

Effect of Preoperative Ketamine and Magnesium Sulfate on Intra & Postoperative Analgesia in Laparoscopic Cholecystectomy: A Comparative Randomized Controlled Study

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Abstract

Background: The pain management using N-methyl-D-aspartate antagonist drugs like ketamine and magnesium sulfate during intraoperative, and postoperative period plays a major role by reducing the opioid usage. A comparative randomized controlled study was assessed to identify the best analgesic drug among two different N-methyl-D-aspartate antagonists in laparoscopic cholecystectomy patients. **Subjects and Methods:** Enrolled patients were equally divided into three groups 20 for each group, First group were administered with normal saline bolus, group 2 with ketamine and group 3 with magnesium sulfate as preoperative analgesic. **Results:** The results showed that ketamine group consumed 53.66% less fentanyl over the controls and 14.64% in magnesium sulfate. Cumulative morphine consumption was 10.2±2 mg in controls, 7.2±2 mg in ketamine and 6.5 ± 2 mg in magnesium groups were resulted a less consumption of postoperative morphine. There are no symptoms like nausea, vomiting, and pruritus was observed. Thus Ketamine and magnesium both were found to be effective in reducing intraoperative and post operative analgesic consumption. **Conclusion:** Therefore, it could be concluded that the preoperative usage of ketamine and magnesium sulfate was safe and reduces requirement of opioid for the major surgeries.

Keywords: Analgesics, Ketamine, Magnesium sulfate, Postoperative pain, Fentanyl, Morphine.

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Introduction

Postoperative pain is a considerable problem for patients which last up to five days. It remains a big challenge for anesthesiologists and acute pain medicine specialists to keep the patient stable under opioid analgesic infusion. In spite of the increasing practice of advanced medical techniques such as multimodal analgesic treatments, regional anesthesia and sustained infusion of postoperative analgesics, the number of patients still suffering from chronic postoperative pain is sizable.^[1] Pain retention or perpetuation is usually the aftereffect of sensitization of central and peripheral neurons in the case of surgery. Therefore a deep analytical understanding of preventive analgesia in relation to the systemic neurons is essential for sustained attenuation of pain processing. Regular investigative and comparative studies are necessary to fully elucidate the mechanisms causing neural sensitization pathways. One such attempt has been made in the current investigation by understanding the comparative effect of ketamine and magnesium sulfate in combination with the regular anesthesia.

Literature says that any major surgeries suppress the immunity of the person in vivo and invitro which may lead to the person's immunodepression after surgery.^[2]

Inadequate pain control results in increased mortality of the postoperative patients.^[3] So, it is important to control pain after surgery needs to be quantified and treat effectively by preventive analgesia.^[4] N-methyl D-aspartate (NMDA) receptors will maintain and induce the central sensitization of pain which can be prevented by administration of NMDA receptor antagonists.^[5] As of now no NMDA receptor antagonists are available in the market for clinical use. However, few of the compounds that have significant NMDA receptor blocking properties are approved to administer in human for several clinical implications. Among the approved NMDA receptors ketamine and magnesium sulfate are the key modulators as adjuvant drugs in chronic pain management and analgesia prevention at lower doses.^[6] Ketamine is phencyclidine derivative that possess the properties of anti-allodynia, anti-tolerance, and antihyperalgesia.^[7] Many clinical conditions like chemotherapy, major surgeries, pathologic pain and chronic diseases involve neuropathic pain and central sensitization. For such conditions ketamine act as best supportive analgesic drug along with opioids. For NMDA receptors ketamine acts as antagonist, two enantiomers of ketamine will be released from the cyclohexane ring of C2 atom that binds to the phencyclidinic site on postsynaptic channels.^[8] Severe pain status an increment doses of the NMDA

receptors controls central sensitization and hyperalgesia, in such case ketamine as adjuvant therapy stops nociceptive transmission to the brain.^[9] Apart from this ketamine also manages the blood pressure, spontaneous breathing and laryngeal reflexes.^[10]

Magnesium sulfate is a versatile drug that uses majorly for preeclampsia patients to prevent seizures and also used for the patients who are suffering from arrhythmia, and asthma.^[11] Usually during surgery magnesium sulfate regimen will administer 30-50 mg/kg initially and then follows a maintenance dose of 6-20 mg/kg/h till completion of surgery.^[12] Many authors in their research said that intraoperative magnesium usage reduced the necessity of anesthetics, muscle relaxants and opioid consumption in first 24hrs.^[13] Similar to ketamine, magnesium also blocks NMDA receptors by inhibiting the calcium ions, and leads to nociceptive action and central sensitization.^[14] The main aim of the present study is to use the lower dose of Ketamine (analgesic dose) or magnesium preoperatively as pre-emptive analgesics, and assessment of the intra operative and postoperative analgesic requirement in patients undergoing laparoscopic cholecystectomy (using Visual Analogue Score, VAS). Also to check the comparisons between efficacies of Ketamine and magnesium as pre-emptive analgesics, if any.

