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Original Article

Evaluating the Effectiveness of Ketamine in reducing Postoperative Nausea and Vomiting in Adults after General Anaesthesia: A Prospective Randomized Controlled Trial

Yachendra V.S.G[1], Girimurugan.N[1], Ameerunnisha Begum[2], Anand.S[2], Surya.R[1]*, Lakshmi.R[3]

[1]Associate Professor, Department of Anaesthesiology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Thandalam, Chennai, Tamilnadu, India
[2]Post Graduate Resident, Department of Anaesthesiology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Thandalam, Chennai, Tamilnadu, India
[3]Professor and Head, Department of Anaesthesiology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Thandalam, Chennai, Tamilnadu, India

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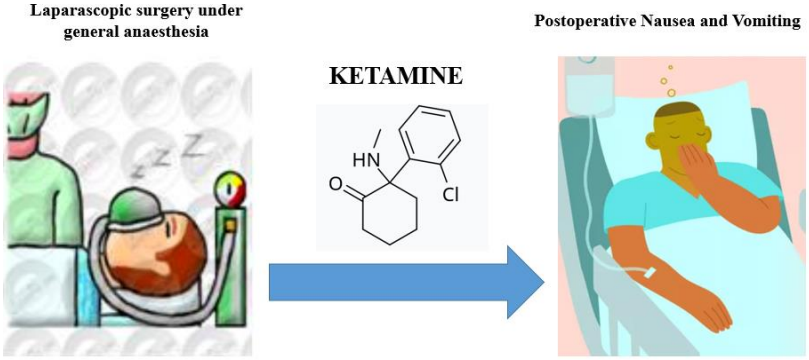
ABSTRACT

Background: Postoperative Nausea and Vomiting (PONV) is defined as any nausea, retching or vomiting occurring during the first 24-48 hours after surgery with a reported incidence of 30% in all post-surgical patients and up to 80% in high risk groups especially in laparoscopic surgeries under general anaesthesia. Many drugs have been tried and tested for abolishing PONV. We evaluated the efficacy of low dose ketamine in decreasing the incidence and severity of PONV following elective laparoscopic surgeries under general anaesthesia.
Method: 40 patients belonging to American Society of Anaesthesiologists Physical status I who were scheduled for elective laparoscopic surgeries under general anaesthesia were recruited and randomized into two groups Group A and Group B. Standard protocol for general anaesthesia were followed for all patients. Patients in Group A received Intravenous ketamine of 0.2mg/kg and Patients in Group B received the saline control half an hour before extubation. The incidence and severity of PONV, number of rescue drug administration, and side effects were recorded for first 24 postoperative hours in different time periods.
Results: Demographic profile were comparable among the groups. The incidence and severity of postoperative nausea were significantly higher in Group B when compared to Group A for the first 6 postoperative hours ($p<0.05$) and thereafter, it was comparable between the groups. The incidence of postoperative vomiting was significantly higher in Group B when compared to Group A for the first 2 postoperative hours ($p<0.04$), and then it was comparable between the groups. The number of rescue medications were significantly higher in Group B when compared with Group A. No complications were noted.
Conclusion: Low dose intravenous ketamine (0.2 mg/kg) administered as a single bolus reduced the incidence and severity of postoperative nausea and vomiting in adults undergoing laparoscopic surgeries under general anaesthesia without any complications.

* Corresponding author: Surya.R
✉ E-mail: suryaratnasamy@gmail.com

GRAPHICAL ABSTRACT



Introduction

Postoperative Nausea and Vomiting (PONV) is defined as any nausea, retching or vomiting occurring during the first 24 to 48 hours after surgery with a reported incidence of 30% in all post-surgical patients and up to 80% in high risk groups.

PONV is a common complication of surgery and anaesthesia. Although it is rarely fatal, PONV is unpleasant and associated with patient discomfort and dissatisfaction with their postoperative care. Patients have reported that PONV avoidance is of greater concern than avoiding postoperative pain. PONV is also associated with delayed discharge from the recovery room and prolonged hospital care [1, 2]. Morbidity associated with PONV includes wound dehiscence, dehydration, electrolyte imbalance, interference with nutrition, and more rarely oesophageal rupture (Boerhaave Syndrome) or aspiration pneumonitis. General anaesthesia using volatile anaesthetics is associated with an average PONV incidence ranging between 20% and 30% [3]. PONV is thought to be multifactorial, involving anesthetic, surgical, and individual risk factors [4, 5]. The PONV incidence in laparoscopic surgeries is higher and ranges from 60-75% [6].

