A Prospective randomized single Blinded controlled study to evaluate the effect of single dose of magnesium sulphate on Postoperative analgesia in abdominal Surgeries patients receiving balanced general anaesthesia

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Abstract
Background: Post-operative pain is the major morbidity of most of the surgeries. This prospective single-blind, randomized, placebo controlled clinical trial was designed to evaluate the effect of Pre-operative IV Magnesium sulphate on Intraoperative and Postoperative pain management and to determine the adverse reactions, as it blocks N-Methyl D Aspartate receptor, among the patients undergoing elective abdominal surgeries under general anaesthesia.

Patients and Methods: This study included 80 adult male and female patients, ASA physical status I and II, undergoing various abdominal surgeries under general anesthesia. Patients were randomly allocated into 2 equal groups. Patients in group M and C each group comprising of 40 patients each.

Group M (MAGNESIUM): Subjects were given Magnesium sulphate 40 mg/kg 100 ml of 9% normal saline over 15 minutes prior to induction

GROUP C (CONTROL): Subjects were given 100 ml of 9% normal saline plain over 15 minutes prior to induction

Results: Results showed that total consumptions of Fentanyl, Atracurium and Tramadol in group M was 155.25 ± 42.61, 50.50 ± 6.77 and 5.0 ± 15.19 mcgm and in group C was 223.75 ± 25.49, 64.50 ± 5.97 and 46.25 ± 13.3 µg P value < .001. (P <0.05. Recovery time was significantly shorter (P <0.05) in magnesium group. Postoperative pain score as well as total analgesic requirement was significantly lower (P < 0.05) in magnesium group compared to control group.

Conclusion: In conclusion, this study suggests that giving magnesium sulphate 40 mgm/kg bodyweight prior to induction provides good quality of analgesia, reduces opioid consumption both intraoperatively and post operatively and decreased need for rescue analgesic post operatively. In addition magnesium sulphate decreases the requirement of neuromuscular blocking agents, without delaying emergence from anaesthesia.

Keywords: Low Dose, Magnesium sulfate; abdominal Surgeries; Anesthesia; post op Analgesia.
Introduction
One of the most common post-operative complications is pain. Pain is an unlike feel due to tissue damage and is there usually after all surgeries. Pain serves a biological function. It signals the presence of damage or disease within the body. In case of postoperative pain; it is the result of the surgery. Thus it is considered as “the fifth vital sign” by the Joint Commission on Accreditation of Healthcare Organization. Effective in 2001, the JCAHO requires adequate assessment, monitoring, and treatment of pain as one of the conditions for accreditation. The major goal in postoperative pain relief is to minimize the dose of analgesic medication and lessen the side effects, while still providing analgesia. Adequate postoperative pain relief leads to early mobilization, shorter hospital stay reduced hospital costs and increased patient satisfaction. Pre-emptive analgesia has been defined as an anti-nociceptive treatment that prevents establishment of altered central processing of afferent input from injuries. The goal of pre-emptive analgesia is to decrease acute pain and development of chronic pain. Therapies that have been tested in pre-emptive trials include NSAIDS, intravenous (I.V) opioids, I.V. ketamine, peripheral local anesthetic, caudal and epidural analgesia, dextromethorphan and gabapentin. Narcotics are the most common analgesics which are used during preoperative period. But the anesthetist is always looking for alternative methods with fewer side effects and cost and one I.V adjuvant medication that has shown potential in pre-emptive analgesia is magnesium sulphate. Hence we designed this study to investigate the effects of magnesium sulfate administration on post operative pain relief and analgesic requirement in patients undergoing abdominal surgeries. Now a day there have been many debates on the role of multi modal analgesia on intraoperative and postoperative pain relief. Magnesium sulphate could be administered with different regimens as bolus only and as bolus followed by infusion.

