## Table of Contents

### Pharmacology

- The Effect of Magnesium Sulfate on Postoperative Pain in Upper Limb Surgeries by Supraclavicular Block Under Ultrasound Guidance ................................................................. 3
- The Impact of Single Low Dose IV Magnesium Sulfate Adjuvant to Ultrasound Guided Transversus Abdominis Plane Block for Control of Post - Cesarean Pain ................................................................. 6
- Magnesium sulfate improves postoperative analgesia in laparoscopic gynecologic surgeries: a double-blind randomized controlled trial....9
1 Pharmacology CE credit.*

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* This program has been prior approved by the American Association of Nurse Anesthetists for 20 Class A CE credits; Code Number 1035464; **Expiration Date 10/31/2020.**
Abstract

Purpose  The purpose of this study was to evaluate whether adding magnesium sulfate to a lidocaine and fentanyl mixture for supraclavicular brachial plexus block would enhance analgesia following surgery on the upper extremity.

Background  The brachial plexus is a network of nerve fibers that supplies sensation and motor function to the upper extremity. It is formed by the anterior rami (divisions) of the cervical spinal nerves C-5, C-6, C-7 and C-8, and the first thoracic spinal nerve, T-1. The supraclavicular approach to the brachial plexus, using an amide local anesthetic, is associated with a rapid onset of anesthesia and a high success rate. It has been used successfully for years to provide anesthesia and analgesia for surgery on the arm, elbow, forearm, wrist, and hand. Different additives to the local anesthetic have been studied for their ability to enhance the efficacy of all types of blocks, including the brachial plexus. Evidence is conclusive that magnesium has analgesic properties, however more information is needed to evaluate its efficacy as an additive to local anesthetics for supraclavicular brachial plexus block. Improving the effects of anesthesia and analgesia for peripheral nerve blockade is important for several well understood reasons:

- improved acute pain management
- sparing the use of opioids
- preventing prolonged postoperative pain
- enhancement of overall recovery
- promoting quality of life

Methodology  This was a randomized, controlled, double blind clinical trial. Data was collected between April and October 2016. Patients with traumatic fractures or tendon damage scheduled for upper extremity orthopedic surgery were randomized into one of two groups:

- **Magnesium Group** - brachial plexus block with 4mg/Kg 1% lidocaine, 50 µg fentanyl and 5 mL 20% magnesium sulfate
- **Control Group** - same brachial plexus block but with normal saline instead of magnesium sulfate

The technique used to perform the supraclavicular block was the same for all participants. Preoperative sedation and monitoring during the procedure was also standardized. A pinprick test was used to evaluate sensory blockade. Patients were tested every five minutes until total analgesia was obtained in the distribution of each of four sensory nerves: median, ulnar, radial, and musculocutaneous. The pinprick test was scored as:

- 0 = no block
- 1 = partial block
- 2 = complete loss of sensation to pinprick
Motor blockade was evaluated on a three point scale:
- 0 = no movement
- 1 = paresis with some movement possible
- 2 = normal movement

Both motor and sensory blocks were recorded every five minutes for the first 30 minutes, every 10 minutes for the next 30 minutes, and every 15 minutes until the end of surgery. When the patient had complete movement of the affected limb, this was considered the end of the motor block. The end of the sensory block was when the patient had a positive result to the pinprick test.

A Visual Analogue Scale (VAS) was used to measure postoperative pain at PACU arrival (hour 0) and hours 1, 2, 4, 8, 16 and 24. Meperidine 0.2mg/Kg was administered IV if the VAS was greater than 3.

Results  
There were 26 patients in each group. No differences were noted in the demographic profiles between groups. The Magnesium Group had a significantly longer time to onset of both motor and sensory block, however the duration of the block was also 18% longer.

At all time points, the Magnesium Group demonstrated significantly lower VAS pain scores compared to Control. The mean time to first dose of rescue analgesia was 8 hours in the magnesium group vs. 4.3 hours in the control group. Total meperidine consumption in the first 24 postoperative hours was almost 25% less in the magnesium group; 17.5 mg versus 23 mg in the control group. There was no hemodynamic instability or serious adverse events observed in either group. One patient in each group had a hematoma at the site of injection.

Conclusion  
This small clinical trial demonstrated that a supraclavicular block for upper extremity surgery with magnesium added to a lidocaine and fentanyl solution provided a superior sensory and motor block compared to only lidocaine and fentanyl alone. Additionally, total postop opioid consumption was significantly less with magnesium added compared to placebo.

