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Evaluation of the pre-emptive analgesic effects of ketamine hydrochloride versus magnesium sulphate in patients undergoing elective abdominal surgeries

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Abstract
Aim: To evaluate the Pre-emptive analgesic effects of Ketamine hydrochloride versus Magnesium sulphate in patients undergoing elective abdominal surgeries compared to control group.
Method: In this study, 90 patients of age 18-70 years undergoing elective abdominal surgeries were randomly allocated into 3 groups of 30 each. Group K received inj. ketamine hydrochloride (0.5 mg/kg), Group M received inj. magnesium sulphate (50 mg/kg) and Group C received normal saline after induction and before surgical incision. Postoperative hemodynamic changes, Visual Analog Scale (VAS) score at 0, 1, 4, 6, 12, and 24 hrs; time of first rescue analgesia, the total amount of analgesia consumed, and adverse effects were recorded.
Result: The VAS scores at all-time intervals were significantly higher in Group C compared to Groups K and M. Time for first rescue analgesia was significantly longer in Groups K and M as compared to Group C ($p<0.0002$). The consumption of Tramadol HCL was significantly lower in Groups K and M (233.00±72.19 and 233.33±97.10 mg) as compared to Group C (370.00±90.25) (P value <0.0001) without any significant side effects. The haemodynamic parameters in Group C showed a higher value at the 2nd hour. However, there were no significant differences between Groups K and M with respect to any parameter studied.
Conclusion: A single Pre-emptive bolus dose of NMDAR antagonists like Ketamine or Magnesium is an easy and reliable method to provide better pain relief after elective abdominal surgeries without any adverse effects.

Keywords: Abdominal surgeries, ketamine hydrochloride, magnesium sulphate, pre-emptive analgesia

Introduction
Pre-emptive analgesia is defined as a treatment that is initiated before surgery in order to prevent the establishment of central sensitization evoked by the incisional and inflammatory injuries occurring during surgery and in the early postoperative period [1].

A Pre-emptive antinociceptive intervention given before the start of surgery would decrease the intensity of postoperative pain, decrease hyperalgesia and central sensitization when compare with a similar intervention given after the start of surgery. Pre-emptive analgesia may also prevent the development of chronic pain [2].

Multimodal analgesia address multiple sites along the pain pathway and may prove to prevent central sensitization in many surgical procedures. Some of the clinical studies results shows that Pre-emptive analgesia is a valid phenomenon.

However, we need to find an answer how to obtained the maximal clinical benefits with the use of Pre-emptive treatment. Evaluation of the true importance of Pre-emptive analgesia will have to await further research with new, more comprehensive approaches [1].

Several drugs, techniques, and combinations are used as Pre-emptive analgesia. There is no conclusive evidence of the superiority of one drug. The choice of drug and technique should be determined according to the clinical characteristics of the patient, type of operation, and the experience of the person.

Techniques like oral administration [3], infiltration [4, 5], intravenous [6, 7], epidural route [8, 9] etc have been used to administer different Pre-emptive analgesic agents.

Drugs with different mechanisms of action such as NSAIDs [10], opioids [11], NMDA receptor antagonists like Ketamine, [7, 12, 13] Magnesium, [7, 14] Paracetamol, [6] or their combinations [5, 6, 15-17] Pregabalin and gabapentin, [3] which are GABA analogs, and local anesthetics [5] have been used as Pre-emptive medication in different surgeries.

Ketamine is an NMDA antagonist with analgesic properties that may be important in the modulation of central sensitization to nociceptive stimulation [2].

In terms of antinociceptive action, the main mode of action of Magnesium involves its action at the N Methyl D aspartate receptor, which prevents central sensitization and attenuates pain hypersensitivity. Administration of magnesium via various route may alleviate pain and perioperative anesthetic and analgesic requirements [18].

The present study was designed to study the efficacy of a bolus dose of Pre-emptive Ketamine HCL and Magnesium sulphate when compared to control group in patients undergoing elective abdominal surgeries, for postoperative pain relief and postoperative consequences, in view of their importance.

