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REPORTS OF ORIGINAL INVESTIGATIONS

Gabapentin does not improve multimodal analgesia outcomes for total knee arthroplasty: a randomized controlled trial

La gabapentine n'améliore pas l'analgésie multimodale pour l'arthroplastie totale du genou : une étude randomisée contrôlée

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Abstract

Purpose *This study assessed whether gabapentin given preoperatively and for two days postoperatively (in addition to patient-controlled analgesia [PCA] morphine, acetaminophen, and ketorolac) is effective in reducing morphine requirements and moderating pain scores when compared with placebo for primary total knee arthroplasty.*

Methods *This single-centre double-blind randomized controlled trial was undertaken in patients who underwent primary total knee arthroplasty. All subjects received acetaminophen 1,000 mg and ketorolac 15 mg po preoperatively. Postoperatively, subjects received PCA morphine, acetaminophen 1,000 mg every six hours, and ketorolac 15 mg po every six hours. Subjects received either gabapentin 600 mg po preoperatively followed by 200 mg po every eight hours for two days or matching placebo. The primary outcome was cumulative morphine consumption at 72 hr following surgery. Secondary outcome measures included pain scores and patient satisfaction.*

Results *There were 52 subjects in the gabapentin group and 49 subjects in the placebo group. The average cumulative morphine consumption at 72 hr postoperatively was 66.3 mg in the gabapentin group and 72.5 mg in the placebo group (difference −6.2 mg; 95% confidence interval −29.1 to 16.8 mg; $P = 0.59$). Mean pain scores at rest, with passive movement, or with weight bearing were similar in both groups at corresponding time periods for the first three days following surgery. In addition, mean patient satisfaction scores and hospital length of stay were similar in the two groups.*

Conclusion *Gabapentin 600 mg po given preoperatively followed by 200 mg po every eight hours for two days has no effect on postoperative morphine consumption, pain*

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

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scores, patient satisfaction, or length of hospital stay. This trial is registered at ClinicalTrials.gov NCT01307202.

Résumé

Objectif *Cette étude a consisté à déterminer si la gabapentine, donnée en préopératoire et pendant deux jours après l'opération (en addition à de la morphine en analgésie contrôlée par le patient [ACP], de l'acétaminophène et du kétorolac), était efficace pour réduire les besoins en morphine ainsi que pour diminuer les scores de douleur par rapport à un placebo pour une arthroplastie totale du genou.*

Méthode *Cette étude randomisée contrôlée à double insu a été réalisée dans un seul centre, auprès de patients subissant une arthroplastie totale du genou primaire. Tous les patients ont reçu 1000 mg d'acétaminophène et 15 mg de kétorolac po avant l'opération. En postopératoire, les patients ont reçu de la morphine en ACP, 1000 mg d'acétaminophène toutes les six heures et 15 mg de kétorolac po toutes les six heures. Les patients ont reçu soit 600 mg de gabapentine po en préopératoire suivis de 200 mg po aux huit heures durant deux jours, soit un placebo correspondant. Le critère d'évaluation principal était la consommation cumulée de morphine à 72 h après la chirurgie. Les critères d'évaluation secondaires étaient les scores de douleur et la satisfaction des patients.*

Résultats *Le groupe gabapentine comptait 52 patients et le groupe placebo en comptait 49. La consommation cumulée moyenne de morphine à 72 h postopératoires était de 66,3 mg dans le groupe gabapentine et de 72,5 mg dans le groupe placebo (différence −6,2 mg; intervalle de confiance 95 % −29,1 à 16,8 mg; P = 0,59). Les scores moyens de douleur au repos, avec un mouvement passif ou avec un mouvement contre résistance, étaient semblables dans les deux groupes à des points dans le temps correspondants au cours des trois premiers jours postopératoires. En outre, les scores moyens de satisfaction des patients et la durée du séjour à l'hôpital étaient semblables dans les deux groupes.*

Conclusion *La gabapentine 600 mg po en préopératoire suivie de 200 mg po toutes les huit heures pendant deux jours n'a aucun effet sur la consommation postopératoire de morphine, les scores de douleur, la satisfaction des patients ou la durée du séjour à l'hôpital. Cette étude est enregistrée sous ClinicalTrials.gov NCT01307202.*

Osteoarthritis is the most common joint disorder worldwide, with the majority of people showing radiographic evidence by age 65 yr.[1] The prevalence of symptomatic osteoarthritis of the knee is 12% for those aged 60 yr or older.[2] Knee pain is a common complaint for which 0.5-1% of people over age 55 yr seek medical consultation annually.[3] While there is some variability, most surgeons require patients to have severe daily pain and destruction of a significant portion of the joint space on radiograph before they are offered total knee replacement (TKR) surgery.[4] The rate of primary TKR surgery increases with age. It peaks for patients in their 70s and is higher in women than in men.[5] Over 500,000 TKR surgeries are performed in the United States annually, and the procedure rate has increased dramatically from 31 to 221 per 100,000 surgeries since it was introduced over 40 years ago.[6]

