The Efficacy of Pregabalin on the Duration of the Spinal Anesthesia and the Early Postoperative Pain After Total Knee Arthroplasty

Original Article

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ABSTRACT

Background: The pain after knee surgery is a great challenge to physicians where lack of adequate analgesia causes many complications. Pregabalin, a gamma amino-butyric acid, has shown analgesic and sedative effects. Therefore, this article examines the effect of a preoperative single dose of oral pregabalin on total knee arthroplasty pain after surgery.

Results: The study results showed that pregabalin was found to prolong the spinal block duration (2-segment regression, L2 regression, and Bromage2 regression time). pregabalin had no significant effect on the sensory nor motor block onset (*P =1.000*) (*P =0.078*) respectively. Pain score at 6hrs and 24hrs was significantly reduced in pregabalin group. In addition, frequency and total narcotic requirements were significantly reduced in pregabalin group.

Conclusion: Premedication with oral pregabalin 150 mg promoted intrathecal bupivacaine efficacy, improved postoperative analgesia, and reduced narcotic requirements.

Key Words: Postoperative pain, pregabalin, spinal anesthesia, total knee arthroplasty.

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INTRODUCTION

Although the hospital stay durations after orthopedic procedures are decreasing overall; Inadequate post-operative pain control can increase hospital costs, delay recovery, and rehabilitation, and result in negative outcomes[1].

Multimodal analgesia is founded on the idea that pain involves multiple pathways. To obtain effective and sufficient postoperative pain relief, various types of analgesics must be combined[2]. Adjuvants of various types (pregabalin, gabapentin, duloxetine, and others) have been utilized to extend spinal anesthesia and reduce postoperative analgesic requirements[3,4].

The use of an analgesic drug before the onset of a painful stimulus is known as preemptive analgesia. It prevents the formation of altered afferent input processing, which worsens post-operative pain[5]. This strategy is used to alleviate postoperative pain, improve analgesic efficacy, and thus reduce the need for narcotics[6].

Pregabalin, a Gamma-aminobutyric acid analog, inhibits voltage-gated calcium influx at nerve terminals, reducing excitatory neurotransmitter release[7,8]; additionally, it progressively reduces central sensitization and hyperalgesia[9]. Preoperative oral pregabalin improves post-operative pain[10-12] and enhances the duration of nerve blockade anesthesia[13].

Previous studies have been conducted to evaluate pregabalin's pain relief and narcotic requirement effects, but very limited studies evaluated its effects on regional anesthesia as the preferred modality for lower limb procedures with less pain and early rehabilitation.

We hypothesize that preoperative oral pregabalin will improve pain and allow early rehabilitation following total knee arthroplasty under spinal anesthesia.

PATIENTS AND METHODS

Methods

A prospective, Parallel groups, randomized, non-funded, and single-institute trial approved by the Ethics committee, (CONSORT) guidelines, and recorded at ClinicalTrials.gov. A signed informed consent was obtained.

The participants were recruited (March 2021 - August 2021).

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Computer□generated codes were blindly randomized with a 1:1 ratio between participants.

Randomization and follow-up were achieved by physicians unaware of grouping. The study included 70 patients with ASA-PS I and II, aged 40 to 70 years, 70-80 kg, 155-170 cm height, both sexes, undergoing elective total knee arthroplasty.

The following are the study's exclusion criteria: Patient refusal, allergy to the medications used in the study, addiction, unable to communicate for the evaluation of postoperative pain, ICU admission, gabapentin or pregabalin medications, contraindications for regional anesthesia (such as coagulopathy and local infection), and patients with psychiatric disorders.

The participants scheduled for total knee arthroplasty after spinal anesthesia have been randomized into:

Pregabalin group (Group P): The participants received oral 150mg of pregabalin capsules 2 hours preoperatively[14].

Control group (Group C): The participants received a placebo.

The participants were transferred to the operating room for spinal anesthesia.

The preoperative clinical assessment was done for all participants before the operative day with routine investigations of ECG, random blood glucose, CBC, INR, PTT, and liver, and kidney function tests.

The participants were monitored with ECG, non-invasive blood pressure, and pulse oximetry before induction of anesthesia.

