Clinical Investigation

Dexmedetomidine versus ketamine infusion to alleviate propofol injection pain: A prospective randomized and double-blind study

Address for correspondence:
Dr. Mayank Gupta,
14, Himvihar Apartment,
Plot No. 8, I.P. Extension,
Delhi - 110 092, India.
E-mail: drm_gupta@yahoo.co.in

Seema Thukral, Priyanka Gupta, Archana Lakra, Mayank Gupta[1]
Department of Anaesthesia, ESI Hospital, Okhla, Delhi, [1]Department of Anaesthesia, Shri Guru Ram Rai Institute of Medical and Health Sciences, Shri Mahant Indiresh Hospital, Dehradun, Uttarakhand, India

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ABSTRACT

Background and Aims: The use of propofol as the most common induction agent and the high prevalence of propofol injection pain (PIP) 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. The aim of our study was to assess the efficacy of single dose intravenous (IV) infusion of dexmedetomidine 0.5 μg/kg compared with ketamine 0.5 mg/kg to alleviate PIP. **Methods:** In this prospective, randomised and double-blind study, 108 patients undergoing elective surgeries under general anaesthesia were randomly allocated to two groups: Group D to receive dexmedetomidine 0.5μg/kg or Group K to receive ketamine 0.5 mg/kg in 20 ml of normal saline over 10 min. Immediately after the infusion, 1% propofol 2 mg/kg IV was injected over 25 s. The patients were assessed for pain every 5 s by asking the question 'does it hurt?' until the loss of consciousness. The pain scoring was done using McCririck and Hunter scale. Statistical analysis was done using SPSS 17.0. **Results:** The incidence of PIP and moderate-severe PIP was higher with Group D (79.6%; 16.7%) compared with Group K (40.7; 1.9%) ($P < 0.001$; 0.016). No patient in either group had arm withdrawal upon propofol injection. The incidence of hypertension and tachycardia was statistically significant in Group K as compared to Group D ($P = 0.027$). **Conclusion:** There was no difference in elimination of the arm withdrawal response and in incidence of moderate to severe PIP between the groups.

Key words: Anaesthesia, dexmedetomidine, ketamine, pain, propofol

INTRODUCTION

Propofol is the most widely used intravenous (IV) induction agent worldwide owing to its smooth induction and rapid recovery characteristics. Propofol injection pain (PIP), a well-known clinical phenomenon has an incidence ranging from 28% to 90% in adults.[1-6] Pain is one of the main pre-operative concerns among patients and analgesia is an important component of balanced anaesthesia technique. A number of techniques, both pharmacological and non-pharmacological, with varying efficacy have been tested and utilised to alleviate PIP.[1-6] Ketamine pre-treatment is a well-established pharmacological technique to mitigate the nociceptive response to propofol injection.[1] However, its bolus administration is associated with increased oro-tracheo-bronchial secretions, tachycardia and hypertension as worrying side effects. Dexmedetomidine is a molecule that is increasingly gaining anaesthesiologists' attention owing to its diverse clinical profile consisting of sedation, anxiolysis, analgesia and sympatholysis.[5,6] The literature evaluating its anti-nociceptive effects

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to mitigate PIP varies with respect to its doses, modes of administration as well as efficacy and there is no direct comparison with ketamine. The routine use of dexmedetomidine infusion as premedication in our institutional practice and lack of similar comparison prompted us to study and compare its anti-nociceptive effect for PIP and intraoperative haemodynamic changes with ketamine infusion immediately prior to propofol injection.

METHODS

After obtaining approval from the Hospital Ethics Committee and written informed consent from the patients, 108 patients aged 20 to 50 years belonging to either sex, American Society of Anesthesiologists (ASA) physical status I and II undergoing elective surgeries under general anaesthesia were included in this prospective, randomised, double-blind study. Patients with a history of drug abuse, psychiatric disease, seizures, uncontrolled hypertension, renal or hepatic impairment, allergy to the study drugs, pregnant females and those who received any kind of analgesic or sedative in the 24 h prior to surgery were excluded from the study. The patients were explained about the procedure in detail in the pre-operative visit prior to obtain written informed consent. No premedication other than the study drug was administered to the patients. The patients were fasted for 8 h preoperatively. In the operating room, monitors, including non-invasive arterial pressure, electrocardiography, and pulse oximetry (using Datex-Ohmeda, Cardiocap/5®, GE Healthcare, Helsinki, Finland), were applied. A 20 gauge IV cannula was secured in the vein on the dorsum of the left hand. Depending upon the drug used for premedication, patients were randomly allocated to two groups (Group D or Group K) using computer generated table with random numbers. The randomisation assignment was kept in sealed opaque envelopes and opened at the time of the study drug preparation. The study drugs, that is, either dexmedetomidine 0.5 μg/kg (100 μg/ml) (Group D) or ketamine 0.5 mg/kg (Group K) were loaded in identical 20 ml syringes labelled as 'study drug' by an independent anaesthesiologist not involved in the study and infused over 10 min using a syringe pump. Immediately after infusion of the study drug, injection propofol 2 mg/kg IV was administered slowly over 25 s. Starting from the time of injection the patients were assessed for pain by asking an open ended question 'does it hurt?' every 5 s until the patient became unresponsive, and the degree of pain was scored as advocated by McCririck and Hunter scale [Table 1]. Both the patients as well as the anaesthesiologist monitoring the response were unaware of the group allocation. The above pain assessment methodology was selected because the PIP starts immediately after injection and McCririck and Hunter scale has been validated previously for evaluation of PIP.[5,7]