A lot of strategies and drugs have been found to be useful in the prevention of postoperative nausea and vomiting. One of the newer drugs found to be effective is low dose ketamine. We assessed the efficacy of low dose ketamine in prevention of PONV in elective laparoscopic surgeries under general anesthesia. The aim of the study was to evaluate the efficacy of low dose ketamine in decreasing the incidence and severity of PONV following elective laparoscopic surgeries under general anaesthesia.

Materials and Methods

After prospective institutional ethical committee approval, this prospective randomised double blind study was done in Saveetha Medical College and hospital in Chennai, Tamilnadu,India in the Department of Anaesthesiology from January 2018 to June 2018 for six months. A total of 40 patients posted for elective laparoscopic surgeries under general anaesthesia meeting the inclusion criteria were included in the study. The Inclusion criteria was adults in the age range of 18 and 45 years old and weight between 40 kilogram and 90 kg, belonging to the American Society of Anaesthesiologists (ASA) Grade I who were sscheduled for elective laparoscopic surgeries under general anaesthesia. The exclusion criteria were ASA grade II and above, preoperative or intraoperative use of drugs with antiemetic properties, in-complete or inconsistent data, regional anaesthesia alone or combined with general anaesthesia, patients with psychiatric illness, contraindication or allergy to ketamine, medical causes of frequent vomiting and patient refusal.

The 100 patients were recruited using simple random sampling and were randomly allocated into two groups by picking computer generated random number lots from a bag by an unbiased person not involved in the study. There two groups were Group A and Group B. Group A was the study group who received ketamine 0.2 miligram per kilogram intravenously as per study protocol and Group B was the control group who did not receive any anti emetic drugs.

The study protocol was practiced as follows in all 100 patients with the stipulated change in the drug for antiemetic based on the group allocated. Following confirmation of inclusion into the study as per the criteria set forth, a written informed consent was obtained. Patient was shifted to the operation theatre on the day of surgery. Baseline monitors including Electrocardiogram (ECG), Noninvasive blood pressure (NIBP), and Saturation ($Sp0_2$) were connected and baseline values recorded. An 18 G venflon was secured and attached to crystalloid solution.

Patient was preoxygenated with 100% oxygen for 5 minutes and the patient was induced with intravenous 2 microgms per kilogram of Fentanyl, 2.5 milligram per kilograms of Propofol and 0.5 milligram per kilogram of Atracurium. After 3 minutes, the patient was intubated with the appropriately sized cuffed endotracheal tube and secured in position after inflation of cuff and ensuring bilateral air entry by 5 point auscultation method. End tidal Carbon-di-oxide (CO_2) monitor was attached and CO_2 levels monitored throughout the procedure.

Intraoperatively, the patient was maintained with fraction inspiration concentration of oxygen (FiO_2) of 50% oxygen and fraction inspiration concentration of Nitrous Oxide (FiN_2O) of 50% Nitrous oxide and 0.6% of isoflurane as the inhalation agent. Neuromuscular blockade was maintained with atracurium boluses every half hourly. Half an hour before the end of the procedure, patients in group A were given a solution contained in a prefilled syringe containing 0.2 mg/kg of ketamine intravenously by the attending anaesthesiologist. The attending anaesthesiologist for patients in group B was given a prefilled syringe containing only saline as placebo to be administered to the patient half an hour before end of procedure. In both cases, the attending anaesthesiologist was blinded to the contents of the syringe to avoid bias.

At the end of the procedure and after adequate recovery from neuromuscular blockade and anaesthesia, the patients were reversed with Neostigmine and Glycopyrolate, extubated, and then shifted to the recovery room. The patients were followed up for 24 hours postoperatively by a blinded observer and any episodes of nausea and vomiting with severity were documented starting from the time of admission to PACU to 24 hours postoperative time period.

Postoperative nausea was defined as an unpleasant sensation associated with awareness of urge to vomit in the postoperative period. Postoperative vomiting was defined as the forceful expulsion of contents of stomach through mouth in the postoperative period. Patients experiencing PONV in the 24 hours of observation were given 4 milligrams of oondansetron intravenously as rescue medication and when required, the number of administrations of rescue medications was recorded. The severity of postoperative nausea and vomiting were observed based on an 11-point verbal numerical rating scale (VRS), in which 0 means no nausea or vomiting and 11 represents intolerable nausea or vomiting.