Every 5 minutes, baseline parameters like systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), heart rate (HR), and oxygen saturation (SpO2) were recorded. Intravenous crystalloid preload was instilled after securing venous access.

Spinal anesthesia was administered to both groups using a 25-G spinal needle. In the midline at the level of (L4toL5) or (L3toL4) 5 ml of 2% lidocaine was administered as local anesthesia via infiltration and a 25-G Quincke /pencil point /spinal needle, all patients were given spinal anesthesia with 3.5mL of bupivacaine 0.5% (hyperbaric). The block level has been assessed by the pinprick test. The participant was excluded if spinal anesthesia failed.

Intravenous crystalloid preload was given at a rate of 10 mL /kg. After the intrathecal injection, the supine position was maintained for twenty minutes. The participants operated with one team and were positioned similarly all through the surgical procedure.

Intravenous ephedrine 4mg was given if the patient's systolic blood pressure dropped by more than 30% or when MAP dropped below 60mm Hg. If the pulse dropped to 45 bpm, 0.5 mg atropine intravenously was given, but no intraoperative sedation was given.

A Pinprick test was carried out to assess sensation level every minute until the peak sensory block was reached. The surgeon then performed an assessment every 10 minutes till the L2 segment recovered sensation.

A 2-dermatome regression was used to define sensory recovery.

The Bromage score was used for motor assessment (3= no movement, 2= flex ankle but without knee flexion, 1= moves ankle and knee but can't elevate straight leg, 0= no weakness)[16]. In addition, the time it took to get to Bromage1 was recorded, and the duration of motor anesthesia was defined as the time it took to get back to Bromage 2.

The post-operative pain was managed with regular simple analgesia. The patient's post-operative pain has been assessed every 2 hours for up to 24 hours using a visual analog score (0=no pain; 10=worst possible pain). An intravenous pethidine 50mg was given every 4 hours (the maximum dose is 300 mg per day) when VAS score was ≥4; And intravenous tramal 50mg was added if VAS score remained ≥4 after the second dose of pethidine[14]. Any adverse effects like hypotension (systolic arterial pressure 90 mmHg), arrhythmia, bradycardia (HR 60 beats/min), nausea and vomiting, dry mouth, mental clouding, palpitations, seizures, or other complications were recorded. In response to bradycardia, 0.5 mg atropine was administered, and 20 ml per kg lactated Ringer was administered in response to hypotension.

The primary outcome: The onset of spinal anesthesia.

The secondary outcome:

1. Recovery time from sensory blockade as 2-dermatome regression of the peak level.

2. Motor block duration.

3. Postoperative pain was assessed by VAS score (0=no pain; 10=worst possible pain) every 2 hours up to 24 hours.

4. Time of the first analgesia request and frequency.

G power software was used to calculate sample size with 90 % power and 0.05 alpha error. Assuming a large effect size difference among the research groups considering the onset of spinal anesthesia (D =0.8), Thirty-five participants in each group were needed as a sample size (a total of seventy participants).

The collected data was revised, coded, tabulated, and introduced to a PC using the Statistical Package for Social Science (SPSS 20). Data were presented, and suitable analysis was done according to the type of data obtained for each parameter.

1. Descriptive: Mean and standard deviation (± SD) for numerical data, Frequency, and percentage of non-numerical data.

2. Analytical: Student T-Test was used for the significance of the difference among the two-study group means, and the Chi-Square test examines the relationship between two categorical variables.

RESULTS

Seventy-nine participants were assessed for eligibility, nine participants were excluded (5 refused and 4 not fulfill the criteria). The seventy participants have been randomized into study groups and completed all assessments (Fig. 1).

No significant difference was found in demographic data (gender, age, weight, height, and operative time) (Table 1).

Table (2) showed no differences in anesthesia onset among groups as the T10 sensory blockade time (*P=1.000*), bromage1 motor blockade time (*P =0.078*), peak sensory level (t7), and peak level time (*P=1.024*).

However, it shows highly significant differences in anesthesia duration among groups as 2-segment regression time, L2 regression time, and Bromage2 regression time.

There was a significant difference in VAS score among groups at 6 and 24hrs (Table 3).

Table (4) and Figure (2) show a highly significant difference among groups in terms of the first analgesic requirement and frequency of the request of narcotics..

