EFFECT OF PREEMPTIVE MAGNESIUM SULPHATE ON PAIN RELIEF AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT

BACKGROUND
The concept of preemptive analgesia was introduced by C. J. Woolf et al demonstrating that a post-injury hypersensitivity results via a central mechanism. The effect of magnesium on perioperative analgesic requirements was first evaluated by Koinig and his colleagues in patients with identical levels of surgical stimulation. Magnesium Sulphate is an antagonist of N-methyl-D-aspartate (NMDA) receptors and its associated channels and regulation of calcium influx into the cell. Magnesium causes modulation of acute pain reducing postsurgical pain intensity and dosage of analgesics. Seyhan et al have reported that magnesium sulphate boluses were effective for postoperative pain relief after gynaecological surgery. Fucs-Budder et al, Kussman B et al used continuous infusion (15 mg/kg/hr.) in addition to initial bolus (50 mg/kg) of magnesium sulphate in their studies, which caused bradycardia and delayed extubation time, which can be attributed to the infusion of Iva Bacak Kochman et al studied effect of low dose $MgSO_4$ (7.5 mg/kg) as analgesic agent after induction in patients undergoing laparoscopic cholecystectomy. This bolus dose of $MgSO_4$ given for control of sympathetic response during intubation also reduced early postoperative pain. Study conducted by O Mentes et al on postoperative analgesic efficacy of single dose $MgSO_4$ (50 mg/kg) after laparoscopic cholecystectomy measured significantly less VAS scores. On this background, our study was done to evaluate the postoperative analgesic efficacy of single dose of magnesium sulphate (50 mg/kg) as preemptive analgesic and measured after laparoscopic cholecystectomy. In addition to VAS scores, total tramadol consumption and time for first rescue analgesia, postoperative haemodynamic parameters and side effects if any were evaluated.

METHODS
After obtaining Institutional Ethical committee clearance and written informed consent from the patients, a randomised prospective study was conducted at King George Hospital, Vishakhapatnam. Randomisation done based on envelope method. Study period was between November 2013 to September 2015. Study contain Sixty patients with ASA Grade I and Grade II of both sexes undergoing laparoscopic cholecystectomy were included in study and divided in two equal groups (n=30 in each group). Patients in magnesium group (group MS) received I.V. $MgSO_4$ 50 mg/kg in 100 mL of 0.9% normal saline during preinduction time and patients in the control group (group NS) received 100 mL of 0.9% normal saline.

STATISTICAL ANALYSIS
Descriptive statistics was done for all data and suitable statistical tests of comparison were done. These included the mean and Standard Deviation (SD) for quantitative variables. Data was also analysed by Student's "t" unpaired test. Significance limit for all was set at $P < 0.05$.

RESULTS
Statistically significant reduction of pain scores in early postoperative period was observed. Significant reduction of postoperative analgesic requirement during the first postoperative day was noted. Intraoperatively, there was significant reduction in mean heart rate as well as mean arterial pressure with MS group when compared to NS group. Less postoperative shivering and PONV observed in MS group. Severe bradycardia and/or hypotension did not occur during or after surgical procedure in any of study patient.

CONCLUSIONS
The present study evaluated preemptive analgesic efficacy of magnesium sulphate on pain relief after laparoscopic cholecystectomy. It was concluded that magnesium sulphate at a dose of 50 mg/kg as a preemptive analgesic is safe. It has good postoperative synergistic effect with analgesics and reduces the postoperative tramadol consumption compared to normal saline group.

KEYWORDS
Analgesia E03.091, Laparoscopy E01.370.388.250.520, Anaesthesia General E03.155.197.

