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Effect of Magnesium Sulphate on Peri-Operative Analgesia

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Conflicts of Interest: Nil

Abstract

Background: Pain and suffering are as much an integral part of life as pleasure and happiness. Relief of pain is one of the greatest objectives of medicine and providing relief from pain has been one of the achievements of the medicine. Magnesium also has antinociceptive effect in animal and human model of chronic pain. These effects are primarily based on the regulation of calcium influx into the cell. The aim of our study was To evaluate the effect of Magnesium Sulfate on perioperative analgesia and to evaluate requirement of rescue analgesia.

Materials and Methods: This prospective randomized double blind study was conducted in 60 patients, aged 15-60 years, of either sex and of ASA grade I and II posted for elective neurosurgical operations. The patients were divided randomly into two groups.

GROUP A (Mg^{++}): Patient who received 10% $Mgso_4$ 50mg/kg

GROUP B (Control): Patient who received isotonic Sodium Chloride solution, in a double blinded fashion.

Induction of anaesthesia:

1. I.v. Propofol (2mg/kg)
2. I.v. Fentanyl (2µg/kg).

After induction, orotracheal intubation was done with the help of Rocuronium (1mg/kg).

Anesthesia was maintained with 0_2 + N_20 + Isoflurane + Propofol (50mcg/kg/min),

After orotracheal intubation patient received either Magnesium sulfate 8mg/kg/h by a continuous IV infusion with a syringe pump over the entire operation period or same volume of isotonic sodium chloride solution.

Intra operative: Normal saline was administered to both group 6ml/kg-1h-1 and 4mlkg/h Post operatively. Intraoperative pulse rate, blood pressures were recorded for every 5 minutes for first 30 minutes then every 15 minutes.

At the end of surgery patients were monitored with N-M junction monitor. When TOF response was >0.90, then patients were reversed & extubated.

Postoperatively, the patients were observed in the recovery room and later in their respective ward for at least 8 hours.

Patients were assessed for pain by 0 – 10 cm linear Visual Analogue Scale. The intensity of pain was assessed. The assessments were made six times for each patient (1, 2, 3, 4, 6, 8 hours after entering the

The following parameters were noted in postoperative period.

1. pain score and sedation score
2. vital parameters like heart rate, systolic and diastolic blood pressure, oxygen saturation

3. any adverse events or side effects

At the end of study, all data was compiled and analyzed using paired and unpaired statistical difference between the two groups.

A p value of <0.05 was taken as statistically significant

Results: The demographic treads in both the groups were comparable. The heart rate, systolic and diastolic blood pressure showed statistically no difference in both the groups.

The total fentanyl requirement was higher in Group A patients than in Group B patients.

Patients who received magnesium sulfate had higher sedation score first hour of postoperative period. But from second postoperative hour onward, both the groups of patients were awake and had similar sedation score.

Conclusion: From the present study it can be concluded that Intraoperative administration of magnesium

- had better hemodynamics stability
- reduces the requirement of analgesia(fentanyl) in Intraoperative and postoperative period
- reduces pain score in postoperative period
- had lesser side effects.

Hence magnesium sulfate can have a role as adjuvant in perioperative analgesia.

Keywords: Magnesium, Pain, Pain score, Sedation score.

Introduction

The definition of pain according to dictionary of biology is "An acutely uncomfortable feeling or sensation of discomfort or distress usually the result of stimuli which are injurious to the body, which may result from dysfunction, stretching or contraction of distensible structures, inadequate or excessive blood supply, bacterial infection, presence of foreign proteins, mechanical or chemical trauma. It is usually associated with impaired function[1]. The IASP defines pain as ″an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such[2].

Surgery is a form of premeditated injury to the body. This process of cutting tissue, traction and tissue injury leads to the stimulation of free nerve endings and specific nociceptors leading to intra operative and postoperative pain. This acute pain has adverse effects on the patients' morals as well as various physiological functions of the body. So adequate control of pain in perioperative period is essential for good outcome as well as it is one of the factors which reduces the hospital stay.

All surgical operations are followed by pain, which may amplify endocrine metabolic responses, autonomic reflexes, nausea, ileus and muscle spasm. which may increase postoperative morbidity. Optimal postoperative pain treatment is therefore mandatory to enable early mobilisation and rehabilitation, to enhance recovery and to reduce morbidity. Despite continuous advances in anaesthesia and postoperative pain relief, however, a review of the literature shows that there are still a significant number of patients who experience severe or moderate pain after surgery.

