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Research Article

The value of epidural magnesium sulfate as an adjuvant to bupivacaine and fentanyl for labor analgesia

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KEYWORDS

Analgesia;
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Abstract *Objective:* We conducted this clinical study to assess the adjuvant effects of single dose magnesium sulfate (Mg) when administered epidurally during labor with fentanyl and bupivacaine.
Methods: Eighty healthy nulliparous women in labor requesting epidural analgesia were divided into two groups. Group 1 received bupivacaine 0.125% with magnesium sulfate 50 mg and fentanyl 50 μg as a loading dose; group 2, received bupivacaine 0.125% and fentanyl 50 μg only. Hemodynamic parameters, motor and sensory evaluation, cervical dilation at time of consenting, the progress of labor, the visual analog pain score (VAS), Apgar score, cord blood acid base status, side effects as nausea, vomiting, itching and respiratory depression were recorded. Fetal heart rate tracings were also documented.
Results: Epidural single dose magnesium sulfate added to bupivacaine and fentanyl in labor resulted in significantly faster onset and longer duration of epidural analgesia (169 ± 50 min) in comparison to those patients who received bupivacaine and fentanyl only (105 ± 41 min), also there was a significant reduction in the number of women requiring additional boluses of bupivacaine when Mg was added ($P = 0.016$). The two groups had no significant differences as regards maternal satisfaction score, maternal and neonatal adverse effects.
Conclusion: Magnesium sulfate added to bupivacaine and fentanyl for labor epidural analgesia resulted in faster onset, longer duration of action and reduced the break through pain.

1. Introduction

Epidural analgesia using local anesthetics is the best method for painless labor, because of its effective pain relief, less maternal stress response, better parturient satisfaction, and the ability to provide anesthesia. The quality of analgesia is better with the combined use of a local anesthetic and an opioid. However, clinical trials aiming to minimize the side effects

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related to epidural local anesthetic administration as motor impairment and sympathetic blockade were and still need to be done [1–4].

Magnesium, the fourth most common cation in the body, has postsynaptic N-methyl D-aspartate (NMDA) calcium channel blocker properties, and has been used successfully to potentiate opioid analgesia and to treat neuropathic pain in animals [5]. Tramer et al. did the first clinical study demonstrating that the administration of magnesium sulfate in the perioperative period was associated with less analgesic requirements in the postoperative period [6]. Other studies examined different routes of magnesium administration such as the intravenous or the intrathecal route, and were found to improve anesthetic and analgesic quality [7]. Epidural magnesium was found to reduce the use of postoperative analgesia without increases in side effects [8,9].

The addition of magnesium to spinal bupivacaine–fentanyl anesthesia improves the duration of spinal analgesia for labor without any side effects [10].

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 [11].

To our knowledge, there were no previous clinical studies which examined the effect of magnesium sulfate administered epidurally as an adjunct to epidural bupivacaine and fentanyl in labor. Therefore, we conducted this clinical study to determine the effects of adding single dose of magnesium sulfate to epidural bupivacaine and fentanyl for labor analgesia.

2. Material and methods

After approval of the Ethics Committee and obtaining informed written consent, we studied 80 healthy (ASA physical status I or II) nulliparous women in active labor. This study was conducted at Saad Specialist Hospital, Saudi Arabia, in the period between January 2010 till January 2012. Women requesting epidural analgesia were considered for inclusion in this study if they presented with a single pregnancy of more than 37 weeks gestation, in early labor (cervix dilation < 5 cm) with normal fetal heart rate. Excluded patients included those with pregnancy-induced hypertension, multiple or high risk pregnancies, breech presentation, multiparty, and gestational diabetes.

Patients were randomly allocated into one of two groups. Group 1 received: 8 mL of bupivacaine 0.125%, Mg sulfate 50 mg (0.5 mL of 10% solution), fentanyl 50 μg (1 mL); group 2 received: 8 mL of bupivacaine 0.125%, fentanyl 50 μg (1 mL) and 0.5 mL normal saline. Randomization was performed by random computer allocation with numbered envelopes. The syringe was prepared by a technician anesthetist who was not involved in the study at the time of randomization. Placement and management of the epidural labor analgesia, and data recordings were done by an anesthesia team who was blinded to group allocation.