Although TKR is indicated for the treatment of pain and disability, the procedure itself is associated with significant postoperative pain. The procedure is considered more painful than many other orthopedic procedures, including total hip replacement.[7] Traditional approaches to postoperative analgesia for TKR involved intravenous patient-controlled analgesia with opioids or epidural analgesia.[8] While effective, these approaches have the disadvantage of exposing the patient to opioid side effects (nausea/vomiting, sedation, pruritus, respiratory depression, and constipation) or epidural side effects (the opioid side effects plus motor blockade, hypotension, urinary retention, and interference with thrombosis prophylaxis therapy because of the risk of spinal hematoma).[9] Regional approaches that allow for unilateral blockade have become increasingly popular. Single-shot femoral nerve blockade has been shown to provide superior analgesia compared with patient-controlled analgesia (PCA) morphine alone and equivalent analgesia to that of continuous femoral block and epidural analgesia. The addition of sciatic nerve block has not been shown to improve outcomes.[10] Lumbar plexus (psoas compartment) block has also proven effective for postoperative analgesia following TKR.[11]

In addition to the primary modes of analgesia, a number of analgesia adjuncts have been shown to improve pain outcomes for joint replacement. Both acetaminophen and nonsteroidal anti-inflammatory drugs reduce pain scores and morphine consumption (by about 30%) after total joint replacement.[12,13] Gabapentin, an anticonvulsant, has an established role in chronic pain management and has been used increasingly in recent years for acute postoperative pain.[14] The mechanism of action of gabapentin is thought to relate to the binding of voltage-gated calcium channels at synapses and not at gamma-amino butyric acid synapses.[15] Meta-analyses that report the role of gabapentin in postoperative analgesia show that it decreases morphine consumption and pain scores following several types of surgery but increases sedation and dizziness.[16-18] In view of these considerations, we undertook a study to determine whether gabapentin, in addition to acetaminophen and ketorolac, administered preoperatively and postoperatively for two days is effective in decreasing morphine consumption, pain scores, and opioid-related side effects following primary unilateral TKA. The primary outcome was cumulative morphine consumption at 72 hr postoperatively.

Methods

This was a single-centre blinded randomized controlled study. Approval was obtained in October 2007 from the Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board, and individual patient written consent was obtained from each participant. The randomization was generated by the local pharmacy using www.randomization.com,[A] incorporating a block randomization method with the block sizes chosen so as to balance the groups after every ten patients. The allocation sequence was managed by the pharmacy and concealed from the outcome assessors. The patients, health care providers, and study personnel were blinded to the treatment allocation, as the study drug and the matching placebo were identical. The study medications were prepackaged in boxes and allocated to study patients according to the randomization sequence.

Participants

Eligible subjects were aged 19-90 yr and scheduled for primary TKA. A research nurse from the Department of Surgery screened patients in the preoperative clinic and obtained their consent. Patients were excluded from the study if they were scheduled for a revision or bilateral arthroplasty and if they had a history of any of the following: renal (creatinine clearance ≤ 60 mL·min^{-1}) or hepatic (alanine aminotransferase, alkaline phosphatase, or bilirubin > the upper limit of normal) impairment; allergy or intolerance to nonsteroidal anti-inflammatory drugs, acetaminophen, morphine, gabapentin, or spinal anesthesia; chronic drug or alcohol abuse; chronic pain syndrome treated with chronic opioids (other than codeine or oxycodone) to a total of 30 mg of morphine equivalence; obstructive sleep apnea not treated with continuous positive airway pressure; seizure disorder; breastfeeding; unable to use patient-controlled analgesia; or unable to provide consent. A consecutive series of eligible subjects was screened and approached to determine if they would participate in the trial. Subsequently, a research nurse approached and recruited those patients who consented to participate. The study took place at the Henderson General Hospital in Hamilton Ontario from May 2008 to March 2010. More than 700 TKRs are performed at this site each year.[19]

All subjects received acetaminophen 1,000 mg *po* and ketorolac 15 mg *iv* two hours preoperatively. At the same time, study participants received the study medication, which was either gabapentin 600 mg orally or matching placebo.

During surgery, patients received a standardized spinal anesthetic with hyperbaric bupivacaine combined with fentanyl and no systemic opioid or local infiltration. The dose and concentration of the spinal medication and the target level of sedation with midazolam and propofol were left to the discretion of the attending anesthesiologist.

