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Dexmedetomidine versus ketamine infusion to alleviate propofol injection pain

Dr Arpita Jena
Assistant Professor, Dept. of Anesthesiology, FM Medical College & Hospital, Balasore.

Dr Ranjan Kumar Mohanty
Assistant Professor, Dept. of Cardiology, SCB MCH Cuttack.

Dr Deepti Swain
Assistant Professor, Dept. of Anesthesiology, SCB MCH Cuttack.

Dr Pradyot Mahali
PG student, Dept. of Cardiology, SCB MCH Cuttack.

Dr Debadas Biswal
Associate Professor, Dept of Anesthesiology, SLN MCH Koraput.
Corresponding author email: debadasbiswal@gmail.com

***Abstract*---**Introduction: Propofol a widely used anesthetic agent administered for induction and maintenance of anesthesia, post operative and ICU sedation and anticonvulsant agent. Pain on injection is a common complain during propofol administration. Many drugs like local anesthetic, opiates, esmolol, clonidine, ketamine have been tried to alleviate propofol injection pain. Here we have compared the effect of dexmedetomidine and ketamine in alleviating propofol injection pain. Materials and methods: 108 patients of either sexes, in the age groups 20-50 years, posted for routine surgical procedure under general anaesthesia were included in the study. The cases were randomly divided into 2 groups of 54 each. Group-D:-Patients received dexmedetomidine 0.5µg/kg in 20 ml Normal saline at a rate of 120 ml / hr Infused over 10 min. Group-K:- Patient received ketamine 0.5mg/kg in 20ml Normal saline at a rate of 120ml/hr infused over 10 mins. Immediately after infusion, 1% propofol in a dose of 2mg/kg IV was given over 20 seconds. Starting from the time of injection, the patients were assessed for pain by asking an open ended question, "Does it Hurts" in every 5 seconds until the patient become unresponsive. Degree of pain score was advocated by "McCririck and Hunter Scale. With the injection of propofol over 20 seconds, patients were fully induced as indicated by loss of verbal contact and eye lash

reflex. This was followed by administration of midazolam 0.05 mg/kg, nalbuphine 0.2 mg/kg and vecuronium as 0.1 mg/kg. The patients were intubated with appropriate sized endotracheal tube. Observation and discussion: Pretreatment with dexmedetomedine and ketamine the incidence of no pain associated with injection of propofol was 18% in group D and 59% in group K. Dexmedetomedine and ketamine infusion in both groups D and K for reduction of pain on injection of propofol was statisatically significant. p=0.00001 ($p < 0.5$). With the exception of pain on injection other side effects were infrequent.

***Keywords*---**Dexmedetomidine, Ketamine, Propofol, Propofol infusion pain.

Introduction

Propofol, 2,6 di-isopropyl phenol is an intravenous anesthetic agent with rapid onset and short duration of action and lack of cumulating effect on repeated administration. There is absence of excitatory effects on induction, maintenance and recovery from anesthesia. Pain on injection, a well known clinical phenomenon with propofol has an incidence ranging from 28% to 90% in adults. A number of methods, both pharmacological and non-pharmacological with varying efficacy have been tested[1,2,3]. Pain on injection is reduced by using a large vein, avoiding veins in the dorsum of the hand, and adding lidocaine to the propofol solution or changing the propofol formulation. Pretreatment with a small dose of propofol, opiates, nonsteroidal antiinflammatory drugs, ketamine, esmolol or metoprolol, magnesium, a flash of light, a clonidine-ephedrine combination, dexamethasone, and metoclopramide all have been tested with variable efficacy.

