Role of Analgesic Adjuncts - Magnesium

LS Ngema

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Department of Anaesthetics
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INTRODUCTION

WHAT IS MAGNESIUM?

Magnesium (Mg) is a nutrient and is the the 4th most abundant mineral in the body, after Sodium, Potassium and Calcium. It is the 2nd most abundant intracellular cation after Potassium. It is a physiological antagonist of Calcium at different voltage-gated channels\(^{(27)}\).

WHAT DOES MAGNESIUM DO\(^{1,2}\)

It activates about 300 enzymes in the body, many of which involve energy production. ATP is fully functional when chelated to Mg. Mg regulates Calcium entry into the cells.

NUMBERS\(^{3,4}\)

- Total body Mg\(^{2+}\) is ≈ 310g (1000 mmol)
  - 50% of this amount is in bone
  - 30% is in cells.
  - 20% in soft tissues
  - 0.3% is in the serum.
- Daily requirements => 200 to 250mg /day
- Normal serum Mg levels => 0.76 to 0.9 mmol/l.
  - Therapeutic levels are => 2 to 4mmol/l
  - Muscle weakness starts at > 5mmol/l

1g MgSO\(_4\) = 98g Mg = 4mmol = 8mEq

BODY CONTROL OF MAGNESIUM\(^{5,6}\)

Mg is absorbed and excreted in the GIT and kidneys. It is reabsorbed in the ascending loop of Henle. Serum [Mg\(^{2+}\)] provides a negative feedback to the Loop of Henle. Mg is maintained at a ratio of 1:5 with K\(^{+}\). K\(^{+}\) deficiency can be difficult to treat in unrecognized Mg deficiency. Mg homeostasis is under PTH and 1,25 Dihydrocholecalciferol control, which increases GIT, bone, and renal re-absorption.
CLINICAL EFFECTS OF MAGNESIUM\textsuperscript{7,8,9,4}

Most of our exposure to the use of magnesium has been in Obstetric Anaesthesia. Magnesium is however not an anticonvulsant.

1. It prevents or reverses causes of seizure activity; that is magnesium reverses vasoconstriction which causes cerebral anoxia which leads to convulsions.
2. It prevents foetal respiratory depression.
3. Mg decreases maternal mortality and morbidity.
4. It is more effective than other agents in blunting the intubation response, with less foetal effect.

Non-medical applications and uses of magnesium\textsuperscript{4,5,6}

- In agriculture: used to correct magnesium deficiency in soil. Mg is an essential element in the chlorophyll molecule.
- Anhydrous magnesium is commonly used as a dessicant in organic synthesis, due to its high affinity for water.
- Used for bath salts in flotation therapy, where high concentrations raise the bath water’s specific gravity. It is also used for sore feet, as a soother.
- Magnesium heptahydrate is used in marine aquaria to maintain large amounts of stony corals, as it stabilizes ions in the saltwater.
- Magnesium is used as a reactive compound in the manufacture of gunpowder (Black powder). It contributes to the violent burn rate (Stoichiometric concentration).
- MgSO$_4$ is used to prepare Copper Sulphate

\[ \text{Cu} + \text{MgSO}_4 + 2\text{H}_2\text{O} \rightarrow \text{H}_2 + \text{CuSO}_4 + \text{Mg(OH)}_2 \]
Medical applications and uses of Magnesium\textsuperscript{7,4,5}

Magnesium has a wide range of applications in medical therapy:

- As Epsom salt it is used as a laxative and topically for treating aches and pains
- MgSO\textsubscript{4} is used as:
  - replacement therapy for hypomagnesemia
  - As a first line anti-arrhythmic agent for Torsade de pointes.
  - For managing Quinidine-induced arrhythmias
- MgSO\textsubscript{4} is used as a bronchodilator after B\textsubscript{2} agonists and anticholinergic agents have been tried, e.g. in severe exacerbations of asthma
- Use in pre-eclamptic and eclamptic patients is described above
- Magnesium has been used to treat tetanus where it has been shown that it reduces spasms and autonomic instability
- Magnesium has been used in patients with spinal injuries to treat or prevent autonomic hyperreflexia\textsuperscript{10}.