Intravenous fluid loading with 500 mL of Ringer's lactate solution was given. Patients were then placed in the sitting position, and local anesthesia infiltration of skin and subcutaneous tissues was done at the level of L2–3 or L3–4 with 2–3 mL of lidocaine 2%. Then, the epidural space was localized with the loss of resistance to air technique using an 18-gauge Tuohy needle. A 20-gauge multi-orifice epidural catheter was then inserted 4 cm into the epidural space in a cephalic direction and aspirated for detection of cerebrospinal fluid or blood. After the catheter was fixed, patients were repositioned with left uterine displacement, and 3 mL of 2% lidocaine with 15 μg of epinephrine as a test dose was injected. In the absence of intravascular or intrathecal placement of the catheter, the study drug was injected 5 min after the test dose.

The time of the injection of study drug was considered as $T = 0$ and assessments were done accordingly. Pain was assessed with a 10-cm linear visual analog scale (VAS) 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 $\leqslant 3$. 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 treated in a similar way in all groups. Management of breakthrough pain was done by a bolus of 8 mL of bupivacaine 0.125% followed by a continuous infusion of bupivacaine 0.125% and fentanyl 2 μg/mL at rate of 10 mL/h and additional top-up doses of 6–8 mL of bupivacaine 0.125% if required.

A maximum of three top-up doses in the first 4 h of the study was given before exclusion of the case from the study. On the first postpartum day, maternal satisfaction was assessed with a 10-cm VAS by an observer blinded to the study drug, 10 being very satisfied.

Sensory levels were checked with changes to cold (ice) at 5, 10,15,30,60, 120, 180, and 240 min after study drug injection. Motor block using a modified Bromage scale (0 = no block, 1 = inability to raise extended leg, 2 = inability to flex knee, and 3 = inability to flex ankle and foot) were also recorded at the same time intervals. With a Bromage score $\geqslant 2$, the infusion rate of bupivacaine was reduced until the Bromage score was found to be $\leqslant 1$. Maternal monitoring included arterial blood pressure and continuous heart rate recording. Cervical dilation at entry of study, duration of first and second stages of labor was recorded. Hemodynamic parameters, motor, and sensory assessments were discontinued after 4 h, but recording of total and hourly administration of the drugs was continued until delivery. Side effects, such as nausea, vomiting, itching, sedation, bradycardia or hypotension were recorded. Hypotension was defined as systolic blood pressure measurement < 100 mmHg and/or $\geqslant 25\%$ baseline decrease and was treated with 5–10 mg of ephedrine and additional doses if needed.

Fetal heart rate was continuously recorded on a cardiotocograph (Hewlett–Packard 80300A, Hewlett Packard, Palo Alto, CA), and were monitored by obstetricians who were blinded to group allocation and rechecked again postpartum for detection of fetal heart rate abnormalities. Analysis compared tracings obtained at least 30 min before epidural and recorded during epidural analgesia. Fetal heart rate abnormalities such as late decelerations, bradycardia (defined as fetal heart rate < 100 bpm lasting for 5 min or more), and decreased fetal heart rate variability (at least two accelerations of 15 bpm lasting 15 s for 40 min) were noted. Fetal conditions were managed according to the situation by oxygen, left or right lateral uterine displacement, ephedrine if needed, cessation of oxytocin, and possible tocolytic treatment, umbilical cord blood–gas were also recorded. Apgar scores at 1, 5 and 10 min were also recorded. Clinical evaluation at 24 h after

Table 1 Demographic data and progress of labor in both groups.

	Group 1 (n = 38)	Group 2 (n = 40)	P value
Age (years)	26.2 ± 2.3	25.3 ± 2.5	0.103
Weight (kg)	73 ± 3.6	75 ± 6.3	0.091
Height (cm)	157 ± 7	161 ± 3	0.001*
Gestational age (weeks)	39 ± 1.5	39 ± 2.1	1.00
Cervical dilatation (cm)	4.2 ± 0.8	4.6 ± 1.1	0.071
Duration of the 1st stage (min)	213 ± 110	229 ± 103	0.509
Duration of the 2nd stage (min)	110 ± 29	120 ± 21	0.084

Values are presented as mean ± SD.
* P value <0.05.

Table 2 Analgesia characteristics and satisfaction score.

