Original Article

Evaluation of efficacy of oral pregabalin in reducing postoperative pain in patients undergoing total knee arthroplasty

Pradeep Jain, Annu Jolly, Vaibahav Bholla, Sweta Adatia, Jayashree Sood

Abstract

Background: Optimal pain treatment with minimal side effects is essential for early mobility and recovery in patients undergoing total knee arthroplasty (TKA). We investigated the effect of pregabalin as an adjuvant for postoperative analgesia provided by opioid-based patient-controlled epidural analgesia (PCEA) in such patients.

Materials and Methods: Forty patients undergoing unilateral primary TKA were randomly assigned to two equal groups, to receive either placebo or pregabalin 75 mg twice a day. The drug was administered orally starting before surgery and was continued for 2 days after surgery. Anesthetic technique was standardized. Postoperatively, static and dynamic pain was assessed by verbal rating score. Mean morphine consumption, PCEA usage, rescue analgesic requirement, and overall patient satisfaction were also assessed. Treatment emergent adverse drug reactions were recorded.

Results: Mean morphine consumption was significantly reduced by pregabalin. Postoperative pain (both static and dynamic) and PCEA consumption too was significantly reduced in the pregabalin group during the first 48 h after surgery. This group needed fewer rescue analgesics and recorded higher overall patient satisfaction. Pregabalin-treated patients had fewer opioid-related adverse reactions like nausea, vomiting, and constipation. Dizziness was noted in two of the patients receiving pregabalin. There was no statically significant difference in the incidence of sedation in the two groups.

Conclusions: Oral pregabalin 75 mg started preoperatively is a useful adjunct to epidural analgesia following TKA. It reduces opioid consumption, improves postoperative analgesia, and yields higher patient satisfaction levels.

Key words: Epidural analgesia, postoperative pain, pregabalin

Introduction

The moderate to severe pain following total knee arthroplasty (TKA) surgery, slows recovery and rehabilitation. Postoperative pain is a model of mixed pain, with nociceptive as well as neuropathic components. Postoperative pain leads to local inflammatory response, stimulation of nociceptors, and nociceptive pain. Surgical stimulus also leads to sensitization of dorsal horn neurons, which is associated with augmentation of pain.[1] This is referred to as central sensitization and represents the neuropathic component.

Several classes of drugs including non-steroidal anti-inflammatory drugs, opioids, and local anesthetics have been used to counter the nociceptive component of postoperative pain. Recent evidence suggests that α_2 d subunit calcium channel ligands, like gabapentin and pregabalin, may aid in providing effective postsurgical analgesia.[2] They mitigate central sensitization by calming down hyperexcited dorsal horn neurons. This discovery has opened up the possibility of using such drugs in the perioperative setting to counter the neuropathic component of postsurgical pain. These drugs were introduced as anticonvulsants, presumably due to their ability to reduce neurotransmitter release from activated epileptic neurons.[2] Similarly, their ability to reduce neurotransmitter release from activated neurons in pain pathways and fear circuits may contribute to their role as an adjuvant in pain management and as anxiolytics.

Pregabalin is a more potent analog of gabapentin with better

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oral bioavailability and potentially more consistent clinical effects.[3] With this background, we designed this study to investigate the efficacy and tolerability of oral pregabalin as an adjuvant for postoperative analgesia with a standardized local anesthetic and opioid-based patient-controlled epidural analgesia (PCEA) regime. The primary goal of the study was to test the hypothesis that the perioperative use of oral pregabalin will reduce consumption of epidural morphine, hence opioid related side effects, after unilateral TKA. Our secondary objectives were to determine whether supplementing epidural analgesics with oral pregabalin can also reduce postoperative pain scores and decrease epidural demand dose requirement. Any significant reduction in rescue analgesic requirements and improvement in overall patient satisfaction were also analyzed.

Materials and Methods

The study was approved by our institutional ethics committee and written informed consent was obtained from all subjects volunteering to participate in the study.

