MAGNESIUM AND CALCIUM: NEW HORIZONS FOR THE ANESTHETIST

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\textbf{ARTICLE INFO} & \textbf{ABSTRACT} \\
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\textbf{Article history} & Magnesium and calcium are the most abundant cations, after sodium and potassium, in the body. Magnesium ions (Mg\textsuperscript{2+}) are involved as a cofactor in about 300 known enzymatic reactions and in several important processes, whereas intracellular calcium regulates many important physiologic functions, including muscle contraction, hormone secretion, glycogen metabolism, and cell division. Of particular relevance to the anesthetist are the effects of calcium on the myocardium, vascular smooth muscle and blood coagulation. Mg\textsuperscript{2+} blocks the N-methyl-D-aspartate (NMDA) receptor and its associated ion channels; this property of Mg\textsuperscript{2+} as an antagonist of NMDA receptors is the basis for studies of its adjuvant effect in perioperative analgesia. The calcium inhibitory effect causes central arteriolar vasodilatation and acts against vasospasm. Magnesium has a stabilizing effect on membranes; it can be used in the treatment of cardiac rhythm disorders. Magnesium sulfate is a safe supplement to a general anesthetic regimen as it reduces the total anesthetic requirements, cost, post-operative pain score and post-operative analgesic requirements. Thus, magnesium seems to have a potential role in anesthesia related to knee surgery, hysterectomy, caesarean section, lumbar surgery, cardiac surgery etc, as suggested by several clinical studies. This clearly indicates that anesthetists may repose increasing confidence in magnesium in the near future. \\
Received 23/06/2014 & \\
Available online 08/07/2014 & \\
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\textbf{Keywords} & \\
Anesthesia; & \\
Calcium; & \\
Ion Channels; & \\
Magnesium; & \\
NMDA Receptors; & \\
Surgery. & \\
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Please cite this article in press as \textbf{Dr. Pallavi Mahajan} et al. Magnesium and Calcium: New Horizons for the Anesthetist. Indo American Journal of Pharm Research.2014:4(06).

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INTRODUCTION

Magnesium is the fourth most abundant cation, after sodium, potassium and calcium, in the body and the second most plentiful intracellular cation. The total body magnesium content is 20-25 g, of which 55% resides in the skeleton and 45% is intracellular. Magnesium intake is 240-370 mg/day in adults, out of which distal small bowel absorption contributes 30-40% of the total. 25% of filtered magnesium is reabsorbed in the proximal convoluted tubule, whereas 50-60% is reabsorbed in the thick ascending limb of the loop of Henle, indicating the efficiency of magnesium reabsorption by the kidneys (Figure 1). Its reabsorption is increased by the factors such as hypomagnesaemia, parathyroid hormone, hypocalcaemia, hypovolaemia and metabolic alkalosis, while hypermagnesemia, acute volume expansion, hyperaldosteronism, hypercalcemia, ketoacidosis and diuretics increase its renal excretion [1]. On an average, 7.32-14.64 mg/day of magnesium is being eliminated by the kidneys. Plasma Mg is tightly regulated between 1.7-2.4 mg/dl. This regulation of plasma levels involves interaction between gut, bone and kidneys [2].

![Figure 1: Overview of magnesium metabolism.](image)

- Daily intake of magnesium: 240-370 mg
- 30-40% absorbed in distal small bowel
- 25% of filtered magnesium reabsorbed in PCT of kidneys
- 50-60% reabsorbed in the thick ascending limb of loop of Henle
- 3-5% excreted in urine

Table 1: Functions of magnesium

- Cofactor in about 300 known enzymatic reactions
- Hormone receptor binder
- Gating of calcium channels
- Transmembrane ion flux
- Regulation of the adenyl cyclase system
- Neuronal activity and neurotransmitter release
- Maintenance of vasomotor tone
- Cardiac excitability
- Effects similar to calcium-entry-blocking drugs
Calcium

