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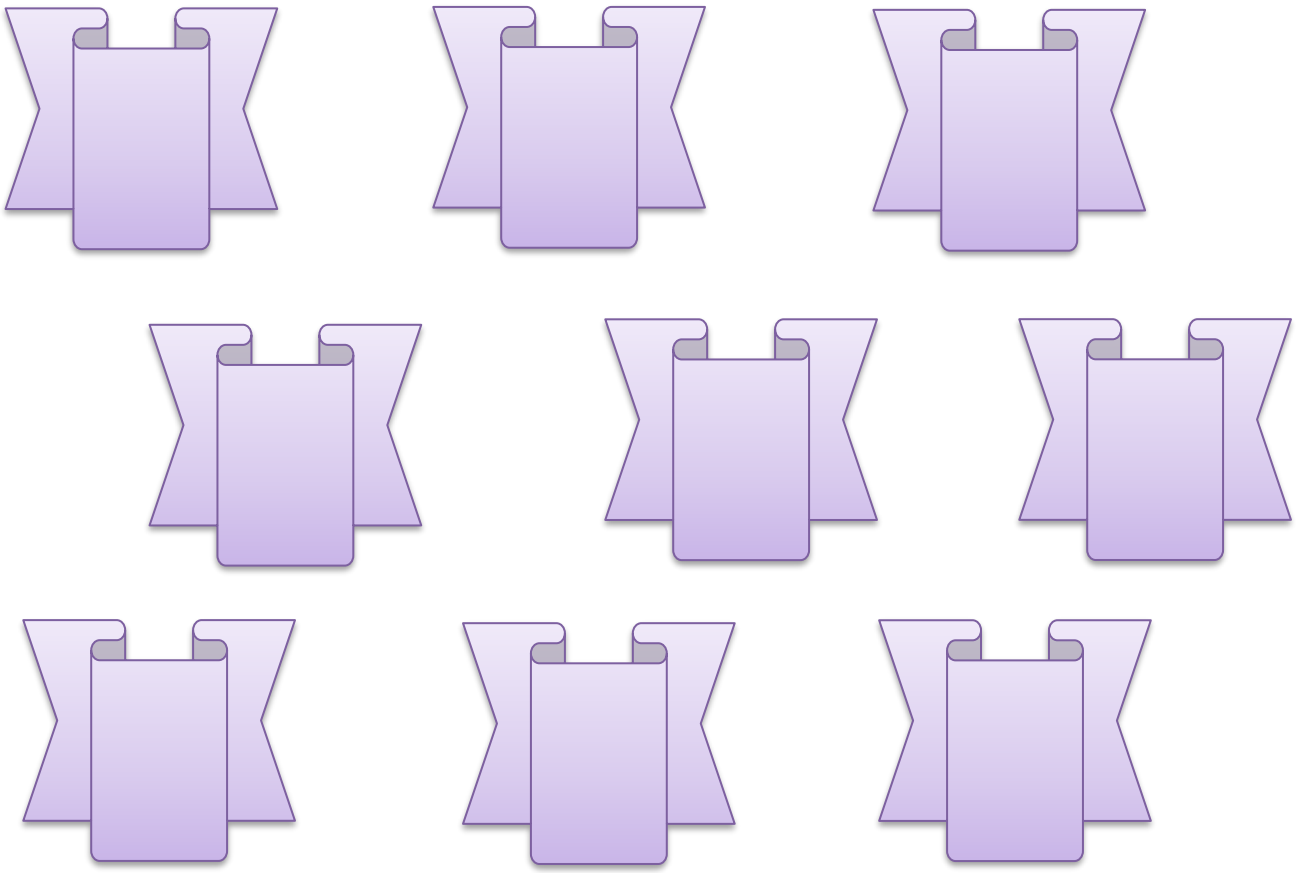

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Original Article

Optimization of The Dose of Pregabalin as Pre-Anaesthetic Medication in Patients Undergoing Total Hip Arthroplasty Under Spinal Anaesthesia: Randomized Controlled Trial

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ABSTRACT

Background and Objective: Total hip arthroplasty [THA] is frequently performed in Egypt for patients with degenerative joint disease. This procedure is performed under general anaesthesia and is associated with severe postoperative pain. Pregabalin has been described as an effective adjuvant for spinal anaesthesia. However, its optimum dose has not been standardized. Herein, we compared two different pregabalin doses [150 and 300 mg] regarding spinal anaesthesia characteristics and postoperative analgesic outcomes.

