

Magnesium as an Effective Adjunct Therapy for Drug Resistant Seizures

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ABSTRACT: Objective: To explore the use of magnesium (Mg), an endogenous ion and enzymatic co-factor used in a variety of medical applications, for the treatment of epileptic seizures resistant to traditional medical therapy. **Background:** For almost a century, Mg has been used as prophylaxis and treatment of seizures associated with eclampsia. Mg is a CNS depressant, with numerous functions intracellularly and extracellularly. However, because of the availability of well studied anticonvulsant drugs, Mg has not been tested widely in the treatment of epileptic seizures. **Methods:** A retrospective chart review of 22 cases of drug resistant epilepsy, where a trial of empiric oral Mg supplementation (mainly in the form of Mg-oxide) was conducted. **Results:** Oral Mg supplementation was associated with a significant decrease in the number of seizure days per month, from 15.3 ± 13.2 (mean \pm SD) to 10.2 ± 12.6 at first follow up (3-6 months, $p=0.021$), and to 7.8 ± 10.0 seizure days/month at second follow up (6-12 months, $p=0.004$). Thirty-six percent had a response rate of 75% or greater at second follow-up. Two patients reported seizure freedom. Most patients were well maintained on MgO 420mg twice a day, or in 2 cases, Mg Lactate, without significant adverse effects, the most frequent being diarrhea (4/22). **Discussion:** These results suggest that oral Mg supplementation may prove to be a worthwhile adjunctive medication in treating drug intractable epilepsy. **Conclusions:** A prospective, double-blinded, placebo controlled study is warranted to evaluate the potential of Mg for the treatment of drug-resistant seizures.

RÉSUMÉ: Le magnésium comme traitement d'appoint efficace dans les crises convulsives résistantes au traitement. Objectif : Le but de l'étude était d'explorer l'utilisation du magnésium (Mg), un ion endogène et un cofacteur enzymatique ayant différentes applications en médecine, dans le traitement des crises épileptiques résistantes au traitement médical traditionnel. **Contexte :** Depuis près d'un siècle, le Mg a été utilisé en prophylaxie et dans le traitement des convulsions associées à l'éclampsie. L'effet du Mg sur le SNC est un effet dépressur et il a également plusieurs fonctions à l'intérieur et à l'extérieur de la cellule. Cependant, le Mg a été peu évalué comme anticonvulsivant à cause de la disponibilité de médicaments dont l'efficacité est déjà bien établie. **Méthode :** Nous avons révisé rétrospectivement les dossiers de 22 patients atteints d'épilepsie réfractaire au traitement médicamenteux qui ont été traités de façon empirique par un supplément oral de Mg (surtout sous forme d'oxyde de Mg). **Résultats :** La prise d'un supplément de Mg par voie orale était associée à une diminution significative du nombre mensuel des crises, soit de $15,3 \pm 13,2$ (moyenne \pm ET) à $10,2 \pm 12,6$ à la première visite de suivi après 3 à 6 mois de traitement ($p = 0,021$) et à $7,8 \pm 10,0$ crises par mois au moment de la deuxième visite de suivi après 6 à 12 mois de traitement ($p = 0,004$). Trente-six pour cent des patients avaient un taux de réponse de 75% ou plus au moment de la deuxième visite de suivi. Deux patients ont rapporté qu'ils n'avaient plus de crises. La plupart des patients étaient stables sous MgO 420 mg deux fois par jour ou, chez deux patients, sous lactate de Mg, sans effets indésirables importants le plus fréquent étant la diarrhée (4/22). **Discussion :** Selon ces résultats, la supplémentation orale en Mg peut s'avérer utile comme médicament d'appoint dans le traitement de l'épilepsie réfractaire au traitement médical. **Conclusion :** Il serait pertinent d'évaluer par une étude prospective, à double insu, contrôlée par placebo, le potentiel du Mg dans le traitement des crises résistantes au traitement médicamenteux.

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The definitive treatment of eclampsia, a syndrome of pregnancy-induced hypertension, proteinuria and new onset seizures, is magnesium (Mg) supplementation, followed by delivery of the fetus. Magnesium has been the widely accepted treatment since first reported in 1925¹, and remains the mainstay of treatment for eclampsia. Eclamptic seizures have been compared, both in semiology and electrographically, to generalized tonic-clonic (GTC) "grand mal" seizures, with controlled clinical trials having demonstrated the clear effectiveness of Mg against eclamptic seizures when compared to conventional anticonvulsants^{2,3}.

