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Dexmedetomidine for Prevention of Propofol Induced Pain: A Prospective, Randomized, Double Blind Controlled Study

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Abstract: Propofol, an intravenous (IV) anesthetic is associated with pain on injection with incidence ranging from 28% to 90% in adults. The aim of present study is to know the anti-nociceptive effect of dexmedetomidine infusion with that of control (Normal saline) infusion immediately prior to propofol injection in alleviating Propofol injection pain (PIP). The present study was a randomized controlled study where in following the approval of the hospital's ethics Committee, 60 consenting adult patients were randomly divided into two groups A and B (n = 30) to receive 20 ml of normal saline as control and 0.5 µg/kg of dexmedetomidine diluted in 20 ml of normal saline respectively. The propofol injection pain was assessed according to the Mc Cririck and Hunter scale. The 27(90%) patients in control group expressed pain compared to 9(30%) patients in Dexmedetomidine Group. In the present study, participants receiving dexmedetomidine 6(20%) patients were determined to be in Grade 1 and 2(6.67%) participants were in grade 2 followed by 1(3.33%) patients were determined to be in Grade 3. There is no significant difference between heart rate, Mean Arterial Pressures and haemodynamic side effects in both groups. Pre-treatment with0.5 µg/kg of dexmedetomidine is effective in alleviating incidence and severity of propofol induced pain, did not cause significant hemodynamic adverse side effects.

Keywords: Propofol, Dexmedetomidine, pain, Anaesthesia, Prevention, haemodynamic changes.

INTRODUCTION

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].

Despite these positive attributes, the high prevalence of propofol injection pain (PIP) pain has an incidence ranging from 28% to 90% in adults [2-3], highlight the significance of finding the ideal combination of drug, dosage and mode of administration of premedicants to alleviate PIP. A number of bolus drugs with variable efficacy have been studied to reduce PIP. Many studies have tried to address this challenge and have explored additional and alternative strategies trials that compared the use of any drug or non-drug interventions (or combinations) with an active or inactive control in adults receiving intravenous propofol [4].

Dexmedetomidine is also an alpha-2 adrenoceptor agonist but is more selective than clonidine and has analgesic and sedative properties [5]. It has been evaluated for reducing the incidence and intensity of propofol-induced pain, but reported results are inconsistent [5-6].

The aim of present study is to know the anti-nociceptive effect of dexmedetomidine infusion with that of control (Normal saline) infusion immediately prior to propofol injection in alleviating Propofol injection pain (PIP). The objective of this study is to assess incidence and grade of propofol induced pain and arm withdrawal response, incidence of hemodynamic changes after single dose intravenous (iv) infusion of dexmedetomidine 0.5 µgms/ kg.

MATERIALS AND METHODS

The present study was conducted on patients admitted in Kakatiya Medical College, Warangal Telangana, undergoing elective surgeries under general anaesthesia after obtaining permission from the

Institutional Ethical Committee. The participants were informed regarding the purpose, procedures, risks and benefits of the study. Written and Informed Consent was obtained from all participants.

The present study was conducted with a total of 60 participants; who were divided randomly into two groups. Group A comprised of 30 patients administered intravenous normal saline 20ml as control and Group B comprised of 30 patients administered intravenous Inj. Dexmedetomidine 0.5µgms/kg diluted in 20ml of normal saline. The present study was conducted from October 2015 to September 2017 i.e.two years. Inclusion criteria is patient willing to participate in surgery**,** Aged between 20 to 50 years**,** ASA I and II undergoing elective surgeries. Exclusion criteria is Patient's refusal to participate in study**,** allergy to the study drug**,** uncontrolled hypertension**,** renal or hepatic impairment**,** psychiatric diseases**,** seizures**,** history of drug abuse and Pregnancy. A detailed history of the patient was taken, complete clinical examination was done to include and exclude patients in accordance with the inclusion & exclusion criteria. The investigations were performed on all participants. Pre-operative assessment of temperature, pulse rate, respiratory rate, blood pressure and conditions of heart and lungs were noted. The noninvasive arterial blood Pressure, ECG, Pulse Rate, SPO2 parameters were monitored in all participants intraoperatively**.**

