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REPORTS OF ORIGINAL INVESTIGATIONS

Randomized controlled trial of gabapentin as an adjunct to perioperative analgesia in total hip arthroplasty patients

Étude randomisée contrôlée de l'ajout de gabapentin pour l'analgésie périopératoire de patients subissant une arthroplastie totale de hanche

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Abstract

Purpose *Gabapentin was investigated as a single-dose adjunct to morphine for postoperative pain management. The primary objective was to determine if gabapentin given preoperatively and for two days postoperatively as part of multimodal analgesia would decrease postoperative morphine consumption in patients undergoing primary total hip arthroplasty (THA).*

Methods *The study group included 102 patients aged 19-90 years who were undergoing primary THA in a single joint with no contraindications to the study medications, no chronic pain syndrome, and no chronic opioid use. Intervention group patients (n = 48) received gabapentin 600 mg po preoperatively and 200 mg postoperatively on the day of surgery. They were continued on gabapentin at 200 mg three times daily for two days. Control group patients (n = 54) received placebo in a similar fashion. Preoperatively, all patients were given 30 mg of ketorolac intravenously and acetaminophen 1000 mg po. Postoperatively, they received intravenous patient-controlled analgesia with morphine, along with ketorolac 15 mg iv and acetaminophen 1000 mg po every six hours.*

Results *The primary outcome was mean (SD) postoperative morphine consumption at 72 hr which was 55.8 (39.2) mg in the gabapentin groups vs 60.7 (37.2) mg for the control group (mean difference, −4.91 mg, 95% confidence intervals [CI]: −21.2 to 11.35; P = 0.550). There were no significant differences between the groups regarding secondary outcomes: pain scores, side effects, range of motion. Patient satisfaction on day 3 was more favourable in the placebo group. Length of hospitalization was marginally shorter in the placebo group.*

This report was previously presented, in part, at the Canadian Anesthesiologists' Society Annual Meeting June 2011.

Author contributions *James Paul* helped design the study, conduct the study, wrote the manuscript and has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files. *Manyat Nantha-Aree* and *Norman Buckley* helped design the study, conduct the study, write the manuscript and have seen the original study data, reviewed the analysis of the data, and approved the final manuscript. *Uswa Shahzad* wrote the first draft of the manuscript, has seen the original study data, reviewed the analysis of the data, and approved the final manuscript. *Ji Cheng* and *Lehana Thabane* helped design the study, analyze the data, write the manuscript and have seen the original study data, reviewed the analysis of the data, and approved the final manuscript. *Antonella Tidy* helped with data collection and has seen the original study data and approved the final manuscript. *Justin DeBeer* helped conduct the study, write the manuscript, and approved the final manuscript. *Mitchell Winemaker*, *David Wismer*, *Dinshaw Punthakee*, and *Victoria Avram* helped conduct the study, write the manuscript and reviewed the analysis of the data, and approved the final manuscript.

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Conclusions *This trial indicated that gabapentin treatment had no clinically important reduction in postoperative morphine consumption at 72 hr in patients undergoing THA. Multimodal analgesia may account for the similar primary and secondary outcomes found in the groups. This trial was registered at ClinicalTrials.gov, number: NCT01307202.*

Résumé

Objectif *L'ajout d'une dose unique de gabapentin à la morphine a été étudié dans la gestion de la douleur postopératoire. L'objectif principal était de déterminer si une administration de gabapentin préopératoire et pendant deux jours en postopératoire dans le cadre d'une analgésie multimodale diminuerait la consommation de morphine postopératoire chez des patients subissant une arthroplastie totale de hanche (ATH).*

Méthodes *Le groupe d'étude a inclus 102 patients âgés de 19 à 90 ans subissant une ATH de première intention sur une seule articulation, sans contre-indications pour les médicaments de l'étude, sans syndrome de douleur chronique et utilisation chronique d'opioïdes. Les patients du groupe interventionnel ($n = 48$) ont reçu 600 mg de gabapentin per os en préopératoire et 200 mg en postopératoire le jour de l'intervention. Le gabapentin a été poursuivi à raison de 200 mg trois fois par jour pendant deux jours. Les patients du groupe témoin ($n = 54$) ont reçu un placebo dans les mêmes conditions. En préopératoire, tous les patients ont reçu 30 mg de ketorolac par voie IV et 1000 mg d'acétaminophène per os. En postopératoire, ils ont reçu une analgésie intraveineuse contrôlée par le patient avec de la morphine, ainsi que 15 mg de ketorolac (IV) et 1000 mg d'acétaminophène per os toutes les six heures.*