Postoperatively, subjects were given intravenous PCA morphine (1-1.5 mg dose, ten minute lockout, and a 20 mg four-hour limit) for three days, acetaminophen 1,000 mg *po*, and ketorolac 15 mg *iv* every six hours. In addition, gabapentin 200 mg *po* every eight hours (600 mg·day^{-1}) or matching placebo were administered for the first two days after surgery.

The primary outcome was cumulative morphine consumption at 72 hr postoperatively. Secondary outcomes included the numerical rating pain score (rated from 0 for no pain to 10 for the worst possible pain) at rest and with passive movement and weight bearing, the incidence of opioid side effects (nausea/vomiting, sedation, and pruritus), gabapentin side effects (dizziness/lightheadedness, and visual disturbances), patient satisfaction (rated as poor, fair, good, or excellent), knee range of motion, and perioperative hemodynamic and respiratory variables (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 breaths·min^{-1}; hypoxia – $SpO_2 < 90\%$). Opioid side effects (nausea/vomiting and pruritus) were rated as follows: 0 = none; 1 = mild – no treatment necessary; 2 = moderate – treatment effective; and 3 = severe – treatment not effective. Sedation was rated as follows: 0 = alert; 1 = occasionally drowsy; 2 = frequently drowsy, easy to arouse; 3 = somnolent, difficult to arouse, and (S) normal sleep. The analgesia outcomes were assessed daily in the morning by the research coordinator. The vital signs data were extracted from the nursing flow sheets, and the range of motion data were obtained from the orthopedic study nurse.

Sample size and statistical considerations

A sample size of 36 patients per group was determined to detect a reduction in morphine consumption by 50% in the treatment group at three days with a two-sided level of significance of 5% and a power of 80%. To account for 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.[16,18] The analysis and reporting of the trial are performed in accordance with the CONSORT guidelines (www.consort-statement.org).[B] All study data

[A] www.randomization.com (last date accessed 01.04.2008).

[B] www.consort-statement.org (last accessed 03.08.2011).

were collected using paper 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 Stata10.1 (StataCorp College Station, TX, USA) and SAS® 9.2 (Cary, NC, USA). The dataset contained both continuous outcomes and binary outcomes. Patient demographics and baseline data were described using number and percentages. For the continuous outcomes (e.g., morphine consumption), treatment groups were compared using Student's two-sample *t* test, and for binary outcomes (e.g., categories of opioid side effects), treatment groups were compared using a logistic regression model and a Chi square test (when the outcome incidence was zero in one treatment group). Continuous outcomes were displayed using box plot displays (quartile 1, median, and quartile 3). The analysis 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 estimates of the difference for continuous variables (odds ratio for binary outcomes), corresponding 95% confidence intervals [CI], and associated *P* values. All reported *P* values are two-sided. The criterion for statistical significance was set *a priori* at alpha = 0.05.

Results

One hundred and forty-five patients were approached to participate in the study. Forty-four of these were excluded and 102 were recruited and randomized to either the gabapentin (52 patients) or placebo (49 patients) treatment group. No patient was lost to follow-up or excluded from the analysis, and no patient's assigned treatment was discontinued early (Fig. 1). Approximately 1,300 patients underwent TKR at our centre during the study period, and about 800 of these were patients with participating surgeons; hence, the screened study sample included about 13% of the total patient population.

The patients were similar with respect to age, sex, body mass index, American Society of Anesthesiologists physical status classification, and medical history (Table 1). The average cumulative morphine consumption at 72 hours was 66.3 mg in the gabapentin group and 72.5 mg in the placebo group (difference −6.2 mg; 95% CI −29.1 to 16.8 mg; $P = 0.59$). At the other time periods, morphine consumption was similar in both groups (Fig. 2). The pain scores at any time period at rest, with passive knee movement, or with weight bearing were similar in the two groups (Fig. 3). In terms of opioid and gabapentin side effects, the total incidence of mild to severe nausea/vomiting

