Original Research Article

Comparative study of epidural fentanyl and epidural fentanyl with magnesium sulphate for post-operative analgesia in patients undergoing lower limb surgeries

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Abstract

Background: Control of post-operative pain is a major concern for the patients and also for the treating physicians. Various analgesic agents such as opioids, nonopioids through various routes such as oral, intravenous, neuraxial, regional for the management of postoperative pain exist. Magnesium has anti-nociceptive properties with additional enhancement of opioid anti-nociception when used epidurally.

Materials and methods: The study was a randomized open labelled controlled trail, conducted in the department of anaesthesiology, Govt. Mohan Kumaramangalam Medical College and Hospital, Salem, Tamil Nadu. The data collection for the study was done between June 2016 to June 2017. The study population included people who were undergoing lower limb surgery for various disease conditions. The key outcome variables assessed were highest sensory blockade, time taken for highest sensory level (min), duration of surgery (min), time for regression to L1 (min), duration of analgesia (min).

Results: Duration of analgesia was longer in the Magnesium sulphate group, with analgesia lasting for 143.4 ±39.57 minutes which was statistically significantly higher compared to Epidural Fentanyl group with 107 (±25.82) minutes. The mean time for regression to L1 was 118 minutes and 119 minutes in group F and FM respectively, there is no statistically significant between two study groups (P value>0.05). There was no statistically significant difference between the groups in the time taken

for the highest sensory level (P value>0.05), the duration of surgery and the time taken for the highest sensory level (P value>0.05).
Conclusion: Magnesium being a relatively harmless and inexpensive molecule, a non-competitive, N-methyl-D-aspartate receptor antagonist with its anti-nociceptive properties has a huge role to play in the coming years for postoperative analgesia.

Key words

Epidural, Fentanyl, Magnesium sulphate, Post-operative analgesia, Lower limb surgery.

Introduction

Control of Postoperative pain is a major concern for the patients and also for the treating physicians [1]. Regional anesthesia is a safe and also an inexpensive technique which has the added advantage of providing postoperative pain relief for a longer time. Autonomic, Somatic and Endocrine responses to postoperative pain are effectively taken care of and blunted by Regional anesthesia [2]. In Epidural administration, the drug is injected into the epidural space of the spinal cord. Effective analgesia for postoperative pain relief after major surgery has been a practical proposition with epidural administration of local anesthetic (LA) and opioid drugs since the early 1980s [3]. Polypharmacological approach for the treatment of postoperative pain has become common nowadays since no single drug can specifically inhibit nociception without associated side-effects. Effective analgesia is an essential part of postoperative management. Various analgesic agents such as opioids, nonopioids through various routes such as oral, intravenous, neuraxial, regional for the management of postoperative pain exist along with various side effects [3-5]. Although conventionally the mainstay of postoperative analgesia is opioid-based, increasingly more evidence exists to support a multimodal approach with the intent to reduce opioid side effects such as nausea and ileus and improve pain scores [1, 3]. Magnesium, besides being one of the plentiful action in the human body, also has anti-nociceptive effects [6, 7]. It has been reported that intrathecal magnesium enhances opioid anti-nociception in an acute incisional model [8]. Epidural magnesium reduces postoperative analgesic requirement [2, 9, 10]. So we carried out our study with the objective of evaluating the efficiency of adding magnesium as an adjuvant with epidural fentanyl for postoperative analgesia.

Objectives

To compare and study the efficiency of epidural fentanyl with combination of epidural fentanyl and magnesium administered postoperatively for lower limb surgery with respect to duration of analgesia, hemodynamic stability and side effects, if any.

Materials and methods

The study was a randomized open labelled controlled trail, conducted in the Department of Anesthesiology, Govt. Mohan Kumaramangalam Medical College and Hospital, Salem, Tamil Nadu. The data collection for the study was done between June 2016 to June 2017, i.e. for a period of one year. The study population included people who were undergoing lower limb surgery for various disease conditions.

The study population were randomized to Intervention group F: fentanyl alone or intervention group FM (Fentanyl plus Magnesium sulphate) using a computer generated random number sequence. The allocation sequence was concealed from the investigator by serially numbered opaque envelops, which were kept in the custody of an independent statistician. The investigator blinding was not possible in the study. The participant involved in the study and the statistician analysing the data were blinded for the intervention. The sample size included 30 subjects in each of the intervention groups, which was assessed basing on the published data, assuming 80% power of study and 5% alpha error, using STAT IC software version 13 [11]. The study was approved by the institutional human ethics committee. Informed written consent was obtained from all the study participants, after explaining the risks and benefits involved in the study and voluntary nature of participation. All the personal data of the participants was kept confidential throughout the study.

After obtaining informed written consent, thorough history and clinical examination was done on each participant.

