USES OF MAGNESIUM SULFATE - REVISITED
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ABSTRACT: HISTORY / BACKGROUND: Magnesium sulfate is the ninth most abundant element in the universe, eighth most abundant element in the earth’s crust. In the human body magnesium activates hundreds of cellular & biochemical reactions. Magnesium is commonly extracted from seawater, where it is the third most common component.

Magnesium was first isolated in 1808 by Sir Humphrey Davy, used the term “magnesium” from the word magnesia. Early use of magnesium was as a curative agent in the form of laxatives & Epsom salts. In 1900 was first used to control eclamptic seizure in parturient.

Richard Wills latter won Nobel Prize in 1915 for describing the nature of the structure of chlorophyll in plants noting magnesium as the central element.

Over the past 100 years, there have been countless research studies investigating the efficacy of magnesium sulfate in various clinical conditions. This article reviews the multifaceted uses of magnesium sulfate in clinical practice.

KEY WORDS: magnesium sulfate, hypomagnesemia, oral & IV preparations.

INTRODUCTION: Magnesium is the most abundant intracellular cation in the human body and the most underdiagnosed electrolyte abnormality in current medical practice. The average sized adult contains approximately 24g (1 mole or 2000meq) of magnesium, one half of total body magnesium is present in bone (53%), 27% in skeletal muscle, 19% in soft tissue, 0.7% in RBC & 0.3% in plasma. Therefore serum magnesium levels can be normal in the face of total body magnesium depletion. (1)

SERUM MAGNESIUM: The normal range for serum magnesium depends on the daily magnesium intake. Recommended dietary allowances of Mg²⁺ - 200 -350mgs (higher requirement in pregnancy). Only 67% of the magnesium in plasma is in the active/ ionized form, and the remaining 33% is either bound to plasma proteins(19% of total ) or chelated with divalent anions such as phosphate and sulfate (14% of the total ).The normal plasma levels are 1.4 to 2.1meq/l. (2), (3)

URINARY MAGNESIUM: Under normal circumstances only small quantities of Mg²⁺ are excreted in the urine. In the presence of deficiency the kidneys conserve Mg²⁺ & urinary magnesium excretion falls to negligible levels (studies have shown that only 5% of filtered Mg²⁺ is excreted where as 70% is reabsorbed in loop of Henle).Hence estimation of urinary Mg²⁺ may be an indicator of magnesium deficiency. (4)

ROLE OF MAGNESIUM IN THE BODY:
- Magnesium is a physiological calcium antagonist, primarily based on the regulation of calcium influx into the cells.
- NMDA antagonist – By blocking NMDA receptors, central sensitization caused by peripheral nociceptive stimulation is prevented. (5), (6).
Magnesium is essential for activation of Na+K+ATPase system, necessary for presynaptic release of acetylcholine from nerve endings.

Mg2+ ions are involved as a cofactor in about 300 known enzymatic reactions in the body such as hormone receptor binding, gating of calcium channels, transmembrane ion flux, regulation of adenyl cyclase system, neuronal activity, vasomotor tone, cardiac excitability.

Biosynthesis of DNA & RNA, protein synthesis & ATP.

Mg2+ affects calcium 5649 metabolism, controls release & action of parathyroid hormone so magnesium deficiency is often associated with hypocalcaemia.

USES OF MAGNESIUM:

- REDUCES ANALGESIC REQUIREMENT: Pain is an important component of post-operative recovery, effective treatment serves to blunt autonomic, somatic & endocrine reflexes with a resultant potential decrease in peri-operative morbidity.

Mg2+ blocks calcium influx & non-competitively antagonizes NMDA receptor channels.

