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Magnesium: The Neglected Electrolyte? A Clinical Review

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Abstract

Magnesium, Mg^{2+}, is the second most abundant intracellular cation after potassium and the fourth most abundant in the body. It was first isolated in 1808 by the English chemist, Sir Humphrey Davy. Magnesium is essential to numerous biochemical reactions. It modulates key physiological processes such as metabolic biochemistry, nucleic acid synthesis, receptor-binding and ion flux. The western diet falls short of the recommended daily allowance of 4.5 mg/Kg/day and important dietary sources are seeds, grains, nuts and green vegetables. It is used as a therapeutic agent in a broad range of pathologies: neurological, cardiovascular, respiratory, gastrointestinal and obstetric. The pharmacokinetics and pharmacodynamics of magnesium, as a drug, are not well understood. Despite its fundamental importance to human physiology, it remains an electrolyte that is not routinely measured as part of the "urea & electrolytes" test and is the most overlooked electrolyte deficiency in hospital inpatients. This review will summarise the importance of magnesium homeostasis, its pharmacological effects and clinical applications.

Keywords

Magnesium, Pharmacology, Pharmacodynamics, Pharmacokinetics, Physiology, Arrhythmias, Eclampsia, Pre-Eclampsia, Phaeochromocytoma

1. Magnesium Intake and Regulation of Balance

A normal adult has approximately 1000 mmol of magnesium (22 - 26 g), the majority of which is stored within the bone (52.9%), followed by muscle (27%) and soft tissue (19%). Normal serum concentration ranges from 0.70 - 1.10 mmol/L [1] [2]. Serum magnesium levels are a poor reflection of total body stores as only less than 1% of total body magnesium is found in blood. This is an important consideration when supplementing in clini-

cal practice [3].

The recommended daily allowance (RDA) for magnesium is 4.5 mg/Kg/day, or 13 mmol/day for a 70 kg individual, with requirements increasing in illness. Magnesium rich foods include seeds, grains, nuts and green vegetables, whilst processed foods tend to lack magnesium. Phytate, fibre and alcohol reduce the absorption of magnesium. Surveys have shown the average Western diet falls short of the RDA [1] [2].

Magnesium is mainly absorbed in the ileum and jejunum [4]. The mechanism of uptake is yet to be fully elucidated, with theories including passive paracellular uptake, passive leak and active extrusion [1] [5] [6].

Plasma magnesium levels are tightly controlled. Whilst the exact mechanism of regulation remains unknown, the renal system plays an essential role. In normal physiology, 80% of plasma magnesium is filtered, of which 95% is reabsorbed, leading to 3 - 5 mmols lost in the urine per day. The kidney is able to increase or decrease the urinary magnesium loss dependent on plasma magnesium concentration but the mechanism behind this is unclear [2].

Several hormones are also known to exert influence over magnesium homeostasis. For example, parathyroid hormone (PTH) promotes magnesium reabsorption in the loop of Henle and distal convoluted tubule [7] [8]. It stimulates gut uptake of magnesium and release of magnesium from bones [9].

The incidence of hypomagnesaemia is higher amongst diabetics, and this is correlated with the severity of hyperglycaemia, suggesting a link between insulin and magnesium [10]. *In-vitro* work has shown increased magnesium uptake in response to insulin in human platelet cells [11]. Studies have produced conflicting results on whether an oral-glucose loading test reduces [1] [12], or causes no change [13], in plasma magnesium in healthy controls.

Insulin's physiological opposite hormone, glucagon, increases magnesium reabsorption in the rat loop of Henle [14] but no change was found in plasma magnesium in humans, in response to intravenous glucagon [15].

These mechanisms are summarised in **Figure 1**. **Table 1** highlights the non-drug and drug causes of hypo- and hypermagnasaemia.

