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Original Research Article

Evaluation of efficacy of low dose IV ketamine for prevention of pain associated with IV propofol injection

Medha Akhilesh Sangawar[1], **Mohana Sharadchandra Shewalkar**[1,*], **Puja Madhukar Shinde**[1], **Soma Chandrashekharan Cham**[1], **Akshay Nagorao Shende**[1]

[1] *Dept. of Anaesthesiology, Government Medical College and Hospital, Nagpur, Maharashtra, India*

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ABSTRACT

Background: Propofol is a widely used intravenous anaesthetic that is known to cause distressing local pain at the site of injection. Ketamine pretreatment is one of the methods proposed to attenuate Propofol injection pain due to its local anaesthetic properties. The present study was undertaken to evaluate the efficacy of low dose (100 mcg/kg) I.V. Ketamine in decreasing I.V. Propofol injection pain by using McCrirrick and Hunter scale.

Materials and Methods: 72 adult patients of ASA Physical status 1 and 2 of either sex undergoing elective surgical procedure under general anaesthesia were randomly allocated into two groups. Group-A (n=36): Pre-treatment with Ketamine 100μg/kg (1ml) and Group- B (n=36): pre-treatment with 0.9% Normal Saline (1ml).

Results: Comparison between group A and group B using McCrirrick and Hunter Evaluation Scale at 5,10 and 15 seconds intervals were statistically highly significant (p value<0.0001). None of the patients in group A experienced moderate or severe pain at all 3 intervals as compared to group B. McCrirrick and Hunter evaluation score mean values were also highly significant at all time intervals between both the groups. Hemodynamic parameters, $EtCO_2$ and SpO_2 were comparable between two groups. There was no incidence of any adverse effects in both the groups.

Conclusion: I.V. Ketamine in a dose of 100mcg/kg with tourniquet as pretreatment before Propofol was useful in significantly reducing the incidence and severity of pain without any adverse haemodynamic effect.

1. Introduction

Propofol was first utilised in clinical practice in the early 1980s and is now the most widely used I.V. anaesthetic for anaesthesia induction, maintenance, and sedation. But pain on injection of Propofol is a very common problem associated with its use which causes unnecessary distress for patients and is concern for practicing anaesthesiologists. Incidence of pain varies between 28% and 90% in adults during induction and it may be very severe in some cases.[1] In children the incidence varies between 28% and 85% with an observation of severity associated with younger age which might be due to smaller size of veins.[2] The mechanisms for pain on propofol injection are multifold and are affected by many factors: Major Factors includes- (a) Site of Injection; (b) size of vein; (c) Speed of injection; (d) Propofol concentration in aqueous phase; (e) the buffering effect of blood.

Although number of techniques,both pharmacological and non-pharmacological with varying efficacy have been

* *Corresponding author*.
E-mail address: shewalkarmohana@gmail.com (M. S. Shewalkar).

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tested and utilised to alleviate Propofol induction pain. For the past decades, numerous ways to minimise the pain induced by Propofol injection were investigated with conflicting results, reducing infusion rate, adding opioids, Aspirin, and Lignocaine, cooling or diluting the Propofol and administering pre-treatment with Ephedrine, Ondansetron, Ketamine, Metoclopramide and Thiopentone are some of them.[3,4]

Ketamine is a phenycyclidine derivative and N- methyl-D-aspartate (NMDA) antagonist and therefore has potent analgesic and local anaesthetic properties by inactivating these receptors either in the vascular endothelium or in the central nervous system. The local anaesthetic property of Ketamine attenuates the afferent pain pathway to reduce the Propofol induction pain rather than central analgesic effect in sub anaesthetic doses.[5] Also, Ketamine has structural similarities to Cocaine therefore, it also produces analgesia via local mechanism.[6] Ketamine is associated with less cardiorespiratory depression than other drugs used for local analgesia.[7] There are many studies on pre-treatment of low dose Ketamine for Propofol injection pain hence we undertook this study which aims at finding whether a extremely low dose of iv Ketamine (100mcg/kg) can be used to decrease the induction pain caused due to Propofol injection. It also aims at finding whether Ketamine causes any haemodynamic changes during induction of anaesthesia.

