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Epidural Magnesium Sulfate Does Increase Cerebrospinal Fluid Ionized Magnesium Concentration of Rabbit: An Experimental Study*

Tavşanlarda epidural kateter yolu ile verilen magnezyum sülfatın spinal beyin omurilik sıvısına geçişinin araştırılması

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Abstract

Aim: This study was designed to investigate the ability of MgSO4, administered by epidural catheter, to pass into cerebrospinal fluid (CSF), and to evaluate motor block effect in rabbits.

Methods: Group 150 (n= 6): 150 mg/mL $MgSO_4$ was administered via epidural catheter, then the catheter was flushed using 0.20 mL of saline. Group 300 (n= 6): 300 mg/mL $MgSO_4$ was administered via epidural catheter, then the catheter was flushed. Group 450 (n=6): 450 mg/mL $MgSO_4$ was administered via epidural catheter, then the catheter was flushed. Rabbit ear arteries were cannulated for arterial blood samples. 0.1 mL CSF sample was taken from cisterna magna. The motor block was scored using Drummond Moore scale. After administration of drug, motor block was evaluated and CSF and plasma were taken at 0, 240, 360 and 480. minutes. Pharmacokinetic parameters were also calculated and statistically evaluated.

Results: In our study, spinal CSF ionized magnesium levels were increased compared to basal Mg^{2+} levels in each group respectively as follows; by 25% for 150 mg, 60% for 300 mg, and 127% for 450 mg. Moreover compared to basal Mg^{2+} levels the plasma ionized Mg^{2+} levels in each group were shown to increase by 13% for 150 mg, 87% for 300 mg, 200% for 450 mg. 450 mg magnesium sulphate administered epidurally generated motor block.

Conclusion: This study has established that epidural administration of MgSO4 increases the spinal CSF ionized Mg^{2+} concentration, epidural $MgSO_4$ passes through systemic circulation, and epidural administration of 450 mg $MgSO_4$ generates motor block in rabbits.

Keywords: Epidural, magnesium sulphate, cerebrospinal fluid, blood-brain barrier, rabbit.

Öz

Amaç: Bu çalışma, tavşanlarda epidural kateter ile verilen magnezyum sülfatın (MgSO4) beyin omurilik sıvısına (BOS) geçiş kabiliyetini araştırmak ve motor blok etkisini değerlendirmek için tasarlanmıştır.

Yöntem: Grup 150 (n= 6): Epidural kateter yoluyla 150 mg/mL MgSO4 uygulandı, ardından kateter 0.20 mL salin ile yıkandı. Grup 300 (n= 6): Epidural kateterden 300 mg/mL MgSO4 verildi, ardından kateter yıkandı. Grup 450 (n=6): Epidural kateterden 450 mg/mL MgSO4 verildi, ardından kateter yıkandı. Arteriyel kan örnekleri için tavşan kulağı arterleri kanülize edildi. Cisterna magna'dan 0.1 mL BOS örneği alındı. Motor blok, Drummond Moore ölçeği kullanılarak skorlandı. İlaç verildikten sonra motor blok değerlendirildi ve 0, 240, 360 ve 480. dakikalarda BOS ve plazma alındı. Farmakokinetik parametreler hesaplandı ve istatistiksel olarak değerlendirildi.

Bulgular: Çalışmamızda spinal BOS iyonize magnezyum seviyeleri her grupta bazal Mg2+ seviyelerine göre sırasıyla şu şekilde arttı; 150 mg için %25, 300 mg için %60 ve 450 mg için %127. Ayrıca bazal Mg2+ seviyeleri ile karşılaştırıldığında,her gruptaki plazma iyonize Mg2+ seviyelerinin 150 mg için %13, 300 mg için %87, 450 mg için %200 arttığı gösterilmiştir. 450 mg magnezyum sülfatın epidural uygulaması motor blok oluşturdu.