It was followed by a standard anaesthesia technique consisting of morphine 0.1 mg/kg, glycopyrrolate 0.2 mg and vecuronium (all IV) as appropriate for the weight of the patient. The trachea was intubated with appropriate sized tube and anaesthesia was maintained with nitrous oxide, oxygen, sevoflurane and intermittent positive pressure ventilation. Intraoperatively, heart rate (HR), blood pressure, oxygen saturation (SpO_2) and end-tidal carbon dioxide were monitored. 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.

Primary outcomes studied were incidence of moderate to severe PIP and arm withdrawal response to propofol injection. Secondary outcomes were incidence of PIP and haemodynamic side effects.

The sample size was calculated based on previous studies.[6] Size of 54 patients in each group was arrived at with 90% power at an alpha value of 0.05 to detect a 25% difference in severity of pain between the two groups. Statistical testing was conducted with the statistical package for the social science system version (SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.,). Age, weight, height and body

Table 1: McCririck and Hunter pain scale

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 behavioural change	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 withdrawal or tears on injection	Severe pain	

mass index (BMI) are presented as mean ± standard deviation and compared utilising Student's *t*-test. Categorical variables are expressed as frequencies and percentages and compared using Chi-square test or Fisher's exact test as appropriate. Non-normal distribution continuous variables were compared using Mann–Whitney U-test. For all statistical tests, $P < 0.05$ was taken to indicate a significant difference.

RESULTS

A total of 108 patients were included in the study and distributed randomly into two groups. All the patients completed the study. Both the groups were comparable with respect to the demographic data and baseline vitals [Table 2]. The incidence of PIP (Score 1 to 3) was significantly higher in Group D compared with Group K. Only 1 patient in Group K had moderate to severe pain compared with nine patients in Group D [Figure 1 and Table 3]. No patient exhibited arm withdrawal upon propofol injection. Two patients had hypotension while no episode of bradycardia occurred in Group D [Table 4]. The Group K had a significantly higher incidence of hypertension and tachycardia compared with Group D [Table 4].

DISCUSSION

Propofol is routinely used in millions of patients every year; however three and one out of every five patients report PIP and severe PIP, respectively.[8] Our study showed that ketamine, when compared with dexmedetomidine pre-treatment was more effective in reducing the incidence and severity of PIP. Previous studies have shown an incidence of moderate to severe pain on propofol injection of 42.5–54% in the control group.[5,6] The incidence of moderate to severe pain during propofol injection was 16.7% and 1.9% in Groups D and K, respectively, suggesting that both of them are effective in reducing moderate to severe PIP. Our results are in accordance to that of Sarkilar *et al*. who found an incidence of 17.6% of moderate to severe pain with dexmedetomidine 0.5 μg/kg pre-treatment following propofol injection in the ipsilateral hand.[9] We observed a higher overall incidence of PIP as compared to other authors with dexmedetomidine.[6,10] This might be due to the pertinent difference in our study design consisting of slow IV administration of dexmedetomidine without venous occlusion. The venous occlusion slows the systemic release of the drug thereby allowing the analgesics to act upon the endothelial nociceptors, the key site of local anti-nociceptive action. A number of studies have combined drug pre-treatment, including ketamine and dexmedetomidine with venous occlusion; however, this has failed to become a standard technique.[11] Because of the lack of convincing studies, the need of additional equipment and time, we chose not to include venous occlusion in our study design. However, the majority (63%) of the patients in Group D in our study had only mild pain. The arm withdrawal response is usually elicited upon experiencing pain of moderate to severe intensity and may result in adverse events such as disconnection of IV drip or removal of IV

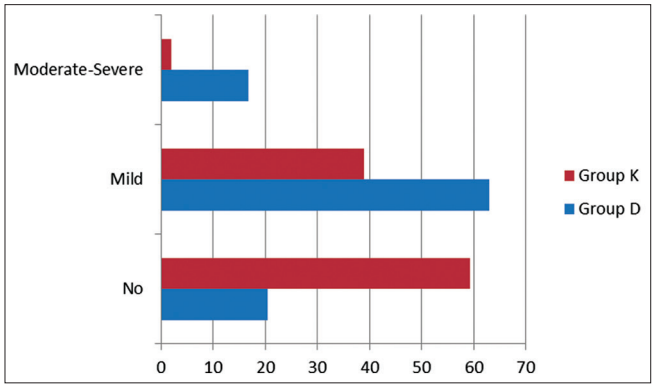

Figure 1: Pain severity

Table 2: Demographic data and baseline vitals

Variable	Group D (*n*=54)	Group K (*n*=54)	*P*
Age (years)	34.04±8.30	31.96±8.71	
Female: male	45/9	40/14	
Weight (kg)	52.94±9.26	51.50±8.02	
Height (cm)	157.13±5.08	155.96±5.27	
BMI (kg/m^2)	21.19±3.07	20.89±3.09	
ASA (I/II)	50/4	54/0	
Heart rate	82.39±11.23	86.28±12.45	0.091
BP	89.46±12.24	87.85±9.16	0.440