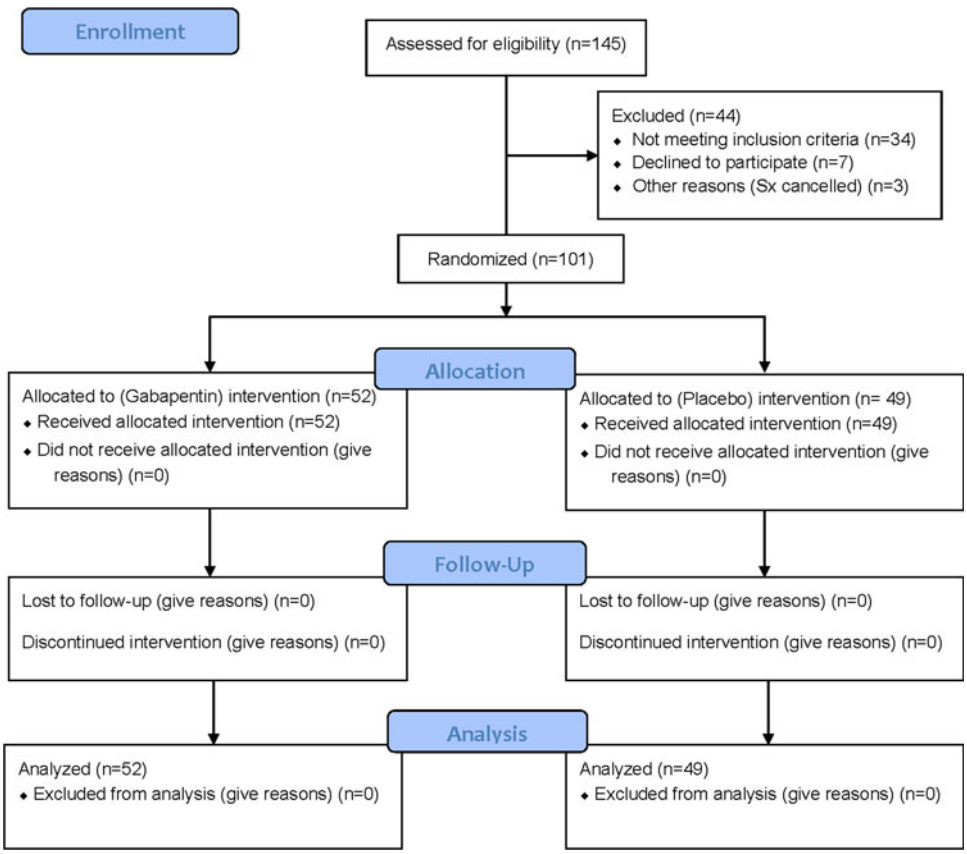

Fig. 1 Patient flow through the study from recruitment to analysis

Table 1 Patient demographics and baseline data

	Gabapentin group ($n = 52$)	Placebo group ($n = 49$)
Age (years), mean (SD)	62.1 (6.4)	63.5 (6.7)
Sex (female), *n* (%)	33 (63.4)	31 (63.3)
Weight (kg), mean (SD)	96.8 (21.2)	93.3 (19.6)
Height (cm), mean (SD)	167.7 (9.4)	168.8 (9.9)
BMI, mean (SD)	34.3 (6.2)	32.9 (6.5)
ASA *n* (%)		
I	1 (1.9)	1 (2.0)
II	17 (32.7)	19 (38.8)
III	32 (61.5)	28 (57.1)
IV	2 (3.9)	1 (2.0)
Arthritic change, *n* (%)		
Osteoarthritis	50 (96.1)	49 (100.0)
Rheumatoid arthritis	1 (1.9)	0 (0.0)
Other	1 (1.9)	0 (0.0)
Medical history, *n* (%)		
Coronary artery disease	4 (7.7)	3 (6.1)
Hypertension	30 (57.7)	22 (44.9)
Smoker	7 (13.5)	13 (26.5)
COPD	1 (1.9)	4 (8.2)
Cerebral vascular disease	1 (2.1)	0 (0.0)
Sleep apnea	4 (7.7)	6 (12.2)
Asthma	4 (7.7)	4 (8.2)
Diabetes	9 (17.3)	3 (6.1)
Oxygen saturation (%), mean (SD)	93.1 (16.5)	97.8 (1.90)
Blood pressure1 (mmHg), mean (SD)	138.1 (16.9)	136.1 (19.3)
Blood pressure2 (mmHg), mean (SD)	79.7 (9.3)	81.4 (12.3)
Heart rate (beats·min^{-1}), mean (SD)	72.5 (10.5)	71.0 (14.9)

BMI = body mass index; ASA = American Society of Anesthesiologists; COPD = chronic obstructive pulmonary disease; SD = standard deviation

was higher in the placebo group than in the gabapentin group (82% *vs* 63%, respectively), and the incidence of moderate to severe pruritus was also higher in the placebo group (16% *vs* 0%, respectively) (Table 2). The incidence of nausea/vomiting requiring treatment (moderate to severe) was lower in the gabapentin group than in the placebo group (42% *vs* 55%, respectively). The incidence of sedation, dizziness, lightheadedness, or visual disturbances appeared similar in both groups. Patient satisfaction ratings were similar for both groups throughout the study period. The knee range of motion at discharge in the gabapentin group was mildly decreased for flexion (97° *vs* 105°, respectively) than in the placebo group but not for extension (3.6° *vs* 2.9°, respectively).