Résultats *Le critère d'évaluation principal était la consommation moyenne (ÉT) postopératoire de morphine à 72 heures: 55,8 (39,2) mg pour le groupe gabapentin contre 60,7 (37,2) mg dans le groupe témoin (différence des moyennes: −4,91 mg; intervalle de confiance [IC] à 95 %: −21,2 à 11,35; $P = 0{,}550$). Il n'y a pas eu de différences significatives entre les groupes pour ce qui concerne les critères d'évaluation secondaires: scores de douleur, effets indésirables, amplitude de mouvement. La satisfaction des patients au 3^{e} jour était meilleure dans le groupe placebo. La durée d'hospitalisation n'a été plus courte que de façon marginale dans le groupe placebo.*

Conclusions *Cette étude a indiqué que le traitement par gabapentin ne réduisait pas de façon cliniquement importante la consommation de morphine postopératoire à 72 heures chez des patients subissant une ATH. L'analgésie multimodale pourrait être responsable de la similitude des critères d'évaluation principaux et secondaires constatée entre les deux groupes. Cette étude a été enregistrée sur le site www.clinicaltrials.gov: NCT01307202.*

Total hip arthroplasty often causes intense postoperative pain. Various methods have been utilized to alleviate the postoperative pain following this surgery, including preemptive analgesia, intrathecal opioids, epidural analgesia, and intra-articular local anesthesia infusion.[1-3] Substantial doses of opioids through patient-controlled analgesia (PCA) systems often provide the bulk of postoperative analgesia. Opioid use, however, can cause increased morbidity including opioid-related adverse effects such as respiratory depression, nausea, vomiting, constipation, and even death.[4,5] For this reason, there has been a gradual shift towards use of alternative or adjunctive methods of controlling postoperative pain, including multimodal analgesia, which incorporates several classes of drugs in the hope of achieving synergistic analgesia while minimizing side effects from any one class of drug.

One such adjunct is gabapentin, or *2-[1-(aminomethyl)cyclohexyl]acetic acid*, which is a structural analogue of gamma-aminobutyric acid.[6] The pharmacological mechanisms through which gabapentin acts at a cellular level remain incompletely understood, but it is surmised that several mechanisms may contribute to its analgesic effects.[6] Gabapentin selectively binds to the $\alpha_2\delta$ subunit of spinal N-type calcium channels, which is likely its analgesic target.[6-8] Previous clinical studies have shown that 1200 mg gabapentin may reduce primary mechanical allodynia in acute inflammation following a thermal injury.[9] It also prevents development of neuronal sensitization[10] and reverses established neuronal sensitization in healthy volunteers.[11,12] Eckhardt *et al.* demonstrated that a 600 mg dose of gabapentin enhanced the analgesic effect of morphine in healthy volunteers.[13] These results were reproduced by Pandey *et al.*, who found that a 600-mg dose of gabapentin more effectively reduces fentanyl consumption and pain scores than 300-, 900-, or 1200-mg doses when given two hours prior to lumbar discectomy.[14]

The efficacy of gabapentin as an analgesic adjunct for postoperative pain is still being established. There is a general lack of consensus with regards to the dosage, indications, side effect profiles, and comparisons between gabapentin and other available pain medications.[15] A meta-analysis of the administration of preoperative gabapentin for postoperative analgesia revealed that when gabapentin is given preoperatively it decreases pain scores and analgesic consumption during the first 24 hr after surgery.[16] It should also be mentioned that the use of gabapentin for both chronic and acute pain is considered 'off label' use of the drug as its manufacturer did not

receive approval from the US Food and Drug Administration or Health Canada for these indications. As a result, there has been ongoing litigation. To date, Pfizer has handled at least two lawsuits with settlements of $325 million and $190 million (USD), respectively. The plaintiffs in these lawsuits claimed that Pfizer encouraged the off-label use of gabapentin and took steps to keep a generic version of the drug off the market.[A]

Despite evidence supporting the use of gabapentin as a possible analgesic for postoperative pain,[14,17-25] there remains a need to determine its efficacy in reducing opioid consumption in various clinical applications. The objective of this study was to determine whether gabapentin, given preoperatively and continued for two days after surgery, could reduce postoperative morphine consumption and avoid morphine-related side effects in patients undergoing primary total hip arthroplasty.