2. Materials and Methods

This prospective double blind randomized control study was conducted at a tertiary care centre after approval from the Institutional ethical committee during a period of 2 years from Jan 2021- Dec 2022. Total 72 Patients of ASA physical status grade I and II, age 18 – 50 years of either sex, weight between 30-90 kg scheduled for elective general surgeries under General Anaesthesia were included in the study. They were randomised into two treatment groups using a predetermined computer - generated randomization allocation plan. Group- A (n=36): Pre-treatment with Ketamine 100μg/kg (1ml) and Group- B (n=36): pre-treatment with 0.9% Normal Saline (1ml). Patients of age group <18 years and >50 yearskgs, patients with anticipated difficult intubation, allergy to Ketamine and/or Propofol, uncontrolled Diabetes, Hypertension, Cardiovascular or Respiratory disorders, Psychiatric or Neurological disorders, patients on sedatives or chronic opioid therapy or antipsychotic therapy or antiepileptic therapy, patients with language or communication difficulties and patient's refusal for consent were excluded from the study. Sample size was calculated using Hypothesis testing of two means AssumptionsSample size has been determined considering difference in proportions for pain as the main outcome measure in two groups.

Pre-operatively, a detailed history was taken, general & systemic clinical examination and laboratory investigations: Complete blood count; Blood sugar fasting & post meal; Kidney function tests (Blood urea & Serum Creatinine); Liver function tests; Serum Electrolytes, X Ray chest & ECG & relevant investigations if any were done. The Informed consent of patient was taken explaining the plan of anaesthesia, risk of anaesthesia and surgery. Patients were advised to remain fasting for 6 hours prior to surgery. Drugs used as night sedation before the day of surgery- Orally: Tab. Diazepam 10mg.

Every patient received Inj. Pantoprazole 40 mg i.v. and Inj. Glycopyrolate 4 mcg/kg as pre-treatment. Patients in both the study groups were preoxygenated with 100% oxygen with face mask for 3 minutes. The study drugs were prepared by an anaesthesia colleague who has not been involved in the study in a total volume of 1ml and was kept in syringe labelled as study syringe.

A pneumatic tourniquet at 70 mmHg was applied on the same arm with the intravenous catheter. The study drug was given intravenously over 10 seconds, i.e., 1 ml of Inj. Ketamine 100mcg/kg in Group A and 1 ml of 0.9% of Normal Saline in Group B. 60 seconds after pretreatment bolus, tourniquet was released and the first 25% of the calculated dose (2.5mg/kg) of Propofol was injected immediately intravenously over 20 seconds. Pain assessment was done 15 seconds after injection of 25% of calculated dose.

The pain score was assessed every 5 seconds till 15 seconds by an anaesthetist who has been blinded to the study using the verbal rating scale (VRS) during injection of Propofol and graded it as 0 to 3 in accordance with scale advocated by McCrirrick and Hunter (1990).

This was considered the end point of our study and the remaining 75% dose of Propofol was injected intravenously for the induction of general anaesthesia. The standard protocol was followed for the later part of general anaesthesia procedure i.e., induction & intubation, securing the tracheal tube, inj. Midazolam (0.03mg/kg) i.v. and inj. Fentanyl (2mcg/kg) i.v., Sevoflurane, muscle relaxant-Vecuronium & IPPV & reversal of anaesthesia.

The haemodynamic parameters (NIBP: SBP, DBP, MAP, HR, SpO_2) were recorded in the perioperative period at various time intervals viz. baseline, after inj. Ketamine or normal saline drug (before release of tourniquet), after release of tourniquet & inj. Propofol (first 25% of the calculated dose), later after complete induction with Propofol, at intubation, 3 minutes and 5 minutes after intubation, at 1 hour and 2-hour post intubation. Haemodynamic parameters were recorded at the following intervals: Tz – Outside OT; TB – Baseline, after taking patient on OT table; Tt -After test drug; Tr - After releasing tourniquet; Tp- After giving 25% Propofol; TI – After induction; TL – At Intubation; T0 – Just after

Table 1: Verbal rating scale by McCrirrick and hunter

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 verbal response or facial grimacing or arm withdrawal or tears on injection	Severe pain	