These effects have prompted the investigation of magnesium as an adjuvant agent for intra & post-operative analgesia. Clinically relevant concentrations of volatile anaesthetics inhibit functioning of NMDA receptors. This inhibition is reversible, concentration-dependent and voltage-insensitive, and results from noncompetitive antagonism of glutamate/glycine signaling. In addition, these effects can be potentiated significantly by co-application of either Mg2+, S (+)-Ketamine interact super additively at NMDA receptors, which may explain the clinical efficacy of the combination.

S. Schulz-Stunner et al, study has shown that usage of Mgso4 as a supplement during remifentanil or propofol and mivacurium anaesthesia has reduced the anaesthetic & relaxant drugs needed.(7)

Kara H. et al, study has shown the mean intraoperative fentanyl requirement was higher in control group than in the magnesium group (p<0.05). Postoperative morphine doses decreased significantly in magnesium group (p<0.05). (8)

Tramer MR et al. performed a randomized, double blind study to assess the role of magnesium on analgesic requirements, pain, comfort & quality of sleep in the post operative period. 42 patients undergoing elective abdominal hysterectomy with general anaesthesia received 20% magnesium sulphate or saline (control) 15ml IV before start of surgery & 2.5ml/h for the next 20h. Postoperative morphine requirement was assessed for 48h using patient controlled analgesia. Compared to control subjects, magnesium treated patients consumed less morphine during the first 6h (p<0.004), had less discomfort on first and second post operative days (p<0.05-0.005) & no change in postop sleeping patterns compared to preoperative patterns. The authors concluded that perioperative use of magnesium sulphate is associated with less analgesic requirement, less discomfort & better quality of sleep in the postoperative period but not with adverse effects.(9)

Systematic review provides convincing evidence that use of magnesium sulfate as an adjuvant to post-op analgesic results in less total analgesic requirement & pain intensity. Meta-analysis on peri-operative IV administration of magnesium sulfate for post-operative pain showed a reduction in opioid consumption & lesser extent of pain scores in first 24 hours post operatively without any reported serious adverse effects. (10). Magnesium combined with Bupivacaine produces a reduction in post operative pain when given intra-articulary after...
Arthroscopic knee surgery in comparison to either Bupivacaine or magnesium alone or to saline placebo. (11).

Mg2+ may have a role in chronic & neuropathic pain. Further exploration regarding Mg2+ in pain is required. An inverse relationship has been demonstrated between the severity of pain with different painful medical & surgical conditions & serum Mg2+ concentrations(12).

**CHANGES IN SERUM MAGNESIUM CONCENTRATIONS DURING ANAESTHESIA:** According to several clinical studies, it was noted that magnesium was lowering during anaesthesia and became normomagnesemic on the 1-3 day after surgery (13). CSF magnesium levels remains unchanged during anaesthesia (p<0.001) & plasma magnesium concentration is not parallel with CSF magnesium concentration (14). Sasaki R et al in their study have concluded that magnesium supplementation is required during anaesthesia when a large amount of fluids are infused (15). Serum magnesium levels after major gastrointestinal & thoraco-abdominal surgery showed a statistically significant (p<0.05) reduction in magnesium levels (16). Spinal anaesthesia unexpectedly reduced CSF total & ionized magnesium concentration in patients undergoing hip arthroplasty, although the mechanism is unclear peripherally infused magnesium sulfate during spinal anaesthesia is unlikely to influence central NMDA receptor activity (17).

**MAGNESIUM IN CARDIAC SURGERY:** After cardiac surgery, magnesium is often administered for prophylaxis and treatment of cardiac arrhythmias. Mg2+, however inhibits platelet function in vitro and vivo in healthy volunteers. Gries A et al concluded that in a randomized, blinded, placebo-controlled study of 24 h after coronary artery bypass grafting, IV magnesium inhibited platelet function in vitro & in vivo (18). Akazawa S et al concluded that a bolus dose of MgSO4 30, 60, 90 mg/kg significantly prolonged AV conduction time during sinus rhythm and QTc interval remained unchanged (19). This finding suggests that MgSO4 in high doses was safe and may be indicated for cardiac arrhythmia and hypertension during sevoflurane anaesthesia. However further study is required for its application in clinical anaesthesia.