Methods

The Hamilton Health Sciences/Faculty of Health Sciences REB (October 2007) and Health Canada approved this study. It was registered on ClinicalTrials.gov (April 2009). It was funded in part through the New Investigator Fund Grant awarded by the Hamilton Health Sciences Corporation. The methods used for this study were the same as those in a similar study performed at the same centre that assessed the efficacy of gabapentin as an analgesic adjunct for total knee arthroplasty.[26]

Population

Inclusion criteria

Patients aged 19-90 years who were undergoing primary total joint arthroplasty in a single hip were eligible to participate in the study. These patients were recruited from the preoperative clinic at the Juravinski Hospital in Hamilton, ON, Canada.

Exclusion criteria

Patients were deemed ineligible to participate if they met any of the following criteria: liver or kidney impairment, history of nonsteroidal anti-inflammatory drug (NSAID)-induced asthma, active gastrointestinal bleeding, chronic opioid analgesic usage (other than codeine or oxycodone) to a total of 30 mg of morphine equivalence, chronic steroid usage, drug or alcohol abuse, obstructive sleep apnea unless receiving continuous positive airway pressure treatment, refusal of or contraindication to spinal anesthesia, patients unable to use a PCA pump, patients under insurance from the Workplace Safety and Insurance Board, pregnancy/breast feeding, or allergy to the study medications. Those undergoing revision arthroplasty and/or bilateral joint arthroplasty were also excluded.

Study design

This study was a randomized, double blind, placebo-controlled trial. The randomization was managed by the local pharmacy using www.randomization.com.[B] They used a block randomization method with the block sizes chosen to balance the groups after every ten patients. The research pharmacist, who was not involved in patient assessment, administered the randomization. All patients, anesthesiologists, surgeons, research personnel, and nursing staff were blinded to the randomization scheme.

The study medication was prepared by the hospital's pharmacy. It was packaged in identical capsules containing either gabapentin or placebo and was labelled with the name of the study. These study medication packages were distributed to the research coordinator by the pharmacy on the day of surgery and remained with the patients during their hospitalization. The preoperative dose and postoperative dosages of the study medication were dispensed from these packages. A statistician/methodologist was consulted prior to commencement of the study for recommendations on designing the data collection sheet.

Intervention

The patients were administered 600 mg of gabapentin or placebo and 1000 mg of acetaminophen orally two hours prior to the surgery. They were also given 30 mg ketorolac intravenously. The gabapentin dose was chosen based on previous clinical trials,[13,14] which showed a therapeutic effect of gabapentin at doses of 300-1200 mg, with higher doses associated with more adverse effects. During the intraoperative period, patients received spinal anesthesia using a mixture of fentanyl 20 μg and 0.5% or 0.75% of bupivacaine. The bupivacaine dose was subject to the anesthesiologist's discretion. Patients did not receive any other intrathecal opioids or local infiltration. They were sedated with midazolam and propofol.

On the day of the surgery (day 1), patients were provided with 200 mg of gabapentin or placebo at 6 p.m. Postoperatively, patients received 200 mg of gabapentin or placebo three times a day, 1000 mg of acetaminophen and

[A] www.reuters.com/article/2014/06/02/us-pfizer-neurontin-settlement-iduskbn0ed1is20140602) (accessed November 2014).

[B] www.randomization.com (accessed November 2014).