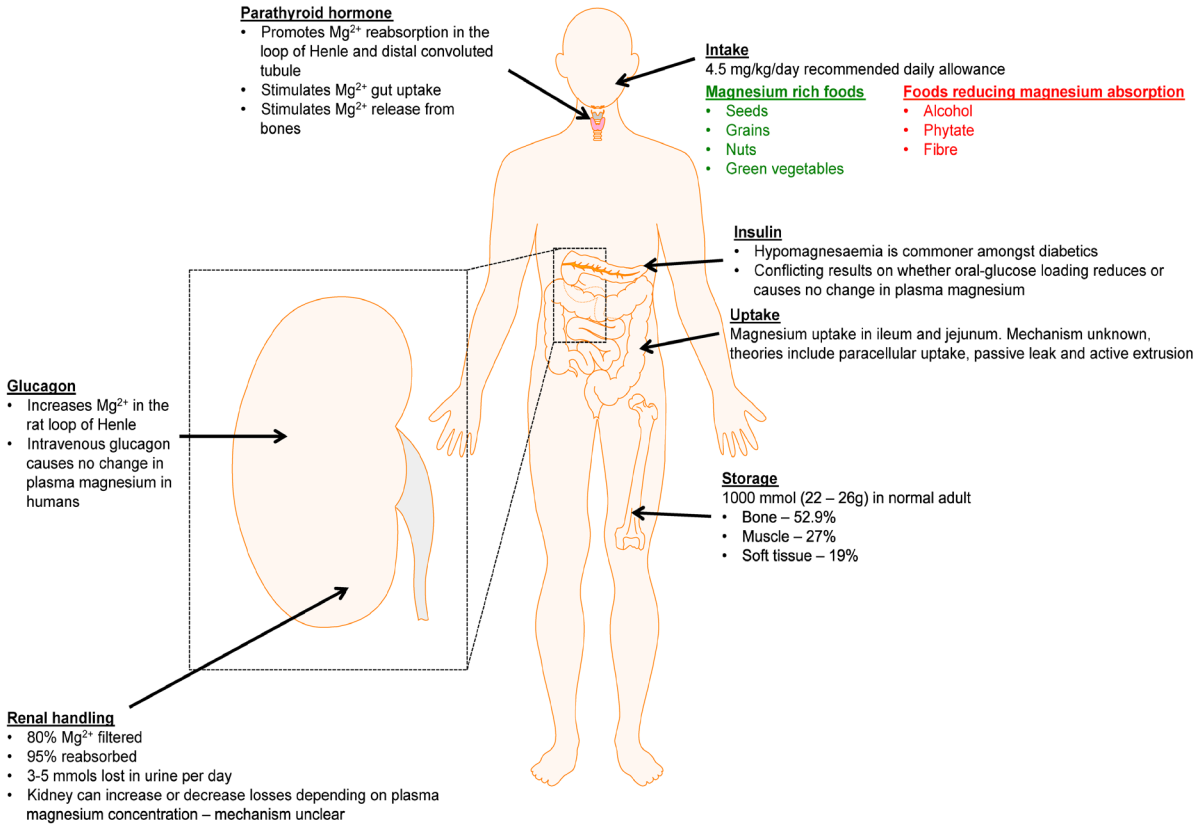

Figure 1. This cartoon illustrates the intake, absorption and regulation of balance of magnesium. Image modified from Motifolio Anatomy Drawing Toolkit available from http://www.motifolio.com/anatomy.html.

Table 1. This table shows the important non-drug and drug causes of hypo- and hypermagnesaemia. Reference: [70].

	Causes of hypomagnesaemia	Causes of hypermagnesaemia
Non-drug causes	Inadequate Mg^{2+} intake	Excessive intake
	High Ca^{2+} intake	Renal failure
	Malabsorption states	Hypothyroidism
	Gastrointestinal losses, e.g. diarrhoea, vomiting	Excessive tissue breakdown, e.g. sepsis, shock, burns
	Polyuria	
	Parathyroid dysregulation	
	Bowel resection	
Drug causes	Diuretics	Lithium
	Laxatives	Mg^{2+} containing antacids (excessive intake)
	Nephrotoxic drugs	Magnesium containing laxatives
	Insulin	

2. Physiological Role of Magnesium

Magnesium is of fundamental importance to hundreds of physiological processes [1] [16] [17], some of which are shown in **Figure 2**.

2.1. Magnesium in Enzymatic Reactions

Magnesium is a catalyst in enzymatic reactions; either Mg^{2+} induces a conformational change in the structure of an enzyme, or it can bind to a substrate, for which the enzyme will have a greater affinity [17].

Adenosine triphosphate (ATP) is a cellular "energy currency" used in several processes, such as fat, protein and nucleic acid synthesis. Enzymes responsible for transferring phosphate from adenosine diphosphate (ADP) or ATP are activated by Mg^{2+} [17].

