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Original Research Article

Comparison of the anti-nociceptive effect of dexmedetomidine with that of clonidine immediately prior to propofol injection in alleviating propofol injection pain

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ABSTRACT

Background: Propofol is the drug of choice for induction of anaesthesia because of its rapid onset and short duration of action, easy titration, and favourable profile for side effects. But three out of five patients experience pain on injection of propofol. Alleviation of Propofol injection pain (PIP) is thus a major concern and several interventions have been investigated to alleviate the pain associated with propofol injection. Clonidine was found to alleviate the pain of injected propofol effectively. Dexmedetomidine is also an alpha-2 adrenoceptor agonist but is more selective than clonidine and has analgesic and sedative properties. The aim of the study was to compare the anti-nociceptive effect of dexmedetomidine with that of clonidine immediately prior to propofol injection in alleviating propofol injection pain.
Methods: A randomized controlled study was conducted on 60 patients admitted in Malla Reddy Institute of Medical Sciences, undergoing elective surgeries under general anaesthesia (GA) for 2 years from October 2015 to September 2017. The patients were randomly divided into two groups (30 each). Group A was administered intravenous injection clonidine 0.5 µg/kg. Group B was administered intravenous injection dexmedetomidine 0.5 µg/kg.
Results: In the present study, difference between the study groups in their mean age, mean weight, gender, ASA grading was not found to be statistically significant. The difference between the groups in incidence of pain on propofol injection was found to be significant statistically. The mean baseline heart rate was declining and mean arterial blood pressure was increasing in both the groups but the difference was not found to be statistically significant.
Conclusions: Pre-treatment with 0.5 µg/kg of IV dexmedetomidine is more effective as compared to IV clonidine in alleviating propofol injection pain.

Keywords: Propofol, Pain, Dexmedetomidine, Clonidine

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, about three out of five patients experience pain on injection of propofol, with one of these patients reporting severe or excruciating pain. Some patients recall the induction of anaesthesia as the most painful part of the perioperative period.[2]

This pain known as Propofol injection pain (PIP), has an incidence ranging from 28% to 90% in adults.[3-8] The quality of pain has been described as extremely sharp, aching, or burning and has been arranged as the seventh most important problem in current practice of clinical anaesthesia.[9] However, the pain of injection is undesirable,

and may cause hand withdrawal and dislodging of the venous cannula.[10,11]

Alleviation of PIP is thus a major concern and several interventions have been investigated to alleviate the pain associated with propofol injection. A systematic review in 2000 suggested pre-treatment using lidocaine (lignocaine) in conjunction with venous occlusion as the most effective intervention.[12] Despite recommendation the technique failed to gain widespread popularity, possibly because of the time needed to apply the tourniquet.

More than 100 new 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.[2]

Among alpha-2-adrenergic receptor (a2-AR) agonists studied, clonidine was found to alleviate the pain of injected propofol effectively.[13] It has also been widely used and investigated as an analgesic adjuvant for anaesthesia and pain therapy. Dexmedetomidine is also an alpha-2 adrenoceptor agonist but is more selective than clonidine and has analgesic and sedative properties.[11] It has been evaluated for reducing the incidence and intensity of propofol-induced pain, but reported results are inconsistent.[10,11]

Need for the study

Routine use of dexmedetomidine infusion as pre-medication and lack of similar comparison prompted us to study and compare its anti-nociceptive effect for PIP.

Aim

The aim of the study was to compare the anti-nociceptive effect of dexmedetomidine infusion with that of clonidine infusion immediately prior to propofol injection in alleviating PIP.

Objective

The objective of this study was to compare the incidence and severity of propofol induced pain and hemodynamic changes between the study groups receiving after single dose IV infusion of dexmedetomidine and clonidine.

