Evaluation of the Efficacy of MgSO\(_4\) as an Adjunct to Ropivacaine and Fentanyl for Labour Analgesia

Abstract

Background and Objective: Epidural analgesia is the most commonly practiced method for labor analgesia. It provides effective pain relief, less maternal stress response, better parturient satisfaction and the ability to provide anesthesia when required. We conducted this study to evaluate the efficacy of Magnesium Sulphate as an adjunct to ropivacaine and fentanyl for labor analgesia.

Materials and Methods: 60 primi parturients, aged more than 18 years, ASA physical status class II, in active labor, requesting labor analgesia were included in this prospective randomised double blind study. Patients in Group F received 7.5 ml 0.2% Ropivacaine + 50 mcg Fentanyl + Normal Saline to make a total volume of 10 ml and in Group FM received 7.5 ml 0.2% ropivacaine + 50 mcg fentanyl + 50 mg MagnesiumSulphate + Normal Saline to make a total volume of 10 ml. Pain was assessed using Visual Analogue Scale (VAS). Time of onset, quality of analgesia and duration of analgesia of bolus dose were noted. Results: Epidural single dose Magnesium Sulphate added to ropivacaine and fentanyl resulted in significantly early onset (2.9 ± 0.7 min v/s 5.2 ± 1.1 min, \(P < 0.001\)) and longer duration of epidural analgesia (107.2 ± 20.1 min v/s 89.9 ± 21.3 min, \(P = 0.002\)) as compared to those patients who received ropivacaine and fentanyl only. There was no significant effect on neonatal outcome (assessed by APGAR Score) and no maternal side effects were recorded. Conclusion: Magnesium sulphate added to ropivacaine and fentanyl for labor analgesia resulted in early onset of analgesia and longer duration of action without any significant side effects.

Keywords: Analgesia, epidural, labour, magnesium sulphate

Introduction

The most commonly practiced method for labor analgesia is regional anesthesia. Of the regional analgesic techniques, epidural analgesia is the most commonly used method during childbirth. It provides effective pain relief, less maternal stress response, better parturient satisfaction and the ability to provide anesthesia when required.[1]

Clinical trials are needed to minimize side effects associated with epidural local anesthetic administration such as motor impairment and sympathetic blockade.[2] Ropivacaine is more selective for sensory fibers when compared with other local anesthetics, producing less motor block.[2] Labor epidural studies using 0.25% ropivacaine solutions lacked harmful maternal and neonatal effects and provided analgesia as effective as 0.25% bupivacaine. A concentration of 0.125% of ropivacaine was sufficient for labor analgesia and it does not cause any motor weakness which can affect the ambulation of the patient or the maternal expulsive efforts.[3]

The quality of analgesia is better when a local anesthetic is combined with an opioid. The rapid onset action of fentanyl is advantageous for labor analgesia and emergency caesarean delivery, however its short duration of action limits its postoperative analgesic effect after single dose.[4] Studies on the use of magnesium sulphate as an adjuvant in labor analgesia are limited. The addition of magnesium to spinal bupivacaine–fentanyl anesthesia improves the duration of spinal analgesia for labor without any side effects.[5] The addition of magnesium to epidurally administered bupivacaine and fentanyl in patients undergoing elective cesarean section with combined spinal-epidural anesthesia helped to improve the quality of postoperative analgesia.[6] To our knowledge, no study has been done so far which evaluated the effect of magnesium sulphate administered epidurally as an

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adjunct to ropivacaine and fentanyl for labor analgesia. Therefore, we planned this study to evaluate the efficacy of epidural magnesium sulphate as an adjuvant to ropivacaine and fentanyl for labor analgesia.

Materials and Methods

After obtaining approval from institutional ethics committee and taking informed written consent from the patients, the study was carried out over a period of 1 year from May 2017 to April 2018, at the Pannadhai Mahila Chikitsalaya, R.N.T. Medical College, Udaipur which was registered under CTRI (CTRI/2018/09/015594).