The study was conducted at a single center between 2008 and 2009. Forty patients undergoing unilateral primary TKA were enrolled. The patients aged between 18 and 75 years of age, within ± 50% of their ideal body weight, with no clinically significant cardiovascular or central nervous system disease, and could operate a patient controlled epidural analgesia (PCEA) device were included in the study. Exclusion criteria were previous history of neuropathic or chronic pain prior use of pregabalin or gabapentin, known allergy to study medications, renal insufficiency, and history of bleeding diathesis or substance abuse.

The study was designed as a double blind, placebo controlled, randomized controlled trial. Patients were randomly assigned to one of the two treatment groups using a computer generated random number list.

The test drug group received pregabalin 75 mg tablets while the control group received matching placebo. Study medication was given orally twice a day, with sips of water, starting 2 h preoperatively, supervised by a staff nurse who had no further involvement. Both the staff nurse and the patient were not aware of the contents of the drug. The same drug was administered at 6:00 AM and 6:00 PM on the first and second postoperative days.

The TKA was performed under regional anesthesia, using a combined spinal epidural block in the lumbar region. Patients in both the groups were administered a mixture of 2.5 ml bupivacaine 0.5% (H) and fentanyl 25 μg spinally. An 18-G epidural catheter was inserted in the L_{2-3} or L_{3-4} interspace for postoperative analgesia. All patients underwent unilateral primary TKA and the average duration of surgery after regional block was 2–2.5 h. The surgery was completed under the effect of the subarachnoid block. The anesthetic technique was standardized in all patients. The fluid replacement was with colloids or crystalloids as per the losses. The average blood loss in unilateral TKA was approximately 250–300 ml, and none of the patients needed a blood transfusion.

Toward the end of the procedure, the patients were given 5 ml bupivacaine 0.25% and were connected to an epidural PCEA device. Postoperative analgesia was provided with an epidural PCEA solution containing bupivacaine 0.0625% and morphine 0.05 mg/ml. The continuous infusion rate was set at 4 ml/h with a bolus dose of 6 ml, set at a lockout interval of 30 min. The use of the PCEA pump was carefully explained to the patient. The primary outcome measure of the study was to compare the total PCEA administered with morphine consumption on days 1 and 2 in both the groups. Daily pain scores assessed on an 11-point verbal rating score (VRS), with 0 = no pain and 10 = worst pain imaginable were also analyzed in both the groups. The pain was rated both at rest (static) and on movement (dynamic) on days 1 and 2. Each day's score was taken as the average of three assessments. The pain scores were recorded at 8:00 AM, 2:00 PM, and 8:00 PM on the first and second postoperative days. A VRS score of greater than 3 was regarded as being uncomfortable by the patient and hindered with limb physiotherapy. Additional secondary outcome measures were the number of PCEA boluses attempted and delivered on days 1 and 2, and the requirement for rescue analgesic doses. Rescue analgesic was given when VRS (static) was greater than 5, in the form of oral diclofenac sodium 75 mg. Overall patient satisfaction was assessed using a 100-mm visual analog scale, ranging from 0 = highly dissatisfied to 100 = completely satisfied. Sedation was scored on a 5-point scale (0 = unarousable, 1 = asleep, 2 = drowsy, 3 = awake, and 4 = agitated).

Postoperative adverse events like nausea and vomiting, dizziness, constipation, urinary retention, dry mouth, and itching were recorded at 24 and 48 h after surgery. Patients with a nausea score greater than or equal to 4 (assessment of postoperative nausea was performed using an 11-point VRS, with 0 = no nausea and 10 = worst nausea imaginable) and those who vomited or requested antiemetics received ondansetron 4 mg i.v.

It was estimated that at least 19 subjects would be required per group in order to detect a difference of 1 in pain score (static/dynamic) between groups with 90% power and 5% probability of type I error. This calculation assumed a

standard deviation of 0.9 for pain score. Pain scores and the other numerical variables of interest were not normal in distribution and were compared between groups by Mann–Whitney U test. Fisher's exact test was employed for intergroup comparison of categorical variables. Two-tailed $P < 0.05$ was taken to be statistically significant. Analysis was done by Statistica version 6 (StatSoft Inc.; Tulsa, OK, USA, 2001) and GraphPad Prism version 4 (GraphPad Software Inc.; San Diego, CA, USA; 2005) software.

