Gabapentin Use in Pediatric Spinal Fusion Patients: A Randomized, Double-Blind, Controlled Trial

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BACKGROUND: Gabapentin has opioid-sparing effects in adult surgical patients, but no reported studies have involved children and adolescents. In a double-blind, randomized, controlled trial, we examined whether gabapentin decreases postoperative opioid consumption for pediatric spinal fusion patients with idiopathic scoliosis.

METHODS: Patients, aged 9 to 18 years, received preoperative gabapentin (15 mg/kg, treatment) or placebo. Anesthesia was standardized. After surgery, all patients received standardized patient-controlled analgesia opioid and continued on either gabapentin (5 mg/kg) or placebo 3 times per day for 5 days. Opioid use was calculated in mg/kg/time intervals. Pain scores and opioid side effects were recorded.

RESULTS: Data from 59 patients (30 placebo and 29 gabapentin) did not differ in demographics. Total morphine consumption (mg/kg/h ± SD) was significantly lower in the gabapentin group in the recovery room (0.044 ± 0.017 vs 0.064 ± 0.031, P = 0.003), postoperative day 1 (0.046 ± 0.016 vs 0.055 ± 0.017, P = 0.051), and postoperative day 2 (0.036 ± 0.016 vs 0.047 ± 0.019, P = 0.018). In addition, gabapentin significantly reduced first pain scores in the recovery room (2.5 ± 2.8 vs 6.0 ± 2.4, P < 0.001) and the morning after surgery (3.2 ± 2.6 vs 5.0 ± 2.2, P < 0.05), but otherwise pain scores were not significantly different. There were no differences in opioid-related side effects over the course of the study.

CONCLUSION: Perioperative oral gabapentin reduced the amount of morphine used for postoperative pain after spinal fusion surgery, but not overall opioid-related side effects. Initial pain scores were lower in the treatment group. Perioperative use of gabapentin seems to be an effective adjunct to improve pain control in the early stages of recovery in children and adolescents undergoing spinal fusion. (Anesth Analg 2010;110:1393–8)

Surgical correction of spinal deformities in children results in challenging postoperative pain control and often a multimodal approach to pain management is necessary. Postoperative pain results from the multilevel surgical injury to boney tissues, decortication, iliac crest bone harvesting, and the corrective forces applied to the spine with instrumentation. Tissue injury initiates activation of both the peripheral and central pain pathways leading to sensitization of the dorsal horn neurons, causing allodynia and hyperalgesia. The relative importance of these different nociceptive mechanisms for the intensity of allodynia and hyperalgesia is often a multimodal approach to pain management. In spinal surgery, peripheral tissue injury provokes modification in the responsiveness of the central nervous system. There is not only peripheral sensitization, a reduction in the threshold of afferent peripheral terminals, but also central sensitization, an increase in the excitability of spinal neurons. This may amplify pain. Anticonvulsants, such as gabapentin, suppress spontaneous neuronal firing and have been effective in treating chronic, centrally mediated neuropathic pain syndromes. The opioids, most often morphine, are used for the treatment of postoperative pain. Traditionally, at Children’s Hospital of Wisconsin (CHW), we have managed the spinal fusion patient with opioids administered by patient-controlled analgesia. Analgesia is often limited by side effects, such as sedation, constipation, pruritus, nausea, vomiting, or respiratory suppression.