Sample size was calculated on the basis of previous study by Hasanein et al. which showed that the VAS in the study group was 0.5 ± 2 compared to 2.5 ± 0.3 in the control group. Based on this study, for our study to have a power of 80% with an α error of 0.05, 9 patients were required in each group. Since this sample size is very small for a biomedical study, based on the central limit theorem, we decided to include 30 patients in each group to study the difference of score of 3 in VAS at a power of 80% and CI of 95%.

Primary objective of the study was to detect the difference in VAS between the two groups. Secondary objectives of the study were the effect of drug on duration of analgesia, maternal expulsive efforts, and neonatal outcome.

Sixty primi parturients aged >18 years, ASA physical status class II, in active labor, requesting labor analgesia were included in this prospective, randomized, double blind, comparative study. Consort flowchart (phases of progress of the clinical trial) is shown in Figure 1.

Patients with known hypersensitivity to study drug, bleeding disorders, local or systemic sepsis, CSF in the epidural catheter during procedure, women with spinal column disorders and those who had undergone spinal surgery, pregnancy induced hypertension, breech presentation, multiparity, gestational diabetes and multiple or high-risk pregnancies were excluded from the study.

After a thorough pre-anesthetic evaluation, patients were randomly allocated into two groups of 30 each using a computer derived random number sequences and the randomization sequences were kept inside sealed opaque envelopes. Group F received 7.5 ml 0.2% Ropivacaine + 50 mcg (1 ml) Fentanyl + Normal saline to make a total volume of 10 ml, Group FM received 7.5 ml 0.2% Ropivacaine + 50 mcg (1 ml) Fentanyl + 50 mg Magnesium Sulphate (1 ml) + Normal saline to make a total volume of 10 ml.

Blinding was done by involving two anesthesiologists one of whom prepared the drugs and performed the epidural block, while another recorded all data in the proforma. Patient, surgeon and ward nurse were also not aware of group allocation. The group allocation was revealed only at the time of data compilation.

The patient was transferred to the operating room where a 20 G cannula was inserted and started on appropriate intravenous fluid. Standard monitoring with pulse oximetry, non-invasive blood pressure monitoring and ECG was applied. After recording baseline blood pressure, oxygen saturation and heart rate, parturients in both the groups were placed in the left lateral position and following strict aseptic techniques, a local infiltration of 2% lignocaine HCl was infiltrated into the intervertebral space at either L3-4 or L4-5 level and epidural space was identified using a loss of resistance technique to normal saline with an 18G Tuohy needle. After locating the epidural space, an 18-gauge multiorifice catheter was threaded through the cranially directed tip of the epidural needle to a depth of 3 cm into the epidural space and negative aspiration of blood or cerebrospinal fluid was confirmed. If there were no signs of an intravascular or intrathecal placement of the catheter, the catheter was secured and the woman was placed in the supine position with left uterine displacement.

Study drug was administered in small aliquots of 1 ml after repeated aspirations considering each dose as test dose. The time of the injection of study drug was considered as T = 0. If the epidural catheter was placed into the intravascular space, it was removed, and the procedure was repeated at a different interspace. If the catheter had been placed in the subarachnoid space, the case will be considered as missed case and was withdrawn from the study.

Figure 1: Consort flowchart
The adequacy of analgesia was assessed with a 10-cm linear visual analog scale (VAS), where 0 refers to no pain and a score of 10 refers to worst imaginable pain, immediately before epidural placement and at 5, 10, 15, 30, 60, 120, 180, and 240 min after injection of the study drug. Onset of analgesia was considered as time to achieve VAS <3. Duration of analgesia was taken as time between T = 0 and breakthrough pain, which was defined as VAS >3, or request for additional analgesia and was treated in a similar way in both groups by a bolus of 7.5 mL of ropivacaine 0.2% + Normal Saline up to volume 10 ml. Analgesia was considered to be adequate if the patient reports acceptable pain relief even if the pain score was not zero. If she says that analgesia is not adequate, an additional 7.5 ml of 0.2% ropivacaine + Normal Saline up to 10 ml volume was administered, and the analgesia was reassessed in the same manner 15 min later. If the analgesia is adequate after the administration of either 10 or 20 ml of medication, the patient was assessed for the presence of motor block in the lower extremities using a modified Bromage scale. If patient complained of pain (VAS >3) even after giving 20 ml of top up doses, she was excluded from the study as this indicates in most likelihood that the catheter was not present in epidural space. The total number of top up doses needed by the patient were also noted. The time of epidural bolus and further epidural top ups was also recorded. Injection-delivery interval (time from administration of study drug to delivery of fetus) was also noted.