Magnesium has been hypothesized to be effective against CNS ischemia and seizures based on its biochemical properties⁴. Magnesium is a known CNS depressant, whose mechanisms of action include: competitive antagonism of N-methyl-D-aspartate (NMDA) receptors, blocking transient receptor potential (TRP)

cation channels, antagonism of calcium channels (and subsequently, synaptic transmission) and increasing membrane surface charge which in turn decreases excitability.

To date, several studies have explored the use of Mg in ameliorating CNS pathology, however, clinical trials have failed to deliver on the promise of the effectiveness of Mg in animal

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studies [see ⁵ for review]. For example, in a large clinical trial, Mg failed to show any benefit in decreasing the morbidity and mortality associated with stroke⁶. Nevertheless, when administered along with adrenocorticotrophic hormone (ACTH), MgSO₄ demonstrated a significant decrease in seizures in children with infantile spasms⁷. However, no clinical trials have investigated the efficacy of Mg in the treatment of recurrent epileptic seizures in adults. We report a small case series illustrating the benefit of oral Mg supplementation in drug intractable epileptic seizures.

METHODS

Charts were reviewed retrospectively, using both electronic and paper medical records, from an outpatient epilepsy clinic at the Toronto Western Hospital; a tertiary center for epileptic patients who are often refractory to conventional pharmacotherapy. All charts depicting the initiation of empiric trials of Mg from August 2005 to January 2011, with at least one follow-up occurring after three months of Mg therapy, were included. Seizure frequency was recorded from patient histories, and reported as seizure days/month, and not the total number of seizures. Several patients reported having several seizures on a daily basis, which are reported here as 30 seizure days/month, the maximum possible. The pre-Mg seizure frequency was taken from the clinic note written on the day of Mg initiation. Mg was usually initiated as MgO 420 mg twice a day, daily, and in some patients, was increased to three times a day, daily. Subsequent follow up notes were used to gauge patient compliance as well as Mg therapeutic and adverse effects. Seizure frequency was pooled into the following groups: 1) Pre-Mg 2) Follow-up at 3-6 months 3) Follow-up at 6-12 Months and 4) Follow-up at 12-18 months.

Statistical analysis consisted of a one-way repeated measures ANOVA with post-hoc analysis using the Holm-Sidak method, and included tests for normality of data, conducted using Sigma-Plot version 11 (Systat Software Inc., San Jose, CA, USA), with a minimum level of significance at $p < 0.05$. Sub group analysis was conducted using a two-way repeated measures ANOVA.

RESULTS

All results are reported in the Table. Both the electronic medical record and paper chart were reviewed for an initial cohort of twenty-seven patients. One patient record was in duplicate, one patient agreed but never took Mg, while three took Mg inconsistently, and thus were not included in the analysis. Twenty-two patients were included in the analysis, 55% female, with an age of 37.1 ± 10.4 years (average \pm SD) at Mg initiation and initial seizure occurring at an age of 15.5 ± 10.0 years (excluding neonatal and febrile seizures). Anti-epileptic drug regimen included 2.8 ± 0.9 drugs and 45% of patients had some sort of neurological surgery, either as a cause or treatment of their seizure disorder.

Average seizure frequency for the group was 15.3 ± 13.2 seizure days/month. At first follow-up (3-6 months), seizure frequency was 10.2 ± 12.6 seizure days/month ($p = 0.021$). At second follow up (6-12 months), consisting of 15/22 patients, seizure frequency was 7.8 ± 10.0 ($p = 0.004$). Only 2/22 patients had a third follow up, with a seizure frequency of 2.5. The only adverse drug event reported was diarrhea, reported by four

patients, three of which were on the MgO three times a day regimen. Two of these patients were switched to Mg-lactate, and subsequently reported increased gastrointestinal tolerability.

Twenty-seven percent (6/22) had a primary seizure disorder (generalized tonic clonic [GTC] or drop attacks) with the remaining 73% (16/22) having partial seizures (complex-partial seizures [CPS] – many of whom had secondary generalization, or simple partial). While Mg seemed more effective at increasing seizure free days/month (i.e. decreasing seizures) amongst the primary epilepsies, sub-group analysis via two-way repeated measures ANOVA comparing the effectiveness of Mg supplementation on primary generalized versus partial seizures revealed no statistical difference ($p > 0.05$).