Results

Forty nine subjects were screened for the study and 40 (81.63%) were found to be eligible. There were no dropouts and all recruited subjects completed the study. The groups were comparable with respect to age, body weight, sex, and American Society of Anaesthesiologists (ASA) physical status [Table 1]. The mean duration of surgery, heart rate, systolic and diastolic blood pressures, and oxygen saturation did not differ between the two groups at any of the measured time points.

The pregabalin treated patients had a mean 24-h morphine consumption of 3.56 mg and 3.3 mg on the first and second postoperative days, respectively. This was significantly lesser than the average morphine consumption of 7.2 mg and 5.97mg on the first and second postoperative days, respectively, in the placebo group [Table 2].

The static VRS pain scores were significantly greater on both the first and second postoperative days in patients receiving placebo than in those receiving pregabalin. A summary of the pain scores is presented in Table 3. The dynamic pain score was greater than 3 (uncomfortable) on both the first and second postoperative days in the placebo group. The pregabalin group had a dynamic pain score of 3.03 on the first postoperative day and 2.37 on the second postoperative day. By the second day, the dynamic pain scores were significantly lower in the study group. Individually, in both the groups, both static and dynamic pain scores declined significantly from the first to the second postoperative day.

Compared to the placebo group, the PCEA requirements were significantly reduced in the pregabalin treatment group for the first 48 h after surgery [Table 4]. In addition, rescue analgesic requirement was significantly less for pregabalin users. Overall patient satisfaction with their postoperative pain management was significantly better in the pregabalin group compared to placebo control.

The potential adverse drug reactions [Table 5], were mostly related to the gastrointestinal system, with 50% patients in the pregabalin group complaining of nausea, vomiting, diarrhea, or constipation. In comparison, 75% patients in the placebo group had similar complaints. Mild dizziness was reported by two patients receiving pregabalin, whereas none in the placebo group had this complaint. The differences in frequency of individual adverse events,

Table 1: Comparison of baseline demographic and clinical characteristics of the two study groups

Baseline variable	Pregabalin group (*n* = 20)	Placebo group (*n* = 20)	*P* value
Age			
Mean ± SD	59.7 ± 8.63	57.1 ± 8.81	0.343
Median (IQR)	60.0 (56.0–67.0)	58.0 (51.0–63.0)	
Weight			
Mean ± SD	67.9 ± 9.38	69.5 ± 8.33	0.560
Median (IQR)	68.0 (60.0–72.0)	68.5 (65.0–74.0)	
Sex			
Male (%)	9 (45.0%)	5 (25.0%)	0.320
Female (%)	11 (55.0%)	15 (75.0%)	
ASA grade			
I	5 (25.0%)	4 (20.0%)	1.000
II	15 (75.0%)	16 (80.0%)	

P value (comparison between the two groups) is from Mann–Whitney U test for age and body weight, and from Fisher's exact test for sex and American Society of Anesthesiologists (ASA) Grade

Table 2: 24-h morphine consumption (mg) on first and second postoperative days in the two study groups

Baseline variable	Pregabalin group (*n* = 20)	Placebo group (*n* = 20)	*P* value
24-h morphine consumption (mg) – Day 1			
Mean ± SD	3.6 ± 1.18	7.2 ± 2.97	<0.001
Median (IQR)	3.6 (2.9–4.2)	6.0 (5.4–8.4)	
24-h morphine consumption (mg) – Day 2			
Mean ± SD	3.3 ± 1.11	6.0 ± 2.40	<0.001
Median (IQR)	3.0 (2.4–4.2)	6.0 (4.8–7.2)	

Table 3: Static and dynamic pain scores assessed through verbal rating on first and second postoperative days in the two study groups

