

# Role of Magnesium---A Step Ahead in Anaesthesia

## Abstract

Mg<sup>++</sup>, a very important intracellular cation, which regulates many intracellular enzyme reactions and thus homeostasis inside the cell. Deficiency of Mg<sup>++</sup> is catastrophic for cell survival Magnesium sulfate has been used in preeclampsia patients in order to prevent seizure. It is also used for the treatment of arrhythmia, asthma and as an anesthetic adjunct, and in patients undergoing surgery for pheochromocytoma. It has high therapeutic index and cost effectiveness. However its potentiating effect on perioperative analgesia and muscle relaxation has drawn attention recently, it has been used as an adjunct in general anaesthesia, to prevent pressor response to laryngoscopy, as an analgesic, and to potentiate muscle relaxation. Mg<sup>++</sup> deficiency is usually associated with hypokalemia and hypocalcemia Correction of Mg<sup>++</sup> ion is an important step to prevent Arrhythmias, intractable hypertension, sudden cardiac arrest. It is a good anticonvulsant and regulates Ca<sup>++</sup> metabolism through parathormone release.

## Mini Review

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### Anita Surana\*

Associate Professor, GBH American Hospital, India

\*Corresponding author: Anita Surana, Associate Professor, GBH American Hospital, Udaipur (Raj), India, Email: anitasurana16@gmail.com

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## Introduction

Ever since the study of magnesium sulfate in clinical anesthesia beginning in 1996, magnesium has drawn attention in the field of anesthesia and pain medicine [1]. Recently, numerous clinical studies, review articles and meta-analyses have been published worldwide [2-8]. In humans Mg<sup>++</sup> is the fourth most plentiful cation after Na<sup>+</sup>, K<sup>+</sup>, and Ca<sup>++</sup> [9]. Intracellularly it is the 2nd most common cation after K<sup>+</sup>, and has a key role in hundreds of physiologic processes [9]. Among the numerous actions of magnesium, the blockade of N-methyl-D-aspartate (NMDA) receptor and calcium channel has an important meaning to anesthesia. Half of the body Mg<sup>++</sup> lies in soft tissues, including muscles, remaining in bones and some in RBCs. Extracellular Mg<sup>++</sup> is both ionized and unionized, it is the ionized form which is physiologically active. It acts as physiological antagonist of calcium.

### Physiological role of magnesium

- It acts as mediator for Na<sup>+</sup>/K<sup>+</sup> ATPase system, thus essential in maintaining trans membrane potential, by maintaining Na<sup>+</sup>/k<sup>+</sup> gradient across the membrane.
- Generation of cAMP via adenylyclase is dependent on Mg<sup>++</sup>.
- Mg<sup>++</sup> controls the release and action of Parathyroid Hormone, thus regulates Calcium metabolism.
- Mg<sup>++</sup> helps in Oxidative Phosphorylation, Glucose utilization and Protein synthesis.

### Homeostasis

Mg<sup>++</sup> homeostasis is maintained and regulated by hormonal and metabolic effect on GI absorption and renal excretion. Normal Serum Mg<sup>++</sup> CONC are 0.7 to 1.05 mmol/l (1.4 to 2.2 meq/l). Mg<sup>++</sup> is mainly excreted by the kidneys. It is reabsorbed in the ascending limb of loop of Henle, Aldosterone increases renal excretion while Parathormone increases gut absorption, and reduces renal excretion. Mg<sup>++</sup> is widely distributed in plant and animal food esp green leafy vegetables, spices, nuts, Soyabean

and shellfish. The average daily intake in western diet is 1.5 mmol/day, of which less than 1% is excreted in urine. Majority of absorbed Mg<sup>++</sup> (99%) goes inside the cell, so chr Mg<sup>++</sup> deficiency will deplete the body stores but plasma conc may be normal. Thus low plasma level indicates decreased total body Mg<sup>++</sup> except in conditions of haemodilution as in massive crystalloid infusion or severe hypoalbuminaemia.

The actions of magnesium on specific systems:

#### A. Cardiovascular system

- Direct depressant effect on myocardial and vascular smooth muscle.
- Inhibits the release of catecholamines from the adrenal medulla, peripheral adrenergic terminals and directly blocks catecholamine receptors.
- As a result, cardiac output and vascular tone are reduced resulting in hypotension and decreased pulmonary vascular resistance.
- Anti-arrhythmic: slows the rate of impulse formation at the SA node, prolongs SA conduction, the PR interval and the AV node refractory period.

#### B. Nervous system

- Reduces the release of acetylcholine at the neuromuscular junction by antagonizing calcium ions at the pre-synaptic junction.
- Causes reduced excitability of nerves.
- Anticonvulsant, as it reduces cell excitability by blocking Ca<sup>++</sup> channels.
- Reverses cerebral vasospasm.