Intubation; T3 – 3 minutes of Intubation; T5 – 5 minutes of Intubation; Th1- At 1st hour; Th2- At 2nd hour. Sedation was given using inj. Midazolam (0.03mg/kg) i.v. and inj. Fentanyl (2mcg/kg) i.v. before induction and intubation the maintenance of anaesthesia was attained using Inhalational Oxygen, Nitrous oxide and Sevoflurane. Muscle relaxation was attained using Inj. Vecuronium Bromide at the dose of 0.08-0.1 mg/kg IV as loading dose and 0.02mg/kg as maintenance dose. Reversal of anaesthesia- At end of Surgery and on regaining efforts of spontaneous respiration Inj. Glycopyrolate 8mcg/kg IV + inj. Neostigmine 0.05mg/kg IV was administered slowly to reverse neuromuscular blockade. Subsequently on regaining consciousness, adequate spontaneous respiration and skeletal motor tone of patient, extubation was done & oral suctioning was done to clear the airway. Patients were monitored for intraoperatively and post operatively for any untoward complications or adverse effects.

2.1. Statistical analysis

Continuous variables were presented as mean ± SD and median and range for non – normalised data. Categorical variables were expressed in frequency and percentages. Categorical variables were compared between two groups by performing Chi square test. For small numbers, Fisher exact test were used wherever applicable. Continuous variables were compared between two groups by performing independent t – test. Comparison of haemodynamic parameters were compared at different time point in each group by performing one-way repeated measure ANOVA test. Comparison of haemodynamic parameters were compared at different time point between two groups by performing independent t–test. P <0.05 were considered as statistically significant. Statistical software STATA version 14.0 was used for data analysis.

3. Observations and Results

During the study period, a total of 72 patients were included and randomly divided into two groups of 36 patients in each group. Both the groups were comparable with respect to demographic profile of the patients and preoperative vitals as shown in Table 1.

The comparison of pain score as per McCrirrick and Hunter evaluation scale between group A and group B at P5, P10 and P15 intervals were statistically highly significant (p value < 0.0001). None of the patients in group A experienced moderate or severe pain at all 3 intervals as compared to group B (saline group) patients, (Table 2).

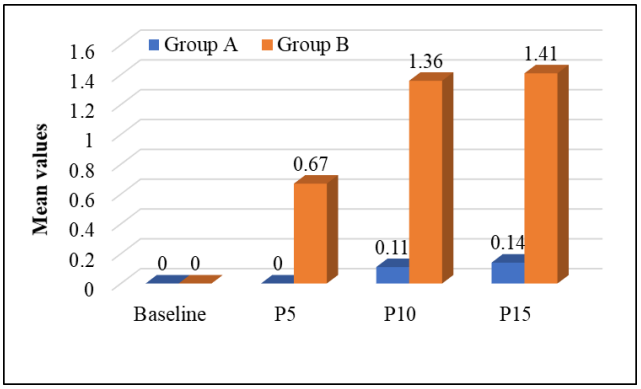

Fig. 1: Comparison of McCrirrick and hunter evaluation for mean of pain score between Group-A and Group-B

McCrirrick and Hunter evaluation score mean values were also highly significant at all time intervals between both the groups as depicted in Figure 1.

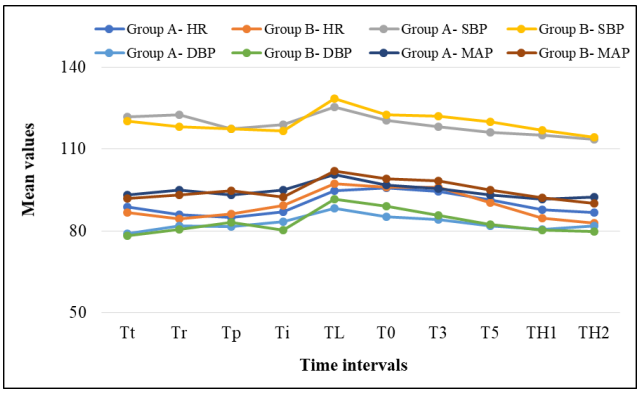

Fig. 2: Comparison of hemodynamic parameters between two groups

Both the groups were comparable and found no significant difference with respect to hemodynamic profile

