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Original Article

The Effect of Intravenous Magnesium Sulphate Treatment on the Spinal Anaesthesia Produced by Bupivacaine in Pre-eclamptic Patients

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Abstract

Objective: In our study, the effect of intravenous magnesium sulphate in normal and pre-eclamptic patients on spinal anaesthesia produced by bupivacaine was investigated.

Methods: Sixty-four pregnant (32 normal and 32 pre-eclamptic) were accepted in this study. Pregnants were divided into four groups as patients given intravenous magnesium sulphate and as control. Spinal anaesthesia was induced with 12.5 mg 0.5% hyperbaric bupivacaine. Intraoperative and postoperative haemodynamic variables, sensorial block periods, onset times of sensorial and motor block, maximum sensorial block levels, the time to reach maximum block level, Bromage scores, consumptions of intraoperative analgesic and ephedrine, the quality of anaesthesia, the duration of spinal anaesthesia and magnesium levels in blood and cerebrospinal fluid were measured and recorded.

Results: The level of magnesium in blood and cerebrospinal fluid was significantly higher in the group given magnesium in pre-eclamptic patients ($p<0.01$). Onset of sensory block times were significantly longer in intravenous magnesium group than in groups 1, 2 and 3 ($p<0.05$). Onset of motor block times were significantly longer and the duration of anaesthesia was shorter in groups given magnesium ($p<0.05$). Although the quality of anaesthesia was similar, supplemental analgesic consumption was significantly higher in pre-eclamptic pregnants given magnesium sulphate than in pre-eclamptic pregnants who were not given magnesium sulphate ($p<0.05$).

Conclusion: Intravenous magnesium sulphate treatment during the spinal anaesthesia produced by bupivacaine extended the onset of sensory and motor block times, shortened the duration of spinal anaesthesia and therefore led to early analgesic requirement.

Key Words: Spinal anaesthesia, magnesium sulphate, bupivacaine, pre-eclampsia

Introduction

The etiology of preeclampsia is a pregnancy pathology that has not yet been fully explained. It is characterized with hypertension, proteinuria and generalized oedema. Because of the elevation in convulsion threshold and antihypertensive effects, magnesium sulphate ($MgSO_4$) is one of the selected drugs in the symptomatic treatment of patients with preeclampsia.

Magnesium level of homeostatic mechanisms and cerebrospinal fluid (CSF) in normal physiology is kept constant within narrow limits (1). Studies have shown that the blood-brain barrier is disrupted, and the magnesium administered intravenously (iv) can pass to spinal space in preeclamptic patients (2, 3). Although magnesium is not a fully effective analgesic, it plays a role in the processing and modulation of pain in medulla spinalis as a N-methyl-D-aspartate (NMDA) receptor antagonist. It has been shown in our previous study that the effects of intrathecal $MgSO_4$ can change the analgesic effects of opioids (4). In addition, it has been shown that when magnesium is administered iv in rats, it stimulates liver microsomal enzyme induction and reduces the effects of local anaesthetics in amide structure (5). However, there is no available study on the effects of iv administered magnesium on the effectiveness of bupivacaine administered during spinal anaesthesia in preeclampsia patients.

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In our study, the effect of intravenous magnesium sulphate in normal and preeclampsia patients on spinal anaesthesia induced by bupivacaine was investigated.

Methods

This study was performed after receiving the approval of Cukurova University Faculty of Medicine Ethics Committee and Ministry of Health. The oral and written informed consents of the patients were also obtained. A total of 64 patients in American Society of Anaesthesiology (ASA) I-II groups and who would give birth by elective caesarean section under spinal anaesthesia were included. Patients who are pregnant with systemic maternal disease (cardiac disease, hepatic-renal disease, bleeding disorders, etc.), foetal abnormalities, placental localization anomalies, unable to receive regional anaesthesia and allergic to any of the study drugs were excluded from the study.