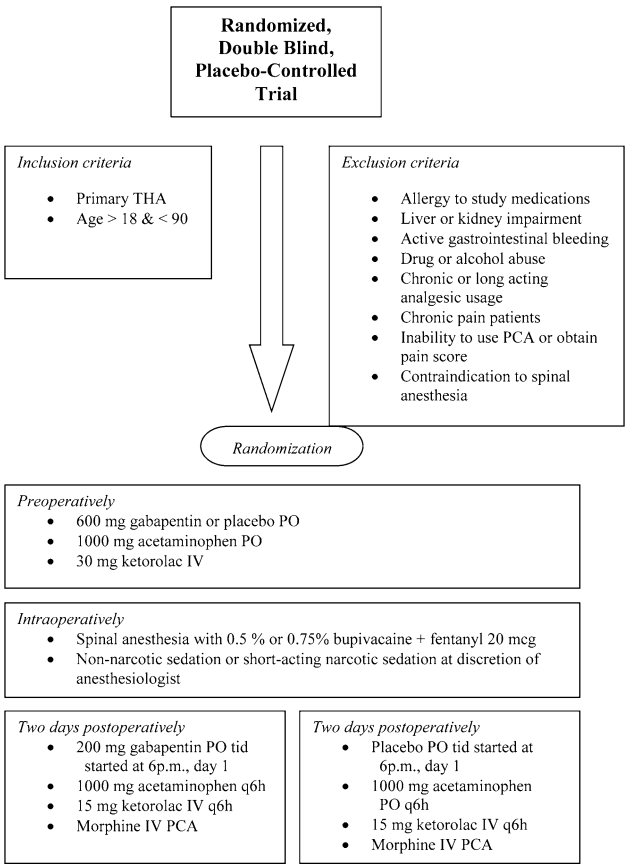

Fig. 1 Summary of methods

15 mg of ketorolac every six hours, and intravenous PCA with morphine. The morphine PCA dose was left up to the anesthesiologist's discretion. The Acute Pain Service usually recommended an initial dose of 1 mg morphine with a ten-minute lockout interval. The postoperative medication regimen, including the PCA, was continued for two days after surgery and was discontinued at 8 p.m. on day 3 (Fig. 1).

Outcome measurements

The primary outcome was cumulative morphine consumption at 72 hr. Secondary outcomes included 1) pain measured with a numerical rating pain scale (0 = no pain to 10 = worst possible pain) at rest, with passive movement, and with weight bearing; 2) incidence of opioid-induced side effects (nausea/vomiting, sedation, pruritus); 3) gabapentin-induced side effects (dizziness/lightheadedness, visual disturbances); 4) patient satisfaction (poor = 1; fair = 2; good = 3; excellent = 4); 5) hip range of motion; 6) hospital length of stay (defined as the interval from time of admission to time of discharge); 7) perioperative hemodynamic and respiratory parameters for which the following parameters applied: bradycardia (heart rate [HR] < 55 beats·min^{-1}, tachycardia (HR > 100 beats·min^{-1}), hypotension (systolic blood pressure [SBP] < 100 mmHg), hypertension (SBP > 160 mmHg), bradypnea (respiratory rate < 10 per min), hypoxia ($SpO_2 < 90\%$). Opioid-induced side effects (nausea/vomiting, pruritus) were rated as follows: 0 = none; 1 = mild – no treatment necessary; (2) moderate – treatment effective; (3) severe – treatment not effective. Sedation was rated as: 0 = alert; 1 = occasionally drowsy; 2 = frequently drowsy, easy to arouse; (3) somnolent, difficult to arouse; (S) normal sleep. The research coordinator assessed the analgesia outcomes daily in the morning. Vital signs were extracted from the nursing flow sheets. Range of motion data were assessed by an orthopedic study nurse.

Sample size determination

We determined that to detect a 50% reduction in morphine consumption in the treatment group at three days with a two-sided level of significance of 5% and a power of 80% we needed a sample size of 36 patients per group. Taking into account anticipated dropouts, we increased the sample size to 50 per group. The 50% reduction in morphine consumption was estimated from previous randomized trials of gabapentin for acute pain.[16,27] This sample size was also based on a baseline morphine consumption of 40 mg·day^{-1}, with a standard deviation (SD) of 30, which was the mean (SD) opioid consumption per day for patients at our institution undergoing total hip replacement.

Statistical analysis

The reporting of this trial was done in accordance with the CONSORT guidelines (www.consort-statement.org).[C] All study data were collected using paper-based case report forms. After the study was completed, the data were scanned into a database using Teleform (iDataFax View, Hamilton ON, Canada). The analysis was performed using STATA 10.1 software (StataCorp., College Station, TX, USA) and SAS 9.2 (SAS Institute, Cary, NC, USA). Our dataset contained both continuous and binary outcomes. Patient demographics and baseline data were described using numbers and percentages. For continuous outcomes (e.g., morphine consumption), treatment groups were compared using Student's two-sample t test. For binary outcomes (e.g., opioid side effects categories), treatment groups were compared using a logistic regression model or Pearson's Chi square statistic (when the outcome incidence was zero in one treatment group). Patient satisfaction was treated as nominal data and compared using a two-sample t-test. Continuous outcomes were displayed using box plots displays (quartile 1, median, and quartile 3). The analysis

[C] www.consort-statement.org (accessed November 2014).