Fanning & colleagues (20) studied the effects of giving 48mmol of magnesium sulfate by continuous infusion during the first postoperative day after cardiac surgery. They found fewer episodes of atrial fibrillation in the group given prophylactic magnesium compared to controls. Overall, magnesium is a cheap & efficacious therapy for treating both supraventricular and ventricular arrhythmias. It may be recommended as a primary therapy for non-life-threatening cardiac arrhythmias.

**MAGNESIUM & SKELETAL MUSCLE RELAXANTS:** The effect of magnesium as muscle relaxant has been known since 1950s. T. Fuchs-Buder et al, T. Okunda et al have investigated the interaction between MgSO4 40mg/kg & vecuronium and concluded that the neuromuscular potency of vecuronium was increased by pretreatment with MgSO4 (21), (22), (23).

Sloan PA and Rasul M have reported a prolonged neuromuscular block with non depolarizing muscle relaxant rapacuronium in the presence of clindamycin & magnesium (24). Hypermagnesemia enhances sensitivity of all NDMR. Use of peripheral nerve stimulator is mandatory to guide further dosing. Ross RM and Baker T determined that clinically relevant infusions of magnesium sulfate produced significant changes in neuromuscular transmission as manifested by diminished “train of four” response to ulnar nerve stimulation in parturient. (25).
DEPOLARIZING MUSCLE RELAXANTS

- Neuromuscular blockade produced by suxamethonium is not potentiated by magnesium therapy.
- Plasma cholinesterase activity is unaffected by magnesium.
- Phase II block produced by suxamethonium, may be potentiated by magnesium therapy.

MAGNESIUM TO ATTENUATE PRESSOR RESPONSE: Magnesium is popularly used to attenuate the pressor response to laryngoscopy & intubation in patients with gestational hypertension /PIH for general anaesthesia. MgSO4-40mg/kg is superior to lidocaine -1.5mg /kg or alfentanil -10mg/kg for control of hypertensive response to intubation & produces less fetal depression than alfentanil. A combination of 30mg/kg of MgSO4 with 7.5mg/kg of alfentanil as a bolus immediately following the induction agent is the method of choice for control of intubation response (26).

ICU & SERUM MAGNESIUM LEVELS: 65% of patients in ICUs reported magnesium deficiency & 20% of hospitalized patients in medical wards (27). Magnesium depletion is the most under diagnosed electrolyte abnormality in current medical practice (28). As magnesium depletion is not evident with hypomagnesemia the incidence is much higher than indicated by the statistical data.

Predisposing conditions for magnesium deficiency

- Diuretics: especially loop diuretics (furosemide & ethacrynic acid) is the leading cause of magnesium deficiency. Drug induced inhibition of sodium reabsorption also interferes with magnesium reabsorption & the resultant urinary magnesium losses can parallel urinary sodium losses. 50% of the patients receiving furosemide showed magnesium deficiency (29); however thiazide diuretics showed deficiency only in the elderly (30). Potassium sparing diuretics such as triamterene did not show magnesium depletion. (31).
- Antibiotics & hypomagnesemia: Aminoglycosides, amphotericin & pentamidine promote Mg2+ depletion. Aminoglycosides block magnesium reabsorption in the ascending loop of Henle & hypo magnesium has been reported in 30% of the patients receiving aminoglycoside therapy (32).
- Diabetes mellitus: magnesium depletion is common in IDDM probably as a result of urinary magnesium losses that accompany glycosuria. (33)
- Secretory diarrhea: can be accompanied by profound magnesium depletion (as lower GIT has high concentration of mg2+ =10-14meq/l) (34).
- Other drugs associated with magnesium depletion: Digitalis, epinephrine, cisplatin & cyclosporine are associated with magnesium depletion. Digitalis & epinephrine shift magnesium into cells where as cisplatin & cyclosporine promote renal magnesium excretion.
- Acute myocardial infarction: 80% of patients with acute MI can have hypomagnesemia in the first 48h after the event. The mechanism is unclear, but may be due to intracellular shift of magnesium caused by endogenous catecholamines excess. (35). Alcohol abuse: Generalized weakness & chronic diarrhea often associated with thiamine deficiency is the reason for hypomagnesemia. Alcohol itself does promote renal magnesium wasting by an effect on renal tubular magnesium reabsorption.
- Prolonged nasogastric suction, short bowel syndrome, malabsorption syndrome & refeeding syndromes are most common causes of magnesium depletion in ICU, occurs due to acute intracellular shift of magnesium secondary to metabolic acidosis (36).
• Large volume resuscitation with hypotonic fluids not containing electrolytes, blood & its products & TPN will promote hypomagnesemia.
• Hypoalbuminemia in critically ill patients have a decrease in total magnesium levels secondary to a decrease in the protein-bound fraction.

