Magnesium

Is There a Signal in the Noise?

THE administration of intravenous magnesium for postoperative pain has been studied for decades. Some studies have demonstrated statistically significant benefits, whereas others have concluded that there is no efficacy. A meta-analysis by De Oliveira et al., in this issue of Anesthesiology, combines the results of many small, inadequately powered studies to provide a big picture. Notably, 18 of 18 studies demonstrated a reduction in postoperative opioid requirements (see De Oliveira figure 10). Unless there has been significant publication bias, the odds that this would occur by chance alone is 1 in 2^18 (i.e., 1 in 262,144 or P < 0.001). On the basis of the published data, perioperative magnesium reduces postoperative use of opioids. There is a signal in the noise! Magnesium does something. Is that something useful?

If patients were more comfortable after surgery, then the utility of perioperative magnesium would be clear. The analysis shows that patients were a little more comfortable after surgery. The authors look at four analgesia endpoints: early pain at rest, early pain with movement, late pain at rest, and late pain with movement. The good news is that magnesium demonstrated analgesic efficacy at all four points. The bad news is that it was a very small effect, less than 1 Visual Analog Scale (VAS) point reduction on average, among the included trials. Is this small effect likely to be clinically useful?

Perhaps we should not be surprised that the reduction in numerical analog score for pain was small. For ethical reasons, all the clinical analgesia trials must provide a rescue analgesic, typically an opioid. If the rescue analgesic is freely available, in the setting of an efficacious intervention, one would expect that pain scores to be nearly equal and the efficacy of the intervention demonstrated by a reduction in rescue medication. Farrer notes that “because the use of rescue outcome requires a definitive action, and may offer a more objective measurement of the patient’s perspective on what represents clinically important analgesia, this outcome represents a logical choice as a definitive standard for the clinical importance of the effect.” This suggests that we should not be too exercised by the modest improvement in numerical analog score associated with magnesium because the analgesic efficacy of magnesium is demonstrated by a reduction in opioid requirement.

Analgesic trials have, by their nature, two primary end points that need to be considered together. The interplay of pain score and opioid use inevitably complicates analysis of analgesic trials. Although analgesic studies state a single primary outcome variable, there is always interaction between measurements of pain and opioid sparing. Mostly, the primary effect is demonstrated in a reduction in rescue medication. In some patients, the opioid-induced side effects are not well tolerated. These patients prefer a higher level of pain to the side effects by the rescue opioid. A metric that combined pain score and rescue medication use would be more universally demonstrative.

The opioid sparing in these studies ranged from 5% to 85%, with an average reduction of 30%. As suggested by Farrer, it logically follows that patients in the magnesium group were more comfortable, and less opioid was required to achieve nearly identical VAS scores. Because less opioid was administered, it would also be expected that the studies would consistently demonstrate a decrease in common opioid side effects, such as postoperative nausea and vomiting. Meta-analysis of the six studies, which reported postoperative nausea and vomiting, did not find any benefit. The authors...
calculated that they only had an 87% power to detect a 15% difference in postoperative nausea and vomiting.

Consideration of candidates to add to our arsenal of medications for postoperative pain is of primary importance. Opioid reduction in the postoperative period is an emerging national priority in the United States. Opioid reduction mitigates not only short-term opioid side effects such as respiratory depression, nausea, pruritus, and constipation, but also long-term consequences of excessive opioid use, which may be of clinically important. Opioids exert powerful effects on immune and endocrine systems, and may promote neoplasia.5,6 Opioid-induced hyperalgesia may also play a role in acute pain and may have overlapping mechanisms with conversion to chronic pain.7

Magnesium is commonly thought of as an N-methyl D-aspartate antagonist although it has other biological effects. Activation of the N-methyl D-aspartate receptor by glutamate is the first step in initiation of central sensitization.8 Prevention of the activation of initiation of central sensitization is conceptually intriguing as an approach to combat chronic pain after surgery. Furthermore, an ever-increasing number of patients are coming to surgery with central sensitization already established who require escalating dosages of opioids.

Although the administration of magnesium for the acute postoperative period is intriguing, future studies should stratify patient populations into opioid-tolerant versus opioid-naive. If we presume that magnesium has an effect on central sensitization, we would expect more efficacy in opioid-naive. If we presume that magnesium has an effect against potential toxicity in adequately controlled trials.

It is important to just know how much magnesium is required over what period of time. Most of the trials included in the current meta-analysis used a 30–50 mg/kg bolus during surgery and some continued with a maintenance infusion. A potentially important finding is that those studies that continued magnesium infusion postoperatively showed a greater reduction of late pain at rest and of opioid requirements. One limitation of the meta-analysis is that it did not include the plasma magnesium concentrations measured in many of the studies. One cannot readily construct pharmacokinetic models to guide dosing without knowing the therapeutic drug concentration. None of the studies measured magnesium concentrations in the cerebral spinal fluid. Central concentrations of magnesium are tightly controlled. In a study by Mercieri et al.,9 an intrathecal catheter was used to draw samples of cerebral spinal fluid from healthy patients with hip arthroplasty. Despite administration of intravenous magnesium, these samples yielded no magnesium in the cerebral spinal fluid. If magnesium does not act within the central nervous system, then where is the site of action? Might magnesium act presynaptically at the dorsal root ganglia to reduce nociceptive transmission?

Why are we only seeing a clear signal now? The majority of the trials included in the meta-analysis were underpowered to detect a signal in the primary outcome variable. Using a two-sided t test, to detect the mean reduction of 0.52 numerical rating score for pain points (the difference in VAS pain at rest in the meta-analysis, e.g., 5–4.48), assuming an SD of 1.5 numerical rating score for pain points with a power of 0.8 would require 132 subjects, 0.9 would require 176 subjects, 0.95 would require 208, and 0.99 would require 307 subjects. The average number of subjects in the included studies was 57. Assuming 28 subjects per group, the studies had just a 25% chance of finding a decrease of 0.52 units at P value less than 0.05.

De Oliveira et al. have used the techniques of meta-analysis to create an adequate sample size to answer the question of whether magnesium has efficacy for postoperative pain. The answer is yes, with the clinically meaningful effect evidenced as reduction in opioid requirement. Few would doubt that ketorolac is an effective analgesic in the postoperative period. A meta-analysis, published by De Oliveira in 2012,10 demonstrated that the reduction in postoperative VAS score with intravenous magnesium is similar to that with ketorolac. The reduction in postoperative opioid requirement with magnesium is greater than that observed with ketorolac or acetaminophen.11 It appears that magnesium may have clinical utility in multimodal analgesia, and that there might even be a role for low-dose magnesium infusions after surgery. Efficacy would need to be balanced against potential toxicity in adequately controlled trials. However, such studies should be done to confirm this signal of efficacy in the analgesic noise.

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References