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Research Article

Dexmedetomidine Versus Ketamine Pretreatment to Alleviate Propofol Injection Pain: A Randomized and Blinded Study

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ABSTRACT

Background: Both ketamine and dexmedetomidine have proven effective in relieving the pain resulting from propofol injection. However, studies comparing them directly are limited. The primary outcome was to compare the incidence of propofol injection pain after dexmedetomidine pretreatment with ketamine pretreatment. Secondary outcome was to study the changes of haemodynamic parameters that arise after the administration of the pretreatment drug till anaesthesia was induced with propofol.

Methods: In this randomized, triple blinded, parallel arm single centre study, we compared pre-treatment with dexmedetomidine 0.5mcg/kg (Group A) and ketamine 0.5mg/kg (Group B). Our primary objective was to compare the incidence of propofol injection pain. The McCririck and Hunter scale was used to evaluate the pain. Secondarily, we compared the changes of haemodynamic parameters that arose after the administration of the pre-treatment drug till induction of anaesthesia with propofol.

Results: Among 168 patients evaluated for eligibility, 140 were included for final analysis with 70 patients in each group. The incidence of propofol injection pain in Group A was 74.3% (52/70) and that in Group B was 42.9% (30/70) (p value <0.001). No pain was reported by 25.7% (18/70) and 57.1% (40/70) patients in Group A and B respectively. Mild and moderate to severe pain was experienced by 58.6% and 15.7% patients in Group A, where as it was 40% and 2.9% patients in Group B respectively.

Conclusion: Ketamine leads to a greater reduction in both the frequency and intensity of pain resulting from propofol injection when compared to dexmedetomidine.

Introduction

Propofol is a commonly employed intravenous anesthetic, and the occurrence of pain following propofol injection varies from 28% to 90%. [1] Numerous pharmacological and non-pharmacological approaches have been suggested to decrease the occurrence and intensity of this pain [1-2]. However, no consistent result has been observed [1, 3].

Ketamine and dexmedetomidine are being increasingly used in the perioperative period as a part of multimodal analgesia technique [4-5]. Both these drugs lower propofol injection pain [1, 3].

Only two studies have directly compared dexmedetomidine and ketamine pretreatment for mitigation of propofol injection pain [1, 6-7.] Based on two studies, a recent meta-analysis favored ketamine pretreatment, but the heterogeneity was 0% [1]. Considering the striking lack of heterogeneity and very limited number of studies, we think that it needs further evaluation in our setup. Thus, the current study was conducted to assess the effectiveness of dexmedetomidine pretreatment versus ketamine

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pretreatment in mitigating pain resulting from propofol injection in elective surgery patients.

Methods

This is a patient, observer and analyzer blinded, randomized, parallel arm study.

We intended to include consenting patients aged 18-60 years, of any gender, ASA Grade I or II, who were scheduled for elective surgeries under general anaesthesia using propofol as the drug for induction. Pregnant or lactating mothers, patients with difficulty in communication, patients with known psychiatric disease or any seizure history and those who were allergic to any of the study drugs were excluded. The study was conducted with permission from the Institutional Ethics Committee, and carried out from December 2020 to June 2021. It was prospectively registered at CTRI (CTRI/2020/11/028996).

Consecutive patients posted for general anaesthesia were screened for eligibility during preoperative visits. Those who provided informed written consent for the study were divided into two groups with the help of a computer generated random selection using block randomization with blocks of variable sizes. Details of the group allocation were sealed within opaque envelopes according to the randomization. The envelopes were arranged in a serial manner. The McCririck and Hunter scale was thoroughly explained in detail to each included patient [6].

The primary outcome was to compare the incidence of propofol injection pain after dexmedetomidine pretreatment with that after ketamine pretreatment. Secondary outcome was to study the changes of haemodynamic parameters that arise after the administration of the pretreatment drug (ketamine or dexmedetomidine) till anaesthesia was induced with propofol.

On the day of surgery, patients were shifted to the operating room, and their electrocardigram (ECG), non-invasive blood pressure (NIBP) and peripheral oxygen saturation monitoring was instituted. An 18 gauge IV cannula was secured in the vein on the dorsum of hands of the patients. The sealed envelopes were taken up from the serial arrangement by a designated anaesthesiology resident who was not involved in the pre-operative, intraoperative or post-operative workup of the patients and the pretreatment drug was prepared by the resident according to the group allocation which was mentioned in the envelopes. According to the randomization sequence, the pretreatment drug was administered to the patients by another designated resident who was not involved in the pre-operative, intra-operative or postoperative workup of the patients. The syringes containing the pretreatment drug did not bear any label or markings that indicated the contents inside. The patients received premedication with inj.dexmedetomidine 0.5μg/kg (Group A) or inj ketamine 0.5 mg/kg (Group B) loaded in identical 20 ml syringes (diluted with sterile water). The study drug was infused over a period of 10 min using an infusion pump.