An 18 Guage IV cannula was secured in the vein on the dorsum of the hand. Patients were randomly allocated into two groups (Group A and Group B). The study drugs, that is either inj Normal saline 20ml (Group A) or inj. Dexmedetomidine 0.5 µgms/kg((diluted with 20ml Normal saline for Group B) were loaded in identical 20 ml syringes labeled as "study drug" and infused over 10 minutes.

Immediately after infusion of the study drug, injection Propofol 2mg/kg IV was administered slowly over 25 seconds. Starting from the time of injection, participants were assessed for pain by asking "does it hurt?" every 5 seconds, until the participant became unresponsive. Degree of pain was scored with Mc. Cririck and Hunter scale which was mentioned below.

Score	Response	Interpretation	Interpretation for stastical analysis
0	Negative response (no) to question	No pain	No pain
1	Pain reported "yes" only in response to the question without any behavioural changes	Mild pain	Mild pain
2	Voluntary complaint of pain or behavioural changes	Moderate pain	Moderate to severe pain
3	Strong vocal response or facilal grimacing or arm withdrawl or tears on injection	Severe pain	

Patients were monitored for hemodynamic effects. Mean arterial blood pressure (MAP) and heart rate (HR) were measured at 2-minute intervals from just before the administration of study drug to 10 minutes after the tracheal intubation (following Inj. Succinylcholine 1-2mg/kg).It was followed by a standard technique consisting of Inj. Fentanyl 1-2 mg/kg, glycopyrrolate 0.2 mg and inj. vecuronium as appropriate for the weight of the patient. Anaesthesia was maintained with nitrous oxide and oxygen. Any episode of bradycardia (HR <60/min or a fall of >20% from basal HR), hypotension (mean atrial pressure <60 mm Hg or a fall of >20% from basal BP), hypertension or tachycardia (rise of >20% from basal values) were recorded and managed as per the standard protocols

STATISTICAL ANALYSIS

Statistical testing was conducted with the MS Excel and statistical package for the social sciences version (SPSS) version 20.0. Socio-demographic data i.e. age, weight, height and body mass index (BMI) and baseline vital parameters are presented as mean (± standard deviation) and were compared utilising the unpaired Student's *t*-test. Categorical variables are expressed as frequencies and percentages and were compared using Chi-square test. For all statistical tests, *P* value of < 0.05 was taken as significant.

RESULTS

The present study was conducted in a sample of 60 participants, who were randomly divided into two groups, comprising of 30 participants each, Group A (Control) (n=30) and Group B (Dexmedetomidine) (n=30). The results are as follows:

Demographic characteristics

Comparison of the characteristics is depicted in Table 1.

Table-1: Comparison of Demographic Characters between the Study Groups

Character	Group A (Control) (N=30)	Group B (Dexmedetomidine)(N=30)	P value
Age (yrs)(Mean+-SD)	35.42(±10.20)	37.58(±12.10)	> 0.05
Gender (M/F)	14/16	16/14	> 0.05
Weight (kg) (Mean+-SD)	58.27(±7.83)	55.67(±7.57)	>0.05
ASA status (I/II)	25/5	26/4	>0.05

SD: standard deviation; ASA status: American society of Anesthesiologist-physical status

Age

The mean age in control group was observed to be 35.42(±10.20) yrs and in Dexmedetomidine group it was observed to be 37.58(±12.10) yrs. The difference in the mean age of the two study groups was not found to be statistically significant. (P>0.05) Thus, the two study groups were observed to be comparable in terms of their age.