Sixty-four pregnant women (32 term pregnancy and 32 preeclampsia cases) were included in this study, and they were divided into four groups with 16 cases in each group. To group 1 (n=16, term pregnancy), 100 mL of 5% dextrose in 15 min; to group 2 (n=16, term pregnancy), $MgSO_4$ (60 mg kg^{-1}) in 100 mL 5% dextrose in 15 min; to group 3 (n=16, preeclampsia), 100 ml of 5% dextrose in 15 min and to group 4 (n=16, preeclampsia) $MgSO_4$ (60 mg kg^{-1}) in 100 mL of 5% dextrose in 15 min were administered iv 45 min before anaesthesia induction. The diagnosis of preeclampsia and iv $MgSO_4$ treatment indication for preeclampsia patients were made by the obstetrics team.

Vascular access was established in all patients who are taken into the operating room following a 6-8 h period of fasting; 2 mL of blood sample was sent to the laboratory to detect the level of magnesium in the blood and 0.9% NaCl infusion was started for hydration. All cases were monitored via electrocardiography, non-invasive automatic blood pressure monitor (Drager Infinity Kappa) and pulse oximetry (Nellcor N-600X Oximax). Systolic and diastolic blood pressures (SAP and DAP), heart rate (HR) and oxygen saturation (SpO_2) were measured and recorded. Age, weight, height, parity, gravida and gestational week data of pregnant women were recorded.

Spinal block was induced in all our patients in sitting position through L3-L4 or L4-L5 intervertebral space. After wiping the area with an antiseptic solution, skin and subcutaneous infiltration anaesthesia with 1% lidocaine was administered. Following local anaesthesia, a 25 gauge (G) quincke-type spinal needle, inserted into a guiding needle, was advanced into the subarachnoid space. CSF sample (0.5 mL) was sent to the laboratory to measure the CSF magnesium levels. Hyperbaric bupivacaine (12.5 mg) was injected into the subarachnoid space to all groups for approximately 30 s. Following intrathecal injection and placing a pillow under the left hip, patients were positioned in the 15-20° supine position and 4-6 mL min^{-1} oxygen was administered via a mask until the birth of the baby.

During the operation, the onset and duration of sensorial and motor block, maximum block levels, the duration to reach maximum block level and the duration of spinal anaesthesia were monitored and recorded in all groups. The pin-prick test was used to assess sensorial block. The absence of pain in the T^{10} level with the pin-prick test was recorded as the onset of sensorial block. Until the 20th min after the spinal injection, the pin-prick test with 1-min intervals was used to determine the last dermatome where no pain was felt and maximum sensorial block level and time were determined. The time between spinal injection and two dermatome regressions in maximum block level was recorded as sensorial block level. Modified Bromage Scale was used to assess motor block. After the spinal injection, the time until the Bromage score reached 3 was recorded as the onset of motor block. After the spinal injection, the time until the motor block was 0 again was recorded as motor block level. Pain assessment of the cases was performed with the verbal rating scale (VRS). VRS values were measured up to the 120th postoperative minute from the moment spinal injection had been induced and the first moment (VRS >3) that the pain was felt on the surgical incision site was determined as the duration of spinal anaesthesia. Anaesthesia quality was evaluated in four forms as excellent, good, fair and poor (1=excellent: no pain, patient is comfortable; 2=good: no pain, patient is restless; 3=good with sedation: requires mild sedation and 4=poor: moderate-to-severe pain or discomfort requiring general anaesthesia).

All side effects pertaining to spinal anaesthesia (nausea, vomiting, hypotension, bradycardia, itching) and SAP, DAP, HR and SpO_2 values were monitored throughout the operation and recorded intraoperatively in the 1^{st}, 5^{th}, 15^{th}, 30^{th}, 45^{th}, and 60^{th} min and postoperatively in the 120^{th} min. When the HR of the patient was <50 beat min^{-1}, it was intervened with 0.5 mg atropine. Ephedrine (10 mg) was administered when SAP falls below 100 mmHg or below 20% of the preoperative value. For pregnant women with intraoperative VRS >3 or who request additional analgesic, 0.5–1.5 μg kg^{-1} of fentanyl was intravenously administered. During the intraoperative period, the total amount of fluid, total dose of ephedrine and additional analgesic requirements of the patients were recorded. The APGAR scores were evaluated and recorded in the 1^{st} and 5^{th} min by a paediatrician.