Immediately after administering the study drug, injection propofol 2 mg/kg and subsequent doses as required were administered intravenously. In this study we avoided any kind of IV premedication (other than the study drugs) which may cause irritation or analgesia before injection of propofol. Commencing from the time of injection of propofol, the patients were assessed for pain by asking the question ‘does it hurt?’ in their own understandable language in every 5 s until the patient became unresponsive. McCririck and Hunter scale was used to score the degree of pain [6]. The highest among the pain scores obtained for each patient was taken into consideration for statistical analysis. The severity of pain was graded as mentioned in (Table 1).

Table 1- McCririck and Hunter pain scale [6]

Numerical Score	Response	Interpretation	Interpretation for statistical analysis
0	Negative response(no) to question	No pain	No pain
1	Pain reported yes only in response to the question without any behavioral change	Mild pain	Mild pain
2	Voluntary complaint of pain or behavioral changes	Moderate pain	Moderate to severe pain
3	Strong vocal response or facial grimacing or arm withdrawal or tears on injection	Severe pain	Moderate to severe pain

Heart rate, systolic, diastolic and mean arterial pressure were recorded just before administration of propofol and these values were used for comparison between the groups. Any episode of hypotension (defined as> or = 20% decrease of MAP in relation to baseline value) was recorded and managed accordingly with IV fluid boluses, vasopressors and blood products as indicated. Any episode of hypertension (defined as a rise of MAP >20% from basal values) or tachycardia (defined as a rise of heart rate of >20% from basal value) were recorded and managed accordingly after determination of the causes for the same. All the data were collected in a predefined proforma.

Immediately following induction of general anaesthesia, inj. glycopyrrolate 0.2mg, inj. fentanyl (1 mcg/kg) and inj. vecuronium (0.1 mg/kg) were administered. The trachea was intubated with appropriate sized tube and general anaesthesia was maintained with sevoflurane 1-2% dial settings titrated accordingly to achieve a MAC of 1.2, as well as 50% nitrous oxide and

50% oxygen along with intermittent doses of IV muscle relaxant, which was titrated to achieve adequate level of muscle relaxation.

Based on a previous study, to detect a difference of 15% in the incidence of propofol injection pain, with a level of significance of 5% and power of study of 80, sample size was calculated to be 59 in each group. [6] Sample size calculation was carried out using the online sample size calculator available at the site https://clincalc.com. Estimating a dropout of 20%, it was decided to include 70 patients in each group.

After completion of study, data were entered in MS Excel spreadsheet™ and decoded after analysis. The statistical analysis was performed using SPSS version 21.0. Kolmogorov Smirnov test and Shapiro-Wilk test were used to find the normality of the data. Continuous variables are depicted as mean ± standard deviation and analyzed with Student's t-test. Categorical variables are represented as frequencies and percentages and assessed using either the Chi-square test or Fisher's exact test when appropriate. Non-normally distributed continuous variables were evaluated using the Mann–Whitney U-test. A significance level of $P < 0.05$ was considered to indicate a statistically significant difference for all statistical tests.

Results

One hundred and sixty eight patients were assessed for eligibility for this study (Figure 1).

The 140 patients meeting inclusion criteria were randomized equally in to two groups and each patient completed the intervention. Thus, the statistical analysis was carried out from data of 140 patients. The demographic characteristics of the study participants in both the groups were comparable (Table 2).

Even though the number of patients with ASA Class II were more than ASA I in each group, the difference did not reach statistical significance.

The incidence of propofol injection pain in Group A was 74.3% (52/70) and that in Group B was 42.9% (30/70) (p value <0.001). The relative risk of pain (95% confidence interval) was 1.73 (1.28- 2.35) in favour of ketamine. No pain was reported by 25.7% (18/70) and 57.1% (40/70) patients in Group A and B respectively (Table 3).