Subjects and Methods

Ethics Approval

This study of ketamine and magnesium sulfate on intra and postoperative analgesia was conducted with the approval of the institutional medical ethics committee of ESIC Medical College, Hyderabad.

Study Design

The present randomized double blind controlled study was conducted between 2008 and 2009 for 15 months in patients undergoing elective laparoscopic cholecystectomy at our Global Hospital. Sixty enrolled patients were selected between the age group of 20-65 yrs of both the sexes. Before enrolling the patients for study, written informed consent was taken from all the patients.

Inclusion criteria

- ASA grade I and II patients scheduled for elective laparoscopic cholecystectomy
- The patients having the age of 20 and above were chosen for study.

Exclusion criteria for patients

- Patients who were having a history of cardiac arrhythmias, psychiatric disorders, neuromuscular disorders, pulmonary, Bronchial asthma and hepatic or renal dysfunction
- Patients with obesity, acid peptic disorders, and high serum magnesium levels
- Few of the excluded patients with preoperative use of opioids, beta blockers and calcium channel blockers
- Patients those are allergic to morphine

Study Design

All the patients were observed for preoperative assessment

by checking the cardiovascular symptoms, any prior medication, allergic to any specific drugs and performed general systemic examination. All the patients were starved for overnight prior to the operation. The patients who meet the eligibility criteria were randomly divided into three groups with 20 patients per each group.

Group I: placebo group received intravenous normal saline

Group II: Ketamine group received 0.5 mg/kg intravenously

Group III: Magnesium sulfate group received 20mg/kg intravenously

The drugs ketamine and magnesium sulfate were diluted in 20ml of normal saline and slowly infused preoperatively to the study group patients for a period of 10 minutes. All the study patients were instructed about the use of visual analogue scale for pain. A standard horizontal 10mm linear visual analogue scale was used to assess pain at rest and on coughing (0 = no pain at all. 10 = worst pain imaginable). All the patients were reviewed with haemogram, CBP, blood sugar & urea, serum electrolytes, magnesium & creatinine, chest X-ray, and electrocardiogram.

Treatment and Evaluation

In the operation theatre all the patients were evaluated with pulse rate (PR), BP, respiratory rate (RR), oxygen saturation (SPO₂), continuous ECG. An intravenous access was secured on each patient with an 18 gauge intravenous catheter. Ten minutes before administering the anesthesia, study drug was given to the respective patients. All the patients were premedicated with intravenous injection of 4mg ondansetron. After preoxygenating the patient with 100% oxygen for 3 minutes, general anesthesia was induced with Inj. propofol 2 mg/kg, and Inj. fentanyl 2 µg/Kg as analgesic. Intubation was facilitated with Inj. vecuronium 0.1mg/kg and the patient's trachea was intubated with appropriate sized endotracheal tube. Anesthesia was maintained with air – oxygen mixture in a ratio of 50:50 with isoflurane. Vecuronium was given whenever required. During operation, heart rate, blood pressure, oxygen saturation and ETCO₂, were monitored continuously and recorded every 15 minutes. Intra operative pain was determined by increase of mean arterial pressure and heart rate more than 20% from base line values and was managed with 0.5-1µg/kg of fentanyl, as boluses till heart rate and mean arterial pressure returned to baseline.

Since administration of magnesium may increase the level of neuromuscular blockade, muscle relaxation was monitored continuously with a peripheral nerve stimulator. Total amount of fentanyl required was recorded. At the end of surgery, neuromuscular paralysis was reversed using neostigmine 0.05mg/kg and glycopyrrolate 8 µg/kg. After full recovery, patients were extubated and shifted to post anesthesia care unit. The patients pulse rate, blood pressure and visual analogue score at rest and on cough were monitored continuously and recorded for next two hours and then shifted to ward as appropriate.