The patients taken to the recovery unit at the end of the operation were monitored for 120 min. The patients were sent to their clinics after the haemodynamic parameters were found stable, the motor block completely disappeared (Bromage 0) and the sensorial block regressed until T_{12} level. On the first

postoperative day, postoperative analgesia consumptions and doses, head and back pain and the presence of motor and neurological deficits of the patients were evaluated and recorded by anaesthesiologists without knowing which group they were in.

Statistical analysis

Power analysis was used to provide reliability in our data and to determine the number of patients. The primary objective was defined as a 20% difference in the duration of spinal anaesthesia. Power (0.9) with a degree of significance (α) calculated to be 0.01 was estimated for all four groups. Statistical Package for the Social Sciences, (SPSS Inc., Chicago, IL, USA) software package was used for statistical analysis. Categorical measurements were summarized as number and percentage; continuous measurements were summarized as mean and standard deviation. Kruskal-Wallis test was used for time-dependent comparison of the measurements between groups. In these comparisons, Mann-Whitney U test, corrected with post hoc test (Bonferroni), was used where statistical difference was present in dual sub-group comparisons. For postoperative follow-up examinations, repeated measurement analysis was used to evaluate whether there were changes in the course of measurements between the groups. For the comparison of the categorical measurement between the groups, chi-square test statistics was used. Statistical significance level in all tests was considered to be <0.05.

Results

When the demographic data of the patients in the groups was compared, no statistically significant difference was determined in terms of age, height, parity, gravida, gestational week and duration of surgery (Table 1). When compared in terms of intraoperative haemodynamic data, SAP and DAP values were statistically higher in groups 3 and 4 than groups 1 and 2 in the 1st, 5th, 15th and 30th min (Table 2).

Following spinal anaesthesia, the onset of sensorial block was significantly longer (p<0.05) in group 4 compared with that in other groups, whereas it was determined that maximum block level and the duration of motor block were similar in all groups and no statistical difference was present. The time to reach maximum block levels were significantly longer in group 4 compared with that in group 1 (p=0.02) and group (p<0.001), and in Group 3 compared to Group 2 (p=0.01). Using pin-prick, when sensorial block duration and anaesthesia time were compared, sensorial block duration was significantly shorter (p<0.023) in group 2 compared with that in group 1. The spinal anaesthesia time was statistically shorter in group 4 compared with that in group 3 (p<0.05). When motor block levels were compared using Bromage scale, the onset of motor block was significantly longer in groups 2 and 4 compared with that in groups 1 and 3 (p<0.03) (Table 3).

When magnesium sulphate levels are considered, $MgSO_4$ in blood levels are significantly higher (p<0.001) in groups 2 and 4 compared with those in groups 1 and 3. $MgSO_4$ in CSF levels, on the other hand, were significantly higher in group 4 compared with those in groups 1, 2 and 3 (p<0.01). It was determined that $MgSO_4$ in CSF levels in groups 1, 2 and 3 was not statistically different (Table 4).

Given the amount of intraoperative intravenous fluids, ephedrine consumption, adverse effects and anaesthesia quality, no statistically significant difference was detected between the groups. It was determined that intraoperative additional analgesic consumption was statistically higher in group 4 cases than in group 2 cases (p=0.017) (Table 5).

Table 1. Demographic data

	Group 1 (n=16)	Group 2 (n=16)	Group 3 (n=16)	Group 4 (n=16)
Age (year)	32.3±4.1	30.4±4.5	30.2±4.1	28.5±5
Weight (kg)	77.8±6.1	83.1±13.9	85.2±17.0	83.3±13.9
Height (cm)	161.3±5.5	164.1±6.9	162.7±4.1	162.2±6.7
Parity	2.1±1.2	2.1±0.9	1.8±0.9	2.2±1.6
Gravida	2.1±1.3	2.6±1.4	2.3±1.3	2.4±1.7
Gestational week	38.2±0.8	38±1.1	37.5±1.1	37.1±1.6
Surgery time	35.0±11.7	32.6±6.6	42.6±11.6	40.8±12.5

All values were given as mean±standard deviation.