Magnesium, the fourth most common cation in the body has numerous physiological activities, including activation of many enzymes involved in energy metabolism and protein synthesis.

Magnesium also has antinociceptive effect in animal and human model of chronic pain. These effects are primarily based on the regulation of calcium influx into the cell, i.e. "natural physiological calcium antagonism" and antagonism of the N-methyl-D-aspartate (NMDA) receptors. Results from in vitro studies indicate that NMDA receptor activation increase cytoplasmic calcium concentration in cultured spinal cord neurons. Change in the intra cellular calcium concentration may lead to persistent changes in the excitability of the dorsal horn

cells and therefore have an important role for pain perception. This study is designed to investigate the effect of magnesium sulfate on postoperative pain relief.

MATERIALS AND METHODS

This prospective randomized double blind study was conducted in 60 patients, aged 15-60 years, of either sex and of ASA grade I and II posted for elective neurosurgical operations.

All the patients were evaluated preoperatively. During the preoperative visit before the elective surgery, the purpose and protocol of the study and use of the visual analog scale (VAS) were explained to the patients. A written valid consent was taken from every patient.

The patients were divided randomly into two groups.

GROUP A (Mg^{++}): Patient who received 10% $Mgso_4$ 50mg/kg

GROUP B (Control): Patient who received isotonic Sodium Chloride solution, in a double blinded fashion.

Inclusion Criteria:

1. Age 15 - 70 years.
2. Weight 40-80 kgs.
3. ASA grade I and II.

Exclusion Criteria:

1. Increased serum Magnesium level (>1mmol/u)
2. Known allergy to drug.
3. Major hepatic, renal or cardiovascular dysfunction especially atrioventricular block.
4. Prior treatment with opioid and calcium channel blockers.

Inj. Fentanyl (0.5mcg/kg) was used as rescue analgesic in intra-operative and post operative period.

Pre-operative medication:

1. Inj. Midazolam (0.02mg/kg),
2. Inj. Glycopyrrolate (0.004mg/kg),
3. Inj. Ondansetron (0.08mg/kg),
4. Inj. Esomeprazole (0.8mg/kg),
5. Inj. Hydrocortisone (2mg/kg),
6. Inj. Dexamethasone (0.16mg/kg),
7. Inj. Phenytoin (2mg/kg) (In patient who received Phenytoin preoperative).

Monitors:

1. Electrocardiography
2. Non invasive blood pressure monitoring
3. Pulse oximetry
4. TOF

Induction of anaesthesia:

3. I.v. Propofol (2mg/kg)
4. I.v. Fentanyl (2μg/kg).

After induction, orotracheal intubation was done with the help of Rocuronium (1mg/kg).

Anesthesia was maintained with 0_2 + N_20 + Isoflurane + Propofol (50mcg/kg/min),

After orotracheal intubation patient received either Magnesium sulfate 8mg/kg/h by a continuous IV infusion with a syringe pump over the entire operation period or same volume of isotonic sodium chloride solution.

Intra operative: Normal saline was administered to both group 6ml/kg-1h-1 and 4mlkg/h Post operatively.

Serum magnesium levels were measured in both groups, preoperative and postoperative.

Rocuronium infusion (10mcg/kg/min) by syringe pump started to maintain TOF between 0-2 which was taken as adequate muscle relaxation.

Intraoperative pulse rate, blood pressures were recorded for every 5 minutes for first 30 minutes then every 15 minutes.

The presence of pain was defined as an increase heart rate and mean arterial blood pressure (MAP) more than 20% from the baseline value after induction and was treated with i.v. fentanyl (0.5mcg/kg) until heart rate and MAP returned to baseline.

At the end of surgery patients were monitored with N-M junction monitor. When TOF response was >0.90, then patients were reversed & extubated.

Postoperatively, the patients were observed in the recovery room and later in their respective ward for at least 8 hours.

