A Perioperative Course of Gabapentin Does Not Produce a Clinically Meaningful Improvement in Analgesia after Cesarean Delivery

A Randomized Controlled Trial

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ABSTRACT

Background: Studies examining the efficacy of a single preoperative dose of gabapentin for analgesia after cesarean delivery (CD) have been inconclusive. The authors hypothesized that a perioperative course of gabapentin would improve analgesia after CD.

Methods: This single-center, randomized, double-blind, placebo-controlled, parallel-group, superiority trial was designed to determine the analgesic efficacy of a perioperative course of gabapentin when added to a multimodal analgesic regimen. Women scheduled for elective CD during spinal anesthesia were randomized to receive a perioperative oral course of either gabapentin (600 mg preoperatively followed by 200 mg every 8 h for 2 days) or placebo. Postoperative pain was measured at 24 and 48 h, at rest and on movement, on a visual analogue scale (VAS, 0 to 100 mm). The primary outcome was pain on movement at 24 h. Neonatal outcomes, opiate consumption, VAS satisfaction (0 to 100 mm), adverse effects, and persistent pain were also assessed.

Results: Baseline characteristics were similar between groups. There was a statistically significant but small reduction in VAS pain score (mean [95% CI]) on "movement" (40 mm [36 to 45] *vs.* 47 mm [42 to 51]; difference, −7 mm [−13 to 0]; $P = 0.047$) at 24 h in the gabapentin (n = 100) compared with control group (n = 97). There was more sedation in the gabapentin group at 24 h (55 *vs.* 39%, $P = 0.026$) but greater patient VAS satisfaction (87 *vs.* 77 mm, $P = 0.003$).

Conclusions: A perioperative course of gabapentin produces a clinically insignificant improvement in analgesia after CD and is associated with a higher incidence of sedation. **(ANESTHESIOLOGY 2015; 123:320-6)**

POSTOPERATIVE pain is one of women's biggest concerns after cesarean delivery (CD).[1] The improvement in analgesia after elective CD in recent decades can be attributed to the widespread adoption of neuraxial anesthetic techniques inclusive of intrathecal opiates and multimodal oral analgesic regimens. An effective analgesic package is integral to an enhanced recovery programme for CD,[2] and good quality pain relief in the perioperative period has been associated with decreased incidences of breast-feeding difficulties,[3] persistent pain, and post-natal depression.[4]

The full package of spinal anesthesia, intrathecal opiates, oral acetaminophen, nonsteroidal antiinflammatory drugs, and systemic opiates, which serves the majority so well, is unfortunately either insufficient or unavailable for a significant minority. The search for useful additions and alternatives to the current standard regimen must continue if we are to cater for such women.

Gabapentin is a perioperative analgesic with proven benefit in a variety of surgeries,[5,6] including settings not dissimilar to CD, such as abdominal hysterectomy.[7] It has documented safety in pregnancy and breastfeeding with much of the data coming from its use as an anticonvulsant[8–10] and from previous studies performed at our institution, designed primarily to assess its analgesic efficacy after CD.[11,12]

In 2010, Moore *et al.*[11] showed improved analgesia after CD associated with a 600-mg preoperative dose of gabapentin. Despite demonstrating 20-mm reduction in visual analogue scale (VAS) pain scores on "movement,"

What We Already Know about This Topic

- Gabapentin is an effective perioperative analgesic adjunct in many contexts, but studies in women after cesarean delivery have been restricted to single doses and have shown mixed results

What This Article Tells Us That Is New

- In 197 women randomized to receive gabapentin, 600 mg before cesarean delivery and 200 mg every 8 h for 2 days postoperatively or placebo, there was a statistically significant but clinically unimportant difference in pain with movement 24 h after surgery
- Sedation was greater in women treated with gabapentin

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24 h after the incision, there was a greater incidence (19 *vs.* 0%) of severe sedation in the gabapentin group, and the study sample was limited to 46 participants. In a subsequent study aimed at identifying an effective dose with less sedative effect, Short *et al.*[12] compared 300 and 600 mg of gabapentin with placebo before CD. However, they failed to replicate the analgesic effect of gabapentin despite a sample size of 42 participants in each arm. *Post hoc* analysis suggested that the study was underpowered, and therefore, no definite conclusion on the efficacy of gabapentin could be drawn.