Patients and Methods: One hundred people who were going to have THA were enrolled in this prospective study. They were split into two groups at random: Group A had 50 people who took 150 mg pregabalin capsules an hour before the surgery, and Group B had 50 people who took 300 mg pregabalin capsules at the same time.

Results: Preoperative patient criteria did not differ between the two groups. Moreover, sensory block criteria, including time to reach the T10 block, peak sensory block level, and time to reach it, were also comparable between the two groups. Nonetheless, the motor block duration increased in Group B. The majority of the recorded pain scores after the operation significantly decreased in Group B during the first postoperative day. Group B showed a significant elongation of the time to the first analgesic request and a significant decline in postoperative morphine consumption.

Conclusion: When THA is done with spinal anaesthesia and 300 mg of pregabalin is taken by mouth, the pain relief is much better than when 150 mg is taken.

Keywords: Pregabalin; Optimal dose; Spinal anaesthesia; Arthroplasty

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INTRODUCTION

Hip joint fractures are the most common type of fragility fracture encountered in orthopedic practice. These pathologies are better managed by total hip arthroplasty [THA], which yields better postoperative functional outcomes than other modalities [1].

Generally, orthopedic lower limb procedures are associated with moderate-to-severe peri-operative pain. This is often associated with increased patient immobilization [2].

Most orthopedic procedures are performed under general anesthesia, the standard anesthetic modality for such procedures worldwide [3]. Nonetheless, it had a relatively short duration, which may limit its analgesic effects after surgery [4].

Numerous adjuvants have been described in the current literature to delay the onset of postoperative pain and decrease postoperative analgesic consumption following spinal anesthesia [5, 6]. Pregabalin is one of these effective adjuvants. It is an analogue for gamma-aminobutyric acid [GABA], frequently prescribed for patients with epilepsy and neuropathic pain [7].

Pregabalin binds to the α2-δ subunit located on voltage-gated calcium channels, leading to a marked decrease in calcium influx and a marked limitation in releasing multiple nociceptive substances, including substance P and other peptides [8]. The preoperative administration of this medication is associated with better control of acute perioperative pain [9]. Some reports also documented its beneficial impact on prolonging anaesthesia during peripheral nerve blocks [10]. Pregabalin is rapidly absorbed following oral administration, with peak plasma concentrations between 0.7 and 1.3 hours. Pregabalin oral bioavailability is approximately 90% and is independent of dose and frequency of administration [11].

The previous trials handling the efficacy of pregabalin as an adjuvant for spinal anesthesia had applied different oral doses [150 and 300 mg] against placebo or other medications [12], and the literature is poor with trials documenting the optimum pregabalin dose that should be administered for such a purpose.

The current trial compared two different pregabalin doses [150 and 300 mg] regarding spinal anesthesia's sensory and motor block characteristics. We hypothesized that increasing the commencement pregabalin dose would enhance the previous parameters.

PATIENTS AND METHODS

This prospective, randomized, double-blind trial was conducted at Mansoura University Hospitals. The research was carried out from April 2021 to October 2022.

Initially, the study protocol was approved by the Institutional Review Board [IRB] of Mansoura University, [code R.21.02.1203], and all patients agreed to the terms of our research after we explained the benefits and possible drawbacks of each intervention. This work has been done according to the Code of Ethics of the World Medical Association [Declaration of Helsinki] for studies that involve people [13]. The study was designed for adult patients aged between 18 and 80 scheduled for THA under spinal anaesthesia in the Mansoura University Orthopedic Surgery Department. Their physical status ranged between I and III, according to the American Society of Anesthesiologists [ASA] [14]. Contrarily, we excluded patients with obesity [BMI ≥ 35], local dermatological infections, known allergies to pregabalin, drug or alcohol abuse, major psychiatric disorders, a history of chronic pain medications, chronic kidney disease, or anticonvulsant medication intake.