Materials and Methods

After obtaining institutional ethical committee approval and written informed valid consent, this randomized controlled study was conducted on 90 patients, 30 in each group.

Patient undergoing elective abdominal surgery under general anesthesia, age 18-70 years, ASA grade I and II of either sex were included in the study. Patients with known allergy to study drugs, obese patients (BMI > 30kg/m2), history of substance or alcohol abuse, history of psychiatric disorder, cardiac disorder, renal dysfunction, pre-existing neurological deficit, respiratory disease, history of treatment of chronic pain syndrome were excluded from the study.

Prior to the procedure pre-anesthetic evaluation was done and detailed history of cardiovascular system, respiratory system, central nervous system, drug therapy and drug allergy were taken. A thorough clinical examination of the patient was performed including general physical examination and systemic examination. Airway assessment was done by mallampatti grading to anticipate the possibility of difficult airway. Routine investigations like complete blood count, serum electrolytes, X ray chest, renal and liver function test, 12 lead ECG, FBS, PPBS, PT, APTT, INR, HbsAg, HIV, urine- routine and micro were done. All the patients were introduced to the VAS scale pre-operatively and instructed of its use as an instrument for measuring postoperative pain.

All patients were premedicated with Tab. Lorazepam 1 mg on the night prior to surgery and kept nil orally for 8 hrs before surgery. In the operating room, an i.v cannula was secured and baseline ECG, Heart rate (HR), Non-invasive Blood pressure (NIBP), end-tidal carbon dioxide ($EtCO_2$), Peripheral Oxygen saturation (SpO_2) were recorded using a multiparameter monitor. Patients were then randomly assigned into one of the three treatment groups:

Group K - Ketamine group (Group K), patients received a bolus dose of inj. Ketamine hydrochloride (0.5 mg/kg) diluted in 10 ml Normal Saline,

Group M: Magnesium group (Group M), patients received a bolus dose of inj. Magnesium Sulphate (50 mg/kg), in 10ml Normal Saline

Group C: Control group (Group C), patients received a bolus dose of 10 ml Normal Saline.

All patients were premedicated with Inj. Glycopyrrolate (0.04 mg/kg) i.v. After preoxygenation with 100% oxygen for 3 minutes, patients were induced with Inj. Fentanyl citrate (2 mcg/kg) + Inj. Propofol (2 mg/kg) i.v. Endotracheal intubation with an adequate-sized cuff endotracheal tube was facilitated after inj. Succinylcholine bromide (1.5 mg/kg) i.v. After checking bilateral air entry, the tube was fixed and connected to the anesthesia machine. Anesthesia was maintained with oxygen and nitrous oxide in a ratio of 1:1, along with Sevoflurane (0.8-1.5%). Maintenance of muscle relaxation was provided by Inj. Vecuronium bromide (0.1 mg/kg) i.v. and followed by a top-up dose of 0.02 mg/kg i.v. intraoperatively. All hemodynamic parameters were monitored.

After completion of the surgery, patient reversed with Inj. Neostigmine sulphate (0.05mg/kg) and Inj. Glycopyrrolate (0.01 mg/kg) i.v. The trachea was extubated once the patient was awake after the establishment of adequate spontaneous respiration. Patients were then shifted to the PACU where further observations were made and recorded.

Postoperative pain assessment was done by using Visual Analog Score at 1st, 2nd, 4th, 6th, 12th and 24 Hrs. Duration of analgesia was defined as the time interval from completion of surgery to the administration of 1st rescue analgesia. Time for 1st rescue analgesia was noted when VAS>5 or if the patient demanded. Inj. Tramadol HCL 2 mg/kg i.v was given as rescue analgesia. Time of duration of analgesia, the total postoperative analgesic requirement in 24 hrs, and hemodynamic measurements were recorded.

Any adverse side effects or complications related to the drugs administered like nausea, vomiting, hallucinations, hypotension, bradycardia etc. were recorded. Nausea & vomiting was treated with Inj. Ondansetron 0.1 mg/kg.