Sonuç: Bu çalışma tavşanlarda epidural MgSO4 uygulamasının spinal BOS'un iyonize Mg2+ konsantrasyonunu arttırdığı, epidural MgSO4'ün sistemik dolaşımdan geçtiğini ve 450 mg MgSO4 epidural uygulamasının motor blok oluşturduğunu ortaya koymuştur.

Anahtar Kelimeler: Epidural, magnezyum sülfat, beyin omurilik sıvısı, kan-beyin bariyeri, tavşan.

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INTRODUCTION

Magnesium (Mg^{+2}) is the fourth most abundant cation in the body and the second most abundant cation in intracellular fluid. The primary neuron transmitters for excitatory synaptic transmission in central nervous system are glutamate and/or aspartate, activate N-methyl-D-aspartate (NMDA) reseptors. It has been shown that physiological concentrations of plasma Mg^{+2} can block NMDA reseptors endogenously and in a non-competetive antagonist. Mg^{+2} in cerebrospinal fluid (CSF) is higher than in plasma. It has been reported that this gradient is due to active transport of Mg^{+2} from blood to CSF (1).

In 1916, Meltzer administered intrathecal $MgSO_4$ for the first time to 12 patients scheduled for surgery. In these patients long duration muscle relaxation and cardiovascular stability was obtained without any need of chloroform (2). In a study of hypomagnesemic cows it has been reported that, after iv Mg^{+2} infusion there was no difference in lumbal CSF Mg^{+2} levels, whereas ventricular CSF Mg^{+2} levels were increased (3). Likewise it has been shown that in mice CSF Mg concentration didn't change when Mg was given intraperitoneally even though plasma Mg level was significantly increased (4). In a study conducted on monkeys it was determined that Mg^{+2} levels were significantly increased in plasma and CSF after intravenous (iv) $MgSO_4$ infusion (5). In healthy humans Mg^{+2} transport from blood to CSF via blood-brain barrier (BBB) is limited (6). In patients with intracranial pressure increase; iv infusion of $MgSO_4$ increases plasma ionised Mg^{+2} concentrations more than 50 %; nevertheless CSF ionised Mg^{+2} levels remain unchanged for 4 hours (7). Kafadar et al (8) investigated Mg^{+2} levels of CSF and plasma in patients with severe head injury and they found that CSF Mg^{+2} levels significantly increased from the first day after trauma untill the fifth day. They also showed that there was no significant change in plasma Mg^{+2} levels. It has been reported that, perioperative $MgSO_4$ iv infusion increased serum Mg^{+2} levels; however CSF Mg^{+2} level was unchanged; moreover perioperative $MgSO_4$ iv infusion did not decrease postoperative analgesic need in abdominal hysterectomy patients (6). In neurosurgery patients, plasma and CSF Mg^{+2} concentrations were determined 30-90-240 minutes after $MgSO_4$ iv infusion and it was shown that at least 90 minutes later CSF Mg^{+2} concentrations were significantly increased. On the other hand, increases in plasma and CSF Mg^{+2} concentration are not compatible. For this reason it has been suggested that, plasma Mg^{+2} concentration can not be used as a determinant for CSF Mg^{+2} concentration changes (9).

It has been reported in one study that intrathecal magnesium administration (50 mg) prolongs analgesic effect duration in pregnant women. However, in that study epidural route of $MgSO_4$ administration is not considered as a component of the study (10).

Epidural Mg^{+2} administration is usually accidental (11,12). Dror et al (11) have reported that after administration of 3 g of $MgSO_4$ accidentally by epidural route, patients had a periumblical burning pain. Moreover, Goodman et al. (12) have reported epidural administration of $MgSO_4$ accidentally to 2 pregnant women (8.7 g in 1 hour and 9.6 g in 6.5 hours); and labour of the parturient which was given the high dose (9.6 g) stopped at first phase and afterwards an emergent cessarian section operation had to be done. However, in both case reports pharmacokinetics of $MgSO_4$ administered by epidural route were not investigated. Konakci et al (13) investigated the motor and sensorial blocking effects of $MgSO_4$ by using neurologic evaluation and somatosensory-evoked potential monitoring and they found that 1 mL of 15 % magnesium sulphate did not produce any neurological effect. They also showed that the dose they have used did not change the plasma levels of magnesium.

