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ORIGINAL RESEARCH

Does Gabapentin Affect Pain Control and Functional Outcome after Total Knee Arthroplasty? A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Introduction: Gabapentin has been used successfully for perioperative pain control in orthopedic, general, cardiothoracic, breast, and spine surgeries. The goal of this study was to determine if perioperative gabapentin reduced postoperative pain and narcotics consumption in patients undergoing total knee arthroplasty (TKA). The purposes of this study were to determine whether 1) gabapentin affected pain control in TKA, and 2) gabapentin affected functional outcomes in TKA.
Methods: Fifty patients were randomized to receive either 600 mg gabapentin or a placebo preoperatively, and either 300 mg gabapentin or placebo postoperatively every 8 hours for 3 days. Postoperatively, patients were asked to rate their pain on the visual analogue scale (VAS) twice daily, narcotics consumption was recorded each day, and patients were asked whether they felt rested or tired upon waking. Knee range of motion (ROM) was recorded twice daily. Narcotics consumption was recorded as morphine dose equivalents (MDE).
Results: Patients in the gabapentin group had significantly lower narcotics consumption than the placebo group on postoperative days 1 and 2 (p=0.014, p=0.037). The groups did not show a significant difference between narcotics consumption on postoperative day 0 (p=0.136). There were no significant differences in pain VAS scores, knee ROM, or feeling rested versus tired at any time points.
Discussion: Perioperative use of gabapentin significantly reduces narcotics consumption on postoperative days 1 and 2 after primary, unilateral TKA. Perioperative use of gabapentin had no significant effect on narcotics consumption on postoperative day 0. Perioperative use of gabapentin had no significant effect at any time point on pain VAS score, knee ROM, and restfulness.
Level of Evidence: I; Randomized controlled trial.
Keywords: Gabapentin; Total knee arthroplasty; Pain control; Functional outcome.

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INTRODUCTION

By 2030, the demand for total knee arthroplasty (TKA) is projected to grow 673%, equal to about 3.48 million procedures [1]. Controlling pain in these patients is

paramount in order to obtain the best surgical outcome. Decreasing pain and narcotics consumption postoperatively allows patients to recover faster and with a better functional outcome [2].

Pain control after total joint arthroplasty has made drastic changes over the past 25 years. Currently, there are many narcotic and nonnarcotic modalities on the market; however, they have yet to be proven in a randomized fashion for TKA [2-4]. A literature search on postoperative pain control after TKA yields numerous studies, each claiming to be a useful regimen for pain control. However, few of these studies are blinded, randomized controlled trials comparing different pain control modalities and their effect on patient outcomes. Because there is no current standard of care for pain control, with TKA, each surgeon develops his or her own multimodal approach based on their experience. Numerous retrospective studies have been performed by individual surgeons describing their approach to pain control and most of them conclude that their method is effective for their patient population [5].

In further studies, gabapentin has been shown to be a useful modality for nonnarcotic pain control. These studies have shown that a single dose of gabapentin preoperatively reduces pain significantly for up to 24 hours postoperatively [6,7]. In addition, administering gabapentin in the acute postoperative setting has resulted in improved pain control and functional outcomes [8]. A previous randomized controlled study performed in Canada and Holland demonstrated significantly decreased morphine consumption postoperatively and improved knee range of motion (ROM) when gabapentin was administered in patients undergoing primary, unilateral TKA. This same study showed gabapentin dosed as low as 300 mg contributed to significant results [9]. A double-blinded, randomized controlled trial showed that giving 300 mg of gabapentin orally at bedtime significantly reduced the number of awakenings overnight and improved patients' overall sleep and function [10]. Citing this study as well as others, the American Academy of Orthopaedic Surgeons lists 300 mg of gabapentin orally at bedtime as their recommendation for all patients undergoing TKA in order to help both sleep and pain control.

In the United States, there have been no randomized controlled studies comparing gabapentin with functional outcome and narcotics consumption in the postoperative period of TKA. The aim of our prospective, randomized, double-blind, placebo-controlled clinical trial was to prove that gabapentin can aid in reducing narcotics consumption and decreasing pain after unilateral, primary TKA. Our secondary goal was to assess whether gabapentin after TKA would aid in functional outcomes, such as postoperative knee ROM and restfulness.