Gender

Control Group was observed to comprise of 14(46.67 %) males and 16(53.33%) females. Dexmedetomidine Group was observed to comprise of 16(53.33%) males and 14(46.67 %) females. The difference in gender of participants of the two study groups was not found to be statistically significant. (P>0.05) and the two study groups were observed to be comparable in terms of gender.

Weight

The mean weight in control group was observed to be 58.27(±7.83) kg and in Dexmedetomidine group it was observed to be 55.67(±7.57) kg. The difference in the mean weight of the two study groups was not found to be statistically significant. (P>0.05) and the two study groups were thus observed to be comparable in terms of their weight

ASA Status

Control Group was observed to comprise of 25 patients classified as ASA-I status and 5 patients classified as ASA-II status. Dexmedetomidine Group was observed to comprise of 26 patients classified as ASA-I status and 4 patients classified as ASA-II status. The difference in ASA status between the two groups was not found to be statistically significant. (P>0.05) and the two study groups were thus observed to be comparable in terms of their ASA physical status.

Incidence of Pain and Severity of Pain on Propanol Injection (PIP):

The 27 patients in control group expressed pain compared to 9 patients in Dexmedetomidine Group

Table-2: Effectiveness of Dexmedetomidine in Reducing Propanol Induced Pain (PIP) among the two study groups

Mc.Crick and Hunter Pain Scale	Group A; Control (N=30)	Group B; (Dexmedetomidine) (N=30)
Grade 0	3(10)	21(70)*
Grade 1	8(27)	6(20)*
Grade 2	15(50)	2(6.67)*
Grade 3	4(13)	1(3.33)*
Total	30(100)	30(100)*

P<0.05 *: Significant

Hemodynamic Parameters

The heart rate (HR), systolic and diastolic blood pressure, Mean arterial pressure (MAP) of the study participants were monitored preoperatively (baseline), time of injection of the study drugs, and till after 2, 4,6,8,10,12,14,16,18 and 20 minutes after injection minutes after administration of study drugs in both groups (Groups A & B).

Heart rate

The mean heart rate in control group and dexmedetomidine group are 85.26± 17.73 and 88.33(± 14.11) bpm respectively. After start of infusion of dexmedetomidine, HR was observed to decrease to 84.53 (± 23.11), in Group B. After 2 minutes, it decreased further to a mean of (82.27± 17.73) bpm and it decreased to 81.70(±17.21) bpm after 4 minutes. Thereafter it showed a slight increase at 6 minutes to 84.60(±16.21) bpm and at 10 minutes a mean HR of 84(±16.77) bpm was observed. At 12 minutes an increase in the mean HR was observed at 85.53(±16.46) bpm which increased to 86.93(±15.15) bpm at 14 minutes. At 16 minutes it decreased slightly to 86.43(±15.42) beyond which it was observed to attain a mean of 85.93(±12.43) at 18 and 85.97(±12.31) bpm at 20 minutes respectively. In control group after propofol injection there is fall in heart rate and it comes to normal in 10 minutes after infusion.

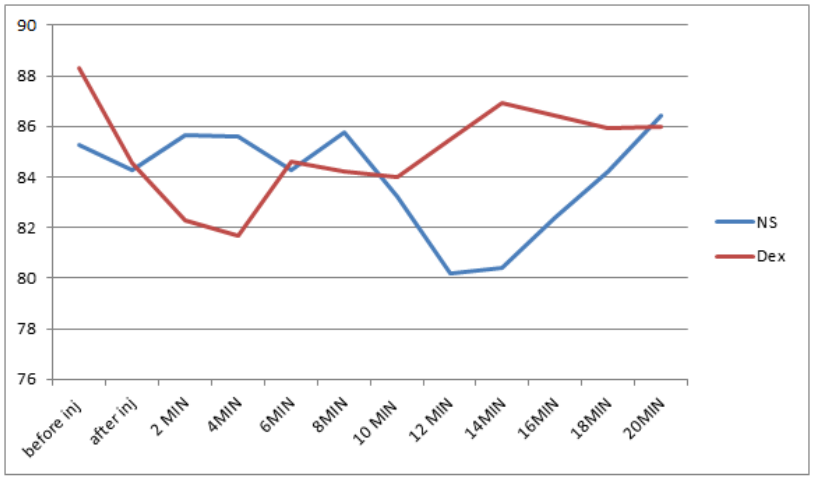

Fig-1: Mean heart rates in two study groups

Mean Arterial Pressure (MAP)