Length of hospital stay was similar for both the gabapentin and placebo groups (3.8 days *vs* 4.4 days, respectively). There were no deaths, and the incidence of other side effects was also similar for both treatment groups. In terms of perioperative hemodynamic and respiratory variables (Table 3), there were no clinically important differences. There was an increased incidence of intraoperative tachycardia for subjects in the gabapentin group (11%) *vs* the placebo group (0%), but mean heart rate values were similar in both groups postoperatively. The incidence of perioperative hypoxia and bradypnea was relatively low (about 10% and 2%, respectively, in the placebo group *vs* 2% and 0%, respectively, in the gabapentin group).

Discussion

This study shows that administration of gabapentin perioperatively (preoperatively and continued for two days postoperatively) with concurrent PCA morphine, acetaminophen, and ketorolac did not reduce morphine consumption or influence pain scores. Since the point estimate for morphine reduction at 72 hr was −6.2 mg (95% CI −29.1 to 16.8), the largest treatment effect would have amounted to about a 10 mg reduction per day, which is of questionable clinical relevance. There was a reduction in overall nausea and vomiting (mild to severe) and moderate to severe pruritus with gabapentin treatment but no reduction in nausea and vomiting that required treatment. Hence, the primary hypothesis for using this drug as an analgesia adjunct (to reduce opioid use and pain) was not supported. Gabapentin treatment was associated with decreased knee flexion at the time of hospital discharge and transient intraoperative tachycardia. Gabapentin treatment did not influence patient satisfaction, hospital length of stay, or other related side effects. While there is ongoing concern regarding gabapentin's sedative effects and the potential to cause dizziness, gabapentin treatment in this study did not increase the incidence of either sedation or dizziness.[14] Although gabapentin is not known to have a direct effect on hemodynamic and respiratory variables, these outcomes were assessed because of the drug's anticipated impact on pain and opioid consumption. While we did not show a reduction in morphine consumption, the incidence of pruritus and nausea (an opioid side effect) was reduced. Given the low incidence of perioperative respiratory depression, this study was likely not powered to detect a difference in respiratory events.[20]

The strengths of this study include the fact that it was conducted at a high volume arthroplasty centre, and gabapentin was evaluated in a blinded fashion in the context of concurrent multimodal analgesia. Apart from the study intervention, the treatment groups were treated similarly regarding anesthetic and perioperative analgesia management. This study also evaluated the potential