The patients were monitored for

1. Pulse rate.
2. Blood pressure. (systolic and diastolic)
3. Oxygen saturation. (Spo_2)

Patients were assessed for pain by 0 – 10 cm linear Visual Analogue Scale. It is a 10 cm long scale of which 0 end is marked as no pain while other end 10 as worst possible pain. The patients were asked to point out the intensity of pain as experienced by them on the scale.

The intensity of pain was assessed. The assessments were made six times for each patient (1, 2, 3, 4, 6, 8 hours after entering the recovery room).

When the patients complained of pain, the VAS score was monitored and if the VAS score was >3, fentanyl (0.5mcg/kg) was given until an adequate level of analgesia was achieved. As our protocol after 8 hours inj Tramadol (50 mg) and inj Ondansetron (4 mg) given by intravenous route.

Because magnesium is widely regarded as a central nervous system depressant, sedation was monitored by using a 4 point rating scale

Sedation Score

1= patient fully awake

2= patient somnolent but responds to verbal command

3= patient somnolent but responds to tactile stimulation

4= patient asleep but responds to pain

The following parameters were noted in postoperative period.

4. pain score and sedation score
5. vital parameters like pulse rate, systolic and diastolic blood pressure, oxygen saturation
6. any adverse events or side effects

At the end of study, all data was compiled and analyzed using paired and unpaired statistical difference between the two groups.

A p value of <0.05 was taken as statistically significant

Results

In our prospective, randomized, double blind, controlled study, 60 patients, between 15 to 70 years of age and ASA grade I or II undergoing elective neurosurgery were divided in to 2 groups, each of 30 and entered into the study. Both the groups undergoing surgery of 3.5 to 4 hrs. duration were studied comparatively, to evaluate the effects of magnesium sulfate on peri-operative analgesia and adverse events if any. The two groups of 30 each were grouped into group A and group B.

Group A- comprised of 30 patients who received 50 mg/kg of 10% $MgSo_4$ I.V. bolus at the time of induction followed by 8 mg/kg/h as continuous intravenous infusion with a syringe pump over the entire operation period till the closure of duramater.

Group B- comprised of 30 patients who received same volume of isotonic sodium chloride solution as I.V. bolus at the time of induction and as continuous intravenous infusion in a similar manner.

Table 1: Demographic Data

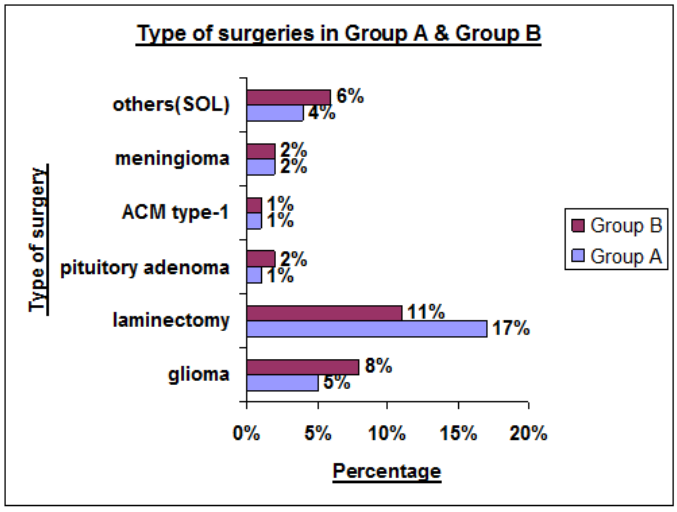
Variables	Group A		Group B		Unpaired t-test applied		
	Mean	SD	Mean	SD	t-value	p-value	Difference is-
Age (years)	36.67	13.74	39.00	15.31	-0.376	0.708	Not significant
Weight (Kgs)	54.63	4.23	55.63	7.94	-0.476	0.636	Not significant
Duration of surgery(minutes)	245.50	11.48	216.50	8.26	0.195	0.846	Not significant
ASA Grade	1.13	0.35	1.10	0.31	0.396	0.694	Not significant

The demographic data such as age, weight and ASA grade of the patients are comparable in both the groups and there

is no significant difference between both the groups(TABLE1)

The mean duration of surgery in both Groups A and B are comparable and there is no significant difference between both the group (TABLE1).

The type of surgery in both groups A and B are comparable and there is no statically significant difference between both groups.