Postoperative Pain management

After completion of surgery patient was given with suppository diclofenac sodium 100 mg followed by 100 mg orally after 12hrs. For all the patients were prescribed to take Tab. Paracetamol 1g Q.I.D orally. For the patients who were

having VAS five and above were administered intramuscularly with 50-100 micrograms/kg Inj. morphine sulphate. Postoperative observation with blood pressure (NIBP), oxygen saturation, visual analogue scores at rest and on coughing (VAS) were recorded at 0, 1, 4, 6 & 24 hours. Requirement of morphine sulfate was also recorder and no other sedative and analgesics were used.

Statistical analysis

All the different parameters of the study patients were analyzed using ANOVA test by using windostat statistical program version 9.1. Kruskal–Wallis one-way analysis of variance was used to calculate the demographic trend, heart rate, blood pressure, serum magnesium levels, oxygen saturation, respiratory rate, end tidal CO2, additional fentanyl requirement, visual analogue scores at rest and on cough, morphine consumption for first 24 hrs. If statistically significant result obtained, Dunnett’s test was performed to determine considerable difference between groups. In addition, t- test was also performed between placebo-ketamine, and placebo-magnesium groups to confirm Dunnett test results. ‘p’ value < 0.05 was considered as statistically significant and the results were expressed as mean ± SEM and median.

Results

Surgery time for the patients was ranged from 78 to 89.2 minutes and all the surgeries were performed by same surgeon and surgical staff. Demographic data of gender, age, weight of the patient and surgery duration was tabulated in table 1, in which no statistical significance was observed in all the three groups. This indicates that the different age groups from 37 to 46 and difference in weights in the study were not faced any complications with operation duration as well as with the ketamine and magnesium sulfate when used as analgesia.

Table 1: Demographic characteristics of patients, and duration of operation among the groups. Values represented as Mean ± SEM.

	Group 1	Group 2	Group 3
Gender (M/F)	9/11	13/7	12/8
Age(yrs)	45.8±15.9	43.0±10.0	37.6±11.0
Weight (kg)	62.3±9.0	63.5±8.51	58.9±8.0
Duration of operation (min.)	78.0±18.5	81.7±23.0	89.2±18.5

All the three groups’ preoperative serum magnesium levels were resulted in normal limits. In figure 1 it is observed that preoperative heart rate was equal in all the groups where as there was a gradual increase all the different time intervals. It is resulted that the mean and standard error of mean for intraoperative heart rate in control group was higher at 45 and 120 minutes with p < 0.05 (0.023, 0.003 respectively) when compared to the other two ketamine and magnesium sulfate groups [Table 2]. At 30 minutes time point heart rate of placebo and magnesium sulfate groups were almost same with 85.5 and 84.3 but no significance was seen.

Table 2: Mean and SEM for preoperative and intraoperative heart rate. (* Indicates statistical significance).

	Group 1	Group 2	Group 3	p - Value
Preoperative	80.0 ± 9.3	80.3 ± 5.6	80.4 ± 11.8	0.9
15 min	79.6 ± 16.0	75.5 ± 11.2	77.7 ± 13.1	0.6
30 min	85.5 ± 15.1	79.9 ± 9.4	84.3 ± 11.1	0.3
45 min	88.3 ± 12.1	80.5 ± 9.8	80.2 ± 8.3	0.023*
60 min	86.5 ± 13.4	81.1 ± 6.2	82.1 ± 12.4	0.2
75 min	85.2 ± 9.6	81.3 ± 7.6	82.6 ± 12.9	0.5
90 min	86.1 ± 9.7	82.4 ± 8.9	82.1 ± 5.6	0.5
105 min	88.7 ± 11.7	84.5 ± 6.3	81.4 ± 6.6	0.3
120 min	90.0	80.0 ± 1.6	79.0 ± 1.0	0.003*

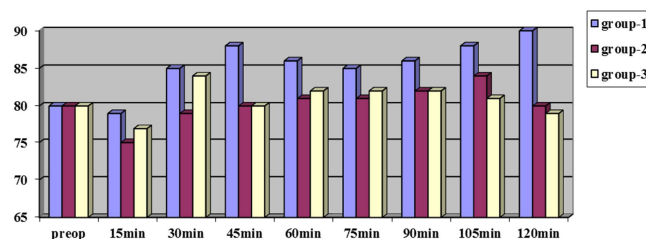


Figure 1: Graphical representation of mean heart rate in all the three experimental groups.

