The Egyptian Journal of Hospital Medicine (July 2018) Vol. 73 (2), Page 6109- 6114

Preoperative Pregabalin Prolongs Duration of Spinal Anesthesia and Reduces Early Postoperative Pain

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ABSTRACT

Background: Various adjuvants have been used to prolong spinal anesthesia, with the additional advantages of delaying the onset of postoperative pain and reducing postoperative analgesic requirements. Pregabalin is an *R*-aminobutyric acid analog that binds to the α2-δ subunit of presynaptic voltage-gated calcium channels.

Objective: The aim of this work is to evaluate the efficacy of a single dose of pregabalin in terms of spinal blockade duration and its potential opioid-sparing effect during the first 24 hours postoperatively

Patients and Methods: There were limitations to the present study. First, since only 1 dosage of pregabalin was evaluated, we could not determine the most effective dosage. Second, clinically meaningful improvements in recovery were not assessed. Adequate postoperative pain control provides early postsurgical mobilization, shortened hospitalization, and increased patient satisfaction. Third, preoperative pain and anxiety scores were not recorded. Pregabalin might affect the preoperative pain, mood, and anxiety scores, and these factors can be related to the postoperative pain score.

Results: The mechanisms by which pregabalin premedication prolongs motor and sensory blocks using local anesthetics in spinal anesthesia are not fully understood. There may be several reasons for the prolongation of spinal anesthesia. Gabapentinoids are an *r*-aminobutyric acid analog that binds to α2-δ subunit of presynaptic voltage-gated calcium channels, and this inhibition decreases postsynaptic excitability by reducing potassium-evoked excitatory transmitter release. These medications provide antiepileptic, anxiolytic, and analgesic features by modulating both GABAergic neurotransmission and calcium influx. Gabapentinoid compounds produce a significant and clinically important improvement in preoperative anxiety scores. Since patients may be anxious in the perioperative period, the anxiolytic effects and euphorigenic effects of pregabalin may be beneficial.

Keywords: Gabapentin, neuropathic pain, adjuvant antiepileptic drug

INTRODUCTION

It reduces the depolarization-induced calcium influx at nerve terminals, with a consequent reduction in the release of several excitatory neurotransmitters, including glutamate, noradrenaline, substance P, and gastrin-releasing peptide [(1)].

The administration of oral pregabalin preoperatively has been reported to reduce acute postoperative pain and to prolong the duration of anesthesia produced by single-injection peripheral nerve blockade [(2)].

However, no clinical study to date has yet fully investigated whether or not pregabalin premedication affects sensory and motor blocks using spinal anesthesia and its effect upon early postoperative pain management.

Preemptive analgesia is analgesic administration that precedes the painful stimulus, thus improving postoperative pain control. It is an antinociceptive treatment that prevents the establishment of altered processing of afferent input, which amplifies postoperative pain.

This technique is utilized in acute postsurgical pain management to improve the efficacy of analgesics and thereby reduce the requirement for opioids [(3)].

Received: 12/7/2018
Accepted: 22/7/2018

In this prospective, randomized, study, we hypothesized that single dose 150mg pregabalin premedication would prolong the sensory blockade of spinal bupivacaine anesthesia in surgeries.

A secondary objective of this study was to determine if premedication with pregabalin also reduces the need for medication to relieve postoperative pain.

AIM of THE WORK

The aim of this work is to evaluate the efficacy of a single dose of pregabalin in terms of spinal blockade duration and its potential opioid-sparing effect during the first 24 hours postoperatively

PATIENTS and METHODS

Type of Study: Randmized controlled double blind consort study

Study setting: Ain Shams University Hospitals

Study period: 5 months from March to July 2018

Inclusion criteria: Surgeries done under spinal anesthesia . Age between 21 and 60 years old. Both genders. ASA I and II.

Exclusion criteria : ASA III and IV. Age younger than 21 or older than 60 years old. Hypersensitivity to any drugs used. Any contraindication to spinal anesthesia

Sampling method: Study Setting: After obtaining approval from the Research Ethical Committee of Ain shams University, this study will be conducted in the operating theatres of Ain shams University Hospitals.

double-blind, and placebo-controlled

Ethical Considerations: The study was performed after ethical committee approval and informed consent from the patients. The study protocol was explained to the patients after taking their consent to the type of anesthesia and surgical procedure.

Study Tools: Spinal needle 25 gauge and the drug pregabalin.

Study Procedure: Preoperative assessment will be done for every patient including: history, clinical examination, laboratory investigations. Patients will be educated about the numeric pain rating scale (NPRS) during the preoperative assessment.

