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The pregabalin effect on opioid consumption and postoperative pain in spinal fusion surgery, a prospective, randomized, controlled study

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ABSTRACT

Background and Aim: Surgical trauma is known to cause peripheral and central sensitization and hyperalgesia, which if untreated can cause chronic postoperative pain after surgery. The current work was conducted to evaluate the effect of preoperative pregabalin 150 mg orally on opioid consumption and acute postoperative pain in spinal fusion surgery.

Methods: Over one-year duration between 2020 and 2021, the current study was conducted. Ninety patients who were scheduled for spinal fusion surgeries (single and double levels) were recruited and randomly subdivided into two equal groups who received either pregabalin or placebo. The primary outcome was the overall amount of consumed morphine in the first 24 hours postoperatively. Secondary outcomes included VAS score at 1 hour, 2 hours, 4 hours and 24 hours postoperative, time to first rescue analgesia and vital signs including heart rate and mean arterial blood pressure intra- and postoperatively.

Results: The overall amount of morphine consumed in the first 24 hours postoperatively was significantly lower in the pregabalin group than the placebo group ($P < 0.001$). Pregabalin group had significantly longer time to rescue analgesia than placebo group ($P < 0.001$). Additionally, within the first postoperative 24 hours, VAS was significantly lower ($P < 0.05$) in the pregabalin group than in the placebo group.

Conclusions: A single dose of 150 mg of pregabalin preoperatively may have the ability to reduce the acute postoperative pain and opioids consumption after spinal fusion surgeries.

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Introduction

Postoperative pain is one of the problems which should be controlled to avoid many complications such as hypertension, tachycardia, decreased alveolar ventilation, poor wound healing and myocardial ischemia [1].

Patients undergoing spinal fusion surgery are at increased risk of acute and persistent postoperative pain and development of postoperative hyperalgesia which may lead to opioid tolerance and causes excessive and continuous use of opioids. Also, postoperative pain usually affects the patients' mobility [2].

Inadequate perioperative pain control leads to central nervous system sensitization and eventually the development of persistent postoperative pain. Many pharmacological agents (including pregabalin) can interrupt that mechanism and help in reducing postoperative pain [3].

Nowadays, the pain management is considered a basic human right and inadequate postoperative pain control can be considered medical negligence [4].

The synthetic chemical pregabalin is generated from the neurotransmitter inhibitor gamma-amino butyric acid. Pregabalin inhibits numerous neurotransmitters release including glutamate, dopamine, serotonin, substance P, and noradrenaline, via binding to the calcium channel's α_2-δ subunit [5]. Many studies suggested that pregabalin has an effective analgesic effect in neuropathic pain, acute postoperative pain and also can reduce the chronic postoperative pain incidence [6].

1. AIM of study

The current work was conducted to evaluate the effect of preoperative pregabalin 150 mg orally on opioid consumption and acute postoperative pain in spinal fusion surgery.

1.1. Primary outcome

Total consumed morphine in the first 24 hours postoperatively, morphine bolus 0.1 mg/ kg was used postoperatively when VAS >4.

1.2. Secondary outcomes

VAS score at rest were recorded at 1 hour, 2 hours, 4 hours and 24 hours postoperatively to assess acute postoperative pain.

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The time to first patient's request for rescue analgesia (morphine).

Vital signs: heart rate and mean arterial blood pressure were recorded intra- and postoperative.

2. Methods

This is a prospective randomized controlled trial that was conducted at the Department of Anesthesia and Intensive Care Asyut University Hospitals in the period between 2020 and 2021. The institutional ethics board of the Faculty of Medicine Asyut University approved this study (IRB: 17,101,526) and was also registered at clinicaltrials.gov **(NCT05083793)**.

2.1. Inclusion criteria

Patients aged 18 to 60 years with an ASA physical status score I or II and scheduled for spinal fusion surgeries were recruited in the study.