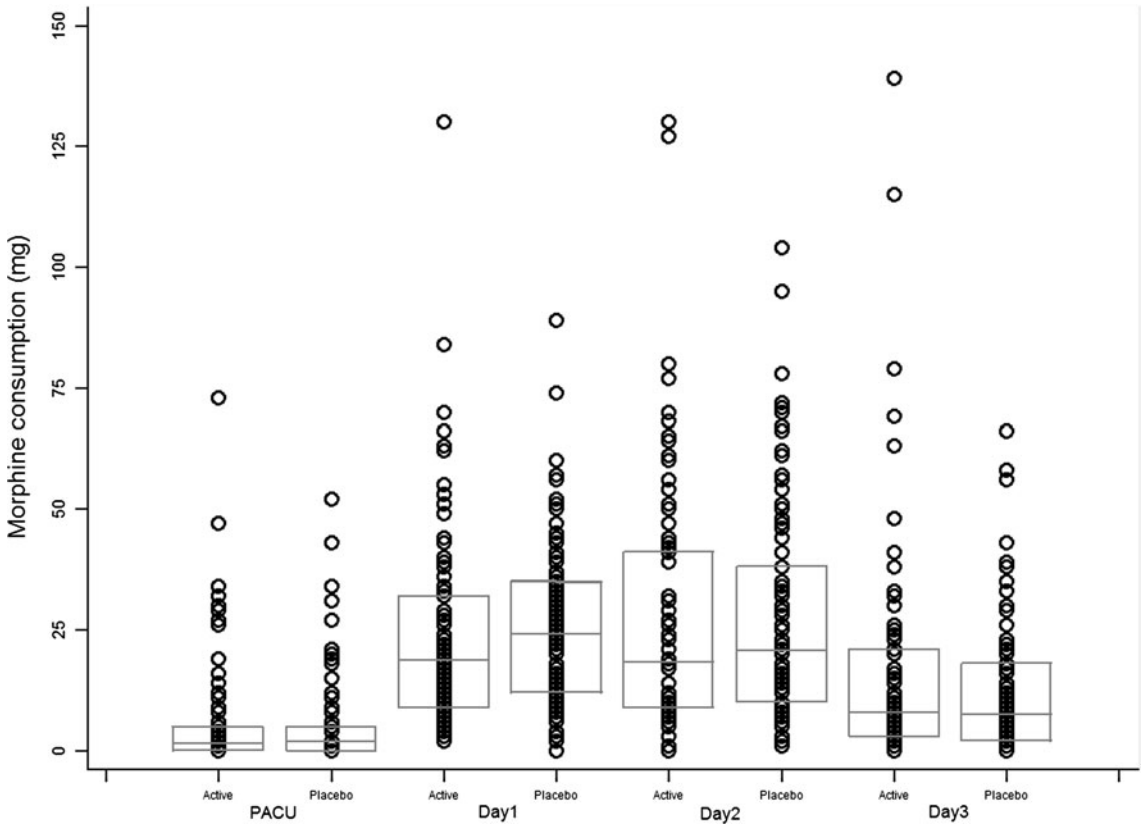

Fig. 2 Morphine consumption via PCA

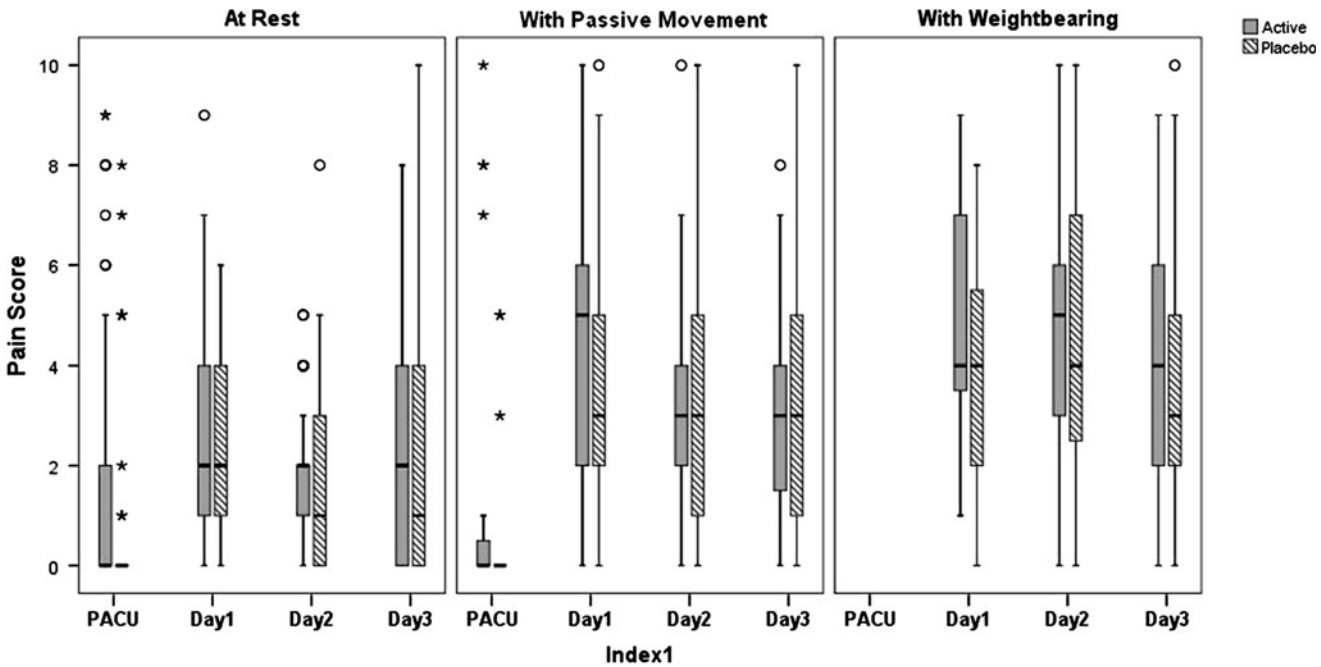

Fig. 3 Pain scores at rest, with passive movement and with weight bearing

impact of gabapentin on perioperative hemodynamic and respiratory variables. The current study is limited by its focus on short-term analgesia outcomes and the fact that there is no assessment of the potential impact of gabapentin on longer-term functional outcomes or on the incidence of chronic post-surgical pain.[21] Further, exclusion of patients