Table 2. Intraoperative systolic and diastolic blood pressures

Time	Group 1 (n=16)	Group 2 (n=16)	Group 3 (n=16)	Group 4 (n=16)
Preoperative				
SAP	124.3±13	128.8±18.7	158.3±12.6	158±17
DAP	79.9±14	80.1±10.4	95.7±18.2	102.1±10.1
1st min				
SAP	106.9±20.9	108±17.8	129.4±20.8*,†	143.2±21.4*,†
DAP	63.6±18.1	55.7±11.8	77.5±20.8*,†	92.3±15.9*,†
5th min				
SAP	103.5±15.3	96.5±9.2	109±22.2*,†	125.5±20.7*,†
DAP	53.5±13.2	45.9±6.8	57.5±17.4*,†	76.8±21.3*,†
15th min				
SAP	100.2±9.6	99.3±13.3	108.6±13.1*,†	107.8±29.9*,†
DAP	49.9±8.6	46±10.6	57.2±14.1*,†	69±18*,†
30th min				
SAP	94.9±3.2	100.4±12.5	108.8±12.3*,†	116.3±19.3*,†
DAP	47.2±8	46.3±10.3	59.8±14.1*,†	65.5±20.1*,†

All values were given as mean±standard deviation.*When compared to group 1, †When compared to group 2; SAP: systolic artery pressure; DAP: diastolic artery pressure

When APGAR scores of new-borns were compared, 1st min APGAR scores were significantly lower in groups 2, 3 and 4 (p<0.041, p=0.004 and p=0.017, respectively) compared with those in group 1. On the other hand, 5th min APGAR scores were significantly lower only in group 4 compared with those in Group 1 (p<0.032) (Table 6).

Discussion

In the regional administration, the increase in CSF concentrations caused by iv administered $MgSO_4$ and the results of the interaction of spinal local anaesthetics and opioids were often the subject of studies. Ko et al. (6) reported that intravenous $MgSO_4$ infusion does not change CSF magnesium level in normal patient groups. Thurnau et al. (3) reported that there is small but statistically significant increase in CSF magnesium levels in preeclampsia patients who were administered $MgSO_4$. Therefore, in our study, both blood and CSF magnesium concentrations are evaluated and tested to see whether iv administered $MgSO_4$ increases CSF magnesium concentration. As a result, it was determined that CSF $MgSO_4$ levels are significantly higher only in group 4 cases in which the blood-brain barrier is disrupted. High CSF $MgSO_4$ levels detected in group 4 was interpreted in favour of the disrupted blood-brain barrier.

Although the magnesium analgesic effect mechanism is not exactly known, it is believed that calcium channels and NMDA receptors play an important role in this effect (7). NMDA receptors have positive modulator sites (NMDA binding site) for excitatory amino acids such as glutamate, whereas they have negative modulator sites (phencyclidine binding sites) for ketamine and magnesium (7). They cause antinociceptive effects by binding these sites. Although there are many studies showing that magnesium infusion reduces anaesthetic and postoperative analgesic consumption during general anaesthesia, there are also some studies reporting the opposite (6, 8-12).

Wilder-Smith et al. (12) studied the effects of magnesium infusion on postoperative pain for 5 h starting from the induction on 24 patients who had undergone elective hysterectomy operation. It is observed that groups that are administered magnesium experienced more pain compared to the placebo group in the 3rd postoperative hour, and it is reported that the number of patients who experienced severe/excruciating pain after the 4th postoperative hour over the entire study was higher. Zarauza et al. (13) reported that they could not obtain a decrease in study agents and morphine consumption when they had studied the effects of $MgSO_4$ on postoperative morphine consumption, nifedipine and nimodipine.