The resulted systolic blood pressure was observed during preoperative and intraoperative at every 15 minutes intervals and it was statistically significant at 45, 60 and 90 minutes in placebo group [Table 3]. It is showed that the p value is less than 0.05 i.e. 0.038*, 0.048*, 0.003* at 45, 60, and 90 min. respectively. Considerable major systolic blood pressure was not observed at all the intervals during operation in all the three groups [Figure 2].

Table 3: Mean and SEM for preoperative and intraoperative systolic blood pressure. (* Indicates statistical significance).

	Group 1	Group 2	Group 3	p - Value
Preoperative	122.2 ± 10.5	124.8 ± 8.2	121.9 ± 8.7	0.5
15 min After intubation	112.2 ± 12.5	105.7 ± 8.2	111.7 ± 13.0	0.1
30min	130.6 ± 14.3	123.5 ± 11.2	125.9 ± 15.4	0.2
45 min	131.7 ± 9.2	123.1 ± 11.2	128.0 ± 10.6	0.038*
60 min	130.9 ± 11.2	122.3 ± 10.9	123.6 ± 11.4	0.048*
75min	128.0 ± 7.3	123.0 ± 7.5	128.8 ± 9.0	0.1
90 min	132.9 ± 5.4	121.1 ± 8.8	132.6 ± 8.1	0.003*
105 min	131.0 ± 1.4	123.0 ± 12.2	127.2 ± 8.8	0.6
120 min	130.0 ± 1.4	120.0 ± 10.583	118.000 ± 14.142	0.724

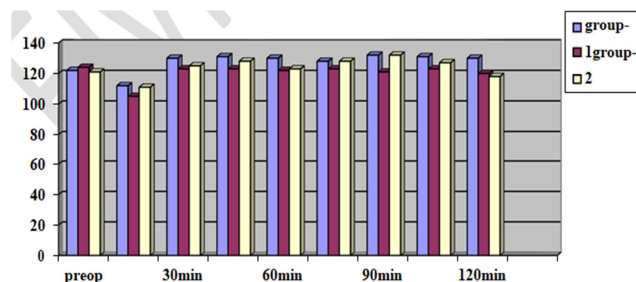


Figure 2: Graphical representation of mean systolic blood pressure in all the three experimental groups.

Similarly as heart rate and systolic blood pressure, the

diastolic blood pressure was also observed preoperatively and intraoperatively. The significance difference of 0.046 was observed at 105 minutes in placebo group of the patients when compared to ketamine and magnesium sulfate groups [Table 4]. At 120 minutes of intraoperative period, the diastolic blood pressure seems to be same with 89 and 89.5 in control and magnesium sulfate groups but no statistical significance was observed [Figure 3].

Table 4: Mean and SEM for preoperative and intraoperative diastolic blood pressure. (* Indicates statistical significance).

	Group 1	Group 2	Group 3	p - Value
Preoperative	76.1 ±7.3	77.5 ±5.0	73.6 ±5.7	0.1
15 min after intubation	70.2 ±10.5	66.8 ±6.2	69.0 ±9.7	0.4
30min	80.4 ±10.0	76.2 ±8.8	76.2 ±9.3	0.2
45 min	79.1 ±10.8	75.2 ±8.7	77.3 ±9.1	0.4
60 min	77.1 ±9.1	77.6 ±10.2	78.0 ±10.7	0.9
75 min	79.3 ±8.8	77.4 ±5.8	77.1 ±8.1	0.7
90 min	79.3 ±8.0	76.7 ±10.0	75.3 ±11.0	0.6
105 min	87.0 ±4.2	74.4 ±4.5	79.0 ±5.8	0.046*
120 min	89.0	80.6 ±11.3	89.5 ±0.7	0.5

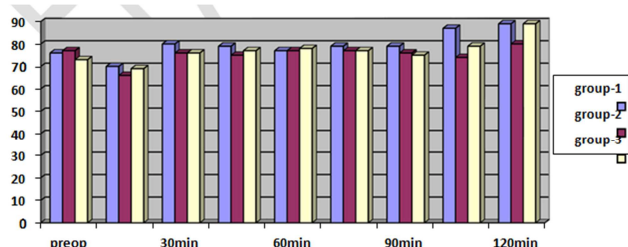


Figure 3: Graphical representation of mean diastolic blood pressure in all the three experimental groups.

During the treatment procedure fentanyl was given as analgesia as well as bolus at the time of surgery. When calculated the additional usage of fentanyl in three groups, it is observed that mean intraoperative usage of fentanyl was more i.e. 51.2 mcg when compared to the ketamine and magnesium sulfate [Table 5]. In group 2 the fentanyl consumption was 23.7 mcg which is 53.66% lesser than control and in group 3 consumption was 43.7 mcg that is 14.6% lesser when compared to the control groups.