2.2. Exclusion criteria

Patients with one or more of the following conditions were excluded from the study; significant cardiac, respiratory, renal and hepatic diseases, pregnancy, psychiatric illness that would impede perception and assessment of pain, chronic pregabalin, opioids or gabapentin users and/or patients' refusal.

2.3. Sample size calculation

Based on the variance in placebo and pregabalin group proportions from the prior trial [7], sample size was determined. At 99% power and 0.01 alpha error, a sample size of 39 people in each group was needed. Final sample size required: 39 + 6 = 45 participants per group, assuming a 10% dropout rate.

The Helsinki Declaration's rules and guidelines were followed in the study's execution.

A table created by an internet randomizer was used for randomization. The participants were randomly assigned into one of the two following groups in a 1:1 ratio:

Pregabalin group; included 45 patients and received oral pregabalin 150 mg one hour preoperatively with a sip of water.

Placebo group; included 45 patients and received placebo one hour preoperatively with a sip of water, which was a starch-filled capsule of the same color and shape and was prepared in the Faculty of Pharmacy Asyut University.

2.4. Pre- and intraoperative anesthesia care

Full history taking and clinical evaluation were done for all patients. Patients were assigned randomly to receive either pregabalin or placebo at the same day of surgery. One hour preoperatively, the patients received one of the study drugs. ECG, heart rate, SaO_2, non-invasive blood pressure and end tidal CO_2 were used as the basic monitoring during anesthesia.

Propofol (1–2 mg/kg), fentanyl (1mcg/kg) and cisatracurium (0.1 mg/kg) were given IV for induction of anesthesia and to facilitate endotracheal intubation. Isoflurane 1–2% was used for maintenance of anesthesia. At the end of surgery, paracetamol 1 gm, ketorolac 30 mg were given intravenously (and every 8 hours postoperatively for 24 hours) and muscle relaxation was reversed. After extubation the patients were transported to the post-anesthesia care unit.

2.5. The following data was recorded

(1) Patients' clinical, demographic and surgical data were recorded.
(2) Patients' vital signs: heart rate and mean arterial blood pressure were recorded intra- and postoperatively.
(3) The time to first patient's request for rescue analgesia (morphine) was recorded.
(4) Total consumed morphine in the first 24 hours postoperatively (morphine bolus 0.1 mg/ kg was used IV when VAS >4).
(5) VAS score at 1st hour, 2nd hour, 4th hour and 24th hour postoperative was recorded.

Visual Analog Score (VAS) was used to evaluate postoperative pain by where a score of 0 represents no pain and 10 is the worst pain. The patient was requested to put a point on the line and the distance was then measured from the left edge (= VAS score) to show the overall severity of pain. VAS was recorded after 1, 2, 4 and 24 hours.

2.6. Statistical analysis

After data collection, SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York) was used to analyze it. To determine whether the data is normally distributed or not Shapiro test was used. Mean ± standard deviation (SD) was used to express normally distributed quantitative data and was compared by Student t test. Median (interquartile range) was used to express abnormally distributed quantitative data and was compared by Mann-Whitney U test.

Nominal data were shown as number (n) and percentage (%) and was compared using Chi^2 test. Level of confidence was kept at 95%, and hence, P value was considered significant if < 0.05.

3. Results

A total of 90 patients were assessed for eligibility. And no one of them was excluded. Finally, 90 patients were equally randomly assigned into two groups (Figure 1).

There were no statistically significant differences (P > 0.05) between both groups regarding clinical and demographic data (Table 1).

Also there was no significant difference (P = 0.134) between the two groups regarding the type of surgical procedures (Table 2).

The mean values of total morphine consumed post-operatively during the first 24 hours were significantly lower (P < 0.001) in the pregabalin group compared to the placebo group (Table 3).

VAS were significantly lower (p < 0.05) in pregabalin group in comparison with placebo group. The *P* values were <0.001 after 1 hr, = 0.002 after 2 hrs, = 0.009 after 4 hrs and = 0.04 after 24 hrs (Table 3).