Responder rates at first follow-up were as follows: 32% (7/22) had a reduction of 75% or greater in the number of seizure days per month, while 41% (9/22) had a reduction of 50% or greater in the number of seizure days per month. At second follow-up, both the 75% and 50% responder rates were 5/14 (36%), suggesting that the efficacy of MgO on seizures may be bimodal i.e. there may be a group of responders and non-responders. Of those who qualified as responders, 3/5 were classified as GTC, one with CPS and one with CPS with secondary generalization. Examination of the anti-seizure drugs did not reveal any obvious trends. This group of five patients were on an average of 2.8 ± 0.8 anti-epileptic medications, the most common being lamotrigine phenytoin, topiramate and valproate, all shared by two patients in the group. Four of the five were on a regimen of MgO twice a day dosing, compared to 68% of the cohort (15/22) who were on a regimen of MgO twice or more per day. Two of the 22 patients (9%) achieved seizure freedom.

Serum Mg levels were not drawn as a part of monitoring oral Mg therapy, however, several patients had serum Mg levels drawn as a part of routine in-patient hospitalizations. Eight patients had pre-treatment serum Mg levels drawn and four patients had post-Mg treatment levels drawn. All levels were within the normal range.

DISCUSSION

Magnesium has been widely used by the obstetrics community for years in the treatment of eclampsia. Other clinical applications of Mg supplementation include ICU protocols, torsades ventricular arrhythmias, parathyroid syndromes, end-stage renal disease, insulin resistance and cardiovascular disease⁸. While toxicity may manifest with respiratory depression and death, most common adverse events are diarrhea and hyporeflexia. Clinical signs of Mg imbalance often do not correlate with serum levels, as less than 1% is found in serum, with the bulk found in bone or intracellularly, where it acts as an important biochemical mediator⁹. When serum levels were measured in the present study, Mg levels were all normal both before and after Mg supplementation. Reports have shown that seizure patients have lower ionized Mg²⁺, and higher ionized Ca²⁺/Mg²⁺ ratios¹⁰, however, Mg levels do not correlate with seizure probability in the treatment of eclampsia¹¹.

Notwithstanding its wide spread clinical use and relatively benign adverse effects, Mg has not been tried for the treatment of patients established epileptic seizures, with the exception of its reported efficacy against infantile spasm as adjunctive

Table: The efficacy of oral Mg supplementation in patients with medically intractable epilepsy

	Sex	Age	Seizure Type	Age @ 1st Sz	NeuroSx	MgDose	AEDs	Seizure Frequency				% Change after 1st f/u	% Change after 2nd f/u
								Initial	1st f/u	2nd f/u	3rd f/u		
1	M	43	SP		No	420 QHS	B, C, H	3	1			-67	
2*	F	36	CPS		No	420 BID	A, E, H	30	5	6		-83	-80
3	F	21	CPS	##6	Yes	420 BID - QID	C, G, I, J	30	30	18		0	-40
4	M	56	CPS	36	Yes	420 BID	B, C, H	30	30	30		0	0
5	M	31	CPS		Yes	420 QHS	B, C, F, O	8	8	8		0	0
6	F	51	CPS		No	420 BID	K	7	0.5	0		-93	
7*	M	31	CPS	28	Yes	420 BID - QID	B, C	7	6	4	3	-14	-43
8	F	31	CPS		No	420 QHS	B, C, H	4	1	4		-75	0
9	M	21	CPS 2° GTC	# 12.5	No	420 BID	F, H, I	30	0			-100	
10*	F	29	CPS 2° GTC	4	Yes	420 BID - QHS	B, N	30	2	2	2	-93	-93
11	F	42	CPS 2° GTC	12	Yes	420 BID	I, K, N	30	30	30		0	0
12	M	27	CPS 2° GTC	4	Yes	420 BID	L, N, P	30	30			0	
13*	F	24	CPS 2° GTC	13	No	420 QHS	B	30	30			0	
14*	F	36	CPS 2° GTC		No	420 QHS - BID	B, C	3.5	3	2		-14	-43
15*	F	28	CPS 2° GTC	11	No	420 BID - TID	C, H, L	3.5	4			14	
16*	F	51	CPS 2° GTC	10	No	420 BID	B, H, I	1	1			0	
17*	M	44	Drop attacks	11	yes	420 BID	B, H, M	5	1			-80	
18*	F	48	GTC	8	Yes	420 BID	L, O	30	30	3		0	-90
19	M	31	GTC		No	420 BID	C, H, M, C	30	4	3		-87	-90
20	F	46	GTC		No	420 QHS	D, L, N	5	1.3	0.3		-74	-94
21	M	48	GTC	20	No	420 QHS	B, H, L	2	3	3		50	50
22	M	42	GTC	25	Yes	420 BID	H, L	2	3	3		50	50

History of febrile seizures in the past; ## History of neonatal seizures in the past; * See patient note below; Seizure frequencies are reported as seizure days per month. Those with several seizures/day are reported simply as 30. Initial, 1st, 2nd, 3rd indicate follow-up visits as detailed in the text.

