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Role of pregabalin as preemptive analgesic in patients undergoing TAH under spinal anaesthesia

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Abstract

Background and Aims: Pre-emptive use of pregabalin helps in the control of postoperative pain by its anti-allodynic and antihyperalgesic activity. The objective was to evaluate whether Pregabalin 150mg when given orally preoperatively has an effect on postoperative pain and analgesic requirement in patients undergoing TAH under spinal anaesthesia.

Methods: Sixty patients presented for TAH under spinal anaesthesia were included in the study. They were randomly distributed to a placebo group and a pregabalin group receiving 150 mg pregabalin capsules 2 h before surgery. Statistical analysis was performed with the help of Statistical Package for the Social Sciences version 11. Group analysis was done using independent student 't' test and Pearson's chi - square test. Rescue analgesia consumption, postoperative pain score and incidence of adverse effects were assessed.

Results: Oral pregabalin significantly decreased the VAS score at 4 h, 6 h, and 12 h postoperatively, prolonged the duration of postoperative analgesia reaching 502.3mins, and decreased consumption of rescue analgesia.

Conclusion: Pre-emptive oral pregabalin reduced the post-operative pain scores and prolonged the time to the first request for rescue analgesics.

Keywords: pre-emptive, pregabalin, TAH, spinal

Introduction

Pre-emptive analgesia refers to the administration of an analgesic treatment before the surgical insult or tissue injury to attenuate or block sensitisation of central and peripheral pain pathway, which amplifies postoperative pain [1]. This 'protective' effect on the nociceptive system, has the potential to be more effective than a similar analgesic treatment initiated postoperative [1].

Perioperative pain is thought to involve primary hyperalgesia (peripheral nociceptor sensitization) and secondary hyperalgesia (central sensitization) [2]. Pregabalin, the gamma amino-butyric acid analogue, appear to have no effect on primary hyperalgesia, but

suppress the tissue damage induced hyperexcitability of dorsal horn neurons and hence decrease secondary hyperalgesia [2]. Analgesic action of pregabalin are mediated through their binding to the alpha-2 delta subunit of voltage gated calcium channels [5]. By reducing the hyperexcitability of neurons in the dorsal horn secondary to tissue damage, pregabalin have been useful in the treatment of postoperative pain, anxiolytic effect of these drug being an added advantage [5].

Pain following hysterectomy is often multifactorial produced from incisional site, deeper visceral structures and pain on movement such as during straining, coughing or mobilization. Abdominal procedure is more invasive than vaginal procedure and produces more pain [8]. Proper management of postoperative pain leads to early mobilization, short hospital stay and increased patient satisfaction.

The primary aim of this clinical trial was to assess the effect of pre-emptive oral pregabalin (150 mg) on postoperative pain and analgesic requirement in patients undergoing TAH under spinal anaesthesia. Postoperative sedation scores due to somnolence effect of pregabalin were measured in both groups as secondary outcome.

Methods

This randomised, placebo controlled clinical study was designed to include 60 female patients (30-60 years), ASA grade I and II, undergoing TAH under spinal anaesthesia. The study protocol was approved from the Institutional ethics committee, registered in the Clinical Trial Registry of India CTRI /2021/01/030736 and a written informed consent was obtained from all the patients.

Patients with allergy to pregabalin, history of intake of NSAIDs within 48hours before surgery, coagulation abnormalities and patients on anticoagulant and antiplatelet medications were excluded from the study.

On the day prior to surgery, a thorough preoperative evaluation was done and Visual Analog Score (VAS) was explained. Two hours prior to surgery, patients were premedicated with Tab. Pantoprazole 40mg and Tab. Alprazolam 0.5mg, and a staff nurse not involved in the study was given the study medicine. Patients were randomly allocated into two groups of 30 each based on computer generated random number table. The patients were unaware as to which group they belonged to.

Group A received Tab. Pregabalin 150mg and Group B received matching placebo.