Magnesium is also crucial in nucleic acid biochemistry. It is a co-factor to restriction endonucleases, exonucleases, polymerases and phosphatases, either as Mg^{2+} or bound to nucleotide triphosphate (NTP) as Mg-NTP [17].

2.2. Magnesium's Effect Platelet Activity and Coagulation

Magnesium inhibited the synthesis and release of pro-aggregation factors cyclooxygenase, lipooxygenase and thromboxane A2 during *in-vitro* work on human platelets [18]. Human *in-vivo* studies confirmed the theory, where magnesium infusions were shown to reduce platelet aggregation [19] and increase bleeding time [20]. It would, therefore, be prudent to monitor for signs of bleeding in hypermagnaesmic patients.

In vitro, magnesium enhanced the activity of factor IXa, increased the binding between factors IXa and VIII and together with Ca^{2+}, caused the activation of factor X [21]. However, the physiological relevance of this remains uncertain as intravenous magnesium did not alter the fibrin-degradation products or antithrombin III complex in human volunteers [22], the INR in human volunteers [23] or the coagulation index in a pre-eclamptic cohort [24].

2.3. Magnesium in Nucleic Acid Biochemistry

Magnesium serves as a co-factor to restrict endonucleases, exonucleases, polymerases and phosphatases, either as Mg^{2+} or bound to nucleotide triphosphate (NTP) as Mg-NTP [17].

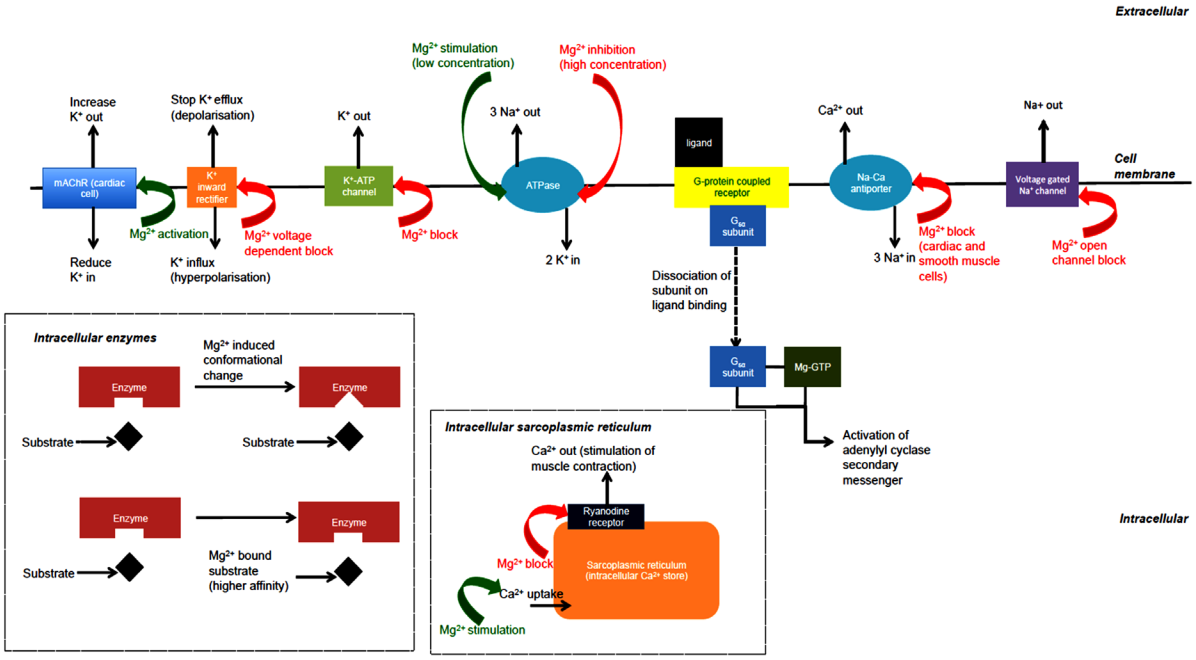

Figure 2. This cartoon illustrates schematically the key mechanisms of how Mg^{2+} modulates ionic transfer across cell membranes, how Mg^{2+} acts as a catalyst to intracellular enzymes and its interaction with the sarcoplasmic reticulum to modulate Ca^{2+} release. Image modified from Motifolio Anatomy Drawing Toolkit available from http://www.motifolio.com/anatomy.html.