Ketamine pretreatment is a pharmacological technique to mitigate the nociceptive response to propofol injection[1]. Its bolus administration is associated with increased oro-tracheo-bronchial secretion, tachycardia and hypertension as worrying side effects. Dexmedetomidine is a molecule that is increasingly gaining anesthesiologists attention owing to its diverse clinical profile consisting of sedation, anxiolysis, analgesia and sympatholysis[2,3]. It has been use by various workers to reduce propofol injection pain. So in this study we assess the efficacy of single dose intravenous infusion of Dexmedetomidine 0.5µg/kg, versus ketamine 0.5mg/kg to alleviate Propofol injection pain(PIP) of patient undergoing elective surgeries under general anaesthesia.

Materials and methods

The study included 108 patients of either sexes, in the age groups 20-50 years, posted for routine surgical procedure under general anaesthesia. Informed consent was obtained from all patients before being included in the study. Patients with history of drug abuse, seizure, hypertension, renal and hepatic impairment, allergy to study drugs, pregnant females were excluded from the study. Antiemetic prophylaxis was given to all patients in the morning before surgery. The cases were randomly divided into 2 groups of 54 each receiving following pre-treatments.

Group-D:-Patients received dexmedetomidine 0.5µg/kg in 20 ml Normal saline at a rate of 120 ml / hr Infused over 10 min. Group-K:- Patient received ketamine 0.5mg/kg in 20ml Normal saline at a rate of 120ml/hr infused over 10 mins.

In the operating room, monitors like non-invasive blood pressure, electrocardiography pulse oximeter and temperature were attached. The study drugs were given by an independent anaesthesiologist not involved in the study and infused over 10 minutes using syringe pump. Immediately after infusion, 1% propofol in a dose of 2mg/kg IV was given over 20 seconds. Starting from the time of injection, the patients were assessed for pain by asking an open ended question, "Does it Hurts" in every 5 seconds until the patient become unresponsive. Degree of pain score was advocated by "McCririck and Hunter Scale.

Numerical score	Response	Interpretation	Interpretation for statistical analysis
0	Negative Resonse (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 bahavioral change	Moderate Pain	Moderate Pain
3	Strong vocal response or facial grimacing or arm withdrawl or tear on injection	Severe Pain	Severe Pain

With the injection of propofol over 20 seconds, patients were fully induced as indicated by loss of verbal contact and eye lash reflex. This was followed by administration of midazolam 0.05 mg/kg, nalbuphine 0.2 mg/kg and vecuronium as 0.1 mg/kg. The patients were intubated with appropriate sized endotracheal tube and anaesthesia was maintained with oxygen, nitrous oxide, isoflurane and intermittent positive pressure ventilation. Intraoperatively heart rate, blood pressure, oxygen saturation, end tidal carbon dioxide were monitored.

Raw data of study parameters was entered into a Eoilinfo 7.1.0.6 version and MS Excel 2017 spreadsheet and analysed using standard statistical software. Categorical variables was analysed using Pearson's chi square test or the Fisher's exact test as applicable. Statistical significance was taken as $p < 0.05$. Normally distributed continuous variables was analysed using the One–way ANOVA followed by the Boneferroni test or the Tukey's B test for the post hoc analysis. Numerical data was expressed as mean and standard deviation. Categorical variables was expressed as percentages.

Observation

Table no- 1. Age wise distribution of patients

Age range	No of patients in years		Mean age in years ±SD	
	Group D	Group K	Group D	Group K
20-30	14(26%)	13(24%)	36.4±7.01	37.2±7.60

31-40	15(28%)	25(46%)		
41-50	25(46%)	16(30%)		

The mean age group-D is 36.4±7.01, Group- K is 37.2+7.60 and statistically in-significant. P= 0.104 (p > 0.05).