METHODS

A randomized controlled study was conducted on 60 patients admitted in Malla Reddy Institute of Medical Sciences, undergoing elective surgeries under general anaesthesia (GA) for 2 years from October 2015 to September 2017. The patients were randomly divided into two groups. Group A comprising of 30 patients administered intravenous injection clonidine 0.5 µg/kg. Group B comprised of 30 patients administered intravenous injection dexmedetomidine 0.5 µg/kg.

Ethics and consent

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

Inclusion criteria

Study participants of age 20-50 years undergoing elective surgeries, belonging to ASA grade I or II were included in the study with their consent.

Exclusion criteria

Patients who refused to participate in study, who are allergic to drugs with uncontrolled hypertension and other medical ailments were excluded from the study.

Procedure

A detailed history along with complete clinical examination, routine lab investigations and pre-operative assessment of temperature, pulse rate, respiratory rate, blood pressure and conditions of heart and lungs were recorded. Intra-operatively, non-invasive arterial blood pressure, ECG and pulse oximetry (pulse rate, SPO_2) were recorded.

An 18 guage IV cannula was secured in the vein on the dorsum of the hand. Depending upon the drug used for premedication, patients were randomly allocated into two groups (group A and group B). The study drugs, that is either injection dexmedetomidine 0.5 µg/kg (group B) or injection clonidine 0.5 µg/kg (group A) were loaded in identical 20 ml syringes (diluted with 20 ml normal saline), labeled as ‘study drug’ and infused over 10 min.

Immediately after infusion of the study drug, injection propofol 2 mg/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.

Patients were monitored for hemodynamic effects. Mean arterial blood pressure (MAP) and heart rate (HR) were measured at 2 min intervals from just before the administration of study drug to 10 min after the tracheal intubation (following injection succinylcholine 1-2 mg/kg). It was followed by a standard technique consisting of injection fentanyl 1-2 mg/kg, glycopyrrolate 0.2 mg and injection 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, $p<0.05$ was taken as significant.

Table 1: Mc. Cririck and Hunter scale.

Score	Response	Interpretation	Interpretation for statastical 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 facial grimacing or arm with drawl or tears on injection	Severe pain	

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 (clonidine) (N=30) and group B (dexmedetomidine) (N=30). The difference in the antinociceptive effect of the two drugs in reducing PIP was found to be statistically significant. ($p<0.05$) i.e.; dexmedetomidine was determined to be significantly more effective than clonidine in reducing PIP among the study participants.

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 min after injection minutes after administration of study drugs in both groups (groups A and B).

Heart rate

The mean baseline HR was observed to be 82.33±10.20 bpm in group A (clonidine) participants and was observed to be 88.33±14.11) bpm in group B (dexmedetomidine) participants.

The mean HR at baseline in both groups was found to be comparable i.e.; the difference in the mean heart rate between the two study groups was not found to be significant statistically ($p>0.05$). Though a decrease in the mean heart rate was observed after infusion of the study drug in both the study groups and in group B it declined further at the end of 2 and 4 minutes, the difference in mean heart rate among both the groups was not found to be significant at observed points of time after infusion of the study drugs ($p>0.05$).

Mean arterial pressure

The mean baseline MAP was observed to be 90.77±18.59 mmHg in group A (clonidine) participants and was observed to be 97.53±9.27 mmHg in group B (dexmedetomidine) participants. At baseline, the MAP in both groups was found to be comparable i.e.; the difference in the mean arterial pressure between the two study groups was not found to be significant statistically ($p>0.05$).

The hemodynamic side effects observed in the two study groups are depicted in Table 6.

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

Table 2: Comparison of demographic and other characteristics between the study groups.

Characteristics	Group B (dexmedetomidine) (N=30)	Group A (clonidine) (N=30)	P value
Age (years) (mean±SD)	34.43±10.20	37.60±12.10	>0.05
Gender (M/F)	14/16	16/14	>0.05
Weight (kg) (mean±SD)	56.27±7.83	58±7.57	>0.05
ASA status (I/II)	28/2	27/3	>0.05

Note: SD: Standard deviation; ASA status: American society of Anesthesiologist- physical status.