After shifting the patients to operating room, subarachnoid block was given with Inj. bupivacaine heavy (0.5%) at a dose of 0.3mg/kg body weight with the maximum dose limited to 20 mg and the level was assessed.

After surgery, all the patients received i.v paracetamol 1g and were shifted to the recovery room. All patients were given Inj. Tramadol 50mg as rescue analgesia, once VAS exceeded 4. The patients were subsequently shifted to ward.

Postoperatively VAS scores were assessed at 0,2,4,6,12 and 24hours after surgery. Total amount of analgesic consumption was recorded. Sedation was assessed by Ramsay sedation scale and any adverse effects like giddiness, nausea, vomiting in first 24hours of postoperative period were noted.

Statistical analysis was performed with the help of statistical package SPSS (Statistical Package for the Social Sciences) version 11. Baseline characteristics of both the groups were tabulated by descriptive statistics (mean, standard deviation) and frequency table. Group

analysis was done using independent student 't' test and Pearson's chi - square test.

Observation & Results

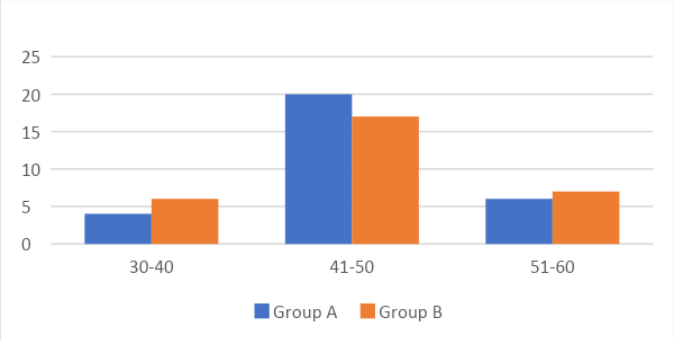
Demographics and dose of Bupivacaine

The groups were comparable with each other with respect to the demographic details and dose of bupivacaine (p >0.05)

	Group A	Group B	P - Value
Age (Years)	43.4	47	0.747
Weight (Kgs)	58.27 ± 5.26	56.57 ± 4.96	0.202
Duration of Surgery (Min)	102 ± 14.67	109 ± 17.68	0.127
Dose of Bupivacaine (Mg)	17.6 ± 1.62	18.1 ± 1.22	0.244

Table 1: Age Distribution of the Study Sample

Age Distribution	Group A		Group B	
	Number of patients	Percentage	Number of patients	Percentage
30-40	4	13.33%	6	20.00%
41-50	20	66.67%	17	56.67%
51-60	6	20.00%	7	23.33%



There is no difference in age between the groups and are comparable.

Weight

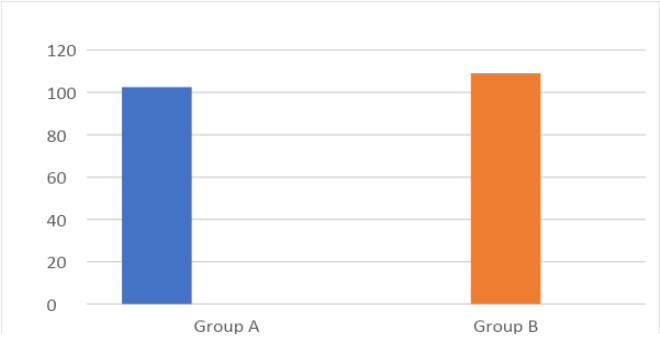
The mean weight of patients in group A was found to be 58.27 kg with a standard deviation of 5.26. Patients in group B were found to have a mean weight of 56.57Kg with a standard deviation of 4.96. The P value calculated was 0.202, which is not significant. This indicates that both groups are comparable in terms of weight.