	Group 1 (n = 38)	Group 2 (n = 40)	P value
VAS before the epidural	8.8 ± 1.1	9.0 ± 1.3	0.467
VAS at 5 min	6.4 ± 2.47	6.6 ± 1.3	0.075
Patients with VAS ⩽ 3 at 5 min (n, %)	4 (10.5%)	5 (12.5%)	0.935
VAS at 10 min	4.1 ± 1.6	6.3 ± 1.3	<0.01*
Patients with VAS ⩽ 3 at 10 min (n, %)	18 (47.4%)	10 (25%)	0.040*
VAS at 30 min	0.5 ± 2	2.5 ± 0.3	<0.01*
Patients with VAS ⩽ 3 at 30 min (n, %)	38 (100%)	34 (85%)	0.039*
Top-up doses in 4 h (mg)	5.2 ± 6.5	9.7 ± 6.9	0.004*
Analgesia duration (min)	169 ± 50	105 ± 41	<0.01*
Satisfaction score	8.6 ± 1.2	8.2 ± 0.8	0.086

Data are presented as mean ± SD, number of patients or percentage.
* P < 0.05.

birth was performed in all neonates by pediatricians blinded to group allocation.

2.1. Statistical analysis

Data were statistically described in terms of mean ± standard deviation (±SD), or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student t test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. Yates correction equation was used instead when the expected frequency is less than 5. P values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

3. Results

Eighty women were included in this study; two patients were excluded as one delivered by cesarean section due to failure to progress, and the other one required replacement of the catheter in the 2nd hour due to catheter displacement. Both groups were comparable regarding demographic data, cervical dilation upon entry, and duration of first and second stages, although there was statistically significant difference in the height (P = 0.001) between both groups, but this difference was not clinically significant (Table 1).

The onset of analgesia was shorter in group 1, VAS becoming significantly less at 10 min (Table 2). At 10 and 30 min the number of patients having pain score < or =3 was significantly higher in group 1 than in group 2 (Table 2). Duration of analgesia was significantly prolonged with the addition of magnesium sulfate, (169 ± 50) min in comparison to only (105 ± 41) min in group 2 (Table 2).

The number of patients requiring additional boluses of bupivacaine during the 4 h of the study is represented in Fig. 1. The additional bolus dose was (bupivacaine 0.125% 6–8 mL). After the start of the study 21 patients in group 1 required no additional doses during 4 h study, versus 10 patients in group 2, which was significantly different (P value 0.016), while 14 patients in group 1 versus 21 patients in group 2 required only one additional bolus dose (P value 0.165), and 3 patients in group 1 versus 9 patients in group 2 required more than one bolus dose (P value 0.141) (Fig. 1).

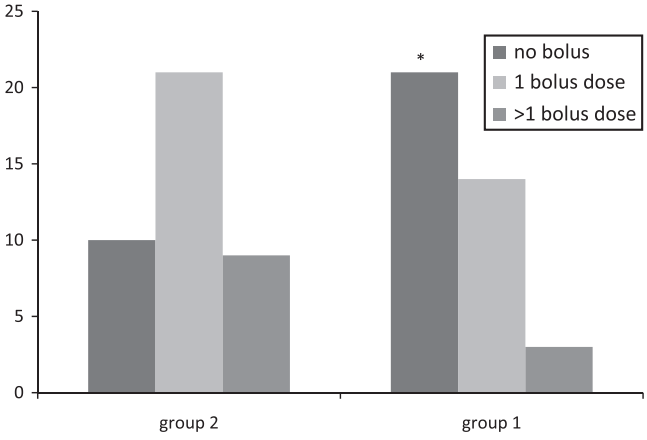
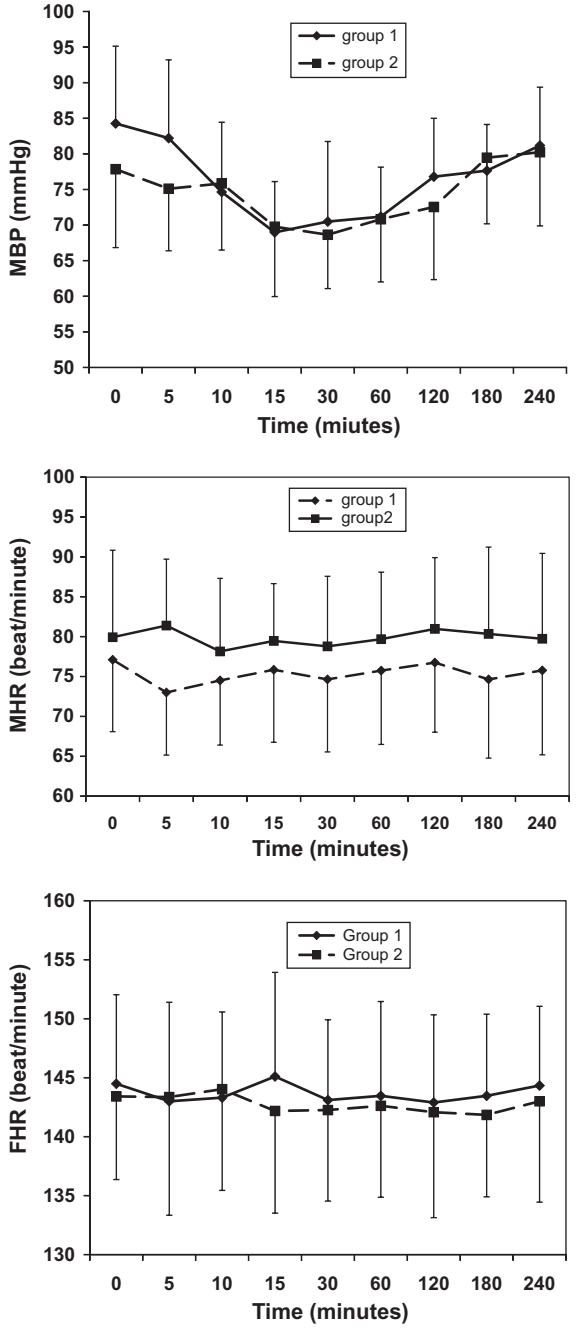