ACM- Arnold chiari malformation, SOL- space occupying lesion

FIGURE1: Types of surgeries

The heart rate at various intervals of time during Intraoperative period found that there is significant difference between both the groups with Group A patients (those who receive magnesium sulfate) having lower heart rate as compares to Group B patients (those who do not receive magnesium sulfate).

The heart rate at various intervals of time during postoperative period as shown implies that there is no significant difference in heart rate in both Group A and Group B in postoperative period.

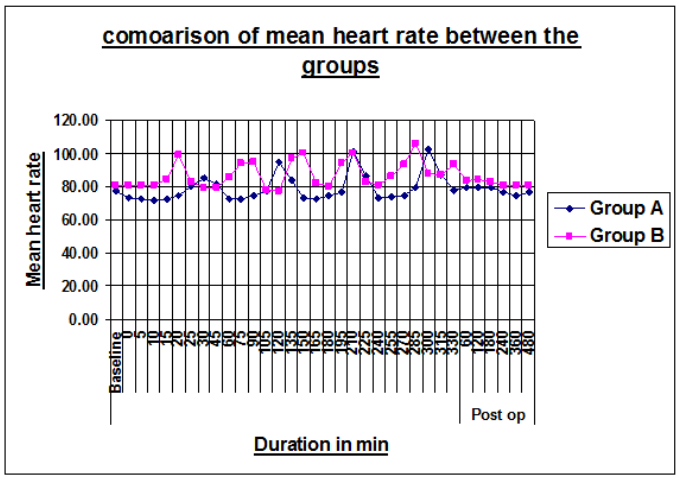


FIGURE 2: Comparison of mean heart rate between the groups.

The mean systolic blood pressure at various intervals of time during Intraoperative period found that there is significant difference between both the groups with Group A patients (those who receive magnesium sulfate) having lower systolic blood pressure as compare to Group B patients (those who do not receive magnesium sulfate).

The mean systolic blood pressure at various intervals of time during postoperative period as shown implies that there is no significant difference in mean systolic blood pressure in both Group A and Group B in postoperative period.

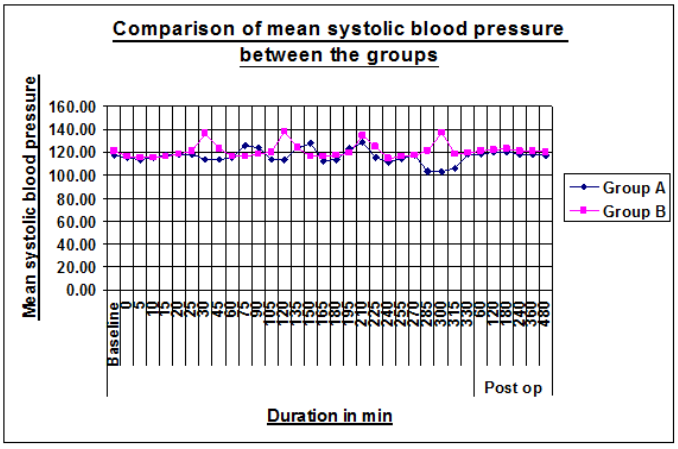


FIGURE 3: Comparison of mean systolic blood pressure between the groups

The mean diastolic blood pressure at various intervals of time during Intraoperative period found that there is

significant difference between both the groups with Group A patients (those who receive magnesium sulfate) having lower diastolic blood pressure as compare to Group B patients (those who do not receive magnesium sulfate).

The mean diastolic blood pressure at various intervals of time during postoperative period as shown in figure 3 implies that there is no significant difference in mean diastolic blood pressure in both Group A and Group B in postoperative period.

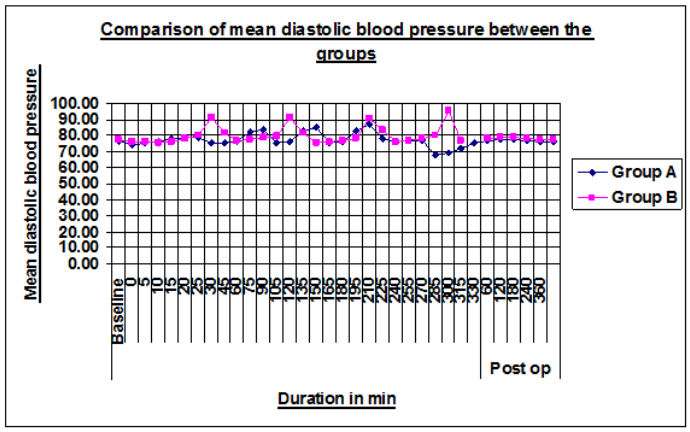


FIGURE 4: Comparison of mean diastolic blood pressure between the groups

The mean fentanyl used in Intraoperative period in both group A and B are comparable and there is no statistically significant difference.