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INTRODUCTION: Laparoscopic cholecystectomy is the gold standard for treatment of symptomatic cholelithiasis.[1] Laparoscopic cholecystectomy procedure offers several advantages such as a reduction in stress response, postoperative pain, short recovery time and cosmetic appearance, but has no overall effect on postoperative mortality.[2,3] The major advantage of laparoscopic cholecystectomy over open cholecystectomy is reduced postoperative pain, though it still remains.[4]

The major goal in postoperative pain management is to minimise the dose of medications and lessen side effects while still providing adequate analgesia.[5] Therapies that have been in trials include NSAIDS, intravenous opioids, intravenous ketamine, peripheral local anaesthetics, caudal and epidural analgesia, dextromethorphan and gabapentin.[6,7,8,9,10] The analgesic efficacy of opioids in the treatment of acute, intense postoperative pain was well accepted.[11] However, to hasten recovery and minimise opioid-related side effects such as sedation, nausea and vomiting and respiratory depression, prophylactic use of opioids in postoperative pain is avoided.[12,13]

AIM AND OBJECTIVES:

AIM: The aim of the study is to evaluate the postoperative analgesic efficiency of magnesium sulphate as preemptive analgesic in patients undergoing laparoscopic cholecystectomy.

OBJECTIVES:

1. To study effect of magnesium sulphate infusion on postoperative analgesic efficiency based on visual analogue scoring.
2. To estimate total tramadol consumption during first postoperative day.
3. To observe the time for first rescue analgesia.
4. To study postoperative haemodynamic variables, heart rate and MAP.
5. To study the drug side effects if any.

RESULTS: Sixty patients were taken into study with ASA grade I and II scheduled for elective laparoscopic cholecystectomy. Patients were randomised based on envelope method. VAS scores were measured at the time of extubation and further on i.e., 0 hr., 2 hrs. and 4 hrs. They were statistically significant with P value <0.05. Lower VAS scores were observed in magnesium group compared to normal saline group. At 8 hrs., 12 hrs., 24 hrs. no statistically significant P value was observed between two groups. (P VALUE >0.05) (Table-1).

Postoperative Duration	MS Group	NS Group	P value
0 HR.	4.6±1.11	5.76±1.30	0.0005*
2 HRS.	4.2±1.3	5.1±1.01	0.004*
4 HRS.	3.6±1	4.13±0.95	0.03*
8 HRS.	3.4±1.1	3.3±0.97	0.71
12 HRS.	2.7±1	2.46±0.99	0.35
24 HRS.	2.6±1.04	2.5±0.92	0.69

Table 1: Comparison of VAS Scores

Postoperative tramadol consumption has significant difference (P<0.05) between magnesium sulphate and normal saline group. Tramadol consumption was more in normal saline group than magnesium group (Table-2).

Groups	MS Group	NS Group	P value
Mean and SD	248±55.5	298.33±66.43	0.002*

Table 2: Tramadol Consumption per Day in mg

Comparison of heart rates in 0 hr., 2 hrs. postoperative period showed a statistically significant P value (P <0.05) (Table-3).

Postoperative Duration	MS Group	NS Group	P Value
0 hr.	75.4±17	85.06±18.93	0.042*
2 hrs.	77±14	89.26±14.07	0.001*
4 hrs.	84±15	84.53±11.81	0.87
8 hrs.	79±9.9	80.06±8.92	0.66
12 hrs.	74.1±12.7	75.46±11.38	0.66
24 hrs.	73.6±10.8	74.12±8.67	0.83

Table 3: Comparison of Heart Rates Among Two Groups

Among two groups, there is a statistical significance in MAP at 0 hr., 2 hrs. (P <0.05). No significance was observed at 4 hrs., 8 hrs., 12 hrs. and 24 hrs. (P >0.05). Magnesium sulphate group has lesser incidence of side effects like shivering and postoperative nausea and vomiting, but more patients experienced sedation than normal saline group (Table - 4 and 5).

Duration	MS Group	NS Group	P value
0 HR.	94.7±8.48	104.55±8.17	0.0001
2 HRS.	98.78±8.07	107.51±8.71	0.0002
4 HRS.	97.8±7.04	99.13±6.61	0.45
8 HRS.	97.97±8.13	98.28±7.75	0.88
12 HRS.	98.13±7.28	98.5±6.71	0.83
24 HRS.	98±5.32	98.2±5.68	0.88

Table 4: Comparison of Mean Arterial Pressure

Side Effects	MS Group	NS Group
Sedation	9/30 (30%)	3/30 (10%)
Shivering	2/30 (6%)	6/30 (20%)
PONV	3/30 (10%)	10/30 (33%)

Table 5: Side Effects of Drug Among Two Groups

MATERIALS AND METHODS:

Procedure: All patients were premedicated with Inj. Glycopyrrolate 0.01 mg/kg, Inj. Midazolam 0.03 mg/kg and Inj. Fentanyl 2 µgm/kg. In group I - Magnesium sulphate at the dose of 50 mg/kg in 100 mL of isotonic 0.9% sodium chloride solution was given intravenously over 15 to 20 minutes immediately before induction of anaesthesia. In group II - Same volume of isotonic 0.9% sodium chloride solution intravenously over 15 to 20 minutes just before induction of anaesthesia. Induction was done with propofol 2 mg/kg. Patients were paralysed with vecuronium 0.1 mg/kg and intubated with appropriate-sized endotracheal tube. During the procedure, patient's

intraoperative pulse, blood pressure and oxygen saturations were measured. Ringer lactate infusion started as 10 mL/kg body wt. with proper monitoring. Pneumoperitoneum was created and maintained with 10-14 mmHg intra-abdominal pressure. After the surgery, all patients were reversed with Inj. Neostigmine 0.05 mg/kg and Inj. Glycopyrrolate 0.02 mg/kg. They were observed until full recovery.

Postoperative Period: Postoperatively, pain was evaluated using a 0-10 visual analogue scale scoring. (VAS scores were measured at intervals starting from emergence from anaesthesia (0 hr.) and at 2, 4, 8, 12 and 24 hrs. after surgery. VAS score of >3 was considered inadequate analgesia. Pain relief in the postoperative period was provided by injection tramadol 50 mg as supplemental doses based on visual analogue scoring. Along with VAS scores, total tramadol consumption per day was noted. The time duration for first rescue analgesia was measured. Postoperative haemodynamic variables were measured.

Inclusion Criteria:

1) Patients who give informed written consent.
2) Patients aged between 20 to 50 years.
3) Patients belonging to ASA grade I and II.

Exclusion Criteria:

1) Patients who refuse to give informed consent.
2) Patients with systemic disorders.
3) Patients taking calcium channel blockers.
4) Heart block/dysrhythmias.
5) ASA grade III and IV.
6) Patient refusal.
7) Psychiatric illness that would interfere with perception and assessments.