Material and Methods
After obtaining the approval from the hospital ethics and scientific committee, this prospective, randomized, single blinded placebo controlled study was conducted in the Department of Anaesthesiology Max Super Speciality Hospital, Saket, New Delhi 80 ASA Grade 1 and 2 patients, aged 18-60 yrs of both gender undergoing elective surgery requiring general anaesthesia were recruited for the study. Informed and written consent was taken in all cases. Patients were randomly allocated by computer generated random number into two groups

Sample size
For the purpose of calculation of sample size, the primary variable of interest is the time to first fentanyl. According to the study done by Usman et al the average time in the control group was 65 minutes with standard deviation of 45 minutes and in the magnesium group (study group) average time to tramadol was 162 minutes with standard deviation of 97 minutes. Using these values and with statistical power of 80% to detect a difference minimum 50 minutes, the sample size in each group, we proposed to cover 40 cases in each group.

Study intervention -patients were be divided into two groups of 40 each
Group M (Magnesium): Subjects were given Magnesium sulphate 40 mg/kg in 100 ml of 0.9% normal saline over 15 minutes prior to induction
Group C (Control): Subjects were given 100ml of 0.9% normal saline plain over 15 minutes prior to induction.

Study duration: The study was conducted from July 2015 to June 2016.

Method of Measurement of Outcome of Interest
Primary Outcome Measurement
Total amount of analgesia required during intraoperative period and in the first 6hrs of postoperative period –
Secondary Outcome Measurement
1. Total amount fentanyl consumed intraoperative/ post operative period,
2. Amount of Fentanyl and rescue analgesics consumed in the postoperative period,
3. Any prolongation of neuromuscular blocking
4. Delay in getting reversed from anesthesia
5. Complication if any arising out of drug

Data Collection Method
Anesthetic Technique

Premedication in form of tablet Alprazolam 0.25 mg and tablet Pantoperazol 40 mg was given to all the patient in the morning 2 hrs prior to the surgery with sip of water. In Preoperative hold area immediate preoperative assessment was done and PAC reviewed. IV line was secured with appropriate bore cannula Study groups (M) received intravenous MgSO$_4$, 40 mg/kg in 100ml 0.9% normal saline over 15 minutes before induction. Prior to induction and after study drug administration iv bolus of 10 ml/kg of crystalloid was infused in over 15 minutes.

After informing patient monitors were setup on patient electrocardiography, comprising heart rate monitoring, pulse oximetry, noninvasive blood pressure, end tidal carbon dioxide, end tidal agent, MAC (minimum alveolar concentration) temperature and neuromuscular junction block monitoring with visual and tactile measurement with TOF monitor.

Preoxygenation was done for 3 minutes. This was followed by 2 mcgm/kg of fentanyl and 0.20mg/kg of midazolam. Patients were induced with propofol upto 2mg/kg dose till the loss of verbal contact, followed by neuromuscular blocking agent preferably atracurium (.5mg/kg) or vecuronium (0.1mg/kg) if former is contraindicated followed by insertion of endotracheal tube.

The control group(C) received 100ml of 0.9% of normal saline over 15 minutes before induction followed by fentanyl (2mcg/kg), midazolam(0.20 mg/kg) and induction with propofol, (2mgm/kg) neuromuscular blockade with atracurium (.5 mg/kg) or vecuronium (.1 mg/kg) if former is contraindicated. After this airway will be secured with endotracheal tube.

Anesthesia was maintained with oxygen + nitrous oxide in 1:1 ratio and sevoflurane as inhalational agent to achieve MAC (minimum alveolar concentration) of 1 to 1.3 in both study group (M) and control group (C). Both the groups also received paracetamol 15 mg/kg during intraoperative period as analgesic agent. Incremental doses of fentanyl 1mcg/kg were given if there were any signs of increase heart rate or blood pressure from the baseline by 20%.Atracurium boluses of.15mg/kg were administered when more than two responses were detected in TOF. After the surgery patient will be reversed with gycopyrolate 10mcgm/kg and neostigmine 70mcgm/kg.

Data collection forms

Assessment was carried out at immediately after shifting patient to PACU and 0, 0.5, 1 2, 4, 6, hrs in the postoperative period.