Table 3: Incidence of Pain on propofol injection (PIP) in the study groups.

Incidence of PIP	Clonidine group		Dexmedetomidine group		P value
	N (%)	%	N (%)	%	
PIP	18	60	9	30	<0.05*

Note: p<0.05*: significant.

Table 4: Effectiveness of clonidine and dexmedetomidine in reducing PIP among the two study groups.

Mc. Crick and Hunter pain scale	Group A (clonidine) (N=30)		Group B (dexmedetomidine) (N=30)		P value
	N	%	N	%	
Grade 0	12	40	21	70	<0.05*
Grade 1	12	40	6	20	
Grade 2	5	16.67	2	6.67	
Grade 3	1	3.33	1	3.3	
Total	30	100	30	100	

Note: p<0.05*: significant.

Table 5: Incidence of side effects in both the study groups.

Incidence of side effects	Group A (clonidine) (N=30)		Group B (dexmedetomidine) (N=30)		P value
	N	%	N	%	
Present	2	6.67	5	16.67	>0.05
Absent	28	93.3	25	83.3	
Total	30	100	30	100	

Table 6: Profile of hemodynamic side effects in the two study groups.

Profile	Group A (clonidine) (N=30)		Group B (dexmedetomidine) (N=30)		P value
	N	%	N	%	
None	28	93.33	25	83.33	<0.05*
Hypotension	1	3.33	0	0	
Hypertension	1	3.33	4	13.33	
Bradycardia	0	0	1	3.33	
Total	30	100	30	30(100)	

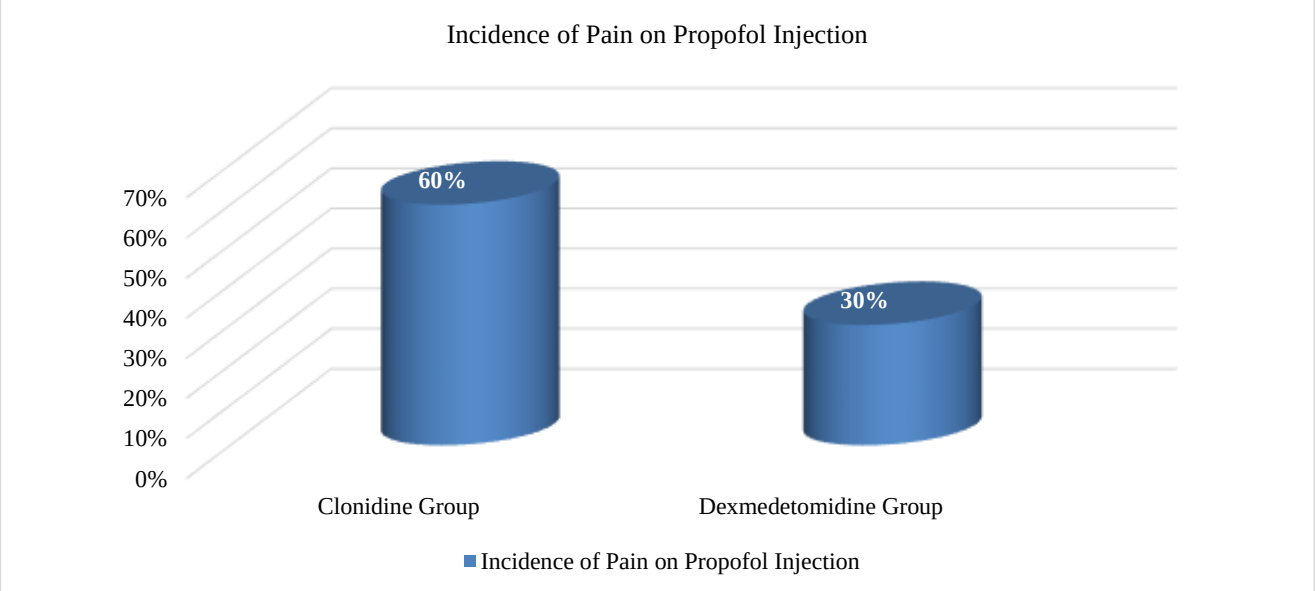

Figure 1: Incidence of Pain on propofol injection (PIP) in both study groups.