Table 1: Demographic characteristics and duration of surgery.

		Control group	Pregabalin group	Test value	*P-value*	Sig.
		No. = 35	No. = 35			
Age	Mean ± SD	63.34 ± 83.83	48.03 ± 2.76	1.080•	*0.284*	NS
Gender	Female	16 (45.7%)	22 (62.9%)	2.072*	*0.150*	NS
	Male	19 (54.3%)	13 (37.1%)			
Height	Mean ± SD	169.97 ± 2.61	169.89 ± 2.08	0.152•	*0.880*	NS
Weight	Mean ± SD	70.60 ± 3.48	70.43 ± 3.58	0.203•	*0.840*	NS
Operation duration	Mean ± SD	134.26 ± 6.71	134.23 ± 5.78	0.019•	*0.985*	NS

P-value > 0.05: Non significant; *P-value < 0.05*: Significant; *P-value < 0.01*: Highly significant
*: Chi-square test; •: Independent t-test

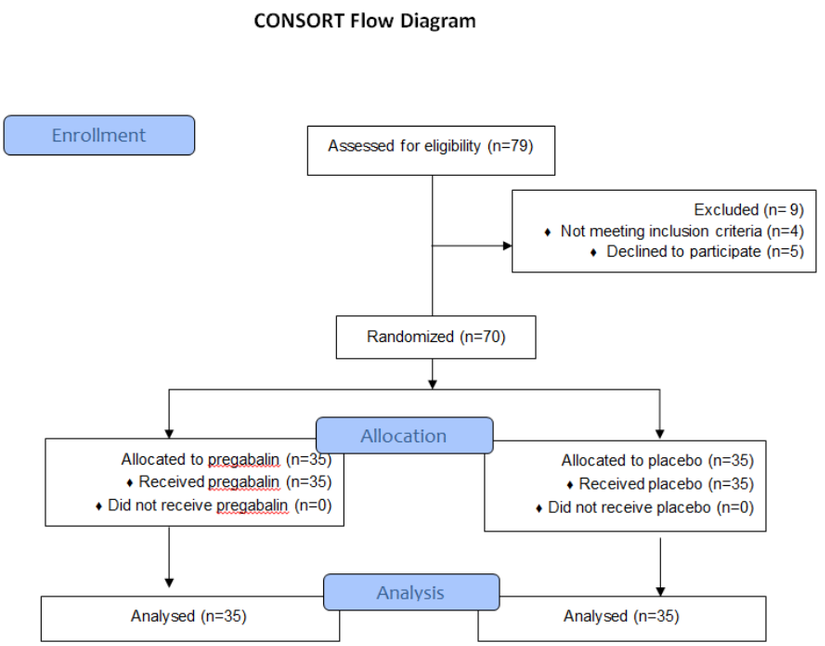

Fig. 1: Consort diagram of the study and control groups.

Table 2: Comparison between two groups according to Time to T10 sensory block, Time to Bromage 1 block, peak sensory level, Time of 2-segment regression, Time for regression to L2 and Time for regression to Bromage 2.

		Control group	Pregabalin group	Test value	P-value	Sig.
		No. = 35	No. = 35			
Time to t10 sensory block	Mean ± SD	5.46 ± 0.51	5.46 ± 0.51	0.000•	1.000	NS
Time to bromag 1 block	Mean ± SD	8.73 ± 0.51	8.44 ± 0.54	1.788•	0.078	NS
Peak sensory level	T7	35 (100.0%)	35 (100.0%)	–	–	–
Time to reach peak sensory level	Mean ± SD	14.04 ± 0.67	13.87 ± 0.73	1.024•	0.310	NS
Time of 2 segment regression	Mean ± SD	74.94 ± 3.59	107.40 ± 8.83	-20.141•	0.000	HS
Time for regression to L2	Mean ± SD	143.00 ± 6.37	173.29 ± 8.48	-16.888•	0.000	HS
Time for regression to bromag 2	Mean ± SD	181.86 ± 11.12	209.00 ± 6.28	-12.575•	0.000	HS

P-value > 0.05: Non significant; *P-value < 0.05*: Significant; *P-value < 0.01*: Highly significant
•: Independent t-test

Table 3: Comparison between two groups according to pain score.