*Patient Notes: 2 - Lamotrigine discontinued secondary to rash at first follow-up. Levetiracetam 500mg twice a day started. 7 - Lamotrigine started and subsequently discontinued during MgO trial. Valproate increased to 1000mg twice a day from 750mg. 10 - MgO dose decreased secondary to diarrhea. 13 - Patient started on prazosin for PTSD. 14 - Patient began having diarrhea with increased dosing and was subsequently decreased. 15 - Started on lorazepam for panic attacks. 16 - Patient started on Mg-Lactate secondary to diarrhea and GI intolerance at first follow-up. 17 - Vigabatrin initiated, then discontinued abruptly due to suspicion of visual field changes; Patient also began course of acupuncture during MgO trial. 18 - Patient was placed on Mg-Lactate secondary to diarrhea and GI intolerance at second follow-up. Abbreviations: f/u - follow-up; CPS - Complex partial seizures; 2° - secondary; GTC - generalized tonic-clonic seizures, SP - simple partial seizures, Sz - seizures, NeuroSx - neurosurgery; EtOH - alcohol abuse and withdrawal; FAS - fetal alcohol syndrome; TBI - traumatic brain injury, VNS - vagal nerve stimulator; SDH - subdural hematoma; SE: status epilepticus; QHS: nightly; BID: twice a day; TID: three times a day; QID: four times a day. AEDs - anti-epileptic drugs: acetazolamide (A), carbamazepine (B), clobazam (C), clonazepam (D), diazepam (E), gabapentin (F), lacosamide (G), lamotrigine (H), levetiracetam (I), oxcarbazepine (J), phenobarbital (K), phenytoin (L), primidone (M), topiramate (N), valproate (O), vigabatrin (P).

therapy with ACTH⁷. It is widely accepted that a low Mg perfusion of *in vitro* brain preparations will readily generate seizures¹². However, animal research on the anti-seizure efficacy of Mg is equivocal. No effect of Mg was reported against maximal electroconvulsive shock (MES) and pentylenetetrazol (PTZ)¹³, or kainate¹⁴ models of seizures *in vivo*. Conversely, other experiments have demonstrated that peripherally administered Mg accumulates in the brain and increases amygdala kindling threshold in the rat¹⁵. It also decreases seizures associated with intracranial NMDA injection when administered both centrally and peripherally¹⁶ and was shown to augment sub-therapeutic VPA in the PTZ model of rat¹⁷. Mg also decreased epileptiform discharges from cortical foci generated by penicillin¹⁸, however, did not suppress epileptiform EEG discharges in eclamptic patients¹⁹, which is a similar finding in penicillin-induced seizure foci in anesthetized cats²⁰.

A randomized clinical trial investigating the neuroprotective effects of continuous Mg infusion in patients with traumatic brain injury did not demonstrate any positive benefits²¹, yet Mg has been successful in the treatment of convulsions associated with porphyria²². Intravenous Mg has been used in the past to successfully treat status epilepticus associated with Alper's Syndrome, a triad of developmental delay, intractable seizures and hepatic failure²³.

Our patient population represents seizure patients who are the most difficult to treat medically. Nevertheless, Mg supplementation was able to significantly decrease the amount of seizure days/month, with two patients reportedly becoming seizure-free. However, there are multiple shortcomings which limit the ability to extrapolate these data. Firstly, this study was an open label, uncontrolled empiric study of the efficacy of Mg in a small population of patients with drug resistant seizures,

heterogeneous medical histories and assorted anti-seizure drug regimens.

Secondly, MgO, one of the most affordable preparations, was used by most patients. However, its limited bioavailability, well-documented in the literature²⁴, is similar to other commonly used Mg compounds²⁵. Magnesium supplementation by mouth may be absorbed throughout the entire length of the small intestine, however, the bulk is associated with uptake in the distal jejunum and ileum, mainly by a passive intercellular process²⁵. Increased bioavailability of organic Mg compounds, such as Mg-Acetate, Mg-Lactate and Mg-Gluconate have been documented using both radio-isotopes and urinary Mg concentrations²⁵, and would be a better preparation for oral Mg delivery in future studies.