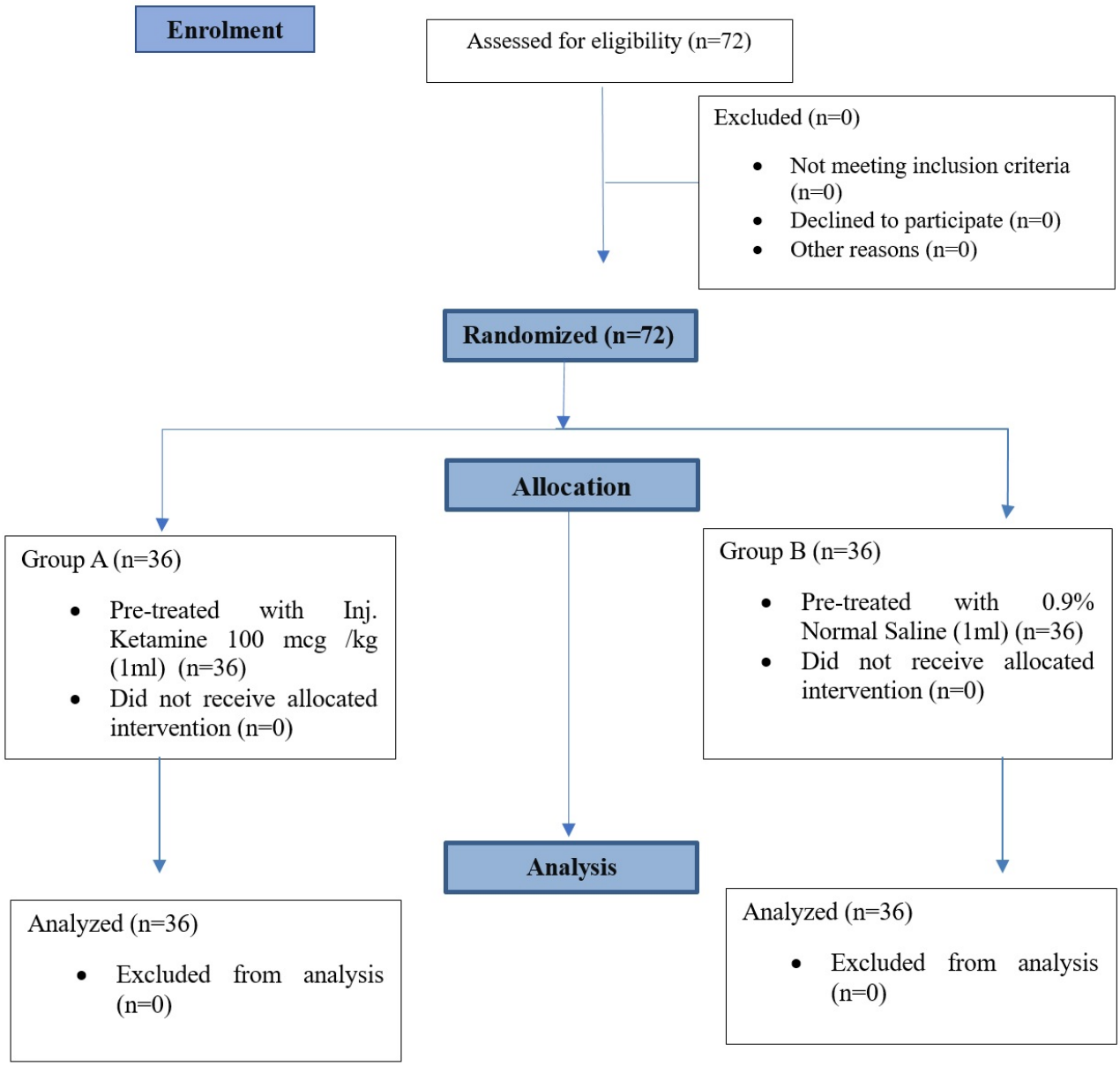

Chart 1: Consort flow chart

Table 2: Demographic profile of the patients and preoperative vitals

Parameters		**Group A**	**Group B**
Demographic data	Age in years	28.72 ± 8.11	33.19 ± 8.54
	Weight (kgs)	56.22 ± 8.27	58.78 ± 9.68
	Gender Male	18 (50.0%)	18 (50.0%)
	Gender Female	18 (50.0)	18 (50.0%)
Preoperative vitals	Heart Rate(/min)	88.75 ± 11.13	86.11 ± 7.84
	SBP (mmHg)	119.41 ± 12.47	120.22 ± 9.78
	DBP (mmHg)	78.02 ± 9.77	78.38 ± 6.70
	RR (/min)	17.91 ± 2.18	18.94 ± 2.30
	SpO_2 (%)	99.22 ± 0.72	99.44 ± 0.60

Table 3: Comparison of pain score as per McCrirrick and Hunter evaluation scale between two groups