		Control group	Pregabalin group	Test value	*P-value*	Sig.
		No. = 35	No. = 35			
Pain score of	Median (IQR)	5 (5 − 6)	4 (3 − 4)	-7.438≠	*0.000*	HS
6 hours postoperative	Range	5 – 6	3 – 4			
Pain score of	Median (IQR)	4 (4 − 5)	3 (3 − 4)	-6.400≠	*0.000*	HS
24 hours postoperative	Range	4 – 5	3 – 4			

P-value > 0.05: Non significant; *P-value < 0.05*: Significant; *P-value < 0.01*: Highly significant
≠: Mann-Whitney test

Table 4: Comparison between two groups as regards first analgesics request, frequency of request of narcotics, total dose of pethidine and total dose of tramal.

		Control group	Pregabalin group	Test value	*P-value*	Sig.
		No. = 35	No. = 35			
First analgesic request min	Mean ± SD	218.29 ± 12.48	333.86 ± 21.35	-27.643•	*0.000*	HS
Frequency of request of narcotics	Mean ± SD	5.23 ± 0.81	3.51 ± 0.51	10.636•	*0.000*	HS
Total dose of pethidine	Mean ± SD	240.00 ± 39.85	127.14 ± 24.53	14.267•	*0.000*	HS
Total dose of tramal	Mean ± SD	121.43 ± 25.10	67.14 ± 24.08	9.232•	*0.000*	HS

P-value > 0.05: Non significant; *P-value < 0.05*: Significant; *P-value < 0.01*: Highly significant
*: Chi-square test; •: Independent t-test

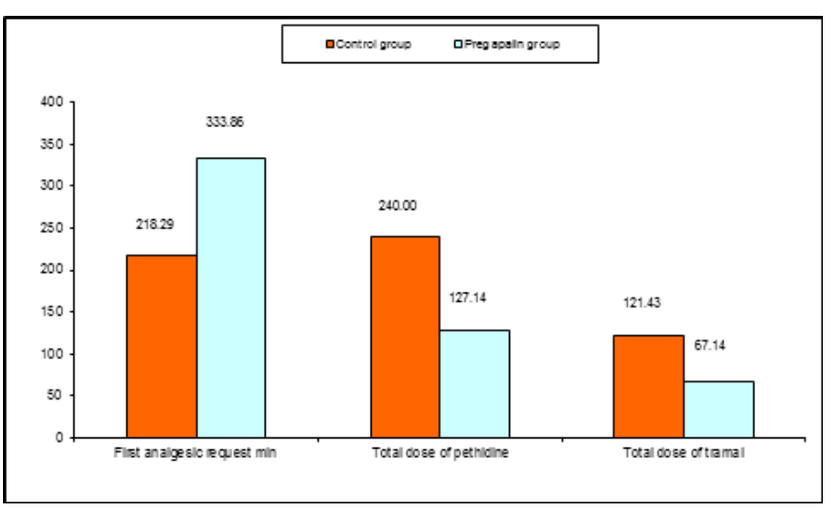

Fig. 2: Comparison between two groups as regards first analgesic request, total dose of pethidine and total dose of tramal.

DISCUSSION

Oral pregabalin 150 mg 2hrs before regional anesthesia was evaluated for its efficacy over the initial postoperative 24 hours post knee arthroplasty where our results revealed that pregabalin statistically didn't affect the sensory nor motor onset of anesthesia (primary outcome), but the sensory blockade duration (2-segment regression time and L2 regression) and motor block (bromage2 regression time) had been prolonged. VAS scores were reduced at 6hrs and 24hrs with delayed first analgesic requests and decreased total narcotic requirements.

Although pregabalin and gabapentin are gamma-aminobutyric acid (GABA) structurally analog, they don't bind to their receptors; But they bind to presynaptic calcium channels and preventing excitatory neurotransmitters release at central nerve terminals, consequently, reducing neuronal firing, central sensitization, potentiate inhibitory modulation at neurons of the dorsal horn, and prolong the spinal anesthesia duration. They don't affect serotonin, dopamine, opioid receptors, or sodium channel activities[9,13,17].

Pregabalin and gabapentin improved postoperative pain control, delayed rescue analgesia, and decreased total narcotic requirements[18,19].

