between groups by applying chi-square test to a contingency table and two ANOVA was applied.

The statistical analysis was done using SPSS version 20.0. The values were represented in Number, proportion (%) and Mean ± SD.

Result

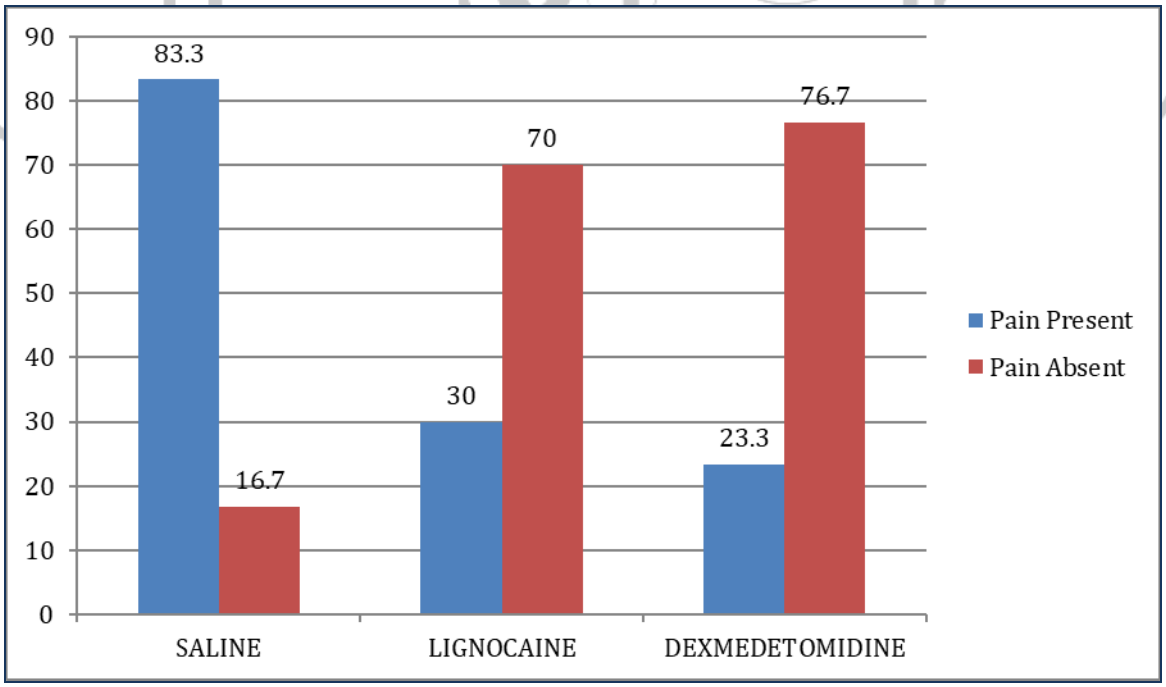
The primary end point of this study was to evaluate incidence and severity of pain on injection of propofol and effects of drugs in attenuating pain. The secondary end point was to assess the recall of pain after surgery.

The patient in all the three groups were comparable and there was no statistically significant difference in age, sex, and weight.

Incidence of pain due to propofol was found to be 83.3% in control group. Premedication with lignocaine showed statistically reduction in incidence of pain to 30%. (P<0.001). Dexmedetomidine also showed statistically significant reduction in incidence of pain to 23.3% (p,0.001). The difference in incidence of pain between group B and group C was not statistically significant (p=0.559) (table 3.).

DEGREE OF PAIN	RESPONSE
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 a behavioural sign or Pain reported spontaneously without questioning
Severe{3}	Strong vocal response or response accompanied

Fig 3. Incidence of pain in different groups



While comparing the severity of pain among three groups, 50 % patient felt severe pain in control group, while none in group B and group C experienced severe pain (table 4.1, 4.2, 4.3). Hence there was statistically significant reduction in severity of pain in group B (p<0.001) and in group C (p<0.001)

Only 16.7% of patients of group A while 70% and 76.7% of group B and group C respectively felt no pain (table 4.1, 4.2, 4.3). Difference in severity of pain in group B and group C was not statistically significant (p <0.82) (table 4.3).