Variable	Pregabalin group (*n* = 20)	Placebo group (*n* = 20)	*P* value
Static pain score – Day 1			
Mean ± SD	2.2 ± 0.69	3.5 ± 1.20	<0.001
Median (IQR)	2.3 (1.67–2.83)	3.3 (2.67–4.00)	
Static pain score – Day 2			
Mean ± SD	1.5 ± 0.48	2.4 ± 0.73	<0.001
Median (IQR)	1.3* (1.17–1.67)	2.3* (2.00–2.67)	
Dynamic pain score – Day 1			
Mean ± SD	3.0 ± 0.72	4.3 ± 1.35	0.001
Median (IQR)	3.0 (2.3–3.7)	4.0 (3.50–4.67)	
Dynamic pain score – Day 2			
Mean ± SD	2.4 ± 0.36	3.4 ± 0.77	<0.001
Median (IQR)	2.3* (2.0–2.5)	3.3* (2.67–4.17)	

P value (comparison between the two groups) in last column is from Mann–Whitney U test, *Denotes P < 0.01 for comparison with corresponding day 1 value by Wilcoxon's matched pairs signed rank test

Table 4: Secondary efficacy variables compared between the two study groups

Secondary efficacy variable	Pregabalin group (*n* = 20)	Placebo group (*n* = 20)	*P* value
PCEA boluses attempted – Day 1			
Mean ± SD	16.5 ± 4.78	39.8 ± 21.44	<0.001
Median (IQR)	16.5 (14.0–20.0)	36.0 (24.5–47.00)	
PCEA boluses attempted – Day 2			
Mean ± SD	15.4 ± 4.69	35.0 ± 24.92	0.001
Median (IQR)	15.5 (11.0–19.0)	27.0* (22.5–38.0)	
PCEA boluses delivered – Day 1			
Mean ± SD	11.9 ± 3.85	23.7 ± 10.23	<0.001
Median (IQR)	12.0 (9.5–14.0)	20.0 (15.5–28.0)	
PCEA boluses delivered – Day 2			
Mean ± SD	11.0 ± 3.68	20.1 ± 7.62	<0.001
Median (IQR)	10.0 (8.0–14.0)	20.0 (16.0–24.0)	
Rescue analgesic doses required (oral diclofenac sodium 75 mg)			
Mean ± SD	0.5 ± 0.76	1.3 ± 1.29	0.031
Median (IQR)	0.0 (0.0–1.0)	1.5 (0.0–2.0)	
Patient satisfaction score – Day 1			
Mean ± SD	52.8 ± 12.30	30.5 ± 11.46	<0.001
Median (IQR)	50.0 (47.5–55.0)	30.0 (25.0–40.0)	
Patient satisfaction score – Day 2			
Mean ± SD	61.5 ± 11.37	41.0 ± 11.65	<0.001
Median (IQR)	60.0# (50.0–65.0)	50.0# (30.0–50.0)	

P value (comparison between the two groups) in last column is from Mann–Whitney U test, */# denotes P < 0.05/< 0.01 for comparison with corresponding day 1 value by Wilcoxon's matched pairs signed rank test, PCEA = Patient controlled epidural analgesia

Table 5: Treatment emergent adverse events encountered in study subjects

Adverse event	Pregabalin (*n* = 20)	Placebo (*n* = 20)
Nausea	5	11
Vomiting	2	10
Constipation	4	4
Diarrhea	—	3
Any of the above gastrointestinal events	10	15
Dizziness	2	—
Itching	2	3
Dry mouth	2	5
Urine retention	1	2

Values denote subject counts within the group. Frequency of individual events did not differ between the groups (*P* > 0.05 by Fisher's exact test)

when compared between the two groups, were statistically insignificant. Antiemetics were required by 3 subjects (15.0%) receiving pregabalin, and 9 patients (45.0%) on placebo; this difference also did not reach statistical significance ($P = 0.082$) although the trend was in favor of pregabalin. Sedation score in the pregabalin group (2.3 ± 0.55; Mean ± standard deviation) was comparable to that in the placebo arm (2.0 ± 0.56).