Further uses include:\textsuperscript{5}

- Used intravenously to prevent cerebral palsy in preterm babies.
- May be given as first aid in barium chloride poisoning. Used topically as a drying agent for abscesses and carbuncles.
- Also used in acne solutions in a cream form.
- Magnesium sulphate is used in warm baths to soothe, relax and relieve herpes outbreak symptoms in genital herpes and Herpes zoster.

MODE OF ACTION

1. Magnesium is a Ca\textsuperscript{2+} antagonist.
2. It competes with calcium to inhibit vasoconstriction.
3. It blocks the NMDA receptor thus decreasing intracellular calcium.
4. Magnesium inhibits Ryanodine receptors decreasing muscle contraction.
5. Also directly inhibits catecholamine release from the adrenal medulla.

PHYSIOLOGICAL EFFECTS OF MAGNESIUM\textsuperscript{7,6}

Cardiovascular System

The LIMIT-2 study in 1992 was the first large scale randomized placebo-control study to show improved outcomes after Myocardial Infarction: smaller infarcts, less arrhythmias and better cardiac function after magnesium was given pre-thrombolysis diminishing reperfusion injury.

1. Improves cardiac output, coronary blood flow and coronary perfusion.
2. Reduces afterload, due to vasodilatation.
3. Changes excitatory threshold and intracellular ionic content causing less arrhythmias on reperfusion.
4. Has a direct depressant effect on myocardial and vascular smooth muscle.
5. Through decreased vascular tone, it decreases pulmonary vascular resistance.
6. It slows the rate of impulse formation at the SA node and prolongs SA conduction, the PR interval and AV node refractory period.

**Nervous System**

Reduces the release of Acetylcholine at the NMJ by antagonising calcium ions at the presynaptic junction.
1. Causes reduced excitability of nerves.
2. Reverses cerebral vasospasm, therefore anticonvulsant.

**Musculoskeletal**

1. Involved in terminating contraction, initiating relaxation in skeletal muscles.
2. In combination with the effects above excessive plasma concentrations can cause muscle weakness.

**Respiratory System**

1. Magnesium is an effective bronchodilator, but does not affect the respiratory drive.
2. Respiratory failure may occur as a result of excessive muscle weakness.

**Genitourinary System**

1. Is a powerful tocoytic, decreasing uterine tone and contractility.
2. Has mild diuretic properties.

**Hematological System**

1. Platelet activity is reduced, resulting in prolonged bleeding time.
PLACING MAGNESIUM IN ANAESTHETICS AND CRITICAL CARE

For more than 100 years, magnesium salts have been used to achieve different purposes like producing general anaesthesia, decreasing MAC\textsuperscript{11} and treatment of Myocardial Infarction.\textsuperscript{7} In the 20\textsuperscript{th} century, magnesium has been used for preventing eclamptic convulsions, and has been recognized as potentiating non-depolarising muscle relaxants.

Discovery of the Calcium channel blocking ability of magnesium, has opened room for studies on a number of its potential benefits in anaesthesia and critical care.

Magnesium is popular as an arteriolar vasodilator with minimal veno dilatation, thus maintaining cardiac filling and cardiac output\textsuperscript{7}.

There is a high percentage Mg deficient patients in hospitals, especially post-operatively.\textsuperscript{12}

Anaesthetising a hypomagnesemic patient may precipitate arrhythmias\textsuperscript{4}. Apart from its use in Torsade, magnesium is recommended for use in Digoxin-induced and ventricular arrhythmias due to other causes, and may be superior to other traditional anti-arrhythmics. In shock-refractory Ventricular Fibrillation, magnesium is given intravenously.

There has been considerable interest in the potential use of magnesium for acute myocardial ischemia\textsuperscript{4}.

Due to its calcium channel blocking properties and suppression of catecholamines, magnesium has been used during surgery for phaeochromocytoma\textsuperscript{7}. Anaesthetists have used magnesium for epidural anaesthesia in quadriplegic patients with autonomic hyperreflexia\textsuperscript{10}.

With the increasing understanding of pain physiology and the NMDA receptor, the use of magnesium for secondary analgesia and as an adjuvant to different regimens is introducing exciting new possibilities for the use of Mg in acute and chronic pain.