Table 4.1 Comparison of pain score between group A and group B

		Pain score				P value
		0	1	2	3	
Group A	N	5	4	6	15	P<0.001
	%	16.7	13.3	20	50	
Group B	N	21	6	3	0	
	%	70	20	10	0	

X^2=26.246

Table 4.2 Comparison of pain score between group A and group C

		Pain score				P value
		0	1	2	3	
Group A	N	5	4	6	15	P<0.001
	%	16.7	13.3	20	50	
Group C	N	23	5	2	0	
	%	76.7	16.7	6.7	0	

X^2=28.683

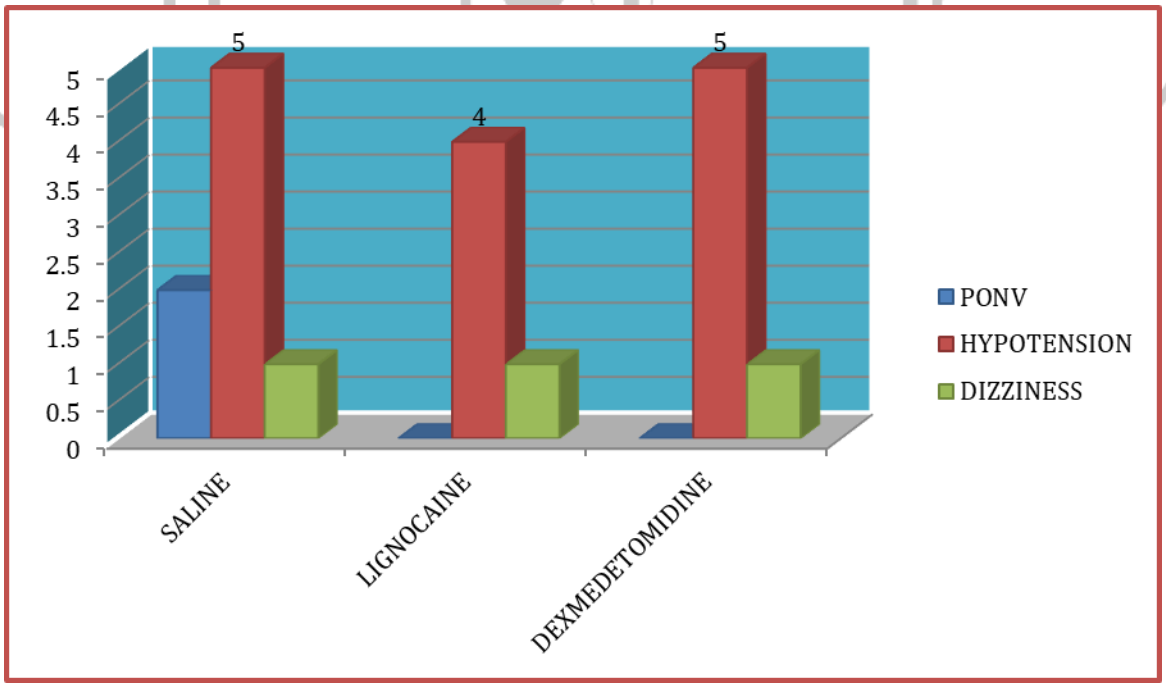
Table 4.3 Comparison of pain score between group B and group C

		Pain score				P value
		0	1	2	3	
Group B	N	21	6	3	0	P<0.001
	%	70	20	10	0	
Group C	N	23	5	2	0	
	%	76.7	16.7	6.7	0	

X^2=0.382

No severe side effects were seen in all the three groups. Although incidence of hypotension and dizziness was comparable in all the groups.PONV was not seen in group B and group C.

Fig 5. Incidence of any side effect



Patients were followed up for two hours in recovery room and asked for recall, if there was pain during injection of propofol during induction. The incidence of recall of pain was reported to be 66.7% in group A (Placebo), 13.3% in group B (Lidocaine)

and 23.3% in group C (Dexmedetomidine). The difference between the incidences of recall of pain between the three groups is shown in table 6. The difference of recall of pain between group A (placebo) and group B was highly significant statistically ($p< 0.001$), difference between group A and group C (Dexmedetomidine) is also highly significant ($p< 0.001$). There was no significant difference between group B and group C ($p>0.05$)

Recall of Pain

		Group A N	%	Group B N	%	Group C N	%	P Value
Recall of Pain	Yes	20	66.7	4	13.3	7	23.3	P*<0.001
	No	10	33.3	26	86.7	23	76.7	P^{Φ} <0.001 $P^{\#}$=0.317

* level of significance between group A&B

Φ level of significance between group A&C

level of significance between group B&C

DISCUSSION

Propofol has been widely used for induction and maintenance of anesthesia, but pain that accompanies propofol injection can be very distressing to the patients [15]. A study reported that incidence of pain on propofol injection is 28% to 90% in adults and 28% to 85% in children [12].

Various interventions have been tried in search of elimination of propofol-induced pain [4, 12, 25], however lignocaine remains most effective. Various studies have recommended using larger veins [13]; decreasing speed of injection [11]; injecting the drug into a fast running IV fluid [26]; diluting it with 5% glucose or 10% intralipid; mixing lidocaine in propofol; pretreating with lidocaine and venous occlusion;pretreating with alfentanyl, fentanyl, or pentothal; cooling propofol to

4°C; injecting cold saline (4°C) before propofol; or discontinuing fluid during the injection.