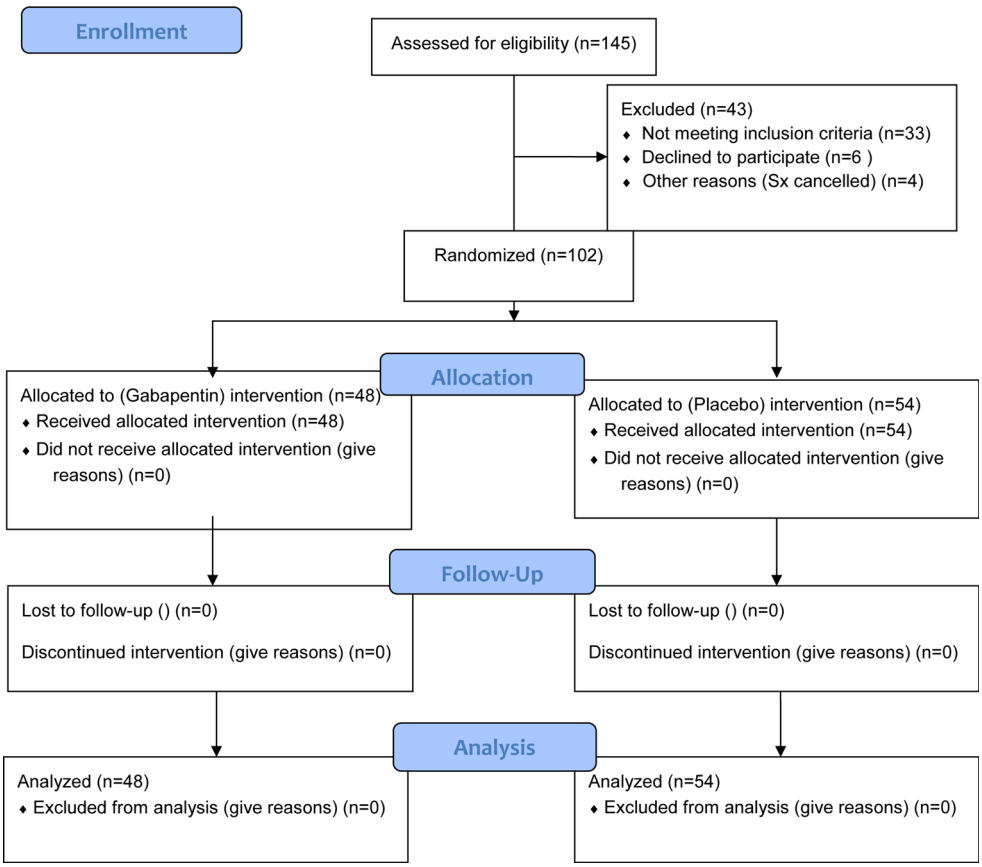

Fig. 2 CONSORT flow diagram: flow of study patients

was performed on an intention-to-treat basis whereby patients were analyzed with respect to the treatment group to which they were randomized regardless of the treatment received. The results of the group comparisons are reported as an estimate of the difference for continuous variables (odds ratio for binary outcomes), corresponding 95% confidence intervals (CIs), and associated *P*-values. All tests were two-sided. *P*-values ≤ 0.05 were considered to indicate statistical significance.

Results

From May 2008 to February 2010, a total of 145 patients were screened upon referral from the patient care team. In all, 43 of these patients either declined to participate or were excluded as per the exclusion criteria. The remainder ($n = 102$) were allocated, following informed consent, to either the gabapentin group ($n = 48$) or the placebo group ($n = 54$) (Fig. 2). The groups were comparable with respect to age, sex, body mass index, and American Society of Anesthesiologists physical status classification at baseline (Table).

Overall, the amount of morphine consumed cumulatively (Fig. 3) at 72 hr was not significantly different between the treatment and control groups. The mean (SD) total morphine consumption for the gabapentin group was 55.8 (39.2) mg *vs* 60.7 (37.2) mg for the control group (mean difference, −4.91 mg, 95% confidence intervals [CI]: −21.2 to 11.35; $P = 0.550$). Furthermore, no clinical significant differences were found between the treatment and control groups regarding the pain scores (Fig. 4), side effects (Fig. 5), or range of motion. The incidence of postoperative hypoxia ($SpO_2\% < 90\%$) was low at 4% in both groups. Patient satisfaction was found to be more favourable in the placebo group – but only on day 3, with a mean difference of 0.34 (95% CI: 0.15 to 0.67) points. The length of hospitalization was somewhat less in the placebo group (4.2 *vs* 4.8 days) with a mean difference of 0.61 day (95% CI: 0.02 to 1.20). A summary of the primary and all of the secondary outcomes collected are shown in the Appendix (available as Electronic Supplementary Material).