The time to patients' request for rescue analgesia for the first time was longer significantly (P < 0.001) in the pregabalin group than in the placebo group (Table 3).

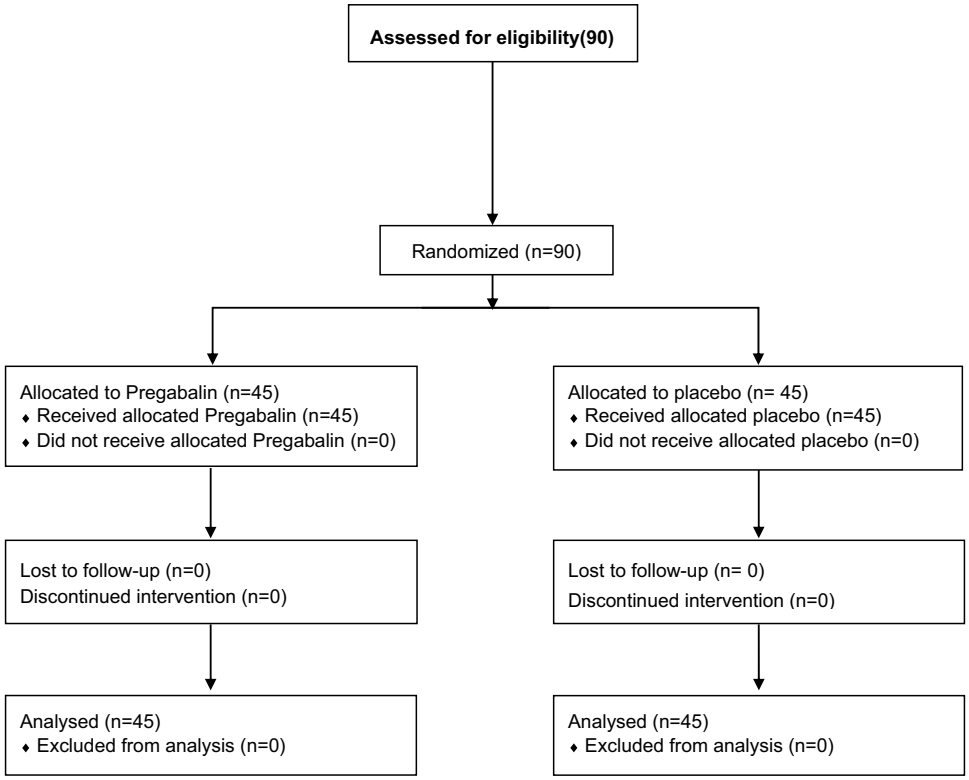

Figure 1. Participant flow diagram.

Table 1. Baseline data of studied groups.

	Pregabalin group (n = 45)	Placebo group (n = 45)	*P* value
Age (years)	41.39 ± 11.23	44.74 ± 10.94	0.15
Sex			0.13
Male	33 (73.3%)	27 (60%)	
Female	12 (26.7%)	18 (40%)	
BMI (kg/m^2)	26.67 ± 2.93	25.65 ± 3.93	0.16
Diabetes mellitus	6 (13.3%)	4 (8.9%)	0.37
Hypertension	4 (8.9%)	8 (17.8%)	0.17
Smoking	7 (15.6%)	8 (17.8%)	0.50
ASA class			0.40
Class-I	34 (75.6%)	36 (80%)	
Class-II	11 (24.4%)	9 (20%)	

Data expressed as mean (SD), range, frequency (percentage). *P* value was significant if < 0.05. ASA: American Society of Anesthesiologists; BMI: body mass index

Table 2. Types of spinal surgeries of studied groups.

	Pregabalin group (n = 45)	Placebo group (n = 45)	*P* value
Types of spinal surgeries			
Single-level spinal fusion	36 (80%)	41 (91.1%)	0.134
Double-level spinal fusion	9 (20%)	4 (8.9%)	

Data expressed as frequency (percentage). *P* value was significant if < 0.05

Table 3. VAS, time to first patients' request of analgesia (min) and total 24 hours' morphine consumption in both groups.

