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Original Research Article

Comparison of efficacy of oral pregabalin and oral paracetamol as pre-emptive analgesics in patients receiving spinal anaesthesia for lower limb surgeries

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ABSTRACT

Introduction: Pre-emptive analgesia is - blockade of afferent nerve fiber before surgical stimulus. Pre-emptive analgesia reduces the physiological consequences of nociceptive transmission provoked by the procedure. Pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Consequently, immediate postoperative pain may be reduced and the development of chronic pain may be prevented. Aim of this study was to evaluate the efficacy of preemptive Pregabalin and Paracetamol and comparison between the two.

Materials and Methods: 120 patients of ASA class 1 and 2 scheduled for lower limb surgeries under spinal anaesthesia were randomly allocated into two groups of 60 each, Group PG received Pregabalin 150 mg & group PA received 1gm Paracetamol, 1 hour before surgeries respectively, Spinal anaesthesia technique was standardized to all patients. Post operative pain was assessed using VAS at 2, 4, 6, 12, 24 hours after surgery. If VAS more than 3, rescue analgesia was given as Inj. Tramadol 1mg/kg. Time of first rescue analgesic & total amount of analgesic over 24 hours noted.

Results: Mean VAS for group PG at 2, 4, 6, 12, and 24 hours after surgery was lower compared to the group PA. Time of first rescue analgesia (4.3±1.2 hrs PG vs 3.3±1.1 Hrs PA) and total number of rescue analgesia for 24 hours period post operatively was significantly lesser for group PG compared to PA.

Conclusion: Pre-operative administration of oral Pregabalin 150mg was an effective adjuvant for acute pain after surgery compared to oral Paracetamol 1000mg.

1. Introduction

Postoperative pain remains a challenging problem and many patients undergoing surgery continue to experience unacceptably high levels of pain post operatively, which is generated through multiple mechanisms.[1]

Effective management of postoperative pain leads to increased patient satisfaction; earlier mobilization and reduced hospital stay. One of the methods used for management of postoperative pain is pre-emptive analgesia - blockade of afferent nerve fiber before surgical stimulus. "Pain signals from damaged tissue are not transmitted to the central nervous system (CNS) through hard-wired pathways. In contrast, nociceptive signals once initiated, will launch a cascade of alterations in the somatosensory system, including an increase in the responsiveness of both peripheral and central neurons. These alterations will increase the response to subsequent stimuli and thus amplify pain".[2]

"Pre-emptive analgesia reduces the physiological consequences of nociceptive transmission provoked by the procedure. Owing to this protective effect on the nociceptive pathways, pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Consequently, immediate postoperative pain may be reduced and the development of chronic pain may be prevented· It modifies the peripheral and central nervous system processing of noxious stimuli, reduces post-operative pain and opoid consumption".[3]

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Based on the multimodal post-operative pain management concept, recent studies shows that pre-emptive use of NSAIDS, Paracetamol or Pregabalin are an effective adjuvant in treatment of post-operative pain and decreases the post-operative opioid use.[4]

"Pregabalin is a structural analogue of gamma amino butyric acid (GABA). It acts by pre-synaptic binding to alpha-2-delta subunit of voltage gated calcium channels that are widely distributed in spinal cord and brain. By this mechanism, Pregabalin modulates the release of several excitatory neurotransmitters, such as glutamate, nor epinephrine, substance-P and Calcitonin gene related peptide. It leads to inhibitory modulation of overexcited neurons and returns them to a normal state. Centrally, Pregabalin could reduce the hyper excitability of the dorsal horn neurons that is induced by tissue damage. Based on these properties Pregabalin was used as pre-emptive analgesia".[5,6]

Paracetamol inhibits both isoform of cyclooxygenase COX-1 and COX-2. Current evidence points to multisite activity in the central nervous system involving inhibition of prostaglandin synthesis and interaction with both serotonergic and cannabinoids pathways. Paracetamol has been used successfully in management of postoperative pain when used pre-emptively and this has been demonstrated by several studies.[7]

Literature search revealed that are very few studies that compare Pregabalin and Paracetamol as pre-emptive analgesic. With this background we planned to study and compare the analgesic effect of both the drugs as pre-emptive analgesic.