After start of infusion of dexmedetomidine, MAP was observed to increase to 99.60 (± 13.52) mmHg in Group B. After 2 minutes, it was observed to decrease to a mean of (99.20 ± 12.85) mmHg and it decreased further to 98.57(±13.64) mmHg after 4 minutes. Thereafter it showed a slight increase at 6 minutes to 99.03(±14.29) mmHg and at 10 minutes a mean MAP of 99.63 (±17.64) mmHg was observed. At 12 minutes a decrease in the mean MAP was observed at 97.23(±18.95) mmHg which increased to 100.10 (±17.90) mmHg at 14 minutes. At 16 minutes, a decrease was observed to 96.53 (±16.54) mmHg beyond which it was observed to attain a mean of 95.43 (±16.06) mmHg at 18 and 95.70 (±15.71) mmHg at 20 minutes respectively. The difference in mean arterial pressure among both the groups was not found to be significant at all observed points of time after infusion of the study drugs.(p>0.05)

Hemodynamic Side Effects

Table-3: Incidence of side effects in both the study groups

Incidence Of Side Effects	Control Group Group A (N=30) N (%)	Dexmedetomidine Group Group B (N=30) N (%)
Present	4((13.33)	5(16.67)
Absent	26(86.67)	25(83.33)
Total	30(100)	30(100)

Table-4: Profile of Hemodynamic Side Effects in the Two Study Groups

Side effects	Control Group Group A (N=30) N (%)	Dexmedetomidine Group Group B (N=30) N (%)
None	26(86.66)	25(83.33)
Hypotension	0(0)	26(86.66)
Hypertension	2(6.67)	4(13.33)
Bradycardia	2(6.67)	1(3.33)
Total	30(100)	30(100)

The difference in the observed incidence of side effects in the two groups under study was not found to be statistically significant. (P> 0.05)

DISCUSSION

Propofol is the most widely used intravenous (IV) anaesthetic agent for induction and maintenance of anaesthetists as well as for sedation inside and outside operation theatre. Propofol is almost an ideal IV anaesthetic agent, but pain on its injection still remains a problem· The pain may not be a serious complication, but most patients remember it as one of the unpleasant encounters with anaesthetists [7].

All phenols irritate skin and mucous membrane. Thus, propofol being an alkylphenol is expected to cause pain in spite of the fact that it is almost isotonic. Propofol Injection Pain has also been described as angialgia[8] meaning that the pain is due to vascular involvement. It is immediate as well as delayed after 10–20 s. 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 [9].

Tourniquets are the most common compressive devices for venous occlusion, but can cause tourniquet-induced hypertension or even ischemia-reperfusion injury. Therefore, venous occlusion before propofol injection may be contraindicated in patients with moderate to severe hypertension. Various other pretreatments have also been evaluated, such as parecoxib with venous occlusion, tourniquet-controlled lidocaine, ondansetron, granisetron intravenous methylene blue, alfentanil, magnesium sulfate, nitroglycerine, lidocaine, and ketamine.

In the present study, the incidence of pain on propofol Injection (PIP) observed in all patients of control Group and in 9 patients of Dexmedetomidine Group. This difference between the groups in incidence of pain on propofol Injection was found to be significant statistically. ($P<0.05$). In the present study, participants receiving dexmedetomidine 6(20%) patients were determined to be in Grade 1 and 2(6.67%) participants were in grade 2 followed by 1(3.33%) patients were determined to be in Grade 3 according to Mc. Cririck and Hunter Pain Scale.In the present study, thus a significantly lesser incidence of propofol induced pain and severity of pain was observed in dexmedetomidine group when compared to control.