Statistical Analysis: Data in the test and table are statistically described in terms of mean± standard deviation. Microsoft Word and Microsoft Excel have been used to generate graphs and tables. For comparing two sets of categorical data, the independent sample t-test was performed. For comparing three sets of categorical data, the Analysis of Variance (ANOVA) test was performed. P values less than 0.05 were considered statistically significant. Statistical analysis was done by using the software Statistical Package for the Social Sciences (SPSS).

Results

All three groups were comparable with respect to age, height, duration of surgery, baseline HR and MAP with no statistical difference between them.

Table 1 shows that all three groups were comparable with respect to heart rate at 0 min, 1st, 4th, 6th, 12th and 24 hours with no statistical difference between them. But at the 2nd hour HR is significantly higher in the control group compared to the K and M groups.

Table 1: Comparison of Heart Rate

Time	Ketamine	Magnesium sulphate	Control	P Value
	Mean± S.D.	Mean ±S.D.	Mean ±S.D.	
BASELINE	79.77±5.66	78.77±5.76	79.13±4.8	0.7710
0 min	79.87±5.78	80.90±6.37	81.00±5.82	0.7207
1 Hr	82.60±8.22	80.87±5.82	81.80±7.94	0.6636
2 Hr	81.13±7.12	81.10±6.38	89.47±6.11	0.0001
4 Hr	82.07±5.64	81.67±8.22	81.77±7.85	0.9761
6 Hr	83.20±4.82	83.03±8.29	82.27±5.67	0.8359
12 Hr	81.90±4.4	80.67±8.13	79.20±4.69	0.2218
24 Hr	78.33±4.7	77.47±3.48	76.9±4.71	0.4386

Table 2: Comparison of Systolic Blood Pressure (SBP)

Time	Ketamine	Magnesium sulphate	Control	P Value
	Mean ±S.D.	Mean± S.D.	Mean ±S.D.	
Baseline	118.37±5.63	118.23±5.78	117.97±6.42	0.9655
0 min	118.70±7.36	119.23±7.61	117.13±7.61	0.5344
1 Hr	120.27±9.54	120.47±6.55	117.20±9.29	0.2594
2 Hr	116.73±6.44	117.33±8.95	121.07±6.25	0.0507
4 Hr	117.23±6.01	117.73±3.89	118.87±6.6	0.5169
6 Hr	119.13±8.91	121.23±6.85	118.57±6.3	0.3473
12 Hr	118.20±7.07	118.27±6.76	120.07±5.37	0.4481
24 Hr	117.67±5.61	117.77±4.84	117.50±4.78	0.9792

Table 3: Comparison of Diastolic Blood Pressure (DBP)

Time	Ketamine	Magnesium sulphate	Control	P Value
	Mean ±S.D.	Mean ±S.D.	Mean ±S.D.	
Baseline	77.40±5.46	75.67±4.93	74.03±4.34	0.0346
0 min	75.87±4.55	75.60±5.26	75.30±4.66	0.9021
1 Hr	76.27±7.27	75.40±4.64	74.70±6.57	0.6256
2 Hr	77.40±5.88	76.63±5.49	80.67±6.87	0.0289
4 Hr	77.03±6.26	77.13±4.57	77.90±6.09	0.8125
6 Hr	77.67±5.59	78.60±5.07	78.50±4.58	0.7391
12 Hr	77.60±4.68	77.73±4.32	77.87±4.33	0.9734
24 Hr	77.43±5.33	77.67±4.62	77.63±4.97	0.9809

Table 4: Comparison of the Mean Arterial Pressure

Time	Ketamine	Magnesium sulphate	Placebo	P Value
	Mean ±S.D.	Mean ±S.D.	Mean ±S.D.	
Baseline	91.06±4.7	89.86±4.81	88.68±4.08	0.1343
0 min	90.14±4.35	90.14±5.10	89.24±4.75	0.6987
1 Hr	90.93±6.90	90.42±4.46	88.87±5.90	0.3649
2 Hr	90.51±5.04	90.2±4.58	101.48±5.81	<0.0001
4 Hr	90.92±3.69	91.29±3.60	90.74±9.62	0.6323
6 Hr	91.49±50	91.34±4.47	91.68±4.63	0.9629
12 Hr	91.13±3.91	91.24±3.05	91.93±3.92	0.6565
24 Hr	90.84±4.01	91.03±3.54	90.92±3.98	0.9819

Table 2, 3 & 4 shows that the SBP, & MAP at the 2nd hour is higher in the control group compared to the K and M Groups.

