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Dr. Kundan Gosavi
Associate Professor,
Department of Anaesthesia,
Grant Medical College,
Mumbai, Maharashtra, India

Dr. Gajanan Admane
Assistant Professor,
Department of Anaesthesia,
Grant Medical College,
Mumbai, Maharashtra, India

Comparison of efficacy of ketamine and dexmedetomidine for prevention of pain due to propofol injection

Dr. Kundan Gosavi and Dr. Gajanan Admane

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Abstract

Background: Propofol is a popular intravenous anesthetic induction agent which produces a smooth, rapid induction with rapid clearance and recovery but Pain on injection with Propofol is a common problem and can be very distressing to the patient. Ketamine is a phencyclidine derivative routinely used as an inducing agent and Dexmedetomidine Hydrochloride, an imidazole compound is the alpha 2 agonist. The present study was undertaken to compare the efficacy of Ketamine (0.5 mg/kg) and Dexmedetomidine (0.5 mcg/kg) in preventing the incidence and reducing the severity of pain on Propofol injection.

Method: 150 patients, ASA I&II, 18-60 year old undergoing elective surgical procedure under general anaesthesia (GA) were randomly assigned into 3 equal groups. Group C, Group K and Group D. In Group C 10 ml Normal Saline, In Group K Ketamine 0.5 mg/kg diluted to 10 ml with normal saline and in Group D Dexmedetomidine 0.5 mcg/kg diluted to 10 ml with normal saline was infused over 10 minutes before injecting Propofol. All study medications were prepared in a 10ML syringe that was covered with black tape by an anaesthesiologist who was not involved in the study. HR, BP, SPO2 and Pain Scores were noted at baseline, after premedication, while injecting study drugs at 3, 5 and 10 minutes and while injecting Propofol at the beginning, after half Propofol was injected, after complete Propofol was injected and at 1, 3 and 5 minutes after completing the Propofol. Incidence and severity of pain and involuntary movements, verbal communication by the patient was watched constantly. Injection pain was graded using a 4-point scale. The pain score was evaluated as '0' when there was no discomfort in the injection area (no pain), '1' when the patient simply answered "yes" without any change in behaviour (slight), '2' when there was a change in behaviour or voluntary complaint of pain (intermediate), and '3' when the patient made a loud sound, grimaced, withdrew his or her arm, or shed tears (severe). Data was recorded in printed proforma. The Proper blinding procedure was followed; All data were tabulated and analyzed by appropriate statistical methods to compare between the three groups.

Results: All 3 groups were comparable with respect to age, weight, gender composition and ASA status. In Group C, there were no changes in vital parameters and pain scores till injecting study drugs, however when Propofol injection was started almost all patients had some degree of pain (2% patients had no pain, 46% patients had mild pain, 34% patients had moderate pain whereas 18% patient had severe pain resulting in limb withdrawal) resulting in transient increase in HR, SBP, DBP and MAP. Once the Propofol injection was completed there was a sudden fall in above mentioned parameters. In Group K, there was a negligible increase in the hemodynamic parameters till infusing ketamine which remained constant throughout the period of injecting Propofol except for the initial few seconds of injecting Propofol which showed a slight surge in HR and MAP but it was not significant. 94% patients had no pain and only 6% of patients complained mild pain while injecting Propofol. Vitals returned to baseline in the post Propofol injection period. In Group D, there was statistically significant but clinically non-significant fall in HR, SBP, DBP, and MAP while infusing Dexmedetomidine. 84% of patients had no pain, 12% of patients experienced mild pain and only 4% of patients experienced moderate pain while injecting Propofol. Vitals continued to fall slowly in the post Propofol injection period. The mean baseline pain scores in all the 3 groups were almost similar and there was no significant statistical difference. Pain scores were compared within the group as well as with each other. When pain scores were compared within the control group at different intervals it was found that increase in pain scores were statistically highly significant at the start of injecting Propofol, when half of Propofol was injected and when complete Propofol was injected as compared to baseline pain scores (P value < 0.001). When pain scores were compared in group K and group D at different intervals, they were statistically not significant (P value > 0.05) at any point of time.