Analgesic schedule in the postoperative period

First demand of analgesia was recorded after patient was shifted to PACU (post anesthesia care unit). Injection fentanyl 1 mcgm/kg was given, if VAS(visual analogue scale) score was still >3 after 20 minutes then another bolus of fentanyl 1mcg/kg was repeated. Rescue analgesia in the form of injection Diclofenac sodium 75mg i/v slowly in 100 ml of normal saline over 15 minutes was given if after 2nd dose of fentanyl patient was still having VAS >3, 2nd rescue analgesia was injection Tramadol, it was given 50mg i/v in 100ml of normal saline slowly over 15 minutes before shifting patient to ward from PACU(post anesthesia care unit) if VAS score was >3. It was be ensured that VAS score was < 3 before shifting patient out from PACU(post anesthesia care unit) VAS scoring was monitored at 0 hr, 0.5hr,1hr, 2hr, 4hr and 6hrs in post anesthesia care unit. If patient complains of pain at any time during 6 hrs in the immediate post operative period, the time and VAS score will be recorded and treatment in the form of appropriate analgesic will be given as mentioned above.

Total analgesics

Total analgesics consumed in 6 hrs post operatively.
The time interval between the injection of analgesic (last dose) during intra-operative period and the first request to postoperative analgesia.

Statistical Methods
Statistical analysis was performed by the SPSS program for Windows, version 17.0. Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired t test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical variables were analysed using either the chi square test or Fisher’s exact test. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

Randomisation was done by a computer generated allocation schedule using allocation concealment to prevent prior knowledge of treatment assignment. Numbers were assigned in strict chronological sequence and study participants were entered in sequence. Each study participant was allocated a unique randomisation number on successful completion of screening. To decrease bias and confounders the decision to accept or reject a participant was made using inclusion and exclusion criteria. Informed consent was obtained from participants prior to obtaining the randomization code. Group allocation was done by an anaesthesiologist who was not aware of the study protocol and did not participate in the study.

Results
Demographic profile
The study groups magnesium sulphate group M and control Group C were comparable with respect to the demographic profile as shown in table 1.

Table – 1: Demographic variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Magnesium group (n=40)</th>
<th>Control group (n=40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40.78 ± 7.64</td>
<td>37.82 ± 5.82</td>
<td>0.056</td>
</tr>
<tr>
<td>Weight</td>
<td>55.52 ± 6.63</td>
<td>54.20 ± 5.35</td>
<td>0.364</td>
</tr>
<tr>
<td>Height</td>
<td>156.10 ± 3.59</td>
<td>156.38 ± 3.79</td>
<td>0.740</td>
</tr>
<tr>
<td>M/F</td>
<td>25/15</td>
<td>20/20</td>
<td>0.260</td>
</tr>
<tr>
<td>ASA/I/II</td>
<td>30/10</td>
<td>33/7</td>
<td>0.412</td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>70.0 ± 13.40</td>
<td>78.50 ± 19.09</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Haemodynamic variables
The baseline and preinduction systolic, diastolic and mean blood pressures were comparable between the two groups. The P value were >1.

![Comparison of MBP at different time points between Cases and Controls](image)
Intraoperative mean blood pressure were significantly lower in group M as compared to control group C from time of skin incision to 75 minutes past the skin incision. P values from skin incision till 75 minutes were < .001 which means they were statically significant except at 45 minutes P value was 0.162, when the values were not significant. After that although the mean blood pressures were lesser in group M as compared to group C upto 120 minutes past skin incision but P value was not significant that means the difference was not statistically significant fig 1.

Total Fentanyl consumed (Intraoperative & Post operative period)
The total fentanyl consumed in group M was 155.25 ± 42.61mcgm and in group C was 223.75 ± 25.49 mcgm which is statically significant, with P value <.001 as shown in (Table.2). Group M (study group) consumed less Fentanyl throughout study duration as compared to control group.

