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Editorial

Multimodal Analgesia

This is the third in a series of issues on postoperative pain management by Mary Golinski, PhD, CRNA. The first two issues addressed regional anesthesia (Issue 12.2) and ketamine (Issue 12.3). This issue looks at the scientific knowledge regarding gabapentin (Neurontin) in multimodal postoperative analgesia. Gabapentin has been known for some time to be useful in the prevention of postop pain but, in my experience, it is little used. I’m guessing a big reason it isn’t used more is the perception that it causes sedation and sleepiness. This can certainly occur, but, we must remember that much of what we do is a balance of stimulation and depression. The stimulation in this case is primarily postoperative pain. But to decide the depression is “caused” by the gabapentin is myopic when the patient has residual inhalation agent, opioids, benzodiazepines, and who knows what else in their system as well. We must remember that all the CNS depressants we’ve administered play some role in the total CNS depression being exhibited. If our patients can benefit from the addition of gabapentin then we must do what we always do, adapt our use of everything else to achieve the overall objective, including a patient that can wake up! In part, this means knowing and using the optimal dose of gabapentin. And, as you’ll see in this issue, in the first hour postop, patients who received the two lower doses of gabapentin were actually less sedated than the placebo group. This fact was probably due, as Dr. Golinski points out in her comment, to the fact that placebo patients had more pain and needed more opioids which also affected their level of alertness.

Most of us are at least somewhat resistant to change. I came up during a time when postop analgesia meant opioids and nothing but opioids. The only choice was wether you would use fentanyl, sufentanil, morphine, Demerol, or some combination. Many of us got really good at opioid only analgesia and it is easy for us. But it is not enough to simply hear the words, “Evidence Based Practice,” we should really do it. And the scientific evidence tells us that multimodal analgesia is superior to opioids alone. NSAIDS, lidocaine infusions, Decadron, dexamethasone, NMDA receptor blockers, gabapentin, and a host of other drugs and techniques provide pain relief, either by themselves or in combination with opioids. The more we learn about all these drugs and techniques and the more we put what we learn into practice the less pain our patients will experience. That is a good day for everyone.

Michael A. Fiedler, PhD, CRNA
Editor
The comparative preemptive analgesic efficacy of addition of vitamin B complex to gabapentin versus gabapentin alone in women undergoing cesarean section under spinal anesthesia: A prospective randomized double-blind study

Abstract

Purpose The purpose of this clinical trial was to compare the postoperative analgesic efficacy of gabapentin and gabapentin plus vitamin B complex after cesarean delivery with spinal anesthesia.

Background Cesarean section produces pain in the same manner as any other invasive surgical procedure. It is the result of tissue trauma inducing neuroendocrine stress responses, catecholamine and inflammatory mediator release, and central sensitization. Noxious stimuli, such as tissue trauma, may induce neuronal sensitization in the dorsal horn of the spinal cord within one hour of surgical trauma. Preventing acute and persistent pain remains an unsolved problem. Evidence suggests that intense postoperative pain is a significant risk factor for the development of chronic postoperative pain. We also know that treating post cesarean pain with opioids can interfere with mother-baby bonding and infant feeding. Opioids themselves can precipitate a hyperalgesia effect under some circumstances, sometimes even after a single administration.

Gabapentin has demonstrated efficacy in decreasing acute postoperative pain and preventing hyperalgesia. It minimally effects other organ systems, and therefore facilitates physical rehabilitation and recovery. The analgesic effects of gabapentin may be due to the inhibition of neurotransmitters released from sensory neurons. It is also hypothesized that vitamins B1 and B12 play an important role in nerve conduction and excitability. Both gabapentin and B vitamins have been studied. For example, gabapentin alone or in combination with B vitamins for alleviation of symptoms in related disease states such as arthritis. Both are FDA approved for specific conditions during pregnancy.