After regression of sensory block (checked by pin prick) to L1, patient group F received 50 µg of fentanyl and group FM received 50 µg of fentanyl plus 50 mg of magnesium sulphate. Patients were monitored for

- Duration of analgesia (as described above)
- Hemodynamic changes – Pulse rate, blood pressure, Respiratory rate, SpO_2
- Side effects – nausea, vomiting, pruritus, shivering etc.

After 30 minutes of monitoring in PACU patients were transferred to post-operative ward. Patients' first analgesic requirement time were recorded. More events related to drug and epidural catheter were observed for 24 hours.

The key outcome variables assessed were highest sensory blockade, time taken for highest sensory level (min), duration of surgery (min), time for regression to L1 (min), duration of analgesia (min). Both the study groups were compared with respect to all the baseline variables. The key outcome parameters and haemodynamic parameters were compared between the two study groups. Quantitative variables were compared by mean and standard deviation, using Independent sample t-test. Categorical variables were compared by using Chi square test. P value < 0.05 was considered as statistically significant. IBM SPSS version 22 was used for statistical analysis [12].

Results

The mean age of study population in group F was 45 years and in Group FM it was 45.6 years, the association of two groups with age was statistically not significant (P value>0.05). There is no statistically significant difference in the ratio of males to females in both the study groups as 22:8 (P value>0.05). Femur fracture cases were more in both the study groups as compared to other fracture types but there is no statistically significant difference between two groups with the type of fractures (P value>0.05) (**Table - 1**).

Among all the highest sensory blockade T6 was the highest proportion in both groups F(60 %) and FM (60%), There is no statistically significant difference among the highest sensory blockades between the two groups (P value>0.05). The mean time taken for the highest sensory level was 14 minutes in group F and it was 12.24 minutes in Group FM, there is no statistically significant difference between the groups in the time taken for the highest sensory level (P value>0.05). The mean duration of surgery was 99 minutes in group F, 92 minutes in group FM, the association of two study groups about the duration of surgery was statistically not significant (P value>0.05). The mean time for regression to L1 was 118 minutes and 119 minutes in group F and FM respectively, there is no statistically significant between two study groups (P value>0.05). The mean duration of analgesia was 107 minutes in group F and 143 minutes in group FM, the difference between the two groups was statistically significant (P value<0.001) (**Table - 2**).

Comparison of pulse rate between two study groups in study population was as per **Table – 3**. Comparison of SBP between two study groups in study population was as per **Table – 4**. Comparison of DBP between two study groups in study population was as per **Table – 5**.

Table - 1: Comparison of Sociodemographic parameters between two study groups in study population (N=60).

Parameter	Group F (N=30)	Group FM (N=30)	Significance
Age (years)	44.92± 4.23	45.6± 4.46	t=0.552; P=0.583
Gender			
Male :Female	22 :8	22 :8	Chi square =0.00; P =1.00
Types of cases			
Fracture Femur	17	17	0.79
Fracture patella	1	1	
Fracture both bone leg or Tibia	8	9	
Split skin graft of leg	2	2	
Achilles Tendon injury	2	1	

Table - 2: Comparison of other parameters between two study groups in study population (N=60).

Parameter	Group F (N=30)	Group FM (N=30)	Significance
Highest sensory blockade			
T10	0 (0%)	3 (12%)	Highest sensory blockade is statistically similar between two groups with P= 0.324
T8	9 (28.0%)	8 (24.0%)	
T6	17 (60.0%)	16 (60.0%)	
T5	4 (12%)	3 (4.0%)	
Time is taken for highest sensory level (min)	13.92±4.50	12.24±3.43	T=1.484; P=0.144
Duration of surgery (min)	99.00±13.31	92.20±15.21	T=1.682; P=0.099
Time for Regression to L1 (min)	118.80±13.41	119.60±17.85	T=0.179; P=0.859
Duration of analgesia (min)	107.00±25.82	143.40±39.57	T=3.852; P<0.001

Table - 3: Comparison of pulse rate between two study groups in study population (N=60).