No published studies have addressed the use of gabapentin for postoperative pain in the adolescent population. Spinal fusion patients are usually receiving potent opioid pain relief postoperatively for 10 to 15 days. Several studies have shown gabapentin to have a positive, opioid-sparing effect in adult surgical patients in a single-dose design, as well as when continued for 1 week after surgery. Gabapentin may have the same opioid-sparing effect in children after surgery. It is often assumed that drug effects differ in children, but in reality, this perception arises because the drugs have not been adequately studied in children. In general, very few studies have considered the possible differences in pharmacokinetic and pharmacodynamic properties of drugs in children, compared with...
adults. Most pharmacodynamic studies on drugs are done in healthy adult volunteers and information is then extrapolated to children. In fact, so little drug testing has been performed in children that they are considered “therapeutic orphans.” Therefore, the aim of this study was to determine the effect of gabapentin on acute pain in the immediate postoperative period, specifically morphine consumption and opioid side effects, in the pediatric spinal fusion patient with idiopathic scoliosis. This study adheres to the Consolidation Standards of Reporting Clinical Trials statements.**16,17**

**METHODS**

An Investigational New Drug number (74317) (January 2006) from the Center for Drug Evaluation and Research with the Food and Drug Administration was obtained, and the study was registered in ClinicalTrials.gov, 06/71, GC138. The protocol was approved by CHW Research and Publications Committee/Human Rights Review Board. Written, informed consent was obtained at preoperative visits from each patient (assent) and parent (consent) for an experimental, randomized, placebo-controlled, double-blind study.

Sixty-three patients were enrolled. Inclusion criteria were children (aged 9–18 years) with idiopathic spinal scoliosis undergoing posterior spinal fusion surgery of at least 9 levels. ASA physical status was III or less. Operations were performed by 1 of 5 surgeons. Exclusion criteria were obstructive sleep apnea; severe, concomitant disease (neuromuscular scoliosis or neurodegenerative disease); current opioid use or admission of illicit drug use; pregnant; anticoagulation therapy; surgery for spondylolisthesis; obesity (body mass index >40); and allergies to morphine, hydromorphone, or gabapentin.

A hospital pharmacy clinical coordinator randomized participants to each study group (gabapentin or placebo), with stratification by surgeon before premedication for surgery. The patients, parents, nursing staff, surgeons, acute pain staff managing the patients, and study principal investigator collecting postoperative data were blinded to group assignment. Recruitment occurred from June 2006 to July 2008. If patients were unable to swallow capsules, liquid was available. Study medication was not provided by the drug manufacturer. Anesthetic technique was standardized. Both groups received preoperative oral midazolam (0.5 mg/kg up to 10 mg). Study drug (gabapentin 15 mg/kg) or placebo was given with premedication in the usual marketed capsule form or liquid, 25 to 30 minutes before being transported to the operating room. Study drug and placebo were identical in appearance. Dosing was based on adult data from several studies**12,18,20** in which 17 to 20 mg/kg gabapentin in a single dose decreased opioid consumption. Pharmacokinetic studies of gabapentin dosing**21** in children for seizure control have shown that doses from 9 to 34 mg/kg/d are well tolerated. Anesthesia was induced by mask sevoflurane in nitrous oxide and oxygen, followed by IV catheter placement. Alternatively, an IV was placed after inhalation of oxygen and nitrous oxide. Anesthesia was then induced with IV propofol and rocuronium to facilitate tracheal intubation. Patients were monitored with somatosensory-evoked potentials and motor-evoked potentials by a neurologist. Anesthesia was maintained in all patients with isoflurane, oxygen, nitrous oxide, sufentanil (1 μg/kg load followed by 0.2–0.4 μg/kg/h), and controlled ventilation. With surgical closure, opioid infusions were discontinued. Patients received morphine (0.1 mg/kg) before emergence. After tracheal extubation and assessment of lower extremity motor function, patients were transferred to the postanesthesia recovery unit (PARU).

Standard patient-controlled analgesia was initiated: demand morphine 0.02 mg/kg/dose every 6 minutes with basal infusion 0.02 mg/kg/h and hourly maximum of 0.12 mg/kg. All patients could receive supplemental opioid in the PARU as needed (0.05 mg/kg/dose morphine) to achieve acceptable comfort levels. Additional gabapentin was administered 3 times per day, starting on postoperative day 1 for 5 days at a dose of 5 mg/kg/dose. IV opioid was continued for at least 2 days postoperatively in all patients. If diet was restricted, small amounts of water were used to facilitate swallowing of the study capsules. Patients in the placebo group received an identical capsule or liquid 3 times daily for 5 days.