Table 2

<table>
<thead>
<tr>
<th>Cases</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Time To First Post Op Demand Of Analgesia In Minutes</td>
<td>32</td>
</tr>
<tr>
<td>Total Intraop Fentanyl Consumed In Micrograms(Mcg)</td>
<td>40</td>
</tr>
<tr>
<td>Post Op Fentanyl Consumed.</td>
<td>40</td>
</tr>
<tr>
<td>Total Fentanyl Consumed</td>
<td>40</td>
</tr>
<tr>
<td>Post Op I/V Tramadol Consumed In</td>
<td>40</td>
</tr>
<tr>
<td>Post Op Diclofenac Consumed</td>
<td>40</td>
</tr>
<tr>
<td>Total Intraop Atracurium Consumed In Milligrams(Mgm)</td>
<td>40</td>
</tr>
</tbody>
</table>

*Comparison between the two groups by unpaired t-test.

Total intraoperative Atracurium used
The total consumption of Atracurium in group M was 50.50 ± 6.77 and group C was 64.50 ± 5.97 , P value being .001 which was statically significant (shown in table:2). The amount of Atacurium used in Group M (study group) was less compared to Group C (Control group).

Postoperative pain assessment
Postoperative pain assessment was done by using VAS scores. The VAS score in postoperative period was assessed at time points of 0 hr, 0.5hr, 1 hr, 2hr, 4 hr and 6 hr. VAS score >3 meant that the patients were experiencing pain and they were given analgesia in the form of fentanyl followed by diclofenac sodium and tramadol as rescue analgesia. VAS scores of patients in group M were significantly lower at 0 hr, 2hr and 6 hr (P values <0.001 at 0 hr, 0.03 at 4 hrs and < .001 at 6 hrs shown in figure 2.

Fig.2
Discussion

Central sensitization is one of the mechanisms implicated in the persistence of postoperative pain. NMDA antagonism inhibits central sensitization both before and after its occurrence unlike opioids which are useful only when administered preemptively. Thus NMDA antagonists have a potential of preemptive analgesia as well as treating established pain states such as post operative pain. Magnesium is a physiological blocker of NMDA receptors.

We decided to evaluate the effect of magnesium sulphate which was given prior to induction, on the first postoperative demand of analgesia and also total requirement of fentanyl both intra operatively and post operatively. In addition to this, our secondary objective was to find out whether magnesium sulphate used preemptively led to decrease in the consumption of neuromuscular blocking agents during the intraoperative period. In our study which was single blinded randomized control study, two groups of 40 patients each were taken, group M (magnesium sulphate) (N=40) received intravenous MgSO₄, 40 mg/kg in 100ml 0.9% normal saline over 15 minutes before induction, whereas patients in the Group C (control) (n = 40) received the same volume of isotonic saline over the same period. Followed by same uniform anaesthetic technique in both the groups.

Number of studies have been done regarding the use magnesium sulphate as analgesic during perioperative period where different dose regimens have been used. Literature is replete with studies of magnesium sulphate for analgesia in perioperative period. Investigators have used single bolus ranging from 30-50 mgm /kg followed by continuous infusion upto 6-20mgm/kg/hr of magnesium sulphate intraoperatively till the end of surgery and single bolus prior to induction and no subsequent infusion during intraoperative period. Koinig H et al first evaluated the effect of magnesium sulphate on the intraoperative analgesia in patients with identical surgical stimulus, here they used bolus dose of 50mgm/kg followed by 8mgm /kg /hr of infusion during intraoperative period and same amount of saline in control group. It was observed that during intraoperative and postoperative periods, the patients in the magnesium group required significantly less fentanyl than those in the control group. Tahiri et al (1) did a study where in they used single dose of magnesium sulphate 50mgm /kg for analgesia in patients undergoing abdominal hysterectomy. Postoperative pain score was lower in magnesium group at 6, 12 and 24 hrs after the operation (P< 0.05). Shamim A et al did study where in they used single dose of magnesium sulphate 50 mgm/kg in patients undergoing cholecystectomy and observed there was a difference in the total Tramadol consumption in the two groups which was statistically significant. Kiran S et al used single dose of magnesium sulphate 50mgm/kg in patients undergoing inguinal surgery. The patients of magnesium sulphate group (Group-I) received magnesium sulphate 50 mg/kg in 250 ml of isotonic sodium chloride solution IV Pain in postop period was significantly lower in magnesium sulphate group in comparison to control group at emergence from anaesthesia.