Pulse rate	Group F (N=30)	Group FM (N=30)	Significance
1 minute	84.16±13.45	81.44±12.07	T=0.753; P=0.455
2 minute	84.16±14.25	81.40±11.56	T=0.752; P=0.456
3 minute	83.84±13.99	80.04± 10.66	T=1.080; P=0.285
4 minute	84.76± 14.12	80.60± 9.10	T=1.238; P=0.222
5 minute	84.64±14.16	79.64±9.05	T=1.488; P=0.143
10 minute	84.36±14.15	79.48±8.19	T=1.493; P=0.142
15 minute	84.16± 13.31	78.60±8.49	T=1.761; P=0.085
20 minute	82.44±12.55	79.60±8.89	T=0.924; P=0.360
25 minute	83.00± 12.43	78.76±9.03	T=1.380; P=0.174
30 minute	83.64±11.93	79.20±8.66	T=1.506; P=0.139
45 minute	82.96±10.02	78.92±6.56	T=1.686; P=0.098
1 hr	84.84±9.41	79.24±6.62	T=2.432; P=0.019
1 hr 15 min	85.17±10.10	79.48±6.97	T=2.287 P=0.027
1 hr 30 min	87.95±9.75	82.00±8.50	T=2.211; P=0.032
1 hr 45 min	89.46±8.92	82.48±7.61	T= 2.435; P= 0.021
2 hr	92.33±11.75	85.88±6.77	T=1.693; P=0.104
2 hr 30 min	95.33± 12.0	86.10±6.99	T=1.675; P=0.122

Table - 4: Comparison of SBP between two study groups in study population (N=60).

SB (mm Hg)	Group F (N=30)	Group FM (N=30)	Significance
1 minute	112.72±11.66	113.6±8.89	T=0.300; P=0.765
2 minute	111.80±12.03	112.00±7.50	T=0.071; P=0.944
3 minute	112.00±11.82	112.64±8.21	T=0.222; P=0.825
4 minute	111.40± 12.49	113.64±7.47	T=0.770; P=0.445
5 minute	112.64±11.01	113.40±8.16	T=0.277; P=0.783
10 minute	112.88±10.8	112.56±7.26	T=0.123; P=0.903
15 minute	113.60±11.18	112.92±7.93	T=0.248; P=0.805
20 minute	113.72±11.18	112.44±5.64	T=0.500; P=0.619
25 minute	112.68±11.64	113.56±5.86	T=0.338; P=0.737
30 minute	112.08±10.34	112.44±6.40	T=0.148; P=0.883
45 minute	114.84±8.28	114.36±5.33	T=0.142; P=0.888
1 hour	116.60±9.79	114.80±5.04	T=0.817; P=0.418
1 hour 15 min	119.26±8.84	115.36±4.91	T=1.909; P=0.062
1 hour 30 min	121.90±7.03	117.62±5.43	T=2.301; P=0.026
1 hour 45 min	126.15±10.14	118.85±5.44	T=2.698; P=0.001
2 hour	130.67±14.97	119.74±6.19	T=2.638; P=0.001
2 hour 30 min	124.67±5.03	119.10±6.61	T=1.332; P=0.210

Table - 5: Comparison of DBP between two study groups in study population (N=60).

DB (mm Hg)	Group F (N=30)	Group FM (N=30)	Significance
1 minute	70.48±7.47	72.92±7.86	T=1.125; P=0.266
2 minute	71.12±7.48	72.32±5.34	T=0.653; P=0.517
3 minute	71.08±7.09	71.40±5.32	T=0.181; P=0.857
4 minute	70.44±7.25	71.76±6.2	T=0.692; P=0.492
5 minute	70.44±8.05	71.88±5.66	T=0.732; P=0.468
10 minute	71.36±7.23	73.56±6.44	T=1.136; P=0.262
15 minute	70.96±6.73	71.44±5.14	T=0.283; P=0.778
20 minute	71.08±7.53	71.00±4.49	T=0.046; P=0.964
25 minute	71.68±6.90	72.04±5.65	T=0.202; P=0.841
30 minute	70.88±6.13	71.40±5.12	T=0.326; P=0.746
45 minute	72.40±5.62	74.20±4.67	T=1.231; P=0.224
1 hr	72.84±5.67	74.36±5.39	T=0.971; P=0.336
1 hr 15 min	74.91±6.65	75.32±4.83	T=0.246; P=0.807
1 hr 30 min	76.52±6.43	77.04±5.17	T=0.299; P=0.766
1 hr 45 min	77.54±6.27	77.50±5.03	T=0.019; P=0.985
2 hr	78.00±7.04	78.42±5.68	T=0.150; P=0.882
2 hr 30 min	74.67±3.06	76.50±6.52	T=0.461; P=0.654

Discussion

We did a randomised controlled trial on 60 subjects undergoing lower limb surgeries divided into 2 groups of 30 each. They either received Epidural Fentanyl or a combination of Epidural Fentanyl with Magnesium sulphate for postoperative analgesia in patients undergoing lower limb surgeries.

Post-operative pain control is a major concern in the post-operative period for the patients. A multitude of therapeutic modalities has been used in the post-operative period for pain control. Magnesium is an inorganic ion that is used for the treatment of eclampsia and pre-eclampsia, hypokalemia, premature labor, myocardial protection after ischemia, asthma crisis, postoperative acute pain control [13, 14] and hemodynamic stability during intubation. Magnesium is a non-competitive, N-methyl-D-aspartate receptor antagonist [15]. Since magnesium blocks the *N*-methyl-D-aspartate receptor and its associated ion channels, it can prevent central sensitization caused by peripheral nociceptive stimulation. There are several products containing magnesium. Magnesium sulfate has been most commonly described in numerous studies [8, 14, 16-18] in anesthesiology.