Table 5: Comparison of VAS score

Time	Ketamine	Magnesium sulphate	Control	P Value
	Mean ±S.D.	Mean ±S.D.	Mean ±S.D.	
0 min	1.07±0.74	1.17±0.59	2.1±1.18	<0.0001
1 Hr	2.97±1.96	2.50±1.48	4.63±1.9	<0.0001
2 Hr	3.40±1.07	3.30±1.53	5.33±1.71	<0.0001
4 Hr	3.70±0.7	3.73±1.01	5.5±1.28	<0.0001
6 Hr	3.67±0.92	3.87±0.97	4.87±2.37	0.0088
12 Hr	3.13±1.04	3.00±0.69	3.9±1.45	0.0043
24 Hr	2.33±0.55	2.47±0.68	3.27±1.08	<0.0001

Table 5 shows that the VAS scores at 0 min, 1st, 2nd, 4th, 6th, 12th and 24th hour is significantly higher in the control group compared to the K and M groups (P-value <0.05).

Table 6: Comparison of the VAS Score between the K and M group

Time	Ketamine	Magnesium sulphate	P Value
	Mean ±S.D.	Mean ±S.D.	
0 min	1.07±0.74	1.17±0.59	0.2827
1 Hr	2.97±1.96	2.50±1.48	0.1508
2 Hr	3.40±1.07	3.30±1.53	0.3854
4 Hr	3.70±0.7	3.73±1.01	0.4415
6 Hr	3.67±0.92	3.87±0.97	0.2086
12 Hr	3.13±1.04	3.00±0.69	0.2810
24 Hr	2.33±0.55	2.47±0.68	0.2033

Table 6 shows that there are no significant differences in the VAS scores between the K and M groups at all-time interval.

Table 7: Comparison of first rescue analgesia

Ketamine	Magnesium sulphate	Control	P Value
Mean ±S.D.	Mean ±S.D.	Mean± S.D.	
3.97±3.19 hr	4.4±4.41 hr	1.1±0.66 hr	0.0002

Table 7 shows that the time to first rescue analgesia administration was significantly lower in the control group (P-value <0.05). There was no significant difference in the time to first rescue analgesia between the K and M group (P-value = 0.3323) TABLE: 8 Comparison of the total analgesic consumption

Table 8: Comparison of the total analgesic consumption

Ketamine	Magnesium sulphate	Control	P Value
Mean ±S.D.	Mean ±S.D.	Mean ±S.D.	
233.00±72.19 mg	233.33±97.10 mg	370.00±90.25 mg	<0.0001

Table 8 shows that the total analgesic consumption was significantly higher in the group C as compared with the K and M groups. (P-value < 0.05), while no difference between ketamine and magnesium group (P=0.4940).

Table 9: Side Effects

Side Effects	Ketamine	Magnesium sulphate	Control
	N (%)	N (%)	N (%)
Nausea/Vomiting	4 (13.33)	4 (13.33)	1 (3.33)
Bad Dreams	1 (3.33)	0	0
Hallucinations	0	0	0
Cutaneous Flushing	0	0	0
Hypotension	0	0	0
Bradycardia	0	0	0
Arrhythmias	0	0	0

Table 9 shows that only 4 out of 30 patients in the K group, 4 out of 30 patients in the M group and 1 patient out of 30 patients in the group C reported nausea and vomiting. 1 patient in the K group reported bad dreams. There were no serious adverse effects like hallucinations, hypotension, bradycardia, or arrhythmias in any patient.

Discussion

Enhanced Recovery after surgery (ERAS) is aimed to improve overall patient care by reducing complications with better intraoperative and postoperative management of pain, to achieve early mobilization and faster recovery. This in turn reduces patients' healthcare costs. The multimodal analgesia technique with NMDA receptor antagonists improves patients' postoperative pain and has some benefits with decreasing the opiate dosage and side effects of individual drugs after abdominal surgery.