Comment  
This study was conducted without many flaws or limitations other than the size of the sample. The researchers used a greater amount of magnesium, 1,000 mg, compared to many other clinical trials. The only adverse event observed was mild nausea after block insertion, however the incidence of nausea was higher in the Control Group. The role of magnesium in anesthesia is not disputed and we have observed its utility in obtunding the sympathetic response to laryngoscopy and endotracheal intubation, in surgery for removal of pheochromocytoma where wide swings in blood pressure and heart rate can be catastrophic, in management of the obstetric, gynecologic, and cardiac surgery.

<table>
<thead>
<tr>
<th>Table 1. Block Characteristics</th>
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<tbody>
<tr>
<td>Sensory block Onset (minutes)</td>
</tr>
<tr>
<td>14</td>
</tr>
<tr>
<td>Sensory block Duration (minutes)</td>
</tr>
<tr>
<td>Motor block Onset (minutes)</td>
</tr>
<tr>
<td>Motor block Duration (minutes)</td>
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</tbody>
</table>
patient, and finally, in the management of
c postoperative shivering. Recently its most valued trait
however is the conclusive evidence that it is an
NMDA receptor antagonist with antinociceptive
properties. And we can safely administer it
intravenously and as an adjuvant for peripheral nerve
blockade. As multimodal analgesia continues to
remain at the forefront for efficacious acute and
chronic postoperative pain management, the role
magnesium plays should not be underestimated. It
may not totally prevent the need for opioids, but it
does appear to reduce the doses needed and therefore
prevent well known adverse effects of high dose
opioids.

Mary A. Golinski, PhD, CRNA

This article is available free full text at the
following url:
http://anesthpain.neoscriber.org/en/articles/
14232.html

Notes: If you’d like a review article on the uses of
MgSO$_4$ in anesthesia Dr. Golinski recommends:

Bansal T. Magnesium: emerging potentials in

DOI: 10.4172/2155-6148.1000547
Pharmacology

**THE IMPACT OF SINGLE LOW DOSE IVMagnesium Sulfate Adjuvant to Ultrasound Guided Transversus Abdominis Plane Block for Control of Post - Cesarean Pain**

Open J Obstet Gynecol 2017;7:269-280
DOI: 10.4236/ojog.2017.73029
Abd Elrahman, TN, Youssry, MA

**Abstract**

**Purpose** The purpose of this study was to determine if magnesium sulfate (MgSO₄) given IV prior to cesarean section, and as an adjunct to transverse abdominis plane (TAP) block, would provide superior postoperative analgesia and reduce opioid consumption for the first 24 hours post-delivery.

**Background** Preemptive analgesia techniques are intended to minimize the neurophysiologic response, known as central sensitization, that occurs due to surgery induced tissue trauma. As a condition of the nervous system and associated with the development of chronic pain, when central sensitization occurs, the nervous system goes through a process called ‘wind-up’ and stays in a persistent state of high reactivity.

Cesarean section is a common obstetric surgical procedure accounting for 21% of births in the developed world. It is also associated with very high levels of postoperative pain and subsequent analgesic requirements. Typically, a multitude of techniques are employed to reduce post-cesarean pain. Transverses Abdominis Plane blocks are becoming more commonplace. Unfortunately, most analgesic techniques are administered following the surgical procedure and therefore lack the advantage of “preempting” pain. This study considered a multimodal analgesia technique employing intravenous magnesium sulfate before surgical incision, combined with a post-incision TAP block. It was theorized this approach might reduce postoperative pain and therefore opioid use, minimize opioids side effects, and decrease the probability of chronic post-cesarean section pain.

**Methodology** This study was conducted as a prospective, randomized, double blind experiment. Subjects were randomized into two groups:

- **Magnesium Group**: 50 mg/Kg MgSO₄ IV over 20 minutes before induction
- **Placebo Group**: 100 mL saline IV over 20 minutes before induction

At the end of surgery when the incision was closed, all patients, both magnesium and placebo, received a TAP block with 20 mL of 0.25% bupivacaine. Women were then transferred to the PACU. In the
PACU each patient received 16 mg lornoxicam IV (an NSAID not available in the USA) and acetaminophen 1 gm IV every 6 hours. Morphine was available for breakthrough pain at any time during the first 24 hours. Pain scores were measured at 2, 6, 12, and 24 hours postoperatively. Time until morphine request, total morphine consumption, first ambulation, and neonatal APGAR scores were recorded in addition to pertinent demographic and surgical data.

**Results**  A total of 60 women completed the study; 30 in each group. There were no differences in demographics between groups including anesthetic, surgical, blood loss, or neonatal outcomes.