Conclusion: Ketamine 0.5 mg/kg and Dexmedetomidine 0.5 mcg/kg both are effective in reducing the incidence and severity of pain of Propofol injection. Their efficacy in attenuation of pain is comparable; However, Ketamine 0.5 mg/kg infusion pre-treatment shows better hemodynamic stability than Dexmedetomidine 0.5 µg/kg infusion pre-treatment.

Keywords: Propofol, ketamine, dexmedetomidine, pain score and hemodynamics

Introduction

Propofol is the most widely used intravenous (IV) anesthetic agent for induction and maintenance of anesthesia as well as for sedation in inside and outside operation theatre^[1]. Propofol is a popular intravenous anesthetic induction agent, especially for brief cases, day surgery or when a laryngeal mask airway is to be used.

Corresponding Author:
Dr. Kundan Gosavi
Associate Professor,
Department of Anaesthesia,
Grant Medical College,
Mumbai, Maharashtra, India

Propofol can also be used in total intravenous anesthesia (TIVA) technique for the maintenance of anesthesia and sedation. Propofol produces a smooth, rapid induction with rapid clearance and recovery [2]. It has also been used for the prevention of emesis, tracheal intubation without neuromuscular blocking drugs and the treatment of pruritis. There are some case reports of epileptiform movements, facial paraesthesia, bradycardia following the administration of Propofol but pain on its injection remains a major problem [3].

Propofol is an alkylphenol (2, 6 di-isopropyl phenol); oil at room temperature and insoluble in aqueous solution but is highly lipid-soluble. Current formulation of 1% (weight/volume) Propofol is available in 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide; also disodium edetate (0.005%) is added as a bacterial growth retardant. In this formulation, the oil droplets containing most of Propofol are large enough to reflect and refract white light significantly, and hence it appears milky [4]. Pain on injection with Propofol is a common problem and can be very distressing to the patient. The incidence of pain varies between 28% and 90% in adults during the induction of anaesthesia and may be severe [5]. In children, the incidence of pain varies between 28% and 85%. The younger the child, the higher is the incidence and severity of Propofol injection pain [5]. This pain is more common in females [6]. Propofol has a higher incidence of pain on injection when compared to other intravenous anesthetic agents.

The pain may not be a serious complication always, but it can clinically cause tachycardia in patients which is very important to avoid in patients of Ischemic Heart Disease, critical stenotic lesions, Coronary Artery Diseases, and many other cardiac pathologies. Profound pain due to Propofol injection may trigger acute myocardial infarction in patients with pheochromocytoma [7].

In paediatric patients, well co-operative children may become uncooperative, pain due to Propofol may cause movements of the limb which may result in sudden removal of an I.V. line. Propofol pain may trigger severe bronchospasm in chronic smokers [8]. Most patients remember it as one of the unpleasant encounters with anaesthetists [1]. All phenols irritate skin and mucous

membrane. Thus, Propofol being an alkylphenol is expected to cause pain although it is almost isotonic. POPI has also been described as angialgia by some, meaning that the pain is due to vascular involvement. POPI 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 [1].

Earlier it was hypothesized that Propofol might indirectly or directly interact with sensory nerve fibers located in the venous adventitia. A recent study claims that nonselective ligand-gated cation channels such as transient receptor potential (TRP) ankyrin 1 (TRPA1) and TRP vanilloid 1 (TRPV1) are the predominant molecular entities mediating activation of peripheral nerve endings by general anesthetics. TRPA1 is an ion channel located on plasma membrane of many cells and is best known as a sensor for irritants, pain, cold, and stretch. It has been shown that 97% of TRPA1-positive sensory neurons also express TRPV1 and that 30% of TRPV1-positive neurons co-express TRPA1 [9, 10].