Table 5: Mean usage of intraoperative fentanyl.

Category	Fentanyl Usage
Group 1 (Control)	51.2 ± 29.7
Group 2 (Ketamine)	23.7 ± 18.9
Group 3 (Magnesium Sulfate)	43.7 ± 24.1

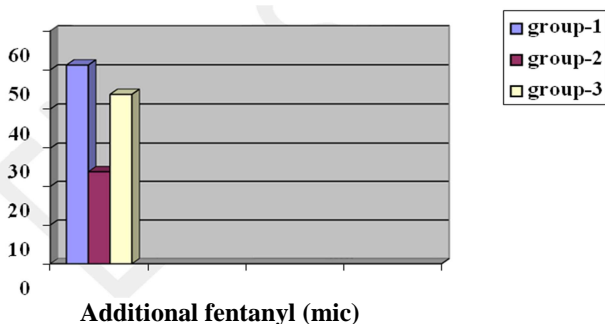


Figure 4: Graphical representation of intraoperative additional fentanyl use in all the different groups.

Postoperative heart rate was checked from 0 hr to 24 hrs for all the patients in three groups. It was resulted that there is no significant difference in the mean post operative heart rate between controls, ketamine and magnesium sulfate groups [Figure 5]. Heart rate in all the three groups was decreased gradually from 90 to 70 from 0 hrs to 24 hrs respectively [Table 6]. This indicates that the heart rate with the ketamine and magnesium sulfate analgesia were not influenced the heart rate of the postoperative patients.

Table 6: Mean and SEM for postoperative heart rate.

	Group 1	Group 2	Group 3	p – value
0 hr	90.2 ± 10.8	87.5 ± 7.5	90.5 ± 9.6	0.545
1 hr	84.3 ± 9.2	83.1 ± 7.4	87.9 ± 8.5	0.188
4 hr	82.1 ± 8.4	85.2 ± 8.7	82.6 ± 10.7	0.529
6 hr	78.3 ± 6.9	78.5 ± 7.2	75.0 ± 6.4	0.208
24 hr	76.5 ± 7.7	74.4 ± 7.5	74.0 ± 6.3	0.509

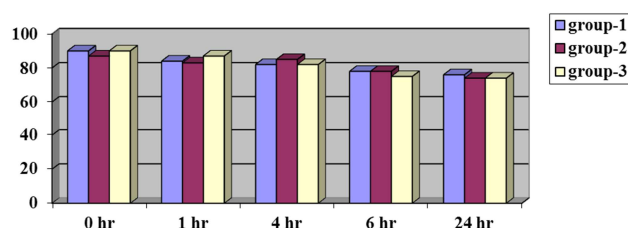


Figure 5: Postoperative heart rate till 24 hrs in three groups.

Postoperative systolic blood pressure was calculated from 0-24hrs in all the three group patients. It is observed at 4th and 6th hrs in control groups was significantly higher when compared to the other two groups [Table 7]. Both the analgesia groups were not shown any significant effect on systolic blood pressure [Figure 6].

Table 7: Mean and SEM for post operative systolic blood pressure

	Group 1	Group 2	Group 3	p – value
0 hr	130.9 ±11.2	126.3 ± 7.0	127.7 ± 7.1	0.239
1 hr	129.3 ± 8.9	129.8 ± 9.4	128.6 ±12.7	0.936
4 hr	131.0 ± 8.3	128.9 ±10.7	122.4 ±11.2	0.027*
6 hr	132.0 ± 8.3	123.2 ± 7.3	122.3 ± 9.4	0.001**
24 hr	120.5 ± 5.4	121.1 ± 6.9	119.7 ± 4.8	0.760

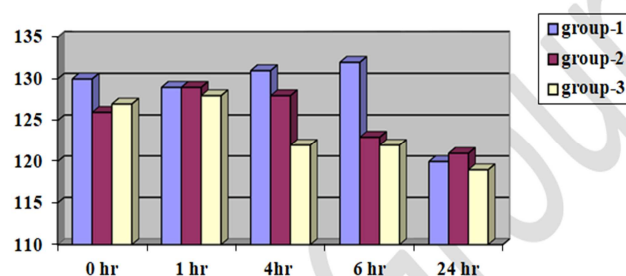


Figure 6: Graphical representation of post operative systolic blood pressure.