Recognizing the limitations of these previous studies and a growing trend in the literature demonstrating the benefit of extending a course of gabapentin into the postoperative period,[5,6] we proposed to conduct a study with adequate power to assess the benefits of a perioperative course of gabapentin compared with placebo. We hypothesized that a perioperative course of gabapentin would improve analgesia after CD.

Materials and Methods

Participants

We obtained written consent from women aged 18 to 55 yr, who scheduled for elective CD of a singleton pregnancy under spinal anesthesia. Patients were excluded if they were American Society of Anesthesiologists physical status III, IV, or V, suffered from epilepsy or chronic pain, were taking anticonvulsants or neuropathic analgesics, had a history of opioid or IV drug abuse, had an allergy or contraindication to gabapentin or other element of the protocol, or had taken antacid therapy in the previous 3 h. This single-center, randomized, double-blind, placebo-controlled, parallel-group, superiority trial was designed to determine the analgesic efficacy of a perioperative course of gabapentin when added to a multimodal analgesic regimen. It was performed between May 2013 and February 2014 in the obstetric unit of a quaternary referral university hospital in Toronto, Canada. It received approval from our institutional research ethics board (13-0039-A, approved on April 10, 2013) and a "no objection" letter from Health Canada. This study was registered with the U.S. National Institute of Health at www.clinicaltrials.gov under NCT01848119.

Intervention and Perioperative Management

Study subjects received either 600 mg of oral gabapentin or placebo 1 h before surgery. Spinal anesthesia was achieved with 1.6 to 1.8 ml of 0.75% hyperbaric bupivacaine, 10 μg of fentanyl, and 100 μg of preservative-free morphine. On completion of intrathecal injection, a 10 ml/kg IV fluid bolus of Ringer's lactate solution was administered, and the patient was positioned supine on the operating table with a left lateral tilt. Noninvasive brachial blood pressures were taken at 1-min intervals, and 100 μg boluses of phenylephrine were used to maintain systolic blood pressure at baseline.

Intraoperative discomfort was treated with up to 100 μg IV fentanyl as required. IV ketorolac 30 mg and 1,300 mg acetaminophen suppositories were administered at the end of the operation. In the postanesthesia care unit, any pain was treated with IV morphine 2 mg every 5 min to achieve satisfactory effect, according to a postanesthesia care unit protocol. Patients then received a postoperative course of 50 mg diclofenac orally every 8 h, 1,000 mg acetaminophen orally every 6 h, and 200 mg gabapentin orally or placebo every 8 h for 48 h to a total of five doses. In the first 24 h, on the postnatal floor, breakthrough pain was treated with a subcutaneous/IV injection of 2 mg morphine or 0.4 mg hydromorphone every hour until satisfactory pain relief was achieved. After 24 h, patients received 10 mg morphine orally or 2 mg hydromorphone on request. Nausea was treated with ondansetron, metoclopramide, or dimenhydrinate according to an institutional protocol.

Blinding

Identical green capsules containing either gabapentin or placebo were prepared by our hospital pharmacy, which was not otherwise involved in the research. The initial dose was prepared by placing a tablet of 300 mg gabapentin or lactose into each of two capsules and sealing them in envelopes that were sequentially numbered according to a computer-generated randomization table. The randomization was done in blocks of six, and subjects were allocated to the two groups in the ratio of 1:1. Each subject, once recruited, was assigned an ascending sequential study number. They were then given the two capsules from the corresponding study envelope with a sip of water at 1 h before the anticipated time of the surgical incision. Each numbered preoperative-dose envelope was accompanied by a medication package containing 10 capsules of either 100 mg gabapentin for the treatment group or lactose placebo for the control group. The nurses caring for each patient then administered two of these capsules every 8 h, according to a standardized schedule.