ASA PS Classification

In both groups (Group A & Group B), 24 patients in each group belonged to ASA-I and 6 patients in each group belonged to ASA-II. The P value was found to be greater than 0.05, hence value is not significant. Therefore, patients in both groups were comparable in terms of ASA classification.

Table 2: Duration of Surgery

Group	N	Mean	Std. Deviation	P -value
Group A	30	102.5	14.67	0.127
Group B	30	109	17.68	0.127



The mean duration of surgery in group A patients were found to be 102.50 minutes with standard deviation of 14.67. Group B patients had a mean duration of surgery of 109 minutes with a standard deviation of 17.68. The P value was found to be 0.127, which is not significant. Hence there is no difference between groups with regard to duration of surgery.

Table 3: Visual analogue scale (VAS) score of Group A vs Group B

Vas	Group A Mean (SD)	Group B Mean (SD)	P Value
0 Hour	1.83 (0.507)	2.03 (0.346)	P.08>0.05 Not Significant
2 Hour	1.93 (0.254)	3.96 (0.928)	P.000<0.05

			Significant
4 Hour	2.6 (0.770)	5.2 (0.379)	P.015<0.05 Significant
6 Hour	2.96 (1.098)	5.7 (0.556)	P.000<0.05 Significant
12 Hour	2.83 (0.913)	5.13 (1.008)	P.039<0.05 Significant
24 Hour	3.43 (1.073)	5.8 (0.664)	P.000<0.05 Significant

All patients were monitored for VAS scores at rest in the immediate postoperative period (0 h), at 2, 4, 6, 12, and 24 hours postoperatively. In the immediate postoperative period (0 h),the mean VAS score was found to be 1.83 in Group A and 2.03 in Group B with no statistically significant difference between the groups. This may be due to the effect of spinal anaesthesia.

The mean VAS scores during postoperative period of 2, 4, 6, 12 and 24 hours in group A patients were 1.93, 2.6, 2.96, 2.83and 3.43 respectively.

In Group B patients the mean VAS scores were 3.96, 5.2, 5.7, 5.13 and 5.8 respectively. In all these time intervals, the P value was less than 0.05 which is highly significant. This shows that there is a significant reduction in the mean VAS scores in patients receiving pregabalin premedication compared to placebo in the first 24 hours after surgery.

Table 4: Time for Rescue Analgesia

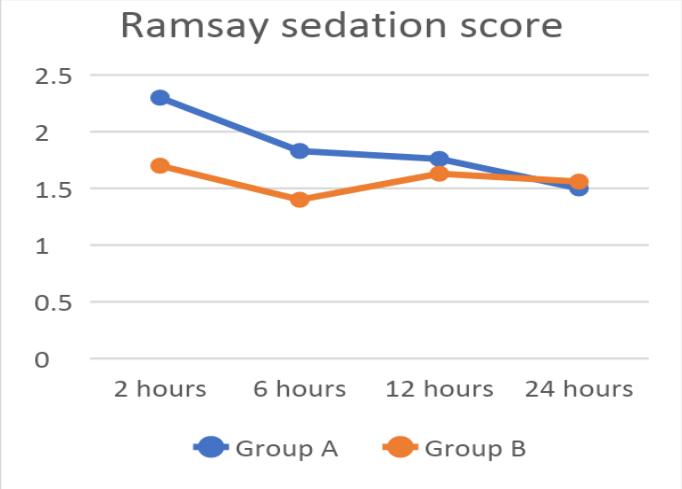
Time For Rescue Analgesia	Group A	Group B	P-Value
	287.38	217.13	<0.001

Duration In Minutes from The End of Surgery	Group A	Group B
Mean	502.3	137.8
SD	101.087	44.483
Range	220-550	60-205

Postoperatively all patients were monitored for VAS scores periodically. When the VAS score at rest is 4 or greater, patients were given Tramadol 50mg intravenously as rescue analgesia. It is the time interval between providing spinal anaesthesia and administration of first dose of rescue analgesia. It was found that this Time interval was 137.8minutes in group B and 502.3 minutes in Group A. The P value was found to be 0.000, which is considered significant. This indicates that Time for rescue analgesia was significantly greater in group A compared to group B. Hence Pregabalin gives prolonged post-operative pain relief compared to placebo group.