The PASS software program was used to calculate the required sample size. Our sample size was estimated based on the data from a pilot study conducted in our department. This study included ten patients with the same previous criteria enrolled into two equal groups. **Group A** included 5 patients who received a 150 mg pregabalin [Lyrica 150 mg cap, Pfizer] capsule one hour before the surgery, and **Group B** included the other 5 patients who received a 300 mg pregabalin capsule [Lyrica 300 mg cap, Pfizer] The time to the first rescue analgesia showed a significant prolongation in group B [379 57.2 minutes] versus 348 26.6 minutes in group A. A sample size of 45 patients in each group was needed to achieve 90% power, and that number was increased to 50 patients for the expected dropouts.

Proper preoperative preparation was done for all participants, including history taking, clinical assessment, preoperative laboratory

workup, and radiological workup. The patients who took part also signed a written consent form that explained the purpose, method, and possible side effects of each intervention. Then, they were randomly assigned into two groups [1:1 allocation ratio] via computer-generated software. According to the commencement pregabalin dose, **Group A** included 50 patients who received 150 mg pregabalin in the form of 2 capsules [Lyrica 150 mg cap, Pfizer + a placebo capsule] one hour before the surgery. **Group B** included the other 50 patients who received 300 mg pregabalin in the form of 2 capsules [Lyrica 150 mg cap, Pfizer] simultaneously. Anesthesiologists who performed the block and health care providers who collected the data were blind to group allocation.

On the day of the surgery, the patients were taken to the operating room, where they were given a preload of ringer solution [7 ml/kg] through an 18-gauge cannula placed in a vein in their forearm. Close monitoring of the patient's blood pressure, pulse oximetry, and electro-cardiogram with three leads were also set up. The spinal anaesthesia was performed under completely aseptic conditions when the patient was in a lateral position. A 23-gauge, sharp spinal needle was inserted into the intervertebral spaces [L3–4] after infiltration of the skin surrounding the entry point with lidocaine 2% [3 ml]. After confirming the free flow of the CSF, inject 2.5 ml of hyperbaric bupivacaine 0.5%. Afterward, the patient was turned to the supine position, and his head was elevated to 15 degrees. The patient was kept in that position for 20 minutes. During that period, basic hemodynamic parameters were monitored, and sensory and motor blocks were assessed.

Both heart rate and mean arterial pressure [MAP] were recorded every three minutes during the initial half hour after spinal anesthesia. A drop in the heart rate below 50 bpm was managed by IV atropine 0.5 mg, while a drop in MAP below 60 mmHg was managed by IV ephedrine 5 mg.

Sensory blockade was tested via the "pinprick test" using a 26-gauge needle that was moved in a caudal-to-cephalic fashion at the midaxillary line. The test was repeated every one minute until reaching the peak sensory level. If the peak sensory level did not go beyond the T10 level, that patient was excluded from the study. In both study groups, the time needed to reach the T10 sensory block, peak sensory level, and the time needed to reach it were recorded.

The motor blockade was evaluated via the "modified Bromage score" [15]. The time needed for the motor block was estimated as the duration between the spinal anaesthesia and achieving a score of 1 [the inability to raise the extended legs against gravity, but the ability to move the ankle and knees were intact]. The duration of motor block was determined by the interval between the highest score obtained and regression to a score of zero after spinal anaesthesia.

After the operation, analgesia was maintained with IV paracetamol [1 gram per 8 hours] in addition to IV ketorolac [30 mg per 12 hours]. The patients were asked to express their pain using the visual analogue scale [VAS], an eleven-point scale ranging from 0 to 10 [0 for no pain and 10 for the worst pain sensation]. VAS was recorded every two hours for the initial six hours following the surgery, then every six hours for the remaining first postoperative day. If the patient reported a breakthrough pain [VAS of 4 or more], IV morphine 3 mg was commenced, and it was repeated every five minutes till desirable or undesirable effects occurred. The incidence of postoperative complications, including nausea, vomiting, pruritis, drowsiness, and urine retention, was also recorded in both groups.

Our study's main goal was to determine if increasing the pregabalin dose would improve the sensory and motor criteria of spinal anesthesia. Secondary objectives included intraoperative hemodynamics, postoperative opioid consumption, and the incidence of complications.