#### C. Musculoskeletal

- It decreases release of acetyl-choline at N-M-J thru its Ca<sup>++</sup> channel blocking effect.

- b) Involved in terminating contraction, initiating relaxation in skeletal muscles, thus it potentiates Non depolarizing neuro-muscular relaxants drugs [10-36]. Some authors have focused on the direct enhancing effects of magnesium on the neuromuscular blockade [37-40].
- c) In combination with the effects above excessive plasma concentrations can cause muscle weakness.

#### D. Respiratory system

- a) Magnesium is an effective bronchodilator but does not affect respiratory drive.
- b) Respiratory failure may occur as a result of excessive muscle weakness.

#### E. Genito-urinary system

- a) Powerful tocolytic, decreasing uterine tone and contractility.
- b) Mild diuretic properties.

#### F. Haematological system

Platelet activity is reduced resulting in prolonged bleeding time, deficiency is associated with platelet hyper-reactivity which plays significant role in MI, Pre-eclampsia and eclampsia. Also required for the utilization of Thiamine.

#### Disorders

**Hypomagnesemia:** Hypomagnesemia can occur frequently, especially after surgery such as abdominal, orthopedic and cardiac operation. From the report of Aglio et al. [10], the incidence of hypomagnesemia was 19.2% before cardiac surgery, peaked to 71% immediately after surgery, and subsided slightly to 65.6% 24 h after then Plasma concentration less than 0.7mmols/L. This is the most under diagnosed electrolyte deficiency in current medical practice. Studies have shown it to be a relatively common disorder, eg\_ 65% of an ICU population and 11% of in patient population [41-61].

#### Causes

##### I. Decrease intake:

- i. Deficiency in diet,
- ii. Mal absorption (as in chr alcoholics, Pancreatic insufficiency pt).

##### II. Inappropriate IV infusions - massive haemodilution

##### III. Increased renal losses:

- i. Drug induced esp Digoxin, Gentamycin, loop diuretics, cyclosporine, cis- platinum etc.
- ii. Batters Syndrome.
- iii. Intrinsic renal dysfunction.
- iv. Hyperaldosteronism.

##### IV. Extra renal losses:

- i. GI tract-prolonged diarrhoea or long term NG suction.

- ii. Primary Hyperparathyroidism.
- iii. Insulin administration.
- iv. Massive citrated blood transfusions.

#### Sign and Symptoms

Hyperirritability, chest pain, Palpitation, Arrhythmia, Hypertension, Angina (Coronary Artery Spasm), Increased Digoxin toxicity in pts on digoxin, due to decrease in K<sup>+</sup> intracellularly and also increased Digoxin uptake by myocardium. Arrhythmias esp Torsades de pointes, Re-entrant Arrhythmias, VT and VF.

#### ECG

Shows prolonged PR and QT interval and T wave changes.

#### N-M Junction

Myoclonus, Cramps Stridor, and Dysphagia, Chvostek's sign, Trousseau's sign due to associated Ca<sup>++</sup> deficiency.

#### Psychiatric Distur

Anxiety, Depression, Confusion, Psychosis.

#### Eleetrolyte distr

Usually accompanied with Ca<sup>++</sup> & K<sup>+</sup> Deficiency. There is intractable K<sup>+</sup> deficiency which is not corrected till you correct Mg<sup>++</sup> deficiency [61].

#### Management

Approximately 10 to 20 mmols/day dietary intake is sufficient, for chronic losses 35 to 70 mmols can be given in 5% dextrose. An amp of Mg<sup>++</sup> contains 50%w/v (500mg/ml) solu. Each ml contains 2mmols, in severe deficiency 8mmols (4ml) ie 2gms in 50 ml of 5% Gdw may be given over 30 min.

#### Hypermagnesaemia

Magnesium from the diet is relatively innocuous as renal elimination of excess magnesium is rapid. Antacids and purgatives often contain magnesium and excessive intake can precipitate hypermagnesaemia. Contamination of water supply has been reported to cause hypermagnesaemia. The most common cause of hypermagnesaemia is iatrogenic as a result of intravenous therapy, particularly if there is co-existing renal failure. Rarer causes include diabetic keto-acidosis and tumour lysis syndrome.

#### Clinical Features

Clinical features of hypermagnesaemia increases in frequency and severity as the serum concentration increases. Initial clinical presentation includes headache, nausea, vomiting and diarrhoea, hypotonia and muscle weakness. Significant neuromuscular block can occur, causing respiratory muscle weakness and ultimately respiratory arrest. Hypotension and bradycardia occur at high plasma concentrations and the ECG may show prolonged AV conduction and widening of the QRS complex, which can progress to severe arrhythmias and finally cardiac arrest.

Serum Mg conc.