Its use in peri-operative pain management is the reason for this talk. Several drugs have been used for pain management, which are not without adverse effects.

Opioids have been the mainstay of pain management but there are issues with their use:
1. Morphine has been associated with immunomodulation, tumor recurrence and a dose-dependent inhibition of pro-inflammatory cytokines.\textsuperscript{13}
Nuclear Factor kappa beta (NF-κB), is a known cytokine, which plays a role in modulating the inflammatory process. In vitro studies have shown that magnesium significantly inhibited endotoxin-induced up-regulation of inflammatory molecules and NF-κB, by antagonising calcium and inhibiting L-type calcium channels\textsuperscript{13,11}

2. Chronic post surgical pain syndromes: Opioids have been shown to induce long term hyperalgesia.
3. Opioid–induced hyperalgesia: It is less of an issue than initially thought, but may still be relevant. Neuroplastic changes in the CNS and PNS lead to nociceptive sensitization.\textsuperscript{11}
4. Opioid tolerance: Morphine use increases the NMDA receptor activity, while decreasing the efficacy of Morphine at the mu receptor\textsuperscript{2}.

NMDA receptor antagonists, Ketamine and magnesium have been shown to prevent occurrence and recurrence of all the above-mentioned phenomena.\textsuperscript{13,2,11}

THE NMDA RECEPTOR, PAIN PATHWAYS AND PAIN STATES

The N-Methyl-D Aspartate Receptor

The NMDA is an inotropic receptor (ligand-gated ion channel), found where speed is important: nerve cells and heart pacemaker cells. The neurotransmitter is glutamate, an excitatory transmitter, which opens calcium channels.

- The NMDA receptor is important in neuronal signaling and neuronal gene expression.
- It is also involved in pain processing, neuronal plasticity and generation of central sensitization after nociceptive stimuli.

NMDA receptor antagonists, like Mg\textsuperscript{2+} and Ketamine, can prevent induction of central sensitization attributed to peripheral nociceptive stimulation – and can abolish hypersensitivity, once it is established.

\textit{Pain States}\textsuperscript{1,2}

There is evidence that NMDA receptors are involved in a number of phenomena that may contribute to the medium to long term changes that are involved in chronic pain states.
Phenomena include:
  o Development of ‘wind up’, facilitation, central sensitization: changes in peripheral receptive fields, induction of immediate early genes and long term potentiation.
  
  o Long term potentiation – refers to changes in synaptic efficacy that occur as part of the memory process, and may play a role in the development of cellular ‘memory’ for pain or noxious inputs.

NMDA receptor antagonists can attenuate these responses - indicating their role in prevention of chronic pain states.

**Intracellular Events**

NMDA receptors are set in a cascade of secondary events in a cell which has been activated. These events lead to intracellular changes which increase the responsiveness of the nociceptive system.

The NMDA receptor in its resting state is ‘blocked’ by a magnesium ‘plug’.

Priming of the NMDA receptor by co-release of glutamate and other peptides, leads to removal of the magnesium plug and subsequent calcium influx into the cell. This leads to secondary events, such as immediate early gene induction, production of NO, activation of a number of messengers, including phospholipases, polyphosphoinositides [IP₃, DAG], cGMP, eicosanoids and phospholipase C.

The 2nd messengers act directly to change the excitability of the cell or involve production of oncogenes which may lead to long term alterations in cell excitability and responsivity.

Prolonged stimulation through sustained and excitotoxic glutamate release may result in cell death. (See figure below).

**Nitric Oxide**

Production of NO is implicated in induction and maintenance of chronic pain states. NO may be one of the factors responsible for cell death, which has been demonstrated to occur under these conditions.
Effects of glutamate on the NMDA receptor in the spinal cord

NO acts as a positive feedback mechanism in the maintenance of pain. Blockade of NO in neuropathic animal models has resulted in a decrease in the behavioural correlates of pain.