We used SPSS [Statistical Package for Social Sciences] version 22 for Windows® [IBM SPSS Inc., Chicago, IL, USA] for data collection, tabulation, and analysis. Categorical data were expressed as numbers [and frequencies] and compared between the two groups using the Fisher exact or Chi-square tests. For numerical data, they were expressed as the mean [with standard deviation] or median [with range]. When comparing two groups, the former was compared using the student t test, while the latter was compared using the Mann Whitney test.

RESULTS

Starting with the demographic characteristics of the two study groups, their ages had mean values of 55.66 and 56.1 years in Groups A and B, respectively. Most of the study participants were women, as they formed 64% of Group A and 70% of Group B. Both age and gender showed no significant differences between the two groups. Additionally, the two groups' ASA physical classes were comparable because class II and class III were the most prevalent, while class I patients made up a smaller percentage of our patients.

When it comes to the spinal anaesthesia parameters, the duration required to reach the T10 sensory block had mean values of 6.74 and 7 minutes [p = 0.584], while the mean time needed to reach the peak sensory level had mean values of 11.54 and 10.56 minutes in the same study groups [p = 0.181], respectively. The peak sensory level was also comparable between the two groups, and it ranged between T6 and T10 in both of them.

In terms of how motor block happens, there was no significant difference between the two groups in how it started [p = 0.096]. Nevertheless, there was a significant prolongation of its duration in Group B [148.8 vs. 132.8 minutes in Group A, p = 0.004] [Table 1].

Group B's heart rates were much lower than the other group's during the first 30 minutes after spinal anesthesia. Although these differences were statistically significant [p 0.05], they were clinically irrelevant from our anaesthetic perspective [Figure 1].

Figure [2] shows that none of the MAP measurements taken in the first half hour after spinal anaesthesia showed a significant difference between the study groups.

Most of the pain scores recorded after surgery went down a lot more in Group B than in Group A during the first day after surgery. Compared to Group A, Group B took significantly longer to ask for their first painkiller and significantly less morphine after surgery [table 2].

There were no significant differences between the two groups in the complications that happened after surgery, except for nausea, which happened more often in Group A [30% vs. 12% in Group B; p = 0.027; table 3].

Table [1]: Demographic characteristics, ASA class, and data related to spinal anesthesia in the study groups

		Group A [n= 50]	Group B [n= 50]	95% CI	P
Age [years]		55.66 ± 9.958	56.10 ± 7.833	-4.00, 3.12	0.807
Gender	Male	18 [36.0%]	15 [30.0%]	-	0.523
	Female	32 [64.0%]	35 [70.0%]		
ASA	I	2 [4.0%]	8 [16.0%]	-	0.135
	II	32 [64.0%]	28 [56.0%]		
	III	16 [32.0%]	14 [28.0%]		
The time to T10 sensory block[min.]		6.74 ± 2.266	7.00 ± 2.312	-1.17, 0.65	0.548
Time from the injection to the peak level [min.]		11.54 ± 4.277	10.56 ± 4.136	-0.69, 2.65	0.181
Peak sensory level [T]	6	3 [6.0%]	5 [10.0%]	-	0.910
	7	11 [22.0%]	9 [18.0%]		
	8	15 [30.0%]	14 [28.0%]		
	9	13 [26.0%]	12 [24.0%]		
	10	8 [16.0%]	10 [20.0%]		
The onset of motor block[min.]		8.60 ± 2.755	7.46 ± 2.998	0.00, 2.28	0.096
Duration of motor block [min.]		132.80 ± 17.961	148.80 ± 27.303	-25.17, - 6.83	**0.004**

Data is expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05. ASA American Society of Anesthesiologists; T thoracic level.