Discussion

Our results indicate that the addition of pregabalin 75 mg twice daily, starting preoperatively and continued for the

first two postoperative days, to our standard institutional postoperative pain relief protocol for patients undergoing TKA, resulted in significant reduction in the postoperative opioid consumption. It also improved analgesia and decreased postoperative epidural demand dose requirement throughout the study period. Correspondingly, the overall patient satisfaction was significantly higher in the pregabalin treated patients.

Improved analgesia and anxiolysis that can be attributed to pregabalin may have contributed to improved patient satisfaction. Pregabalin targets the α_2 d subunit of voltage-gated channels.[2] The reduction in calcium flow through the channels decreases neuronal transmission in activated neuronal circuits, which may lead to decreased pain perception and analgesia.[3]

Although structurally similar to gabapentin, pregabalin has demonstrated greater analgesic efficacy in rodent models of neuropathic pain.[3] According to the results of the rodent model of chronic neuropathic pain, the analgesic potency of pregabalin is two-to-four fold greater than that of gabapentin. In the literature, however, there are no comparative studies on the analgesic potency of the two gabapentinoids in humans. It exhibits predictable linear pharmacokinetics across its therapeutic dose range with low intersubject variability. The adverse effect profile of pregabalin is also encouraging, with the most common effects being dizziness and somnolence.[4] It does not cause any hemodynamic changes. It is rapidly and extensively absorbed after oral dosing in the fasted state, with maximal plasma concentration occurring 1 h after single or multiple doses and steady state being achieved within 24 to 48 h after repeated administration.[5] The oral bioavailability of pregabalin is high at >90% and is independent of dose. It is only slightly metabolized by the liver and does not interact wtih P-450 enzymes, which results in a lack of pharmacokinetic interaction. Up to 98% of the administered dose is eliminated unchanged by the kidneys.[6] Furthermore, the administration of pregabalin with food has no clinically relevant effect on the amount of pregabalin absorbed, thus providing for a dosing regimen that is uncomplicated by meals.[5] These features make pregabalin an easy drug to use in clinical practice.

The use of pregabalin in acute postoperative pain management has been evaluated in recent studies. In the first trial investigating the postoperative analgesic effect of pregabalin, a dose of 300 mg pregabalin administered after dental operation was more effective in attenuating acute postoperative pain than placebo. It also had a longer duration of analgesia than ibuprofen.[7] However, adverse effects were more frequent in patients receiving pregabalin 300 mg. The most common of these adverse effects were dizziness, somnolence, and vomiting. Tippana and coworkersl[8] analyzed 22 randomized, controlled trials examining the analgesic efficacy, adverse effects, and clinical value of gabapentinoids (pregabalin and gabapentin) in postoperative pain. They concluded that gabapentinoids effectively reduce postoperative pain, opioid consumption, and opioid-related side effects after surgery. In another study, Jokela and colleagues[9] observed that preoperative administration of 300 mg pregabalin, followed by the same dose repeated after 12 h in patients undergoing laparoscopic hysterectomy decreases oxycodone consumption. They also noted that the improved analgesia is associated with an increased incidence of adverse effects such as dizziness and blurred vision. In a subsequent study by Jokela and colleagues,[10] premedication with pregabalin 150 mg in patients undergoing day case gynecological surgery resulted in an improved quality of analgesia, but there was no difference in the amount of postoperative analgesics required or the degree of drowsiness.

At variance with these observations, Paech and colleagues[11] reported that a single preoperative dose of 100 mg pregabalin was ineffective in reducing acute postoperative pain or improving recovery after minor surgery involving only the uterus. This could possibly be attributed to a single small dose (100 mg) as against the recommended 150 mg/day.[12]

Mathiesen and others[12] administered pregabalin 300 mg to 120 patients undergoing hip arthroplasty under spinal anesthesia. The drug was given preoperatively. They observed a 50% reduction in 24-h postoperative morphine requirement. Agarwal and co-workers[13] observed that a single preoperative dose of pregabalin 150 mg is an effective method for reducing postoperative pain and fentanyl consumption in patients undergoing laparoscopic cholecystectomy. They suggested further trials to study the dose–response and the effect of continued therapy. Our study adds a further dimension to this evolving perioperative analgesic role of pregabalin by initiating therapy preoperatively and continuing it postoperatively for 48 h.