Materials and Methods

The present study was a prospective, double-blind, randomized controlled study on 150 ASA I & II patients undergoing elective surgical procedures under general anaesthesia. After obtaining prior institutional ethical committee clearance, the patients were visited pre operatively, full pre anaesthetic check-up was done. An informed written consent was taken from all the patients under this study. Patients between 18 to 60 age group who are ASA I & II and elective surgeries under general anaesthesia were included in this study. Patient who are ASA III and above, pregnant females, patients with any hepatic or renal disease, known history of hypersensitivity to the study drugs were excluded in this study.

150 patients were randomly divided into one of the three groups (50 in each group) by computer. The drug solution was administered by an anesthesiologist who was blinded to the constituents of the drug. The data was collected in a pretexted proforma meeting the objectives of the study.

Study groups were as following

Table 1: Study groups- drugs; dosages and timing of infusion

Group	Study Drug: doses and final volume	Time and rate of injection
C	10 ML Normal Saline	After premedication as an infusion over 10 minutes
K	0.5 Mg/Kg Ketamine diluted to 10 ML with Normal Saline	After premedication as an infusion over 10 minutes
D	0.5 Mcg/Kg Dexmedetomidine diluted to 10 ML with Normal Saline	After premedication as an infusion over 10 minutes

History, Investigations, Preanaesthetic check-up, Consent for Surgery and Anaesthesia, NBM status of the patients were noted and confirmed. Written informed consent for the study was obtained. Patients were instructed to lie in a supine position, with arms by the side of body. NIBP, ECG and pulse oximeter were attached and baseline readings of Heart Rate, Blood Pressure, and SPO2 were obtained. Oxygen supplementation was started at the rate of 6 litres/minute. Intravenous line was secured with 20Gangiocath in a large, obviously visible peripheral vein on dorsum of a forehead. All study medications were prepared in a 10ML syringe that was covered with black tape by an anaesthesiologist who was not involved in the

study not involved in the study. Routine premedication with injection Ondansetron (0.08mg/kg), Glycopyrrolate (0.004 mg/kg), Fentanyl (2mcg/kg) and Midazolam (0.02mg/kg) was done. After premedication HR, BP, SPO2 and Pain Scores were noted. This was followed by administration of study drugs over 10 minutes by an infusion pump as mentioned in the chart above. Multiple readings of HR, BP, SPO2 and Pain Scores were noted at 3, 5 and 10 minutes. Propofol injection at 0.2 ml/sec was started, multiple readings of HR, BP, SPO2 and pain scores were noted at the beginning of Propofol injection, after injecting half Propofol, after injecting complete Propofol and at 1, 3 and 5 minutes after injecting complete Propofol.

Incidence and severity of pain and involuntary movements, verbal communication by the patient was watched constantly. Injection pain was graded using a 4-point scale mentioned below. Another anesthesiologist who was unaware of the group assignment assessed the intensity of pain after beginning Propofol injections. At the loss of corneal reflex and when patients were able to be ventilated by bag and mask, Injection Vecuronium 0.1 mg/kg was injected. After 5 minutes of oxygenation, patients were intubated by direct laryngoscopy with appropriate laryngoscope blade and ET tube of appropriate size. ETCO₂ was checked, bilateral air entry was confirmed. Patients were kept on a closed circuit on controlled ventilation. Anaesthesia was maintained with the help of a mixture of oxygen, nitrous oxide, and Sevoflurane. Vecuronium topups were given intermittently. At the end of the surgery, residual neuromuscular blockade was antagonized with 0.05 mg/kg of Neostigmine and 0.008 mg/kg of Glycopyrrolate. Extubation was done when the patients were fully awake and obeying commands. Patients were shifted to the recovery room and a well-trained staff nurse was told to monitor the patient for half an hour, Patients were shifted toward thereafter.

Monitoring and observations

Degree of pain

From the start of the injection until the loss of consciousness, each patient was told to inform if he/ she was feeling the pain of injection every 5 seconds to measure the degree of pain. The pain score was evaluated as '0' when there was no discomfort in the injection area (no pain), '1' when the patient simply answered "yes" without any change in behaviour (slight), '2' when there was a change in behaviour or voluntary complaint of pain (intermediate), and '3' when the patient made a loud sound, grimaced, withdrew his or her arm, or shed tears (severe).