Outcomes and Assessments

Before surgery, we collected baseline data regarding patient characteristics, gestational age, parity, previous pregnancies, and deliveries. Intraoperatively, we recorded type of incision, whether uterine exteriorization was performed, and whether a supplemental analgesic or antiemetic was required. A respiratory therapist who was responsible for the infant was present for all deliveries, and we recorded their assessment of Apgar score at 1 and 5 min, as well as umbilical cord blood gases and the need for advanced resuscitative measures. We also documented the need for neonatal intensive care unit admission at any point during the study period.

We performed postoperative visits at 24 and 48 h after surgical incision. During these assessments, we recorded

VAS pain at "rest" and on "movement," VAS satisfaction with pain management, side effects, breast-feeding difficulties, and opiate consumption. The patient recorded the VAS scores by marking along a 100-mm line. The VAS scales were annotated for pain (0, no pain; 100, worst pain imaginable) and satisfaction (0, unsatisfied; 100, completely satisfied). They were instructed to report their pain at rest as that pain felt when lying still and to sit up from the lying down position to evoke the pain they felt on movement. We assessed the following side effects: nausea, vomiting, sedation, dizziness, pruritus, and difficulties balancing. Patients were asked to rate each of these as "not present," "mild," "moderate," or "severe." Morphine milligram equivalents were calculated, so that opiate consumption could be compared between patients regardless of which opiate they had received within the protocol. Telephone interviews were conducted at 2 and 6 weeks postoperatively to assess for the presence of persistent pain at the surgical site.

The primary outcome measure was VAS pain on movement at 24 h postoperatively. The secondary outcomes were VAS pain at rest at 24 h, VAS pain at rest and on movement at 48 h, neonatal outcomes (Apgar scores, umbilical arterial pH, need for intubation, positive pressure ventilation, or admission to the neonatal intensive care unit), opiate consumption, VAS satisfaction at 24 and 48 h, adverse effects, and persistent pain.

Study Population Size

To achieve 80% power to detect a difference of 10 mm on the VAS scale between treatment and control arms at 24 h, we needed a total of 184 patients (92 in each treatment arm). This calculation assumed a type I error of 0.05 and a common SD of 24 mm in each group. The SD was estimated from previous studies[11,12] in which the SD ranged from 17 to 24 mm. Therefore, to ensure that we had sufficient power, we aimed to recruit and randomize 204 patients to account for a 10% potential loss to follow-up.

Statistical Analysis

Data were analyzed using an intention-to-treat analysis. Demographic and clinical characteristics of study participants are presented as mean and SD for continuous factors and frequencies and proportions for categorical factors. Hypothesis testing was two tailed. Data on continuous outcomes are presented as mean values with 95% CIs and analyzed using Student independent two-sample *t* test assuming unequal variance. Data on categorical outcomes are presented as frequencies with percentages and were analyzed using chi-square test. Where continuous data were found to be nonnormally distributed according to skewness or kurtosis statistics greater than 1, medians and interquartile ranges are reported, and nonparametric Mann–Whitney U tests were conducted. A *P* value of less than or equal to 0.05 was used to indicate statistical significance.

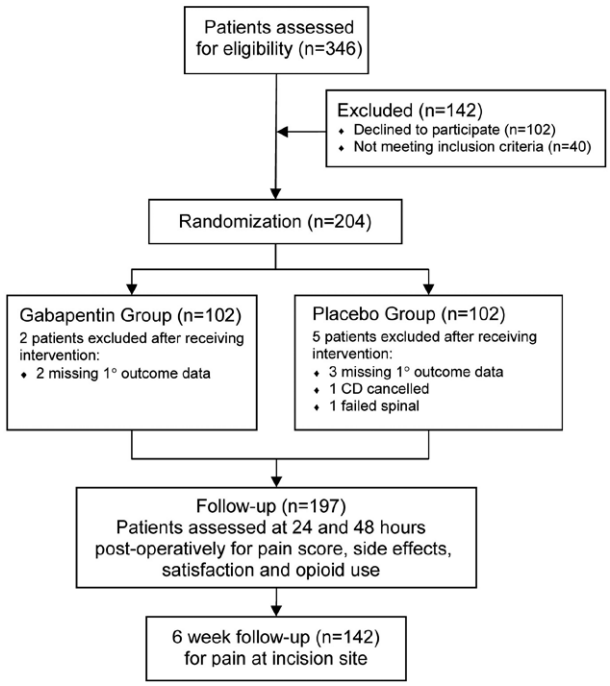

Fig. 1. Trial profile. CD = cesarean delivery.