The resultant postoperative diastolic blood pressure was significantly high (81.3) at 6th hour in control group when compared to ketamine and magnesium sulfate groups [Table 8]. The diastolic blood pressure was low in control groups at 0 and 1st hour if compared to other two groups but there was a gradual increase in the rate at 4th and 6th hrs.

Though there was a decrease to 76 at 24th hour still higher in diastolic blood pressure over the other two groups [Figure 7].

Table 8: Mean and SEM for post operative diastolic blood pressure

	Group-1	Group-2	Group-3	p-value
0 hr	77.4 ± 8.8	78.950 ± 6.901	75.150 ± 6.777	0.287
1 hr	77.4 ± 7.5	78.550 ± 6.724	79.550 ± 10.526	0.715
4 hr	80.5 ± 7.6	78.000 ± 9.581	75.150 ± 8.087	0.146
6 hr	81.3 ± 5.7	75.850 ± 7.095	73.350 ± 4.987	0.000**
24 hr	76.5 ± 5.6	74.700 ± 6.868	74.950 ± 6.039	0.773

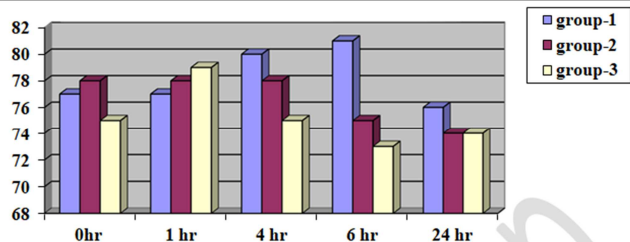


Figure 7: Graphical representation of post operative diastolic blood pressure.

A visual analogue score was measured for all the patients to assess the intensity of the pain after surgery from 0 to 24 hrs at rest. It is observed that three of group 1 and group 3 patients underwent slight pain at first hour where as four of group 2 patients underwent pain 4th hour [Figure 8]. But there was no observed statistical significant pain in any group at resting period [Table 9].

Table 9: Mean and SEM for visual analogue score at rest.

	Group-1	Group-2	Group-3	p-value
0 hr	1.400 ± 1.984	0.850 ± 1.899	0.850 ± 1.461	0.539
1 hr	3.250 ± 1.410	2.700 ± 1.174	3.300 ± 1.261	0.269
4 hr	2.300 ± 1.342	3.300 ± 1.838	2.250 ± 1.410	0.061
6 hr	2.100 ± 0.968	1.400 ± 0.940	2.000 ± 1.376	0.108
24 hr	0.200 ± 0.410	0.100 ± 0.308	0.250 ± 0.444	0.472

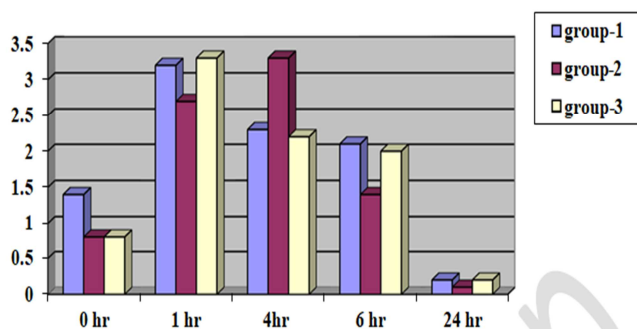


Figure 8: Graphical representation of visual analogue score at rest.

Similarly VAS at cough was also assessed in all groups from 0 to 24hrs. The resultant score was high at 4th hour in ketamine group which is statistically significant when compare to placebo and magnesium sulfate group [Table 10]. There was also observed increment in pain at cough in the first hour of magnesium sulfate group, still there is no statistical significance [Figure 9].

Table 10: Mean and SEM for Visual analogue score on cough.

	Group-1	Group-2	Group-3	p-value
0 hr	2.750 ± 2.989	1.650 ± 2.300	2.300 ± 1.922	0.366
1 hr	5.700 ± 1.720	4.950 ± 1.761	6.150 ± 1.899	0.111
4 hr	4.000 ± 1.777	5.400 ± 2.210	3.750 ± 1.916	0.023*
6 hr	3.600 ± 1.635	3.400 ± 1.569	3.450 ± 1.849	0.927
24 hr	1.050 ± 0.945	0.650 ± 0.745	0.950 ± 0.887	0.320

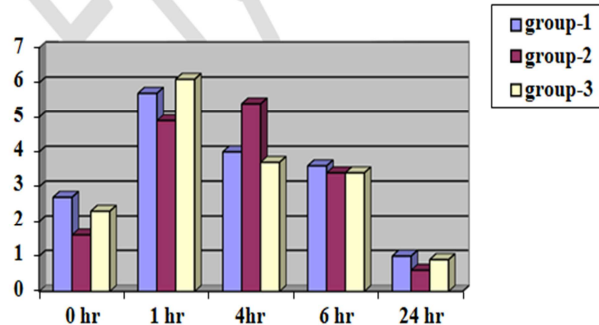


Figure 9: Graphical representation of postoperative visual analogue score at cough.