Table 2: Mc Crick and hunter pain scale

Pain Score	Verbal or Motor Response	Degree of pain
0	Responds as No	No
1	Responds as yes but no change in behavior	Mild
2	Voluntary complain of pain or change in behavior	Moderate
3	Loud sound, Grimace, withdraws hands or sheds tears	Severe

Monitoring of vital parameters:

Vital parameters as HR, Blood Pressure, Oxygen Saturation were recorded at 0, 3, 5 minutes after Injecting study drugs, Immediately after the beginning of injecting Propofol, after injecting half Propofol, after injecting complete Propofol and at 1, 3 and 5 minutes after injecting complete Propofol. If Systolic BP fell to less than 80 mm of Hg then fluid Rate was increased, if SBP > 160 mm of Hg then an additional dose of 2 ml Propofol was given. If HR became less than 50 then Atropine 0.6 mg was injected, If HR became more than 120 then 2 ml of additional Propofol was given. If HR became more than 125 then additional (0.5 mcg /kg) Fentanyl was given. A constant watch was kept for the development of any complications like nausea, vomiting, bradycardia, hypotension, laryngospasm, swelling at the injection site, skin rash, etc.

Data was recorded in printed proforma. The Proper blinding procedure was followed; all data were tabulated and analyzed by appropriate statistical methods. Considering previous studies, the incidence of Propofol induced pain 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.

Observation and Results

Statistical analysis

- Data obtained was compiled on an MS Office Excel Sheet (v 2010, Microsoft Redmond Campus, Redmond, Washington, United States).
- Data were subjected to statistical analysis using Statistical package for social sciences (SPSS v 21.0, IBM).
- Descriptive statistics like frequencies and percentage for categorical data, Mean & SD for numerical data has been depicted.
- Normality of numerical data was checked using the Shapiro-Wilk test & was found that the data followed a normal curve; hence parametric tests have been used for comparisons.
- Intergroup comparison (>2 groups) was done using one way ANOVA followed by pair wise comparison using post hoc test.
- Intragroup comparison was done using repeated measures ANOVA (for >2 observations) followed by post Hoc test.
- A Comparison of frequencies of categories of variables with groups was done using chi-square test.
- For all the statistical tests, $p < 0.05$ was considered to be statistically significant, keeping α error at 5% and β error at 20%, thus giving a power to the study as 80%.
- The analysis was further represented by various line graphs and diagrams for comparison of various parameters between the study groups.
- 150 patients under this study were categorized into 3 groups (Group C, Group K and D). They comprised both sexes with age ranging from 18-60 years.
- Group C= Group Control
- Group K= Group Ketamine
- Group D= Group Dexmedetomidine

Results

150 patients were recruited in the study, the patients were randomly divided in three groups of 50 patients.

The current study showed no significant differences in demographic data that included age, gender and also with regards to ASA.

Table 3: Demographics

	Group C (n=50)	Group K (n=50)	Group D (n=50)
Age (year)	41.4 ± 13.75	39.74 ± 13.83	38.64 ± 14.20
Gender (M/F)	24/26	25/25	24/26
Weight	58.66 ± 9.73	55.12 ± 9.84	57.62 ± 10.97
ASA (I/II)	24/26	26/24	25/25