2.4. Magnesium in Hormone-Receptor Binding

G-protein coupled receptors are ubiquitous and involved in many organ systems, serving cardiovascular, endocrine, neurological and reproductive functions [25] to name but a few. Upon activation of receptors with the $G_{s\alpha}$ subunit, the $G_{s\alpha}$ subunit dissociates and binds to magnesium-bound guanosine triphosphate (Mg-GTP), which is responsible for activation of adenylyl cyclase, the second messenger transduction system responsible for hormonal signal transmission [26].

2.5. Magnesium in Intracellular Calcium Regulation

Calcium influx into muscle cells triggers release of calcium from its intracellular store, the sarcoplasmic reticulum, via the activation of ryanodine receptors. This stimulates muscle contraction in both cardiac and skeletal muscle [27] [28]. Magnesium blocks this process via inhibition of the ryanodine receptors [27] [28] and it stimulates calcium uptake into the sarcoplasmic reticulum [29]. By competing with calcium binding sites on muscle filaments [30] [31], magnesium acts as a physiological antagonist to calcium [31].

The Na-Ca antiporter is essential in lowering intracellular calcium concentration after depolarisation [32], and this too is modulated by magnesium. Mg^{2+} inhibits this antiporter via competition with Ca^{2+} in cardiac cells [33] and smooth muscle cells [34], showing a role for magnesium in regulation of ion transfer across cell membranes.

2.6. Magnesium in Ionic Transfer across Cell Membranes

Magnesium is responsible for modulating ionic transfer of sodium or potassium via several pathways [35].

Intracellular Mg^{2+} causes an open-channel block of voltage-gated sodium channels, blocking the outward sodium current [36], which has been proposed as having a role in modulation of depolarisation [35].

Magnesium plays a role in potassium channels. Many cells contain a potassium inward rectifying channel that is responsible for influx of potassium under hyperpolarisation but stopping efflux under depolarisation. This behaviour is known as inward rectification and is responsible for prolonging depolarisation, which is of relevance in cardiac function and egg fertilisation. The inward rectification is caused by rapid closure of the potassium channel with a voltage-dependent block by intracellular Mg^{2+} [37].

Magnesium further affects inward rectification via modulation of the muscarinic acetylcholine receptor in cardiac cells. Activation of this receptor causes K^+ efflux and slows pacemaker activity. Depletion of intracellular Mg^{2+} not only increases the K^+ efflux but also reduces the K^+ influx. Mg^{2+} also participates in the initial activation of the muscarinic potassium channel via G-protein binding [38].

Cardiac muscle, skeletal muscle and insulin-secreting cells exhibit potassium-selective single membrane channels, inhibited by adenosine triphosphate (ATP), known as K^+-ATP channels [39] [40]. This K^+-ATP channel is blocked by intracellular Mg^{2+} [41] [42]. In cardiac muscle, this channel is activated under anoxia and causes a shortened plateau of the ventricular action potential and thus reduced contraction. This may be a protective mechanism preventing a dramatic fall in intracellular ATP, critical for cellular processes [40] [43]. In insulin-secreting cells, this channel has a role in initiating insulin release [40]. Its role in skeletal muscle remains unclear [40].

The symptoms of hypomagnesaemia are shown in **Table 2**.

3. Pharmacokinetics of Magnesium

Information on the pharmacology of magnesium is limited. Chuan *et al.* conducted a pharmacokinetic model, using a population approach, upon a cohort of 116 patients who received magnesium sulphate for pre-eclampsia with measurement of serum magnesium concentration. Their model estimated, along with interpatient variability (co-efficient of variation); a systemic clearance of 4.28 L/h (37.3%), a volume of distribution of 32.3 L (32.1%), a baseline concentration of 0.811 mmol/L (18.5%) and a half-life of 5.2 hours [44]. Similar pharmacokinetic modelling by Lu et al. on 51 pre-eclamptic patients given magnesium sulphate estimated a volume of distribution of 24.0 L (39%) [45].

4. Magnesium as a Drug

Magnesium's important therapeutic roles are summarised in **Table 3**.

