Original Article

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Anaesthesia Section

Pre-emptive Analgesic Efficacy of Low Dose Ketamine versus Magnesium Sulfate in Patients undergoing Major Abdominal Surgeries under General Anaesthesia: A Randomised Clinical Study

KAVITA JAIN[1], SURENDRA KUMAR SETHI[2], SOURABH BAGRA[3], VEENA PATODI[4]

ABSTRACT

Introduction: Pre-emptive analgesia has been proposed to result in better pain management, reduced analgesic consumption, and improved patient satisfaction.

Aim: To evaluate pre-emptive analgesic efficacy of intravenous ketamine and intravenous magnesium sulfate in patients undergoing major abdominal surgeries under general anaesthesia by administering it 10 minutes before the incision.

Materials and Methods: This randomised, double-blind, clinical study, was conducted in JLN Medical College, Ajmer, Rajasthan, India, from November 2019 to November 2020. The study included 100 patients, aged 18-60 years of American Society of Anaesthesiologist (ASA) physical status I and II were randomly allocated into two groups. Group K (n=50) received intravenous (i.v.) ketamine infusion 0.3 mg/kg in 100 mL normal saline over 10 minutes. Group M (n=50) received i.v. magnesium sulfate ($MgSO_4$) infusion 30 mg/kg in 100 mL normal saline over 10 minutes. The duration of analgesia, total amount of rescue analgesic consumed in 24 hours, haemodynamics, and side-effects were noted. The quantitative data was presented as mean±standard deviation and were compared by student's t-test.

Results: Duration of analgesia was significantly prolonged in group K (67.96±9.20 min) as compared to group M (30.60±6.44 min) (p-value <0.001). The total dose of rescue analgesic consumption in 24 hours was lesser in group K (1180±388.09) as compared to group M (1280±453.56) (p-value=0.236). Haemodynamics and side-effect profile were comparable in the two groups.

Conclusion: In major abdominal surgeries under general anaesthesia, patients getting ketamine had longer duration of analgesia compared to magnesium sulfate, had an improved quality of recovery after surgery and less serious adverse events in the Postanaesthesia Care Unit (PACU). Ketamine reduces the need for intraoperative opioids and could suppress the pressure response to endotracheal intubation.

Keywords: Haemodynamic effect, Postanaesthesia care unit, Recovery, Rescue analgesic, Side-effects

INTRODUCTION

Perioperative pain management poses a significant challenge for an anaesthesiologist. Various modalities may provide effective postoperative analgesia which include systemic or regional analgesic methods. Opioids are commonly used for the treatment of postoperative pain; however, they are associated with side-effects like Postoperative Nausea and Vomiting (PONV) and respiratory depression [1]. So, the opioid-sparing regimens in postoperative pain management may help to reduce both postoperative pain and PONV [2]. The analgesics given in the preoperative period improves pain relief and reduces opioid consumption as well as their associated side-effects. This has been also shown to improve the standard of recovery process with reduction in duration of hospital stay, postoperative morbidity, and shorter period of convalescence after surgery [2].

Pre-emptive analgesic is a preventive analgesia technique which prevents the phenomena of central hyperexcitability, central sensitisation, central neuroplasticity stimulated by injuries due to incision and inflammation occurring during surgery as well as early postoperative period via the mechanism of pain perception pathway [3]. This may lead to better pain management, reduced analgesic consumption, and improved patient satisfaction.

Ketamine, an N-Methyl-D-Aspartate (NMDA) antagonist, inhibits central pain sensitisation at subanaesthetic doses, and various studies have been undertaken to establish the role of low dose ketamine as an analgesic for postoperative pain. The low-dose intravenous (i.v.) infusion has been considered an effective method for both centrally mediated analgesic properties with minimal effect on consciousness and cognition [4-6]. Magnesium sulfate ($MgSO_4$) is also an NMDA receptor antagonist with antiociceptive effect and has been investigated as a possible adjuvant for intraoperative and postoperative analgesia [7-9].

It was hypothesised that pre-emptive low dose ketamine as an intravenous (i.v.) infusion would lead to enhanced postoperative analgesia with minimal haemodynamic changes and side-effects when used as an alternative to magnesium sulfate.