	Pregabalin group (n = 45)	Placebo group (n = 45)	*P* value
Total 24 hr morphine consumption (mg)	8.67 ± 2.20	14.45 ± 2.50	<0.001*
Time to first request of analgesia (min)	210.1 ± 7.3	167.16 ± 12.2	<0.001*
Postoperative VAS			
At 1 hour	2.75 ± 1.04	3.88 ± 1.77	< 0.001*
At 2 hours	2.22 ± 1.04	3.06 ± 1.43	0.002*
At 4 hours	2.33 ± 1.15	3.00 ± 1.20	0.009*
At 24 hours	2.49 ± 1.08	2.98 ± 1.21	0.04*

Data was expressed in form of mean (SD). *P* value was significant if < 0.05. VAS: visual analogue score.

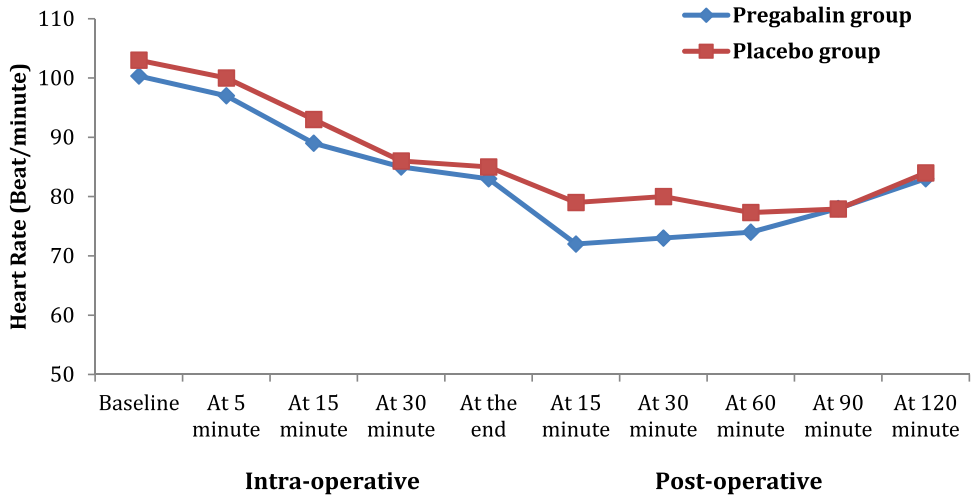

Figure 2. Change in the heart rate during the current study.

There were no statistically significant differences (P > 0.05) between both groups regarding heart rate and mean arterial blood pressure (Figures 2, 3).

4. Discussion

As good postoperative pain control is necessary, the use of pregabalin as a part of multimodal analgesia to be an adjuvant for acute pain control is progressing [8,9]. The current study was conducted to evaluate the analgesic effect of pregabalin 150 mg oral administration preoperatively on total opioid consumption and acute postoperative pain in spinal fusion surgery. Ninety patients scheduled for spinal fusion surgeries were recruited in the study. They were randomly subdivided into two groups (pregabalin or placebo).

The main finding of the current study was significantly lower morphine consumption in the first 24 hours postoperatively in the pregabalin group. Also VAS was significantly lower at different times of postoperative assessment among the pregabalin group in comparison to the placebo group, and the time to patients' request for rescue analgesia for the first time was longer significantly in the pregabalin group than in the placebo group.