4.1. Magnesium in the Central Nervous System

Magnesium has been used as a therapeutic agent in acute pain. A recent meta-analysis conducted on twenty randomised trials examined the effect of perioperative intravenous magnesium upon postoperative pain. Magnesium was superior to placebo in reduction of opiate consumption by a mean of 10.52 mg of morphine, as well as a reduction in pain scores at rest and with movement [46]. This may be due to magnesium's role as an NMDA-receptor blocker, similar to ketamine's analgesic properties [47].

There may be a role of magnesium in the treatment of chronic pain. A double-blinded randomised controlled trial found intravenous and oral magnesium therapy in patients with chronic low back pain lowered pain scores and increased range of movement compared to pre-treatment [48].

In long-term care patients with primary insomnia, magnesium, in conjunction with other oral supplements, improved sleep quality, sleep time, ease of getting to sleep, hangover on awakening and alertness the following day [49].

Table 2. This table shows the symptoms of hypomagneaemia. Reference: [71].

Range (mmol/L)	Range (mmol/L)	Symptoms
Mild	0.7 - 1.0	-
Moderate	0.5 - 0.7	-
Severe	<0.5	Weakness
		Convulsionscardiac arrhythmias
		ECG changes
		Nystagmus
		Positive Chvostek and Trousseau sign

Table 3. This table shows the potential therapeutic uses of magnesium.

System	Condition	Evidence base
Central nervous system	Acute pain	• Perioperative IV magnesium reduced opiate consumption postoperatively and led to reduced pain scores [46]
	Chronic pain	• IV and PO magnesium increased range of movement and reduced pain scores in chronic back pain with a neuropathic component [48]
	Memory dysfunction	• Increased brain magnesium enhanced learning and memory in rats [72] but no research in humans to date
	Neuromuscular blockade	• Potentiates the effects of non-depolarising neuromuscular blocking agents [73]-[76] • Blunts the serum potassium rise induced by suxamethonium [77]
	Postoperative shivering and thermoregulation	• Reduction in hypothermic shivering threshold from 36.6˚C to 36.3˚C (not clinically significant) [78], some reports of reduced postoperative shivering [79]-[81] but not borne out in a systematic review [82]
	Insomnia	• PO supplementation gave improved sleep quality, sleep time and ease of getting to sleep [49]
Cardiovascular system	Arrhythmias	• Treatment for torsades de pointes, digoxin toxicity, most atrial and ventricular arrhythmias where hypokalaemia is present [50] • Superior to amiodarone in cardioversion of atrial tachyarrhythmias in intensive care [51]
	Myocardial infarction	• Reduced infarct size in canine model [83] • LIMIT-2 study showed reduced 28-day mortality in magnesium treated group [84] • Larger and more recent ISIS-4 and MAGIC-2 trials showed no survival benefit [85] [86]
	Cardiothoracic surgery	• Prophylactic magnesium reduced incidence of postoperative atrial fibrillation from 28% to 18% [53] and ventricular arrhythmias by 48% [54] • Magnesium in cardioplegic solution reduced postoperative ischaemia [55]
	Phaeochromocytoma anaesthesia	• Case series reported 15 out of 17 cases with good haemodynamic stability at induction and tracheal intubation, with 4 cases requiring additional pharmacological support for blood pressure control during tumour handling [59]
Respiratory system	Acute severe asthma	• Scottish Intercollegiate Guidelines Network (SIGN) and British Thoracic Society (BTS) 2012 recommend intravenous magnesium for patients with acute asthma, non-respondent to inhaled short-acting beta-2 agonists, inhaled anticholinergics, corticosteroids and oxygen [60] • Reduced admission rates in acute severe asthma but not in non-severe [61]
	Respiratory muscle weakness	• Improved respiratory muscle power in hypomagnesaemic patients given supplementation [62]
Gastrointestinal system	Mendelson's syndrome	• Magnesium trisillicate is superior to cimetidine in achieving a higher gastric pH [66] in prophylaxis against Mendelson's syndrome (pulmonary aspiration of gastric contents in obstetric anaesthesia)
Obstetrics	Eclampsia	• Reduced risk of maternal death and seizure recurrence compared to diazepam [67]
	Pre-eclampsia	• Reduced risk of developing eclampsia compared to placebo, phenytoin and nimodipine [68]

4.2. Magnesium in the Cardiovascular System

Magnesium is established in the treatment of cardiac arrhythmias, particularly torsades de pointes, digoxin toxicity and most atrial and ventricular arrhythmias where hypokalaemia is present [50]. In fact, a randomised control trial showed magnesium sulphate to be superior to amiodarone in cardioversion of atrial tachyarrhythmias in intensive care patients [51].