MATERIALS & METHODS

Study Design

This study was a prospective, randomized, double-blind, placebo-controlled trial comparing postoperative pain and narcotic usage in patients undergoing a unilateral, primary TKA. This study was approved by the Clinical Research Institute at Texas Tech University Health Sciences Center and registered at *www.clinicaltrials.gov* (NCT01680549). Prior to surgery, each patient received written and oral informed consent with information regarding the risks and benefits of surgery, purpose of the study, and the side

effects of both the placebo and gabapentin.

Inclusion criteria were age greater than 25 years; diagnosis of primary osteoarthritis of the knee; undergoing unilateral, primary TKA; and defined as American Society of Anesthesiologists (ASA) class I, II, or III. The exclusion criteria were severe joint malalignment greater than 20 degrees of varus or valgus, use of gabapentin preoperatively, history of chronic pain defined as currently receiving treatment from a pain specialist, patients currently taking narcotic pain medications prior to surgery, history of substance abuse of narcotics or alcohol, impaired kidney function defined as baseline creatinine greater than 1.5, history of epilepsy, known allergy to gabapentin, history of depression or suicidal ideations, and any person contraindicated for general anesthesia.

Fifty patients were enrolled in the study between October 2012 and December 2015 (Figure 1). Thirteen were withdrawn from the study. Four patients failed to receive a preoperative dose of the study drug; 3 patients asked to be withdrawn from the study on postoperative day 1; 1 patient claimed to be allergic to gabapentin and was withdrawn from study after receiving the preoperative dose of the study drug; 1 patient developed a small bowel obstruction requiring a nasogastric tube for decompression; 1 patient was unable to swallow the study drug; 1 patient admitted to daily narcotic usage postoperatively; 1 patient had a painful traumatic Foley insertion; and 1 patient developed postoperative vasovagal syncope and was withdrawn for concern of this being a side effect of the study drug. The patients were divided into 2 groups by an unblinded pharmacist on a 1-to-1 basis using the randomization software Random Allocation Software (version 1.0 developed by M. Saghaei, MD). Table 1 represents the participants' mean age at the time of their surgery, mean body mass index (BMI), the ratio of ASA classes in each group, and the ratio of men to women in each group. The pharmacist prepared the drugs for the placebo and gabapentin study groups. The patients and primary investigators were blinded to the study groups. The size, shape, and color of the drugs given were similar.

Perioperative Protocol

General endotracheal anesthesia was implemented for all patients in the study. Intraoperative anesthesia was controlled with desflurane and supplemented with fentanyl only when needed for pain control during the procedure. The amount of volatile anesthesia and opioids used intraoperatively was titrated to the patient's weight and age while maintaining balance with respect to any existing medical comorbidities. At the completion of surgery, general endotracheal anesthesia was discontinued and the patients were extubated after spontaneous ventilation was established. Postoperatively, the patient was transferred to the postanesthesia care unit where they were allowed to recover until they were stable and coherent enough to be transferred to the floor. Preoperatively, each group received 200 mg of celecoxib orally, 1000 mg of acetaminophen intravenously, and 10 mg of oxycocdone orally. Intraoperatively and prior to placement of the permanent implants, each group received a capsular block using ketorolac 15 mg, morphine 2 mg, ropivicaine 1% 20 mL, and epinephrine 0.3 mg. Postoperatively, each group received a femoral nerve block using 0.5% ropivicaine for 1 day, administered by our department of anesthesia, scheduled acetaminophen 1000 mg intravenously every 6 hours for 4 doses, tramadol 50 mg orally every 6 hours as needed, while

receiving acetaminophen intravenously, hydrocodone 7.5/325 or 7.5/500 orally every 4 to 6 hours as needed for pain, and hydromorphone 0.5 to 1.0 mg intravenously every 2 hours as needed for pain. The preoperative, intraoperative, and postoperative medications are the primary investigators' standard of care.

Study Drug Administration

The study group received gabapentin 600 mg orally within 2 hours before surgery and gabapentin 300 mg orally every 8 hours postoperatively for 3 days. The control group received a placebo orally within 2 hours before surgery and a placebo orally every 8 hours postoperatively for 3 days.