10-12.5 mmol/L cardiac arrest

5-7.5mmol/L respiratory paralysis

4-5mmol/L muscle weakness & loss of tendon

Reflexes

## Management

Most cases of symptomatic hypermagnesaemia can be prevented by anticipation. Patients receiving parenteral magnesium should be frequently monitored and patients with renal failure should not receive magnesium containing medication. If renal functions are normal, cessation of therapy often allows prompt restoration of normal levels which can be assisted with fluid therapy and diuretics. Haemodialysis or filtration may be required in renal failure or in the presence of severe systemic effects. IV calcium gluconate (2.5-5mmol) can antagonise the actions of magnesium and therefore is useful in the immediate management of patients with severe hypermagnesaemia, followed by inducing diuresis or dialysis.

## Magnesium in Anaesthesia and Critical Care

Although magnesium is not a primary analgesic in itself, it enhances the analgesic actions of more established analgesics as an adjuvant agent. The role of magnesium for peri-operative analgesia has been investigated by many authors. Magnesium sulfate has been reported to be effective in perioperative pain treatment and in blunting somatic, autonomic and endocrine reflexes provoked by noxious stimuli [11-13]. It has a role in chronic neuropathic pain also. Ryu et al. [52] compared magnesium sulfate and remifentanyl during middle ear surgery. In this study, either drug when combined with sevoflurane provided adequate level of hypotensive anesthesia, however, the magnesium group had more favorable postoperative courses showing better analgesia and less shivering and nausea/vomiting after surgery. In addition, sevoflurane was required less to maintain surgical anesthesia in patients receiving magnesium sulfate than those receiving remifentanyl. Seyhan et al. [15] reported that magnesium sulfate reduced propofol, atracurium and postoperative morphine consumption in gynecologic surgical patients. In another study employing gynecologic patients undergoing laparotomy under TIVA, pain scores, analgesic consumption and shivering incidents were lower in the magnesium group compared with control. Gupta et al. [16] also reported that magnesium reduced the requirements for propofol, rocuronium and fentanyl in spinal surgical patients. It is conceivable that the intraoperative use of magnesium sulfate may mitigate remifentanyl-induced hyperalgesia in patients receiving TIVA.

Magnesium sulfate can play a beneficial role also in spinal anesthesia when administered via both intravenous or intrathecal route. Magnesium can prevent the induction of central sensitization from peripheral nociceptive stimuli at the spinal action site by blocking NMDA receptors in a voltage-dependent manner [17]. With the same mechanism, when small doses of magnesium sulfate was added to local anesthetics for spinal anesthesia, the duration of anesthesia was prolonged, postoperative analgesic requirement was reduced and the side effects of high doses of local anesthetics and opioids were decreased. Clinical studies also showed that intrathecal magnesium sulfate added to fentanyl

prolonged labor analgesia without any increase in side effects [20,21]. Intraoperative use of magnesium sulfate can be associated with decreased incidences of nausea and vomiting after surgery [14,29], which could have been due to the lower consumption of volatile anesthetic (sevoflurane) [14,30] rather than any antiemetic effect of magnesium sulfate. Recently magnesium has been highlighted on its efficacy to attenuate cardiovascular responses associated with tracheal intubation [44,45].

However anaesthetising hypomagnesaemic pt can precipitate arrhythmias, severe hypotension due to myocardial depressant action combined with anaesthetic drugs, and also relaxation of vascular smooth muscles leads to decrease in SVR, PVR, it dilates coronary arteries, but suspected role in MI pts is controversial according to MAGIC and ISIS4 trials [61]. It also blocks catecholamine receptors but Mg<sup>++</sup> is required for ionotropic effect of Adrenaline [61]. Effective in Tachyarrhythmias, digoxin induced arrhythmias, VT, VF. In pts with A-V block, avoid Mg<sup>++</sup> as it may ppt asystole or worsen arrhythmias. Its role in pheochromocytoma is well established. Mg<sup>++</sup> given during surgery due to its Ca<sup>++</sup> channel blocking property. Initially 40 to 60 mg/kg iv, followed by 2 gm/hr. Mg<sup>++</sup> is very effective in pre-eclampsia and eclampsia, tetanus and cerebral vasospasm. It potentiates all N-M blocking drugs, no effect on suxamethonium but repeated doses may lead to phase 2 block. Used with caution in pts with muscle disease like Myasthenia gravis and Muscular dystrophies. It is a good bronchodilator, but excessive doses may lead to respiratory failure due to muscle weakness.

## Conclusion

Magnesium sulfate is an old drug, but has multiple characteristics which are very useful for anesthesiologists. When it is used appropriately to enhance analgesia and muscle relaxation in surgical patients, it can contribute to improvement in the outcome of surgical patients. Strict haemodynamic monitoring and blood chemistry is required to prevent hypermagnesaemia (during supplementing MgSO<sub>4</sub>) which is mostly iatrogenic, otherwise it is a safe drug to be used peri-operatively and also in ICU pts.

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