Singh *et al.* [19] found in a study done by them that there is a high prevalence of acute postoperative pain in patients undergoing abdominal surgeries. Tissue trauma during abdominal surgeries modifies the central processing pathway for pain perception. These changes decrease the stimulus threshold and amplify postoperative pain. The induction and maintenance of such central sensitization may be dependent on the activation of NMDA receptors. Therefore, NMDA antagonists like ketamine and magnesium sulphate should prevent central sensitization and improve postoperative pain relief.

We studied the effect of a single Pre-emptive dose of two drugs inj. ketamine 0.5 mg/kg and magnesium sulphate 50mg/kg after abdominal surgeries and compared whether the antinociceptive treatment given before the incision is more effective than a placebo.

Singh *et al.* [13], compared the Pre-emptive effect of three different doses of ketamine, 0.5 mg/kg, 0.75 mg/kg, and 1.00 mg/kg for Laparoscopic cholecystectomy and concluded that a lower dose of 0.5 mg/kg is an optimal dose in these patients, devoid of any adverse effects and hemodynamic changes.

Heydari *et al.* [6] studied inj. PCM 15 mg/kg, inj. ketamine 0.25 mg/kg and inj. magnesium 7.5 mg /kg, Helmy *et al.* [15] used 0.3 mg /kg of inj. ketamine and 30 mg/kg of inj. magnesium sulphate and Thakur *et al.* [16] used inj. ketamine 0.5 mg/kg and inj. magnesium 20 mg/kg, as a pre-emptive analgesia for different surgeries. Taheri *et al.* [7] and P. Sudha Poornima *et al.* [14] studied a dose of 50 mg /kg of inj. magnesium sulphate before induction.

In our study, we found that there were no significant hemodynamic changes between the K and M groups. However, in the control group, we recorded hemodynamic changes at 2nd hour.

Thakur *et al.* [16] recorded a significantly higher postoperative SBP in the control group in the 4th (P-value 0.027) and 6th hour (P-value 0.001) and significantly higher DBP at the 6th hour in the control group (P-value- 0.0001) when compared to ketamine and magnesium groups in patients who underwent laparoscopic cholecystectomy. Singh *et al.* [13] found that the HR, SBP, DBP, and RR were significantly more in the control group at most times postoperatively than the ketamine group. Poornima *et al.* (14) found a statistically higher HR and MAP in the control group compared to the magnesium group till the 2nd postoperative hour.

The VAS scores recorded postoperatively in our study were comparable in the K and M groups but were significantly higher in the immediate post-operative period in the control group. The VAS score at the 1st hour was 2.97±1.96, 2.50±1.48, 4.63±1.9 in the K, M and control groups respectively (p<0.0001) and 3.13±1.04, 3.00±0.69, 3.9±1.450 (p<0.0043) in the 12th hour in the K, M and control groups respectively.

Helmy *et al.* (15) measured a statistically higher VAS score in the control and magnesium group as compared to ketamine. Thakur *et al.* [16] found a significantly higher VAS score at cough in the ketamine group in the 4th postoperative hour compared to the magnesium and control groups but at rest, there was no significant difference between the three groups. The mean of postoperative pain using the VAS system was significantly lower in ketamine than magnesium and paracetamol [6]. Veronica *et al.* [17] found rest and dynamic pain scores were higher in the immediate postoperative period in the control group than the other two groups.

A study done by Singh *et al.* [13] showed that the mean visual analog scores were lower in the ketamine group than the control group. Taheri *et al.* [7] and Poornima *et al.* [13] concluded that postoperative pain scores were significantly lower in the magnesium group than placebo.

The time to first rescue analgesia in our study was 3.97±3.19 hrs in Group K, 4.4±4.41 hrs in Group M and 1.1±0.66 hrs in the control group. It was statistically significant (p<0.0002). The total analgesic consumption of rescue analgesia, inj. Tramadol was 233.00±72.19 mg in the K group, 233.33±97.10 mg in the M group, and 370.00±90.25 mg in the control group which was statistically significant (p<0.0001) and also suggests that there is no statistical difference between the ketamine and magnesium groups.