Postoperative Management

A standard postoperative physical rehabilitation protocol was initiated on the day of surgery, postoperative day 0. A certified physical therapist saw the patient 2 to 3 times daily. During a therapy session, the therapist

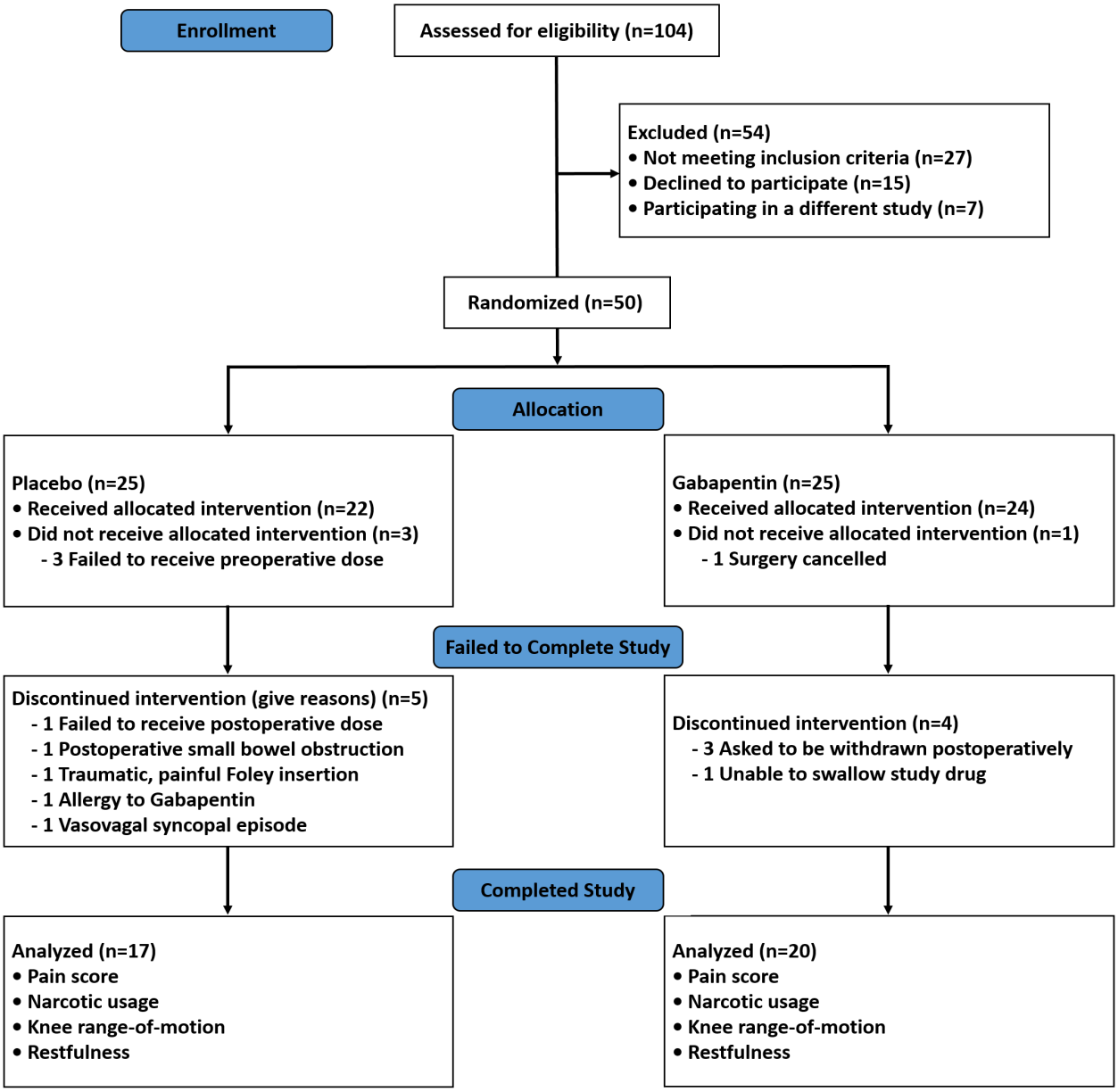

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

Table 1. Demographic Data for Placebo and Gabapentin Groups.

Parameter	Placebo (n=17)	Gabapentin (n=20)	P Value
Men:Women	7:10	9:11	0.82
Mean age (SD) (yrs)	63 (11)	61 (10)	0.63
Mean BMI (SD) (kg/m^2)	33.7 (5.7)	33.8 (5.8)	0.97

works with the patient on knee ROM, gait training, and hamstring and quadriceps strengthening. Patients were discharged when pain was controlled and after approval of a physical therapist. Based on physical therapy recommendations, patients were discharged to either their home with home physical therapy, an inpatient rehabilitation center, or a skilled nursing facility. All patients were discharged with hydrocodone 7.5/325 or 7.5/500 tablets, 1 to 2 tablets by mouth every 4 to 6 hours as needed for pain with 4 refills.