Pain Scores

Table 4: Pain scores in study groups

TIME	Group C	Group K	Group D	C vs K P value	C vs D P Value	K vs D P Value
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	One way ANOVA followed by post hoc		
Baseline	0.06 ±0.31	0 ±0.000	0.08 ±0.396	>0.05	>0.05	>0.05
After Premedication	0 ±0.000	0 ±0.000	0 ±0.000	>0.05	>0.05	>0.05
During Injecting Study Drug	0 ±0.000	0 ±0.000	0 ±0.000	>0.05	>0.05	>0.05
3 minutes After Study Drug	0 ±0.000	0 ±0.000	0 ±0.000	>0.05	>0.05	>0.05
5 minutes After Study Drug	0 ±0.000	0 ±0.000	0 ±0.000	>0.05	>0.05	>0.05
10 minutes After Study Drug	0 ±0.000	0 ±0.000	0 ±0.000	>0.05	>0.05	>0.05
During Injecting Propofol	2.08 ±0.85	0.06±0.240	0.3 ±0.58	.000**	.000**	>0.05
After Injecting half Propofol	1.74 ±0.77	0 ±0.000	0.16 ±0.37	.000**	.000**	>0.05
After Injecting Complete Propofol	1.32 ±0.62	0 ±0.000	0.08 ±0.27	.000**	.000**	>0.05
1 minute After Propofol	0.08 ±0.34	0 ±0.000	0 ±0.000	>0.05	>0.05	>0.05
3 minutes After Propofol	0 ±0.000	0.02 ±0.141	0 ±0.000	>0.05	>0.05	>0.05
5 minutes After Propofol	0 ±0.000	0 ±0.000	0 ±0.000	>0.05	>0.05	>0.05

Table 5: Proportions and intensity of pain in different groups during injecting propofol

Pain Score	Group C (50)	Group K (50)	Group D (50)	C vs K P value (Z test)	C vs D P value (Z test)	K vs D P value (Z test)
0 (NO Pain)	1	47	42	<0.001	<0.001	>0.05
1 (Mild Pain)	23	3	6	<0.001	<0.001	>0.05
2 (Moderate Pain)	17	0	2	<0.001	<0.001	>0.05
3 (Severe Pain)	9	0	0	<0.001	<0.001	>0.05