Score	Number of Patients					
	At P5 interval		At P10 interval		At P 15 interval	
	Group A	Group B	Group A	Group B	Group A	Group B
None (0)	36 (100%)	18* (50%)	32 (88.89%)	9* (25%)	31 (86.11%)	8* (22.22%)
Mild (1)	0 (0%)	12* (33.33%)	4 (11.11%)	14* (38.89%)	5 (13.89%)	14* (38.89%)
Moderate (2)	0 (0%)	6* (16.67%)	0 (0%)	4* (11.11%)	0 (0%)	5* (13.89%)
Severe (3)	0 (0%)	0 (0%)	0 (0%)	9* (25%)	0 (0%)	9* (25%)
Total no. of patients with pain	0 (0%)	18* (50%)	4 (11.11%)	27* (75%)	5 (13.89%)	28* (77.78%)

*P value < 0.0001 Highly Significant.

of the patients as depicted in Figure 2. Also, the mean $EtCO_2$ and SpO_2 values remained within normal range and were comparable. No incidence of any adverse effects was seen in any patients of both the groups.

4. Discussion

Propofol is the primary choice for many anaesthesiologists for day care surgery due to its rapid induction and clear - headed recovery. It is known to produce hypnosis in one arm brain circulation time with minimal excitation.

Propofol being a drug belonging to Phenol group has the disadvantage of irritating mucous membrane and skin. The mechanism of pain due to Propofol has been attributed to release of kininogen from the vein wall with triggering of local kinin cascade.

In anaesthesia practice, patients judge the quality of anaesthesia by recall of any pain or discomfort during the surgery. The experience of pain upon on administration of Propofol is reported to occur in 70% of the patients when only Propofol is used for induction. So, avoiding pain on Propofol injection is highly desirable as pain appears to be a limiting factor to an otherwise useful drug.

We used the tourniquet at 70 mmHg for 60 seconds which was considered as an important tool in isolation of arm vein from rest of circulatory system to study the peripheral action of the drug in absence of its central action. It also allows the analgesics to act upon the endothelial nociceptors, the key site of local anti-nociceptive action.

Pretreatment with Ketamine is a well-established pharmacological technique to mitigate the nociceptive response of Propofol injection. Ketamine (a Phenylcyclidine derivative) has potent analgesic and local anaesthetic properties. Ketamine as a NMDA receptor antagonist may activate these receptors either in vascular endothelium or in the central nervous system. Ketamine has strong analgesic effect at small dose.[8] Ketamine also has structural similarities to Cocaine therefore it also produces analgesia via local mechanism.Ketamine is associated with less cardiorespiratory depression than other drugs use for local analgesia.

It is observed that pain on injection of Propofol can be immediate or delayed. C.H. Tan et al postulated that immediate pain probably results from a direct irritant effect whereas delayed pain resulted from an indirect effect via kinin cascade. Delayed pain has a latency of 15 to 20 seconds.[9]

So, we chose to conduct a time graded response evaluation so as to determine the action of Ketamine on both immediate and delayed pain caused due to Propofol injection.

After giving 25% of total calculated dose of Propofol, the pain score was assessed for every 5 seconds till 15 seconds. At 5 seconds interval, 12 patients (33.33%) experienced mild pain and 6 patients (16.67%) experienced moderate pain in group B (Saline group) as compared to none in group A (Ketamine group). No patient experienced severe pain in both the groups. Thus, total patients who experienced pain in group B was 18 patients (50%) as compared to none in group A which was statistically highly significant (p value <0.0001). At 10 seconds interval, 4 patients (11.11%) experienced mild pain in group A as compared to 14 patients (38.89%) in group B. Moderate pain was reported by 4 patients (11.11%) of group B whereas severe pain was experienced by 9 patients (25%) patients in group B as compared to none in Group A. Thus, total number of patients experiencing pain were 27 patients in group B (75%) as compared to only 4 patients in group A (11.11%), (p value<0.0001). Whereas at 15 seconds interval, mild pain was experienced in 5 patients (13.89%) in group A as against 14 patients (38.89%) in Group B. Moderate pain was reported by 5 patients (13.89%) of Group B as compared to none in Group A. No patient experienced severe pain in group A as compared to 9 patients (25%) in Group B. Thus, total patients who experienced pain were 28 patients in group B (77.78%) as compared to 5 patients (13.89%) in group A, which was statistically highly significant, (p value <0.0001). None of the patients in group A experienced moderate or severe pain at all 3 intervals as compared to group B patients. These results are similar to the studies conducted by Yamini T et al,[7] Sadaawvy I et al[10] and Zahedi H et al.[11]

More patients experienced pain with higher severity at 15 seconds as compared to at 5 seconds. This delayed pain can be attributed to indirect effect via the kinin cascade.