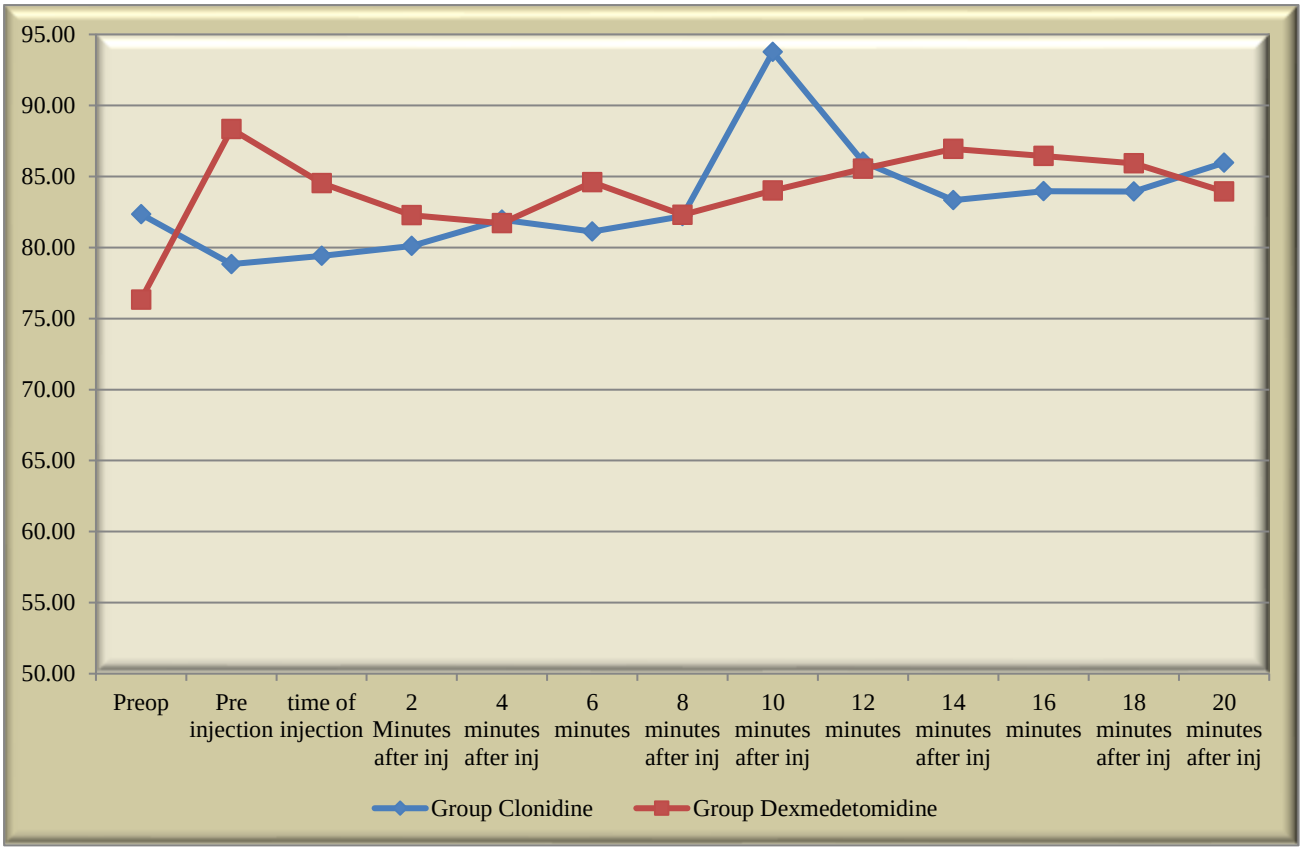

Figure 2: Mean heart rate variability in both the study groups.