Figure 1 The number of women requiring additional boluses of bupivacaine during the 4 h of the study: *P < (0.016).



Values are expressed as mean ± SD. There was no significant difference between the two groups at any time points ($p > 0.05$).

Figure 2 Changes in maternal heart rate (MHR), maternal blood pressure (MBP), and fetal heart rate (FHR) in each group.

Although there was a tendency at higher satisfaction score in group 1 in the 1st postpartum day, there was no statistically significant difference between the two groups; group 1: (8.6 ± 1.2) versus (8.2 ± 0.8) in group 2, (*P* value 0.086).

3.1. Maternal data

Maternal hemodynamic data are shown in Fig. 2. There was no significant difference in maternal MAP, HR, and neonatal HR between the two groups at any time points ($P > 0.05$).

3.2. Side-effects

Although no significant difference was seen, there was a trend that the incidence of side-effects (pruritus and shivering) was higher in group 2. No significant difference was observed in other side-effects such as nausea, vomiting, motor block, respiratory depression, and hypotension between the two groups. Furthermore, none of the parturient in both group required certain treatment during labor (Table 3).

3.3. Neonatal data

Neonatal data are presented in (Table 4). Umbilical arterial blood pH, umbilical arterial blood oxygen partial pressure, arterial blood carbon dioxide partial pressure and base deficit, lactate concentrations, and Apgar scores at 1, 5 and 10 min were comparable between the two groups. Although the neonatal birth weight was significant statistically between both groups but clinically it was within the normal range.

4. Discussion

This study demonstrated the additive analgesic effect of epidural magnesium sulfate, administered with bupivacaine and fentanyl.

In our study, onset of analgesia was shorter among patients receiving magnesium sulfate. We defined good analgesia as a VAS $\leqslant 3$ and recorded VAS at 5 and 10 min to determine the number of cases reporting VAS scores $\leqslant 3$ at these time intervals. Our results showed that the addition of magnesium has an effect both on the number of women with a VAS $\leqslant 3$ and on the mean VAS at 10 min. Also, the addition of magnesium to 0.125% bupivacaine prolonged the analgesia by approximately 1 h; (169 ± 50 min) versus (105 ± 41 min) in the group received magnesium and the group who did not receive magnesium respectively. Also, the break through pain and the top up doses needed in 4 h were reduced significantly by adding magnesium to epidural bupivacaine and fentanyl.

A study was done to determine the effects of adding magnesium sulfate to epidural bupivacaine and fentanyl in patients undergoing elective caesarean section using combined spinal-epidural anesthesia, patients who received magnesium had good intraoperative conditions as well as good quality of postoperative analgesia [12].

Magnesium was compared with clonidine, as an adjuvant to epidural bupivacaine in lower abdominal and lower limb surgeries. Rapid onset of surgical anesthesia without any side-effects occurred with magnesium concluding that magnesium may be a good alternative to epidural bupivacaine [13].

Noxious stimulation causes the release of neurotransmitters, which attach to different amino acid receptors, including NMDA receptors, Stimulation of these receptors results in entry of calcium into the cell and causes a series of central sensitization and long-term potentiation in the spinal cord [14]. Excitation of NMDA receptor may be of value in determining the duration of acute pain [15]. Therefore, antagonists of NMDA receptor help in the prevention and treatment of post-traumatic pain [16]. Non-competitive NMDA receptor antagonists have an effect on pain when used alone, but it has also been shown that they can have the analgesic properties of opioids [17,18]. In this way, the injection of both mag-

Table 3 Maternal data in both groups.