Age, sex, and Body Mass Index (BMI) of the patients were analyzed using T-TEST and expressed as mean and standard deviation. A p-value of less than 0.05 was considered to be statistically significant. The PONV incidence in the study and control groups was compared using the chi-square test and the difference considered significant if the p-value was less than 0.05.

Results and Discussion

100 patients were recruited for the study and analyzed for the study without any loss of follow up. The demographic parameters were comparable among the groups, as listed in Table 1. All the surgeries included were elective laparoscopic surgeries like interval

appendectomy, cholecystectomy, ovarian cystectomy, and inguinal hernia repair.

The Incidence of postoperative nausea was significantly higher in the first 6 postoperative hours since arrival to PACU between the two groups and after which, it was observed to be comparable among the two groups, as provided in Table 2 ($p<0.02$).

The incidence of postoperative vomiting was significantly higher in the first 2 postoperative hours since arrival to PACU between the two groups and after which, it was observed to be comparable among the two groups, as shown in Table 3 ($p<0.04$).

The severity of postoperative nausea in the first 6 postoperative hours were significantly higher in Group B when compared with Group A, as indicated in Table 4 ($p<0.05$).

The number of rescue analgesics (ondonsetron) to treat PONV in the first 24 hours were significantly higher in Group B when compared to Group A, as presented in Table 5 ($p<0.05$).

Side effect profile like sedation, psycho mimetic behavior, hallucination, hypotension requiring vasopressors, headache, and nystagmus were not observed in both the groups. Postoperative nausea and vomiting are a common entity faced in anaesthesia practice. One of the main reasons given for this is the higher use of intraoperative opioids with inhalation agents, both of which have been implicated to cause PONV [4].

Table 1: Demographic parameters among both the groups

Serial No.	Demographic parameters	Group A (n=20)	Group B (n=20)	P-value
1	Age (Years)	45.3 ± 8.6	45.1 ± 8.9	0.89
2	Sex (M/F)	9(45%)/11(55%)	8(40%)/12(60%)	1.09
3	BMI (Kilograms per square meters)	26.3 ± 1.6	27.1 ± 1.1	0.76
4	Duration of Surgery (Minutes)	124 ± 7	132 ± 8	0.95
5	Duration of Anaesthesia (Minutes)	130 ± 8	138 ± 9	0.86

Table 2: Incidence of postoperative nausea (%) in the first 24 postoperative hours among the two groups in the post anaesthesia care unit (PACU)

Serial No.	Time periods in first 24 postoperative hours	Group A (n=20)	Group B (n=20)	P-value
1	On arrival to PACU	4/20 (20%)	9/20 (45%)	0.001
2	0 to the 2nd hour	3/20 (10%)	8/20 (40%)	0.001
3	The 2nd to the 4th hour	1/20 (5%)	5/20 (25%)	0.001
4	The 4th to the 6th hour	2/20 (10%)	5/20 (25%)	0.02
5	The 6th to the 12th hour	2/20 (10%)	2/20 (10%)	0.65
6	The 12th to the 18th hour	1/20 (5%)	1/20 (5%)	0.65
7	The 18th to the 24th hour	0/20 (0%)	1/20 (5%)	0.09

Table 3: Incidence of postoperative vomiting (%) in the first 24 postoperative hours among the two groups in the post anaesthesia care unit (PACU)

Serial No.	Time periods in first 24 postoperative hours	Group A (n=20)	Group B (n=20)	P-value
1	On arrival to PACU	1/20 (5%)	5/20 (25%)	0.01
2	0 to the 2nd hour	1/20 (5%)	3/20 (15%)	0.04
3	The 2nd to the 4th hour	1/20 (5%)	2/20 (10%)	0.08
4	The 4th to the 6th hour	1/20 (5%)	1/20 (10%)	0.9
5	The 6th to the 12th hour	0/20 (0%)	0/20 (0%)	1
6	The 12th to the 18th hour	0/20 (0%)	1/20 (5%)	0.1
7	The 18th to the 24th hour	0/20 (0%)	1/20 (5%)	0.1

Table 4: Severity of postoperative nausea (median and range) in the first 24 postoperative hours among the two groups in the post anaesthesia care unit (PACU)