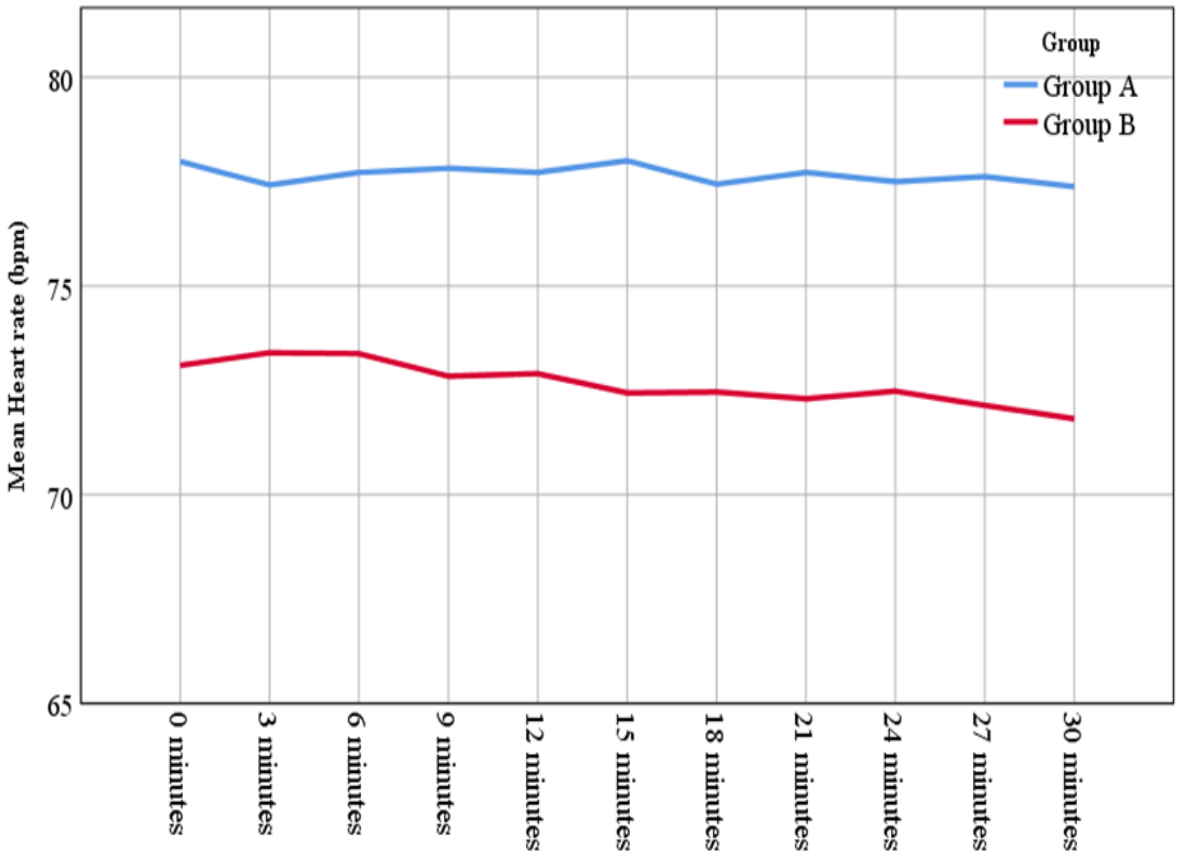

Figure [1]: Heart rate readings in the two study groups

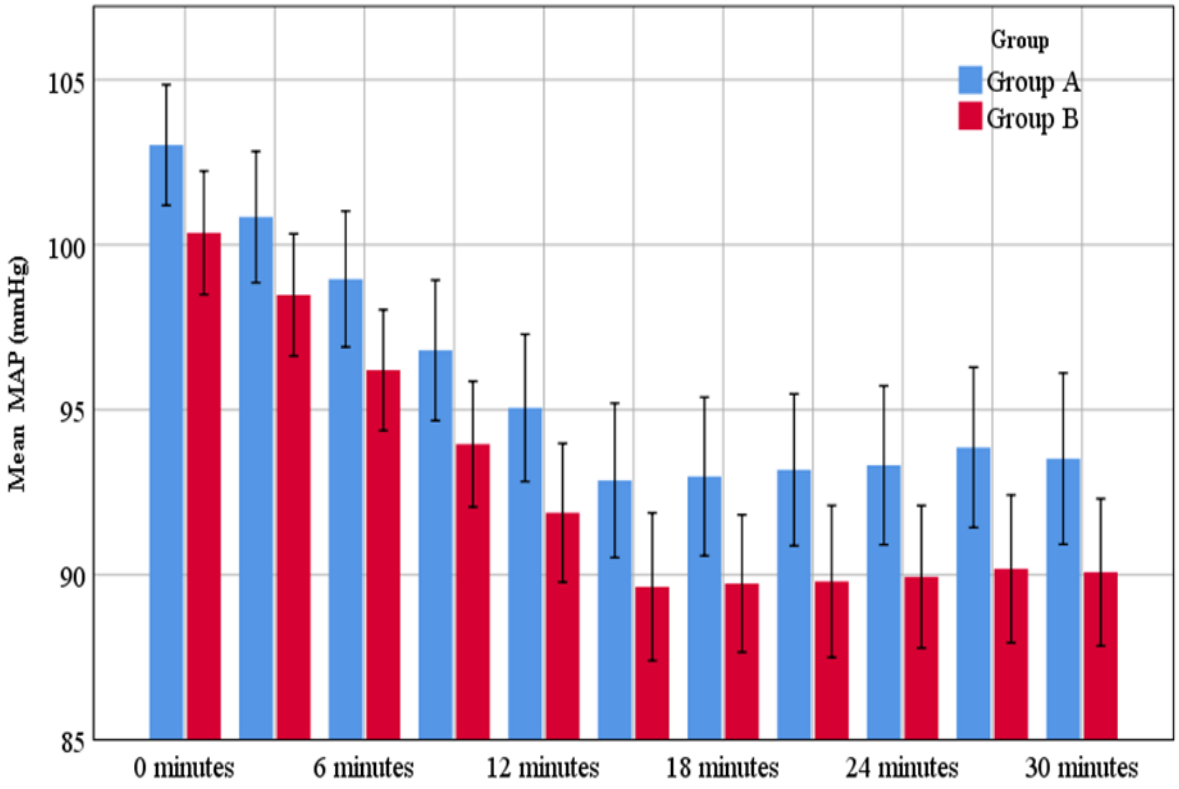

Figure [2]: MAP readings in the two study groups

Table [2]: Postoperative pain score, the first request of analgesia, and total morphine consumption in the study groups

		Group A [n= 50]	Group B [n= 50]	95% CI	P
VAS	2 hours	0.16 ± 0.510	0.06 ± 0.314	-0.07, 0.27	0.239
	4 hours	3.46 ± 1.432	2.48 ± 1.147	0.47, 1.49	**0.001**
	6 hours	3.72 ± 1.213	2.84 ± 0.934	0.45, 1.31	**0.000**
	12 hours	4.54 ± 1.110	4.10 ± 0.789	0.06, 0.82	**0.045**
	18 hours	4.38 ± 1.398	3.76 ± 1.135	0.11, 1.13	**0.020**
	24 hours	4.60 ± 1.552	3.94 ± 1.346	0.08, 1.24	**0.036**
Time of the first request of analgesia [hours]		8.20 ± 4.522	10.52 ± 4.929	-4.20, -0.44	**0.021**
Morphine [mg]		8.40 ± 2.100	7.26 ± 2.849	0.15, 2.13	**0.030**

Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05. VAS; visual analogue score.

Table [3]: Postoperative complications in the study groups

	Group A [n= 50]	Group B [n= 50]	Odds ratio	P
Pruritus	9 [18.0%]	5 [10.0%]	0.51	0.249
Nausea	15 [30.0%]	6 [12.0%]	0.32	**0.027**
Vomiting	7 [14.0%]	2 [4.0%]	0.26	0.081
Drowsiness	7 [14.0%]	10 [20.0%]	1.54	0.424
Urine retention	7 [14.0%]	3 [6.0%]	0.39	0.182

Data is expressed as percentage and frequency. P is significant when < 0.05.

DISCUSSION

This is the first time a trial has been done to figure out the best dose of pregabalin to use with spinal anaesthesia in THA procedures. We looked at how 150 mg and 300 mg of pregabalin worked one hour before spinal anesthesia. First, the reader could not find any statistically significant differences between our study groups in any of the preoperative parameters. This denotes our proper randomization technique. Additionally, this should also negate any bias skewing our findings in favor of one group rather than the other.