Arachidonic Acid Production

The production of arachidonic acid metabolites as part of the cascade occurs following NMDA receptor activation – the peripheral effects of NSAIDS act on this pathway. There appears to be a role for spinal administration of NSAIDS –which either act directly on receptors like NMDA, neurokinin or influence intracellular metabolite production.
Central Sensitization\textsuperscript{8,9,14,1,2}

Post injury there can be increased responsiveness to normally innocuous mechanical stimuli: This zone of secondary hyperalgesia in uninjured tissue surrounding the site of injury (allodynia).
  - There is no change in the threshold to thermal stimuli. These changes are believed to be a result of processes occurring in the dorsal horn of the spinal cord following injury.
  - This is the phenomenon of Central sensitization.

In the presence of pain, the CNS is not hard wired. Nociceptive stimuli, such as surgery, result in changes to the response properties of the dorsal horn neurons. With clinical pain associated with nociceptive input there is not a simple stimulus-response relationship, but a ‘wind up’ of spinal cord neuronal activity.

  - Wind up is dependent on activation of the NMDA receptor and therefore is subject to modification by agents acting on the receptor.
  - This ‘wind up’ may make these neurons more sensitive to other input. It is a component of central sensitization.

Other changes in the dorsal horn have been noted with central sensitization
  - Expansion in the receptive field size so that a spinal neuron will respond to stimuli that would normally be outside the region that responds to nociceptive stimuli.
  - There is an increase in the magnitude and duration of the response to stimuli which are above the threshold in strength.

  - There is a reduction in threshold so that normally non-noxious stimuli activate neurons which normally transmit nociceptive information.
  - These changes may be important both in acute pain and in the development of chronic pain.

The development of ‘wind up’ phenomenon has led to a surge of interest in approaches like pre-emptive analgesia, rationale behind the concept lies in an attempt to reduce development of subacute or chronic pain by abolishing or reducing acute pain, thus preventing the occurrence of changes associated with ‘wind up’\textsuperscript{15}.

Nerve damage results in enhancement of calcium flux, Nitric Oxide production, and protein kinase C production. Protein kinase C has a potent effect in increasing activity at the NMDA receptor – thus causing a vicious cycle
Intrathecal or systemic administration of morphine for neuropathic pain may increase NMDA activity, while decreasing the efficacy of morphine at the mu opioid receptor at the same time. Morphine administration for neuropathic pain may progressively contribute to increasing pain.

Morphological changes have been demonstrated within the dorsal horn following injury.
- Peripheral nerve injury leads to a redistribution of central terminals of myelinated afferents, with sprouting of these terminals, from Lamina IV to Lamina II.
- If functional contact is made between terminals, which normally transmit non-noxious information, with those that normally receive nociceptive information—this provide a framework for pain and sensitivity to light touch—Allodynia, post nerve injury.

**Opioid Receptors**

These receptors are widely used, and are generally efficacious in pain management. Opioid receptors are found pre- and post-synaptically in the dorsal horn—75% are presynaptic.

Activation of presynaptic opioid receptors leads to reduction in the release of neurotransmitters from the nociceptive primary afferent.

Changes that occur with inflammation and neuropathy can produce significant changes in opioid sensitivity that involve a number of mechanisms.

These include:
- Interference with opioid analgesia by Cholecystokinin (CCK),
- Loss of opioid presynaptic receptors
- Formation of a morphine metabolite, Morphine-3-glucuronide, which may antagonize action normally produced by opioid receptor activation.

It has also been demonstrated that the NMDA receptor is involved in the development of tolerance to opioids. Animal studies showed that administration of NMDA antagonist reduces development of tolerance to morphine and prevents the withdrawal syndrome in morphine-tolerant rats.
MAGNESIUM AS AN ADJUVANT TO ANAESTHESIA AND ITS PROPOSED ROUTES OF ADMINISTRATION

Adjuvant analgesics are a group of drugs marketed with a non-pain indication, but found to be useful in treating pain conditions\(^4\). Use of adjuvant analgesics and non opioids may improve efficacy while reducing opioid related side-effects.