Table no. 2 (Sex distribution of patients)

SEX	GROUP-D	GROUP-K
Male	21	23
Female	33	31

The Male and Female ratio in each group were comparable and having no statistically difference. p = 0.69 (P > 0.05)

Table no. 3 (Weight distribution of patients)

Weight in kg	No. (%)		Mean weight± SD (Kg)	
	Gr. D	Gr. K	Gr. D	Gr. K
40-50	7(13%)	11(20%)	59.9±7.7	57.3±8.9
51-60	20(37%)	25(46%)		
61-70	27(50%)	18(34%)		

The Group-D having mean wt of 59.9±7.7 and Group-K having mean wt of 57.3±8.9 and was not statistically significant. P = 0.19 (p > 0.05)

Table no.4 Pain score during injection of propofol (Mccririck and hunter pain score)

Pain score	Number (%)	
	Group- D	Group- K
0	10(18%)	32(59%)
1	35(65%)	20(37%)
2	6(11%)	1(2%)
3	3(6%)	1(2%)

There was no pain in 59% patients in group K where as in Group-D patient it was 18%.This was found to be statistically significant as P= 0.00001 (p < 0.05). The incidence of no pain or mild pain was 96% in group K where as it was 83% in group D which is statistically significant as p=0.00001.

Table no. 5. Pulse rate at various intervals (beats/min.) Mean ± SD

Time of reading	Group- D	Group – K
Pre op	83.93 ± 4.67	86.87 ± 6.20
2 min after induction	75.30 ± 4.37	89.40 ± 7.89
5 min after induction	81.04 ± 3.25	91.13 ± 6.71
Post Recovery	85.16 ± 4.17	89.76 ± 6.44

Changes in pulse rate after induction of propofol was slightly more in Group K as compared to Group D which was statistically in-significant.

Table no. 6. Systolic blood pressure at various intervals (mmHg) Mean ± SD

Time of reading	Group - D	Group – K
Pre op	120.8 ± 5.6	116.5 ± 7.4
2min after induction	111.1 ± 6.8	112.5 ± 4.5
5 min after induction	119.2 ± 3.85	123.9 ± 3.2
Post Recovery	121.4 ± 4.8	123.9 ± 3.2

The systolic blood pressure at various intervals in Group K was slightly higher than Group D, but was comparable and statistically in-significant.

Table no.7. Diastolic blood pressure at various inervals (mmHg) Mean ± SD

Time of reading	Group - D	Group – K
Pre op	80.9 ± 4.3	77.5 ± 4.7
2 min after induction	75.3 ± 5.8	79.8 ± 3.4
5 min after induction	79.4 ± 4.8	79.6 ± 3.5
Post Recovery	81.8 ± 4.0	79.9 ± 2.9

The diastolic blood pressure was low in Group D as compare to Group K, but was comparable and statistically in-significant.

Table no. 8. Side effects

Variables	Group-d	Group-k
No side effects	50 (92.6%)	45 (83.3%)
Bradycardia	2 (3.7%)	0 (0%)
Hypotension	2 (3.7%)	0 (0%)
Hypertension	0 (0%)	4 (7.4%)
Tachycardia	0 (0%)	5 (9.2%)

Discussion

Induction of anesthesia with propofol is often associated with pain on injection. Multiple drugs and distraction techniques have been investigated to reduce the pain on injection of propofol. Pretreatment with a small dose of propofol, opiates, nonsteroidal antiinflammatory drugs, ketamine, esmolol, metoprolol, magnesium, a flash of light, a clonidine-ephedrine combination, dexamethasone and metoclopramide all have been tested with variable efficacy. Here a study was done to evaluate the effect of pretreatment of dexmedetomidine and ketamine on the propofol infusion pain.

The two groups are demographically comparable. The mean age of patients in group D and group K was 37.24 and 36.43yrs respectively and there was no statistically significant difference between the two groups. $P = 0.104$ ($p > 0.05$). Out of 108 patients, 44 were males and 64 were females the male : female ratio in

groups D was 21:33, in group K was 23:31. There was no statistically significant difference between the two groups with respect to sex. P= 0.69 (p > 0.05). Mean weight of patients in group D was 59.8kgs and group K was 57.3 kgs and the two groups were statistically comparable. P = 0.19 (p > 0.05).