Outcome Measures

Data collection began in the hospital on postoperative day 0. On postoperative days 0, 1, and 2, self-reported pain scores were collected based on visual analog scale (VAS) scores. In addition, narcotic pain medication consumption was recorded, as well as whether or not the patient felt rested or tired upon waking. Postoperative knee ROM based on physical therapy notes was recorded as well. VAS scores were recorded by having the patient make a mark on a continuous line 100 mm long. The far left end was marked as "No Pain"; the far right end was marked as "Very Severe Pain." The mark was measured in millimeters from the left end of the scale and recorded as the patient's VAS score. Narcotic usage was reported in morphine dose equivalents (MDE) based on a conversion using a morphine dose equivalent calculator. The conversion was milligrams of hydromorphone intravenously and milligrams of hydrocodone orally into milligrams of morphine intravenously. The equianalgesic ratios were 1 mg hydromorphone intravenously equates to 6.67 mg morphine intravenously, and 1 mg hydrocodone orally equates to 0.33 mg morphine intravenously [11]. Restfulness was recorded by asking patients to choose whether they felt rested or tired upon waking. Knee ROM was recorded from physical therapist notes and reported as arc of ROM in degrees.

Statistical Methods

Statistical analysis was performed using StataSE 13.1 (College Station, TX). An initial power analysis determined that to achieve a 30% change in VAS scores, we would need 34 subjects in each group, 68 subjects total. Assuming an average 5% dropout rate, we planned on enrolling 72 patients for this study. Sample size estimates for the comparison of the mean VAS scores were calculated using the 2-sample *t*-test formula and incorporated the following assumptions: Alpha = 0.05, power = 80%, mean of the control group = 45 with standard deviation = 17, as previously reported [7]. We performed a midpoint analysis of our data through 50 patients, showing a statistically significant difference with a large effect size between the groups with regards to narcotic usage on postoperative days 1 and 2. Given this

significant difference along with a large effect size, the study was discontinued.

Wilcoxon matched-pairs signed-ranks test was used to compare changes from days 0, 1, and 2 within groups in all outcome variables, and Kruskal-Wallis Rank Test was used to compare differences between groups at each time point in regards to MDE, VAS scores, and knee ROM. Additionally, chi-squared and risk ratios were calculated for the risk of poor sleep quality. Significance level was set at 0.05. Pain scores, narcotics consumption, and knee ROM were summarized as mean ± SD. Sleep quality was summarized as frequency and percentage of patients that awoke rested or tired.

Sources of Funding

There was no external funding source for our study.

RESULTS

Thirty-seven patients were included in the final analysis: 17 received placebo and 20 received gabapentin. No patients were found to have adverse side effects directly related to the gabapentin or placebo drugs. A summary of outcomes for the placebo and gabapentin groups can be found in Table 2. There was no significant difference between groups in narcotics consumption on day 0 (χ^2=2.23, p=0.136). There was a significant difference between groups in narcotics consumption on days 1 (χ^2 =6.07, p=0.014) and 2 (χ^2=4.33, p=0.037) (Figure 2). Patients in the placebo group consumed 25.02 (17.28) MDE and 21.62 (17.28) MDE on postoperative days 1 and 2, respectively, while patients in the gabapentin group consumed 11.53 (13.9) MDE and 11.61 (10.78) MDE. The effect size (Cohen's d) on postoperative days 1 and 2 (day 1: 0.73; day 2: 0.71) was large with respect to narcotic consumption. Both placebo and gabapentin groups increased significantly in narcotic usage from day 0 to day 1 (placebo: z=–3.57, p<0.001; gabapentin: z=–2.76, p=0.006), and from day 0 to day 2 (placebo: z=–3.41, p<0.001; gabapentin: z=–3.14, p=0.002). There were no significant differences found in subjective pain perception at any time points (day 0, p=0.548, day 1, p=0.255, and day 2, p=0.579) based on VAS scores (Figure 3). There was no significant difference in knee ROM between groups at any time points (day 0, p=0.234; day 1, p=0.476; day 2, p=0.792) (Figure 4).

Table 2. Demographic Data for Placebo and Gabapentin Groups.