The quality of analgesia throughout labor was assessed by the scoring system by Yadav P et al.[7] in which quality of analgesia was assessed by asking parturients to grade from zero to three [Grade 0 = Failure, Grade 1 = Incomplete, Grade 2 = Good, Grade 3- Excellent].

Block height was assessed by loss of sensation to cold using a spirit swab, Motor block using a Modified Bromage score: Grade 0, No motor block; Grade 1, Inability to raise extended leg, able to move knee and feet; Grade 2, Inability to raise extended leg and move knees, able to move feet; Grade 3, Complete block of motor limb, balance (Romberg’s sign), ability to stand (trial walk) were assessed twice at 15 minutes intervals and then motor Bromage score was assessed at 30-min interval until study was completed.

Vital parameters of the parturient—Heart rate, Blood Pressure, Respiratory Rate were recorded every 5 min for the first 30 min, then every 30 min until study was completed. Hypotension was defined as systolic blood pressure measurement <100 mmHg and/or >25% baseline decrease and was treated with 6 mg of mephentermine and additional doses if needed. Bradycardia was defined as heart rate <60/min and it was treated with Inj atropine 0.4 mg iv.

Fetal heart rate was recorded continuously on Cardiotocograph and any evidence of fetal heart rate decelerations were monitored by obstetricians who were blinded to study. Analysis compared the tracings obtained at least 30 mins before epidural placement and recorded during epidural analgesia. Fetal heart rate abnormalities if occurred were maintained accordingly. Neonatal assessment was done by assessing the APGAR score at 1 and 5 min.

Side effects such as nausea, vomiting, itching, sedation, bradycardia, or hypotension were also recorded.

The collected data was entered and analyzed by using MS Excel (Microsoft), Epi-info6 (AG Dean, KM Sullivan, MM Soe). Categorical data were presented as number (proportion) and compared with Chi-square test. Continuous variables were presented as Mean ± SD and compared using t-test. P value <0.05 was considered statistically significant.

**Results**

Demographically, patients in both the groups were comparable as depicted in Table 1.

Epidural analgesia was initiated when the mean cervical dilatation was 3.20 (95% CI; 2.87–3.528) in group F and 3.3 (95% CI; 3.034–3.626) in group FM. The effacement of cervix (%) at the time of initiation of labor analgesia was 57.50 (95% CI; 54.04–60.96) and 59.33 (95% CI; 56.6–62.06) in group F and group FM, respectively. On comparison, these data did not attain any statistically significant difference. (P > 0.05) [Table 1].

At the initiation of labor analgesia, the mean VAS score was 9.13 (95% CI; 8.86–9.40) in group F and 9.03 (95% CI; 8.66–9.39) in group FM (P = 0.660). The mean VAS score remained lower in group FM as compared to group F throughout the study period although statistically significant difference was reached only at 10 mins and 15 mins (P < 0.05) [Table 2].

The mean time of onset of analgesia (VAS ≤3) was significantly less in group FM as compared to group F respectively [mean 2.93 (95% CI; 2.64–3.24) in group FM] vs [mean 5.23 (95% CI; 4.83–5.63) in group F], P < 0.05 [Table 2].

The mean duration of analgesia of bolus dose, defined as the time until parturient request for additional analgesia, was found to be significantly more with addition of magnesium in group FM as compared to group F [107.2 (95% CI; 99.31–115.09) vs 89.90 (95% CI; 82.46–97.34), P = 0.002] [Table 2]. This also implies that the mean first top up time was also significantly more in group FM (107.2 ± 20.1) as compared to Group F (89.9 ± 21.3).