Table 5: Sedation Scores and Other Adverse Events

Adverse Effects	Group A	Group B
Nausea	1	4
Vomiting	0	3
Giddiness	3	0



Postoperatively all patients were assessed for the level of sedation using Ramsay sedation score periodically at 2, 6, 12 and 24 hours. Sedation scores were significantly higher in group A at 2h and 6h postoperatively. The mean sedation scores at 2 and 6 hours of postoperative period in group A were 2.3 and 1.83. In Group B, the scores were 1.7 and 1.4 respectively. However, the scores at 12 and 24 hrs were not statistically significant among the 2 groups. Overall mean (SD) sedation scores

of group A when compared with group B at 24h were significant (P= 0.0001).

Table 5 shows the incidence of side effects in the two groups. In group B, 4 patients had nausea and 3 patients had vomiting while in Group A, only 1 patient had nausea and 4 patients had giddiness**.** These values were not statistically significant (P = 0.078). This may be due to increased doses of tramadol in the placebo group.

Discussion

The concept of pre-emptive analgesia to reduce the magnitude and duration of postoperative pain was paved in 1983 by Woolf who showed evidence for a central component of post injury pain hypersensitivity in experimental studies. Though pregabalin was first identified as treatment for neuropathic pain, pregabalin has been reported to be as effective for acute postoperative pain control.

The amino butyric acid analogues such as Pregabalin contain analgesic components and are anti-nociceptive. It is postulated that CNS sensitivity may lead to post-operative pain growth. Administering amino butyric acid analogues before surgery, before inflammatory trauma, or surgical stimulation may reduce the degree of sensitivity of the CNS.

The pathogenesis of postoperative pain includes inflammatory, neurogenic, and visceral mechanisms.

Multimodal approach to control postoperative pain is considered as a best therapeutic option. Post-operative pain is the reason for several complications like delayed recovery, metabolic alterations, anxiety and stress to the patients and patient dissatisfaction.

The main aim of multimodal analgesia is to reduce the dosage and side effects of opioids by replacing with drugs which act by different mechanisms.

This study was done to assess whether pregabalin given preoperatively has a role in reducing acute postoperative pain.

The results of my study showed that pregabalin 150mg given two hours before surgery significantly reduces postoperative pain scores, analgesic requirement, prolongs the time for requirement of first analgesic dose without increasing the incidence of side effects except for giddiness.

Bafna et al studied 90 adult patients undergoing gynecological surgeries under spinal anaesthesia. The patients were randomly classified into 3 groups: a placebo group, a gabapentin (600mg) group, and a pregabalin (150mg) group. They showed that the oral use of either pregabalin or gabapentin prolonged the mean duration of effective analgesia of subarachnoid block, prolonged the mean duration of motor block, and improved postoperative analgesia without a significant increase in the incidence of side effects or complications. Pregabalin showed a significantly longer duration of effective analgesia than gabapentin.

A study conducted by Agarwal et al evaluated the effectiveness of a single dose of Pregabalin 150 mg pre-operatively in patients undergoing laparoscopic cholecystectomy. Patients receiving pregabalin showed significant reduction in VAS scores in the first 24 hrs post surgery which is similar to the results obtained in this study.

There might be a limitation in our study , in that we used only one dose of oral pregabalin. but it was arrived at by analyzing the observations of previous studies, in that increased doses had more adverse effects and lower doses were ineffective in providing adequate analgesia.

Conclusion

This study demonstrates that a single oral dose of pre-emptive pregabalin 150mg reduces the postoperative pain scores and total dose of analgesic consumption in patients undergoing total abdominal hysterectomy under spinal anaesthesia.

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