In the current study we investigated the hypothesis that $MgSO_4$, administered in various doses by epidural catheter would: 1. pass to CSF, 2. pass to blood, 3. cause motor block in rabbits.

METHODS

Eighteen New Zeland albino, male rabbits weighing 2000 to 3000 g were chosen for the study in Dokuz Eylül University Animal Research Laboratory. The animals were housed at least one week before the experiment in a room that has standard laboratory conditions (air-conditioned room with 12 h light–dark cycles, with a the temperature of 20-22°C, and relative humidity of 50- 60%) They were allowed to be fed water and food freely. The study protocol was approved by the Animal Research Committee of Dokuz Eylul University.

Anesthesia:

The marginal vein of the right ear was cannulated and an infusion of Lactated Ringer solution (Lactated Ringer Eczacıbaşı-Baxter H.U. San. ve Tic. A.Ş, İstanbul, Türkiye) was started with a rate of 4 mL kg h^{-1}. The induction of anesthesia was performed with intramuscular ketamine (50 mg kg^{-1}) (Ketalar, Pfizer İlaçları Ltd. Şti, İstanbul, Türkiye). Cefasoline (Cefamezin, Eczacıbaşı Sağlık Ürünleri San. ve Tic. A.Ş, İstanbul, Türkiye) was administered at a dose of 10 mg/kg intramuscularly for two days and twice a day for surgical prophylaxis.

Placement of Epidural Catheter

The animals were turned to prone position under ketamine anesthesia and epidural catheter (Portex®, SIMS Portex Ltd, Hythe, England) was inserted into the sacral canal. This technique was performed according to the method described previously by Arkan et al (14). The animals were evaluated 1 hour later with Drummond and Moore (15) scale to check if there was any neurological deficit due to catheter. The animals which passed this evaluation as having no hind limb limitation were included in the study. Afterwards, 1mL of 1 % lidocaine was administered to the animals via epidural catheter and after that the catheter was flushed with 0.2 mL of saline (14). Epidural placement of catheter was confirmed by observation of motor and sensitive block 5 minutes after drug administration. Afterwards, animals were transported to care unit and 2 hours later they were allowed to be fed. 24 hours after epidural catheter placement, the catheter fixation and connection sites were checked. The animals whose catheters were displaced due to any reason, or had infection, neurological deficit or worsening of general condition were excluded from the study.

Preparation of Magnesium Sulphate Solution

99.5% pure $MgSO_4$ (Sigma-Aldrich Corporation, Steinheim, Germany) was dissolved in distilled water. The tubes were vortex-mixed (Reax top, Heidolph Instruments GmgH & Co. KG, Schwabach, Germany) for 5 min. Final concentrations were 150, 300 and 450 mg/mL. After that, they were all wrapped with aluminum folio to protect the solutions from light. pH of the prepared $MgSO_4$ solutions were measured with pHmeter device (InoLab® 720, WTW Wissenschaftlich-Technische Werkstätten GmbH, Munich, Germany) at 26.5 °C.

Study Groups:

Subjects were randomly allocated into 3 groups:

Group 150 (n= 6): 1 mL of 150 mg/mL $MgSO_4$ (~ 0.6 mmol elemental magnesium) (pH: 6.20) solution was administered via epidural catheter and then the catheter was flushed using 0.20 mL of saline.

Group 300 (n= 6): 1 mL of 300 mg/mL $MgSO_4$ (~ 1.2 mmol elemental magnesium) $MgS0_4$ (pH: 6.16) solution was administered via epidural catheter and then the catheter was flushed with 0.20 mL of saline.

Group 450 (n=6): 1 mL of 450 mg/mL $MgSO_4$ (~ 1.8 mmol elemental magnesium) $MgS0_4$ (pH: 6.10) solution was administered via epidural catheter and then the catheter was flushed with 0.20 mL of saline.

Neurological Evaluation:

Motor block was evaluated 0., 240., 360., 480. minutes after administration of drug through epidural catheter, and was scored using Drummond Moore scale (15); 0 point: Free movements in the hind limbs without limitations.1 point: Loss of body support in the hind limbs and asymmetry or limitations in walking. 2 points: Loss of body support in the hind limbs. 3 points: Total hind limb paralysis.

Spinal Cerebrospinal Fluid and Plasma Collection:

One day after epidural catheter placement and following neurological assessment, animals were anesthetized by mask induction with halothane (2-3 % inspired) in oxygen, and anesthesia was maintained with halothane (0.5-1 % inspired) in oxygen. Gas mixture was continuously monitored via anesthetic gas monitor (Anesthesia Gas Monitoring 1304, Bruel&Kjaer, Copenhagen, Denmark) in order to ensure constant gas mixture. The artery of the right ear was cannulated with 22 G catheter for blood sampling.

Anesthetized animals were turned to prone position and median muscle structures at the back of their neck were divided. A 0.1 mL of spinal CSF sample was taken from cisterna manga by passing through atlantooccipital ligament. Simultaneously, 0.25 mL of arterial blood was taken from each animal using an insulin syringe

prewashed with heparin. Spinal CSF and plasma were obtained at 0, 240th, 360th and 480th minutes. All samples were placed into an ice-filled box and kept there until the measurement time.

Ionized Mg^{+2} concentrations in spinal CSF and plasma were measured by Stat Profil M (Nova Biomedical Corp., Waltham, USA). Magnesium electrode measurement interval was 0.3-30 mmol L^{-1} in plasma. The detection limit of the assay was 0.0995mmol.L^{-1}.

Calculation of Pharmacokinetic Parameters:

Plasma and spinal CSF ionized Mg^{+2} concentration-time graphs were drawn for each subject. The peak concentration in plasma/spinal CSF (C_{max}) and time to reach C_{max} (t_{max}) were determined directly from the individual plasma/spinal CSF concentration-time profiles. Area under the plasma/spinal CSF concentration-time curve $(AUC)_{0-480}$ was calculated using the noncompartmental model.

Statistical Analysis:

Statistical analysis was performed using SPSS (18.0 version) for windows. The results were given as median±standard deviation (SD). The data were tested for normality with the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Kruskall- Wallis test was used for independent group comparisons and multiple comparison tests were calculated with the formulas written below.

Test statistic= $1/s^2(å R_i^2/ni - N*(N+1)/4)$

$S^2= 1/N-1 (å R (X_{ij})^2 - N*(N+1)^2/4)$

For multiple comparisons;

$½Ri/ni - Rj/nj ½ > Test sta._{table} * (Test sta._{calculation})^{1/2}* (1/n_i+1/n_j)^{1/2}$

Treatments *i* and j are considered different if the following inequality is satisfied (16).

Multiple comparisons were made manually. There is no software program for this comparisons. P value <0.05 was considered as significant.

RESULTS

The average weight of the animals were determined as 2408±262, 2450±327, 2516±248 g in Group 150, Group 300 and Group 450 respectively. There was no significant difference between groups.

Plasma Ionized Magnesium

Plasma Mg concentrations were increased in all groups after $MgSO_4$ administration compared to base-line values. This increase was statistically significant in Group 300 at 240th and 360th minutes and in Group 450 at all time points (* p<0.05). Between groups' base-line values no statistically significant difference were detected (Table 1).

Plasma ionized magnesium mean value of Group 150 at 480th minute was significantly lower than Group 300 and Group 450 (* p<0.05) (Table 1).Plasma magnesium area under curve ($AUC_{Plasma\ (0-480)}$) mean values in Group 150; Group 300; and Group 450 were calculated respectively as follows: 2.36±0.37 mmol. min. L^{-1}; 3.71±0.26 mmol. min. L^{-1}; and 4.93±0.54 mmol. min. L^{-1}. Mean values of $AUC_{Plasma(0-480)}$ were compared between groups ; in Group 450 ionised magnesium $AUC_{Plasma(0-480)}$ mean value was significantly high. (p< 0.05). $AUC_{Plasma(0-480)}$ mean value was also significantly high in Group 300 than Group 150 (# p=0.02) (Table 3).

Spinal cerebrospinal fluid ionized magnesium

After $MgSO_4$ administration, CSF Mg concentrations were increased compared to base-line values in all groups. But statistically significant increases were detected only in Group 450 at all time points (* p<0.05). We couldn't find any significant difference between Group 150 and Group 300. Between groups' base-line values no statistically significant difference were detected (Table 2).Mean values of spinal CSF ionised magnesium area under curve ($AUC_{CSF(0-480)}$) in group 150; group 300; and group 450 were calculated respectively as follows: 3.45±0.62 mmol. min. L^{-1}, 3.05±0.44 mmol. min. L^{-1}, 4.76±0.47 mmol. min. L^{-1}. Mean values of $AUC_{CSF(0-480)}$ was compared between groups; in Group 450 ionised magnesium $AUC_{CSF(0-480)}$ mean value was significantly high (* p< 0.05) (Table 3).

Neurological Evaluation:

Motor block results at 0. minute were not significantly different between groups. Motor block was not detected in Group 150 and Group 300 at any of the

time points. At all time points Group 450's mean motor block values were significantly higher than other groups (* $p<0.05$)(Table 4).

DISCUSSION

Our study has showed that magnesium sulphate administered by epidural route increased spinal CSF ionised magnesium concentration, could pass systemic circulation and that 450 mg of epidural magnesium sulphate administration caused motor block.

In our study the initial magnesium measurement time was at 240th minute. It was reported that 30 minutes after magnesium administration via intravenous or intramuscular route, serum ionized magnesium concentration reached equilibrium (17). Fuchs-Buder et al (9) have reported that after intravenous magnesium administration (60 mg kg^{-1} $MgSO_4$) to CSF in neurosurgical patients, time for equalization of magnesium concentration between blood and CSF was approximately 240 minutes.

In our study, spinal CSF and plasma ionised magnesium concentration in rabbits were found as 0.30-0.39 mmol/L and 0.29- 0.31 mmol/L, respectively. The ratio of CSF and plasma ionised magnesium level was 1.18 (0.35/0.29=1.18). This finding is similar to Frossini et al (18)' s results which is 1.26 in concious rabbits. Basal CSF total magnesium concentration in dogs were 2.1-2.4 mEq/L = 1.05- 1.2 mmol/L (19). Basal CSF and serum magnesium concentration in rats were reported as 18.84±19.70 µg/mL= 0.74-0.77 mmol/L and 15.72-16.86 µg/mL= 0.61-0.66 mmol/L, respectively. In rabbits, basal CSF magnesium concentrations were found as 0.90±0.20 mmol/L and plasma levels as 0.72 ± 0.13 mmol/L (18). We found that CSF magnesium concentrations are higher than plasma concentrations and this finding is similar to other studies. We measured ionized magnesium concentrations but in these studies the investigators measured total magnesium levels. This could be the reason that their results are 2 or 3 times greater than our measurements.

In our study spinal CSF ionised magnesium maxium concentration compared to basal ionised magnesium concentration was increased in 150 mg, 300 mg and 450 mg groups by ; 28%, 66% and 127%, respectively. Plasma ionised magnesium maximum concentration was increased compared to basal ionised magnesium concentration in 150 mg, 300 mg and 450 mg groups by 24%, 87 % and 200%, respectively. These findings have shown that ionised magnesium has dose dependently increased both in plasma and spinal CSF. Likewise, Oppelt et al. (19) have showed in their study using i.v $MgCl_2$ in dogs that CSF Mg^{+2} concentration has increased by a maximum of 21% and plasma maximum concentration increased at a ratio of 300-400%. Furthermore, Hallak et al. (20) have determined in their study that, after administration of 432 mg/kg of $MgSO_4$, Mg^{+2} concentration in hippocampus increased after 2 hours at a ratio of 41%. In an another study, Tsuda et al. (21) studied neuron protective effects of $MgCl_2$ in global cerebral ischemia model in rats and they showed that 24 hours after reperfusion hippocampus Mg^{+2} concentration increased at a ratio of 28%. Feria et al. (22), however, have showed that subcutaneous 600 mg/kg $MgSO_4$ administration in rats caused a 32% increase in spinal CSF Mg^{+2} concentration. McKee et al. (23) studied neuron protective effets of i.v $MgSO_4$ in acute cerebral trauma patients and in that study they measured total and ionised magnesium concentration in CSF and found an increase of 15% in total Mg^{+2} concentration and an increase of 11% in ionised Mg^{+2} concentration. In another study, Kafadar et al (8) investigated Mg^{+2} levels of patients with severe head injury and they showed that CSF Mg^{+2} levels were increased and the highest levels were found at the first day after trauma. McCarthy et al. (24) studied intrathecal administration of 60 µg/h of $MgSO_4$ infusion in rats and they showed that spinal CSF magnesium concentration increased at a ratio of 144%, whereas serum magnesium concentration did not show any increase. On the other hand, controversial with these findings, Ko et al. (6) have reported that iv administration of $MgSO_4$ did not increase CSF Mg^{+2} concentration. However, in that study CSF Mg^{+2} concentration measurement was performed nearly 120 minutes later in comparison to our study. In an another study, Kim et al. (25) have reported that, after 5 day infusion of $MgSO_4$ they produced a hipermagnesemic state in rats and they showed that although the plasma Mg^{+2} concentration was increased by 3 times that of the inital concentration, there was no increase in brain paranchymal Mg^{+2} concentration. The researchers explain that a low number of subjects and technical faults account for this. Brewer et al. (7) studied intracranial hypertensive patients, they administered 5 g (20 mmoL) $MgSO_4$ infusion in 30 minutes and have showed no

increase in CSF ionised Mg^{+2} concentrations. We think that the difference between the studies is due to administration of various types of magnesium salts. 1 g of $MgCl_2$ contains 118 mg of magnesium (=9 mEq= 4.5 mmoL), whereas 1 g of $MgSO_4$ contains 98 mg of magnesium (= 8.12 mEq= 4.06 mmoL) (26).

In our study, since the calculated AUCs from plasma and spinal CSF Mg^{+2} concentration-time curves drawn from administration of varied doses of magnesium into epidural space, and maximum concentrations were linearly correlated , this shows that the drug could pass from epidural space to plasma and spinal CSF, and that the amount passed into spinal CSF is associated with plasma concentration and/or drug concentration in epidural space. Furthermore, Oppelt et al. (19) studied dogs and administered iv $MgCl_2$ and showed while plasma concentrations were increasing rapidly, the increase in CSF Mg^{+2} levels was relatively very slow (reached maximum concentration at 5 hours) and it increased only by 21% compared to the control value. Sun et al (4) gave intraperitoneal Mg^{+2} to mice and reported that there was no significant change in CSF Mg^{+2} concentration while plasma concentration increased significantly. Since CSF magnesium measurements following iv magnesium sulphate administrations were confusing and remained unchanged except for a very few number of reports in literature, we considered that increased CSF Mg^{+2} levels might have been due to Mg^{+2} passage through duramater following epidural administrations.

In this study it is shown that high concentrations of magnesium causes motor block and this motor block is associated with the CSF ionised magnesium concentration. Akutagawa et al. (27) reported that magnesium ions increase the firing threshold of both myelinated and unmyelinated nerves by the mechanism of decreasing the negative surface charge of bivalent cations and increase the transmembrane potential (eg., causing hyperpolarisation). As a result of these findings they reported that magnesium prolongs the motor block duration. Furthermore, Gündüz et al. (28) have reported that the motor block duration was not prolonged with the concomitant administration of iv magnesium sulphate (150 mg), whereas adding magnesium into local anesthetic solution in high dose (150 mg) prolonged the motor block duration. Also, Thurnau et al. (29) showed in their study that i.v infusion of magnesium sulphate increased the CSF magnesium concentration by 15% and blood magnesium concentration by 384%, however they did not see any motor block, so they concluded that magnesium blood concentration has no effect on motor block formation.

In our study we did not determine motor block in subjects that were administered 14.7 – 29.4 g of magnesium (Group 150, Group 300). Lejuste (30) has reported a case of accidental intrathecal administration of 1000 mg of $MgSO_4$ (4.06 mmoL) and 90 minutes long motor block and recovery without any sequela. Dror et al. (11) reported that after accidental epidural administration of 3 g $MgSO_4$ (12.18 mmoL) patient felt a periumblical burning pain and had no motor block. Furthermore, Goodman et al. (12) have reported two accidental epidural administrations of magnesium sulphate to two partiurients (8.7 g (35.32 mmol, 145 mg/min) in one hour and 9.6 g (38.97 mmol, 24.61 mg/min) in 6.5 hours) and the labour was stopped at the first phase in the parturient that was administered high dose magnesium (9.6 g), so an emergent ceaserian operation had to be done. Nevertheless, there was no motor block in both patients. We think the reason for the lack of motor block in all of the three cases could be that the epidurally infused dose of magnesium is low.

The motor block of magnesium differs from the block produced by local anesthetics. This difference is because the mechanism of action is not similar in magnesium and local anesthetics. Karasawa et al. (31) has reported that, after administration of intrathecal magnesium sulphate (12.3 % [4.1 mg/kg] or 24.6 % [8.2 mg/kg]) and lidocaine (4% or 8%) to rats they produced different types of motor paralysis, magnesium produced a spastic type and lidocaine a paralytic type. Although they have not performed a histopathological examination, they have discussed this result according to the thesis on which the inhibition of the inhibitory interneurons that affect motor neurons by high concentrations of Mg^{+2}. Bahar et al (32) have reported in their study involving the administration of intrathecal $MgSO_4$ (total 1260 µg) in order to investigate behaviours of rats and magnesium toxicity, that $MgSO_4$ could cause spinal analgesia and sedation, however this effect only takes several hours. Chanimov et al. (33) have reported that

repeated intrathecal bolus administration of $MgSO_4$ for 30 days did not cause any neurological injury, which has shown hystopathologically that there is no significant hystopathologic injury in spinal cord. Likewise , Simpson et al. (34) have shown that intrathecal administration of 45-60 mg of $MgSO_4$ in dogs, did not caused any spinal cord injury hystopathologically. Furthermore, it is reported that accidental administration of 1000 mg of $MgSO_4$ intrathecally caused 5 hourmotor block and recovery without any sequeale (30). Controversial to all these findings, Saeki et al. (35) performed spinal ischemia in rabbits and administered intrathecal magnesium at doses of 1, 2, 3 mg/kg and showed that these doses produced injury at intermediate zone of lamina V-VII in spinal gray matter and this caused motor dysfunction. Jellish et al (36) performed 30 minutes of spinal cord ischemia and injected 3mg/kg $MgSO_4$ intrathecally before the ischemia. The investigators found that intrathecal $MgSO_4$ improved the motor function and decreased the neuron loss after spinal cord ischemia. Taira et al. (37), however showed in the model of transient spinal ischemia in rats that the interneuron injury in lamina III-VII caused paraparesis without producing any motor neuron injury.

Limitations of our study is that we could not show hystopathologically whether high dose $MgSO_4$ administration via epidural route could cause spinal cord injury. Furthermore, we could not calculate the magnesium elimination half time administered through epidural route because rabbit cerebrospinal fluid was collected only 4 times. Also, the C_{max} and t_{max} values are not reliable enough due to limited sample collection time.

In conclusion, administration of magnesium sulphate via epidural route increases spinal CSF ionized magnesium concentration and can also pass to systemic circulation and epidural administration of 450 mg magnesium sulphate causes motor block.

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