The quality of analgesia was better in group FM. 86.7% parturients of group FM considered analgesia as excellent while 13.3% labeled it as good. Whereas in group F, 63.4% parturients labeled it as excellent and 36.6% as good.
Height of sensory block achieved in both groups was comparable [9.27 (95% CI; 8.81–9.72) in group F vs 9.33 (95% CI; 8.84–9.81) in group FM, P = 0.840).

There was no motor block in any patient and therefore Modified Bromage Score was 0 in all the patients, Rhomberg’s sign, SLR (straight leg raising test) and trial walk. The time taken from injection of study drugs to the delivery of baby [Injection Delivery Interval] was similar in both the groups [142.73 (95% CI; 125.72–159.74) in group F vs 149 (95% CI; 137.61–160.39) in group FM, P = 0.279).

There was no statistically significant difference in hemodynamic variables i.e. HR, SBP, DBP between both the groups at any time intervals (P > 0.05).

The quality of maternal expulsive efforts as judged by obstetrician was comparable in both groups and did not have any statistical significance (P > 0.05). It was excellent in 33.3% of parturients in Group F and 50% in Group FM. The efforts were good in 63.33% and 50% of parturients in group F and FM, respectively [Table 3].

There was no statistical difference in the APGAR score of neonates between both the groups at 1 and 5 mins [Table 4].

None of the participants in both the groups had any side effects like nausea, vomiting, hypotension, hypersensitivity reaction, pruritis, respiratory depression, urinary retention, weakness in limbs, or shivering.

**Discussion**

Neuraxial adjuvants are used to improve or prolong analgesia, increase the speed of onset of neural blockade (reduce latency) and decrease the adverse effects associated with high doses of a single local anesthetic agent. Neuraxial adjuvants include opioids, sodium bicarbonate, vasoconstrictors, alpha-2 adrenoceptors agonists, cholinergic agonists, NMDA antagonists, and GABA receptor agonists.\(^4\)

This study demonstrated the adjuvant effect of Magnesium sulphate along with epidurally administered ropivacaine and fentanyl. In our study, there was a statistically significant difference in the time of onset of analgesia between both the groups. Moreover, all the patients in Group FM achieved a VAS score of ≤3 within 5 mins while only 63.4% of patients in group F achieved this within 5 mins. *Ghatak et al.\(^9\) (2010)* in their study on lower abdominal and lower limb surgeries observed that the time to onset of analgesia was least in magnesium adjuvant group (11.80 ± 3.21 mins), intermediate in clonidine group (16.93 ± 3.43 mins) and highest in control group (18.73 ± 2.79 mins). This difference in the groups was statistically significant. *Hasanein R et al.\(^1\) (2013)* observed that the onset of analgesia was shorter when magnesium was used as an adjuvant to bupivacaine and fentanyl [4.1 ± 1.6 mins in group 1 vs 6.3 ± 1.3 mins in group 2]. Earlier onset of analgesia with addition of epidural magnesium was also noted in studies by *Shahi V et al.\(^9\) (2014)* and *Pradhan A et al.\(^10\) (2017)*.

Noxious stimulation causes the release of neurotransmitters, which attach to different amino acid receptors, including NMDA receptors.\(^1\) Activation of these receptors produces influx of calcium into the cell and initiates a series of central sensitization and long-term potentiation in the spinal cord. NMDA receptors signaling may be important in determining the duration of acute pain.\(^1\) Magnesium non-competitively antagonizes the NMDA receptors and can have an effect on pain when used alone or as an adjunct to local anesthetic.\(^10\) It also accentuates the analgesic property of opioids.

In our study, the difference in VAS scores at 10 and 15 mins between the two groups was statistically significant. Thereafter the VAS score remained lower in group FM.
in comparison to group F but did not attain any statistical significance. In study by Hasanein R et al.[13] (2013), the difference in VAS scores became statistically significant at 10 mins. They also noted that at 10 and 30 mins, the number of patients having VAS ≤3 was significantly higher in the group where magnesium was used as an adjuvant with epidural bupivacaine as compared to the other group. Their results were similar to our study as the same amount of MgSO4 was used in both studies. Shabana R[14] (2014) Nagre AS[15] (2017) also reported that VAS was significantly lower in patients who received combined levobupivacaine and MgSO4 as compared to those who received levobupivacaine alone.