Calcium is the fifth most common element in the body and the most prevalent cation. An average human body contains about 1 kg of calcium, of which about 99% present in the skeleton. Physiologically, calcium may be classified into intracellular and extracellular. Intracellular calcium has role in many important physiologic functions, including muscle contraction, hormone secretion, glycogen metabolism, and cell division [5]. Extracellular calcium provides calcium ion for the maintenance of intracellular calcium, and is essential for many biological processes that include bone mineralization, cardiac automaticity; excitation-contraction coupling in myocardial, smooth and skeletal muscle; blood coagulation; neuronal conduction; synaptic transmission; hormone secretion, mitotic division and plasma membrane potential. It stabilizes the plasma membranes and influences permeability and excitability. Calcium is also a major intracellular messenger needed for normal cellular function and required by many enzymes for full activity. Of particular relevance to the anesthetist are the effects of calcium on the myocardium, vascular smooth muscle and blood coagulation [6].

Biomembranes

All biomembranes consists of a phospholipid bilayer, which contains proteins, glycoproteins, cholesterol and glycolipids. The presence of membrane proteins permits each type of membrane to perform specific functions. These membrane proteins are of two types: integral proteins, all or part of which penetrate the phospholipid bilayer, and those which do not interact with the hydrophobic core of the bilayer, are known as peripheral proteins.

These proteins in the plasma membrane selectively absorb nutrients, expel wastes, and maintain the proper intracellular ionic composition, in all the cells. These proteins anchor the membrane to intracellular cytoskeletal fibers and the extracellular matrix. They also participate in the interactions and communication between cells [7].

Calcium Channels

The voltage-sensitive calcium channel in the surface membrane is the major route of entry of calcium, whose activation by depolarization gives rise to the slow inward current. Calcium enters the cell by this route with each action potential and triggers the release of large amounts of Ca\(^{2+}\) from intracellular stores causing an immediate increase in cytosolic Ca\(^{2+}\) concentration. The release and uptake of calcium takes place by an intracellular calcium store, e.g. the sarcoplasmic reticulum. The sarcoplasmic reticulum Ca\(^{2+}\) release channel appears to be the major source for changes in cytoplasmic Ca\(^{2+}\) concentration required to produce cardiac contraction or relaxation in the mature heart (Figure 2). In the developing heart, the membranes of the sarcoplasmic reticulum are less abundant, which suggests that cardiac mechanics are regulated primarily by trans-sarcolemmal Ca\(^{2+}\) flux. Chemical messengers such as hormones and neurotransmitters are the mechanisms that are responsible for the repetitive changes in the cytoplasmic Ca\(^{2+}\) concentration [8].

Figure 2: Calcium regulation in the heart.

Calcium channels and transporters involved in initiating contraction (solid arrows) by calcium-induced calcium release mechanism and subsequent relaxation (dotted arrows) in myofibres. Dashed line- calcium activation of myofibrils.

NMDA receptors

The N-methyl-D-aspartate (NMDA) receptor can be considered one of the fundamental neurotransmitter receptors in the brain. Named for its most potent exogenous agonist, the NMDA receptor belongs to a family of ionotropic receptors for the excitatory amino acid glutamate and is characterized by high affinity for glutamate, a high unitary conductance, high calcium permeability, and a
voltage-dependent block by Mg$^{2+}$. Activation of NMDA receptors by the neurotransmitter glutamate requires glycine as an essential coagonist. Glutamate and glycine molecules bind different subunits of the receptor; two of each is thought to be required for maximum activation of the receptor. NMDA receptor activation leads to opening of an ion channel that is selective for cations, resulting in the influx of Na$^+$ and Ca$^{2+}$ and efflux of K$^+$. Although most glutamate receptors are cation selective, few are permeable to calcium ions. Its exceptional calcium permeability is the first of two key properties of the NMDA receptor that form the basis for its regulatory role in synaptic plasticity. Entry of calcium into the postsynapse via the NMDA receptor (Figure 3) permits coupling of electrical synaptic activity to biochemical signaling via activation of Ca$^{2+}$ dependent enzymes and downstream signaling pathways. In this way, calcium influx through the NMDA receptor can lead to long-term changes in synaptic strength and other cellular modifications, including alterations in synaptic structure or connectivity. The second key biophysical property of the NMDA receptor, and the one that bestows its proposed role in learning and memory, is that it is blocked by Mg$^{2+}$ in a voltage-dependent manner. At resting membrane potential, NMDA receptors are blocked by Mg$^{2+}$; however, if excitation by synaptic inputs causes sufficient depolarization of the neuron, the Mg$^{2+}$ block is relieved and those NMDA receptors which have glutamate bound will open [9].