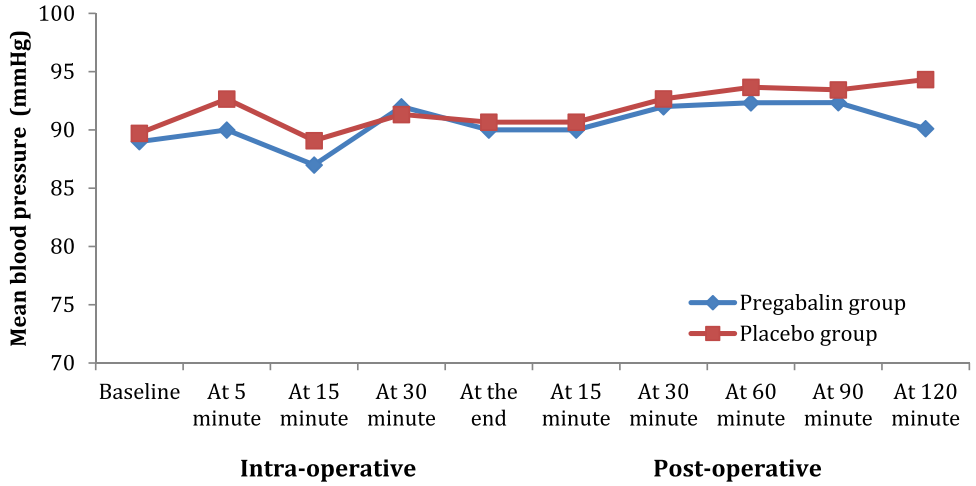

Figure 3. Change in mean blood pressure during the current study.

In accordance with this study, Akdogan et al. (2021) studied 126 patients undergoing TKR (total knee replacement) retrospectively, 65 patients was given two hours preoperatively 150 mg of pregabalin and 61 patients didn't. All patients were given the same pain management method postoperatively. Pain at rest was evaluated by using VAS several times postoperatively. The results showed that VAS scores at the all times (postoperatively between the 4th and the 48th hours) and the total amount of tramadol consumed were significantly less in the pregabalin group [10].

Also Hu J et al. (2018) stated that single preoperative dose of pregabalin significantly decreased the postoperative pain and 24-hour postoperative opioid consumption [11].

Similarly, Kheirabadi et al. (2020) stated that Pregabalin 75 mg taken orally prior to lower limb orthopedic surgery can decrease the intensity of postoperative pain, reduce the need for postoperative opioids and increase the patient satisfaction [12].

Campbell R et al. (2021), in a recently published meta-analysis, concluded that the gabapentinoids when added to multimodal analgesia perioperatively can reduce the consumption of opioids after lower limb arthroplasty, and also decrease the postoperative nausea, vomiting and pruritus [13].

In another meta-analysis done by Yao Z et al. (2014), they concluded that pregabalin had postoperative analgesic and opioid-sparing effects after gynecological surgery at rest and at movement [14].

Also, Li et al. (2019) showed evidences that the perioperative administration of oral pregabalin may lead to postoperative pain relief in a safe way [15].

Eman A et al. (2014) studied 40 patients undergoing abdominal hysterectomy and were divided into two groups: one group received preoperative oral pregabalin and the other group received placebo. In accordance with our results they showed significant decrease in the overall amount of morphine consumed in the first 24 hours postoperatively and also lower VAS scores at different times of postoperative assessment among pregabalin group in comparison to the placebo group. Also there were no significant differences between both groups regarding vital signs. Contrary to our study they found that the time to first analgesic demand showed no significant difference between the studied groups [16].

5. Conclusion

Pregabalin 150 mg as a single oral dose can reduce pain and the total opioids consumed postoperatively in patients undergoing spinal fusion surgeries.

5.1. Recommendations

It is recommended to confirm these results with future multi-center studies. Also, long duration of follow-up and assessment of the effect of pregabalin on functional outcome of those patients are recommended in the future studies.

5.2. Limitations

There are few limitations in this study. Firstly, VAS scores were used to assess pain rather than quantitative sensory testing (QST) which is a better tool since it can assess and quantify hyperalgesia with a stimulus-response gradient.

Secondly, despite recent research showing sex differences in perception of pain, we didn't consider this difference. At the same time, our study was designed as a randomized trial, and this point is a point of strength. In addition, sample size was calculated before enrollment of participants.

Disclosure statement

No potential conflict of interest was reported by the authors.

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