In recent years, intrathecal administration of magnesium has been reported as an effective analgesic and as an adjunct to intrathecal lignocaine anesthesia. It is possible that analgesic effect of magnesium occurred at the supra-spinal level and might be related to its systemic absorption. But Ko SH et al.[16] failed to observe postoperative analgesic effect with 50 mg/kg intravenously administered magnesium sulphate, and they reported that perioperative administration of magnesium did not increase cerebrospinal fluid (CSF) magnesium concentration. When compared with these doses, our epidural dose is too low for the systemic effect. Although there is no study about the physicochemical properties of magnesium in relation to its penetration to spinal meninges, another probable mechanism for epidural usage may be related to the diffusion of magnesium from the dura. The addition of intrathecal magnesium 50 mg to spinal anesthesia prolongs the period of anesthesia without additional side-effects.[8]

The mean duration of analgesia of bolus dose in our study was statistically significantly higher in group FM compared to group F (P = 0.002). Hasanein R et al.[13] (2013) also found that the duration of analgesia was significantly prolonged with the addition of epidural magnesium sulphate to bupivacaine and fentanyl (169 ± 50 min vs 105 ± 41 mins). Shahi V et al.[8] reported in their study that the time from epidural medication to first epidural top up was longest (587.8 ± 64.3 min) in dexmedetomidine group followed by magnesium group (266.3 ± 60.9 min) and control group (157.3 ± 23.8 min). The differences among groups were highly significant (P < 0.001). Although supplementation of epidural dexmedetomidine leads to significantly prolonged duration of analgesia but magnesium added as an adjuvant also potentiates the duration of analgesia when compared to control group (0.5% bupivacaine alone). Shabana R et al.[14] and Nagre AS et al.[15] in their studies also noted prolongation of duration of analgesia with addition of magnesium to epidurally administered levobupivacaine.

Therefore, all the studies quoted earlier, using magnesium as an adjuvant in epidural analgesia supports our study. Although no study has been done so far using MgSO4 with ropivacaine and fentanyl for epidural analgesia, so we do not have any reference point for this.

In our study all patients in both the groups had a Modified Bromage score of 0 at all the times. Rhomberg’s sign was negative in all the patients in both groups. All patients tested negative for the Straight Leg Raising test. Trial walk was positive in all the patients in both the groups throughout the study period. Chhetty YK et al.[16] (2013) and Hasanein R et al.[13] (2013) also reported no patient with motor blockade in their respective studies which was in accordance with our study. The absence of motor block is attributed to the use of very low concentration of local anesthetic agent. At low concentration, the Aβ and C fibers carrying pain are blocked whereas the Aα fibers responsible for motor block are spared. Moreover, ropivacaine causes less motor block as compared to bupivacaine or levobupivacaine.

Obstetrician graded 33.33% of parturients in group F and 50% of parturients in group FM as having excellent expulsive efforts. Similarly, 63.33% parturients in group F and 50% in group FM were considered as having good expulsive efforts. The difference in quality of maternal expulsive efforts was statistically insignificant (P > 0.05).

Epidural analgesia did not appear to have an immediate effect on neonatal status as determined by APGAR score in our study. Similar observations were made by Hasanein R et al.[13] and chhetty YK et al.[16] in their studies.

An ideal labor analgesia technique should not have any unpleasant side effects, but the use of various drugs at times may lead to their ill effects. In our study, no parturient had hypotension, hypersensitivity reaction, pruritis, nausea, vomiting, urinary retention, respiratory depression, weakness in the limbs or shivering.

Limitations
1. In our study, epidural bolus along with subsequent top ups on maternal request were given as facilities for continuous epidural infusion and PCEA were not available in our institute
2. A comparison of intermittent boluses versus continuous infusion technique would give a better estimation of local anesthetic consumption.

Conclusion
Addition of 50 mg of magnesium sulfate with ropivacaine and fentanyl shortens the time to onset and prolong the duration of analgesia without any maternal and neonatal adverse outcome.

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Nil.
Conflicts of interest

There are no conflicts of interest.

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