Serial No.	Time periods in first 24 postoperative hours	Group A (n=20)	Group B (n=20)	P-value
1	On arrival to PACU	3.5 (2-6)	6 (4-10)	0.001
2	0 to the 2nd hour	4 (3-6)	6.5 (4-10)	0.02
3	The 2nd to the 4th hour	5 (5-5)	4 (3-6)	0.04
4	The 4th to the 6th hour	3 (3-3)	4 (3-5)	0.05
5	The 6th to the 12th hour	2 (2-2)	2 (2-2)	0.09
6	The 12th to the 18th hour	2 (2-2)	2 (2-2)	0.09
7	The 18th to the 24th hour	0 (0-0)	1 (1-1)	0.1

Table 5: Incidence of number of rescue medications for postoperative nausea (%) in the first 24 postoperative hours among the two groups in the post anaesthesia care unit (PACU)

Serial No.	Rescue analgesics	Group A (n=20)	Group B (n=20)	P-value
1	The first dose	6/20 (30%)	10/20 (50%)	0.001
2	The second dose	2/20 (10%)	5/20 (25%)	0.02
3	The third dose	0/20 (0%)	1/20 (5%)	0.05

Though a lot of drugs and treatment strategies exist to prevent and treat PONV, it continues to be a problem especially following laparoscopic surgeries under general anaesthesia [5-7]. Ketamine is a NMDA antagonist which is commonly used in anaesthesia for providing anaesthesia and perioperative pain control. But recently, it has been claimed that ketamine has an antiemetic property through unknown mechanisms [8-10]. Ketamine being an excellent analgesic can reduce pain in the immediate postoperative period reducing the opioid requirements of the patient and thereby reduce the PONV incidence [8]. In our study, we tried to show that the use of 0.2 milligram per kilogram of intravenous ketamine can reduce the PONV incidence significantly in this subset of surgery.

In our study, patient demographics, type of surgical procedure, and anesthetic administered were similar between groups making comparison for the incidence of PONV statistically possible. In our study, we found that the incidence of postoperative nausea was significantly higher incidence and severity in control group in comparison with the ketamine group in the first 6 postoperative hours ($p<0.05$), and then the same was comparable between the groups. The incidence of postoperative vomiting was significantly higher in the control group in comparison with the ketamine group for the first 2 postoperative hours ($p<0.04$), and thus it was comparable among the two groups. Our results were comparable with Adriaenssens *et al.* [8], Stabhuag *et al.* [9], and Javery *et al.* [10]. This clearly means that ketamine in sub anaesthetic doses has an antiemetic property. The number of rescue antiemetic medications was significantly higher in control group when compared to ketamine group. This observation was similar to study conducted by Stabhuag *et al.* [9].

Although ketamine is well-known for its anaesthetic and analgesic property, it is also known for its side effects profile like sedation, psycho mimetic behavior, hallucination, hypotension requiring vasopressors, headache, and nystagmus. In our study, we did not observe any of the side effects of ketamine in both groups. This observation could be due to the low dose of ketamine of 0.2 milligram per kilogram used in our study. Another contributing reason could be the time of ketamine administration was half an hour before extubation and only one bolus of low dose of ketamine was administered in our study, and hence, the administered drug would have got metabolised by the time the patients reached PACU. The studies conducted by Adriaenssens *et al.* [8] and Javery *et al.* [10] have also observed similar findings in terms of side effect profile of ketamine.

Our study was not devoid of limitations. First, our study was done with small sample size in Asian population. Hence, randomized trials with larger sample size comparing different ethnicity with different susceptibility to PONV should be conducted in future. Next, our study used only a single bolus of low dose of ketamine and observed that PONV was reduced for first 6 postoperative hours. Hence, studies in which low dose of ketamine administered as bolus and continuous infusion should be carried out whether the antiemetic effect of ketamine can be prolonged for the next 48 of postoperative period.

Conclusion

Low dose intravenous ketamine (0.2 mg/kg) administered as a single bolus reduced the incidence and severity of postoperative nausea and vomiting in adults undergoing laparoscopic surgeries under general anaesthesia without any side effects.

Conflict of Interest

No potential conflict of interest was reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of this article and agreed to be responsible for all the aspects of this work.

Orcid

Yachendra V.S.G.
https://orcid.org/0000-0002-0218-8284
Girimurugan.N
https://orcid.org/0000-0003-4772-2193
Ameerunnisha Begum
https://orcid.org/0009-0008-3264-8860
Anand.S
https://orcid.org/0009-0002-4351-0898
Surya.R
https://orcid.org/0000-0003-1021-5833
Lakshmi.R
https://orcid.org/0000-0003-4984-4688

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