Pregabalin and gabapentin are used in multimodal analgesic regimes as adjuvants for pain management in a different way than opioids and NSAIDs; they have an opioid-sparing effect (30%-62%) postoperatively with higher patient satisfaction[20].

Pregabalin has the same anxiolytic, anti-hyperalgesic, and anti-convulsant properties as gabapentin, moreover fewer adverse events.

The sedative effect of pregabalin increased in a dose-dependent way[21]. The preoperative 75mg and 150mg pregabalin decreased pain after dental and jaw surgeries with limited sedative effect[22,23], where 300mg pregabalin increased side effects[24].

Adverse effects of gabapentin such as confusion, somnolence, dizziness, and ataxia may limit its use[20].

Oral pregabalin takes 1.5 hours to reach the peak plasma level and the absorption is dose-independent, also, it has a half-life of 5.5hrs to 6.7hrs and could cross the blood-brain barrier as a lipophilic drug[25].

Buvanendran *et al*. stated that cerebrospinal fluid pregabalin concentrations after oral intake decreased the central hyperexcitability for 6 hours and increased the pain threshold during movement[26].

Perioperative pregabalin improves post-operative pain and reduces opioid consumption, it also has anxiolytic and euphorigenic effects; The time, dose, and frequency are still unclear[27-29].

After reviewing the previous literature in orthopedic and other surgeries under regional and general anesthesia[9, 25, 27-31], oral pregabalin 150 mg has been chosen as an effective and safe dose[14].

Cho and his colleagues reported that 150mg of oral pregabalin 1 hour before spinal anesthesia for ACL repair and another dose after 12 hours reduced NRS score during rest and passive movement in comparison to the control[31].

After hip arthroplasty under spinal anesthesia, preoperative 300mg pregabalin improved post-operative pain and decreased narcotic requirements to half compared to control, but sedation and vomiting were significant[27].

Kim and his colleagues compared the effects of oral 75mg and 150mg pregabalin 1 hour before and 12 hours after spine surgery and reported that pregabalin 150mg improved post-operative pain score and opioid requirement for 48 hours compared to control and 75mg pregabalin group, with limited adverse events[32].

The time for rescue analgesia was compared in gynecological surgeries after spinal blockade among 150mg pregabalin and 600mg gabapentin and reported that the duration of spinal block and the need for rescue analgesia in both groups were longer than in control. The first analgesic requirements were (535±32) in pregabalin group when compared with our results (334±20), different bupivacaine doses and different procedures might be the cause[33].

Preoperative oral 150mg pregabalin was reported to increase the sensory blockade duration and reduce narcotic requirements after upper limb surgery under infraclavicular nerve block[34]. Another study evaluated 75, 150, and 300mg preoperative oral pregabalin with the same circumstances against control and concluded that 150mg and 300mg pregabalin prolonged the sensory blockade duration and reduced narcotic requirements with fewer adverse events in the 150mg pregabalin group[13].

In comparison to our study, preoperative oral 75mg pregabalin 1 hour before ACL reconstruction after regional anesthesia and 12 hours postoperatively were ineffective in improving post-operative pain and narcotic requirements. The low dose of pregabalin might be the cause[30].

Limitations:

There were some limitations to the current study. First, we failed to pick out the best pregabalin dosage because

only one was tested. Second, Longer-term research on functional recovery is required. Third, there were no preoperative pain or anxiety levels registered. Pregabalin may influence anxiety, mood, and pain levels, all of which are linked to postoperative pain levels.

CONCLUSION

Premedication with oral pregabalin 150mg promoted intrathecal bupivacaine efficacy, improved postoperative analgesia, and reduced narcotic requirements.

ABBREVIATIONS

ACL--- Arthroscopic anteriorcruciate ligament.

ASA-PS---American Society of anesthesiologists Physical status.

ICU--- Intensive care unit.

MAOIs---Monoamine oxidase inhibitors.

OR--- Operating room.

PONV---Postoperative nauseaand vomiting.

SNRIs---Serotonin and norepinephrinereuptake inhibitors.

SSRIs---Selective serotonin reuptake inhibitors.

TKA---Total knee arthroplasty.

VAS---Visual analog score.

CONFLICT OF INTEREST

There are no conflicts of interest.

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