	Placebo (n=17)			Gabapentin (n=20)		
	Day 0	Day 1	Day 2	Day 0	Day 1	Day 2
Morphine (mg)	7.4±9.03	25.02±22.8	21.62±17.28	4.16±9.02	11.53±13.9	11.61±10.78
Pain (VAS)	33.6±26.3	34.9±26.6	38.0±15.9	40.0±26.1	46.3±30.5	39.6±28.8
ROM (degrees)	53.12±17.72	66.81±20.54	67.47±23.13	57.85±17.7	62.74±19.44	65.94±15.2
Sleep						
Rested, n (%)	6 (35.3)	9 (52.9)	10 (58.8)	11 (55)	15 (75)	13 (65)
Tired, n (%)	11 (64.7)	8 (47.1)	7 (41.2)	9 (45)	5 (25)	7 (35)

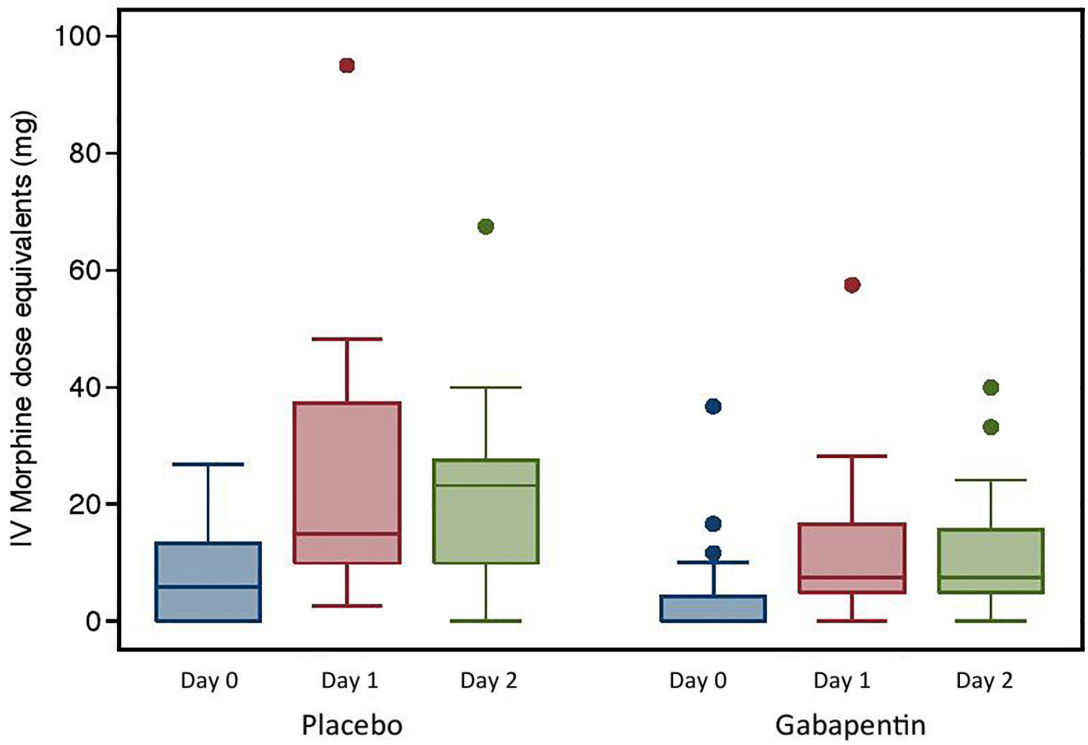

Figure 2. Box plot comparing morphine dose equivalents between groups on postoperative days 0, 1, and 2. Lines in the middle of the boxes represent median, boxes represent 25th and 75th percentiles, whiskers indicate 95% confidence interval, and dots represent outliers.