Descriptive Statistics

Mean, Standard deviation (+ SD) and range for parametric numerical data

Frequency and percentage of non-numerical data.

Analytical Statistics:

Independent sample t-test will be used to assess the statistical significance of the difference of a parametric variable between the two independent means of the two study groups.

Chi square test is used to examine the relationship between two qualitative variables but when the expected count is less than 5 in more than 20% of the cells; Fisher's Exact Test is used.

P-value: Level of significance: P>0.05: Non significant (NS). P<0.05: Significant (S). P<0.01: Highly significant (HS).

RESULTS

Table (1): Comparison between groups according to Time to T10 sensory block, Time to Bromage 1 block and Mean of maximal sensory level.

	Group A: Pregabalin (N=25)	Group B: Control (N=25)	t-test	p-value
Time to T10 sensory block	5.05±1.34	5.15±1.03	1.034	0.790
Time to Bromage 1 block	7.52±1.44	8.34±1.44	0.139	0.106
Mean of maximal sensory level	T7	T7	0.000	1.000

This table shows no statistically significant difference between groups according to Time to T10 sensory block, Time to Bromage 1 block and Mean of maximal sensory level.

Table (2): Comparison between groups according to Time of 2-segment regression, Time for regression to L2 and Time for regression to Bromage 2.

	Group A: Pregabalin (N=25)	**Group B: Control (N=25)**	**t-test**	**p-value**
Time of 2-segment regression	91.46±13.49	69.11±11.23	4.033	<0.001**
Time for regression to L2	160.68±14.94	133.90±17.20	4.258	<0.001**
Time for regression to Bromage 2	204.04±17.30	173.25±32.55	3.183	<0.001**

This table shows highly statistically significant difference between groups according to Time of 2-segment regression, Time for regression to L2 and Time for regression to Bromage 2.

Table (3): Comparison between groups according to pain score.

Pain score	**Group A: Pregabalin (N=25)**	**Group B: Control (N=25)**	**t-test**	**p-value**
At 6 h postoperative	3.19±1.24	4.33±1.03	3.226	0.014*
At 24 h postoperative	1.65±0.72	2.27±0.72	2.658	0.011*

This table shows statistically significant difference between groups according to pain score at 6 h and at 24 hrs.

Table (4): Comparison between groups according to first analgesics request (min.).

First analgesics request, min	**Group A: Pregabalin (N=25)**	**Group B: Control (N=25)**	**t-test**	**p-value**
Mean±SD	416.12±126.90	210.94±38.73	4.880	<0.001**

This table shows highly statistically significant difference between groups according to first analgesics request.

Table (5): Comparison between groups according to total dose of pethidine (mg).

Total dose of pethidine, mg	**Group A: Pregabalin (N=25)**	**Group B: Control (N=25)**	**t-test**	**p-value**
Mean±SD	36.77±17.41	50.00±0.00	5.152	<0.001**

This table shows highly statistically significant difference between groups according to total dose of pethidine.

Table (6): Postoperative adverse effects during the first 24 hours.

Adverse effects	Group A: Pregabalin (N=25)	Group B: Control (N=25)	t-test	p-value
Dizziness	4 (16%)	2 (8%)	0.189	0.664
Drowsiness	0 (0%)	0 (0%)	0.000	1.000
Dry mouth	5 (20%)	5 (20%)	0.000	1.000
Nausea/ vomiting	3 (12%)	4 (16%)	0.011	0.917

This table shows no statistically significant difference between groups according to adverse effects.

DISCUSSION

We investigated whether pregabalin premedication prolonged the duration of a sensory block as well as the time to the first request for postoperative analgesics. This study showed that oral pregabalin administered 2 hours before spinal anesthesia prolongs both sensory

and motor blocks induced by spinal bupivacaine anesthesia. The time to the first request for postoperative analgesics was delayed, and lower rescue analgesic

requirements were observed during the early postoperative 24 hours. The length of the delay to the first request for postoperative analgesics was significantly related to the total dose of postoperative analgesics required.

Meta-analyses have demonstrated that pregabalin leads to a reduction in postoperative pain scores [(4)].

However, only a limited number of studies have been published to date about the efficacy of pregabalin in regional anesthesia, and the effect of administration of a single dose of preemptive pregabalin on the effectiveness of spinal anesthesia has not been fully reported to date.