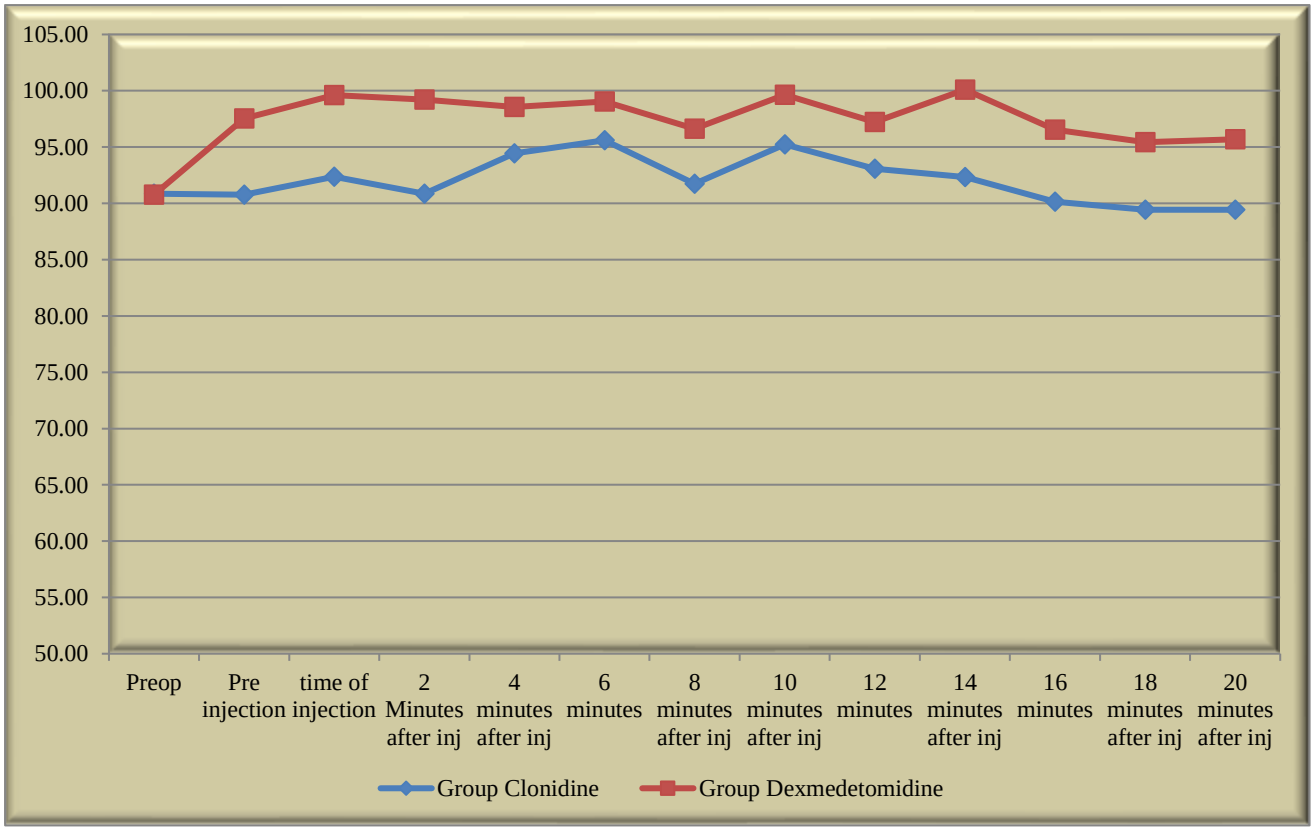

Figure 3: Mean arterial pressure in both the study group.