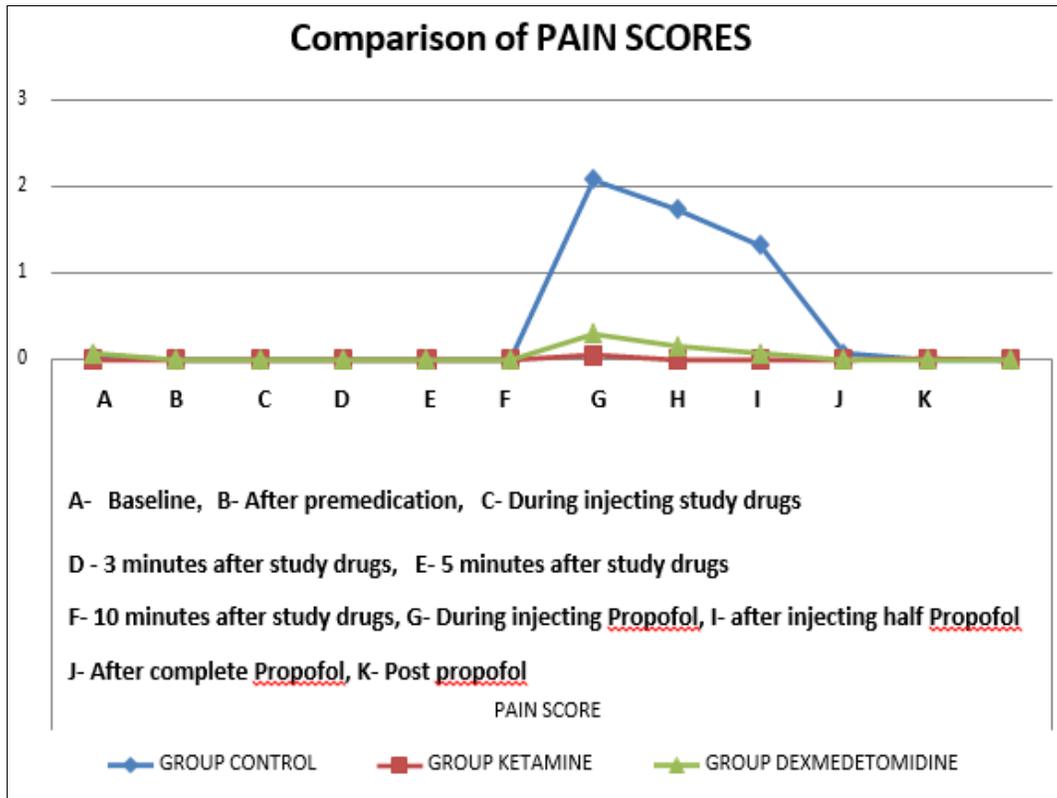


Fig 1: Pain score variation in study groups

In group C, the mean pain scores were relatively much higher when compared to other study groups. The mean pain score was 2.08 ±0.853 when Propofol injection was started, later it decreased to 1.74 ±0.777 when half of the Propofol was injected, it further reduced to 1.32 ±0.621 when complete Propofol was injected. 1 patient in group C had painless Propofol injection (Pain score 0), 23 patients experienced mild pain (Pain Score 1), 17 patients experienced moderate pain (Pain Score 2) and 9 patients in

this group experienced severe pain (Pain Score 3). In group K, pain scores were the best among the 3 groups. The mean pain score while injecting Propofol in group K was 0.06 ±0.240 which was much lesser than the pain score in group D (0.3 ±0.580) and in group C (2.08 ±0.853), thus showing the efficacy of ketamine in significantly reducing the pain of Propofol injection out of 50, 47 patients in group K experienced a painless injection of Propofol and only 3 patients experienced mild pain (Pain Score 1) on Propofol

injection. No patient experienced moderate or severe pain on Propofol injection in this group. No patient complained of pain in group K thereafter.

In group D, the mean pain score was 0.3 ± 0.580 while injecting Propofol which was much better than 2.08 ± 0.853 of group C but slightly higher than 0.06 ± 0.240 of group K. Out of 50, 42 patients in group D had painless Propofol injection, 6 patients experienced mild pain (Pain Score 1) and 2 patients experienced moderate pain (Pain Score 2). Mean pain score was 0.16 ± 0.370 when half of the Propofol was injected which was better than 1.74 ± 0.777 of group C but higher than 0 ± 0.000 of group K. On Further continuing Propofol injection the mean pain score was reduced to 0.08 ± 0.274 which was better than 1.32 ± 0.621 of group C but slightly higher than 0 ± 0.000 of group K. There was no incidence of pain thereafter. When the efficacy of group K was compared with the efficacy of group C in reducing Pain while Propofol injection was started, half of Propofol was injected and when complete Propofol was injected, it was found that Ketamine was highly efficient in reducing the pain of Propofol injection (P value < 0.001). Once the complete Propofol was injected there was no significant difference in pain scores among these groups. When the efficacy of group D was compared with the efficacy of group C in reducing Propofol pain while Propofol injection was started, half of Propofol was injected and when complete Propofol was injected, it was found that Dexmedetomidine was also highly efficient in reducing the pain of Propofol injection (P value < 0.005). Once the complete Propofol was injected there was no significant difference in pain scores among these groups. When group K was compared with group D, it was found that difference in reducing Propofol pain among these 2 groups was insignificant (P value > 0.05) when compared while injecting Propofol, after injecting half Propofol, and thereafter.

Mean Heart Rates

While Infusing normal saline in control group, the mean HR almost remained same whereas mean HR was increased in group K (from 84.62 ± 12.07 to 86.26 ± 14.22) while infusing ketamine and decreased in group D (from 81.92 ± 12.61 to 77.3 ± 12.22) while infusing Dexmedetomidine. This increase in mean HR in group K when compared to a decrease in mean HR in group D was found to be statistically significant (P value < 0.05). However, the variation in mean HR in group K and Group D as compared to Control group was not found to be statistically significant (P Value > 0.05) during injecting study drugs.