BP – Blood pressure; BMI – Body mass index; ASA – American Society of Anaesthesiologists

Table 3: Pain scores

Pain score	Frequency (%) (*n*=54)		*P*
	Group D	Group K	
0	11 (20.4)	32 (59.3)	<0.001
1	34 (63)	21 (38.9)	0.012
2	5 (9.3)	0 (0)	0.057
3	4 (7.4)	1 (1.9)	0.363

Table 4: Side effects

Variable	Frequency (%)		*P*
	Group D	Group K	
No	52 (96.3)	42 (77.8)	0.013
Bradycardia	0 (0)	0 (0)	
Hypotension	2 (3.7)	0 (0)	0.495
Hypertension	0 (0)	6 (11.1)	0.027
Tachycardia	0 (0)	6 (11.1)	0.027

cannula with associated bleeding, loss of venous access and jeopardising sterility as well as patient safety. The moderate to severe pain is also associated with more physical and psychological distress with a higher propensity to be remembered by the patient in the post-operative period. Therefore, we chose moderate to severe pain and its counterpart arm withdrawal response as the primary outcome. The putative mechanism behind PIP is still not fully understood.[9,12] It may be due to the constituent phenol group mediated stimulation of nociceptors and free nerve endings in the endothelial wall. A number of recent studies have negated any influence of propofol administration upon the bradykinin generation as has been postulated earlier.[13,14] A number of drugs with different anti-nociceptive mechanisms some acting peripherally, some producing analgesic modulation at spinal and supraspinal level while others having dual mechanism of action have been employed with varying efficacy to reduce the PIP.[8] Lignocaine, a well-established agent used to reduce the PIP has a failure rate ranging up to 33%.[15] A standard anaesthesia protocol consisting of fixed site (dorsum of hand) and size (20g) of IV cannula was followed as the incidence and intensity of the PIP varies with the site and size of IV cannula.[8]

Ketamine produces analgesia both by local mechanism due to its structural similarity with local anaesthetic cocaine and also by analgesic modulation via NMDA and μ-opiate receptors at the neuraxial level.[16] The dose of 0.5 mg/kg ketamine was selected on the basis of a study conducted by Barbi *et al*. who found this dose to be effective in reducing PIP.[17] Others have used lower doses, such as 0.4 mg/kg and found it to be effective in reducing PIP; however, they combined this with venous occlusion.[18] The inadequate safety and efficacy profile of the existing techniques results in a never ending quest of newer drugs such as dexmedetomidine which is a highly selective α2-agonist with the added advantages of systemic analgesia, sedation, anxiolysis and sympatholysis without the risk of respiratory depression.[6] The dexmedetomidine anti-nociceptive action is thought to be mediated via analgesic modulation at the level of the dorsal horn by activation of α-2B-adrenoceptors and inhibition of substance P release.[19] The finding that dexmedetomidine 0.5 μg/kg as the proper dosage to reduce the PIP by Lee *et al*. formed the basis for selecting this as our study dose.[5] Sarkilar *et al*. in their study on the PIP also found dexmedetomidine 0.5 and 1 μg/kg to be equally effective.[9] We chose to administer dexmedetomidine and ketamine as 10 min infusions to avoid acute haemodynamic changes associated with their rapid bolus injection.[19] Sapate *et al*. in their study to compare dexmedetomidine with lignocaine to alleviate the PIP used IV bolus as the mode of dexmedetomidine administration.[10] However, they utilised a lower dose of 0.2 μg/kg along with venous occlusion to prevent/slow the systemic release. Rapid IV bolus injection of dexmedetomidine is associated with biphasic BP response with initial hypertension (α-2B adrenoceptor mediated) followed by prolonged hypotension (α-2A adrenergic receptor mediated), bradycardia and even sinus arrest.[20,21] We in the present study did not observe any hypertensive response or bradycardia subsequent to dexmedetomidine infusion. Only two patients in the Group D had hypotension, and the incidence of the same was comparable among the groups. The slow IV administration in our study may have mitigated the initial transient hypertensive response as well as the bradycardia and hypotension seen with dexmedetomidine. We observed a statistically significant incidence of intraoperative hypertension and tachycardia in six patients in the ketamine group.

CONCLUSION

Ketamine 0.5 mg/kg slow IV infusion immediately before the propofol injection appears to be more effective in reducing the incidence and severity of the PIP than dexmedetomidine 0.5 μg/kg infusion pre-treatment. There was no difference in elimination of the arm withdrawal response and in incidence of moderate to severe PIP between the groups.

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Conflicts of interest

There are no conflicts of interest.

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