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Review Article:

EMERGING ROLE OF MAGNESIUM IN MODERN ANAESTHESIA, ANALGESIA, OBSTETRICS & CRITICAL CARE.

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Abstract:
Magnesium is a ancient cation but it can be used successfully as adjuvant to Local anaesthetic agent.iIt can be used successfully in various Surgeries like neurosurgery, cardiac surgery,as induced hypotensive agent,in FESS Surgeries, used for attenuation of pressure response to laryngoscopy& intubation,also to prevent postoperative sore throat.It can be used in critical care,& in obstetrics to prevent Eclampsia.In present article various uses of Magnesium sulfate discussed.

Introduction

Magnesium is the second most abundant intracellular cation[1,2] and the fourth when the extracellular medium is also considered[1]. It is involved biological reactions, such as[3]: hormone binding to receptors, flow of trans-membrane ions, regulation of the adenylate kinase system, muscle contraction, neuronal activity, vasomotor tone, cardiac excitability, release of neurotransmitters, and calcium binding to calcium channels.
In 1906, Haulbold and Meltzer reported sensorial and mo-tor blockades in humans after the intrathecal administration of magnesium; in 1950, magnesium was used in anesthesia, mainly to control seizures in gravidas. Currently, it has several applications in anesthesia, obstetrics, and critical care[3-5]. The objective of present review was to access the physiology, pharmacology, and reduction in plasma levels of magnesium, as well as some of its applications in obstetrics, anesthesia, analgesia,& critical care

PHYSIOLOGY AND PHARMACOLOGICAL EFFECTS

Magnesium is an intracellular cation with multiple functions: it participates in energy metabolism, since it is a cofactor in glucose metabolism, and a cofactor of nucleic acid, protein, and fatty acid degradation enzymes[5,6]; it regulates the flow of transmembrane ions[5]; and it mediates the activity of several enzymes[5,7]. Magnesium is considered a natural physiologic calcium antagonist, having several regulatory mechanisms, such as[1-3,8-11]: com-petitive antagonist affecting type L calcium channels, inhibition of the enzyme Ca^{2+}-ATPase, and it is a cofactor for all enzymes that participate in phosphate transferences that use ATP. In high concentrations, it inhibits the enzyme Na^{+}/K^{+}-ATPase[5]. Magnesium is absorbed in the jejunum and ileum at a propor-tion of 11% to 65% of the ingested amount[12]. The kidney is the main regulator of the levels of magnesium in the body, being capable of eliminating almost 100% of the filtered magnesium in case of overload[5].

Medicnot elucidated completely the mechanism of ac-tion of magnesium sulfate used therapeutically[13]. Some of the following proposa) and the amplitude of terminal end-plate potential[9].**b)**

Mechanism of action:

It is an antagonist of NMDA glutamate receptors[1,2,5,10,11]; this receptor is responsible for central sensitization[10]. Binding of this receptor has analgesic, anticonvulsant, and sedative properties[5].

c) It can increase the synthesis of prostacyclins and inhibit angiotensin converting enzyme,leadingto vasodilation[11].

d) It decreases the release of catecholamines after sympathetic stimulus[1,5,9,11]. It has been used in the treatment of pheochromocytoma-related hypertensive episodes during surgeries or outside the surgical environment[5].

e) In asthma patients, it inhibits the release of histamine and acetylcholine[5,16], and it potentiates the effects of beta-adrenergic agents[5]. It is indicated only in severe cases because it decreases the rate of hospitalizations and the length of stay in the intensive care unit, but it has little be-neficial effects in moderate and mild cases[16].

Formulation

For Intramuscular, intravenous use each ml of magnesium sulfate (heptahydrate) 500 mg , provide 4.06 meq of mgso4 & water for injection.PH- 5.5-7.No preservative, no bacteriostatic agent added.