	Group 1 (n = 38)	Group 2 (n = 40)	P value
Pruritus (n, %)	1 (2.6%)	3 (7.5%)	0.645
Nausea (n, %)	3 (7.9%)	4 (10%)	0.943
Vomiting (n, %)	1 (2.6%)	2 (5%)	0.964
Hypotension (n, %)	3 (7.8%)	4 (10%)	0.531
Respiratory depression (n)	0	0	1.000
Bromage scale (n): 0, 1, 2, 3	37, 1, 0, 0	33, 5, 2, 0	0.089

Values are presented as number or percentage.

Table 4 Neonatal data in both groups.

	Group 1 (n = 38)	Group 2 (n = 40)	P value
Birth-weight (kg)	3.3 ± 0.4	3.5 ± 0.3	0.014*
Apgar score at: 1, 5 and10 min	<7	0/0/0	1.000
Umblical arterial blood acid–base status			
pH	7.37 ± 0.03	7.37 ± 0.03	1.000
PO_2 (mmHg)	15.2 ± 4.2	15.0 ± 2.2	0.791
PCO_2 (mmHg)	52 ± 5	53 ± 2	0.245
Base excess (mmol/L)	−3.20 ± 2.4	−3.03 ± 2.5	0.760
Lactate concentration (mmol/L)	4.1 ± 1.3	4.3 ± 1.1	0.456

Values are presented as mean ± SD.
* P value <0.05.

nesium and an opioid is expected to cause a significant reduction in opioid administration for postoperative pain relief. Many studies showed that systemic administration of magnesium is accompanied by reduction in analgesic requirement and less postoperative pain [15,19]. The proper mechanism of the interaction between the NMDA receptor complex and opioid anti-nociception has not been cleared, but it has been shown that magnesium supplement helps the analgesic effect of opioids and delays the development of tolerance [18,20].

No study showed the physicochemical properties of magnesium in relation to its penetration to the spinal meninges, but there may be a mechanism for epidural usage, which may be related to its diffusion from the dura mater.

In our study, epidural administration of magnesium had an additive analgesic effect to bupivacaine and fentanyl during labor analgesia, in comparison with the bupivacaine fentanyl only.

In two cases reported by Goodman et al. [21], larger doses (8.7 g, 9.6 g) of magnesium sulfate were accidentally administered into the epidural space and did not result in any neurologic complication. Also another report showed that an accidental intrathecal injection of 1000 mg of magnesium resulted in a transient motor block followed by a complete resolution with no neurological complication at long-term follow-up [22].

We reported neither episodes of maternal bradycardia nor sedation in either group probably due to small dose of opioid used in both groups.

In our study the addition of magnesium sulfate to epidural bupivacaine and fentanyl did not seem to impact fetal heart rate or fetal outcome, as monitored by Apgar scores and umbilical cord blood–gas values.

In other studies, it was reported that the addition of intrathecal magnesium 50 mg to spinal anesthesia is safe and prolongs the period of anesthesia without additional side-effects [20,23].

Also, Banwait and colleagues had evaluated the effect of single epidural bolus dose of magnesium when added to epidural fentanyl for postoperative analgesia in 60 patients underwent total hip replacement under combined –spinal epidural anesthesia and they concluded that; the administration of epidural magnesium (75 mg) with epidural fentanyl (1 μg/kg) for postoperative analgesia resulted in significantly increased duration of analgesia when compared with epidural fentanyl (1 μg/kg) alone and that the addition of magnesium reduces the requirement of breakthrough analgesics with no increased incidence of side effects [24].

The concern of neuromuscular blockade after intravenous injection of magnesium is emphasized in the literature [25], but no effect was noted on motor function in our study (as tested by modified Bromage score) when magnesium was administered epidurally.

Magnesium role in preventive analgesia was studied in patients underwent abdominal hysterectomy by continuous infusion of magnesium sulfate epidurally before the start of anesthesia and it was found to provide an analgesic-sparing effect which improved the postoperative analgesia in a time period that exceeded five half-lives of the drug without any increase in the adverse effects [26].

In conclusion, single dose epidural magnesium is a useful adjuvant to bupivacaine 0.125% and fentanyl in labor epidural analgesia. Further studies should point to different dosages of magnesium and different surgical settings.

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