Table 3. Spinal anaesthesia onset data

Time (min)	Group 1 (n=16)	Group 2 (n=16)	Group 3 (n=16)	Group 4 (n=16)
Sensorial block onset time	3.01±1.6	3.18±1.2	2.75±1.1	5.6±1.8¶
Sensorial block time	58.8±21.6	45.1±9.5*	46.1±9.6	51±16.3
Motor block onset time	5.01±0.9	6.01±2.01*	5.2±0.1	6.2±1.5¶
Motor block time	126±36.5	139.4±19.8	140.1±31	120.9±34.2
Time to reach maximum block level	6.31±2.6	5.31±1.3	7.5±2.5†	8.98±3.2*,†
Maximum block level	T 3.5 (T 2-4)	T 3 (T 2-4)	T 3.5 (T 2-4)	T 3 (T 2-4)
Spinal anaesthesia time	105.6±39	98.3±27.2	100.7±22.4	85.3±24.9¶

All values were given as mean±standard deviation. P<0.05; *When compared to group 1, †When compared to group 2, ¶When compared to group 3

Table 4. $MgSO_4$ levels in blood and cerebrospinal fluid in groups

	Group 1 (n=16)	Group 2 (n=16)	Group 3 (n=16)	Group 4 (n=16)
Blood $MgSO_4$ level (meq/L)	1.81±0.34	2.91±0.48*	1.88±0.36	3.69±1.22†
CSF $MgSO_4$ level (meq/L)	2.87±0.1	2.80±0.15	2.79±0.21	3.08±0.19†

All values were given as mean±standard deviation. *When compared to groups 1 and 3, †When compared to groups 1, 2 and 3; CSF: cerebrospinal fluid

Table 5. Patients' ephedrine, fluid, analgesic requirements and side effects

	Group 1 (n=16)	Group 2 (n=16)	Group 3 (n=16)	Group 4 (n=16)
Given IV fluid amount (mL)*	2760±868	2375±543	2425±657	2075±628
Ephedrine requirement¶	3 (18.9%)	1 (6.3%)	3 (18.9%)	0 (0%)
Intraoperative additional analgesic requirement¶	2 (12.5%)	0 (0%)	2 (12.5%)	5 (31.3%)
Nausea¶	2 (12.5%)	3 (18.9%)	6 (37.8%)	3 (18.9%)
Hypotension¶	1 (6.3%)	2 (12.6%)	1 (6.3%)	0 (0%)

Values were given as *mean±standard deviation, ¶number of patients and %.

Table 6. New-born APGAR scores

	Group 1 (n=16)	Group 2 (n=16)	Group 3 (n=16)	Group 4 (n=16)
APGAR 1. min	8.5±0.81	8±0.6*	7.5±1*	7.2±1.7*
APGAR 5. min	9.6±0.5	9.3±0.4	8.8±1.2	9.2±1.2*

All values were given as mean±standard deviation. *When compared to group 1

However, there are also many studies showing that there is a decrease in intraoperative anaesthetic and analgesic consumption, postoperative pain and analgesic consumption of magnesium application (14, 15). Apan et al. (16) reported that magnesium that was administered right after spinal anaesthesia caused a decrease in analgesic consumption for 24 h. In our study, it was determined that spinal anaesthesia duration was statistically shorter in group 4 that underwent magnesium treatment than group 3 that did not undergo magnesium treatment; therefore, it was determined that the case group with the most analgesic requirement was group 4. When we investigate the reasons of the differences in literature on magnesium effectiveness, the underlying reason may be that magnesium has different interactions with different drugs. For example, potentialization data attracts attention in many studies examining the interaction between magnesium and opioids; antagonistic effect on amide group with local anaesthetic interaction stands out (9-11).

The drug administered during spinal anaesthesia, the dosage, density, subarachnoid injection speed, added adjuvant, metabolic rate and the patient's position during the application may change block level. To prevent the differences that may be caused by these effects, spinal anaesthesia was administered primarily in all groups in the sitting position using the same local anaesthetic, same dose and technique. However, the results pertaining to the dose and effectiveness of intravenous $MgSO_4$ we used before spinal anaesthesia in our study were different. In a study where the effectiveness of three different magnesium doses was compared (17), it was reported that a dose of 40 mg kg^{-1} was sufficient to reduce postoperative morphine consumption. It was reported that adding an infusion dose of 10 mg kg^{-1} h^{-1} caused an increase in this effect, and an infusion dose of 20 mg kg^{-1} h^{-1} did not provide a further benefit. To provide an increase in effective prophylaxis and analgesia in our study, $MgSO_4$ was administered iv in 60 mg kg^{-1} 100 mL 5% dextrose within 15 min. The magnesium dose we administered is compatible with the doses reported in the study above.