In our investigation, we preferred to commence pregabalin before the operation rather than post-operatively. We wanted to see if its preoperative administration had a beneficial effect on the criteria for spinal anesthesia. Also, we believe in the concept of preemptive analgesia, which entails the administration of the analgesic agent before tissue trauma or a painful stimulus. The preemptive concept hinders the changes in afferent nociceptive inputs, leading to better control of postoperative pain [16, 17]. We used the time "one hour" before surgery, as the peak serum pregabalin concentrations are obtained within one hour of its oral administration [18, 19].

In the first 30 minutes after spinal anesthesia, Group B's [higher dose of pregabalin] heart rates were much lower than the other group. Similarly, **Kohli *et al.*** reported that preemptive pregabalin 1 hour before hysterectomy under spinal anaesthesia was associated with a significant drop in heart rate compared to placebo [20]. the decreased stress and anxiety of the patient with pregabalin intake [21, 22] may explain these findings.

This study found that increasing the oral dose of pregabalin didn't make a big difference in how long it took for T10 sensory block to happen or when motor block started. The study by **Park *et al.*** confirmed the previous results. They found that taking 150 mg of oral pregabalin didn't change the time needed for the T10 sensory block or the time needed for the motor block significantly compared to the control group [23]. **Khetarpal *et al.*** also found that taking 300 mg of pregabalin before the start of sensory or motor blockages didn't make a big difference compared to controls [p > 0.05] [24].

As the dose of pregabalin went up in our study, we saw that the motor block lasted for a much longer time. The previous results may suggest that the length of the motor block caused by oral pregabalin may increase with the dose. In a previous study that compared pregabalin [150 mg] to controls, the authors noted a significant increase in the time needed for regression to a Bromage score of two in the pregabalin group [198.1 vs. 168.2 minutes in the controls—p = 0.000] [23]. **Omara *et al.*** confirmed the previous findings regarding the increased duration of the motor block with pregabalin intake [7].

The mechanism by which pregabalin enhances the motor block of spinal anaesthesia is still obscure. Its action on voltage-gated calcium channels could alter calcium influx and modulate GABAergic neurotransmission, which could explain the previous findings.

Our findings showed decreased postoperative pain scores in association with an increased pregabalin dose. Patients in the 300-mg pregabalin group also showed a prolongation of the time needed for first rescue analgesia. Consequently, total morphine consumption also diminished. This may be explained by the fact that Pregabalin binds to the 2-subunit located on voltage-gated calcium channels, resulting in a marked limitation in the release of multiple nociceptive substances [8].

Multiple studies have shown that spinal anaesthesia makes the painkilling effects of pregabalin stronger. **Park *et al.*** also said that pain scores after surgery went down a lot in the first day after surgery. Also, people used a lot less pethidine and tramadol when they took 150 mg of pregabalin beforehand [23]. **Omara *et al.*** reported that the same dose given before surgery led to a significant decrease in postoperative pain scores and the need for analgesics, as well as a significant increase in the time until the first rescue analgesic was needed [7]. In another study, the 300-mg dose was linked to a big drop in pain scores after Orthopaedic procedures compared to the control group. Even the time to the first top-up epidural dose was significantly prolonged in the pregabalin group, and postoperative diclofenac consumption markedly decreased in the same group [24].

In the current study, the number of complications after surgery was almost the same in both groups, except for nausea, which was much more common in Group A. This could be because people in the same group reported more pain or took more opioids. One should also notice a slight increase in drowsiness associated with an increased pregabalin dose. This could be secondary to pregabalin's sedative and anxiolytic effects, which are more pronounced with increased doses [10]. One should also mention that 300 mg is the highest safe single dose reported in previous pain management reports [24], ensuring that these effects were side effects of the drug and not caused by toxic levels.

Even though our trial dealt with a unique topic that has not been discussed much before, it has some problems. The main limitations are the relatively small sample size, single-center experience, and lack of long-term follow-up to assess the impact of dose increases on the incidence of chronic post-surgical pain. These drawbacks should be handled in the upcoming studies.

Conclusions: Based on the preceding findings, the oral administration of 300 mg of pregabalin is associated with significantly better outcomes after THA under spinal anaesthesia compared to the 150-mg dose. The larger dose is associated with a better postoperative analgesic profile manifested in decreased opioid need, longer time to rescue analgesia, and lower pain scores, without significant complications or drug-toxicity-related events. Therefore, the 300-mg dose should be used in such settings.

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