Discussion

The objective of this study was to determine whether multiple doses of gabapentin administered preoperatively and for two days postoperatively would help reduce postoperative morphine consumption in patients

Table Patient demographics and baseline characteristics

Parameter	Gabapentin group ($n = 48$)	Placebo group ($n = 54$)
Age (yr)	60.9 (9.1)	60.5 (8.5)
Female sex	20 (41.6)	24 (44.4)
Weight (kg)	89.7 (20.2)	83.1 (14.8)
Height (cm)	171.2 (11.6)	171.30(9.9)
Body mass index	30.5 (6.0)	28.3 (4.4)
ASA classification		
I	2 (4.1)	2 (3.7)
II	23 (47.9)	35 (64.8)
III	21 (43.7)	17 (31.4)
IV	2 (4.1)	0 (0.0)
Arthritic change		
Osteoarthritis	48 (100.0)	54 (100.0)
Rheumatoid arthritis	0 (0.0)	0 (0.0)
Past medical history		
Coronary artery disease	2 (4.1)	1 (1.8)
Hypertension	23 (47.9)	18 (33.3)
Smoker	11 (22.9)	15 (27.7)
COPD	0 (0.0)	3 (5.5)
Cerebral vascular disease	1 (2.0)	0 (0.0)
Sleep apnea	1 (2.0)	2 (3.7)
Asthma	4 (8.3)	1 (1.8)
Diabetes	2 (6.2)	3 (5.5)
Oxygen saturation %	96.9 (2.1)	93.6 (18.8)
Blood pressure 1 mmHg	136.1 (16.7)	133.1 (15.5)
Blood pressure 2 mmHg	83.2 (17.1)	78.9 (7.7)
Heart rate beats·min^{-1}	73.4 (12.9)	71 (12.2)

Data are mean (SD) for interval data and number (%) for categorical data

ASA = American Society of Anesthesiologists; COPD = chronic obstructive pulmonary disease

undergoing total hip arthroplasty. The results of the trial indicated no difference in morphine consumption between the gabapentin and placebo groups. Also, there were no differences in pain scores, opioid side effects, or hip range of motion. Gabapentin treatment did not increase the incidence of either sedation or dizziness. Although gabapentin is not known to have a direct effect on hemodynamics and respiration, these outcomes were assessed because of the drug's anticipated impact on pain and opioid consumption. If gabapentin was successful in reducing pain and opioid consumption, it could lead to more stable hemodynamics and reduced respiratory depression. Although small numerical differences were found in the length of hospitalization, intraoperative hypertension and tachycardia, and patient satisfaction on the third postoperative day, none was clinically significant.

The strengths of this study are that it was conducted at a high-volume arthroplasty centre and that gabapentin was evaluated in a randomized, blinded fashion. This study is one of the largest acute pain gabapentin trials to date. The limitations of the current study are that it focused on short-term analgesia outcomes, and the PCA opioid dose was left to the discretion of the anesthesiologist, which could have created a potential difference between the treatment groups.

The results of this study contrast with other studies and several meta-analyses that demonstrated that gabapentin effectively reduced opioid consumption and pain scores.[16,27,28] Our results, however, are consistent with a recent study by the same investigators on patients undergoing total knee arthroplasty. One of the key differences with both of these studies is that gabapentin was assessed in the context of multimodal analgesia (concurrent acetaminophen and an NSAID). It appears that the adjunctive properties of gabapentin may be negated by other analgesics, and there is a limit to how much you can lower opioid consumption with analgesia adjuncts. Two recent randomized controlled trials of mastectomy patients treated with placebo or gabapentin reconfirmed that gabapentin can reduce pain scores and opioid consumption, although neither of these trials used other regular analgesia adjuncts such as acetaminophen or