Results

The study was conducted from May 2013 to February 2014, and during this period, we approached 346 women. Of these, 142 women either declined or were found ineligible, which resulted in the recruitment of 204 patients into the study.

Figure 1 displays the trial profile. Seven women were excluded from analysis after randomization, two from the gabapentin and five from the placebo group. These were due to deviation from the protocol, lost outcome data, and patient withdrawal. The two patients excluded due to protocol deviation were both from the placebo group. One of these did not deliver by cesarean, and the other one was excluded due to failure to establish spinal anesthesia. One hundred ninety-seven patients were included in this intention-to-treat analysis. Fifty-five patients could not be contacted after discharge and so could not be included in the analysis of persistent pain at 2 and 6 weeks. Table 1 outlines the baseline data showing that maternal and neonatal characteristics were similar in both groups, and there were no differences in any other clinical variables.

Visual Analogue Scale Pain Scores

At the primary outcome, pain on movement at 24 h after incision, the mean VAS pain score showed a statistically significant but small reduction: 7 mm (95% CI, 13 to 0; $P = 0.047$) in the gabapentin group (fig. 2). The mean VAS pain score was 40 mm (95% CI, 36 to 45) in the gabapentin group compared with 47 mm (95% CI, 42 to 51) in the control group. The mean VAS pain score seen at rest at the same time point in the gabapentin group also demonstrated

Table 1. Baseline Maternal Characteristics at Enrolment

Variables	Gabapentin (n = 100)	Placebo (n = 97)	*P* Value
Age (yr)*	35.9 (3.9)	34.7 (4.5)	0.09
BMI (kg/m²)*	30.8 (5.1)	31.3 (5.6)	0.53
Gestational age (wk)*	38.7 (0.8)	38.6 (0.9)	0.73
Gravida†	3 (2–3)	2 (2–3)	0.015
Parity†	1 (0–3)	1 (0–4)	0.21
Repeat CD‡	76 (76.0)	70 (72.2)	0.54
Exteriorization‡	77 (78.6)	69 (71.1)	0.23

* Results are presented as mean (SD) (unequal variance, independent two samples *t* test). † Results are presented as median (interquartile range) (nonparametric Wilcoxon rank sum test). ‡ Results are presented as n (%) (chi-square test for association).

BMI = body mass index; CD = cesarean delivery.

a statistically significant but small reduction compared with the control group (13 mm [95% CI, 10 to 16] *vs.* 19 mm [95% CI, 15 to 23]; difference, −6 mm [95% CI, −11 to −1]; $P = 0.017$). There were no statistically significant differences seen between groups at the 48-h pain measurements.

Adverse Effects

Most adverse effects were evenly distributed across the groups (table 2), but there were significant differences in the incidence of sedation. At 24 h, 55 patients (55%) who had received gabapentin reported sedation compared with 38 patients (39%) in the control group (difference, 16%; $P = 0.026$). Table 3 details the severity of sedation as categorized by patients at 24 h after their surgery. In the gabapentin group, 8% of patients reported their sedation as severe, at 24 h, compared with 2% in the control. At 48 h, the incidence of sedation was similar in each group with nine patients (9%) in the gabapentin group reporting sedation of any severity compared with 11 (11%) in the control group (difference, −2%, $P = 0.59$). No patient in either group reported severe sedation on the second postoperative day.

Fewer patients in the gabapentin compared with the control group complained of pruritus at 48 h: 18 (17%) *versus* 33 (34%); difference, −17%; $P = 0.010$. There was no difference seen between groups at 24 h for this side effect.

VAS Satisfaction, Supplemental Intraoperative Analgesia, Opiate Consumption, Persistent Pain, and Neonatal Outcomes

Patients who had received gabapentin reported a statistically significant increase in mean VAS satisfaction score at 24 h when compared with the control group (87 mm [95% CI, 83 to 90] *vs.* 77 mm [95% CI, 72 to 82]; difference, 10 mm; $P = 0.001$). No statistically significant difference was observed between groups with regard to VAS satisfaction at 48 h.