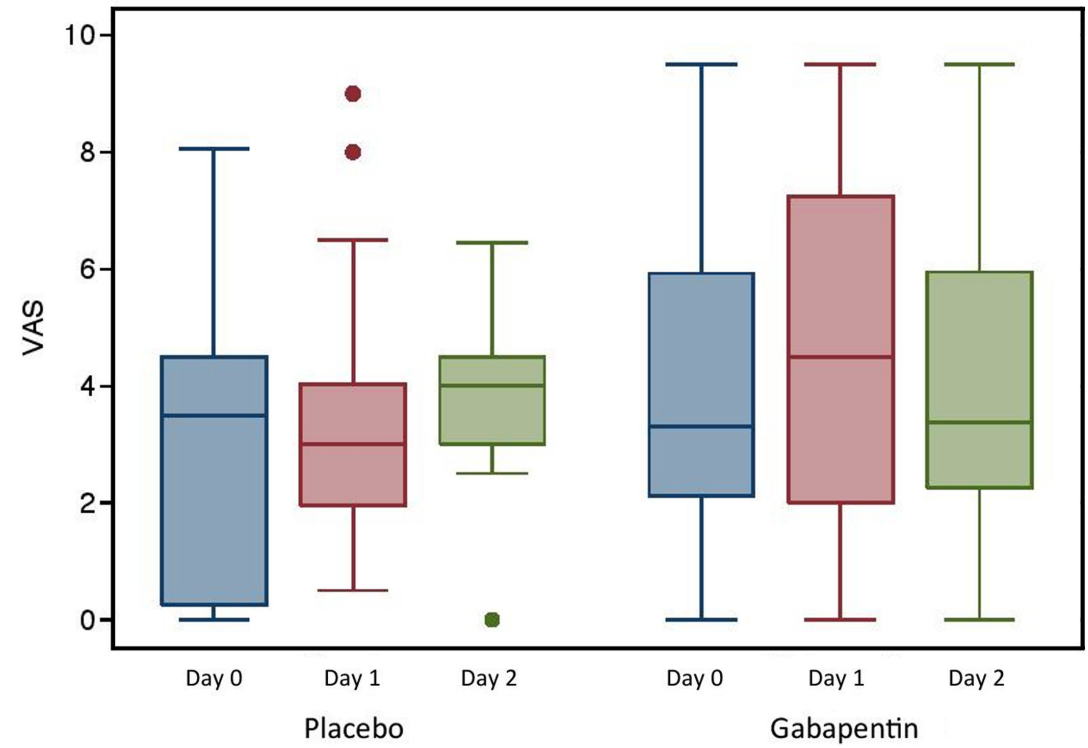

Figure 3. Box plot comparing visual analogue scale scores between groups on postoperative days 0, 1 and 2. Lines in the middle of the boxes represent median, boxes represent 25th and 75th percentiles, whiskers indicate 95% confidence interval, and dots represent outliers.

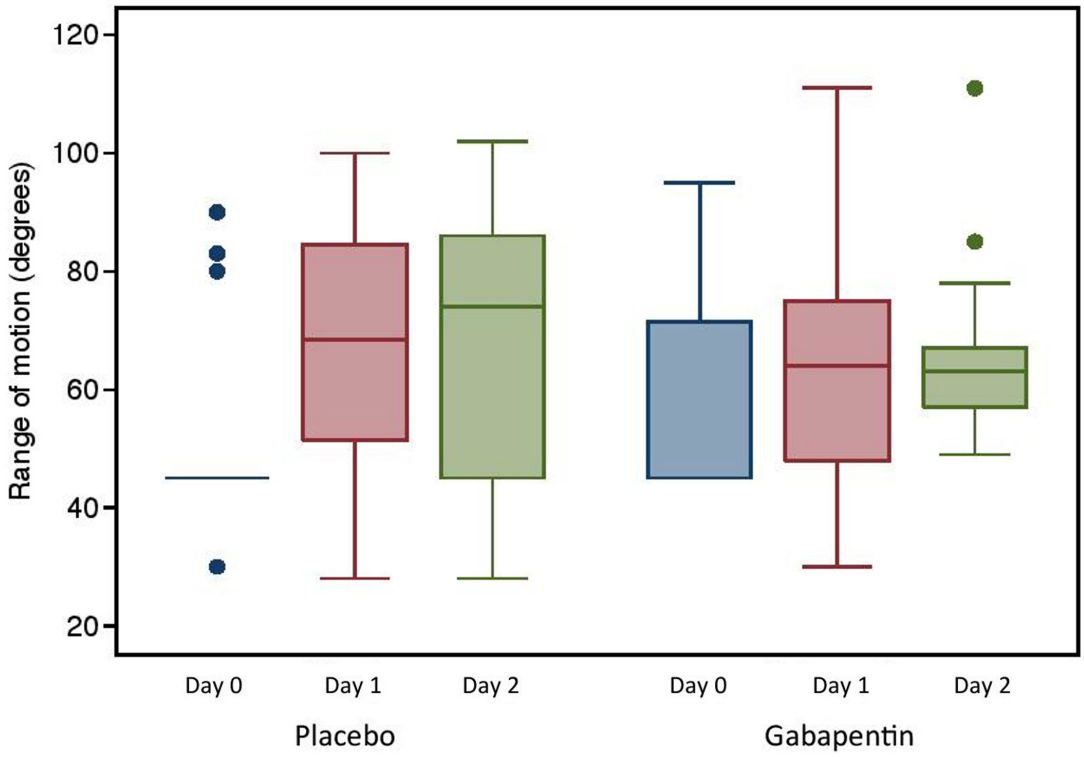

Figure 4. Box plot comparing knee range of motion between groups on postoperative days 0, 1 and 2. Lines in the middle of the boxes represent median, boxes represent 25th and 75th percentiles, whiskers indicate 95% confidence interval, and dots represent outliers.