When analgesia was inadequate, the pain management team increased opioid doses following a standard decision-making tree. Diazepam was allowed to treat muscle spasm at a dose of up to 0.1 mg/kg/dose every 6 hours, as needed. Side effects, including nausea, vomiting, constipation, urinary retention, and pruritus, were recorded and treated by administration of ondansetron, diphenydramine, or bladder catheterization. Sedation was measured using the CHW sedation scale**22** as follows: 6 = agitated, anxious, or in pain above baseline; 5 = spontaneously awake without stimulus; 4 = drowsy but easily arouses to consciousness with light touch or verbal stimulus; 3 = arouses to consciousness but with moderate stimulus; 2 = arouses slowly to consciousness with sustained, painful stimulus; 1 = arouses but not conscious with painful stimulus; and 0 = unresponsive to painful stimulus. If excessive sedation was encountered, the opioid was stopped until the sedation score was ≥4.

Data collected included vital signs, pain scores in the PARU, and pain scores across shifts. All pain scores were assessed using a verbal numeric rating scale (0–10) and were measured multiple times per shift, with patient movement and rest. Sedation scores were recorded every 4 hours. Opioid consumption across shifts and cumulative amounts per day (mg/kg/h, hydromorphone doses were multiplied by 5 to obtain morphine equivalents in 1 patient who received hydromorphone) were recorded. Oxygen supplementation, days of bladder catheterization, and time to first bowel movement were noted. Nausea was assessed by verbal report or emesis; both were treated with ondansetron and the number of doses was recorded. The frequency of sedation scores <4, using the CHW sedation scale, or frequency of respiratory depression, as defined by <8 breaths per minute, was noted as well. Data safety monitoring board investigated safety after 30 patients were enrolled. No issues with safety were determined, and the study continued until completion.
Statistical Analysis
Opioid consumption was the primary outcome measure used to evaluate efficacy. Therefore, a power analysis was performed by extrapolation from adult studies using morphine consumption as a primary measure of improved pain control. 12,18,23 Turan et al. 20 showed that gabapentin in adult spinal fusion surgery decreased the amount of morphine consumption by 38% in the first 24 hours after surgery. This demonstrated an effect size equal to 2.66 for reduction in morphine use. For our sample size, we assumed children would show more variability in morphine use and so doubled the SDs from the study by Turan et al. for the power analysis. Assuming a power of 0.8, a sample size of 30 in each group was considered adequate to demonstrate the hypothesized effect at a significance of 0.05. Descriptive statistics were included to examine sample and between-group characteristics. Variables were examined for normality (Kolmogorov-Smirnov). Categorical data were examined with \( \chi^2 \) tests or Fisher exact tests. Between-group differences were examined with independent sample 2-tailed \( t \) tests (continuous and normally distributed data) or Mann-Whitney \( U \) test. Pain scores were analyzed with 2-way repeated-measures analysis of variance, with Bonferroni post hoc comparisons. Significance of tests was \( P < 0.05 \) for all analyses. Data were analyzed using SPSS, version 11.5 (SPSS, Chicago, IL).

RESULTS
Sixty-three consecutive patients were evaluated for enrollment in the study (Fig. 1, CONSORT [Consolidated Standards of Reporting Trials] flow diagram). After enrollment, 4 patients were subsequently excluded: on day 1 after surgery, 2 patients (gabapentin group) refused to participate, 1 citing unpleasant feelings with the study drug and 1 because of a skin rash. On the day of surgery, 1 patient (placebo group) was excluded because the surgeon changed the procedure to anterior spinal fusion. After completion of the study protocol, 1 patient (gabapentin group) was excluded on the basis of study violation, resulting in data for 59 patients, 30 in the placebo group and 29 in the gabapentin group.