Figure 3: N-methyl-D-aspartate (NMDA) receptor. The binding of glutamate (Glu) and glycine (Gly) activates the receptor. It is thus a ligand-gated ion channel which permits the movement of Ca$^{2+}$, Na$^+$ and K$^+$ across the post-synaptic membrane. It is blocked by Mg$^{2+}$. The receptor is composed of multiple subunits out of which only two are shown for simplicity. Antagonists of NMDA receptors: 1- ketamine, 2- memantine, 3- xenon.

Effects of magnesium

Action on membrane and membrane pumps

Mg$^{2+}$ acts as a stabilizer of cell membrane and intracytoplasmic organelles by intervening in the activation of membrane Ca-ATPase and Na-K ATPase involved in transmembrane ion exchanges during depolarization and repolarization phases [10]. Low Mg$^{2+}$ levels impair the action of ATPase pumps, thus leading to reduction of intracellular ATP and hence, increased concentrations of sodium and calcium, whereas decreased concentrations of potassium within the cell [11].

Action on ion channels

Magnesium also acts as a regulator of various ion channels. Decreased intracellular Mg$^{2+}$ concentration alters conduction and cellular metabolism; by causing potassium out flux [11]. Mg$^{2+}$ also exerts its effect on L-type potential-dependent calcium channels in the membrane and sarcoplasmic reticulum (the main site of intracellular calcium storage). A competitive antagonist action is directed against calcium influx, as Mg limits the outflow of calcium from the sarcoplasmic reticulum by inhibiting the calcium activation dependent on the sarcoplasmic channel [12]. Hence, Mg$^{2+}$ is a calcium channel blocker and a modulator of calcium channel activity, which means that an increase in intracellular calcium occurs during hypomagnesemia [13].

Action on NMDA receptors

Mg$^{2+}$ blocks the NMDA receptor and its associated ion channels; it can prevent central sensitization caused by peripheral nociceptive stimulation [3]. Magnesium also has antinociceptive effects in human models of pain [14]. These effects are primarily based on the regulation of calcium influx into the cell, i.e., ‘natural physiological calcium antagonism’ and antagonism of the NMDA receptor [4]. The property of Mg$^{2+}$ as an antagonist of NMDA receptors is the basis for studies of its adjuvant effect in perioperative analgesia. The inhibiton of calcium by magnesium causes dilatation of central arterioles and reduces vasospasm. Mg also causes
inhibition of NMDA receptors and thus, leads to increased production of vasodilator prostaglandins that are responsible for its anticonvulsant action [12]. High doses of magnesium salts produce a tocolytic and hypotensive effect in preeclampsia [15]. In an animal model, magnesium lowered maternal arterial pressure, while maintaining uterine arterial flow and fetal oxygenation [16]. Magnesium is proposed as a neuroprotective agent in a number of forms of neurological injury [17], and for neuronal protection of the premature fetus [18].

**Therapeutic effects of magnesium**

Historically, magnesium sulphate (MgSO₄) has been considered as a general anesthetic. Though magnesium was considered as a central nervous system depressant, its anesthetic effect was primarily due to progressive respiratory and cardiac depression which was followed by cerebral hypoxia, whereas no central nervous system depression was seen even at a very high concentration of serum magnesium, on maintaining respiratory support [19]. Magnesium inhibits catecholamine reuptake by the adrenal medulla, thus, reducing the sensitivity of adrenergic receptors causing peripheral vasodilatation and decreases antiarrhythmic effects, therefore, used in pheochromocytoma surgery [20].