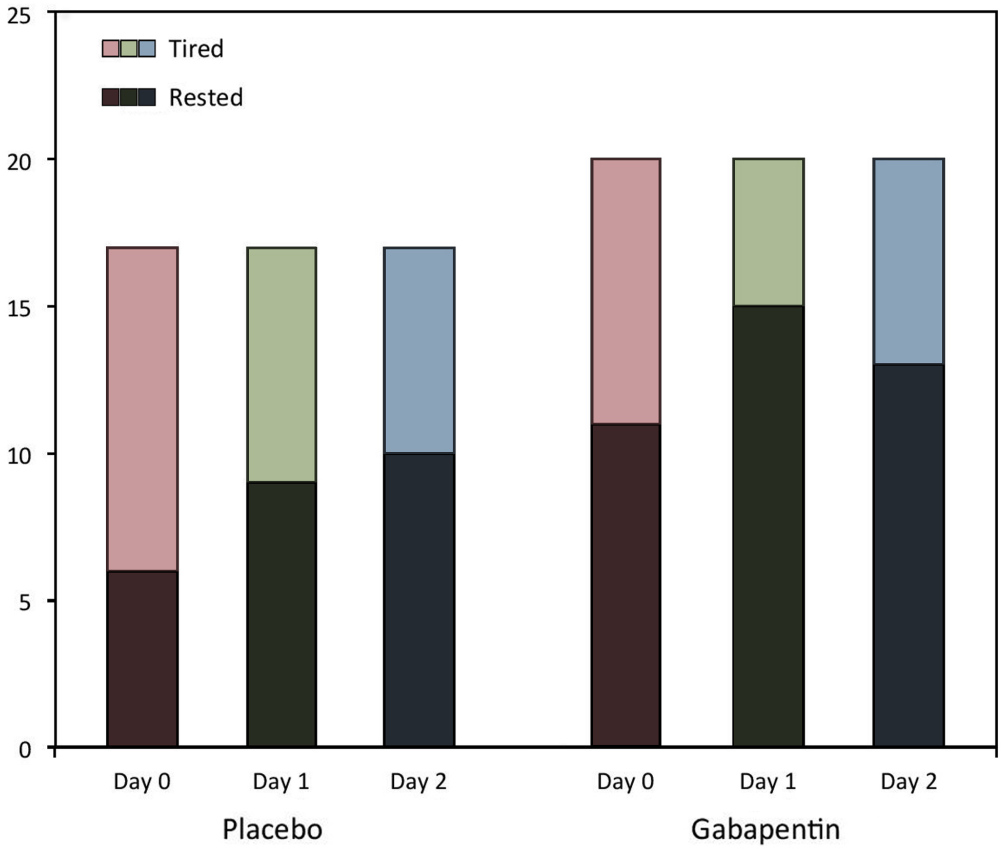

Figure 5. Comparison between groups of number of patients self-reporting feeling rested or tired upon awakening on postoperative days 0, 1 and 2.

There were no differences in self-reported sleep quality between groups at day 0 (RR=0.69, 0.38-1.26, p=0.231), day 1 (RR=0.53, 0.21-1.32, p=0.161), and day 2 (RR=0.85, 0.37–1.93, p=0.699) (Figure 5).

DISCUSSION

This prospective, randomized, double-blind, placebo-controlled trial showed a statistically significant difference in narcotics consumption between groups on postoperative days 1 and 2 after primary, unilateral TKA. There was no difference in narcotics consumption shown on postoperative day 0, which, after further consideration, is not unexpected as all patients received a 24-hour femoral nerve block per the primary investigators' protocol. There was no significant difference at any time point between groups with regards to postoperative subjective pain scores, knee ROM, and self-reported sleep quality.