Table 2 Primary and secondary outcomes

	Gabapentin group ($n = 52$)	Placebo group ($n = 49$)	Treatment effect (95% CI)	P value
Primary outcome				
Morphine consumption (mg)				
PACU	6.9 (10.5)	5.7 (10.0)	1.2	
Day 1	27.9 (22.9)	27.0 (19.0)	1.2	
Day 2	30.2 (30.3)	30.1 (22.9)	0.1	
Day 3	17.5 (22.3)	15.5 (16.2)	2.1	
Cumulative at 48 hr	56.5 (48.2)	57.2 (36.6)	−0.7	
Cumulative at 72 hr	66.3 (54.0)	72.51 (47.1)	−6.2 (−29.1, 16.8)	0.59
Secondary outcomes				
Pain scores				
Pain score at discharge from PACU				
At rest	1.7 (2.9)	0.7 (1.9)	1.0	
With passive movement	1.5 (3.2)	0.5 (1.5)	1.0	
Pain scores at rest				
Day 1	2.7 (0.3)	2.2 (1.9)	0.4	
Day 2	1.7 (1.4)	1.7 (1.8)	0.1	
Day 3	2.2 (2.2)	2.0 (2.5)	0.2	
Pain scores with passive movement				
Day 1	4.7 (2.7)	3.7 (2.7)	1.01	
Day 2	3.3 (2.0)	3.6 (2.8)	−0.34	
Day 3	3.2 (2.5)	3.2 (2.6)	0.1	
Pain scores with weight bearing				
Day 1	9.5 (3.0)	8.2 (3.9)	1.32	
Day 2	5.6 (3.4)	5.7 (3.7)	−0.07	
Day 3	4.4 (2.6)	4.1 (2.8)	0.39	
Patient satisfaction good to excellent				
Day 1	3.1 (0.7)	3.1 (0.9)	0.0	
Day 2	3.2 (0.7)	3.1 (0.9)	0.2	
Day 3	3.2 (0.8)	3.2 (0.8)	0.0	
Side effects and morbidity				
Nausea/vomiting				
Mild to Severe	33(63.5)	40 (81.6)	0.4	
Moderate to Severe	22 (42.3)	27 (55.1)	0.6	
Severe	10 (19.2)	8 (16.3)	1.2	
Sedation				
Mild to Severe	35 (67.3)	35 (71.4)	0.8	
Moderate to Severe	11 (21.2)	8 (16.3)	1.4	
Severe	5 (9.6)	3 (6.1)	1.6	
Pruritus				
Mild to Severe	17 (32.7)	20 (40.8)	0.7	
Moderate to Severe	0 (0.0)	6 (12.2)	N/A	
Severe	0 (0.0)	2 (4.1)	N/A	
Dizziness/lightheadedness	29 (55.8)	28 (57.1)	1.0	
Visual disturbance	12 (23.08)	7 (14.3)	1.80	
Death	0 (0.00)	0 (0.0)	N/A	
Other side-effects	22 (42.2)	23 (46.9)	0.8	
Range of motion				
Knee range of motion at discharge				
Flexion, degrees (°)	97.2 (18.8)	105.1 (15.4)	−7.6	
Extension, degrees (°)	3.6 (5.1)	3.0 (4.2)	0.7	
Hospitalization				
Length of stay (days)	3.9 (1.3)	4.4 (1.9)	−0.5	

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

Treatment effect was reported as difference between gabapentin group and placebo group for interval data, and odds ratio for categorical data

Pain score is based on a numerical rating scale (rated from 0 for no pain to 10 for the worst possible pain). Patient satisfaction is rated as poor, fair, good, or excellent

CI = confidence interval; SD = standard deviation; PACU = postanesthesia care unit