**Commonly Used Adjuvant Analgesics\(^{11}\)**

- Among the N-Methyl-D-Aspartate antagonists, Ketamine use perioperatively is both efficacious and preventive, as an adjuvant analgesic, with good safety and tolerability profiles.
- Magnesium is beneficial, especially in abdominal surgery, while toxicity from its use is rare, with routine monitoring.
- Gabapentin reduces post-operative pain, but with dose-dependent dizziness and sedation. Pregabalin is another studied adjuvant.
- Dexamethasone and Methylprednisolone give analgesia plus antiemesis. Use is limited by steroid-related side effects.
- Clonidine, though opioid sparing, is associated with a severe bradycardia, and hypotension in many studies\(^{11}\). Dexmedetomidine is also an analgesic adjuvant.
- Lidocaine is an amide local anaesthetic with antinociceptive and antinflammatory properties. When given intravenously, it is effective in chronic neuropathic pain conditions.\(^{11}\)
Magnesium has been used alone or in combination with other drugs to potentiate the actions of these drugs. There have been many proposed routes of magnesium administration:

- From enteric, where it is used as a salt for bowel carthasis (laxative) to topical use, as has been mentioned in the text above.
- Magnesium has been used intravenously as magnesium sulphate, especially in obstetrics, to prevent convulsions, while lowering blood pressure\(^7\).
- Magnesium is also used in Intravenous Regional Anaesthesia (IVRA), where it is used in an attempt to reduce tourniquet pain\(^{15,16}\) and to prolong the effects of lignocaine.
- Spinal and epidural use of magnesium with opioids and local anaesthetics to reduce the anaesthetic requirements has been researched with different outcomes\(^{14,12}\).
- Intravenous use of magnesium in general anaesthesia as an adjunct to anaesthetic agents like non-depolarising neuromuscular agents, Propofol and Remifentanil, to reduce anaesthetic requirements\(^{17,18}\).
- During regional anaesthesia, intravenous magnesium has been used to reduce the post operative Morphine/ Fentanyl requirements in PCA’s (patient controlled analgesia), or PCEA’s (patient controlled epidural analgesia).
- Magnesium has been used as a local infiltration drug with local anaesthetics.
- The use of magnesium for post operative pain management after major thoracic surgery in thoracic epidural analgesia (TEA) has been explored\(^{20}\).
- Caudal use, patches and pumps are other possibilities for routes of magnesium use. However, these routes are not covered in this talk.

**Use of Magnesium in Acute versus chronic pain**\(^{8,9,19,1}\)

- Studies have shown that there is room for magnesium use in acute and chronic pain management.
- Most studies reviewed in this talk have been done on magnesium use in acute peri-operative pain.
- Only one case report has been reviewed on use of magnesium for management of chronic pain\(^3\).
- As explained in the pain pathways in the text above, there is room for use of magnesium in the prevention and treatment of chronic pain- ‘central sensitization’ and ‘wind up’.
- Magnesium has taken part in the application of the concept of pre-emptive analgesia, the blockade of the pain pathways before the nociceptive stimulus sets in.
A META ANALYSIS OF RANDOMISED CONTROL TRIALS ON MAGNESIUM USE

Table 1 shows an analysis of 14 randomised controlled trials on magnesium.

In 2007, a systematic review of randomised control trials was done on intramuscular and intravenous magnesium use in the peri-operative period.

A meta analysis of 14 trials was done, in which different molecular forms of magnesium were used on patients peri-operatively, with the endpoint of assessing:

- Post operative pain intensity
- Post operative analgesic requirement
- Post operative shivering
- And serum magnesium levels

- Of the 14 trials, only 4 reported a significant reduction in post operative pain intensity in patients treated with magnesium, compared with placebo, in the 24 hour period post operatively – (29%).
- Other trials had either shown no difference, or even more pain in magnesium treated patients.
- 8 Trials (57%) had shown a significant reduction in post operative analgesic requirement, that is, opioids.
- Post operative shivering was never reported in any of the magnesium treated patients.
- Magnesium levels were elevated in all 7 trials that reported them.

Conclusion

- The 2007 systematic review concluded that trials did not show convincing evidence that perioperative magnesium may have favourable effects on post operative pain intensity.
- However, there was strong evidence that peri-operative magnesium administration did reduce post operative analgesic requirements.

Limitations of the Systematic Review

The studies did not use a uniform molecular form of magnesium; others used Magnesium laevulinate, others Magnesium gluconate, while others were using Magnesium sulphate.
A large variety of dosing regimens led to inconsistent findings. Many trials had used Magnesium sulphate intravenous bolus plus infusion whilst others had used an intravenous bolus only.