Methodology This study was conducted using a double blind, randomized, experimental design in 128 women scheduled for elective cesarean section. Inclusion criteria were ages 17 - 40 years, ASA physical status I or II. Exclusion criteria included hepatic, renal, or cardiovascular disease; contraindication to regional anesthesia; long-term opioid, psychotropic, or analgesic drug use; or history of chronic pain. Participants were randomized into two groups:

- **Group G** 300 mg gabapentin PO 30 minutes prior to incision
- **Group GB** 300 mg gabapentin & vitamin B complex PO 30 minutes prior to incision.

Vitamin B complex included: 10 mg B1 (thiamine), 4 mg B2 (riboflavin), 4 mg B6 (pyridoxine) and 40 mg nicotinamide.
The anesthetic was standardized and all patients received intravenous lactated Ringer’s solution 5-7 mL/Kg prior to an L4-5 subarachnoid block. Upon confirmation of clear CSF, 12.5 mg isobaric bupivacaine was injected.

The primary outcome variables measured were the time from administration of the spinal anesthetic to the first request for analgesia after surgery and the total analgesic consumption in the first 12 postoperative hours. Secondary outcomes measured were the incidence of PONV and sedation levels. The Ramsay sedation scale was used to measure the degree of sedation (1 = anxious, 2 = calm and oriented, 3 = calm and drowsy).

Pain intensity was evaluated using a 1 to 10 Visual Analogue Scale (VAS) in the PACU, then at 2, 4, 8, and 12 hours postoperatively. If the VAS was >4 and the patient requested an analgesic, a diclofenac 100 mg suppository was administered. Intravenous meperidine 25 mg was given for breakthrough pain (VAS >4) if there was no relief after the suppository.

**Result**

The demographic profiles did not differ in terms of age, weight, height, or duration of surgery. There was no difference in the mean time to the first analgesia request. However, the total dose of meperidine consumed in the first 12 postoperative hours was significantly lower in the gabapentin+vit B group compared to the gabapentin only group. In fact, 64 participants (98.5%) in the gabapentin+vit B group did not require any meperidine. Their VAS pain scores were lower or their pain relieved by administering diclofenac alone compared to 58.5% of patients in the gabapentin only group that requested analgesia in addition to diclofenac (P=0.029). Furthermore, the frequency of requests for analgesia was significantly less in the gabapentin+vit B group (P=0.034). The incidence of PONV and degree of sedation was comparable between groups. No infants suffered any adverse effects and APGAR scores did not differ between groups.

**Conclusion**

The gabapentin+vit B group had a reduced total analgesic requirement during the first 12 hours following cesarean delivery with spinal anesthesia compared to gabapentin alone.

**Comment**

I selected this article because I believe there is more to discover regarding the efficacy of gabapentin as a component of multimodal pain management. I was even more intrigued after searching the scientific literature for the role that B vitamin and B vitamin complex may have in the prevention of acute pain after surgery. The incidence of prolonged postsurgical pain following cesarean section has been reported to be approximately 20%. We probably don’t think about post C-section pain in the same way as pain after a laparotomy for example, but we should. After all, the surgery entails the same incisions through the layers of the abdominal wall starting with the skin, underlain by subcutaneous tissues, connective tissue i.e. fascia, muscles, and the peritoneum. Understanding the anatomy, innervation and blood supply, and pregnancy induced hormone changes, it should not surprise us that pain following...
cesarean can be severe and predispose to a chronic pain state. We do know however that vitamins B6 (pyridoxine) and B12 (cyanocobalamin) are important in reducing levels of the amino acid homocysteine in the blood. Homocysteine in turn is associated with inflammation. Other research has shown that B vitamins in complex carbohydrates are important in diminishing pain, particularly nociceptive pain that includes, but not limited to, myofascial pain. In addition, current research has explored the effects of vitamin B1 (thiamin) and its role in reducing the systemic inflammatory response. Experts have concluded that some B vitamins may be clinically effective in treating numerous other painful conditions such as lumbago and sciatica by acting as an analgesic. Also notable are the findings from the National Institutes of Health that link vitamin B3 (niacin or niacinamide) with improved range of motion, reduced pain, and reduced inflammatory responses due to their enhancement of physiologic glucocorticoid secretion.