Serum ionised magnesium is known to fall in patients undergoing cardio-pulmonary bypass [52]. Meta-analyses, have shown a reduction in postoperative atrial fibrillation from 28% to 18% with magnesium treatment [53] and a reduced risk of ventricular arrhythmias by 48% [54] compared to placebo in cardiac surgery. Magnesium in the cardioplegic solution is protective of the myocardium [55] and reduces the incidence of periopera-

tive ischaemia [56] compared to controls.

Phaeochromocytoma is known to cause cardiovascular instability during induction of anaesthesia, tracheal intubation and tumour handling [50]. *Ex-vivo* work on cat adrenal glands showed the importance of calcium in co-ordinating catecholamine release from the adrenal gland [57], and it is probably via antagonism of calcium that Mg^{2+} is able to inhibit adrenal catecholamine release [58]. James discussed the clinical relevance of this in a case series, where magnesium sulphate was used as the primary anti-adrenergic agent in 17 phaeochromocytoma anaesthetics. Catecholamine levels were reduced from time of induction to tumour handling by magnesium sulphate in the 5 cases where measurements were taken. Fifteen of the seventeen cases had good haemodynamic stability at induction and tracheal intubation, with 4 cases requiring additional pharmacological support for blood pressure control during tumour handling [59].

4.3. Magnesium in the Respiratory System

The joint Scottish Intercollegiate Guidelines Network (SIGN) and British Thoracic Society (BTS) guidelines of 2012 on the management of asthma recommend intravenous magnesium should be considered for patients with acute asthma, non-respondent to inhaled short-acting beta-2 agonists, inhaled anticholinergics, corticosteroids and oxygen [60].

A Cochrane review found magnesium therapy was beneficial in reducing admission rates in acute severe asthma, with an improvement in the peak expiratory flow rate. These results were not seen in non-severe acute asthma [61].

Magnesium may have some direct effect upon respiratory muscle power as hypomagnesaemic patients display an improvement in respiratory muscle power when magnesium is replaced [62].

4.4. Magnesium in the Gastrointestinal System

Mendelson's syndrome is the pulmonary aspiration of acidic liquid gastric contents intra-operatively or early postoperatively in obstetric anaesthesia, leading to dyspnoea, cyanosis and shock [63] [64]. Antacid therapy has been an established treatment in the prophylaxis against Mendelson's syndrome [65] and magnesium trisillicate is superior to cimetidine in achieving a higher gastric pH [66].

4.5. Magnesium in Obstetrics

Magnesium is efficacious in the termination of seizures associated with eclampsia. A recent Cochrane review showed intravenous or intramuscular magnesium reduced the risk of maternal death and seizure recurrence (risk ratios 0.59 and 0.43 respectively) compared to diazepam. There was no impact on perinatal or neonatal mortality, with fewer babies needing admissions greater than 7 days in the magnesium group [67].

In pre-eclampsia, a Cochrane review showed magnesium reduced the risk of developing eclampsia compared to placebo or no drug therapy in six trials (risk ratio 0.41), and to a lesser extent when compared to phenytoin in three trials (risk ratio 0.08) and nimodipine in one trial (risk ratio 0.33) [68]. It should be noted that rates of progression from pre-eclampsia to eclampsia were as low as 1.9% in the Magpie trial [69], the largest trial on the matter.

5. Summary

Magnesium is fundamental to numerous physiological processes. Physical manifestations of hypomagnesaemia reflect the multitude of systems that depend on this unique electrolyte.

This article discussed magnesium homeostasis, important roles magnesium plays in enzyme interactions, nucleic acid synthesis and facilitating ionic transfer across cell membranes. Overall, the pharmacology of magnesium as a drug is not well known but the clearance, volume of distribution and half-life has been described by modelling data in humans.

Finally, we have discussed established indications for magnesium in the treatment of eclampsia, cardiac dysrhythmias, acute severe asthma and prevention of adrenergic surge in phaeochromocytoma surgery. We have explored more novel applications of magnesium in the prevention of perioperative complications, such as; aspiration in obstetric surgery, postoperative pain and arrhythmias following cardiac surgery.

Magnesium is often overlooked as an electrolyte, which deserves greater appreciation.

Statement of Conflict of Interest

None.

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