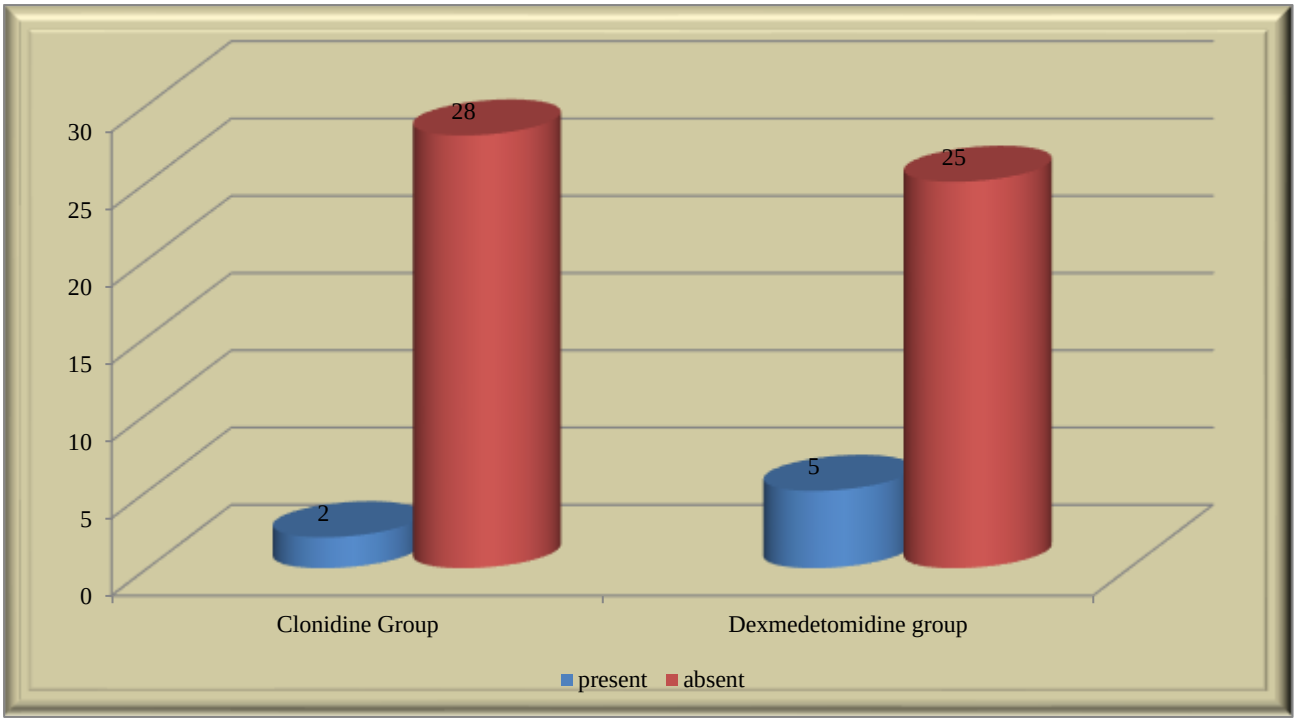

Figure 4: Incidence of hemodynamic side effects in both the study groups.

DISCUSSION

Propofol is the most widely used 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.[14]

The pain may not be a serious complication, but most patients remember it as one of the unpleasant encounters with anaesthetists.[14]

About 60% of patients experience pain on injection with standard propofol alone-that is, without any preventive measures.[2]

Demographic characteristics

In the present study, the difference between the study groups in their mean age and weight was not found to be statistically significant with p value>0.05. Similarly, no statistically significant difference was found between the two groups in terms of gender and ASA grading with p>0.05 (Table 2).

The findings are in concurrence with the study done by Singh et al they assessed the efficacy of pre-treatment with various drugs to alleviate the propofol injection pain.[6] Similar findings were obtained by He et al in their study, where they evaluated the effect of dexmedetomidine (DEX) for reducing the incidence and severity of PIP.[15] There were no statistically significant differences observed among the seven groups with regard to age, weight, gender, or ASA class (p>0.05).