ROLE OF MAGNESIUM IN VARIOUS CLINICAL SITUATIONS
• Pheochromocytoma: The rational for the use of magnesium sulphate infusion in the anaesthetic management of pheochromocytoma is its antiadrenergic, antihypertensive & antiarrhythmic action. By its calcium channel blocking properties the release of catecholamines is inhibited. Should be used with caution in patients with pheochromocytoma, complicated with impaired myocardial contractility. (37).
• An initial bolus dose of 40-60 mg/kg IV followed by an infusion of 2g/hr + 2g incremental has been effective in controlling CVS responses.
• Tetanus: Magnesium reduces spasms & automatic instability, However reports of hypotension, bradycardia, hypocalcaemia & respiratory muscle paralysis requiring ventilation may result. A proposed regimen for the management of tetanus is 5g magnesium sulphate IV over 20mts followed by 2g/hr, incremental 0.5g/hr until relief of spasms or loss of patellar reflexes.
• Acute severe asthma: Magnesium produces bronchodilation by smooth muscle relaxation & dilates the pulmonary vessels, there by improves peak expiratory rates especially in children. To be considered in refractory cases of impending respiratory failure.(38).Okayama & colleagues studied the effect of 1.2g of magnesium sulfate over 20mts in patients with mild asthma exacerbations produced a significant increase in FEV1 before any treatment was given .(39) . Mangat & colleagues investigated the role of inhaled magnesium sulfate in acute asthma attacks. They compared nebulised salbutamol (2.5mg) with 3cc of a 3.2% solution (95mg) of magnesium sulfate in a randomized double-blind trial involving 33 patients .They found that the increase in peak flow rates were comparable in both groups of patients with moderate to severe asthma exacerbations.(40)
• In ventricular arrhythmias: Effective in abolishing tachyarrhythmias, recommended for treatment of digoxin induced ventricular arrhythmias unresponsive to other treatments. A bolus dose of 2g given over 10mts is recommended.(41)
• Bupivacaine induced arrhythmias: Recommended in bupivacaine toxicity (42), (43).
• Pre-eclampsia & Eclampsia: Magnesium sulfate is the drug of choice for prevention & treatment of eclamptic seizure. It is more effective than Phenytoin or nimodipine. Progression from pre-eclampsia to eclampsia has been shown to be significantly lower when treated with magnesium & a trend towards lower maternal mortality.(42)
• Mechanism of action: acts as a potent cerebral vasodilator, reverses cerebral vasospasm. It blocks Ca influx through NMDA subtype of glutamate channel
• Anticonvulsant & CNS depressant
• Reduces cerebral irritability.
• Antihypertensive & antiadrenergic drug
• Obtunds pressor response to intubation & laryngoscopy with GA.
• Reduces hyperactivity of NMJ by reducing pre-synaptic release of acetylcholine & also sensitivity of post junctional membrane to Ach
• Relaxes uterine smooth muscle & blood vessels
Magnesium is a unique calcium antagonist & acts to reduce intracellular calcium results in arterial relaxation, is a potent vasodilator of uterine & mesenteric arteries & aorta but has minimal effect on cerebral arteries.(43)