Magnesium potentiates the neuromuscular blockade produced by non-depolarising neuromuscular blocking agents. It decreases the amount of acetylcholine released from the motor nerve terminal, leading to decreased excitability of the muscle fiber itself and reduction in the amplitude of the end plate potential [21]. It decreases catecholamine release from the adrenal medulla and adrenergic nerve endings, so obtunds the pressor response to laryngoscopy and intubation and also reduces postoperative shivering [22]. And also minimizes changes in arterial pressure and heart rate. This is a particularly attractive option in preeclamptic patients requiring general anesthesia for Caesarean section [18].

Magnesium has a stabilizing effect on membranes; it can be used in the treatment of cardiac rhythm disorders. The best indication is for the treatment of torsades de pointes [23] but magnesium is also indicated for ventricular arrhythmias related to digitalis toxicity. In critically ill patients, Magnesium proved more effective than amiodarone for the conversion of acute atrial tachyarrhythmias [24].

Magnesium has bronchodilator effects apparently related to its calcium antagonist properties that inhibit the contraction of smooth muscle fibres [25]. Magnesium should not be used routinely in the treatment of moderate asthma, but intravenous magnesium sulfate may be useful in addition to the usual therapy for refractory asthma [11].

Magnesium also plays a role in tetanus. In individuals with severe tetanus, in the absence of mechanical ventilation, spasm-related respiratory failure is the most common cause of death, whereas in ventilated patients, it is tetanus-associated autonomic dysfunction. Magnesium infusion reduces the requirement for other drugs to control muscle spasms and cardiovascular instability, but it does not reduces the need for mechanical ventilation in adults with severe tetanus [26].

**Clinical evidence of magnesium in anesthesia**

1. Magnesium has been reported to produce general anesthesia and to enhance the activity of local anesthetic agents. Magnesium sulfate as a hypotensive anesthesia technique led to better operative field, reduction in the duration of surgery and reduced blood loss [27]. The possible mechanisms for reduction of the anesthetic requirements include; antagonism of NMDA receptors in the CNS by magnesium, and reduction of catecholamine release by sympathetic stimulation, thus decreasing peripheral nociceptor sensitization or the stress response to surgery. In addition, the actions of magnesium at the neuromuscular junction include: a reduction in acetylcholine release from motor nerve terminals, a decrease in the depolarising action of acetylcholine at the endplate and depression of muscle fibre membrane excitability [28].

2. MgSO₄ is co-administered with propofol, it potentiates the anesthetic effect and NMDA antagonism of propofol [29, 30]. It has vasodilator and hypotensive effect and therefore potentiates the hypotensive effect of propofol [31].

3. It also has variety of neuroprotective actions in the central nervous system after induction of experimental ischemia [32]. The CNS depressant effect of anesthetic agents may be potentiated when they are used concurrently with magnesium sulfate [33].

4. Studies have reported that preoperative administration of magnesium sulfate reduces intra- and post-operative analgesic requirements in patients undergoing knee surgery or abdominal hysterectomy [33].

5. A bolus of 4 gm magnesium resulted in a rapid but transient decrease in arterial blood pressure in hypertensive patients, whereas normotensive patients did not have any significant change in blood pressure [31]. Moreover, Tramer et al [34] has shown that patients treated with magnesium did not show any significant hemodynamic difference compared with control patients in the intra-operative and post-operative period.

6. Intravenous magnesium causes significant reductions in rocuronium, vecuronium or mivacurium consumptions during total intravenous anesthesia with continuous magnesium administration. Magnesium act competitively in blocking the entry of calcium in presynaptic endings. Presynaptic release of acetylcholine and its effects on the postsynaptic muscle receptors were reduced by magnesium [35].

7. An interaction between magnesium sulfate and the non-depolarizing neuromuscular blocking agents has been documented for many years. This was also observed in patients undergoing cardiac surgery, where administration of magnesium sulfate results in a (30–35 min) prolongation of the neuromuscular blockade induced with intubating and maintenance doses of cisatracurium [36].