Pain of propofol infusion is vascular pain experienced by patient as aching, burning and crushing in nature. Propofol has a phenol group irritating to the skin, mucous membrane and venous intimal layer. Mechanism of pain is due to activation of kallikrein-kinin system by propofol probably bradykinin. Sarlikar et al.found that an incidence of 17.6% of moderate to severe pain with dexmedetomidine 0.5µg/kg pre-treatment following propofol injection in the ipsilateral hand [4]. We observed higher incidence of PIP with dexmedetomidine. This might be due to slow IV infusion without venous occlusion. Venous occlusion slows the systemic release of the drug allowing the analgesics to act upon the endothelial receptors, site of local nociceptive action. A number of studies had combined drug pre-treatment with ketamine and dexmedetomidine with venous occlusion; however this has failed to become a standard technique[5]. We had choosen not to occlude venous occlusion in our study design. In this study there was an incidence of mild pain in 37%, moderate pain in 2% and severe pain in 2% cases where as 59% had no pain in Group K. The incidence of PIP in Group D were mild in 65%, moderate in 11% and severe in 6% cases and no pain in 18% cases. Comparing the incidence of no pain in propofol infusion, group K reported higher positive response as compared to group D and the results were statistically significant, p value being 0.00001.

Ketamine produces analgesia due to its structural similarity with local anaesthetic cocaine and analgesic modulation via NMDA and µ-opioid receptors at the neuraxial level[6]. The dose of 0.5mg/kg ketamine was selected on the basis of a study by Barbi et al. who found this dose to be effective in reducing PIP[7]. Few have used lower doses such as 0.4mg/kg and found to be effective in reducing PIP, however they combined it with venous occlusion[8].

Dexmedetomidine a highly selective α2-agonist has systemic analgesia, sedation, anxiolysis and sympatholysis without the risk of respiratory depression[3].The antinociceptive action is mediated via analgesic modulation at the dorsal horn by activation of α-2B adrenoceptors and inhibition of substance P release.[9] Dexmedetomidine 0.5µg/kg to reduce PIP by Lee et al. formed the basis for selecting this is our study dose. Sarkilar et al. in their study on the PIP also found dexmedetomidine 0.5 and 1 µg/kg to be equally effective[4].

We had chosen to administer dexmedetomidine and ketamine as 10 min infusions to avoid acute hemodynamic changes associated with their rapid bolus injection.[9] Sapate et al. compared dexmedetomidine with lignocaine to alleviate the PIP and used IV bolus as the mode of dexmedetomedine administration.[10] However they utilised a lower dose of 0.2 µg/kg along with venous occlusion to prevent systemic release. Rapid IV bolus injection of dexmedetomidine is associated with biphasic blood pressure response with initial hypertension (α-2B adrenergic receptor mediated) followed by prolonged hypotension (α-2A adrenergic receptor mediated), bradycardia and even sinus arrest.[11,12] In the present study only two patients in the Group D had hypotension and two patients had

bradycardia. The slow iv infusion in our study might have mitigated the initial transient hypertensive response as well as the bradycardia and hypotension seen with dexmedetomidine. We also observed six patients had hypertension and seven patients had tachycardia which was statistically significance incidence intra operatively.

In Group D the baseline heart rate was 83.93±4.67 and post recovery was 85.17±4.17 where as for Group K was 84.11±6.20 and 89.76±6.44 respectively. Heart rate did not change significantly after an induction dose of propofol. Only 9.2% patients in Ketamine infusion had tachycardia and only 3.7% patients had bradycardia in group D and is statistically in-significant. $p = 0.092$ ($p > 0.05$). Similarly in Group K 7.4 % patients had hypertension and in Group D only in 3.7% patients had hypotension and is statistically in-significant. $p = 0.169$ ($p > 0.05$).

So to conclude ketamine 0.5 mg/kg slow iv infusion immediately before propofol injection appeared to be more effective in reducing the incidence and severity of the PIP than pre-treatment with dexmedetomidine 0.5µg/kg infusion with minimal side effects in both the groups.

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