WHO recommends Magnesium sulphate therapy for prevention of eclampsia in women with severe PIH.
Dosage regimen: Loading dose -4-6gms IV, Maintenance dose 1-3g/h
Therapeutic range: 2-3.5mmols/h (therapy continued post partum for 48hrs)

IN ACLS: according to 2010 AHA guidelines magnesium sulfate can facilitate termination of torsades de pointes (irregular/polymorphic VT associated with prolonged QT interval). ACLS providers may administer an IV/IO bolus of magnesium sulfate at a dose of 1-2g diluted in 10ml dextrose in water (class II b, LOE C). However routine administration of Mgso4 in cardiac arrest is not recommended (class III, LOE A) unless torsades de pointes are present. (44)

Magnesium and Acute cerebral injury
Recent evidence suggests that Mg2+ plays a critical role in the injury process after traumatic brain injury.
Magnesium not only has direct effects on cellular metabolism, but also in regulating other proposed secondary injury factors (45)
- Magnesium reduces the brain oedema formation, also useful in maintaining BBB integrity.
- Magnesium acts at NMDA receptor & protects neurons from deleterious effects of excitatory amino acids & thus reduces cytotoxic brain oedema (46).
- Magnesium as a neuroprotective agent in cases of SAH, acute ischemic stroke (47) (to receive Mg2+ with in 12 hrs of stroke). Decline in serum ionized Mg2+ was shown to be correlated with the severity of brain injury.
- Studies have shown a significant correlation between low CSF magnesium & the intensity of the residual neurologic deficit (48)
- Several epidemiologic studies suggest a decrease in stroke rates & death from stroke among those with diets rich in magnesium.(49)

MAGNESIUM & SEPSIS: Magnesium deficiency in sepsis is associated with poor out come. In a recent clinical study, patients with ionized hypomagnesemia at any time had more severe organ dysfunction & higher mortality rates (50). The important role of magnesium in sepsis might be attributed to its effects on immunological functions.

MAGNESIUM IN ACUTE MYOCARDIAL INFARCTION
It has been postulated that supplemental magnesium therapy may benefit in acute MI in several ways
- Magnesium limits myocardial damage, perhaps by inhibiting calcium influx into ischemic myocardial cells (51).
- Improves distal blood supply to ischemic myocardium by producing vasodilation (52).
- Magnesium increases the threshold for depolarization of cardiac myocytes and may have antiarrhythmic effects beneficial to these patients.(53)
- Magnesium infusion reduces peripheral vascular resistance and subsequently may increase cardiac output without increasing cardiac work.(54)
Magnesium may inhibit the platelet aggregation which is important in the pathogenesis of acute MI. (55)

MAGNESIUM IN PRE-TERM BABIES: Magnesium to prevent cerebral palsy in pre-term babies in antenatal period. Risk of cerebral palsy & gross motor dysfunction in preterm infants was reduced by 30%. (56).

ASSOCIATED ELECTROLYTE ABNORMALITIES WITH MAGNESIUM DEPLETION (57)

- HYPOKALEMIA: 40% of cases of magnesium depletion are associated with hypokalemia. Magnesium repletion is often necessary before potassium repletion
- HYPOCALCEMIA: 22% of cases of magnesium depletion is associated with hypocalcemia is due to impaired parathormone release combined with impaired end organ release. Hypocalcemia due to magnesium depletion is refractory to correction unless magnesium deficits are corrected.
- HYPOPHOSPHATEMIA: 30% of cases of magnesium depletion is associated with hypophosphatemia; this is due to enhanced renal loss.