Mary A Golinski PhD, CRNA

Notes: For more information about B vitamins visit http://www.b12-vitamin.com/b-complex/
Pharmacology

**Gabapentin as an Adjuvant Therapy for Prevention of Acute Phantom-Limb Pain in Pediatric Patients Undergoing Amputation for Malignant Bone Tumors: A Prospective Double-Blind Randomized Controlled Trial**

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**Abstract**

**Purpose** The purpose of this study was to discover if gabapentin, added to an established opioid regimen, would reduce acute perioperative pain and the occurrence of phantom limb pain in pediatric patients having lower limb amputations for malignant non-metastatic bone tumors.

**Background** The incidence of phantom limb pain in adults undergoing limb amputation ranges between 50% - 90%. The rate of occurrence in the pediatric population is not established and may be even higher. Typically, this pain occurs within a few days following amputation and is described as burning, gnawing, and stabbing. Its existence is associated with numerous psychological and physical problems that can and often do affect recovery and quality of life. The cause of phantom limb pain is not completely understood. Opioids such as morphine are often prescribed however they are not always effective, and increasing the dose increases the probability of serious adverse effects. Minimal research has been conducted in the pediatric population on the alleviation of pain after limb amputation for cancerous tumors. The researchers questioned whether the preoperative administration of gabapentin, in addition to an opioid regime, would reduce postoperative phantom limb pain pediatric patients.

**Methodology** This was a prospective, randomized, controlled study. Patients younger than 18 years of age diagnosed with unilateral lower limb primary malignant bone tumor who poorly responded to chemotherapy were randomized into two groups: a gabapentin group and a placebo group. Beginning three days prior to surgery, each patient was given either gabapentin or placebo. The dosing regimen was as follows:

- 300 mg gabapentin or placebo, one capsule on day one
- 300 mg gabapentin or placebo, one capsule twice on day two
- 300 mg gabapentin or placebo, one capsule three times a day, from day 3 preop until 30 days postop

All patients were placed on a standard cancer related pain control regime that consisted of intradermal morphine and oral oxycodone during their entire hospitalization. Baseline pain intensity was documented using a visual analog scale (VAS).

Amputations were performed with a standardized general anesthetic that included remifentanil. Pain was measured using the VAS every morning while hospitalized beginning on POD 1. Characteristics of
phantom pain described by each patient was recorded. Follow up continued for 60 days after surgery.

**Result**  
A total of 102 patients who met inclusion criteria were evaluated. Of these, 57 were excluded (lack of consent, benign or metastatic tumors). A total of 45 were randomized resulting in n = 23 in the gabapentin group and n = 22 in the placebo group. All completed the study. Demographics were similar between groups. Most had an osteosarcoma and 2 in each group had Ewing’s sarcoma.

Baseline pain intensity measured with a VAS on the day of hospitalization, day of randomization, and day of surgery, was not significantly different between groups. Both groups responded favorable to preoperative morphine and oxycodone.

The numbers of patients with phantom-limb pain after surgery were significantly fewer in the gabapentin group on postoperative days 7, 14, 30, and 60 (P<0.05). Pain intensity scores were similar between groups on postoperative days 1 - 4. However, on postoperative days 4 - 9 the gabapentin group demonstrated a steady decrease in pain intensity compared to the placebo group (P < 0.05). From days 10-14, pain intensity did not differ between groups and both groups pain scores decreased. There were no serious adverse effects in either group however two patients in the placebo group experienced a tingling sensation in the phantom limb triggered by urination. This disappeared at approximately two months postoperatively.

**Conclusion**  
Gabapentin reduced acute postoperative pain intensity and the incidence of phantom limb pain for up to 60 days postoperatively compared to placebo. There were no adverse effects in either group.