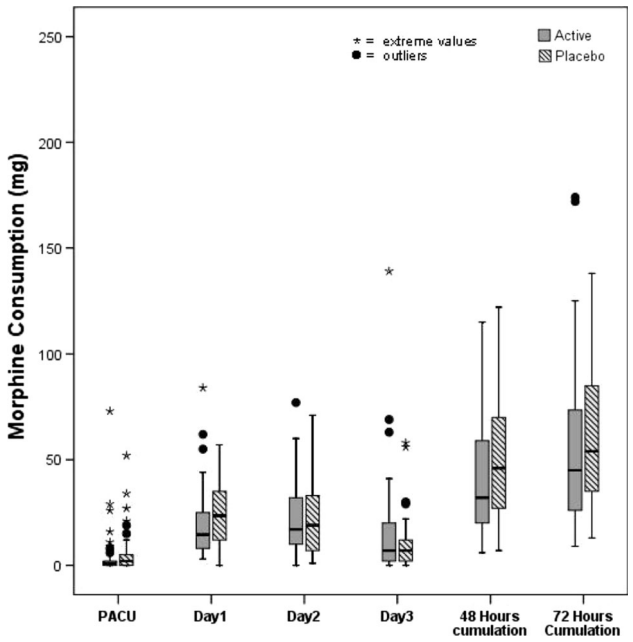

Fig. 3 Morphine consumption through patient-controlled analgesia. There were no significant differences found in morphine consumption between the gabapentin and placebo groups in the postanesthesia care unit (PACU) on the day of surgery (day 1) or postoperatively (days 2 and 3) or in cumulative consumption at 48 or 72 hr

NSAIDs.[29,30] Another recent trial of patients undergoing arthroscopic rotator cuff repair showed mixed results in that gabapentin reduced the pain scores at 24 hr but not opioid consumption.[31] Similarly, gabapentin did not reduce opioid consumption or reduce pain scores in a randomized controlled trial of thoracotomy patients who also received multimodal analgesia with acetaminophen and ketorolac.[32] In the majority of the other, previous studies, the effect on perioperative opioid consumption was evaluated using single-dose gabapentin,[14,17-25] whereas the current study evaluated the effectiveness of multiple-dose gabapentin. Another difference between the gabapentin acute pain trials is the dose of gabapentin used. Dosages have varied among the studies, ranging from a single preoperative dose of 300 mg up to 1800 mg·day^{-1}. We chose this dose because it is commonly used in clinical practice and was proven effective in a recent pilot study.[25] Higher dosages of gabapentin may be necessary when multimodal analgesia is employed.

All patients had access to morphine via PCA, which likely explains the similarity of the pain scores. Even if gabapentin proves to be an effective analgesic adjunct for this surgery, one would expect patients to titrate their morphine to a similar level of analgesia.