In the systematic review by Pascale Picard et al [4], incidence of pain following propofol injection was 70%, in the absence of other pretreatments. Similarly, H. Zahedi, *et al* [5] reported overall incidence of pain to be 82.2% in the saline group and concluded that pain intensity was significantly less in patients receiving drugs for pretreatment than those receiving saline (*P*=0.001). A.Turan et al [7] conducted a similar study and found the incidence of pain in saline group (group I) was 86.66% and that in group II (dexmedetomidine) was 33.3% and in group III (lignocaine) was 23.33%. In study, i.v. 0.25 mcg/kg dexmedetomidine was found to be equally effective in reducing the pain associated with the i.v. injection of propofol when compared with 0.5 mg /kg lidocaine. Meenu Gupta et al [27] in 2006 in a randomized, double blinded study found that incidence of pain after premedicating with 1% lignocaine to be 40% as compared to 76% in case of placebo. Ahmad et al in 2013 [19] incidence of moderate to severe pain at 15seconds after the injection of propofol was 56% in the saline group which was greatly reduced to 14% in the lignocaine group. Ozgul. U et al in 2013 [18] in a prospective, randomized, double-blinded study concluded that pre-treatment with alkalinized lignocaine appears to be effective in reducing the pain during propofol injection.A large meta-analysis conducted by Pascale Picard et al [4] suggested that lidocaine is most effective in preventing pain when given before propofol.

In our study incidence of pain on propofol injection in placebo group was 83.33%. And that of lignocaine and dexmedetomidine group was 30% and 23.3% respectively. However, Ayoglu et al in 2007 [22] compared dexmedetomidine with lidocaine in reducing the pain of propofol and found pretreatment with dexmedetomidine is not effective in reducing injection pain of propofol. The different doses and the different application and assessment method of the intensity of propofol pain and rates of injection of the study drug may have been the main reason of these various results.

Lu Y et al in 2013[20] in their study concluded that dexmedetomidine significantly reduced pain due to propofol injection when compared to saline group like our study. Gamze Sarkılar et al [21] in 2012 studied effect of dexmedetomidine on pain caused by injection of propofol and that infusions in pre-anesthetic sedative doses of 0.5 µg/kg and 1 µg/kg of dexmedetomidine decrease the incidence of propofol injection pain compared to placebo.Incidence of recall of pain was found to me maximum in group A (66.7%) ,like Meena Gupta et al found in there study to be 84% in placebo group. the difference in lignocaine and dexmedetomidine group was found to be statistically insignificant.Incidence of side effects were negligible in most of the studies.Lidocaine, in addition to being a local anesthetic, alleviates the pain on injection of propofol by two other mechanisms: firstly lidocaine inhibits bradykinin generation [Scott et al[1], Nakane M et al[16,12] lidocaine mixed with

propofol decreases its pH, also resulting in a lower concentration of propofol in the aqueous phase and, therefore, less pain (Eriksson et al [17] The latter mechanisms come into play when lidocaine is premixed with propofol. Even lidocaine, however, which can be considered as the gold standard, fails to alleviate pain in all cases. Moreover, the administration of lidocaine may be undesirable in certain circumstances. There has been a report of anaphylactic shock developing immediately after intravenous administration of lidocaine without preservative added to the propofol to alleviate pain on injection [28]

Dexmedetomidine is alpha 2-adrenoreceptor agonist. Possible mechanism involved in decreasing propofol pain by dexmedetomidine might be venous alpha$_1$ and alpha$_2$-stimulation resulting in release of vasodilator prostaglandins that antagonize the veno-constrictor response. This modulates the sympathetic response of venous smooth muscle and may be important in endothelial dysfunction caused by propofol [Callow ID et al, 1998]. There are other studies that suggest that dexmedetomidine has also shown to promote peripheral anti-nociception. Dalle et al (2001) [23] suggested a novel role for inwardly rectifying hyperpolarization-activated conductance in peripherally mediated anti-nociception. Turan et al [7] suggested a possible mechanism of dexmedetomidine in decreasing propofol pain,might be venous a_1- and a_2-stimulation, resulting in release of vasodilator prostaglandins that antagonize the veno-constrictor response.

CONCLUSION

The study showed that lidocaine 0.5mg/kg and dexmedetomidine 0.25 µgm/kg significantly reduces the incidence of pain during propofol injection more than placebo ($p< 0.001$). There was no significant difference in pain score between groups B and C. the difference of pain score between group A and that of group B and C was significant ($p >0.05$). Addition of pretreatment drugs did not have any serious side effects or any cardiovascular instability in comparison to control group.

- Hence in our opinion dexmedetomidine effectively reduced pain on propofol injection.
- The effects of lignocaine and dexmedetomidine are comparable statistically.
- It can be effectively used as an alternative to lignocaine for the purpose of reducing propofol injection pain especially where use of lignocaine is undesirable.

INTEREST OF CONFLICTS: NONE

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