Alleviation of PIP

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. PIP has also been described as angialgia meaning that the pain is due to vascular involvement. It is immediate as well as delayed after 10-20 sec.[16,17]

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.[18] PIP seems to be independent of gamma-aminobutyric acid A receptors and a study by Fischer et al identified TRPV1 and TRPA1 as key molecules for propofol-induced excitation of sensory neurons.[19]

In the present study, the incidence of PIP observed in group B (dexmedetomidine) patients was observed to be 9/30 (30%) and in group A (clonidine) the incidence of PIP was observed to be 18/30 (60%) as shown in Table 3. This difference between the groups in incidence of pain on propofol Injection was found to be significant statistically (p<0.05). Thus, a significantly lesser incidence of propofol induced pain and severity of pain (as assessed by pain score) was observed in dexmedetomidine group than in clonidine group (Figure 1). The findings of our study are in concurrence with the finding of study done by He et al where they compared the efficacy and safety of lidocaine and dexmedetomidine in preventing PIP in their study.[20]

Both dexmedetomidine and lidocaine significantly decreased pain after administration of propofol in Chinese patents undergoing elective surgery. A recent study reported that dexmedetomidine effected strong analgesia through inhibition of the spinal ERK1/2 signaling pathway.[21] These studies suggest that it has an important role in nociceptive transmission at the spinal level.

The findings of our study are in contradiction with the findings of the study done by Ayoglu et al it was demonstrated that pre-treatment with 0.25 µg/kg DEX was not effective in reducing propofol injection pain whereas in our study 0.5 µg/kg DEX was effective in reducing PIP.[10] Turan and his colleagues also showed that pre-treatment with 0.25 mg/kg DEX decreased propofol injection pain as effectively as pre-treatment with lidocaine 0.50 mg/kg.[11]

Hemodynamic parameters

In the present study, the mean baseline heart rate was declining and mean arterial blood pressure was increasing in both the groups but the difference was not found to be statistically significant with p value >0.05 (Figure 2 and 3).

Ahmed et al in their study observed that there was transient rise in heart rate in patients suffering from pain of verbal rating scale (VRS) score 2-3 in both the groups, but no changes in blood pressure were noted.[5]

Lee et al also observed the increase in blood pressure seen during dexmedetomidine administration is due to vasoconstriction of the α_2 B-adrenoceptor, which is located on the smooth muscle cells of certain peripheral blood vessels. Similar results were observed in our study.[7]

In the study by He et al none of the patients who received DEX 0.25, 0.5, or 1 mg/kg infusion developed bradycardia or hypotension.[15] Therefore, they concluded that 1 mg/kg DEX is safe for the general population, which is again in contrary to our study where four patients were observed to have hypertension and one patient had bradycardia.

Hemodynamic adverse effects

In our study, clonidine group showed lesser hemodynamic adverse effects incidences compared to that of the dexmedetomidine (Table 5 and 6). Among the observed side effects, 1 incidence of hypotension and hypertension was recorded in clonidine group whereas for the patients who received dexmedetomidine, 4 incidences of hypertension and 1 of bradycardia was recorded.

In the study by Sapate et al no adverse effects like oedema, pain, wheal response at the site of injection were observed in the study.[22]

Pre-treatment with DEX has been reported to cause significant hemodynamic adverse side effects but it was contrary to the observations of the present study where both the drugs under study did not cause significant hemodynamic side effects.

Limitations

The present study was single centred, conducted for a period of 2 years and included relatively smaller sample size. In order to obtain more accurate results that can be precisely projected on the general population, multicentred studies with larger sample size is required.

CONCLUSION

In the present study we have found that 0.5 µg/kg of dexmedetomidine is more effective than 0.5 µg/kg clonidine in alleviating incidence and severity of PIP. Both clonidine and dexmedotomidine did not cause significant hemodynamic adverse side effects. Thus, both were also observed to have an acceptable safety profile in terms of hemodynamics. Therefore, we conclude that 0.5 mcg/kg of dexmedetomidine is more effective than 0.5 mcg/kg of clonidine in alleviating propofol induced pain with comparable safety profile.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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