Ayoglu H *et al*. [6] determined the efficacy of dexmedetomidine compared with lidocaine in reducing the pain of propofol and rocuronium injection pain. In their study it was demonstrated that pre-treatment with 0.25 µg/kg DEX was not effective in reducing propofol injection pain whereas in our study 0.5µg/kg DEX was effective in reducing PIP. Yet the research done by Turan[5] and his colleagues contradicted this, showing that pretreatment with 0.25 mg/kg DEX decreased propofol injection pain as effectively as pretreatment with lidocaine 0.50 mg/kg.

He L *et al*.[10] evaluated the effect of dexmedetomidine (DEX) for reducing the incidence and severity of propofol injection pain .Their study demonstrated that the reduction of propofol injection pain through pretreatment with DEX depended on the DEX dose, 0.5µg/kg dexmedetomidine was effective in reducing propofol injection pain. Another finding in the study was that the interval between DEX and propofol infusion influenced the analgesic effect of DEX on propofol injection pain. DEX was most effective when 1 µg/kg was injected 5 min before propofol injection.

Dexmedetomidine has an analgesic effect by controlling the nociceptive signal transmission at both the central nervous system of the supraspinal and spinal levels, while accelerating antinociception in the periphery. Although the mechanisms of its analgesic effect have not been fully elucidated, many studies have shown that it acted by inhibiting the release of substance P from the dorsal horn of the spinal cord [11]. A recent study reported that dexmedetomidine effected strong analgesia through inhibition of the spinal ERK1/2 signaling pathway [12]. These studies suggest that it has an important role in nociceptive transmission at the spinal level

In the present study, the mean baseline heart rate and MAP was found to be comparable. After infusion of the study drug of dexmedetomidine, the mean heart rate was observed to decrease at the end of 2 minutes and at 4 minutes in (group B); thereafter it showed a slight increase at 6, 10 (time of propofol injection) 12,14,16 and 18 minutes. In the present study, at baseline, the Mean arterial pressure in both groups was found to be comparable. After infusion of the study drug of dexmedetomidine the mean arterial pressure increased and was. The difference in mean arterial pressure among both the groups was not found to be significant at all observed points of time after infusion of the study drugs.($p>0.05$). In the present study, significant changes in hemodynamic parameters were observed in 5/30 (16.67%) patients of Group B, bradycardia in one and hypertension was observed to develop in 4 participants.

Ahmed A *et al*. [13]. in their study observed that there was transient rise in heart rate in patients suffering from pain of verbal rating scale score 2-3 in both the groups, but no changes in blood pressure were noted. Lee SH *et al*. [2] evaluated, 0.5 µg/kg of dexmedetomidine mixed with propofol is a proper dosage for reducing injection pain while controlling hemodynamic changes as was utilized in the same dose of dexmedetomidine in the present study, with comparable results.

Thukral S *et al.* [14]**.** in their study observed that two patients had hypotension while no episode of bradycardia occurred in Dexmedetomidine. In the study by He L *et al*. [10] none of the patients who received DEX 0.25, 0.5, or 1 mg/kg infusion developed bradycardia or hypotension. This is comparable to our results of our study.

The decline in heart rate is attributable to the baroreceptor reflex response to the increase in blood pressure. In this study, there were smaller decreases in blood pressure in all groups that were administered dexmedetomidine (0.25-0.75 µg/kg) compared to saline administration. The reason for this is unclear, but considering the marked decrease in blood pressure seen in the saline group, the blood pressure increasing effect of dexmedetomidine may be a counterbalance to the blood pressure decreasing effect of propofol.

CONCLUSION

The results of the present study show that 0.5 µg/kg of dexmedetomidine is effective in alleviating

incidence and severity of propofol induced pain, did not cause significant hemodynamic adverse side effects.

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