Visual analogue pain scores (VAS) were no different between groups at the two hour point. But the Magnesium Group VAS at hours 6 and 12 was statistically significantly lower than the placebo group; though the clinical significance is debatable (Table 1).

**Table 1. VAS Pain Scores**

<table>
<thead>
<tr>
<th></th>
<th>Magnesium</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hours</td>
<td>51</td>
<td>59</td>
<td>0.07</td>
</tr>
<tr>
<td>6 hours</td>
<td>40</td>
<td>54</td>
<td>0.012</td>
</tr>
<tr>
<td>12 hours</td>
<td>26</td>
<td>35.5</td>
<td>0.005</td>
</tr>
<tr>
<td>24 hours</td>
<td>23</td>
<td>24</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Notes: VAS from 0 to 100 (worst pain).

The mean time until the first rescue analgesia requirement was longer in the Magnesium Group; 3.3 hours vs 2 hours in the Placebo Group (P = 0.002).

The total dose of morphine consumed during the first 24 postoperative hours was lower in the Magnesium Group, 6 mg, compared to the placebo Group, 10 mg (P = 0.001). Patients also ambulated two hours sooner in the Magnesium Group; 4 hours vs. 6 hours (P = 0.004).

**Conclusion**  A preemptive dose of intravenous magnesium sulfate 50 mg/Kg combined with an ultrasound guided TAP block resulted in analgesia superior to placebo. The Magnesium Group also used less morphine, started walking earlier, and did not exhibit any maternal or fetal complications following cesarean section delivery.

**Comment**  I wrote this abstract with a keen understanding that in the USA, regional anesthesia is the most common method of providing anesthesia for non-emergent cesarean section delivery. This study was conducted in a Medical College Hospital in Saudi Arabia, and it appears anesthesia for elective surgical delivery differs from what we consider standard of care. Upon searching the literature, I found the most common indications for general anesthesia for C-section are urgency (35% of cases in a non-teaching hospital), maternal refusal of regional techniques (20%), inadequate or failed regional attempts (22%), and regional contraindications including coagulation or spinal abnormalities (6%). Obstetric indications, such as placenta previa, were in the past considered absolute indications for general anesthesia however there exist multiple reports of these cases being performed safely under regional anesthesia. We can expect that we will take care of a moderate number of women, who for varying reasons, will have a general anesthetic for cesarean delivery. The point I
am trying to make is that we can gain useful information from this study for our general anesthetic C-section cases.

Magnesium sulfate has potentiating effects on perioperative analgesia. The characteristics of magnesium allow the reduction of overall anesthetic doses including opioids, which we know are associated with numerous adverse effects including causing a predisposition to prolonged post-surgery pain. Magnesium sulfate has a high therapeutic index and is very cost effective. Considering these features, the appropriate use of magnesium sulfate has potential to improve surgical outcomes, including C-section outcomes, as well as increase patient satisfaction.

Although the women in this study had general anesthesia, this should not preclude us from considering magnesium as an analgesic adjunct for cesarean section with neuraxial anesthesia. This study found at hours 6 and 12 post-delivery, the Magnesium Group exhibited lower pain scores than Placebo Groups and both groups had TAP blocks. Clearly if a lidocaine spinal anesthetic was administered, the effects of the spinal would be long gone at hours 6 and 12. Additionally, at the dose of magnesium administered, there was no skeletal muscle weakness or reduction in APGAR scores. All patients recovered without complications and newborns did not have any untoward sequelae.

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This article is available free full text at the following url:
http://file.scirp.org/Html/1-1431359_74727.htm

Notes on MgSO₄:
The normal range of magnesium in plasma is 0.7-1.1 mmol/L (1.4-2.2 mEq/L). Magnesium sulfate is effective in perioperative pain treatment and in blunting somatic, autonomic, and endocrine reflexes provoked by noxious stimuli. It also:
• depresses the CNS, produces anticonvulsant effects
• blocks peripheral neuromuscular transmission - decreases amount of acetylcholine released at end-plate by motor nerve impulse
• slows rate of SA node impulse formation in myocardium and prolongs conduction time

Magnesium is 30% protein bound and 100% excreted unchanged in the urine.
Pharmacology

**Magnesium Sulfate Improves Postoperative Analgesia in Laparoscopic Gynecologic Surgeries: A Double-Blind Randomized Controlled Trial**

J Clin Anesth 2016;34:379-384
DOI: 10.1016/j.jclnane.2016.05.0006
Sousa A, Rosado G, Neto Jde S, Guimarães G, Ashmawi H

**Abstract**

**Purpose** The purpose of this study was to measure the postoperative analgesic effectiveness of magnesium sulfate and compare it to nonsteroidal anti-inflammatory drugs (NSAIDs) and placebo in women undergoing laparoscopic gynecologic surgery.