Postoperative morphine requirement as a pain medicine was observed in all the three groups. It was seen in the graph that morphine consumption in ketamine group used less until 4th postoperative hours. Whereas no significant consumption was observed in placebo and magnesium groups. Within the postoperative 24hrs morphine requirement was less in magnesium group then follows ketamine group and highest consumption was observed in placebo group [Table 11, Figure 10].

Table 11: Mean and SEM for Morphine requirement in the postoperative period

	Group-1	Group-2	Group-3	p-value
0 hr	0.975 ± 1.773	0.225 ± 1.006	0.600 ± 1.492	0.275
1 hr	3.150 ± 2.001	2.025 ± 2.137	3.375 ± 2.058	0.095
4 hr	1.350 ± 1.941	2.400 ± 2.251	1.125 ± 1.999	0.124
6 hr	1.425 ± 2.034	0.675 ± 1.649	0.600 ± 1.492	0.261
24 hr	3.525 ± 1.634	1.875 ± 2.170	0.825 ± 1.719	0.000**

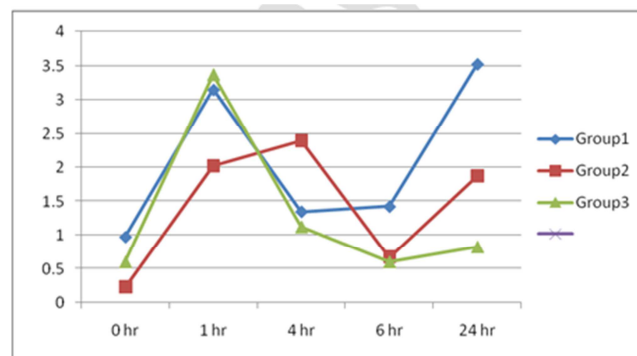


Figure 10: Comparison of total morphine requirement in three groups.

Cumulative morphine consumption was less in treatment groups i.e. ketamine and magnesium. Ketamine group consumption was 30% less where as 36% less in magnesium group when compared to the placebo group [Table 12, Figure 11].

Table 12: Mean and SEM of cumulative morphine consumption in three groups.

Category	Morphine Usage
Group-1	10.2 ± 2.5
Group-2	7.2 ± 2.0
Group-3	6.5 ± 2.8

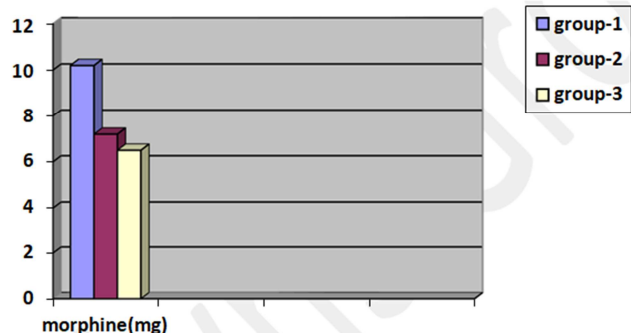


Figure 11: Cumulative consumption of morphine in three groups.

Intraoperative and postoperative side effects were observed in all the three groups. There were no significant symptoms observed in all the three group except hallucination in three ketamine group patients [Table 13].

Table 13: Comparison of incidence of intraoperative and postoperative side effects.

	Group 1	Group 2	Group 3
Delayed recovery	0	0	0
Pruritus	0	0	0
Urinary retention	0	0	0
Hallucinations	0	3	0
Nausea & vomitings	0	0	0

Discussion

In the present study, we have observed the laparoscopic cholecystectomic patients intra and postoperative effect on usage of Preoperative ketamine and magnesium sulfate as analgesia by comparing with control groups. A major criterion of the study is to reduce the pain, opioid consumption, shorter recovery and fentanyl consumption without any side effects. Our results revealed that the usage of a bolus of ketamine (0.5mg/kg) and magnesium (20mg/kg) were more efficient in post operative pain management, cumulative morphine consumption and reduced fentanyl consumption. It is also resulted that the systolic, diastolic blood pressure was maintained in a controlled manner at intra and postoperatively. In addition, visual analogue score was lower in both the treatment groups when compared to controlgroup.