Table 1 presents demographic data. No differences were identified between groups for all variables evaluated (all \( P \) values >0.05). There were no CHW sedation scores <4; therefore, all patients received study medication through day 5.

Morphine consumption was calculated for each postoperative day in all patients. Given that morphine was discontinued by the end of day 4 in all but 5 patients, data on morphine use and pain assessments are presented through day 4. Total morphine consumption was significantly lower in the gabapentin group on the day of surgery, postoperative day 1, and postoperative day 2. On the day of surgery, patients in the placebo group used 0.064 ± 0.031 mg/kg/h morphine, whereas those in the gabapentin treatment group used only 0.044 ± 0.017 mg/kg/h (\( P = 0.003 \)). This trend continued on postoperative day 1 with the placebo group using 0.055 ± 0.017 mg/kg/h and the treatment group using 0.046 ± 0.016 mg/kg/h (\( P = 0.051 \)). On postoperative day 2, the placebo group used 0.047 ± 0.019 mg/kg/h morphine and the treatment group used 0.036 ± 0.016 mg/kg/h (\( P = 0.018 \)). No differences were found for days 3 through 5. Data are graphically displayed in Figure 2. An examination of the cumulative morphine consumption through day 2 showed that overall usage was significantly less in the gabapentin group (M 0.126 ± 0.038 mg/kg/h) than in the placebo group (M 0.165 ± 0.061 mg/kg/h, \( P = 0.005 \)).

A repeated-measures analysis of variance yielded a significant interaction between condition (placebo versus gabapentin) and time of measurement (\( F = 6.6 = 9.8, P < 0.001 \)) on pain scores. The first pain score, taken in the PARU, was significantly lower in the gabapentin group (M 2.5 ± 2.8 vs 6.0 ± 2.4, \( P < 0.001 \)). Scores were also lower for the gabapentin group on the morning after surgery (M 3.2 ± 2.6 vs 5.0 ± 2.2, \( P < 0.05 \)) but otherwise did not differ throughout the remainder of the study (Fig. 3).

No differences were found between groups for any of the measures of morphine-related side effects (Table 2). Although mean numbers of ondansetron (2.9 ± 3.6 vs 4.1 ±
Figure 2. Total morphine consumption. Data are shown as mean (mg/kg/h ± SD), *P < 0.05.

Figure 3. Postoperative pain scores. Data are shown as mean (SD), P < 0.05.
epidural opioids for postoperative pain control with significance.

gabapentin group, differences did not reach statistical significance.

Several studies have shown gabapentin to have opioid-sparing effects in postoperative surgical adult patients in a single-dose design. A single dose of 600 mg in healthy adult volunteers showed that gabapentin improved pain scores and decreased opioid requirements at 4 hours in mastectomy patients and within the first 24 hours in adults undergoing spinal fusion surgery. Based on our findings, we would only recommend early use of gabapentin with a preoperative initial oral loading dose and continued use for 2 days; at the maintenance dose used, benefit was not seen after 48 hours. Future studies should begin to explore other dosing regimens of gabapentin in pediatric spinal fusion. A limitation to the study is that idiopathic spinal fusion patients are usually female, with ages ranging from 9 to 15 years. Other patients, such as neurogenic scoliosis, pectus excavatum repair, or developmentally delayed patients undergoing surgical procedures, whose use of potent opioids poses significant respiratory risk, may also benefit from a preoperative gabapentin load, as did these healthy patients. Again, this warrants further study.

In conclusion, an initial preoperative loading dose and continued use of oral gabapentin decreased early total morphine consumption and pain scores in pediatric patients undergoing spinal fusion up to 2 days after surgery. Continued maintenance dosing of gabapentin beyond 2 days did not show benefit in pain management in this group of patients.