8. In the intensive care unit, magnesium sulfate infusion was associated with decreased sufentanil requirements [30].

9. Levaux et al [37] used MgSO₄ as an adjuvant for postoperative analgesia after major lumbar surgery and they observed that the postoperative opioid consumption and pain scores were lower in the magnesium group than the control group. Apan et al [38] showed that postoperative MgSO₄ infusion reduces analgesic requirements and prolongs the time to first analgesic request in patients undergoing spinal surgery under spinal anesthesia.
10. MgSO₄ administered before induction of anesthesia increases minimum alveolar anesthetic concentration of sevoflurane and reduces cardiovascular responses to intubation [39].
11. MgSO₄ acts as an adjunct to lidocaine and improves the quality of anesthesia and analgesia in intravenous regional anesthesia [40].
12. It has an established role in blunting the laryngoscopic intubation response [41].

**Evidence for risk of Magnesium and calcium in anesthesia**

It was reported and also confirmed experimentally, lengthening of neuromuscular blockade occurs in patients treated with magnesium. It was also found in two prospective studies that in a group treated with magnesium a lower use of curare was done during surgery. Magnesium potentiated neuromuscular blockade effect of d-tubocurarine, decamethonium and succinylcholine, in a rat phrenic nerve-diaphragm preparation [12]. More frequent recourse of anticholinesterases is required to counteract prolonged curarization due to neuromuscular blockade [34]. Magnesium administrations to obstetric patients, who are at increased risk of preterm birth, provide neuroprotection to preterm babies [42]. Magnesium sulfate, though sometimes used as a tocolytic to slow uterine contractions during preterm labour, but it may produce complications for both mother and baby [43]. Babies who have been exposed to magnesium for a prolonged period of time may be listless or floppy at birth, as magnesium sulfate causes muscle relaxation. As the drug clears from the baby’s system, this effect typically passes away. Magnesium sulfate should not be administered in women with medical conditions like myasthenia gravis or muscular dystrophy that could be made worse by the side effects.

Many studies suggest that general anesthetics, either volatile or intravenous, can induce cell death by apoptosis in a concentration and time-dependent manner in different types of cells, including neurons, in various animal models. The volatile anesthetics, especially isoflurane, can induce apoptosis by increasing the cytosolic and mitochondrial calcium concentrations and decreasing the endoplasmic reticulum calcium concentration by over-activation of the inositol 1,4,5-triphosphate receptor (InsP₃R) or ryanodine receptor (RYR) calcium channels. In addition, increased calcium influx from the extracellular space can cause calcium release from the endoplasmic reticulum via calcium-induced calcium release by subsequent activation of the InsP₃Rs and/or RYRs. An elevated cytosolic Ca²⁺ concentration can induce apoptosis by: 1) activating apoptotic-related enzymes, such as calpain; 2) causing an overload of mitochondrial Ca²⁺ resulting in the collapse of the mitochondrial membrane potential and release of cytochrome c from the mitochondria into the cytosolic space which activates caspase 9 and 3 and subsequent apoptosis; and 3) inhibiting normal protein synthesis as a result of the depletion of endoplasmic reticulum calcium stores by excessive calcium release via either the InsP₃R and/or the RYR [44]. The disruption of intracellular calcium homeostasis is a convergent path toward general anesthetic-induced neuroapoptosis.

**CONCLUSION**

Magnesium balance is affected by calcium, although there is some evidence to the contrary, and the relationship between dietary calcium and magnesium may vary with age and sex [45]. Magnesium is an affordable and commonly used drug having diverse applications. Most of its physiological effects are due to its calcium channel blocking properties. The bottom line is that MgSO₄ is a safe supplement to a general anesthetic regimen with propofol, fentanyl and rocuronium, as it reduces the total anesthetic requirements, cost, post-operative pain score and post-operative analgesic requirements. Magnesium is a calcium competitor with many of the actions of the dihydropyridines, but with a broader spectrum of action that includes inhibition of transmitter release and NMDA receptor antagonism. Further research should be carried out so that more evidence will be available to finally establish the role of magnesium salts in anesthesia.

**ABBREVIATIONS:**

- LTCC, L-type Ca²⁺ channel; SR, sarcoplasmic reticulum; IP₃R, inositol triphosphate receptor; RyR, ryanodine receptor; SERCA, sarcoplasmic reticulum Ca²⁺-ATPase; [Ca²⁺]ᵢ, intracellular calcium concentration; MCU, mitochondrial calcium uniporter; NCX, Na⁺/Ca²⁺ exchanger.

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