The exact mechanism of action of gabapentin remains unknown. Several hypotheses proposed for its nociceptive role are that gabapentin increases the concentration and probably the rate of synthesis of GABA in the brain; gabapentin reduces the release of several monoamine neurotransmitters; gabapentin increases serotonin concentrations in the blood [12].

To our knowledge, this is the first prospective, randomized controlled trial involving gabapentin in pain control for patients undergoing primary, unilateral TKA in the United States. A similar study in Denmark investigating the use of gabapentin in TKA for perioperative pain control showed no differences in narcotics usage or VAS among groups, but did show that patients receiving gabapentin reported feeling more rested and reported higher levels of dizziness [13]. Pandey et al. [14] conducted a prospective, randomized controlled trial in patients undergoing lumbar discectomy using various doses of gabapentin preoperatively. They found that patients receiving the FDA's lowest recommended dose of gabapentin preoperatively, 300 mg, had significantly lower VAS scores and consumed less narcotics in the first 24 hours postoperatively [14]. A review article by Clivatti et al. [8] looked at 26 various studies involving the use of gabapentin perioperatively for pain control. Their review showed that a single dose of gabapentin improves pain control for 24 hours postoperatively in several different types of surgeries; however, orthopedic surgery was not represented in this article [8].

While there remains no universally accepted postoperative pain control protocol for TKA, it is widely believed that a multimodal approach is more effective. One prospective study involving pain control with TKA compared periarticular injections to patient-controlled epidural anesthesia and femoral nerve block (PCEA/FNB) [15]. The study showed that the only difference between the 2 groups was that patients in the PCEA/FNB group had less pain with ambulation. This study also showed that the periarticular injection group experienced similar pain but had fewer side effects compared to PCEA/FNB group, specifically respiratory depression, nausea, vomiting, ileus, urinary retention, hypotension, and cognitive changes [15]. A study in spine surgery showed that patients who received a multimodal approach of perioperative oral agents including gabapentin had less opioid consumption, lower pain ratings, and experienced

less drowsiness and nausea than patients receiving intravenous, patient-controlled analgesia alone [16]. In a retrospective study comparing multimodal, pre-emptive analgesia to postoperative analgesia alone after total joint arthroplasty, patients in the multimodal group had a significantly decreased length of hospital stay, experienced less nausea, used less intravenous narcotics, were less likely to miss physical therapy sessions, and were less likely to be discharged to an extended care facility [17].

One concern when performing investigative drug studies is the potential side effects of the drugs being studied. The most common side effects reported for gabapentin are dizziness, drowsiness, sedation, nystagmus, fever, fatigue, viral infections, ataxia, diplopia, xerostomia, and irritability [18]. The side effect of sedation could be a confounding variable in regards to pain control. It is possible that patients in the gabapentin group were too sedated or drowsy to ask for pain medication, resulting in a lower amount of narcotics consumed in this group. One prospective study using prebagalin, a drug similar to gabapentin, in TKA showed patients experienced higher levels of postoperative confusion and sedation [19]. While our study did not specifically look for confusion, sedation, or dizziness, no adverse events related to these side effects were reported. One patient was removed from the study due to a small bowel obstruction, and a second patient was removed from the study due to an episode of vasovagal syncope. After unblinding, it was determined both of these patients were in the placebo group. In fact, no patients in the gabapentin group were reported to have an adverse event postoperatively.

Opioid-related adverse side effects are well known and can contribute to inferior outcomes in TKA [20]. One study reviewing 20 articles showed opioid-related adverse drug events (ORADEs) were not only common, but also very costly for hospitals [21]. Overall occurrence rate of ORADEs were as high as 13.6% per hospital stay. The same article showed that patients who experienced ORADEs had longer and more expensive hospital stays and even experienced higher mortality rates [21]. Although our study did not address the added benefits of reduced narcotics usage, it has been shown in previous studies that patients who consume less intravenous opioids have fewer side effects associated with these drugs and shorter hospital stays [16,17]. These 2 factors alone can significantly improve surgical outcomes and diminish the cost of hospital stays for patients undergoing primary, unilateral TKA.

Although our study had a relatively small sample size, there was a statistically significant difference with a large effect size between narcotics consumption on postoperative days 1 and 2. Our study failed to show a difference in subjective pain scores, knee ROM, and restfulness between groups. Based on this study, we believe that adding gabapentin to a multimodal pain management regimen can significantly reduce postoperative narcotics consumption in patients undergoing primary, unilateral TKA.

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