The present study was conducted to evaluate pre-emptive analgesic efficacy of low dose i.v. ketamine and i.v. magnesium sulfate in patients undergoing major abdominal surgeries under general anaesthesia. The primary outcome measure was duration of analgesia, while secondary outcome measures were postoperative Visual Analogue Scale (VAS) scores, total dose of rescue analgesic consumed in 24 hours, haemodynamic changes, postoperative sedation score and side-effects (postoperative nausea or vomiting, respiratory depression, hallucinations, hypotension and bradycardia).

MATERIALS AND METHODS

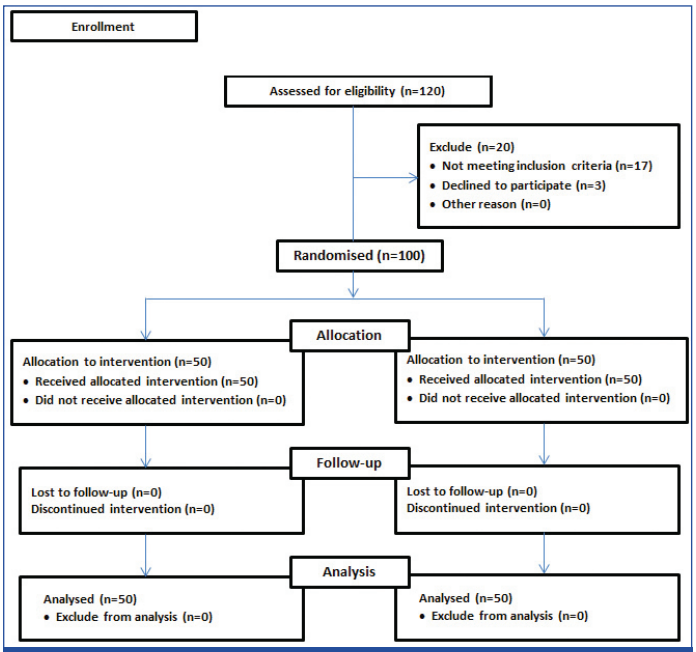
This randomised, double-blind, clinical study, was conducted in JLN Medical College, Ajmer, Rajasthan, India, from November 2019 to November 2020. This study is registered with Clinical Trials Registry-India (CTRI/2019/10/028829). The Institutional Ethics Committee had approved the study (978/Acad-2/MCA/2019).

Sample size calculation: Based on the study by Helmy N et al., sample size was determined taking into consideration that a sample size of 50 patients per group would give a power of 80% and type 1 error of 0.05 [10].

Inclusion criteria: All patients aged 18-55 years of either sex, with American Society of Anaesthesiologists (ASA) physical status I or II, scheduled to undergo major abdominal surgeries under general anaesthesia were included in the study.

Exclusion criteria: Patients who refused to participate in study, had history of diabetes mellitus and hypertension, patients allergic to study drugs, with neuropsychiatric illness and on chronic pain medications were excluded from the study.

The study population was randomly divided into two groups with 50 patients in each, using computer generated tables of random numbers with allocation concealment using sealed opaque envelope technique [Table/Fig-1].



[Table/Fig-1]: CONSORT flow Diagram.

- Group K (n=50): Patient received i.v. ketamine infusion 0.3 mg/kg in 100 mL normal saline over 10 minutes
- Group M (n=50): Patients received i.v. magnesium sulfate infusion 30 mg/kg in 100 mL normal saline over 10 minutes.

The study drug solutions were prepared by a resident anaesthesiologist who has not participated in the study later on. After the study drug infusion, all the study parameters were recorded by an anaesthesiologist who was blinded to the group to which the patient belonged.

Study Procedure

Preanaesthetic evaluation was done on the day before surgery. All patients were kept nil per oral for 8 hours prior to surgery. The patients were explained about the procedure and informed written consent was taken. After arrival of the patients in operation theatre, vital parameters, such as Heart Rate (HR), Non Invasive Blood Pressure (NIBP), Respiratory Rate (RR), temperature, Electrocardiogram (ECG) and oxygen saturation (SpO_2) were recorded. A 20G i.v. cannula was secured on either arm and i.v. fluid (ringer lactate solution) was started. Glycopyrrolate 0.2 mg i.v. was given as a premedication. All the patients received the study drug infusion as per group allocation before induction of anaesthesia. After preoxygenation with 100% oxygen for 3 minutes, anaesthesia was induced with i.v. propofol (1%) 1.5-2.5 mg/kg till loss of response to verbal commands. The i.v. succinylcholine 1.5 mg/kg was given thereafter to facilitate tracheal intubation with an adequate-sized, cuffed endotracheal tube followed by loading dose of atracurium (0.5 mg/kg), an intermediate acting neuromuscular blocking agent. Anaesthesia was maintained with oxygen: nitrous oxide (50:50), sevoflurane (0.8-2%) and intermittent boluses of atracurium on controlled mechanical ventilation. The vital parameters were monitored throughout the procedure.