In our study, both groups were comparable in terms of baseline characteristics such as age, gender distribution, type of cases taken up for surgery. Subjects with Fracture of Femur were more common in both the study groups. Duration of analgesia was longer in the Magnesium sulphate group, with analgesia lasting for 143.4 minutes with SD of 39.57 minutes which was significantly higher statistically compared to Epidural Fentanyl group with 107 minutes (±25.82). Similar to our study, Arcioni R, et al. (2007) [16] in their randomized, double-blinded placebo-controlled trial on patients undergoing orthopedic surgery, observed that supplementation of spinal anesthesia with combined intrathecal and epidural $MgSO_4$ significantly reduces patients' post-operative analgesic requirements.

Similar to our study, Bilir A, et al. [2] (2007) in their study noted that the time to first analgesic requirement time was slightly longer when magnesium was co-administered, although not significant statistically. In their study, compared with Group F, patients in Group FM received smaller doses of epidural fentanyl (P, 0.05). The cumulative fentanyl consumption in 24 h was higher in Group F compared to Group FM (P, 0.05) in their study. Arcioni R, et al. (2007) [14], in their study found that post-operative morphine consumption was 38% lower in patients receiving spinal anesthesia plus epidural $MgSO_4$, 49% lower in those receiving spinal anesthesia plus intrathecal $MgSO_4$ and 69% lower in the intrathecal-epidural combined group relative to control patients receiving spinal anesthesia alone. Buvanendran A, et al. (2002) [19] in their study observed that in patients receiving spinal analgesia for labor, the addition of magnesium sulfate to the opioid fentanyl prolonged analgesia with no increase in side effects.

Dabbagh A, et al. (2007) [20] in their study observed that Intravenous magnesium sulfate can serve as a supplementary analgesic therapy to suppress the acute postoperative pain, leading to fewer morphine requirements in the first 24 h but Ko SH, et al. (2001) [17] in their study observed that Perioperative intravenous administration of magnesium sulfate did not increase CSF magnesium concentration and had no effects on postoperative pain. Tramer MR, et al. (1996) [21] in their study showed that the perioperative application of intravenous magnesium sulfate is associated with the smaller analgesic requirement, less discomfort, and a better quality of sleep in the postoperative period. But most of these studies were on intravenous magnesium sulphate, so we carried out our study with epidural supplementation which resulted in larger benefits.

Magnesium does not effectively cross the blood-brain barrier when given IV, but Intrathecal magnesium potentiates opioid anti-nociception and the safety of intrathecal magnesium has been demonstrated in humans [19]. There was no associated increase in adverse events in their study but Larger doses of intrathecal magnesium were not studied because of the limitations on cephalad spread when hyperbaric solutions are injected in the sitting position.

All other parameters were comparable between both the groups such as duration of surgery, highest sensory level of blockade attained and time is taken for it, time for regression in our study. Similar to our study, Bilir A, et al. [2]

(2007) in their study noted that there was no difference in the quality of sensory and motor block before and during the surgery was noted between groups. Systolic, diastolic, mean arterial blood pressures, heart rates, and oxygen saturation remained stable, and there was no significant difference between the groups. The Pulse rate was higher in the Epidural Fentanyl group compared to Combination of Epidural Fentanyl with Magnesium sulphate, which was not statistically significant. There was no statistically significant difference in Systolic blood pressure between the two groups except at 1 hr 30 minutes, 1 hr 45 minutes, 2 hrs after surgery. There was also no statistically significant difference in Diastolic blood pressure between the two groups at all intervals.

Lysakowski C, et al. (2007) [22] in their systematic review of randomized trials similar to our study observed that Perioperative magnesium supplementation has a role in postoperative analgesia, although the evidence was not conclusive.

There are a number of limitations in our study because of practical and economic constraints as for example, we did not evaluate the pain scores and amount of top-up analgesia needed and hence their comparison could not be done.

Conclusion

Magnesium being a relatively harmless and inexpensive molecule, a non-competitive, N-methyl-D-aspartate receptor antagonist [15] with its anti-nociceptive properties by blocking the *N*-methyl-D-aspartate receptor and its associated ion channels, can prevent central sensitization caused by peripheral nociceptive stimulation and has a huge role to play in the coming years for postoperative analgesia. In conclusion, supplementation of fentanyl with epidural magnesium for postoperative epidural analgesia in lower limb surgeries provided a pronounced increase in epidural fentanyl analgesia without any significant side-effects. But there is a need for further studies to address different dosages of magnesium in different surgical settings.

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