The mean values of pain scores at 5 seconds (P5) were 0 in group A as compared to 0.67± 0.75 in Group B. While at 10 seconds (P10) it was 0.11±0.31 in Group A and 1.36±1.12 in group B respectively. At final recording time of 15 seconds i.e., P15 mean values for pain scores were 0.14±0.35 in group A as compared to 1.41±1.10 in group B. The P values were statistically highly significant at all time intervals, (p value <0.0001). These findings are comparable with the previous studies.[7,12,13]

The haemodynamic parameters (NIBP: SBP, DBP, MAP, HR, SpO_2) were recorded in the perioperative period at various time intervals. The changes in heart rate in both groups were found statistically insignificant. A similar transient rise in mean Systolic blood pressure was seen in both groups at laryngoscopy and intubation and it was maintained till 5 minutes post intubation which can be attributed to stress response of Laryngoscopy and intubation (from 119.05±10.91 mmHg to 125.33±10.96 mmHg in Group A and 116.44±7.31 mmHg to 128.47±9.85mmHg in Group B. There was also a sequential fall in Systolic blood pressure in both the groups after giving 25% of total dose of Propofol and complete dose of Propofol in both the groups which was also statistically insignificant. The changes in systolic blood pressure in both the groups were not clinically significant and hence did not require any treatment. Propofol induces a decrease in the arterial blood pressure after induction of anaesthesia. This is due to the decrease in the peripheral vascular resistance, inhibition of both the sympathetic activity and myocardial contractility. We did not find significant sympathomimetic effect of Ketamine (100 mcg/kg) in our study which can be attributed to low dose of Ketamine. There was a transient rise in Diastolic blood pressure during laryngoscopy and intubation in group A from 83.38±7.92 mmHg to 88.41±7.91 mmHg. Similar changes were seen in Group B (from 80.27±9.27 mmHg to 91.55±6.02 mmHg) which was not statistically significant.

MAP changes were seen during laryngoscopy and intubation in both the groups. The rise in MAP values in both groups were statistically insignificant. In Group A there was an increase in MAP from 95.05±7.65 mmHg to 100.67±7.90 mmHg after laryngoscopy. Similarly, in Group B there was an increase in MAP from 92.35±7.86 mmHg to 102.08±6.38 mmHg post laryngoscopy and intubation. Also, the mean $EtCO_2$ and SpO_2 values remained within normal range and were comparable. These results are comparable with earlier studies.[12,14,15]

We did not find any adverse effects like rash and pruritis associated with Propofol in both the groups. No patients had emergence reactions (dreams, hallucinations, delayed recovery and looking dissociated from surroundings) or increased secretions in Ketamine group which can be attributed to low dose of Ketamine used and also the use of Glycopyrrolate in pre-anaesthetic medication. These results are similar to the studies done by Khadka B et al[12] and Polat R et al.[14]

5. Conclusion

The number of patients with pain were 50% in saline pretreated group as against to none in Ketamine group at 5 seconds' stage. With further passage of time the number of patients with pain increased in control group to 75% and 77.7% at 10 seconds and 15 seconds interval as compared to mere 11.11% and 13.89% in Ketamine pretreated patients at similar time interval. None of the patients of Ketamine pretreated group experienced moderate or severe pain after Propofol administration. Use of I.V. Ketamine in a dose of 100mcg/kg as pretreatment with tourniquet before Propofol was found useful in significantly reducing the incidence and severity of pain related to Propofol administration as an induction agent.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Author biography

Medha Akhilesh Sangawar, Associate Professor https://orcid.org/0009-0006-6590-4379

Mohana Sharadchandra Shewalkar, Junior Resident https://orcid.org/0009-0009-6086-7486

Puja Madhukar Shinde, Junior Resident https://orcid.org/0009-0006-3299-2608

Soma Chandrashekharan Cham, Associate Professor https://orcid.org/0009-0006-0717-3432

Akshay Nagorao Shende, Junior Resident III Year https://orcid.org/0009-0009-7556-4488

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