DISCUSSION: The result being comparable with the study done by Hammad et al who done study on postoperative pain in patients undergoing upper abdominal surgery found VAS scores of 4.2-4.7 during 0-3 hrs. postoperatively in $MgSO_4$ group compared with 5.3-6.2 in control group ($P < 0.05$).[14] In our study, the analgesic duration was extended for 4 hrs. due to less manipulation of splanchnic viscera than open laparotomy. The results of Bhatia et al found administration of intraoperative $MgSO_4$ as an adjuvant analgesic in patients undergoing open cholecystectomy resulted in better pain relief and comfort in the first postoperative day with better sleep quality during postoperative period without any significant adverse effects that was due to $MgSO_4$ supplemented as both bolus dose 50 mg/kg and infusion of 15 mg/kg/hr. till end of surgery,[15] where as in our study, it was given in the preoperative period as a single bolus at 50 mg/kg dose. Benhaj Amor M et al evaluated the effect of intra and postoperative magnesium sulphate infusion on postoperative pain in abdominal surgery. The results of the study support the use of magnesium sulphate as an adjuvant for postoperative analgesia in abdominal surgery till 24 hrs. postoperatively.[16] Kiran S et al studied that the administration of intravenous magnesium sulphate 50 mg/kg preoperatively significantly reduces postoperative pain in patients undergoing inguinal surgery. They found statistically significantly lower VAS scores in magnesium sulphate groups at 2 hrs., 4 hrs., 8 hrs., 12 hrs. and 24 hrs., respectively. This can be attributed to less manipulation surgical procedure.[17] Study done by Iva Bacak Kocman et al studied in laparoscopic cholecystectomy patients by comparison between two doses of 5 mg/kg and 7.5 mg/kg obtained VAS scores were significantly lower in both groups during first postoperative period due to low dose that will blunt only sympathetic response where as in our study a single dose 50 mg/kg was given as preemptive analgesic by which postoperative analgesia extended over 4 hrs. This was also supported by study done in gynaecology patients by Ryu J H et al who gave magnesium sulphate as a bolus dose 50 mg/kg and also continuous infusion by 15 mg/kg/hr. had better VAS scores both at rest and at movement at 24 hrs. and 48 hrs. after surgery.[18] In a study done by O Mentes et al, the postoperative analgesia lasted for 12 hours, because they used patient controlled analgesia device, but in the present study, postoperative analgesia lasted for 4 hours because of single bolus administration of $MgSO_4$. In our study, the tramadol consumption was higher in NS group (298.33±66.43) than with MS group (248±55.5) with statistically significant P value <0.05. This was supported by study done by Levaux C et al who observed that postoperative opioid consumption was lower in the magnesium group (50 mg/kg) both at first night's sleep and global satisfaction scores.[19] Tauzin Fin P et al study showed that intravenous magnesium sulphate reduces tramadol consumption when used as a postoperative analgesic in radical prostatectomy.[20] Study results are comparable as in our study that cumulative mean tramadol dose after 24 hrs. was 226 mg in the magnesium group where as in normal saline group consumption of tramadol was 446 mg with significant P value of 0.001. These results were comparable to study done by Benhaj et al where morphine consumption was significantly higher in control group than MS group on first postoperative day with mean and standard deviation of 52±4 mg and 30±3 mg with significant P value of 0.0002.[16] Hamad Usmani et al also supported the study by evaluation of perioperative Magnesium Sulphate in patients undergoing upper abdominal surgery found that total tramadol consumption was 105±31 mg in normal saline group compared to 80±24 mg in magnesium group with P value <0.05.[14] The results of our study was similar to results obtained by Shasikiran et al that rescue analgesic requirement less in magnesium group than normal saline group.[17] Seyhan TO et al conducted a double-blinded study in gynaecological patients with $MgSO_4$ 40 mg/kg bolus followed by 10 mg/kg/hr. infusion lead to significant reduction in postoperative morphine consumption probably due to continuous infusion of $MgSO_4$ throughout surgery, but in the present study, $MgSO_4$ was given as single bolus dose.

Rescue analgesia was given when VAS score was >3 in both the groups. In our study, the patient in MS group received first dose of Inj. Tramadol 1 mg/kg as rescue analgesia after a mean±SD of 82.33±22.90 mins. in postoperative period compared to NS group who received tramadol 44.33±22.7 mins. This is statistically significant with P value of 0.01. Results are comparable with study done by Hammad et al who had a mean requirement of first dose of tramadol had a mean time of 162 in magnesium group compared to NS group, it is 65 mins.[14] Gautam Piplai et al showed in their study the time for first postoperative analgesic requirement was significantly longer in group MS than group NS P value <0.05).[21] Benhaj et al had done a study with 48 patients. The time of the first demand of morphine was significantly longer in MS group than in NS group respectively (18±5 mins. vs. 7±1 mins., p=0.03), this is because of abdominal surgery that need early analgesic supplementation.[16] The MAP values were significantly lower in MS group with P value 0.0001 and 0.0002 at 0 hr. and 2 hrs. respectively compared to NS group. This can be explained by lesser incidence of pain in MS group and ability of $MgSO_4$ to maintain stable haemodynamics. The observation of Gautam Piplai et al was similar. They found significantly higher MAP in normal saline group.[21] It is known that magnesium induce hypotension directly by vasodilatation as well as indirectly by sympathetic blockade and inhibition of catecholamine release. However, we did not observe any hypotensive episode in our patients treated with magnesium sulphate. Transient fall in blood pressure was observed in both the groups, which can be attributed to use of propofol as an induction agent. None of our patients had any significant bradycardia that required treatment.

CONCLUSION: The present study evaluated preemptive analgesic efficacy of magnesium sulphate on pain relief after laparoscopic cholecystectomy. It was concluded that magnesium sulphate at a dose of 50 mg/kg as a preemptive analgesic is safe. It has good postoperative synergistic effect with analgesics and reduces the postoperative tramadol consumption compared to normal saline group.

LIMITATIONS: Magnesium concentration in serum and cerebrospinal fluid was not measured in the present study. Another limitation of the study was the lack of correlation between plasma magnesium concentration and total body content.

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