After completion of the surgery, the neuromuscular blockade was reversed with i.v. neostigmine 0.04 mg/kg and glycopyrrolate 0.01 mg/kg followed by tracheal extubation after achieving spontaneous respiration and adequate muscle power. Postoperatively, all the patients were shifted to recovery room.

- **Visual Analogue Scale (VAS):** Pain intensity was assessed using VAS at 0, 2, 4, 6, 12 and 24 hours postoperatively where time 0 hour was taken as the time when the patient was shifted to postoperative recovery room. The first dose of rescue analgesia was given (paracetamol 1g i.v.) over 30 minutes when the VAS ≥3 or on patient demand. The total dose of rescue analgesia given during 24 hours was noted.
- **Haemodynamic parameters:** This include heart rate and Mean Arterial Pressure (MAP) which were observed and recorded at 0,2,4,6,12, and 24 hours.
- **Sedation:** Postoperative sedation was assessed using Ramsay Sedation Scale (RSS).

STATISTICAL ANALYSIS

Statistical analysis was performed with the Statistical Software for the Social Sciences (SPSS) version 21.0 (Inc., Chicago, IL, USA). The categorical data was presented as numbers (percent) and were compared between groups using Chi-square test. The quantitative data was presented as mean±standard deviation and were compared by Student's t-test. Probability was considered to be statistically significant p-value <0.05.

RESULTS

Demographic profile (mean age, sex, weight and ASA physical status) were comparable between two groups (p-value >0.05) [Table/Fig-2].

Parameters	Group K (Mean±SD)	Group M (Mean±SD)	p-value (Student's paired t-test)
Age (years)	39.64±8.96	37.34±11.50	0.267
Gender			
Male	16	18	0.833
Female	34	32	
Weight (kgs)	60.40±6.26	59.44±6.24	0.444
American Society of Anaesthesiologist (ASA)			
Grade I	47	48	1
Grade II	3	2	

[Table/Fig-2]: Demographic profile.
p-value <0.05 was considered as statistically significant

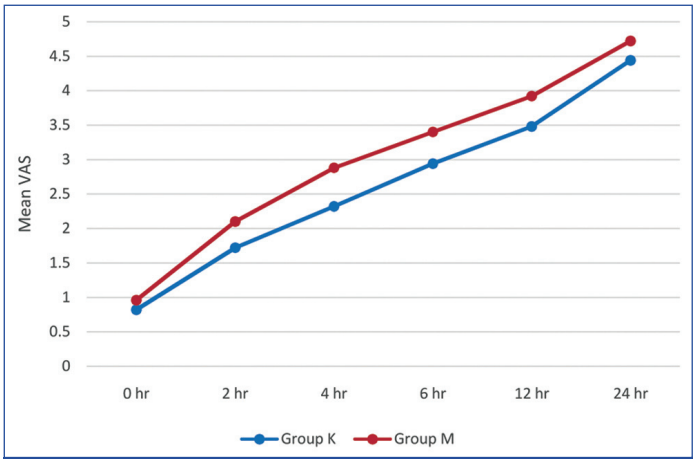
The mean VAS at 0,2,4,6,8 and 12 hours postoperatively were significantly higher in group M (p<0.05). The VAS >3 achieved earlier in group M as compared to group K before giving rescue analgesia but at 24 hrs it was comparable in both groups [Table/Fig-3].

The mean duration of analgesia was significantly prolonged in group K (67.96±9.20 min) when compared to group M (30.60±6.44 min) (p-value <0.05). The total dose of rescue analgesic required in first 24 hours was lesser in group K (1180.00±388.09 mg) than group M (1280.00±453.56 mg) [Table/Fig-2]. Although the total dose of rescue analgesia required was lesser in group K but it was statistically insignificant (p-value=0.236) [Table/Fig-4].