One trial used Magnesium gluconate intravenous bolus plus infusion, while the other had used magnesium laevulinate intravenous bolus plus infusion.

Studies that followed the 2007 meta analysis, from 2008 to 2011, have all used magnesium sulphate, in different doses and regimens, which gives them some form of uniformity and consistency in their findings\textsuperscript{7,10}

Table 1 shows the analysis of the randomised control trials’ findings after the use of magnesium in different surgical settings, and the outcomes on post operative pain intensity and analgesic requirements, the summary of which has been discussed above.\textsuperscript{12}
<table>
<thead>
<tr>
<th>Quality of data reporting</th>
<th>All magnesium regimens were given intravenously (no. of analyzed patients)</th>
<th>Comparison</th>
<th>Postoperative analgesic requirements and pain intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rel.</td>
<td>R</td>
<td>C</td>
<td>B</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>41</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>42</td>
<td>2</td>
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<td>43</td>
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<td>44</td>
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<td>0</td>
<td>1</td>
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<tr>
<td>45</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>47</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>49</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Group 1: see “MgSO₄ IV bolus”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Randomization: 0 = none; 1 = yes, not specified; 2 = yes, adequate. Concealment of treatment allocation: 0 = none; 1 = yes. Blinding: 0 = none; 1 = patient or investigator or observer.
STUDIES ON THE USE OF MAGNESIUM AS AN ADJUNCT FOR PERI-OPERATIVE PAIN MANAGEMENT

Since the meta-analysis 2007 several new studies indicate Mg may be more promising than shown in the first Meta analysis.

A follow up meta-analysis of the recent studies, was done in 2011\textsuperscript{11}, by Lui and Ng, which comprises 6 studies on the use of Magnesium as an analgesic adjuvant, in different surgical settings:

- 5 Studies confirmed the, that the use of magnesium as an adjuvant, does decrease the Morphine requirement post operatively. One study showed no difference in pain scores between groups.
- An interesting question arises: Is there a just right dose for magnesium if it is to be used as an analgesic adjuvant?

Studies done in 2004\textsuperscript{16}, and in 2011\textsuperscript{15}, have shown the efficacy of magnesium when used with intravenous regional anaesthesia, in reducing tourniquet pain and improving the quality of the block, and reduces the overall failure rate of IVRA. It also extends the time for analgesia, which is a limitation in this technique.

Single bolus dosing of magnesium, has proven effective in pain management for minor cases, like inguinal surgery\textsuperscript{20}, and stripping of varicose veins\textsuperscript{9}, decreasing the need for post-operative analgesia. Of note was that, single bolusing seems not to work for post operative pain in ambulatory surgery, where the patients were expected to mobilize early post-op\textsuperscript{9}. (Statistical result below.)
Assesment of pain in postoperative period
(Visual analogue scale) (1-10)

<table>
<thead>
<tr>
<th></th>
<th>Group I (Mean±SD)</th>
<th>Group II (Mean±SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergence of anaesthesia</td>
<td>1.86±.70</td>
<td>1.96±0.53</td>
<td>0.138</td>
</tr>
<tr>
<td>After 2 hrs</td>
<td>1.22±.76</td>
<td>1.82±.96</td>
<td>0.001</td>
</tr>
<tr>
<td>4 hrs</td>
<td>1.32±.84</td>
<td>1.88±.44</td>
<td>0.000</td>
</tr>
<tr>
<td>8 hrs</td>
<td>2.74±1.43</td>
<td>3.84±1.46</td>
<td>0.000</td>
</tr>
<tr>
<td>16 hrs</td>
<td>1.36±.69</td>
<td>2.00±.76</td>
<td>0.000</td>
</tr>
<tr>
<td>24 hrs</td>
<td>0.78±.68</td>
<td>1.30±.46</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*P<0.05 significant, *P>0.05 insignificant