**Comment**  
My intent in writing this abstract was to inform CRNAs of current pediatric research involving non-opioid treatment modalities for phantom limb pain, and, ultimately, to offer suggestions for treatment approaches. Osteosarcoma is a rare form of bone cancer mostly affecting children, adolescents, and young adults. It usually develops after age ten and before age 30. Approximately 400 children, adolescents, and young adults in the USA are diagnosed with osteosarcoma each year. Phantom limb pain most commonly develops during the growth spurt of the teen years. As noted in the introduction, the cause of phantom pain is unclear, but is theorized to originate in the spinal cord and brain. During diagnostic imaging, portions of the brain that had been neurologically connected to the nerves of the amputated limb show activity when the person feels phantom pain. Many experts believe phantom pain may be at least partially explained as a response to mixed signals from the brain. Damaged nerve endings, scar tissue at the site of the amputation, and the physical memory of pre-amputation pain, have been hypothesized to influence phantom limb pain. Some researchers have found that people who had significant pain in a limb before amputation are more likely to have it afterward. The brain appears to be
holding on to the memory of the pain and keeps
sending pain signals, even after the limb is removed.

Gabapentin’s current use is related to its effect in
minimizing neuropathic pain. With neuropathic pain,
the nerve fibers themselves might be damaged,
dysfunctional, or injured. These damaged nerve fibers
send incorrect signals to other pain centers. There
may be a direct connection, therefore, to phantom
limb pain. It is well accepted that the intensity of pain
following amputation is extremely high, however,
most studies have focused on adult patients. We know
one risk factor for the development of chronic pain
after surgery, including phantom limb pain, involves
the intensity of preoperative pain. The synergic effects
of gabapentin may have decreased the requirement
for opioids thereby minimizing adverse effects related
to opioids.

Mary Golinski, PhD, CRNA
Role of Preemptive Gabapentin on Postoperative Analgesia After Infraumbilical Surgeries Under Subarachnoid Block – A Randomized, Placebo-Controlled, Double-Blind Study

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Tomar GS, Singh F, Cherian G

Abstract

Purpose The purpose of this study was to compare the postoperative analgesic efficacy of three different doses of preoperative gabapentin in patients undergoing inguinal hernia repair with spinal anesthesia. The secondary purpose was to determine whether 400, 800, or 1,200 mg doses of gabapentin resulted in any adverse drug effects.

Background Inguinal hernia repair is associated with moderate to severe acute postsurgical pain and is therefore a risk factor for the development of chronic pain after surgery. The incidence of prolonged pain following hernia surgery ranges from 0.7% to 37%. Unfortunately, approximately 3% of these individuals develop severe prolonged pain. Minimizing acute pain in these patients has potential to prevent chronic pain.

Gabapentin is structurally related to gamma-aminobutyric acid (GABA) and has antihyperalgesic and antinociceptive properties. It acts by binding subunits of the calcium ion channels which prevents central sensitization and hyperalgesia. Due to these unique properties, it has been studied for reducing opioid requirements following surgery, and for preventing the development of chronic postsurgical pain. Compared to other non-opioid analgesics gabapentin has minimal to no effects on gastric mucosa, renal function, or platelet count and function. The authors hypothesize that PO gabapentin might reduce acute post inguinal hernia pain and minimize development of chronic pain. Because the optimal dose to accomplish this has not been established, this research attempted to find an optimal dose.

Methodology This was a prospective, randomized, double-blind, placebo controlled clinical trial. Healthy patients, ASA I and II, scheduled for inguinal hernia surgery with spinal anesthesia were randomized into one of four groups. Each group received either a placebo or gabapentin at differing doses two hours prior to surgery:

- Placebo
- Gabapentin 400 mg
- Gabapentin 800 mg
- Gabapentin 1,200 mg

Anesthetic technique was standardized. Each patient received a subarachnoid injection and 3 mL of hyperbaric 0.5% bupivacaine. No other analgesics or anxiolytics were administered pre- or intraoperatively. Postoperative pain assessments were performed without knowledge of which group the patient was in using a visual analogue scale. Time to first rescue analgesic and side effects were recorded from the
PACU until 24 hours postop. If rescue analgesia was required, IVPCA fentanyl 0.2 µg/Kg IV with a 10 minute lockout was used for the first 24 hours. The PCA was discontinued after 24 hours. If additional analgesia was necessary, patients could take diclofenac 75 mg. PACU length of stay, based on the modified Aldrete score, was recorded.