The mean heart rate in postoperative period revealed that there was no statistically significant difference in both the groups K and M (p-value >0.05) [Table/Fig-5].

Similarly, the mean MAP postoperatively revealed that there was no statistically significant difference in both groups K and M (p-value >0.05)

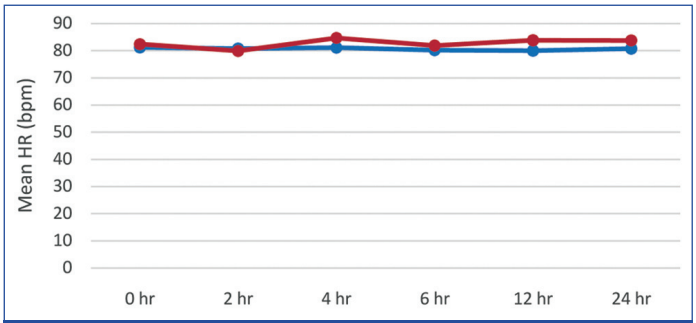
[Table/Fig-6]. Haemodynamics and side-effect profile were comparable in the two groups.



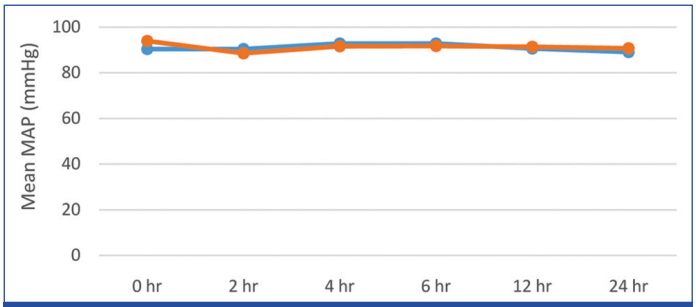
[Table/Fig-3]: Comparison of mean VAS in two groups.
p-values=0.025 at 0 hr; p-value=0.005 at 2 hrs, p-value=0.0005 at 4 hrs; p-value=0.0005 at 6 hrs; p-value=0.0008 at 12 hrs; p-value=0.120 at 24 hrs

Parameters	Group K (n=50)	Group M (n=50)	p-value
Mean duration of analgesia (min)	67.96±9.20	30.60±6.44	<0.001
Mean total dose of paracetamol over 24 h (mg)	1180.00±388.09	1280.00±453.56	0.236

[Table/Fig-4]: Duration of analgesia and rescue analgesic consumed in 24 hours.



[Table/Fig-5]: Comparison of mean heart rate.



[Table/Fig-6]: Comparison of MAP (mmHg).

The postoperative mean sedation score (RSS) in Group M was found to be significantly higher at time from 0 hr to 2 hrs as compared to group K (p-value <0.001) [Table/Fig-7]. The difference in mean sedation score was statistically insignificant from 4 hours onwards till 24 hours (p-value >0.05).

Sedation score at time interval	Group K (N=50)		Group M (N=50)		p-value (Unpaired t-test)
	Mean	SD	Mean	SD	
0 hr	1	0	1.94	0.24	<0.001
2 hrs	1	0	1.96	0.48	<0.001
4 hrs	1	0	1.04	0.20	0.156
6 hrs	1	0	1	0	-
12 hrs	1	0	1	0	-
24 hrs	0	0	1	0	-

[Table/Fig-7]: Comparison of mean Ramsay sedation score.

DISCUSSION

The findings of the present study showed that mean duration of analgesia was significantly longer in group Ketamine (67.96±9.20 min) than group magnesium sulfate (30.60±6.44 min). The pre-emptive doses of both ketamine and magnesium sulfate might be responsible for the postoperative analgesia which was found to be more with ketamine compared to magnesium sulfate. The analgesic efficacy of ketamine is due to its action as NMDA receptor antagonist as well as action on all opioid receptors with different affinities. Similarly, the mean VAS scores were significantly higher in group magnesium sulfate till 12 hours and the total dose of paracetamol as rescue analgesic required in first 24 hours was lesser in group ketamine (1180.00±388.09 mg) than Group M (1280.00±453.56 mg).