Postoperative sedation score in recovery room

<table>
<thead>
<tr>
<th>Group</th>
<th>Sedation score (mean ± SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-I (n=50)</td>
<td>1.86±0.64</td>
<td></td>
</tr>
<tr>
<td>Group-II (n=50)</td>
<td>1.40±0.49</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Single bolus magnesium, not showing desired effect when patients needed to ambulate. Is the effectivity of magnesium dose dependent?
The dosing of magnesium seems to be crucial for its maximum effectiveness as an adjuvant in combating pain. Of interest is the 2009 study, by Lee and Kwon\textsuperscript{21}, who showed the preferential use of 45mg/kg of magnesium sulphate over 30mg/kg, in Caesarean section patients, for the prevention of recall, and pain management pre-neonatal delivery. “Magnesium-45” patients showed better BIS scores, with less Fentanyl, Midazolam and Atracurium requirements, than the “Magnesium-30” group, (Table 2).

\begin{table}[h]
\centering
\caption{BIS values from induction of anaesthesia to delivery. Values were expressed as mean (sd). \textsuperscript{*}$P<0.05$, \textsuperscript{\dagger}$P<0.001$ when compared with pre-magnesium sulphate and \textsuperscript{\ddagger}$P<0.01$, \textsuperscript{\S}$P<0.001$ when compared with the Mg 45 group.}
\begin{tabular}{lccc}
\hline
 & Control group & Mg 30 group & Mg 45 group \\
 & (n=24) & (n=23) & (n=25) \\
\hline
Pre-induction & 97 (9) & 97 (8) & 98 (8) \\
Pre-magnesium sulphate & 53 (9) & 54 (9) & 54 (8) \\
2.5 min after surgery & 56 (8) & 55 (10) & 56 (10) \\
5 min after surgery & 61 (9) & 59 (7)* & 58 (10) \\
7.5 min after surgery & 64 (9)\textsuperscript{\dagger,\S} & 62 (8)\textsuperscript{\dagger,\S} & 56 (8) \\
10 min after surgery & 66 (8)\textsuperscript{\dagger,\S} & 64 (7)\textsuperscript{\dagger,\S} & 55 (8) \\
Pre-delivery of neonate & 67 (8)\textsuperscript{\dagger,\S} & 63 (9)\textsuperscript{\dagger,\S} & 55 (7) \\
\hline
\end{tabular}
\end{table}

Pre-operative administration of magnesium reduced intraoperative requirements of Midazolam, fentanyl and atracurium. Furthermore, magnesium effectively attenuated the BIS and arterial blood pressure increases pre-neonatal delivery.\textsuperscript{21}
One case report has reviewed the role of magnesium in chronic pain\(^8\). Post Herpetic neuralgia causes debilitating pain in patients who have suffered from Herpes zoster. Transforaminal epidural magnesium was injected, with local anaesthetic. VAS score dropped to as low as 15/100, with patient being pain-free for a period of 6 months. Limitation to this report: It was only performed on one patient and cannot be inferred to the population at large.

Epidural administration of magnesium has proven beneficial compared to clonidine in time to achieving a T6 block\(^{22}\), (see below). Even though Clonidine showed a longer duration of the block and better pain scores than magnesium, magnesium showed some activity over and above the benefits it shared with Clonidine, that is, abolishing shivering. Clonidine is expensive and not readily available.

<table>
<thead>
<tr>
<th>Landmark</th>
<th>Group A (N=30)</th>
<th>Group B (N=30)</th>
<th>Group C (N=30)</th>
<th>Statistical significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Time taken to achieve T6 block (min)</td>
<td>18.73</td>
<td>2.79</td>
<td>11.80</td>
<td>3.21</td>
</tr>
<tr>
<td>Time to 1st epidural top-up (min)</td>
<td>150.87</td>
<td>35.80</td>
<td>161.67</td>
<td>30.10</td>
</tr>
<tr>
<td>Time to 2nd segment regression (min)</td>
<td>123.00</td>
<td>28.08</td>
<td>130.33</td>
<td>33.94</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A (n=30)</th>
<th>Group B (n=30)</th>
<th>Group C (n=30)</th>
<th>Statistical significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>24</td>
<td>19</td>
<td>22</td>
<td>2.105</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td>3.60</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>3.60</td>
</tr>
<tr>
<td>Shivering</td>
<td>4</td>
<td>0</td>
<td>7</td>
<td>7.664</td>
</tr>
<tr>
<td>Sedation</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>15.181</td>
</tr>
</tbody>
</table>

Epidural magnesium, when co-administered with Bupivacaine, produces a rapid onset of block, while addition of clonidine to epidural Bupivacaine prolongs the duration of the block.
Time to T6 block was the shortest in the magnesium group. Differences in intensity of operative pain started to show in 45 minutes into operation. Magnesium can be an alternative to Clonidine.²³

In 2007 a study by Arcioni, et al¹, looked at the use of magnesium in different routes, intrathecal, epidural, combined spinal epidural, to reduce post operative analgesic requirements. (See below for the impressive result of using magnesium on PCA Morphine consumption).