**Result**  A total of 130 patients were assessed for eligibility. Ten were excluded resulting in 120 participants, 30 in each group. Demographic profiles were similar in all four groups (age, weight, duration of surgery in minutes, and perioperative vital signs).

Pain, as measured by visual analogue scale (VAS), was significantly less intense with any dose of gabapentin at hours 2 through 24 (P<0.001 for all except hour 24 P<0.03). Time until the first request for additional analgesia was significantly longer with any dose of gabapentin compared to placebo (P<0.0001). The mean time until the first request for additional pain medication in each group was:

- Placebo 116 min
- Gabapentin 400 mg 160 min
- Gabapentin 800 mg 164 min
- Gabapentin 1,200 mg 169 min

When rescue analgesia was needed, the total dose of IVPCA fentanyl used was significantly less in the gabapentin 1,200 mg group compared to the other gabapentin groups or the placebo group (P<0.0001). Pain scores, need for rescue analgesia, pruritus, and total opioid use was similar across gabapentin groups and less than the placebo group.

Sedation during the first postoperative hour was greatest in the gabapentin 1,200 mg group and least in the gabapentin 400 mg group. The placebo group was not the least sedated, but was intermediate between the two gabapentin groups (P<0.0005). At four hours postop sedation was statistically significantly different between groups, but both gabapentin and placebo groups had little if any sedation.

Overall, somnolence was greater in the gabapentin 1,200 mg group than in either the other gabapentin or placebo groups (P = 0.019). However, at four hours postop, sedation differed little between groups. Postoperative Nausea and Vomiting was more likely in the placebo group (P≤0.05).

**Conclusion**  Preoperative PO gabapentin 400, 800, or 1,200 mg resulted in significantly lower VAS pain scores, compared to placebo, following surgery for inguinal hernia repair with spinal anesthesia. Because of low postoperative pain scores in the gabapentin groups, requirements for rescue analgesia with IVPCA fentanyl and/or oral diclofenac was minimally. Additionally, PONV was significantly less frequent in the gabapentin groups compared to placebo. Preemptive oral gabapentin 400 mg reduced opioid consumption, reduced the side effects of fentanyl during the first 24 hours postoperatively, and improved the recovery profile.

**Comment**  This was a tightly controlled clinical trial with a rigorous design. It appears that more anesthetists are incorporating gabapentin in a multimodal non-opioid
postoperative pain management regime. Due to its mechanism of action and our greater understanding of pain, this certainly makes sense and there is great potential for this drug to be used routinely. This is exciting.

It was interesting to note that there was less somnolence and sedation in the gabapentin 400 mg and 800 mg groups than in the placebo group during the first hour in the PACU. This was most likely the result of the greater opioid doses required to relieve pain in the placebo group. This difference had disappeared by the fourth hour.

It would have been beneficial to follow up on these patients at the 3, 6, and 12 month postoperative timeframe. It is well accepted that moderate to severe acute pain following inguinal hernia is common, and uncontrolled acute pain is a strong predictor of chronic postsurgical pain. A limitation I noted was the lack of gender profile in the demographics of the study participants. The literature shows that men are eight times more likely to develop an inguinal hernia than are women however women do get hernias.

Mary Golinski, PhD, CRNA

Notes: Observer’s Assessment of Activity and Sedation Scale (OAA/S)

1. not responding to mild prodding or shaking; is asleep
2. responds after mild prodding or shaking
3. responds to high tone/repeated name
4. lethargic response to name spoken in normal tone
5. awake alert

Gabapentin Prescribing Information: