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Artificial Intelligence in the ICU

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Using iMg Testing for Clinical Management in the ICU

An overview of ionised serum magnesium as an important biomarker for critically ill patients and how iMg testing is utilised at Mater Intensive Care.

Ionised Serum Magnesium - An Important Biomarker

Magnesium is the fourth most common cation in the body and the second most abundant intracellular cation, exceeded only by potassium. The bulk of it is found in the intracellular space, with the greatest proportion in bone, around one-third in muscle and the rest in soft tissue. Only around 1% of magnesium is found in extracellular fluid where it takes part in several physiologic processes. The magnesium contained in blood exists in different states. Around half is in its ionised form, with the remainder bound to albumin or complexed with anions.

Although in health, there is a good correlation between total and ionised magnesium levels, this is not likely to be the case in critically ill patients. The levels of bound magnesium can fluctuate significantly, often in a very unpredictable way, particularly in the critically ill. This can be because of changes in serum protein levels or in the number of anions in the blood. There are also several drugs administered and clinical states encountered by critically ill patients that can affect magnesium levels, including acid-base disturbances, refeeding syndrome, pancreatitis, diuretics, aminoglycosides, proton pump inhibitors and calcineurin inhibitors, to name a few.

Although dysmagnesaemia is common in critically ill patients, there are relatively few studies looking at the relationship between ionised and total magnesium levels in the ICU. In a study by Johansson et al. (2007)), there was a weak correlation between total and serum magnesium, with 25% of patients having low ionised magnesium in the presence of normal total magnesium and 9% having high ionised magnesium despite normal total magnesium. Escuela et al. (2005) also found that total magnesium levels were a poor reflection of ionised magnesium. In another paper by Yeh et al. (2017), only 18% of low total magnesium levels were considered below the normal range for ionised magnesium. This suggests that up to 80% of patients could be receiving unnecessary magnesium supplementation. Another study in critical care noted that in patients with low total magnesium levels, only 30% of these also had low ionised magnesium (Huijgen et al. 2000). Outside of the critical care population, when looking at acute myocardial infarction patients compared to controls, ionised magnesium has been found to be a more useful monitor in detecting alterations in magnesium levels (Kyriacou 2008). This body of evidence suggests that ionised serum magnesium is an important marker in identifying critically ill patients who may be vulnerable to complications due to magnesium deficiency.

Clinical Complications Due to Hypomagnesaemia and Hypermagnesaemia

Abnormalities in serum magnesium levels are common in critically ill patients. Hypomagnesaemia is more frequent than hypermagnesaemia, occurring in up to 70% of patients admitted to the ICU. Low magnesium levels are mainly secondary gastrointestinal losses (such as nasogastric suctioning, malabsorption, diarrhoea, pancreatitis) and renal losses (renal diseases, osmotic diuresis, acidosis, hypercalcaemia, fluid therapy, drugs). As magnesium is involved in a myriad of physiologic processes, dysmagnesaemia can affect multiple systems and have significant consequences.

Some of the most serious effects of altered magnesium levels are abnormalities in the cardiovascular system. Hypomagnesaemia can result in atrial and ventricular arrhythmias, hypertension, vasospasm and sudden death. Hypermagnesaemia is associated with bradycardias, heart block, hypotension and cardiac arrest. Magnesium deficiency may also increase the risk of post-operative atrial fibrillation in a cardiac surgery population. Abnormal magnesium levels can also have a significant impact on the neuromuscular system. Low levels are associated with seizures, tetany, laryngospasm, paraesthesias, migraine, cramping and hyperreflexia. On the contrary, hypermagnesaemia can lead to muscle weakness and flaccid paralysis with respiratory muscle weakness and coma. Other complications associated with altered magnesium levels include nausea, anorexia, haemostatic abnormalities and metabolic abnormalities, including hypokalaemia, hypocalcaemia and insulin resistance.

The relationship between magnesium levels and mortality varies in the literature, but there is evidence to suggest that both hyper and hypomagnesaemia can affect patient outcomes. In a paper by Chernow et al. (1989), mortality was higher in postoperative intensive care patients with low magnesium levels. Rubeiz et al. (1993) found a similar relationship between magnesium levels and mortality in acutely ill medical patients. In contrast, Guerin et al. (1996) did not find an association between low admission levels of magnesium and death. Mortality was increased in the hypermagnesaemic group, but this only included six patients. In keeping with Guerin, Soliman et al. (2003) found no association between admission magnesium levels and outcome. However, patients who went on to develop ionised hypomagesaemia during their critical care stay had worse outcomes. In addition to increased mortality, patients with hypomagnesaemia are more likely to experience other electrolyte disorders, require organ support and have a longer ICU stay (Safavi and Honarmand 2007).

Measuring iMg Levels in Intensive Care Patients

Despite disorders of magnesium being relatively common in the ICU, the recent VITA-TRACE survey found that up to 25.4% of respondents did not routinely perform any form of measurement of magnesium levels more than once a week (Vankrunkelsven et al. 2021). This was even though 63.4% gave regular parenteral magnesium supplementation. Ionised magnesium levels are less routinely used in comparison to total magnesium in clinical practice. This is likely because there are no standardised diagnostic reference levels available. There are also relatively few manufacturers offering point-of-care devices that measure ionised magnesium levels in the blood (Dent and Selvaratnam 2022).

Point-of-care devices that offer ionised magnesium levels use methods based on ion-selective electrodes. They allow accurate detection of ionised magnesium from whole blood with a rapid turnaround time and require only a small volume of blood. Monitoring ionised magnesium in critically ill patients is beneficial as it is the physiologically active component (Dent and Selvaratnam 2022; Scarpati et al. 2020). However, despite the many benefits of ion-selective electrodes, magnesium-specific electrodes are vulnerable to interference from other cations. Correction equations may need to be applied based on calcium concentrations. Ionised magnesium levels vary with pH, and the measurements can also be affected by temperature and dilution of the sample (Dent and Selvaratnam 2022; Scarpati et al. 2020). These factors are more commonly found in a critically ill population than the general hospital cohort.

iMg Testing at Mater Intensive Care

The Mater Intensive Care service is a mixed medical and surgical ICU, admitting critically ill patients from all disciplines within the Mater and Rotunda Hospitals and those referred from outside the hospital. There is a prioritised service to the national Cardiothoracic, Heart and Lung transplantation programme, Acute Spinal Injury services, and supra-regional services such as Vascular Surgery and Extra-Corporeal Membrane Oxygenation. The ICU has 18 beds with 1300 admissions annually, a bed occupancy of 107% and an average length of stay of 4.4 days. The HDU has 16 beds and admits approximately 1200 patients annually, has a bed occupancy of >100% and average length of stay of two days.

“ionised serum magnesium is an important marker to identify critically ill patients who may be vulnerable to complications due to magnesium deficiency”

Ionised magnesium levels are measured in all patients admitted to the Mater ICU. As a mixed medical and surgical unit, it cares for a variety of patients at risk of disorders of magnesium and the associated clinical consequences. As mentioned previously, hypomagnesaemia is common in critical care. Many patients will receive ICU therapies that interfere with magnesium homeostasis. These include diuretics, proton pump inhibitors, aminoglycosides and fluid therapy. As a result, monitoring ionised magnesium in all comers is beneficial and allows the detection of hypomagnesaemia and treatment before clinical consequences develop. There are also patient groups with specific indications for magnesium in whom the ability to rapidly measure levels is advantageous.

As a cardiothoracic centre, the Mater ICU routinely cares for patients who have undergone cardiopulmonary bypass. Evidence suggests that magnesium may reduce the risk of postoperative atrial fibrillation in this patient group. In the 2019 guidelines on cardiopulmonary bypass in adult cardiac surgery, its use can be considered prophylaxis for atrial fibrillation (Kunst et al. 2019). Hence, at Mater, the team routinely administers magnesium in these patients to prevent or treat atrial fibrillation and other tachyarrhythmias. The hospital also runs a heart and lung transplant programme. In addition to post-operative arrhythmias, these patients are prescribed calcineurin inhibitors as part of their post-transplant immunosuppression regime. Calcineurin inhibitors increase the risk of hypomagnesaemia, so it is useful to have the facility to routinely monitor ionised magnesium in these two groups.

Sepsis is a common admission category to the Mater ICU, as with many ICUs. There is evidence to suggest that magnesium supplementation in patients with severe sepsis can improve lactate clearance and reduce the length of stay. In a study by Noormandi et al. (2020), supplementation was targeted to the upper limit of normal magnesium levels. More recent observational evidence implies that magnesium use may be associated with reduced mortality in critically ill patients with sepsis. This was irrespective of admission magnesium level (Gu et al. 2023). Khalili et al. (2021) found that magnesium supplementation reduced the incidence of vancomycin plus piperacillin-tazobactam-induced acute kidney injury in critically ill patients. This antibiotic combination would not be uncommonly used in our patients with sepsis. They targeted a serum magnesium level of 3mg/dl (1.24 mmol/L). Detecting asymptomatic hypomagnesaemia and correcting it may also reduce the incidence of acute kidney injury in critically ill patients (Barboas et al. 2016). More evidence and recommendations for target levels are required before adopting this into routine clinical practice but measuring ionised magnesium and supplementing levels to maintain them in the normal range is standard practice in our unit.

Another group of patients that benefit from magnesium supplementation are those admitted with acute severe asthma. Magnesium may have bronchodilator effects. Its use in acute severe asthma may reduce the rate of intubation, and it may also reduce hospital admission in those with minimal response to standard treatment. Recent guidelines recommend considering a single dose if the initial response to bronchodilator treatment has been poor (BTS/SIGN Guideline 2016). The ability to monitor ionised magnesium levels allows administration in this situation while avoiding respiratory fatigue and muscle weakness associated with magnesium toxicity.

The Mater ICU also has an affiliation with the Rotunda Maternity Hospital. Within that remit, it cares for critically ill obstetric patients, some of whom may be at risk of eclampsia.

Measuring ionised magnesium in these patients helps prevent hypomagnesaemia, reduces the risk of eclampsia and prevents the complications associated with hypermagnesaemia during treatment. Magnesium can accumulate in patients with renal failure. The ability to perform repeated bedside measurements in these patients can also help prevent the development of hypermagnesaemia.

Magnesium Supplementation Dosing and Monitoring

The initial dose of magnesium administered depends on the clinical situation. If the patient is asymptomatic and found to be hypomagnesaemic after measuring ionised magnesium, the dose would be titrated to the result to aim for a normal level. The standard order for the Mater ICU is a magnesium dose of 10 to 20 mmol (2.5 to 5 grams). In other specific clinical situations, the dose depends on best evidence or guideline recommendations. For example, in acute severe asthma, the British Thoracic Society suggests considering 1.2 to 2 grams of magnesium (BTS/SIGN Guideline 2016). For torsades de pointes, a dose of 1 to 2 grams is generally given. In pre-eclampsia, the magnesium dose given in the MAGPIE trial to prevent eclampsia was 4 grams (Altman et al. 2002).

When magnesium has been administered, ionised magnesium levels are used to monitor the response to treatment. In some situations, this is to ensure adequate supplementation. For example, in patients at risk of or being treated for new-onset arrhythmias, the target would be an ionised magnesium level greater than 1 mmol/L. The ability to monitor ionised magnesium is also used to reduce the likelihood of hypermagnesaemia and its consequences in patients requiring supplementation, for example, during the treatment of asthma or pre-eclampsia. As mentioned earlier, it can be helpful to prevent magnesium toxicity following supplementation in patients with renal failure, in whom magnesium can accumulate.

Conclusion

Magnesium is one of the most abundant cations in the body. It is mainly found in the intracellular space, but it is the free-ionised extracellular magnesium that is physiologically active. Abnormal magnesium levels are common in critically ill patients. There is a poor correlation between total and ionised magnesium levels in critically ill patients, and it is likely that ionised magnesium is more useful and specific in this patient population. Evidence suggests that using ionised magnesium can avoid unnecessary supplementation in critical care patients and that levels are correlated with outcomes. Ionised magnesium can be measured in whole blood at the bedside with a quick turnaround time. Routine measurement can identify at-risk patients and allow tailored treatment for specific indications in the ICU, including atrial fibrillation, in real time while avoiding complications of dysmagnesaemia in a complex patient cohort.

Disclaimer

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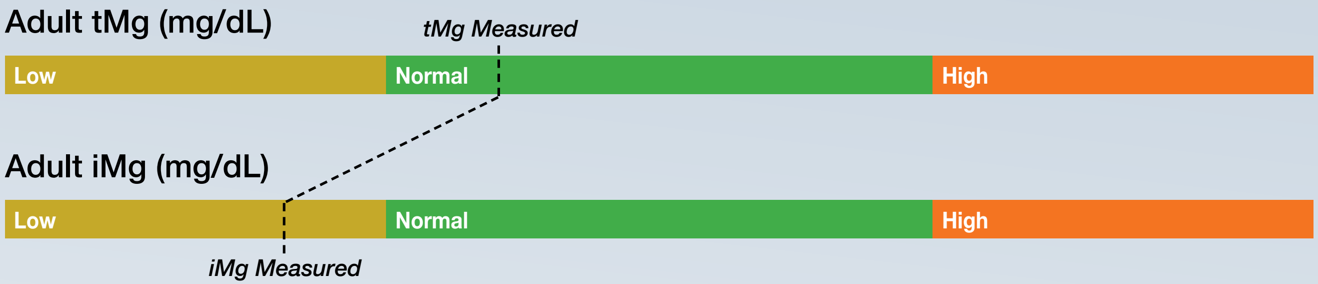
ICU Patient Studies Show Critical Importance of Ionized Magnesium

Patients Undergoing Continuous Renal Replacement Therapy (CRRT)

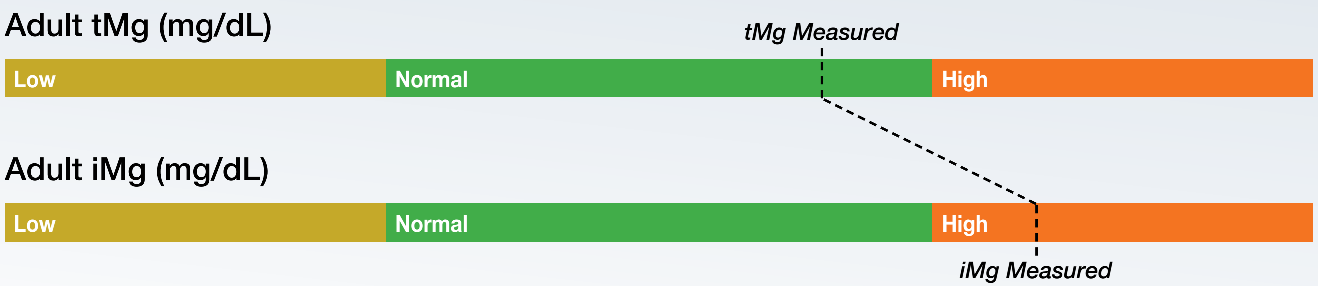
Hutten et. al.[1] found that patients receiving CRRT with citrate anticoagulation had normal tMg levels, but low iMg levels. This is due to magnesium ions being bound by citrate, and the citrate-magnesium complex being measured as tMg. These patients are actually hypomagnesemic but would not be recognized as such if only tMg were measured.



1.Hutten et al., Ionized and not total magnesium as a discriminating biomarker for hypomagnesaemia in continuous venovenous haemofiltration patients. *Nephrol Dial Transplant*, 2021.

Surgical ICU Patients

Yeh et. al.[2] found that 21% of tMg tests which were reported as normal were hypermagnesemic based on iMg. This exposes patients to potential risks associated with undetected hypermagnesemia, including prolonged days on the ventilator, muscle weakness, QT prolongation, and cardiac arrhythmia. In addition, there were many patients with low tMg and normal iMg, which led to unnecessary Mg supplementation and repeat blood draws.



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