Bafna et al. [(5)] compared the time to the first analgesic request for the groups of single dose 600mg gabapentin and 150mg pregabalin premedication in gynecological surgeries under spinal anesthesia. Both medications prolonged the mean duration of effective analgesia of a spinal bupivacaine block, but pregabalin showed significantly longer duration of effective analgesia. In the pregabalin group, the analgesic effect was maintained for 535 minutes (±32.8), which was a longer duration than our result (404 minutes (±123.2)). This might be because of the dose of bupivacaine and the difference between the types of surgery. The efficacy of perioperative administration of gabapentinoids (gabapentin and pregabalin) has been investigated in various surgeries, and clinical studies have confirmed the potential of gabapentinoids as an adjuvant for pain treatment, mostly in acute and persistent postoperative pain.

Gabapentin is a useful adjunct for the management of postoperative pain since it provides analgesia through a different mechanism than opioids and therefore makes a reasonable addition to a multimodal analgesic treatment plan. The use of gabapentin might be limited by its negative side effects, such as dizziness, somnolence, confusion, and ataxia.

Pregabalin has antihyperalgesic, anticonvulsant, and anxiolytic properties similar to those of gabapentin, but with fewer side effects as well as dose-independent absorption.

Preemptive usage of pregabalin in infraclavicular nerve blocks has been reported to result in early initiation of the motor block and prolongation of sensory block. Unlike in our study in spinal anesthesia, the duration of the motor block was not prolonged. In addition, 150 and 300mg doses of pregabalin premedication showed no differences as anxiolytic agents in peripheral nerve blocks. White et al found that preoperative pregabalin administration (70–300mg) increased perioperative sedation in a dose-related fashion. Single dose of preemptive pregabalin administration was also shown to reduce postoperative pain in third molar dental surgery (75mg) as well as double-jaw surgery (150mg) under general anesthesia. However, greater side effects were seen with 300mg pregabalin in patients for dental surgery under general anesthesia. Thus, the basis of previously published studies as well as our own pilot study, we determined that a dose of 150mg pregabalin premedication was most appropriate for this study. In addition, we observed no significant difference in the postoperative adverse effects between the 2 groups during the first 24 hours following surgery.

The mechanisms by which pregabalin premedication prolongs motor and sensory blocks using local anesthetics in spinal anesthesia are not fully understood. There may be several reasons for the prolongation of spinal anesthesia. Gabapentinoids are an *r*-aminobutyric acid analog that binds to α2-δ subunit of presynaptic voltage-gated calcium channels, and this inhibition decreases postsynaptic excitability by reducing potassium-evoked excitatory transmitter release. These medications provide antiepileptic, anxiolytic, and analgesic features by modulating both GABAergic neurotransmission and calcium influx.

Gabapentinoid compounds produce a significant and clinically important improvement in preoperative anxiety scores.

Since patients may be anxious in the perioperative period, the anxiolytic effects and euphorigenic effects of pregabalin may be beneficial.

In this study, a single dose of 150mg pregabalin 2 hours before spinal anesthesia showed sufficient efficacy during the first postoperative 24 hours. Pregabalin has an elimination half-time estimated to range from 5.5 to 6.7 hours, which is independent of the dose and frequency of administration [(6)].

On the other hand, the duration of bupivacaine is approximately 2 to 3 hours. ***Buvanendran et al.*** [(7)] found that 6 hours after a single dose of 300mg pregablain oral administration, the cerebrospinal fluid pregabalin level is high enough to reduce central nervous system hypersensitivity. Evoked pain during movement is enhanced by central neuronal sensitization [(8)] and the persistent pregabalin effects observed in our study were likely the result of preoperative pregabalin preventing central nervous system sensitization.

There were limitations to the present study. First, since only 1 dosage of pregabalin was evaluated, we could not determine the most effective dosage. Second, clinically meaningful improvements in recovery were not assessed. Adequate postoperative pain control provides early postsurgical mobilization, shortened hospitalization, and increased patient satisfaction. Third, preoperative pain and anxiety scores were not recorded. Pregabalin might affect the preoperative pain, mood, and anxiety scores, and these factors can be related to the postoperative pain score.

We investigated the effects of single dose preoperative administration of 150mg pregabalin 2 hours before spinal anesthesia and demonstrated that it prolonged the duration of both sensory and motor blocks. The mean time to the first postoperative analgesic request was delayed by 200 minutes, and the dosage of postoperative analgesics was significantly decreased in the first 24 hours following urogenital surgery relative to the control group. After further assessment of individual pregabalin dosages and types of surgery, these results can be used to improve the quality of acute postoperative recovery.

CONCLUSION

Premedication with a single dose of 150mg pregabalin before surgery promoted the efficacy of intrathecal bupivacaine and improved postoperative analgesia in patients undergoing operation under spinal anesthesia..

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