**Methodology** This was a double-blind, randomized, controlled clinical trial. The study sought to answer the question: “how does magnesium infused during anesthesia reduce postoperative morphine consumption and pain scores compared to ketorolac or placebo?” Participants were randomized into one of three groups:
- **Ketorolac Group**
- **Magnesium Group**
- **Placebo Group**

The Ketorolac Group received IV ketorolac 30 mg followed by a saline infusion. The Magnesium Group received IV magnesium sulfate 20 mg/Kg followed by an infusion of magnesium 2 mg/Kg/hour. The Placebo Group received IV saline 20 mL bolus following by a saline infusion. After a standardized anesthesia induction, the bolus doses of each drug was administered over 20 minutes and infusions followed. Infusions were discontinued at the end of the surgical procedure and each woman received dipyrone 30 mg/Kg IV bolus [Editor’s Note: dipyrone is a non-opioid analgesic unavailable in the USA]. A PCA morphine device was set up prior to leaving the operating room. At PACU admittance, and at 20, 30, and 60 minutes, pain was measured using two different methods: the VAS scale and a descriptive verbal scaling tool. Also documented was time to the first morphine rescue, average pain intensity, total...
consumption of morphine, agitation and sedation scores, episodes of PONV, respiratory depression, and pruritus. Once discharged from the PACU, patients were follow for 24 hours. Also measured was hospital length of stay.

**Results**  A total of 54 patients completed the trial, 18 in each group. The majority were ASA physical classification II and had a laparoscopic hysterectomy. There were no significant differences between group demographic profiles specific to age, weight, time to hospital discharge, surgery duration, or anesthesia duration. There were no cardiovascular, respiratory, or adverse neurologic events in any group.

There were no statistically significant differences between the Magnesium and Ketorolac Groups in:

- time to first PACU morphine dose ($P = 0.07$)
- morphine consumption in PACU ($P = 0.83$)
- 24 hour morphine consumption ($P = 0.70$)
- intraoperative remifentanil dose ($P = 0.41$)

Additionally, there were no differences in average pain scores between the Magnesium and Ketorolac Groups in the first 60 minutes and the 24th postoperative hour ($P = 0.64$ and 0.42 respectively).

Significant differences were found, however, between the Magnesium and Placebo Groups. Average VAS pain scores in the first 60 minutes postoperatively and at hour 24 were lower in the Magnesium Group than the Placebo Group. Total morphine consumption in the first 24 postoperative hours was also lower in the Magnesium Group compared to Placebo.

**Conclusion**  Magnesium sulfate administered intravenously during anesthesia for laparoscopic gynecologic surgery reduced postoperative morphine consumption and pain scores in a manner similar to ketorolac. There were no reports of any serious adverse effects in any group.

**Comment**  While not common, NSAID drugs like ketorolac are associated with gastrointestinal bleeding and perforation, platelet inhibition with altered clotting, and renal impairment. The incidence of these serious adverse events has declined over the years due to revisions of dosing guidelines, a better understanding of who is at the greatest risk, and when NSAIDs would be most problematic. The risk for adverse events increases, however, with high doses taken over greater than five days, and in subsets of the population such as the elderly. Acute renal failure has been reported after ketorolac use but was reported as reversible after discontinuation of the drug. As with other nonsteroidal anti-inflammatory drugs, ketorolac may trigger allergic or hypersensitivity reactions.

Contraindications to ketorolac use include a history of, or current risk of, gastrointestinal bleeding, renal failure, compromised clotting processes, hypersensitivity to aspirin or other NSAIDs, labor and delivery, and nursing.

A study conducted by Choi et al\(^1\) described pain characteristics after total laparoscopic hysterectomy. It was reported that visceral pain dominated over incisional pain constantly for the first 72 postoperative hours, and shoulder pain was less severe on the day of operation but increased to the maximum severity at
the 24th postoperative hour. The essential point is this surgery hurts and there are a significant number of women who have contraindications to NSAIDs and need an alternative that can manage their pain like NSAIDs can. Some of the same characteristics that predispose to problems with NSAIDs exist for opioids too. In this study, magnesium was shown to be just as good as ketorolac for managing postoperative pain without serious adverse effects. Magnesium may be an excellent alternative when NSAIDs place a patient at risk for postoperative problems and should be considered as part of multimodal analgesia.

Mary Golinski, PhD, CRNA

Bibliography