One patient in the gabapentin group (40 μg) and three in the placebo group (25, 50, and 75 μg respectively) were given supplemental intraoperative fentanyl. There were no statistically significant differences between groups in either opiate consumption at 24 and 48 h or incidence of persistent

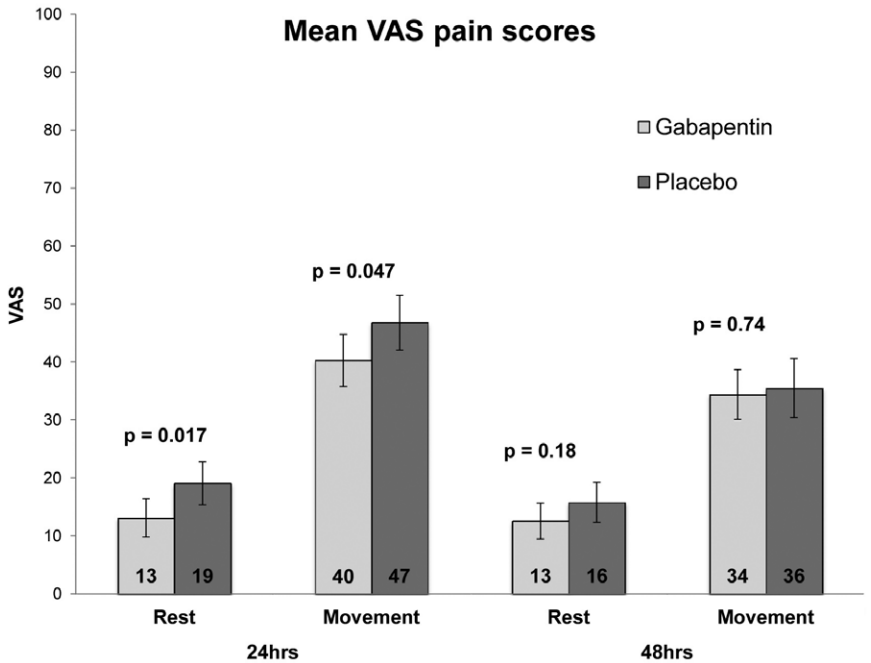

Fig. 2. Mean pain scores reported by subjects, on a visual analogue scale (VAS, 0 to 100 mm), in the gabapentin and placebo groups at "rest" and on "movement," at 24 and 48 h after surgical incision. The respective mean VAS pain scores are given at the base of each *bar*, the 95% CIs for those values are illustrated as *error bars*, and the *P* value for each comparison is provided above the respective pair of measurements. At the primary outcome, pain on movement at 24 h, there was a small but statistically significant reduction in pain experienced by patients who had received a perioperative course of gabapentin.

Table 2. Opiate Consumption, Satisfaction, Persistent Pain, and Side Effects

	Gabapentin (n = 100)	Placebo (n = 97)	Difference between Groups	*P* Value
24-h opiate consumption*	10 (4 to 20)	10 (4 to 14)	—	0.97
48-h opiate consumption*	10 (10 to 20)	10 (10 to 20)	—	0.19
24-h VAS satisfaction†	87 (83 to 90)	77 (72 to 82)	10 (1 to 18)	0.001
48-h VAS satisfaction†	86 (82 to 90)	81 (77 to 86)	5 (–4 to 13)	0.15
Pain at 2 wk‡	30/83 (36)	40/81 (49)	–13 (–28 to 2)%	0.09
Pain at 6 wk‡	4/71 (6)	3/71 (4)	1 (–6 to 9)%	>0.99
Side effects at 24 h§				
Nausea	38 (38)	42 (43)	–5 (2 to 8)%	0.45
Vomiting	24 (24)	26 (27)	–3 (–15 to 9)%	0.65
Sedation	55 (55)	38 (40)	15 (2 to 30)%	0.026
Dizziness	41 (41)	42 (43)	–2 (–16 to 12)%	0.74
Pruritus	72 (72)	77 (79)	–7 (–19 to 5)%	0.23
Balance difficulties	27 (27)	29 (30)	–3 (–16 to 10)%	0.65
Side effects at 48 h§				
Nausea	4 (4)	6 (6)	–2 (8 to 4)%	0.53
Vomiting	1 (1)	1 (1)	0 (–3 to 3)%	0.99
Sedation	9 (9)	11 (11)	–2 (–11 to 6)%	0.59
Dizziness	11 (11)	16 (17)	–6 (–15 to 4)%	0.26
Pruritus	18 (17)	33 (34)	–16 (–28 to –4)%	0.010
Balance difficulties	16 (16)	17 (18)	–2 (–12 to 9)%	0.77