We in our study used single bolus dose of 40 mgm/kg intravenous to find out whether this dose provides adequate analgesia and to see if there are any complications at this dose. It was given prior to induction and we recorded time to first demand of analgesia post operatively in both magnesium group (M) and control group (C) and compared VAS score of magnesium and the control group at 0hr, .5hr, 1hr, 2hr, 4h and 6hr post operatively.

Both the magnesium group and control group were comparable with respect to demographic profile like age, weight, height, ASA class table and sex distribution.

First Post operative Demand of Analgesia

Shamim A et al in their study on magnesium sulphate as analgesia in patients undergoing cholecystectomy found that the patients who had received magnesium sulphate demanded analgesia
very late as compared to patients who had received normal saline in the post operative period. In the magnesium group mean time to first demand of analgesia in the postoperative period was 131.72 ± 140.11 minutes while as patients in control group demanded very early, mean time being 49.33 ± 93.33 minutes (15). Usmani H et al in their study on the role perioperative magnesium sulphate on the postoperative pain in patients undergoing upper abdominal surgeries observed that the first post operative demand of analgesia (tramadol) was delayed in patients of magnesium group with mean time being 162 ± 97 minutes and in the control group (patients who did not receive magnesium sulphate) mean time was 65 ± 47 minutes. Piplai G et al in their study of effect of magnesium sulphate on post operative opioid consumption observed that time to first analgesic requirement was significantly longer in the magnesium group than the control group. The mean time to first analgesic requirement in magnesium group was 50.5 minutes and mean time to first post operative analgesia in control group was 68.1 minutes (P< 0.05).

We found in our study that first demand of analgesic in postoperative period in patients of group M was significantly delayed, average time to first demand of analgesia in Magnesium group (group M) was 144.94 ± 123.22 minutes where as average time to first demand of analgesia in patients of control group (group C) was 30.68 ± 24.69 minutes. Our results are comparable to the studies done by Shamim A et al, Usmani H et al and Piplai G et al.

**Total Analgesia consumed intraoperatively (fentanyl)**

Studies have shown that total opioid consumed in patients where magnesium sulphate was used pre operatively, reduced during intraoperative period.

Koinig H et al in their study on magnesium sulphate observed that during intraoperative period magnesium group required significantly less fentanyl than those in control group, the intraoperative fentanyl consumption in control group was 0.089 ± 0.02mcg/kg/min versus magnesium group 0.058 ±0.01mcg/kg/min; P< 0.05. Piplai G et al evaluating effect of magnesium sulphate on the opioid consumption, observed that total intra operative fentanyl requirement in magnesium group was 0.45(0.11) mcg/kg/hr and in the control group was 1.14(0.26) mcg/kg/hr, (P value < 0.001). Schultz-Stubner et al observed that on using magnesium sulphate as part of balanced general anaesthesia there was significant reduction in remifentanil consumption from 0.14 in control group to 0.09 μg/ kg/min in magnesium group (P< 0.01) and kara et al demonstrated a significant decrease in the intraoperative opioid consumption for patients who received magnesium sulphate. Gupta et al in their study on magnesium sulphate as adjuvant in general anaesthesia observed that fentanyl dose required intraoperatively was significantly lower in the magnesium group A than in the control group B (p < 0.05).

We found in our study that total fentanyl consumed intraoperatively in magnesium group was 118.75 ± 22.44 mcgm and in the control group 173.50 ± 23.04 mcgm P value < 0.001. Our results are comparable to study done by Koinig H et al, Piplai G et al, Schultz-Stubner et al, Kara et al, Gupta K et al.