White and co-workers[14] attempted to study the effect of pregabalin on preoperative anxiety and sedation levels. They concluded that preoperative pregabalin (75–300 mg p/o) increased preoperative sedation in a dose-related fashion, but failed to reduce preoperative state anxiety, postoperative pain, or to improve the recovery process after minor elective surgery procedures. Analogous to the findings of other investigators,[7,9] pregabalin resulted in more frequent side effects (excessive sleepiness and dizziness). The authors

commented that their inconsistent findings with respect to the ability of pregabalin to improve the management of postoperative pain may be related to a variety of potentially confounding factors. The most likely explanation relates to the type of surgical procedures and the use of multimodal analgesic regimens, as well as the timing of the drug administration (e.g. preoperative vs. postoperative).

White and coworkers administered only a single dose of the medication before surgery, the dose was variable, and the maximum dose was 300 mg. In variance with this trial,[14] our study protocol followed an extended dosing schedule; a low preoperative dose of 75 mg pregabalin was followed by 75 mg twice a day, for the first two postoperative days. The nature of surgeries conducted in the two trials too was radically different. White and colleagues evaluated the effect of pregabalin in elective, ambulatory, superficial procedures, as opposed to major orthopedic surgery. They followed a multimodal analgesic regimen, including local anesthetic infiltration at incision sites. The decreased postoperative pain in their patients may have contributed to a higher incidence of sedation.

In a more recent study, Buvanendran and colleagues[15] investigated the effect of perioperative pregabalin in reducing chronic pain after TKA. They administered pregabalin 300 mg before TKA and continued it for 14 days after TKA (50-150 mg twice daily). They observed that perioperative pregabalin administration reduces the incidence of chronic neuropathic pain after TKA, with less opioid consumption and better range of motion during the first 30 days of rehabilitation. However, in the doses tested, it is associated with a higher risk of early postoperative sedation and confusion. They attributed the improved analgesia to presurgical administration of a large initial dose and/or a continued large dose for 10 days after TKA. The investigators commented that the increased sedation was due to the 300 mg initial dose of pregabalin, which was administered abruptly, without the slow escalation that is standard practice with pregabalin (or gabapentin). The authors advocated large clinical studies with lower doses and shorter duration to determine the optimal dose and duration of pregabalin administration in this and other surgical pain models.

A limitation of our current study is that we did not have a dose–response curve before choosing the dose used in the study. We decided our dose of pregabalin (75 mg preoperatively followed by 75 mg bd for the first 48 h after surgery) based on the experience of previous investigators. Paech and others[12] reported ineffective analgesia after a single dose of 150 mg pregabalin. Other workers[7,9,12,14] reported improved analgesia with 300 mg pregabalin, but in all these studies, the improved analgesia was associated with significant side effects like sedation and dizziness. Most of the previous models of acute postoperative pain have not evaluated the effect of repeated dosing of pregabalin. Pregabalin achieves steady-state concentration over a 24–48 h period.[5] We observed a significant improvement in analgesia by starting with 75 mg pregabalin preoperatively and continuing the same dose twice a day for the first two postoperative days. Pregabalin was used as an adjuvant to our standard pain relief protocol with PCEA pump, and not as the sole analgesic. The incidence of side effects was quite low in our patients, and those encountered were mostly mild and did not cause inconvenience to the patients greatly.

Conclusion

The perioperative administration of pregabalin reduces opioid consumption, improves postoperative analgesia, and yields higher patient satisfaction levels in primary TKA. In addition to this operation, we believe that as a component of multimodal analgesia, pregabalin needs to be studied as an adjunct to epidural analgesia following other types of lower extremity surgery.

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