24 and 48 h represent 24 and 48 h after surgical incision, respectively.
* Results are presented as median morphine milligram equivalents (interquartile range) (Mann–Whitney U test). † Results are presented as mean VAS satisfaction (95% CI) (unequal variance, independent two samples *t* test). ‡ Due to some loss to follow-up the results for pain at 2 and 6 weeks are presented as number of patients reporting persistent pain at the surgical site/ number of patients successfully contacted for follow-up (%). § Results are presented as n (%) (chi-square for association or Fisher exact test if small cell sizes).
VAS = visual analogue scale.

pain at 2 and 6 weeks (table 2). There were no differences in neonatal outcomes (table 4).

Discussion

These results demonstrate that a perioperative course of gabapentin produces a 7-mm reduction in the pain on movement, as measured on a VAS, in the first 24 h after CD. It is also associated with an increase in level of satisfaction of 10 mm when measured on the same scale. These "improvements" are small and of questionable clinical significance.

The question of what constitutes a clinically meaningful difference in pain intensity has attracted much attention in the medical literature and is of particular relevance when interpreting the clinical implications of results of studies such as ours. The work by Farrar *et al.*,[13–15] in particular, has increased our understanding of this issue and gone much of the way to quantifying the size of such a "clinically important difference (CID)" in pain outcomes. In a cancer-related model of pain, they used a reference standard for a CID as the difference in pain intensity that determined whether a patient had received enough pain relief in order not to require additional "rescue medication." The within subject cutoff for percentage pain intensity difference (%PID) that was, once balanced for

Table 3. Severity of Sedation at 24 Hours

Sedation	Gabapentin Group (n = 100)	Placebo Group (n = 95)	*P* Value*
0	45 (45)	57 (60)	
1	23 (23)	10 (11)	
2	24 (24)	26 (27)	0.018
3	8 (8)	2 (2)	

Results are given as n (%).
* Overall chi-square test for comparison of the distribution of severity of sedation in the gabapentin and control groups.
0 = no; 1 = mild; 2 = moderate; 3 = severe sedation.

Table 4. Neonatal Outcomes

	Gabapentin Group (n = 100)	Placebo Group (n = 97)	*P* Value
Birth weight (g)*	3,408 (450)	3,347 (506)	0.37
Apgar score (1 min)†	9 (9, 9)	9 (9, 9)	0.23
Apgar score (5 min)†	9 (9, 9)	9 (9, 9)	0.46
Umbilical arterial blood pH‡	7.3 (0.07)	7.3 (0.10)	0.77
Positive pressure ventilation§	3 (3.0)	3 (3.1)	>0.99
NICU admission§	1 (1.0)	4 (4.1)	0.21
Breast-feeding difficulties§	16 (17.6)	17 (19.3)	0.76

Positive pressure ventilation refers to the need for this respiratory intervention during initial resuscitation of the newborn or at any point after that during the inpatient study period. NICU admission refers to the need for care on the NICU at any point during the inpatient study period.
* Results are presented as mean (SD) (unequal variance, independent two samples *t* test). † Results are presented as median (interquartile range) (nonparametric Wilcoxon rank sum test). ‡ Results are presented as mean (SD) (nonparametric Wilcoxon rank sum test). § Results are presented as n (%) (chi-square test or Fisher exact test if small cell sizes).
NICU = neonatal intensive care unit.

sensitivity (73.4%) and specificity (69.6%), best able to predict adequate pain relief (accuracy, 72.3%), as defined in this way, was greater than or equal to 33%PID. Another study by Todd *et al.*[16] set out to determine the absolute value on a VAS of a minimal CID in pain severity in the context of minor trauma patients in the emergency department. It concluded that an improvement of less than 13 mm, measured on a VAS, was not clinically important. Both of these attempts to define a clinically significant difference have by necessity involved an assessment of within-subject differences. This is a different context to the comparison of the group means used in our study to evaluate the treatment effect of gabapentin. Although not ideal, these standards still can help evaluate the clinical significance of our findings.

