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Analgesic Effect of Oral Preemptive Pregabalin in Patients Posted for Urogenital Surgeries under Subarachnoid Block: A Randomised Controlled Trial in SMS Medical College and Hospital

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Abstract

Background and Aims

Preemptive analgesia is an analgesic administered preceding the painful stimulus, thus improving postoperative pain control. Oral pregabalin has been used previously in acute pain management but less study are present for its analgesic effect as a premedicant in spinal anesthesia.

Aim

The aim of this study is to assess and compare postoperative pain relief and regression of sensory

blockade between oral pregabalin and placebo group in patients undergoing urogenital surgeries.

Methods

Forty-four patients undergoing urogenital surgery under spinal anaesthesia were randomly allocated into two groups, group A and group B. Group A patients received oral pregabalin 150 mg and group B patients received placebo two hours prior to surgery. Then the patient was taken into surgery and spinal anaesthesia was given. The patients were monitored for regression of sensory blockade as well as for post operative analgesia. Side effects were looked for.

Result

The time required for first rescue analgesia was more in group A (pregabalin group) compared to group B(placebo group). There was no significant difference between the two groups regarding vitals intraoperatively. A significant difference was found in sensory regression, sensory blockade regressed late in group A. Number of analgesic required were also less in group A in first 24 hours surgery. No significant difference was found in side effects between the two groups.

Conclusion

A single dose oral premedicant pregabalin 150 mg two hours before surgery provided a longer analgesia post surgery, reduced the requirement of analgesics and improved the efficacy of bupivacaine given intrathecally.

Keywords

Preemptive analgesia, spinal anaesthesia, pregabalin

Trial registered under Clinical trial registry of India

Registration Number - CTRI/2021/02/030888

Introduction

Spinal anesthesia is a commonly used technique for infra-umbilical surgeries. It provides faster and effective onset of sensory and motor block along with prolonging postoperative analgesia. The patient remains awake and problems associated with airway management are minimisedor completely avoided.

From time immemorial, acute and chronic pain management has always been in the minds of medical professionals. Short and long acting local anaesthetics have been used widely for central neuraxial blocks.

Preemptive analgesia is analgesic administered preceding the painful stimulus, thus improving postoperative pain control. It is a treatment, anti-nociceptive in nature, and thus prevents the establishment of altered processing of afferent input, which amplifies postoperative pain.(1) The adjuvant drugs to local anaesthetics improve the quality and duration of subarachnoid block in terms of anaesthesia, analgesia and patient safety. It increases patient satisfaction along with comfort to a great extent. (2,3)
Pregabalin is a newer generation gabapentinoid (4). It's use as an oral adjuvant to spinal anesthesia for prolonging postoperative pain relief has not been done to a great extent.

With this background, this study is designed to see the effect of preemptive oral 150mg pregabalin on postoperative pain relief and time taken for regression of sensory blockade.

Materials and methods

Patients and exclusion criteria- Patients between the ages of 35 and 70 years with American society of Anesthesiologists grade I or II scheduled to undergo urogenital surgeries under spinal anaesthesia were included in this study. Patients were excluded if

they were known to be allergic to any medicine used in study, had a history of drug or alcohol abuse, were taking opioidor sedative medications, and had a history of psychiatric conditions. Patients with a history of taking pregabalin or gabapentin were also excluded. Patients with failure of spinal anesthesia and requiring general anaesthesia were excluded.

Anesthesia and data collection- After receiving due permission from institutional ethics committee and a written informed consent from the patients, forty-four consecutive patients posted for elective urogenital surgeries under spinal anaesthesia were divided randomly into two groups. Each group had 22 patients in it. It was a randomised, placebo-controlled double blind trial. Patients were randomised into two groups using a sealed envelope method.

Both the patient and anesthesiologist were double-blinded to the treatment, and all records were recorded by an anesthesiologist blinded to group allocation. Identical capsules of either pregabalin or placebo were prepared and a doctor who was not involved in the preoperative evaluation administered the capsule according to randomization sequence. Two hours prior to surgery, the control patients (group B) receivedplacebo and the pregabalin patients (group A) receivedcapsules containing 150 mg of pregabalin. Oxygen saturation, blood pressure and electrocardiography were monitored upon arrival to the operating room and subsequently every 5 minutes. Vitals were noted just before lumbar puncture. Spinal anesthesia was performed at L3-L4 interspace with the patient in left lateral position by using a 25 Gauge Quincke needle under strict aseptic conditions. Free flow of cerebrospinal fluid was verified before injection of the anesthetic solution 2.5 ml volume. All patients were immediately placed in a supine position following the injection. Monitoring was done using continuous electrocardiography (lead II & V), heart rate, non-invasive blood pressure and continuous pulse oximetry and patients were given 4.0 L/min of oxygen by venti-mask.

Any episode of hypotension or bradycardia intraoperatively was recorded.

When adequate spinal block achieved, the time from the end of intrathecal injection to readiness for surgery was recorded. Then the patient was then positioned for planned surgery.

Hypotension was defined as a mean arterial blood pressure < 60 mm of Hg or a decrease in systolic blood pressure by 30% from baseline values and was treated by incremental doses of mephentermine 6 mg IV and IV fluid as required.

Bradycardia was defined as fall in heart rate below 50 beats per minute and was treated with incremental doses of atropine 0.6 mg IV. Sensory blockade was assessed using a pinprick test in at the midaxillary line on both sides of the chest. Pinprick tests were performed every 1 minute until maximum sensory blockade was achieved in the relevant body segment and subsequently every 5 minutes for the next 30 minutes. Thereafter, assessments were performed every 15 minutes until recovery of sensation in the L2 segment. The time to T10 sensory block, peak sensory level, and time from the injection to the peak level were recorded. Recovery time from the sensory blockade was defined as a 2- dermatome regression of anesthesia from the maximum level. Time taken from intrathecal drug administration to patient's first demand of rescue analgesia (On VAS 4) was taken as total duration of analgesia. Postoperatively, the pain was assessed by using visual analog scale (VAS) between 0 and 10 (0 = no pain, 10 = most severe pain). It was assessed at 6

hours and 24 hours of surgery in both the groups. Patients with a VAS score of 4 or more received 75mg diclofenac intravenously. This time from intrathecal injection to first administration of rescue analgesic (total duration of analgesia) was noted.

The times of the first request for postoperative analgesia and the number of injections were recorded. Patient were monitored for 24 hrs for any adverse effects. The incidence of adverse effects or complications such as hypotension, bradycardia, drowsiness (no eye opening in response to a verbal command), dizziness, dry mouth, and nausea or vomiting was recorded. End point of study was 24 hours from the time of intrathecal injection.

Statistical analysis

Statistical analysis was performed with the SPSS, version 21 for Windows statistical software package (SPSS inc., Chicago, IL, USA). The Categorical data was presented as numbers (percent) and were compared among groups using Chi square test. The quantitative data was presented as mean and standard deviation and were compared by student's t-test. Probability was considered to be significant if less than 0.05.

Results

A total of 44 patients were assessed for the study. Statistical analysis was performed with the SPSS, version 21 for Windows statistical software package (SPSS inc., Chicago, IL, USA). The Categorical data was presented as numbers (percent) and were compared among groups using Chi square test. The quantitative data was presented as mean and standard deviation and were compared by students t-test. Probability was considered to be significant if less than 0.05. There was no substantial difference among the groups with regard to age and sex with male predominance (Table 1). No complication was seen with regards to surgical procedure.

The mean duration of 2-dermatome regression from peak sensory block levels in pregabalin group (89.32 ± 11.37 minutes) was significantly longer than in placebo group (63.18 ± 10.18 minutes) with a p value of less than 0.001 (Figure 2).The time for regression to L2 sensory block levels was also significantly prolonged in pregabalin group with a p value 0.001 (Table 2). The post operative VAS scores were noted frequently upto 24 hours (Figure 1). Upto four hour postoperatively, the VAS score were significantly lower in pregabalin groups. The 6-hour and 24-hour VAS score difference was not significant among the 2 groups. The time to the first request for postoperative supplemental analgesia was significantly prolonged in pregabalin group (413.64 ± 82.03 minutes) as compared to placebo group (201.36 ± 17.61 minutes) with a resultant p value of less than 0.001). The number of rescue analgesics required was significantly lower in pregabalin group than in placebo group (p value-0.019) (Table 3). The frequencies of side effects including dry mouth, dizziness, drowsiness, nausea and vomiting were similar in both the groups (Table 4).

Discussion

From time immemorial, acute and chronic pain management has continued to be on the mind sof medical professionals. Pain is one of the most common and most important complaints in medicine. Pain is produced from higher brain centre processing. It is a sensory experience which is generated from nervous signal.(4) Postoperative pain when not managed well, brings along with it a number of negative consequences including increased morbidity, impaired physical function and quality of life, slower recovery, increased cost of care, prolonged opioid use during and after

hospitalisation, impaired sleep, impaired physical function etc.(5,6)

And to avoid the above – mentioned consequences, the effective management of postoperative pain is a very important aspect in patient sunder going any surgery (7).

Inourstudy, forty -four patients who underwent urogenital surgeries under subarachnoid block were given preemptive oral pregabalin and placebo and effects with regards to sensory blockade and VAS score were studied.

Our study showed that the regression of sensory block was prolonged in pregabalin group. There was also a reduction in postoperative VAS scores and the number of rescue analgesics required in first 24 hours in pregabalin group.

There have been various studies demonstrating comparison between gabapentin and pregabalin and studies showing analgesic effect of pregabalin but the effectiveness of a single dose preemptive pregabalin in analgesia as well as efficacy of spinal has not been fully studied till date.

In a study done by Rahmawy G E et al.(8), authors concluded that preoperative oral pregabalin 150 mg causes earlier onset of peak sensory and motor block with increased duration of analgesia and decreased incidence of PDPH in patients undergoing elective surgeries under spinal anaesthesia.

In another study done by Kohli M et al(9), the duration of analgesia in 300 mg pregabalin group was 202.42 minutes and in150 mg pregabalin group was 175.38 minutes which was statistically highly significant. Prolongation of analgesia was correlating with the half life of pregabalin which is 4.6 hrs to 6.8 hrs.

There was a statistically significant difference among the two groups in terms of rescue analgesics required with more number required in placebo group. Our studies concurred with the study done by Park et al (10) in 2016 in which patients undergoing urogenital surgeries under spinal anaesthesia were given oral pregabalin 2 hours prior to surgery. The patients of pregabalin group had lesser requirement of analgesic postoperatively.

The mechanism of action of pregabalin in reducing pain is similar to gabapentin. Its main site of action is voltage gated sodium channel. These are present on presynaptic membrane in the peripheral and central nervous system. Pregabalin acts on alpha-2-delta subunit of these channels on presynaptic membrane(11). Binding affinity and potency of pregabalin is six times more than gabapentin. Pregabalin produces an inhibitory modulation of neuronalexcitability (12), particularly, in areas where synaptic connections are dense such as the neocortex, amygdala, and hippocampus(13,14). A study done in 2006(15) successfully demonstrated that preemptive pregabalin caused a significant reduction in postoperative VAS scores. A yet another study done in 2010(9) involved the use of 150 mg pregabalin in patients undergoing below umbilical surgeries under spinal anaesthesia demonstrated that pregabalin group had lower VAS scores than the placebo group.

The mechanisms by which pregabalin premedication prolongs motor and sensory block using local anaesthetic in spinal anaesthesia are not fully understood. It would be unwise to make a direct comparison with other studies as either the mode of anaesthesia was different or the time of administration of drug was different or the parameters studied weren't exactly the same. In our study, the time taken for two

segment regression and the time taken for regression to L2 was significantly prolonged in pregabalin group. Park et el(10) compared the time of 2 segment regression as well as the time for regression to L2 and concluded that the time taken for regression of sensory block was prolonged in pregabalin group than in placebo group.

We believe that since the patients were anxious preoperatively, the anxiolytic and sedative effects of pregabalin would have helped.

In contrast to our study, the study done by Rahmawy GE et al.(8) two segment regression in control was 72.2±7.1min and in pregabalin 74.3±1.4min and the difference was statistically not significant.

And yet another study done by Fassoulaki A et al.(16) showed that there was no statistically significant difference among groups (gabapentin and placebo) in time taken for regression of sensory level to L4. Our study does not compare with the results of above studies.

There were limitations to the present study. First, since only one dose of pregabalin was evaluated, we could not determine the most effective dosage. Secondly, as dizziness was one of the side effects, sedation score should have been studied. Thirdly, clinically meaningful improvements in recovery were not recorded.

Conclusion

We conclude from our study that oral preemptive pregabalin premedication in a dose of 150mg when compared to placebo showed

The total duration of analgesia was prolonged in pregabalin group

The number of rescue analgesics needed was less in pregabalin group

A reduction in post operative VAS score was observed in pregabalin group.

The regression of sensory block was prolonged in pregabalin group

The difference in side effects between the two groups was not substantial.

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	Group A	Group B	p value
Age distribution in years(mean±SD)	60.00±7.14	56.59±11.69	0.546(NS)
Gender distribution (female/male)	2/20	1/21	1.00 (NS)
Duration of surgery in minutes (mean±SD)	80.23±39.35	70.68±35.20	0.402 (NS)

Table 1: Demographic characteristics and duration of surgery (S-Significant, NS-Non-significant)

	Group A Mean±SD (minutes)	Group B Mean±SD (minutes)	p value
Regression of sensory blockade by two segments	89.32±11.37	63.18±10.18	<0.001 (S)
Regression of sensory blockade to L2	148.64±15.21	133.86±14.22	0.001 (S)

Table 2: Regression of sensory blockade (S-Significant, NS-Non-significant)

	Group A	Group B	p value
VAS score at 2 hours postoperatively	0.00±0.00	2.55±0.51	<0.001 (S)
VAS score at 4 hours postoperatively	3.00±0.93	3.82±0.39	0.004 (S)
VAS score at 6 hours postoperatively	4.05±0.84	3.95±1.17	0.769 (NS)
VAS score at 24 hours postoperatively	2.00±0.82	2.05±0.72	0.845 (NS)
Time of first dose of rescue analgesic in minutes	413.64±82.03	201.36±17.61	<0.001 (S)

Table 3: VAS score and time to first request of postoperative analgesic (S-Significant, NS-Non-significant)

	Group A		Group B	
	No.	%	No.	%
Drowsiness	1	4.54	0	0.00
Nil	11	50.00	14	63.63
Dry Mouth	4	18.18	4	18.18
Dizziness	4	18.18	1	4.54
Nausea/vomiting	2	9.09	3	13.63
Total	22	100.00	22	100.00
Result (P value)	0.499 (NS)			

Table 4- Side effects (S-Significant, NS-Non-significant)

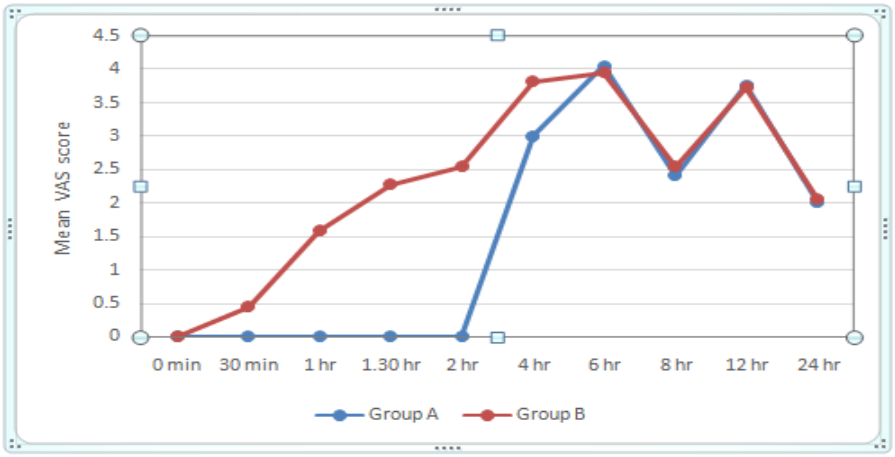

Figure 1: VAS scores at different intervals

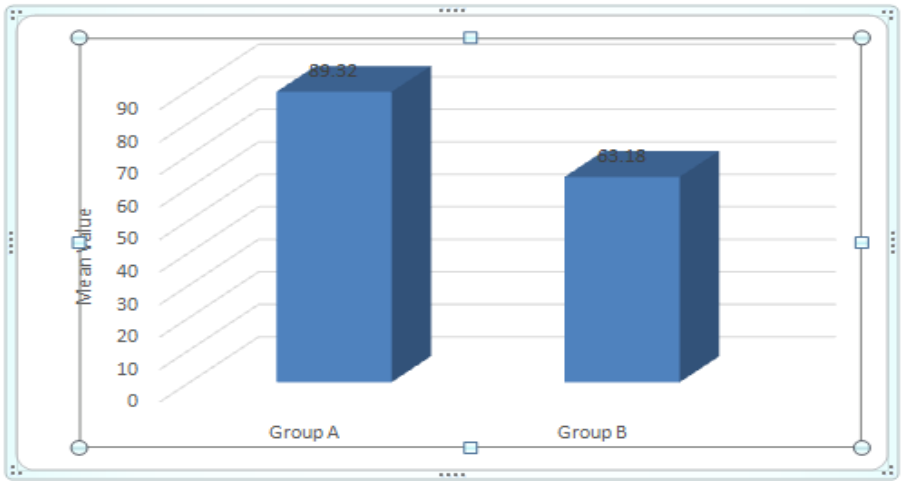

Figure 2: Time of two segment regression from highest level