**DISCUSSION**

The goals of this study were to determine the effects of gabapentin on morphine consumption, self-reports of pain and opioid side effects, in the pediatric spinal fusion patient with idiopathic scoliosis. Our results demonstrate that preoperative gabapentin with continued administration is effective in reducing morphine consumption and pain scores in the early postoperative period. Benefits were observed for the immediate postoperative period through day 2, and no benefits were observed after the second postoperative day. No significant differences in opioid side effects were found between the gabapentin and placebo groups.

Our findings based on a pediatric sample are similar to those from studies that have demonstrated benefits of gabapentin in the early postoperative period in adults. Several studies have shown gabapentin to have opioid-sparing effects in postoperative surgical adult patients in a single-dose design. A single dose of 600 mg in healthy adult volunteers showed that gabapentin improved pain scores and decreased opioid requirements at 4 hours in mastectomy patients and within the first 24 hours in adult spinal fusion patients.

It is clinically meaningful that children and adolescents can also experience the postsurgical benefits of gabapentin. Postoperative pain in this patient population is often difficult to manage. Multimodal therapy with the addition of other analgesics has not gained widespread application for spinal fusion patients. Nonsteroidal antiinflammatory drugs are often used for treatment of postoperative pain, but there are concerns that these drugs interfere with bone healing. Others have used transdermal clonidine and epidural opioids for postoperative pain control with variable results. Studies on the safety of gabapentin in the chronic pain patient have demonstrated adverse effects including dizziness, somnolence, confusion, headache, nausea, ataxia, and weight gain. These side effects usually diminish with time but may, in fact, be troublesome in an acute, postoperative spine patient.

It was postulated that a decrease in the amount of opioid needed to control pain would lead to fewer opioid-related side effects. This was not demonstrated in our patients. These findings are similar to the study by Turan et al., after which our study was modeled, in which statistical significance was found in only 2 of the 8 adverse side effects measured. Our study may have been affected by specific ward nursing protocols that are followed in the postoperative spinal fusion patient. Foley catheters are frequently used for 3 to 5 days in these patients and oxygen is supplemented for 1 to 3 days. It is also possible that the study was underpowered for the detection of any opioid side effects, because the sample size was based on opioid consumption as the primary outcome variable. In addition, the gabapentin dose of 5 mg/kg 3 times per day perhaps was not high enough to show significant reductions of both opioid use and side effects. This warrants further study.

This study is the first to show, in children, that a preoperative, initial oral load of gabapentin with continued use reduced the amount of morphine consumed and decreased pain scores in the first 48 hours after idiopathic spinal fusion surgery. Based on our findings, we would only recommend early use of gabapentin with a preoperative initial oral loading dose and continued use for 2 days; at the maintenance dose used, benefit was not seen after 48 hours. Future studies should begin to explore other dosing regimens of gabapentin in pediatric spinal fusion. A limitation to the study is that idiopathic spinal fusion patients are usually female, with ages ranging from 9 to 15 years. Other patients, such as neurogenic scoliosis, pectus excavatum repair, or developmentally delayed patients undergoing surgical procedures, whose use of potent opioids poses significant respiratory risk, may also benefit from a preoperative gabapentin load, as did these healthy patients. Again, this warrants further study.

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**REFERENCES**


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**Table 2. Morphine-Related Side Effects**

<table>
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<th>Gabapentin</th>
<th>Placebo</th>
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<tr>
<td>Oxygen, d</td>
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<td>2.7 ± 1.9</td>
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<tr>
<td>Foley, d</td>
<td>4.3 ± 0.9</td>
<td>4.5 ± 0.9</td>
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<tr>
<td>Bowel movement</td>
<td>3.8 ± 1.2</td>
<td>3.9 ± 0.8</td>
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<td>postoperative day</td>
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<td>3.7 ± 0.7</td>
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<td>Day oral analgesics</td>
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<td>2.0 (0–6.0)</td>
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<td>Number of diphenhydramine doses</td>
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All data presented as mean ± sd or median (upper-lower quartiles). All P values >0.05.
Gabapentin for Pain Control in Pediatric Spinal Fusion Patients