Molecular Formula: Mgso4,7H20

Molecular weight:246.67

HYPOMAGNESEMIA & CRITICAL CARE

The human body has 21 to 28 grams of magnesium[5]. It is distributed as follows: 53% in the bones, 27% in the muscles, 19% in the soft tissues, 0.3% in the red blood cells, and 0.3% in the plasma[5,6]. Fifty-five per cent of plasma magnesium is ionized and 45% is bound to plasma pro-teins or broken into divalent anions, such as phosphate and sulfate[6]. Its plasma concentration ranges from 1.6 to 2.3 mg.dL^{-1} [5,6]. Since magnesium is an abundant intracellular ion and it is present in the plasma in very low amounts, measuring its plasma levels is not adequate to evaluate real deficiency or overload[5].

Body magnesium stores are better assessed by measuring the urinary excretion in patients without renal failure[5,6]. Under normal circumstances, a small amount of magnesium is elimi-nated in the urine[6]. The urinary retention test is performed by collecting 24-hour urine after the intravenous infusion of 6 g of magnesium sulfate[6]. When more than 70% of the amount administered is recovered from the urine, the presence of de-ficiency is unlike[5], but when less than 50% is recovered from the urine, body stores are probably deficient[6].

Hypomagnesemia is seen in 10% to 20% of hospitalized internal medicine patients[6], and 60% of patients in Intensive Care Units (ICU)[6,7], 7% of admissions for ketoacidosis, 30% of admissions to the neonatal ICU, and up to 70% after coronary revascularization in adults[5]. The presence of hypo-magnesemia in the surgical ICU has been associated with increased mortality[7].

Coronary Critical care patients

Clinical signs of hypomagnesemia are non-specific[6], and they are associated with cardiac arrhythmia[8], reduction in cardiac index[8], reduction in neuromuscular excitability[7], disorientation[9], seizures[9], and psychosis[9]. It is the main cause of refractory hypokalemia[7].

Sepsis, diabetic patients

Critical patients have a tendency to develop hypomagnesemia for several reasons: deficient intake, increased losses, and re-distribution in the body[5]. The main cause of hypomagnesemia is the use of diuretics and it is seen in 50% of chronic furosemide users[6]. Other possible causes include[5]: total parenteral nutrition; pancreatitis; burns; extracorporeal circulation; use of beta-agonists, aminoglycosides, and amphotericin B; diarrhea; acute tubular necrosis; and hypoparathyroidism.

Treatment consists on correcting the underlying cause, when-ever possible, and replacement of magnesium[5]. Intestinal absorption of magnesium is erratic and the intravenous route should be preferred for therapeutic use[5,7]. Six grams should be administered in 24 hours[5,7] and, in critical patients, serum levels should be maintained above 2.0 $mg.dL^{-1}$ [7].

Obstretic Uses

Magnesium sulfate has been used in obstetrics since 1925 for prevention of seizures in eclampsia[17,18], with the advantage of decreasing peripheral vascular resistance without changing uterine blood flow[5].

It has been postulated that the **anticonvulsant** property of mag-nesium sulfate is due to the blockade of NMDA receptors[5,14].

a)CNS & Neuromuscular junction effects:

Considerations on the real effects of magnesium in the treat-ment of eclampsia-related seizures have been made, since its effects in the neuromuscular junction can mask the real effects of magnesium in the central nervous system[19]. Doses used to depress the activity of the neuromuscular junction have been used in gravidas[20], and small alterations or even no changes on the electroencephalogram have been reported in some studies with women without eclampsia[21], with eclampsia[22], and in animal models[23]. Studies with Doppler flowmetry have demonstrated cerebral vasodilation[2,5] and reversion of cere-bral vasospasm[2,15] after the administration of magnesium.

The therapeutic serum level for the treatment of seizures ranges from 4.2 to 8.4 $mg.dL^{-1}$ which can be achieved by the intramuscular administration of 6 g followed by 2 g/hour; intravenous administration of 3 to 4 g (up to 1 g/min) or a combination of both routes[19]. Two administration schedules of magnesium are widely used: Pritchard's and Zuspan's[18].

b)Prit-chard's schedule

It starts with a 14-gram dose, 4 g IV and 5 g in each gluteal region[18]. Maintenance is achieved with 5 g every 4 hours in the gluteal region[18].

c)Zuspan's schedule

Bolus 4 g IV[18], followed by continuous infusion of 1 g/hour[18]. Elevated plasma levels are associated with adverse effects (Table I); therefore, it is necessary to observe some clinical parameters to guarantee the safety of its use[17]. Those para-meters

include: diuresis of 25 $mL.h^{-1}$, positive patellar reflex, respiratory rate greater than 12 bpm, and unchanged vital signs (blood pressure, heart rate, and level of consciousness)[17]. Magnesium decreases by 52% of the risk of seizures when compared to diazepam, and 67% when compared to phenytoin[24]. This study increased the use of magnesium from 2% to 40% in patients with preeclampsia in the United Kingdom[19]. Benzodiazepines are indicated for the treatment of seizures

Table I -

Clinical Manifestations of Hypermagnesemia Serum levels in $mg.dL^{-1}$

	Symptom
5-9	Therapeutic
10-15	Areflexia
15-20	Respiratory arrest
≥ 25	Cardiac arrest

only postpartum[17], in the absence of magnesium sulfate[17], or when treatment with magnesium sulfate has failed[2].

Further studies on this area will focus on aquaporin 4[19], a wa-ter channel-bound protein found in the final portion of astrocyte axon, whose levels are increased in cerebral edema[19]. Magnetic resonance imaging studies have documented cerebral edema of the white matter of the posterior region of the brain eclampsia patients[25]. This change has also been documented in animal models of eclampsia[25]. The expression of aquaporin 4 is increased in pregnancy[26], and the use of magnesium sul-fate decreases cerebral expression of this protein, which can attenuate cerebral edema in eclampsia patients[27].

Magnesium has been used as the standard drug for tocoly-sis during treatment of premature labor, and other drugs have been compared to it[28]. The mechanism of action has not been completely elucidated, but it seems to be secondary to calcium antagonism by competing for the binding site of this ion[28]. The loading dose for tocolysis ranges from 4 to 6 g intravenous over 15 to 30 minutes, followed by maintenance with 2 to 6 g IV/hour[28]. Several patients treated with magnesium devel-op minor adverse reactions, such as: feeling hot, scotomata, nausea, vomiting, blurred or double vision, and lethargy[5,28]. Adverse effects can be reverted by the intravenous adminis-tration of 1 g of calcium gluconate[5].

ANESTHESIA & CRITICAL CARE CONSIDERATIONS :

The indications of magnesium sulfate in anesthesia have been increasing over the years to include situations out of the gynecological field[5]. It has analgesic and sedative properties with potential neuro- and cardioprotective effects, although it is not know the mechanisms of those actions[5,29].

Myocardial & cerebral Ischemia

acute myocardial infarction (AMI), 80% of the patients develop hypomagnesemia in the first 48 hours, probably secondary to the high serum levels of catecholamines[6]. Magnesium

deficiency leads to cell depolarization and promotes tachycardia[6]. Two studies using magnesium in patients with AMI, LIMIT 2 and ISIS 4, showed antagonic mortality results[5]. Only LIMIT 2 showed a reduction in mortality, but magnesium was used before spontaneous or pharmacologic recovery of the occluded vessel[5]. The prophylactic use to prevent hypomagnesemia during extracorporeal circulation is controversial, although reduction in the incidence of ventricular tachycardia and atrial fibrillation has been shown[5].

Neuronal ischemia leads to the outflow of ATP from the cell and inflow of calcium, which triggers the release of toxic metabolites, culminating with cell death[5]. Blockade of glutamate NMDA receptors inhibits the cellular inflow of calcium and contributes for neuronal protection[3,29-31]. Other probable actions for cerebral protection include: reduction in the presynaptic release of excitatory neurotransmitters[32], blockade of calcium channels[32,33], suppression of anoxic depolarization[32], antioxidant effects[31,32], an increase in cerebral blood flow[29,30,32,33]. Besides, cellular energy preservation is also seen, since magnesium is bound to ATP in the cytosol.

Two studies demonstrated antagonic results in patients with cerebral ischemia, IMAGE and FAST-MAG[32]. A 90 $mg.kg^{-1}$ dose reduced infarction volume after middle cerebral artery embolus by 48% when administered in the first six hours[32]. It is possible that the doses used in the IMAGE study have not been enough to cause an increase in the concentration of magnesium in cerebral cells[15].

Attenuation of stress response to intubation:

Magnesium has been used to attenuate the cardiovascular re-sponse to tracheal intubation[5]

This effects is, probably, secondary to a reduction in the release of catecholamines after sympathetic stimulation[1,3,5,11,34,35]. A 40 $mg.kg^{-1}$ dose has shown similar efficacy to that of 10 $\mu g.kg^{-1}$ of alfentanil as well as greater effectivity than 1.5 $mg.kg^{-1}$ of lidocaine[5]. It is a complementary drug in the treatment of hypertensive episodes during the surgical treatment of pheochromocytoma, since it inhibits the release of catecholamines from the adrenal glands[5].

Effects on Neuromuscular junction & interaction with Relaxants:

Magnesium inhibits the release of acetylcholine in the neuromus-cular junction and behaves as a neuromuscular relaxant, poten-tiating the effects of non-depolarizing neuromuscular blockers[5]. A 40 $mg.kg^{-1}$ dose of magnesium reduces the ED_{50} of vecuronium by 25%[5]. When magnesium is administered before induc-tion, it prevents succinylcholine-induced increase in potassium levels[9,36]. This drug limits muscular fasciculation, but does not interfere with the time of recovery of succinylcholine[36].

The analgesic potential of magnesium is partially secondary to the blockade of NMDA receptors, but also to a reduction in the release of catecholamines[11]. The potential to reduce the MAC of volatile anesthetics has been confirmed in laboratorial studies with rat models[1,5,37], and it can be as high as 60%[1]. Schutz-Stubner et al.[3] demonstrated a reduction in the need of remifentanil and fentanyl when one intravenous dose of 50

$mg.kg^{-1}$ of magnesium was used in humans. Collateral effects were not observed with this dose[3].

Magnesium as adjuvant to local anaesthetic agent in spinal, Epidural ,caudal anaesthesia and peripheral nerve blockages.

Magnesium is successful adjuvant to LA by its NMDA antagonism effect,it prolonge sensorimotor blockage .

A) adjuvant to LA in spinal anaesthesia

Sarika sarkar etal use different doses of Mgso4 as adjuvant to bupivacaïne & compare with Fentanyl in spinal anaesthesia & concluded that Mgso4 is good adjuvant to bupivacaïne in spinal anaesthesia and improve sensorimotor blockage charesteristics in spinal anaesthesia & dose dependably,prolonged postoperative analgesia (39)

Satish Kumar Chaudhary etal use different doses of Mgso4 in spinal anaesthesia and concluded that Mgso4 improve spinal bupivacaïne effects.(40)

B) Adjuvant in Epidural anaesthesia

Sonali Banwait,sujata Sharma have compare 75 mg of Mgso4 & 1 mcg/kg of Fentanyl as adjuvant to LA & showed that epidural magnesium decreases Verbal rating scale, prolonge duration of Analgesia.(41)

Tanmay Ghatak etal evaluated 50 mgmgso4/ 150 mcg clonidine as a adjuvant to epidural Bupivacaïne & concluded that Mgso4 group showed no shivering, Rapid onset, without adverse effects.(42)

C) **Mgso4 as adjuvant to LA in paediatric caudal Anaesthesia**

Hegar Reface etal compare 1 mcg/ Kg of Dexmedemidine/ 50 mgMgso4 and showed that both adjuvants improve sensorimotor blockage charesteristics , post-op Analgesia of LA.(43)

D) **Mgso4 in Peripheral nerve blockage**

James MF shown mechanism of action of Mgso4 in Peripheral nerve blockage as it interferes with release of neurotransmitter in synaptic cleft& potentiates LA action.(44,45)

ElshamaHA etal use mgso4 in femoral nerve blockage & concluded that Mgso4 potentiates action of LA.(46)

Hasan etal. had used mgso4 in thoracic paravertebralblock with bupivacaïne for analgesia in MRM surgery & concluded effective roleof mgso4 in block(47)

Goyal P had used mgso4 in bracheal plexus blockage & shown analgesic properties of mgso4.(48)

Topical magnesium sulfate to prevent postoperative sore throat.(POST)

Narinder Singh etal proved thàt topical Mgso4 prevent POST effectively.(49)

SunilRajan,George Malayil etal showed ketamine/ mgso4 nebulization can attenuate POST.(50)

Magnesium in cardaiac Anaesthesia

Magnesium is very useful for maintenance fluid infusion & for prevention of arrhythmias.
Mansoor Jannati etal use1.5-2 gr of Mgso4 in cardiovascular surgery in Iv/ oral formulation & concluded that decrease in prevalence of arrythmia by costeffective method.(51)

Robie Soliman have given 15mg/kg/ hr of magnesium infusion 20 min before induction & found decrease in Tropornin I ,CK-MB level,lower ECG changes, increase E/A peak ratio,Enddiastolic volume, Cardiac index.there was decrease in Heart rate,mean Pulmonary artery Pressure Pulmonary vascular Resistance, pharmacological & Mechanical support in group magnesium than in control group.(52)

A Roscoac,A.Ahmed etal done survey of perioperative use of Mgso4 in cardiovascular surgery in Uk & concluded that Mgso4 is advantageous in cardiac surgery.(53)

Magnesium in Neuroananaesthesia
Magnesium is used successfully as adjuvant to general anaesthesia for resection of tumors.

Charu Mahajan etal have given lignocaine 1.5-2 mg/ kg bolus following 2 mg/ kg/ hour in lignocaine group
In Mgso4 group Mgso4 50 mg/ kg bolus following by 25 mg/ kg/ hour as.adjuvant in supratentorial resection of tumor,& access post-op Analgesia, opioid requirements ,VAS,S100 B levels.They have found decrease VAS, fentanyl consumption in lignocaine & Mgso4 group then in saline group.but 24 hr S100 B level was decrease in Mgso4 group which suggests neuroprotective Effects of Mgso4.S100B is calcium binding protein having Alpha& beta subunits.Beta units present in glial& Schwan cells.Increase level of it in brain injury & poor outcome.so decrease level of it suggests Enhanced recovery after surgery (ERAS)in Mgso4 group.(54)
Magnesium for induce hypotension
Magnesium causses induced hypotension & very useful to prevent blood loss.
N M Elsgarnouby use Magnesium infusion for FESS surgery to prevent blood loss.They used 40 mg/ kg bolus following 15 mg/ kg/ hr.It decrease blood loss, MAP,HR,Anaesthetic requirements of fentanyl, Vecuronium,sevoflurane.They have access blood loss by Boezaart score.(55)
SaudersGM,Sim Km, used Magnesium as hypotensive agent in oral& faciomaxillary Surgery . They used 40 gr/ hr to maintain 55+/-5 mm of Hg then5 gr/ hr until 30 min before end of surgery.(56)
Mgso4 for attenuation of Pressure response in laproscopy surgery
Shruti Kamble etal compare Mgso4 with clonidine for attenuation of Pressure response to pnuemoperitonium in the laproscopy surgery & concluded that mgso4 successfully attenuate pressure response(57)
Mgso4 as adjuvant in pheochromocytoma

Pits Miller etal use mgso4 successfuly to control blood pressure in recetion of pheochromocytoma.(58)

In nutshell,Magnesium sulfate has been used in obstetrics with good results inhibiting of premature labor and in the treatment of eclampsia-related seizures. This drug is potentially analgesic and sedative and it could be used as adjuvant during general anesthesia, reducing the blood pressure response to tracheal intubation and decreasing the need of anesthetic agents.It could be safely used as adjuvant to local anaesthetic agent in spinal, epidural,caudal, Anaesthesia, various peripheral blockages.It is used in cardiac Anaesthesia since recently it is started to be used in various neurosurgery, laproscopic surgery,for induce hypotension,& nebulization of it prevents postoperative sore throat,haorseness of voice following endotracheal intubation.so it is a single cost-effective drug with multiple uses..

REFERENCES

1. Telci L, Esen F, Akcora D et al. Evaluation of effects of magnesium

in reducing intraoperative anaesthetic requirements. Br J
Anaesth 2002;89:594-598.
2. Bahar M, Chanimov M, Grinspun E et al. Spinal anaesthesia induced
by intrathecal magnesium sulphate. Anaesthesia 1996;51:627-633.
3. Schutz-Stubner S, Wettmann G, Reyle-Hahn SM et al. Magnesium as part of
balanced general anaesthesia with propofol, remifentanil and mivacurium:
a double-blind, randomized prospective study in 50 patients. Eur J Anaesthesiol 2001
;18:723-729.
4. Chanimoy M, Cohen ML, Grinspun Y et al. Neurotoxicity after spinal
anaesthesia induced by serial intrathecal injections of magnesium sulphate.
An experimental study in a rat model. Anaesthesia 1997;52:223-228.
5. Alday Muñoz E, Una Orejón R, Redondo Calvo FJ et al. Magnesium
anestesia y reanimación. Rev Esp. Anestesiol Reanim2005;52:222-234.
6. Marino PL. Magnésio. In: Marino PL. Compêndio de UTI. Porto Alegre:
Artmed, 2000;529-538.
7. Nácul FE. Distúrbios eletrolíticos em medicina intensiva. In: Nácul FE.
Medicina intensiva - abordagem prática. Rio de Janeiro: Revinter,2004;309-318.
8. Roscoe A, Ahmed AB. A survey of peri-operative use of magnesium sulphate
in adult cardiac surgery in the UK. Anaesthesia 2003;58:363-365.
9. Pascarella PJ e Pineda M. Efectos del sulfato de magnesio en la respuesta
hemodinamica durante la laringoscopia e intubación traqueal.Rev Venez Anestesiol
1998;3:8-12.
10. Kara H, Sahin N, Ulusan V et al. Magnesium infusion reduces perioperative pain.
Eur J Anaesthesiol 2002;19:52-56.
11. Elsharnouby NM, Elsharnouby MM. Magnesium sulphate as a technique of hypotensive
anaesthesia
. Br J Anaesth 2006;96:727-731.

12. Booth CC, Babouris N, Hanna S et al. Incidence of hypomagnesaemiain intestinal malabsorption
. Br Med J 1963;2:141-144.
13. Glover ML, Machado C, Totapally BR. Magnesium sulfate administered via continuous IV infusion in pediatric patients with
refractory wheezing. J Crit Care 2002;17:255-258.
14. Ganem EM e Castiglia YMM. Anestesia na pré-eclampsia. Rev Bras Anestesiol 2002;52:481-497.
15. McKee JA, Brewer RP, Macy GE et al. Analysis of the brain bioavail- ability of peripherally
administered magnesium sulfate: A study in humans with acute brain injury undergoing prolonged
induced hyperma-gnesemia. Crit Care Med 2005;33:661-666.
16. Barbosa FT, Barbosa LT, Cunha RM et al. Uso do sulfato de magnésio por via venosa e nebulização para o tratamento da asma agudana emergência. Rev Bras Ter Intensiva 2007;19:369-373.
17. Gonçalves MM. Doença hipertensiva específica da gravidez. In: Ratton JLA. Medicina intensiva.
São Paulo:Atheneu, 1997;66-76.
18. Cardoso RL, Correa CM. Pacientes obstétricos em UTI. In:
Nácul FE.Medicina intensiva - abordagem prática. Rio de Janeiro: Revinter, 2004;542-548.
19. Euser AG, Cipolla MJ - Magnesium sulfate for a treatment of eclampsia:
a brief review. Stroke, 2009;40:1169-1175.
20. Ramanathan J, Sibai BM, Pillai R et al. Neuromuscular transmission
studies in preeclamptic women receiving magnesium sulfate. Am JObstet
Gynecol 1998;158:40-46.
21. Somjen G, Hilmy M, Stephen CR. Failure to anesthetize human subjects
by intravenous administration of magnesium sulfate.
J Pharmacol Exp Ther 1966;154:652-659.
22. Sibai BM, Spinnato JA, Watson DL et al. Effect of magnesium sulfate
on electroencephalographic findings in preeclampsia-eclampsia. Obstet Gynecol 1984;64:261-266.
23. Koontz WL, Reid KH. Effect of parenteral magnesium sulfate on penicillin
-induced seizure foci in anesthetized cats. Am J Obstet Gynecol1985;153:96-99.
24. The Eclampsia Trial Collaborative Group. Which anticonvulsant for
women with eclampsia? Evidence from the collaborative eclampsia trial.
Lancet 1995;345:1455-1463.
25. Karumanchi SA, Lindheimer MD. Advances in the understanding of eclampsia.
Curr Hypertension Rep 2008;10:305-312.26. Quick AM, Cipolla MJ. Pregnancy
-induced up-regulation of aquaporin-4 protein in brain its role in eclampsia. FASEB J 2005;19:170-175.

27. Ghabriel MN, Thomas A, Vink R. Magnesium restores altered qua-porin-4 immunoreactivity following
traumatic brain injury to a pre-injury state. Acta Neurochir Suppl 2006;96:402-406.
28. Lewis DF. Magnesium sulfate: the first-line tocolytic. Obstet Gynecol Clin North Am 2005;32:485-500.
29. Wadhwa A, Sengupta P, Durrani J et al. Magnesium sulphate only slightly reduces the shivering threshold in humans. Br J Anaesth2005;94:756-762.
30. Simpson JI, Eide TR, Schiff GA et al. Intrathecal magnesium sulfate protects the spinal cord from ischemic injury during thoracic aortic
cross-clamping. Anesthesiology 1994;81:1493-1499.
31. Breen TW, Yang T. The changing role of magnesium sulphate therapy. Curr Opin Anaesthesiol 1999;12:283-287.
32. Dohi K, Ohtaki H, Shioda S et al. Magnesium sulfate therapy in patients with acute neuronal damage: the problem of intravenous admin-istration. Crit Care Med 2005;33:698-699.
33. Bilotta F, Rosa G. Magnesium sulfate and neuroprotection. Anesth Analg 2003;96:1838.
34. Pivalizza EG. Magnesium sulfate and epidural anesthesia in pheochromocytoma and severe coronary artery disease. Anesth Analg1995;81:414-416.
35. Ramirez Paesano C, Gonzalez O, Rodriguez B et al. Laringoscopia e intubación traqueal: uso de sulfato de magnesio para atenuar la respuesta cardiovascular refleja. Rev Venez Anestesiol 1998;3:66-71.
36. Stacey MR, Barclay K, Asai T et al. Effects of magnesium sulphate on suxamethonium-induced complications during rapid-sequence induc-tion of anaesthesia. Anaesthesia 1995;50:933-936.
37. Altan A, Turgut N, Yildiz F et al. Effects of magnesium sulphate &clonidine on propofol consumption, haemodynamics and postopera
recovery. Br J Anaesth 2005;94:438-441.
38. Lysakowski C, Dumont L, Czarnetzki C et al. Magnesium as an ad
to postoperative analgesia: a systematic review of randomized
trials. Anesth Analg 2007;104:1532-1539.
39.Sarika Sarkar,chhavi Drevedi, Comparison of different doses of Mgso4/ Fentanyl as adjuvant to bupivacaïne for infraumbilical surgery under subarachnoid blockage.Indian journal of Anaesthesia 2015, vol 59, issue 8,page471-475.
40.Satishkumar Chaudhary,Shelly Rana, Mgso4 at 2 different doses as adjuvant to bupivacaine in infraumbilical orthopaedic surgery under spinal anaesthesia.Ain shams journal of Anaesthesia,2016, volume 9, issue 3,page416-421.
41.Sonali Banwait,Sujata Sharma,Rajesh Sood, Evaluation of single bolus dose of magnesium as adjuvant to epidural fentanyl for postoperative Analgesia.Saudi journal of Anaesthesia 2012,jul -sep6(3): 273-278.
42Tanmay Ghatak,,Girish chand, Evaluation of effect of Mgso4 & clonidine as adjuvant to epidural Bupivacaine, Indian Journal of Anaesthesia, volume 54, issue 4,308-313.