Table 3 Perioperative hemodynamic and respiration data

	Gabapentin group ($n = 52$)	Placebo group ($n = 49$)	Treatment effect
Hypotension (SBP < 100 mmHg)			
OR	23 (45.1)	24 (49.0)	0.9
PACU	23 (45.1)	22 (44.9)	1.0
Day 0	13 (25.0)	15 (30.6)	0.8
Day 1	13 (25.0)	11 (22.5)	1.2
Day 2	7 (13.5)	5 (10.2)	1.4
Day 3	0 (0.0)	3(6.1)	N/A
Overall	36 (69.2)	34 (69.4)	1.0
Hypertension (SBP > 160 mmHg)			
OR	14 (27.5)	16 (32.7)	0.8
PACU	2 (3.9)	3 (6.1)	0.63
Day 0	0 (0.0)	1 (2.3)	N/A
Day 1	2 (3.9)	1 (2.0)	1.9
Day 2	1 (1.9)	2 (4.1)	0.5
Day 3	4 (7.7)	4 (8.2)	0.9
Overall	18 (34.6)	20 (40.8)	0.8
Bradycardia (HR < 55 beats·min^{-1})			
OR	15 (28.9)	13 (26.5)	1.1
PACU	15 (28.9)	22 (44.9)	0.5
Day 0	3 (5.8)	5 (10.2)	0.5
Day 1	0 (0.0)	1 (2.3)	N/A
Day 2	0 (0.0)	0 (0.0)	N/A
Day 3	0 (0.0)	0 (0.0)	N/A
Overall	23 (44.2)	25 (51.0)	0.8
Tachycardia (HR > 100 beats·min^{-1})			
OR	1 (1.9)	1 (2.0)	0.9
PACU	1 (2.0)	2 (4.1)	0.5
Day 0	6 (11.5)	0 (0.0)	N/A
Day 1	4 (7.7)	3 (6.1)	1.3
Day 2	9 (17.3)	6 (12.2)	1.5
Day 3	10 (19.2)	6 (12.2)	1.7
Overall	16 (30.8)	13 (26.5)	1.2
Bradypnea (RR < 10 breaths·min^{-1})			
OR	0 (0.0)	0 (0.0)	N/A
PACU	0 (0.0)	1 (2.1)	N/A
Day 0	0 (0.0)	0 (0.0)	N/A
Day 1	0 (0.0)	0 (0.0)	N/A
Day 2	0 (0.0)	0 (0.0)	N/A
Day 3	0 (0.0)	0 (0.0)	N/A
Overall	0 (0.0)	1 (2.1)	N/A
Hypoxia (SpO_2 < 90%)			
OR	0 (0.0)	0 (0.0)	N/A
PACU	0 (0.0)	0 (0.0)	N/A
Day 0	1 (1.9)	1 (2.1)	0.9
Day 1	0 (0.0)	2 (4.1)	N/A
Day 2	0 (0.0)	2 (4.1)	N/A
Day 3	0 (0.0)	1 (2.1)	N/A
Overall	1 (1.9)	5 (10.2)	0.2

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

OR = operating room; SD = standard deviation; PACU = postanesthesia care unit; SBP = systolic blood pressure; RR = respiratory rate; HR = heart rate; SpO_2 = pulse oximetry; CI = confidence interval

with chronic pain may have eliminated a patient group who might have benefited from this analgesia adjunct.[14] Lastly, although the study sample represents a select proportion of the total population of patients who underwent TKR during the study period, there is a possibility that our study patients may not have been a representative sample of the total population of patients, and thus, our results may not be generalizable to that population.

Our results contrast with the results of other studies and several meta-analyses which show that gabapentin is effective in reducing opioid consumption and pain scores.[16-18] While it is not entirely clear why gabapentin was not an effective adjunct for primary TKA when compared with other studies, there is considerable heterogeneity in terms of timing and dose of gabapentin in previous trials. To date, the dose of gabapentin studied has varied from a single preoperative dose of 300-1,200 mg to 1,800 mg·day^{-1} for 48 hr.[17] For our study, we chose 200 mg every eight hours or 600 mg·day^{-1}. We selected this dose as it was used commonly in clinical practice and was shown to be effective in a recent pilot study.[22] Further, this study is differentiated by the use of gabapentin concurrently with acetaminophen and ketorolac as analgesia adjuncts. A number of studies in the meta-analyses do not report the use of analgesia adjuncts in addition to gabapentin. It is possible that the incremental benefit of gabapentin is negated by the impact of multimodal analgesia whereby there is no further room to decrease opioid consumption or pain scores. In a recent randomized trial by Clarke *et al*. involving the use of perioperative gabapentin in 36 patients undergoing primary TKA, the results showed a reduction in morphine consumption for up to 48 hr but no reduction in pain scores.[22] Like our study, results of the trial by these investigators also showed a reduction in the incidence of pruritus in the gabapentin group. This study differed from ours in that patients were treated with preoperative femoral and sciatic nerve blocks, and the dose of gabapentin ranged from 300-900 mg·day^{-1} depending on the treatment group. Beyond some differences in methodology (different gabapentin regimens, the use of regional blocks, and no acetaminophen use) the differences in the

results of this study may have been partially due to the fact that the study was not double-blinded. Morphine consumption could be influenced by the PCA dosage and lockout used, and knowing that a patient received gabapentin could possibly have influenced the decision regarding the PCA dosage of morphine to administer.[23]

In summary, we failed to show that gabapentin is an effective analgesia adjunct (in terms of reducing opioid consumption and pain scores) for patients undergoing primary TKA in the context of multimodal analgesia. While results of our study did show a reduction in mild nausea (not requiring treatment) and moderate to severe pruritus, this positive benefit may not be sufficiently compelling to recommend this drug for this indication. Further studies are necessary to investigate the potential longer-term impact of gabapentin on functional status and the incidence of chronic pain.

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