![Figure 3: Intergroup comparison of intensity of operative pain as measured using a VAS at different time intervals. The difference in intensity of operative pain between groups was statistically significant at 45 minutes (P<0.05) by using two-way repeated measures analysis of variance (ANOVA). Data are given as mean (SD)](image)
Intravenous magnesium given during spinal anesthetic reduced post operative pain and analgesic consumption, without complications.\textsuperscript{24} The total PCA consumption was reduced in the magnesium group for up to 48 hours post operatively—See figure and graph below.

**Table 4** Average VAS pain scores. Values are presented as medians and inter-quartile ranges. Group M, Mg group; Group S, saline group. *\textit{P}<0.05 compared with Group S

<table>
<thead>
<tr>
<th></th>
<th>Group M (n=20)</th>
<th>Group S (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediately postoperative</td>
<td>0 (0–3)</td>
<td>0 (0–13)</td>
</tr>
<tr>
<td>Postoperative 30 min</td>
<td>0 (0–10)</td>
<td>15 (0–35)</td>
</tr>
<tr>
<td>Postoperative 4 h</td>
<td>30 (20–40)*</td>
<td>50 (45–64)</td>
</tr>
<tr>
<td>Postoperative 24 h</td>
<td>20 (10–30)*</td>
<td>38 (32–45)</td>
</tr>
<tr>
<td>Postoperative 48 h</td>
<td>12 (5–15)*</td>
<td>29 (22–35)</td>
</tr>
</tbody>
</table>

**Fig 3** The total amount of PCA drug. The concentrations of morphine and ketorolac are 0.7 and 1.5 mg ml\textsuperscript{−1}, respectively. Group M, Mg group; Group S, saline group. Values are presented as means (sd). The error bars indicate 1 sd.*\textit{P}<0.05 compared with Group S.
CONCLUSION

Practical points to consider
Intravenous administration of magnesium is not without its own adverse effects, like: pain on injection, flushing, nausea and vomiting. These are counter acted by adding local anaesthetics, dilution and slow injection of magnesium sulphate. A small dose of Midazolam helps patients not to remember the discomfort.

In conclusion:
Should Magnesium Sulphate be considered a “wonder drug”?
  o It acts on most organ systems that involve that most feared experience-PAIN.
  o It potentiates drugs and minimizes side effects by minimizing their requirements.
  o Magnesium is easy to monitor, levels are part of the routine tests we do.
  o It has the easiest antidote that is not a scheduled drug, with an effective result- Calcium.
  o The use of magnesium sulphate in regional anaesthesia and in conjunction with a general anaesthetic seems to be the best option for our setting, since they are the commonest routes applicable.

  o 50mg/kg body weight bolus with 15mg/kg /hr intraoperative infusion proves to be effective with no side effects, in most studies.

In war zones it is the best stoichiometric concoction.
  o All studies in this talk have excluded use of magnesium on opioid resistant patients and patients with chronic pain.
  o It has been proven that magnesium works well at certain doses in opioid naïve patients, for acute pain management..

Recommendations are:
  o To further research the effectiveness of magnesium in patients on chronic opioid therapy.
  o Future directions of adjuvant analgesics include incorporating adjuvants into a practical regime based on procedure–specific multimodal analgesia, and to elaborate perioperative opioid– sparing benefits into prevention of chronic postsurgical pain^{11}.
REFERENCES


**ADDITIONAL READING**


The difference in cumulative fentanyl consumption was significant from 2 to 24 hours post operatively between the magnesium and the control groups.\textsuperscript{13} There were no side effects reported.

Co-administration of epidural magnesium for postoperative epidural analgesia provided a pronounced reduction in patient-controlled epidural fentanyl consumption.