43.Hagar Reface,Amol Hanafy,Elela,Dexmedetomidine/ Mgso4 as adjuvant to Bupivacaine induced caudal block in children.open acess maced journal med.scijan 15,7(1):73-76.
44.James MF.(1992)clinical use of Magnesium infusion in Anaesthesia& Analgesia,74:129-136.
45.James MF(2009)Magnesium as an emerging during Anaesthesia, British journal of Anaesthesia 103:465-467
46.ElShamaHA, Ibrahim M,Eldesukg HI, Mgso4 in femoral nerve blockage as adjuvant to bupivacaine, Egyptian journal of Anaesthesia 30:169-173.
47.Hasan MF,Marhan, Effects of adding Mgso4 to bupivacaine on clinical profile of ultrasound guided thoracic paravertebralblock in patients of Modified Radical Mastoidectomy.Egyptian journal of Anaesthesia 2015:31:23-27
48.Goyal P,Jaiswal R,HoodaS,Role of Mgso4 for bracheal plexus Analgesia.Internet journal of Anaesthesia 2008,21:1
49.Narinder singh, Jeetinder Makkar.Role of topical magnesium in postoperative sore throat, systematic review.Indian journal of Anaesthesia,2019, volume 63, issue 7,520-529.
50.Sunil Rajan, George Malayil , comparison of Mgso4/ NS nebulization for attenuation of Postoperative sore throat, hoarseness of voice,cough.Anaesthesia essay & reaserch,2017, volume 11, issue 2287-293.
51.Mansour Jannati,Sharbanoo Shahbazi , Laleh Eshaghi. Comparision of oral/ IV Magnesium in prevention of hypomagnesemia& arrythmia after CABG. Journal of cardiovascular surgery.2018,33(5).448-453.
52.Robie Soliman,Walid. Abukhudair,periopeffects of mgso4 in patients with concentric LVH undergoing cardiac surgery.double blind Randomised study.Annals of cardiac Anaesthesia,2019, volume 22, issue 3,246-253.
53.A.Roscac,A B Ahmed, survey of perioperative use of Mgso4 in adult Cardiac surgery in UK. Anaesthesia/ vol 58, issue4
54.Charu Mahajan,Rajeeb Mishra,Bhagya Ranjan Jena,effects of magnesium & lignocaine on postcraniotomy pain.Saudi journal of Anaesthesia 2/19, volume 13, issue 4,page299-305.

55.N M Elsharnousby, Magnesium as a hypotensive anaesthetic agent , British journal of Anaesthesia,june2006, volume 96, issue 6,page 727-731

56.Saunders GM,Sim Km.Is it feasible mgso4 as hypotensive agent in oral & faciomaxillary Surgery? Ann.Acaf Med Singapore 1998, volume 27 , page 780-785.

57.Shruti Kamble,Genesh C.Anandswamy ,, comparison of Mgso4/ clonidine for attenuation of Pressure response to pnuemoperitonium in laproscopic cholecystectomy.Anaestheaia, Essay, Reaserch jan- March2017:11(1),67-71.

58.Pit Miller,Primus E.Use of Mgso4 as anaesthetic management of pheochromocytoma.west indian med joirnal 2000 march49(1),73-75.

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