Veronica *et al.* [17] found that in the KetMag group, patients had significantly delayed administration of the first dose of morphine and also consumed significantly less morphine at 6 and 12 hours after surgery than the ketamine and control group. Thakur *et al.* [16] concluded that the post-operative consumption of morphine was reduced significantly in the treatment groups, 7.2±2.0 mg in the K group, 6.5±2.8 mg in the M group and 10.2±2.5 mg in the control group. Helmy *et al.* [15] found that the first request for postoperative analgesia was statistically longer (82±12 mins in the K group, 36±5 mins in the M group, 33±7 mins in the C group, p< 0.05) and total dose of pethidine required during the first 24 hours was statistically lower in the K group as compared to the M and C groups (82±33 mg in the K group, 137±39 mg in the M group, 140±38 mg in the C Group (p< 0.05). Heydari *et al.* [6] found that the patients in ketamine group requested opioid later than the magnesium and paracetamol groups (p< 0.05) and that the mean dose of opioid use at the end of recovery was also significantly lower than the other two groups (p< 0.05).

Singh *et al.* [13] showed that the mean duration for rescue analgesia was significantly more in the groups that received different doses of ketamine (2.1 hrs in Group A, 1.85 hours in Group B. 1.98 hours in Group C and 0.37 hours in Group D) and also the postoperative analgesic consumption was significantly less than control group. The first analgesic demand time was longer and rescue analgesic dose was less in Ketamine group than control [12, 19].

Taheri *et al.* [16] found that the pethidine consumption was significantly lower in the magnesium group throughout 24 hours after surgery compared to the control group (16.75±18.23 mg vs 68.0±17.42 mg, p< 0.0001). Poornima *et al.* [14] conclude that Tramadol consumption in 24 hours was significantly low in the magnesium group than control group (248±55.5 mg vs 298.33±66.43, p< 0.002) and also time of first dose was longer in the magnesium group.

We, in our study, did not record any serious adverse effects in the K and M groups. Nausea and vomiting were found in four patients in K and M group which was treated with inj. Ondansetron while bad dreams in one patient in ketamine group. Thakur *et al.* [16] reported no serious systemic effects except hallucinations in three ketamine group patients. Helmy *et al.* [15] reported no statistically significant differences between the K, M and control groups in postoperative nausea and vomiting. Heydari *et al.* [6] found that there was no significant difference between the ketamine, magnesium, and paracetamol groups in the vomiting frequency and metoclopramide use. Veronica *et al.* [17] found no differences between the KetMag, ketamine and control groups in postoperative nausea and vomiting or hallucinations. Singh *et al.* [13] reported hallucinations in the ketamine group. Parikh *et al.* [17] reported nausea and vomiting in four patients in the control group.

Dahl *et al.* [20] conducted a study using ketamine as a Pre-emptive analgesia and concluded that there is no reduction in the postoperative analgesic requirement and failed to demonstrate the Pre-emptive effect.

A systematic review and meta-analysis reported a beneficial effect of ketamine and magnesium sulphate for different surgeries and demonstrated that ketamine in the dose range of 0.15 - 1 mg/kg reduced the postoperative pain, opioid consumption and prolonged the time to first analgesic request.

The perioperative administration of magnesium sulphate could reduce postoperative analgesic consumption and reduce postoperative nausea, vomiting and shivering [21, 22].

Our results indicate that a bolus dose of ketamine and magnesium given before skin incision decreases postoperative pain, reduces postoperative analgesic consumption and delays patients' request for analgesia after abdominal surgeries.

Conclusion

We conclude that pre incision administration of a single bolus dose of NMDA receptor antagonists, ketamine hydrochloride, and magnesium sulphate is a simple, easy, and effective method to control postoperative pain without any systemic side effects in patients undergoing elective abdominal surgeries. Its delayed the time for the first rescue analgesia and decreased the total consumption of postoperative analgesic requirement.

Conflict of Interest

Not available

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Not available

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