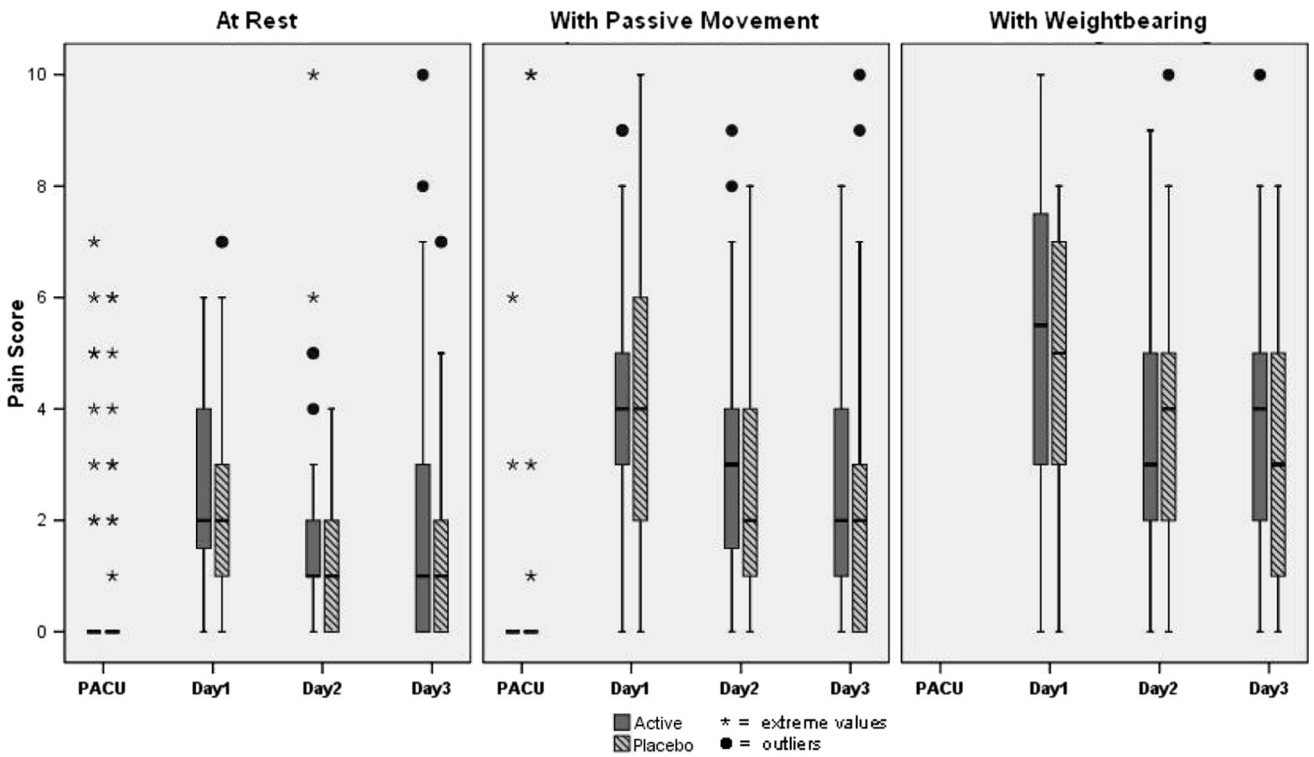

Fig. 4 Pain scores at rest, with passive movement, and with weight bearing. There were no significant differences in pain scores between the gabapentin and placebo groups at any time point

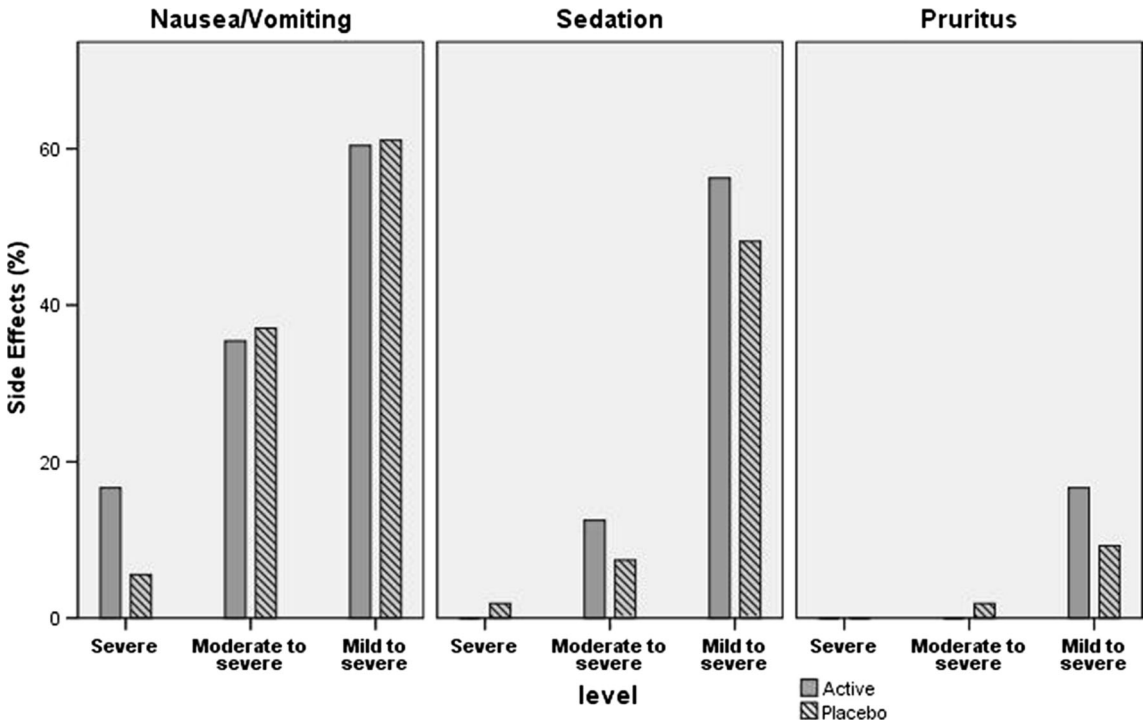

Fig. 5 Side effects (nausea/vomiting, sedation, and pruritus. No significant differences were found between the gabapentin and the placebo groups for the incidences of nausea/vomiting, sedation, or pruritus

In summary, perioperative gabapentin (when started preoperatively and administered as 200 mg *tid* daily for three days) was not shown to be superior to placebo in terms of postoperative morphine consumption, pain scores, or side effects in patients who are treated concurrently with multimodal analgesia (i.e., morphine, acetaminophen, and ketorolac). In the future, larger studies are necessary to investigate gabapentin's impact on side effects (the current and previous trials were powered only for pain and analgesia consumption), potential longer-term impact of gabapentin on functional status, and the incidence of persistent postsurgical pain.

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Competing interests None declared.

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