Helmy N et al., compared the pre-emptive analgesic efficacy of low dose ketamine (0.3 mg/kg) and magnesium sulfate (30 mg/kg) in parturients undergoing caesarean section under general anaesthesia. The time for first analgesic request was found to be significantly longer in ketamine group (82.00±12.00 min) compared to magnesium sulfate group (33.00±7.00 min), along with lower VAS scores in ketamine group till 6 hours, postoperatively [10].

Ghazi Saidi K and Hajipour A, lower VAS pain scores and lesser morphine consumption over 24 hours postoperatively in the ketamine group than in the control group (normal saline) [11]. However, they had not compared the duration of analgesia, although the above findings show an increase in postoperative duration of analgesia in terms of lower VAS and prolonged time to rescue analgesic request.

Kwok RF et al., compared pre-emptive low-dose ketamine (0.15 mg/kg) administered either preincision or after wound closure in patients undergoing gynaecological laparoscopic surgeries [12]. They found that preincisional ketamine reduced postoperative pain over 6 hours, increased time to first analgesic requirement along with reduced postoperative analgesic requirement, which also concurs with the index study.

Similarly, Behdad A et al., evaluated postoperative pain and analgesic requirement in patients undergoing appendectomy under general anaesthesia with pre-emptive low-dose ketamine (0.5 mg/kg) administered 10 min before the surgical incision [13]. They found significantly lower VAS scores in the ketamine group compared to the control group, with a prolonged time for the first analgesic request and reduced rescue analgesic consumption in first 24 hours in ketamine group.

Bhatia A et al., evaluated the efficacy of magnesium sulfate (preoperative loading dose of 50 mg/kg followed by 15 mg/kg/hr continuous infusion till the end of surgery) on postoperative pain, discomfort and sleep along with postoperative analgesic requirement in patients undergoing open cholecystectomy under general anaesthesia when compared to placebo group [14]. They found that patients in both groups had similar pain scores and analgesic requirement during the first 24 hrs postoperatively. In the index study, magnesium sulfate group also showed similar pain score and analgesic requirement.

Zakine J et al., compared the effects of ketamine administration on morphine consumption in major abdominal surgeries [15]. Postoperative VAS scores were significantly lower in the PERI group (receiving intraoperative and postoperative ketamine for the first 48 hours after surgery) than the intragroup (receiving intraoperative ketamine administration only and control group receiving placebo). They concluded that low dose ketamine leads to a significant decrease in morphine consumption with improved postoperative analgesia especially when it was continued for 48 hours postoperatively. Although, the mean postoperative RSS was significantly higher in group M till 2 hours, but patients remained in arousable sedation (RSS <3). Inadequate intraoperative and postoperative analgesia leads to haemodynamic instability i.e. tachycardia with or without concurrent hypertension in patients under general anaesthesia.

These were effectively managed with the pre-emptive administration of ketamine and magnesium sulfate in the index study. None of the patients had any significant side-effect during postoperative period.

Limitation(s)

The visual analog scale is subjective and varies with the level of understanding between patient and anaesthesiologist. Both ketamine and magnesium sulfate were used in single pre-emptive dose not followed by infusion, which did not infer the long term benefits to the patient as an analgesic.

CONCLUSION(S)

Both low dose i.v. ketamine and magnesium sulfate can be effectively used as a pre-emptive analgesic but ketamine provides longer duration of analgesia in comparison to magnesium sulfate. Low dose i.v. Ketamine and magnesium sulfate also reduce pressor response due to endotracheal intubation and reduced rescue analgesic consumption along with, stable haemodynamic, and show no side-effects.

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PARTICULARS OF CONTRIBUTORS:

1. Senior Professor, Department of Anaesthesia, JLN Medical College, Ajmer, Rajasthan, India.
2. Associate Professor, Department of Anaesthesia, JLN Medical College, Ajmer, Rajasthan, India.
3. Senior Resident, Department of Anaesthesia, JLN Medical College, Ajmer, Rajasthan, India.
4. Senior Professor, Department of Anaesthesia, JLN Medical College, Ajmer, Rajasthan, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Surendra Kumar Sethi,
Flat No. 202, Shiv Enclave, Ajmer, Rajasthan, India.
E-mail: drsurendrasethi80@gmail.com

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