The mean fentanyl used in postoperative period in both Group A and Group B are comparable and there is no statistically significance difference. The total mean fentanyl requirement in perioperative period in Group A is 328.00±38.09 mcg, which is lesser than Group B i.e. 420.50±86.55 mcg. There is statistically significant difference between both the groups regarding to total fentanyl requirement(FIGURE 4).

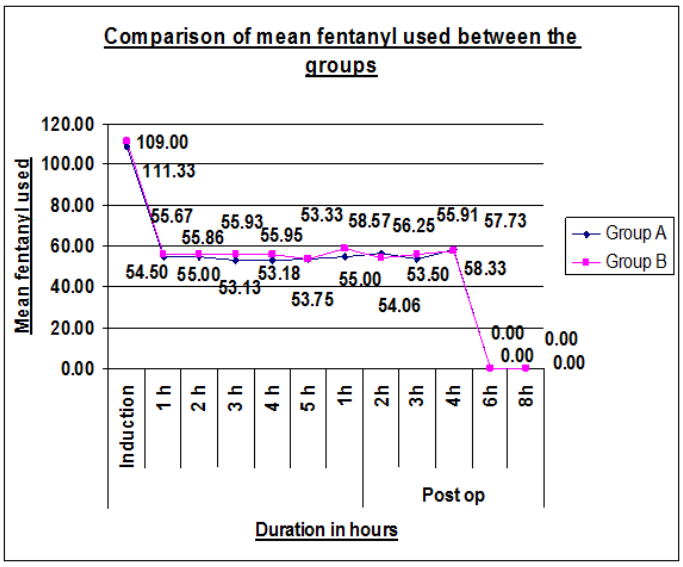


FIGURE 5: Comparison of mean fentanyl used between the groups

Table 2: Comparison of Mean Pain Score (By Visual Analouge Score) Between the Groups

Duration in hours	Mean Pain Score ($\bar{X} \pm$ SD)		p value	Difference
	Group A	Group B		
1h	1.00 ± 1.36	1.77 ± 02.06	0.0928	Not significant
2h	2.07 ± 1.72	3.17 ± 1.70	0.0156	Significant
3h	3.10 ± 1.63	3.73 ± 1.36	0.1096	Not significant
4h	0.93 + 1.14	2.00 + 1.97	0.4126	Not significant
6h	0.17 ± 1.05	0.70 ± 1.42	0.1036	Not significant
8h	0.00 ±	0.00 ±	0.0000	Not significant

By Student 't' Test P<0.05 Significant

At 1 hour post operative, there is no statistically significant difference in mean VAS between both groups A and B. though Group B has got higher VAS than Group A.

At 2 hour postoperative, there is statistically difference in mean VAS between Group A and Group B with VAS in Group B is more than Group A(TABLE 2) During rest of postoperative periods at 3, 4, and 6 hours the mean VAS is

more in Group B than Group A, which are statistically not significance.

At 8 hour postoperative VAS was statistically not significant in both groups.