This difference of proportion of patient not experiencing pain was statistically significant (p value 0.00016). Among the patients experiencing pain, the incidence of mild pain was more than moderate to severe pain in both the groups (Table 3). Though higher proportion of patients experienced mild pain, its proportion was significantly lower in patients in Group B. The proportion of patient experiencing moderate to severe pain was statistically significantly high in Group A. The proportion of patients experiencing mild, moderate and severe pain is mentioned in (Table 3).

The baseline heart rate, systolic, diastolic and mean blood pressure was similar in both the groups (Table 2). The heart rate, systolic, diastolic and mean arterial pressures were significantly higher in Group B at the end of study drug infusion (Table 4).

The haemodynamic parameters of the patients during the study period are provided in (Table 4). There was no bradycardia or sinus arrest following dexmedetomidine infusion. Three patients in the Group A had hypotension, whereas none in Group B. Six patients in Group B had hypertension, whereas none in Group A.

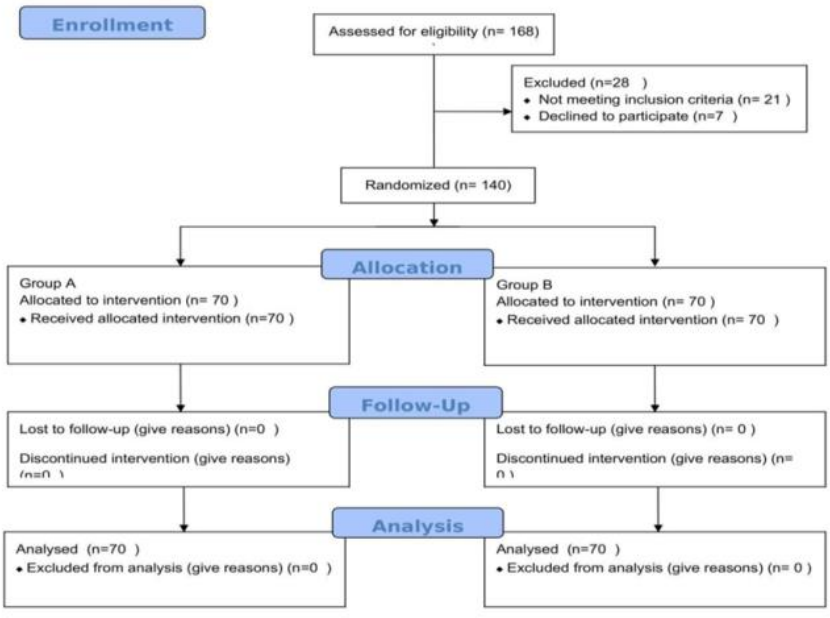

Figure 1- Patient flow diagram

Table 2- Demographic details of patients

Variables	Group A (n=70)	Group B (n=70)	P value
Age (years)	40.17 ± 12.19	38.67 ± 11.54	0.46
Gender (M/F)*	48/22	44/26	0.48
Weight (kg)	66.6 ± 10.76	67.4 ± 9.6	0.64
ASA Class (I/II)*	19/51	14/56	0.32
Baseline HR (beats/minute)	74.83 ± 5.83	76.27 ± 5.74	0.06
Baseline MAP (mmHg)	89.84 ± 7.22	89.38 ± 5.57	0.99

ASA- American Society of Anesthesiology, F- Female, HR- Heart rate, M- Male, MAP- mean arterial pressure, *- absolute numbers

Table 3- Intensity of pain among both the groups

Pain	Group A (n=70)	Group B (n= 70)	P value
No pain	18 (25.7%)	40 (57.1%)	0.00016
Mild pain	41 (58.6%)	28 (40%)	0.0278
Moderate to severe pain	11 (15.7 %)	2 (2.9%)	0.0088

Table 4- Comparison of haemodynamic between both the groups after study drug injection

Variables	Group A	Group B	P value
Heart rate (beats/minute)	75.33 ± 5.89	79.77 ± 7.64	<0.001
SBP (mmHg)	116.77 ± 9.33	121.57 ± 11.25	0.031
MAP (mmHg)	88.43 ± 7.29	92.58 ± 8.80	0.003
DBP (mmHg)	74.26 ± 7.97	78.09 ± 9.06	0.016

DBP- Diastolic blood pressure, MAP- Mean arterial pressure, SBP- Systolic blood pressure

Discussion

The primary outcome of this study was to compare the incidence of propofol induced pain between dexmedetomidine and ketamine pretreatment. The occurrence of pain from propofol injection was notably higher in the Dexmedetomidine group when compared to the Ketamine group. Similar observations have been made by other authors [6-7].