CLINICAL MANIFESTATIONS OF MAGNESIUM DEPLETION: Clinical manifestations are often non-specific, normally associated with other electrolyte abnormalities may present with cardiac manifestations like ischemia, refractory arrhythmias & digitalis toxicity. Most characteristic manifestation of magnesium deficiency is termed as “Reactive central nervous system disorder”

Which presents with ataxia, slurred speech, generalized seizures & obtundation. The symptoms are precipitated by loud noises or bodily contact which is due to reduced magnesium levels in CSF & it resolves with magnesium infusion. (58)

Diagnosis: As serum magnesium levels are insensitive marker of magnesium depletion, retention test is done for suspected cases of magnesium deficiency (when serum Mg2+ levels are normal) However this test is unreliable in the presence of impaired renal function or in the presence of ongoing renal magnesium wasting

REPLACEMENT STRATEGIES

ORAL & PARENTERAL PREPARATIONS OF MAGNESIUM

Oral preparations are used for daily maintenance therapy (5mgs/kg in normal individuals) & for correcting mild asymptomatic magnesium deficiency. (59), (60)

Parenteral preparations are preferred for treating symptomatic or severe magnesium deficiency (intestinal absorption of oral magnesium is erratic)

ORAL PREPARATIONS
- Magnesium chloride enteric coated tablets 4meq/ml
- Magnesium oxide tablets 400mgs & 140mgs or 1meq/ml
- Magnesium gluconate- 500mgs

Mgso4 is the standard IV preparation, each gram of Mgso4 has 8meq (4mmol) of elemental magnesium. A 50% solution (500mgs/ml) is diluted to 10% (100mgs/ml) or 20% (200mgs/ml) in saline.

REPLACEMENT PROTOCOLS
MILD / ASYMPTOMATIC HYPOMAGNESEMIA (serum magnesium 1-2mEq/kg)
• Replace 1mEq/kg for the first 24 hrs & 0.5 mEq/kg daily for the next 3 to 5 days
• If serum magnesium is more than 1mEq/L, oral preparations can be used for replacement therapy.

MODERATE HYPOMAGNESEMIA (serum magnesium < 1mEq/kg)
• Add 6g Mgso4 (48 mEq Mg) to 250 or 500 ml isotonic saline & infuse over 3 hrs.
• Follow with 5g Mgso4 (40 mEq Mg) in 250 or 500 ml isotonic saline over the next 6 hrs.
• Continue with 5g Mgso4 every 12 hrs by continuous infusion over the next 5 days.

SEVERE / LIFE THREATENING HYPOMAGNESEMIA - This condition is associated with serious cardiac arrhythmias or generalized seizures
• Infuse 2g Mgso4 (16 mEq Mg) IV over 2-5 mts
• Follow with 5g Mgso4 (40 mEq Mg) in 250-500ml isotonic saline infused over next 6 hrs.
• Continue with 5g Mgso4 every 12 hrs by continuous infusion for the next 5 days.

It is important to follow the bolus dose with a continuous infusion. Serum magnesium levels may normalize after 1 to 2 days, but it will take several days to replenish the total body magnesium stores.

CONCLUSION:
• Serum magnesium is not a sensitive marker of total body magnesium stores, serum magnesium levels can be normal in patients who are magnesium depleted. Therefore urine magnesium is a better marker of magnesium depletion.
• Magnesium depletion is probably very common in ICU, especially in those with secretory diarrhea, on treatment with furosemide & aminoglycosides.
• Refractory hypokalemia is associated with hypomagnesemia in ICU. Magnesium repletion is often necessary in these cases before the serum potassium return to normal.
• The usefulness of the drug ranges from attenuation of pressor responses to an adjuvant for intra & post –op analgesia. Though precise data regarding pain relief / nociceptive action is not substantial it is known to reduce the doses of analgesics & also does not prolong the activity of other analgesics. However further explorations regarding pain relief property of magnesium is required.

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