TABLE 3: Comparison of Mean Sedation Score between the Groups

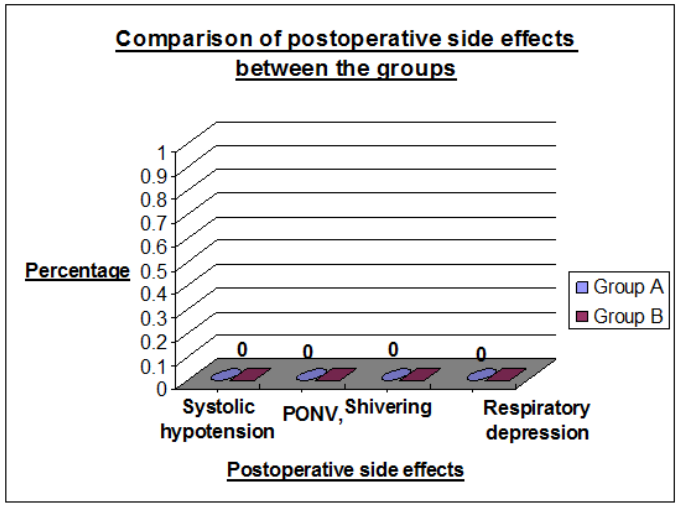
Duration in hours	Mean Sedation Score ($\bar{X} \pm SD$)		p value	Difference
	Group A	Group B		
1h	1.43 ± 0.50	1.03 ± 0.18	0.0001	Significant
2h	1.00 ± 0.00	1.00 ± 0.00	0.056	Not significant
3h	1.00 ± 0.00	1.00 ± 0.00	0.056	Not significant
4h	1.00 ± 0.00	1.00 ± 0.00	0.056	Not significant
6h	1.00 ± 0.00	1.00 ± 0.00	0.056	Not significant
8h	1.00 ± 0.00	1.00 ± 0.00	0.056	Not significant

By Student't' Test P<0.05 Significant

The mean sedation score at 1 hour postoperatively is higher in Group A than Group B, though there is statistically no significant difference between both the Groups.

After 1 hour postoperative, the mean sedation score remained 1(patient fully awake) in both the Groups A and B and is statistically not significance (TABLE 3)

Table 4: Postoperative Side Effects between the Groups



Discussion:

The study conducted to assess the efficacy of magnesium sulphate as perioperative analgesia comprised of 60 ASA grade I or II patients aged 15-70 yrs weighing between 40-80 kgs undergoing elective neurosurgery.

The 60 patients were randomly assigned into two groups A and B, each comprising of 30 patients.

Group A- comprised of 30 patients who received 50 mg/kg of 10% $MgSo_4$ I.V. bolus at the time of induction followed by 8 mg/kg/h as continuous intravenous infusion with a syringe pump over the entire operation period till the closure of duramater.

Group B- comprised of 30 patients who received same volume of isotonic sodium chloride solution as I.V. bolus at the time of induction and as continuous intravenous infusion in a similar manner.

The observations and results are analysed using student 't' test and compare under following headings.

- Demographic data
- Mean heart rate during Intraoperative and postoperative period
- Mean systolic and diastolic blood pressure during Intraoperative and postoperative period
- Total fentanyl requirement during entire surgical period
- Postoperative pain assessed by VAS
- Postoperative sedation assessed by sedation score
- Other complication if any

Demography:

The mean age in Group A is 36±13.74 yrs and in Group B is 39±15.31 yrs, which are comparable. There is statistically no significance difference between both the groups with respect to age.

The mean weight in Group A 54.63±4.23 kgs and in Group B is 55.63±7.94 kgs, which are comparable. There

is statistically no significance difference between both the groups with respect to weight.

The type of surgery is also comparable in both the group without any statistically significance.

The mean duration of surgery was 245.5 minutes in Group A and 216.5 minutes in group B, which are comparable. There is statistically no significant difference between both the groups with respect to mean duration of surgery.

Comparison of Heart Rate:

The heart rate during intraoperative period at various intervals of time was comparable. There is significant difference between both the groups. Group B having higher heart rate as compare to Group A. but in postoperative, there is no significant difference in heart rate in both Group A and Group B.

This correlate with study conducted by **N. Oguzhan et al (2008)[3].** who evaluated the effect of magnesium sulphate infusion on sevoflurane consumption, hemodynamics and perioperative opioid consumption in lumbar disc surgery. The groups of patients who received magnesium sulphate 30 mcg/kg bolus followed by 10 mcg/kg/h had lesser heart rate when compared with the groups which did not receive magnesium sulphate (though there was statistically no significance between both the groups.)

Comparison of Blood Pressure:

There is statistically no significant difference between both the groups A & B with respect to systolic and diastolic blood pressure and both the groups are comparable.

This result correlates with the study conducted by **N. Oguzhan et al (2008)[3]** in which he found that the blood pressure in both the control and test group were comparable and there was no statistically significant difference between both the groups A & B with respect to blood pressure.