One recent meta-analysis of incidence of pain between patients pre-treated with dexmedetomidine and ketamine reported a risk ratio of 1.93 (1.51- 2.47) with I2 0 % (p value < 0.00001) in favour of ketamine [1]. Both the studies reported a strikingly similar effect size. In fact, we also observed a similar result. Estimates of different studies may vary depending on random sampling error or due to heterogeneity. Heterogeneity may be due to differences in treatment, study population, design and method of data analysis [8]. The methodology and plan of data analysis of the two studies comparing dexmedetomidine and ketamine and that of our study is similar. Homogeneous or nearly homogeneous result suggests that the treatment probably will have a similar effect when applied to new subjects [8].

Though not many studies have directly compared ketamine with dexmedetomidine, many authors have evaluated the effect of pre-treatment of ketamine or dexmedetomidine in various dosages [1, 9-10]. These studies suggest that pre-treatment with ketamine is an effective modality, albeit the magnitude of the effect varies among studies. Similar trend is also observed for dexmedetomidine. Studies with lower doses of ketamine and dexmedetomidine reported acceptable alleviation of propofol injection pain; however venous occlusion was also used [11-14]. Venous occlusion causes slowing of the systemic release of the drug. This causes the analgesics to effectively exert their action on the endothelial nociceptors. These nociceptors form the prime site of local anti-nociceptive action [6]. This might have enhanced the local antinociceptive effect of dexmedetomidine and ketamine, resulting in lower pain. However, venous occlusion has not been considered to be a routine, standardized technique [15]. Thus, we did not include venous occlusion in the present study.

In our study, patients who received dexmedetomidine pretreatment, 58.6% experienced mild pain and 15.7% experienced moderate to severe injection pain of propofol. Whereas, in the ketamine pre-treatment group, a lower value of 46% of the patients experienced mild pain and only 2.8% complained of moderate to severe pain. Our results are similar to a previous study where they found that dexmedetomidine pretreatment group reported mild pain in 63% and moderate to severe pain in 16.7% of patients [6]. Whereas, in the ketamine preteratment group, an incidence of mild pain of only 38.9% and moderate to severe pain of 1.9% [6]. Thus, ketamine not only reduces occurrence of pain, it reduces the severity in those experiencing it. In another study with ketamine pretreatment, the authors found a much lower incidence of mild pain though equivalent incidence of moderate to severe pain [12]. This might be attributed to the effects of venous occlusion in their study design. In another study with dexmedetomidine pre-treatment the authors found a much lower incidence of mild pain [16].

Thus, the data about the efficacy of these drugs in reducing the severity of pain is conflicting. The reasons for it need to be evaluated.

In our study design, we decided to administer dexmedetomidine and ketamine as an infusion over 10 minutes. This was used to avoid any acute haemodynamic changes that may occur following a rapid bolus injection of these drugs. Rapid IV bolus injection of dexmedetomidine causes a biphasic blood pressure response. This comprises of an initial hypertensive phase (due to α 2B adrenoceptor stimulation) which is later followed by a hypotensive phase of longer duration (due to α 2A adrenergic receptor stimulation), bradycardia and also, in certain conditions, sinus arrest [17].

We did not observe any hypertensive response, bradycardia or sinus arrest following dexmedetomidine infusion. Only three patients in the dexmedetomidine group had hypotension, however, the incidence of hypotension was comparable among the groups. The slow IV administration in our study may have decreased the initial transient hypertensive response as well as the bradycardia and hypotension typically experienced with the use of dexmedetomidine. There was an incidence of hypertension and tachycardia at induction in six patients in the ketamine group which was statistically significant. Ketamine is known to cause both hypertension and tachycardia [18].

Our findings should be extrapolated in the context of some inherent limitations of our study. Our study is a single hospital study and thus the influence of institutional practice or our patient population may have influenced the outcome. Though our study was statistically adequately powered to answer the primary objective, the study sample was not large enough to determine the safety of the two drugs. Thus, no succinct recommendations can be made regarding the safety profile of the two groups.

Conclusion

We conclude that ketamine leads to a greater reduction in both the frequency and intensity of pain resulting from propofol injection when compared to dexmedetomidine. As a secondary measure, we noted that patients who received ketamine exhibited statistically significant increases in heart rate, systolic and diastolic blood pressure, as well as mean arterial pressure compared to dexmedetomidine.

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