Mean Arterial Pressure

There was a surge in MAP in group C and group K when the Propofol infusion was started (MAP 99.33 ± 11.11 in group C and 98.33 ± 10.1574 in group K) but MAP did not rise much in group D (MAP 85.22 ± 11.156). This increase was transient and MAP started to fall in all 3 groups as the infusion of Propofol was continued. In group C, MAP was 100.24 ± 9.240 after half of Propofol was injected, 93.04 ± 8.647 after complete Propofol was injected, 89.88 ± 9.439 1 minute After Propofol injection, 87.8 ± 9.702 3 minutes after completing Propofol injection, 87.76 ± 9.328 5 minutes after completing Propofol injection. In group K MAP was 97.3 ± 10.691 after injecting half of Propofol, 95.16 ± 10.796 after injecting complete Propofol, 96.14 ± 11.964 ,

93.96 ± 10.891 and 95.3 ± 8.603 1,3 and 5 minutes after completing Propofol injection. In group D, MAP fell to 83.76 ± 11.510 after injecting half of Propofol, 82.58 ± 10.763 after injecting complete Propofol, 81.48 ± 9.643 , 81.74 ± 11.220 and 80.98 ± 9.898 at 1,3 and 5 minutes after injecting complete Propofol.

Discussion

In the present study, It was observed that all the baseline and post premedication hemodynamic parameters (HR, SBP, DBP, MAP and SPO2) and pain scores were comparable among the study groups with statistically insignificant P values. It was observed that after study drug infusion there were no significant changes in hemodynamic parameters (HR, SBP, DBP, MAP and SPO2) and Pain scores in the control group. Whereas HR, SBP, DBP and MAP were slightly above the baseline.

Values in group K and slightly below the baseline values in group D. So, it can be concluded from this study that Dexmedetomidine infusion causes dose-dependent suppression of the central sympathetic outflow and it also explains the findings of episodes of bradycardia and hypotension in Group D. All these changes in parameters were well within the acceptable limits. When compared statistically, these changes in group K and group D were found to be highly significant (P value < 0.001). There were no significant changes in Pain Scores and SPO2 values in any of the above mentioned groups. 3 patients in group C had tachycardia (HR > 120) so a repeat dose of 1 mg Midazolam was given. 2 patients had episodes of bradycardia in group D so injection Atropine 0.6 mg bolus was given. 2 patients in group C and 1 patient in group K had SBP > 160 mm of Hg while injecting respective study drugs so Injection Esmolol 30 mg bolus was given.

During injecting Propofol: It was observed that there was sudden, transient increase in mean HR, SBP, DBP, MAP and Pain scores in group C probably because of sympathetic stimulation due to pain of Propofol injection (n=50, No pain= in 1 patient, mild pain = in 23 patients, moderate pain = in 17 patients and severe pain = 9 patients).

When observed in group K, there was a slight increase in HR and MAP in the initial period but as Propofol was continued and readings were noted till completing Propofol injection, these parameters returned to the baseline values. (n=50, No pain= in 47 patient, mild pain = in 3 patients, moderate and severe pain = 0 patient). In group D, there was no statistical difference in the pain scores when compared to group K (n=50, No pain= in 42 patients, mild pain = in 6 patients, moderate pain = in 2 patients and severe pain = 0 patient). However, hemodynamic parameters like HR, SBP, DBP and MAP were on the lower side than the baseline values in this group and when compared with group K they were statistically significant.

9 subjects in group C had a pain score of 3 during injecting Propofol so Sevoflurane was started which was continued till pain score became less than 2. 3 subjects in group C had a pain score of 1 even after finishing complete dose of Propofol so an additional 20 mg Propofol was given to induce the case.

Once the Propofol injection was over and muscle relaxant was injected, values of these parameters were noted for 5 minutes at different intervals. There were no changes in SPO2 and pain scores post Propofol injection, however,

mean HR, SBP, DBP, and MAP started falling immediately in group C whereas it continued to fall in group D. group K showed no significant changes in these parameters post Propofol injection.

Conclusion

Based on the findings of our study, it can be concluded that Ketamine 0.5 mg/kg and Dexmedetomidine 0.5 mcg/kg both are effective in reducing the incidence and severity of pain of Propofol injection. Their efficacy in attenuation of pain is comparable; However, Ketamine 0.5 mg/kg infusion pre-treatment shows better hemodynamic stability than Dexmedetomidine 0.5 µg/kg infusion pre-treatment.

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