**Post Operative Analgesia Consumed**

A number of studies have revealed that administration of magnesium sulphate prior to induction reduced post operative requirement of opioid. Koinig H et al in their study found that fentanyl consumed by magnesium group postoperatively was 0.0031±0.0018 mcg/kg/min and by control group was 0.021± 0.013 mcg/kg/min ; P < 0.01. Shamim A et al in their study found that post op tramadol consumption between the magnesium group and the control group was statistically significant, tramadol consumption in control group was 106.83 ± 20.98 and in magnesium group 79.70± 24.14mgm; P=0.000. Study done by Rezae M et al using single dose of magnesium sulphate 50mg/kg in
lower segment caesarean section observed that mean post operative analgesic consumption (morphine) was less in magnesium group than in the control group ( P = 0.006) after 24 hrs. Piplai G et al evaluating effect of magnesium sulphate on the post operative opioid consumption, observed that cumulative postoperative opioid consumption was significantly less in magnesium group at 24 and 48 hr after operation (p < 0.024, p < 0.007). Tahiri et al evaluated the effect of single dose of magnesium sulphate given prior to induction on post operative analgesia and found pethidine requirement was significantly lower in magnesium group throughout 24 hour after the surgery. The pethidine consumption in magnesium group was 16.75 ± 18.23mgm and in control group 68.0 ± 17.42 mgm; p = 0.0001 which is statistically significant. Usmani H et al in their study on the evaluation of perioperative magnesium sulphate i/v on the post operative pain observed that total requirement of tramadol in magnesium group was 80 ± 24 mgm and in control group 105±31mgm P < 0.05, which is statistically significant.

We found in our study that total postoperative fentanyl consumed by magnesium group was 36.25 ± 22.61 and by control group was 51.25 ± 13.81 P< 0.001 which is statistically significant. Hence our results are comparable with the studies done on magnesium sulphate by Koinig H et al, Shamim A et al, Rezae M et al, Piplai G et al, Tahiri et al and Usmani H et al.

In our study the Visual analog score at (0, 0.5, 1, 2, 4 and 6 hr) among two groups are shown in table 12 figure 12, the VAS scores of patients in magnesium group were significantly lower at 0 hr, 2hr and 6 hr (P values <0.001 at 0 hr, P = 0.003 at 4 hrs and P < .001 at 6 hrs (shown in table 13, figure 13). However at 30 minutes, 1 hr and 4 hrs the VAS score between group M (magnesium) and group C (control) were having P values of .349, .575 and .238 which were statistically not significant meaning thereby that at these values the VAS score were comparable because of opioids or rescue analgesics been given to patients. Our results are comparable with the study done by Shamim A et al, Kiran S et al, Rezae M et al and Asadollah S et al. However Usmani H et al observed that pain at 6hrs post operatively in magnesium group was similar in both magnesium and control group, contrary to our study. This difference can be possibly explained by the fact that analgesics are given whenever VAS score was more than 3, resulting in lowering of VAS and relief of pain leading to comparable VAS at various time intervals during study period.

We found in our study that total amount of non depolarizing muscle relaxant consumed in magnesium group was 50.50 ± 6.77 which was significantly less than control group 64.50 ± 5.97; P < 0.001. The time to first incremental dose of neuromuscular blocking agent in magnesium group was 39.62±19.19 minutes and in control group was 23.55±3.47 minutes; P < 0.001 which is statistically significant. Our results are comparable with the results of Piplai G et al.

In conclusion, this study suggests that on giving magnesium sulphate 40 mgm/kg bodyweight prior to induction provides good quality of analgesia, reduces opioid consumption both intraoperatively and post operatively and decreased need for rescue analgesic post operatively. In addition magnesium sulphate decreases the requirement of neuromuscular.
blocking agents, without delaying emergence from anaesthesia.

References