A study conducted by Rodríguez-Rubio L, et al.^[15] administration perioperative magnesium sulfate as adjuvant, that reduced the need of opioids, propofol, and neuromuscular blockings. Similarly the present study used

magnesium sulfate as adjuvant drug which showed the reduction in usage of fentanyl and cumulative morphine consumption. Another research by Dabbagh A, et al. in lower limb orthopedic surgery patients, when administered magnesium sulfate intravenously that showed suppression of postoperative pain and led to less usage of morphine for first 24 hrs.^[16] In support to Dabbagh A, et al. study our clinical trial also yielded the similar results with 3.5 mg/kg of morphine in placebo group at 24th hour whereas 1.8 and 0.8 mg/kg in ketamine and magnesium groups.

Lower dose of intraoperative and postoperative ketamine usage in major abdominal surgery improved postoperative analgesia, incidents of nausea and decreased in morphine consumption.^[17] The present case of lower ketamine dose i.e. 0.5 mg/kg the results showed decrease in fentanyl and morphine consumption. Also there are no observed side effects like pruritus, nausea, vomiting, etc. except hallucination in three patients. Visual analogue score for the pain in ketamine and magnesium groups was not there at rest but there is a slight pain at 4th and 1sthour pain at cough respectively. Several studies indicate that Ketamine has persistent effect on central nervous system sensitization.^[18] However, we observed a decrease in morphine requirement during only upto 4 hrs after surgery. This may be due to insufficient dose of ketamine for therapeutic plasma levels or short duration of pharmacokinetic effects of ketamine.

The results regarding intraoperative and post operative analgesic need after magnesium supplementation are contradictory. Generally there is a significant decrease in serum magnesium levels intra and post operatively in almost all surgeries.^[19] Contrastingly in a study by Koinig H, et al. showed that administration of magnesium lead to a significant reduction of intra and postoperative analgesic requirements.^[20] Similarly in the other study by Tramer MR, et al. showed that perioperative administration of magnesium sulfate was associated with smaller analgesic requirement, less discomfort, and a better quality of sleep in the postoperative period but no adverse effects and cumulative morphine consumption after 48 hrs was 30% less in magnesium treated patients.^[21]

In our study administration of magnesium sulfate decreased intraoperative fentanyl consumption by 14% and cumulative morphine consumption for the 1st 24 hrs by 36% when compared with control group, but the difference in reduction of morphine consumption for first four post operative hours when compared to control group was not significant. This may be due to no interaction between opioids and magnesium. The cumulative consumption of morphine for the 1st 24 hours of post operative period was about 6% less than Ketamine group and 36% less than control group. Decrease in serum magnesium levels in control and Ketamine groups intra and post operatively may explain the increase in analgesic requirements in these groups compared to morphinegroup.

When observed the heart rate, there is no significant difference in both preoperative and intraoperative patients in all the three groups. The mean systolic blood pressure was high in control groups of preoperative as well as 4th and 6th hrs of postoperative period. Similarly mean diastolic blood pressure was observed to be high in preoperative control groups. And postoperative DBP was increase at

6th postoperative hour. This indicates the use of adjuvant usage of ketamine and magnesium maintained a very good systolic and diastolic blood pressure. This study suggests that ketamine and magnesium sulfate drugs when administered as adjuvant therapy for the laparoscopic cholecystectomy patients helped in reduced usage of other pain management drugs.

Conclusion

In conclusion, patients those who underwent cholecystectomy surgery were not having any symptoms like nausea, vomiting, and pruritus in all the three groups. Intraoperative and postoperative pain was reduced by using lower doses of ketamine i.e. 0.5mg/kg and magnesium sulfate i.e. 20mg/kg as preoperative analgesic drugs. It is also observed that the ketamine effect was more efficient in comparison with magnesium by means of reducing analgesic requirement during the intraoperative period and during the first four hours of post operative period. Magnesium was succeeded in reducing the cumulative morphine consumption in first 24hrs of postoperative period. With the present study we can suggest that the Preoperative usage of lower doses of ketamine and magnesium sulfate (NMDA receptor blockers) was safe and reduces requirement of opioid for the major surgeries.

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