Comparison of Fentanyl Requirements:

The mean Fentanyl used during induction, intraoperative period and postoperative in both the Group A and B are comparable. There is statistically no significance difference between both the groups. The total Fentanyl requirement in perioperative period in Group A is 328±38 mcg and in Group B is 420±86.55 mcg which is much lesser and statistically significant.

Hence the total analgesic requirements in patient receiving magnesium sulfate (Group A) are lesser than those who did not receive magnesium (Group B).

This correlates with the study conducted by **H Koinig et al (1998)[4]** who evaluated the role of magnesium sulfate in intraoperative and postoperative analgesia in arthroscopic knee surgery patients. The patients who received 50 mg/kg i.v. bolus of $MgSo_4$ followed by 8 mg/kg/h intraoperatively as infusion had lesser requirement of Fentanyl both in intraoperative and postoperative periods than in control patients who received equal volume of isotonic saline.

Our result also correlate with the study conducted by **L. Telci et al (2002)[5]** who evaluated the effects of magnesium sulfate in reducing intraoperative anaesthetic requirement in elective spine surgery. They found that patients who received magnesium had lesser remifentanil requirement.

The result of study conducted by **H. Kara et al (2002)[6]** who evaluated postoperative analgesic requirement in elective post-hysterectomy patients show that patients who received magnesium sulfate perioperatively reduces Fentanyl consumption than those who did not.

Also in elective laparoscopic cholecystectomy, intraoperative magnesium sulfate infusion reduces post operative tramadol consumption than those patients who had not received magnesium sulfate infusion as studied by **O. mentes et al (2008)[7].**

Similarly **Martin et al** in 1996 in his study evaluated the role of magnesium sulfate in post operative analgesia in elective abdominal hysterectomy and found that morphine requirement were less in magnesium treated patients than in control patients during first 48 hours which was more pronounced in first 6 hours.

Comparison of Postoperative Analgesia:

The mean VAS is higher in group B than in group A during 1,2,3,4 and 6 hour though there is no statistically significant difference between both the groups. This implies that magnesium treated patients have lower pain score than in control patients in post operative period.

Our result correlate with a study conducted by **H Koinig et al (1998)**[4] who evaluated the role of magnesium sulfate in reducing intra and post operative analgesia requirement in arthroscopic knee surgery patients. He demonstrated that the magnesium treated patients have lower VAS score than those patients who had not received magnesium sulfate.

Also **Levaux et al (2003)**[8] in there study on effect of intraoperative magnesium sulfate on pain relief after major lumbar orthopedic surgeries found that magnesium treated patients had lesser pain Similarly Christopher **Lysakowski et al (2007)**[9] who studied magnesium as adjuvant for postoperative analgesia found that serum levels were increased in patients who received magnesium sulfate and serum levels were decreased in those who received placebo.

Comparison of Sedation Score:

The mean sedation score at 1 hour postoperative period is higher in Group A than in Group B. but after 1 hour the mean sedation score remained same with patients remaining awake in both the groups without any statistical significance.

Our study correlated well with the finding of **H. Kara et al (2002)** [6] who evaluated the role of magnesium sulfate in perioperative pain reduction in patients undergoing elective hysterectomy. He found that the postoperative sedation score were similar in both the groups without any **statistical significant difference.**

Comparison of Side Effects:

Our study demonstrated no side effects such as postoperative nausea and vomiting, systolic hypotension, shivering or respiratory depression in both magnesium treated and placebo treated patients which correlate well with the study conducted by **H Koinig et al (1998)**[4] who found no side effects of magnesium sulfate in postoperative period.

Also **Bhatia A et al (2004)**[10]in his study found no significance side effects in postoperative period in his study which evaluated the role of magnesium on analgesic requirement, pain discomfort and sleep during postoperative period.

Conclusion:

This study was undertaken to evaluate the effect of magnesium sulfate on perioperative analgesia, to evaluate the requirement of rescue analgesia and to study the side effect of magnesium sulfate if any.

From the present study it can be concluded that Intraoperative administration of magnesium

- had better hemodynamics stability
- reduces the requirement of analgesia(fentanyl) in Intraoperative and postoperative period
- reduces pain score in postoperative period
- had lesser side effects.

Hence magnesium sulfate can have a role as adjuvant in perioperative analgesia.

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