At the primary outcome, the reduction of 7 mm in mean VAS pain observed in the treatment group when compared with the control group represents a 15% (7 of 47) reduction. Therefore, this can be judged as a clinically insignificant difference when either of the aforementioned standards is applied. Although the 6-mm reduction seen at rest at 24 h does not meet the "13-mm standard," it represents a 32% reduction in the mean pain from the control group and narrowly misses the "33%PID" standard.

Adverse Effects

We observed a moderately increased (55 *vs.* 39%) incidence of sedation at 24 h and no difference at 48 h. However, Moore *et al.*[11] observed severe sedation, in the first 48 h after CD, in 4 of the 21 (19%) patients who received 600 mg gabapentin preoperatively compared with none of the 23 who received placebo. Short *et al.*[12] designed their subsequent study, partly, in the hope that they could demonstrate benefit at half that dose and without the problematic sedative effect. They documented rates of severe sedation of 4.8 and 7.1% associated with single preoperative doses of 600 and 300 mg, respectively. They could not convincingly explain this apparent lack of dose–response relationship. Our current larger study demonstrated a rate of severe sedation in the first 24 h associated with gabapentin that was four times (8 *vs.* 2%) that observed in the control group.

All other side effects were similar with the exception of "pruritus" at 48 h. As opiate consumption in the first 48 h was also similar between the groups, it is unlikely to be responsible for the decrease in pruritus observed in the treatment group. Gabapentin has a documented antipruritic effect in other contexts,[17,18] and it is possible that this only became evident, in our study, once the strong pruritic effect of intrathecal morphine had subsided.

Although we did not find evidence of neonatal harm, we were not powered to assess for this, and the effects for which we assessed were exclusively severe in nature. It would have been useful to include a more sensitive measure such as a neonatal neurobehavioral assessment. However, it is still reassuring that any major effect, should it exist, is not large enough to be detected in the 197 deliveries included in our study.

Limitations

The average pain experienced by our study population was only mild to moderate, and this pays testament to the quality of the standard analgesia. Given that we were able to identify an effect, albeit small, in the context of such excellent standard pain relief, it would seem worthwhile to assess for an effect of gabapentin in those patients likely to experience severe postoperative pain. It is a legitimate criticism of our study that we did not make an attempt to focus on such patients. The predictive tools currently available for predicting pain post-CD are limited but do exist. A future examination of gabapentin could use the three-item questionnaire identified by Pan *et al.*[19] to identify a high-risk population for postcesarean pain.

Our study was limited by the use of the VAS to assess pain. VASs are easy to use but have been shown to be an imprecise measure of pain in the postoperative setting.[20] The search goes on for a well-validated and clinically practical measure of pain in the postoperative setting. We used a self-reported measure of sedation, but it would have added valuable information if we had included an objective measure of this troublesome side effect. Also, if it had been feasible to use opiate–intravenous patient-controlled analgesia at our institution, it would have provided a more accurate measure of opiate consumption.

This study was also limited by the absence of definitive evidence for an optimal analgesic dose of gabapentin in this context. We based our treatment regimen on the trend in the literature from other surgeries, but this may not have been sufficient for our study population.

Conclusions

In summary, a perioperative course of gabapentin reduces pain by a small amount and increases patients' satisfaction in the first 24 h after CD, but it is associated with an increase in sedation. These results do not support the introduction of gabapentin into the standard analgesic package, but it may be possible to identify a subgroup of women, at higher risk of experiencing severe postcesarean pain, who would receive a clinically significant benefit, and this warrants further investigation.

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Competing Interests

The authors declare no competing interests.

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