Similarly, the ability of Mg to penetrate the blood brain barrier in therapeutically relevant concentrations has been the subject of some debate [see REF⁵ for review]. Using Mg²⁸Cl, Oppelt et al, (1963)²⁶ concluded that Mg uptake into the CSF from the blood was an active process, keeping CSF concentrations greater than serum concentrations, and this was not affected by increasing Mg concentrations 3-4 fold. Similarly, Sun and colleagues (2009)²⁷ found no increase in CSF Mg when MgSO₄ was injected intraperitoneally, in mice.

And yet, several groups have noted increased CSF Mg when supplemented parenterally, including pre-eclamptic patients²⁸ and neurosurgical patients undergoing ventriculostomy drainage²⁹ or craniectomy³⁰. Similarly, rats injected intraperitoneally with MgSO₄ had significantly elevated CSF Mg levels at four hours, which coincided with elevated hippocampal seizure thresholds³¹.

In all studies, including those where CSF Mg did not significantly increase, a significant rise in serum Mg was noted. However, when Mg levels were measured in this study as part of routine inpatient hospitalization, levels were all within normal limits. The usefulness of Mg levels prepared by the clinical laboratory is questionable, given that 99% of magnesium is intracellular [bone (53%); soft tissues (46%)] with 1% in the blood²⁶. Of the 1%, only the free ionized form is capable of transport across the blood brain barrier.

Future studies should include a blinded, placebo controlled protocol, with appropriate long term follow up, using organic Mg preparations such as Mg-Acetate, lactate or gluconate, and should coincide with monitoring of CSF Mg in attempt to correlate Mg levels with anti-seizure effectiveness. Monitoring intracellular red blood cell magnesium is another possible assay which may correlate with a decrease in seizures, and less invasive than obtaining CSF.

Standard anti-seizure medications are known for their wide adverse side-effect profile, whereas the adverse events associated with Mg supplementation, which is quite inexpensive, are relatively benign and easily monitored. Given these data, clinical trials of the efficacy of Mg supplementation to routine anti-seizure therapy in medically responsive epilepsy are warranted.

REFERENCES

- Lazard EM. A preliminary report on the intravenous use of magnesium sulfate in puerperal eclampsia. *Am J Obstet Gynecol.* 1925;9:178-88.
- Duley L, Henderson-Smart DJ, Walker GJ, Chou D. Magnesium sulphate versus diazepam for eclampsia. *Cochrane Database Syst Rev.* 2010;8(12):CD000127.
- Duley L, Henderson-Smart DJ, Chou D. Magnesium sulphate versus phenytoin for eclampsia. *Cochrane Database of Syst Rev.* 2010;6(10):CD000128.
- Goldman RS, Finkbeiner SM. Therapeutic use of magnesium sulfate in selected cases of cerebral ischemia and seizure. *N Engl J Med.* 1988;319(18):1224-5.
- Sen A, Gulati A. Use of magnesium in traumatic brain injury. *Neurotherapeutics.* 2010;7(1):91-9.
- Muir KW, Lees KR, Ford I, Davis S, Investigators. IMEiSIS. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial. *Lancet.* 2004;363(9407):439-45.
- Zou L-P, Wang X, Dong C-H, Chen C-H, Zhao W, Zhao R-Y. Three-week combination treatment with ACTH + magnesium sulfate versus ACTH monotherapy for infantile spasms: A 24-week, randomized, open-label, follow-up study in China. *Clin Ther.* 2010;32(4):692-700.
- Kanbay M, Goldsmith D, Uyar ME, Turgut F, Covic A. Magnesium in Chronic Kidney Disease: Challenges and Opportunities. *Blood Purif.* 2010;29(3):280-92.
- Elin RJ. Magnesium metabolism in health and disease. *Dis Mon.* 1988;34(4):161-218.
- Sinert R, Zehtabchi S, Desai S, Peacock P, Altura BT, Altura BM. Serum ionized magnesium and calcium levels in adult patients with seizures. *Scand J Clin Lab Invest.* 2007;67(3):317-26.
- Aali BS, Khazaeli P, Ghasemi F. Ionized and total magnesium concentration in patients with severe preeclampsia-eclampsia undergoing magnesium sulfate therapy. *J Obstet Gynaecol Res.* 2007;33(2):138-43.
- Mody I, Lambert JD, Heinemann U. Low extracellular magnesium induces epileptiform activity and spreading depression in rat hippocampal slices. *J Neurophysiol.* 1987 Mar;57(3):869-88.
- Krauss GL, Kaplan P, Fisher RS. Parenteral magnesium sulfate fails to control electroshock and pentylenetetrazol seizures in mice. *Epilepsy Res.* 1989;4(3):201-6.
- Mikati MA, Injibar H, Kurdi RM, et al. Effects of magnesium sulfate in kainic acid-induced status epilepticus. *J Med Liban.* 2006;54(4):200-4.
- Standley CA, Irtenkauf SM, Cotton DB. Anticonvulsant Effects of Magnesium Sulfate in Hippocampal-Kindled Rats. *J Biomed Sci.* 1995;2(1):57-62.
- Cotton DB, Hallak M, Janusz C, Irtenkauf SM, Berman RF. Central anticonvulsant effects of magnesium sulfate on N-methyl-D-aspartate-induced seizures. *Am J Obstet Gynecol.* 1993;168(3 Pt 1):974-8.
- Safar MM, Abdallah DM, Arafa NM, Abdel-Aziz MT. Magnesium supplementation enhances the anticonvulsant potential of valproate in pentylenetetrazol-treated rats. *Brain Res.* 2010;1334:58-64.
- Borges LF, Gücer G. Effect of magnesium on epileptic foci. *Epilepsia.* 1978;19(1):81-91.
- Sibai BM, Spinnato JA, Watson DL, Lewis JA, Anderson GD. Effect of magnesium sulfate on electroencephalographic findings in preeclampsia-eclampsia. *Obstet Gynecol.* 1984;64(2):261-6.
- Koontz WL, Reid KH. Effect of parenteral magnesium sulfate on penicillin-induced seizure foci in anesthetized cats. *Am J Obstet Gynecol.* 1985;153(1):96-9.
- Temkin NR, Anderson GD, Winn HR, et al. Magnesium sulfate for neuroprotection after traumatic brain injury: a randomised controlled trial. *Lancet Neurol.* 2007;6(1):29-38.
- Sadeh M, Blatt I, Martonovits G, Karni A, Goldhammer Y. Treatment of porphyric convulsions with magnesium sulfate. *Epilepsia.* 1991;32(5):712-5.
- Visser N, Braun K, Leijten F, van Nieuwenhuizen O, Wokke J, van den Bergh W. Magnesium treatment for patients with refractory status epilepticus due to POLG1-mutations. *J Neurol.* 2011;258(2):218-22.
- Firoz M, Graber M. Bioavailability of US commercial magnesium preparations. *Magnes Res.* 2001;14(4):257-62.
- Coudray C, Rambeau M, Feillet-Coudray C, et al. Study of magnesium bioavailability from ten organic and inorganic Mg

- salts in Mg-depleted rats using a stable isotope approach. *Magnes Res.* 2005;18(4):215-23.
26. Oppelt WW, MacIntyre I, Rall DP. Magnesium exchange between blood and cerebrospinal fluid. *Am J Physiol.* 1963;205(5):959-62.
27. Sun L, Kosugi Y, Kawakami E, Piao YS, Hashimoto T, Oyanagi K. Magnesium concentration in the cerebrospinal fluid of mice and its response to changes in serum magnesium concentration. *Magnes Res.* 2009;22(4):266-72.
28. Thurnau GR, Kemp DB, Jarvis A. Cerebrospinal fluid levels of magnesium in patients with preeclampsia after treatment with intravenous magnesium sulfate: a preliminary report. *Am J Obstet Gynecol.* 1987;157(6):1435-8.
29. McKee J, Brewer R, Macy G, Borel C, Reynolds J, Warner D. Magnesium neuroprotection is limited in humans with acute brain injury. *Neurocrit Care.* 2005;2(3):342-51.
30. Fuchs-Buder T, Tramèr MR, Tassonyi E. Cerebrospinal Fluid Passage of Intravenous Magnesium Sulfate in Neurosurgical Patients. *J Neurosurg Anesthesiol.* 1997;9(4):324-8.
31. Hallak M, Berman RF, Irtenkauf SM, Evans MI, Cotton DB. Peripheral magnesium sulfate enters the brain and increases the threshold for hippocampal seizures in rats. *Am J Obstet Gynecol.* 1992;167(6):1605-10.