With respect to magnesium effectiveness, Dayıoğlu et al. (18) reported the effects of added magnesium to bupivacaine and fentanyl for spinal anaesthesia in knee arthroscopy. They found that 50 mg intrathecal $MgSO_4$ that had been added to spinal anaesthesia did not affect the time to reach maximal sensorial block level but prolonged the duration of sensorial block. El-Kerdawy et al. (19), on the other hand, in a similar study investigated the epidural magnesium infusion and intrathecal magnesium added to combined spinal epidural anaesthesia that is used in lower limb orthopaedic surgeries and reported that postoperative analgesic consumption was significantly reduced in both groups.

Different results were received with added opioids as an adjuvant to local anaesthetics in the studies mentioned above. In the study conducted by Chan-Jong et al. (20), in which spinal anaesthesia was provided with a single local anaesthetic, it was reported that the sensorial block onset time was 2.5±1 min, maximum block level was approximately T_3, the time to reach maximum level was 8.1±2 min and the onset time of motor block was 6±1.9 min for normal pregnant women who had undergone a caesarean section under spinal anaesthesia provided with 12.5 mg hyperbaric bupivacaine. In our study, while the results pertaining to the patients who did not receive $MgSO_4$ treatment showed similarity with the study conducted by Chan-Jong et al. (20), in preeclampsia magnesium-treated patient group, the significantly longer time to reach maximum block level and motor block onset than dextrose-treated group may be the result of magnesium- bupivacaine interaction.

Another factor affecting the duration of sensorial block in spinal anaesthesia is metabolic rate of local anaesthetics. Amide-type local anaesthetics are metabolized by hydroxylation with cytochrome P_{450} 3A and 2C isoforms in liver microsomes and N-debutilation process. Saito et al. (21) showed that $MgSO_4$ infusion induces NADPH- P_{450} reductase and cytochrome b_5 in the rat liver microsomes. Thus, it increases the activity of cytochrome P_{450} 3A and 3B and therefore increases bupivacaine metabolism and clearance. This study of Saito's explains why the sensorial block time in magnesium-administered group 4 was shorter in our study. Similarly, Hung et al. (21) showed that they compared the magnesium effects on the block provided with amide-type local anaesthetics (lidocaine, bupivacaine and ropivacaine) in the rat sciatic nerve; proprioception, nociception and motor sensory loss were obtained back in a shorter time and duration of local anaesthetic effect was reduced in magnesium-treated groups. Finally, Ünlügenç et al. (22) compared the effects of 50 mg magnesium, 25 μg fentanyl and saline added to10 mg of 0.5% bupivacaine in spinal anaesthesia for patients who had undergone caesarean section. They identified that the sensorial and motor block times were similar but shorter in the magnesium-treated group compared with those in the placebo group. They have concluded that in spinal anaesthesia administration, adding 50 mg of magnesium to 10 mg of 0.5% bupivacaine does not affect the duration of spinal anaesthesia. As in the studies mentioned above, an inverse relationship was revealed between high CSF magnesium levels and duration of spinal anaesthesia in our study.

Preeclampsia may cause changes in the APGAR scores (23). In our study, whereas 1st min APGAR scores were significantly lower in groups 3 and 4 compared with those in group 1, 5^{th} min APGAR scores were significantly lower only in group 4 compared with those in group 1.

In our opinion, the only thing that could be a limitation to this study is that hypotension caused by sympathetic block-

ade created with spinal anaesthesia may get worse because of $MgSO_4$ treatment. In our study, we did not observe fluid therapy and haemodynamic monitoring with significant hypotension.

Conclusion

Intravenous $MgSO_4$ treatment during the spinal anaesthesia produced by bupivacaine extended the onset of sensorial and motor block times, shortened the duration of spinal anaesthesia and therefore led to early analgesic requirement.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Çukurova University Faculty of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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