2. Aims and Objectives

1. Assessing the analgesic efficacy of pre-emptive Pregabalin and pre-emptive paracetamol in terms of duration and quality.
2. To compare post -operative analgesia of both drugs.
3. Adverse effect of either drug.

3. Materials and Methods

3.1. Source of Data

After obtaining clearance from institutional ethical committee this prospective randomized comparative study was conducted at Shri B. M Patil Medical College Hospital, Vijayapur on 120 patients posted under spinal anaesthesia for lower limb surgeries from December 2017 to August 2019.

3.2. Sample size calculation

With Anticipated Mean Difference of VAS score between study groups as 2.5 and Anticipated SD as 3.25, the minimum sample size per group is 60 with 90% power and 1% level of significance.

Total is 120

By using the formula:

$$n = \frac{n = (z_\alpha + z_\beta)^2\ 2\ SD^2}{MD^2}$$

Where Z = Z statistic at a level of significance

MD = Anticipated mean difference

SD = Anticipated Standard deviation

3.3. Inclusion criteria

1. Patients from age 20-65yrs undergoing elective surgery
2. ASA grade I and II

3.4. Exclusión criteria

1. Uncooperative and unwilling patient
2. Hypersensitivity to drugs
3. History of neurologic or seizure disorder
4. Surgeries lasting for more than 3 hours

4. Methodology

Informed and written consent was taken from selected patients. Following approval of institutional ethics committee, 120 patients were taken up for receiving spinal anesthesia for lower limb surgeries, all the patients were evaluated thoroughly on the previous day of the surgery. A detailed history, complete physical examination and routine investigations were done for all patients and patients were explained about visual analogue score.

4.1. Randomization

The study population of 120 with age and sex matched were randomly selected and divided by computer generated random number tables into two groups with 60 patients in each group.

Group PG- Received Pregabalin 150 mg orally 1 hour prior to surgery with 5ml of water.

Group PA- Received Paracetamol 1gm orally 1 hour prior to surgery with 5ml of water.

Patient was monitored preoperatively, for baseline pulse rate, non invasive blood pressure (NIBP) and SPO2. Once the patient is inside the OT, IV line is secured; preloading with 10ml/kg/hr of ringer lactate was done.

Under aseptic precautions, after painting with betadine and spirit and draping the patient, lumbar puncture at L_3-L_4 interspace using a 25/26G Quincke's spinal needle with patient in left lateral/sitting position is done. Bupivacaine heavy(0.5%) at a dose of 0.3mg/kg body weight is injected into the subarachnoid space after noting the clear free flow of CSF, with the operating table in horizontal position. Patients are turned supine immediately and are given supplemental oxygen 2-4L/min, and level of block checked.

Intraoperative SPO2, pulse rate and blood pressure were monitored.

Post operative pain was assessed with using visual analogue score at 2, 4, 6, 12, 24 hours after surgery.

4.2. Rescue analgesia

VAS consists of a 10 cm line anchored at one end by a label such as "NO PAIN" and at other end by a label "WORST PAIN IMAGINABLE" The patient simply marks the line to indicate the pain intensity and the provider then measures the length of line to mark a point scale. All the patients will be instructed about VAS and to point out the intensity of pain on the scale. (0-No Pain, 10-Worst Pain).

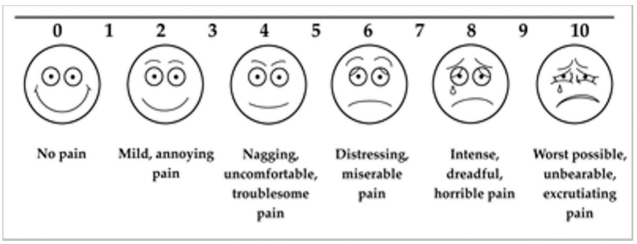

Fig. 1: Visual analogue score

If visual analogue score is more than 3, analgesia was given in the form of Inj Tramadol 1mg/kg. Time of first analgesic given post operatively and the total amount of analgesic given in 24 hours were noted.

4.3. Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of N, mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and data was analyzed by Chi square test for association, Comparison of means using t test, ANOVA and diagrammatic presentation.

5. Results

The mean age in group PG and PA were 41.70±13.96 and 40.23±12.62 respectively and comparable between both the groups (p value-0.547). The both groups were comparable statistically as far as sex is concerned. The number of ASA grade I patients in group PG were 38 and in group PA were 36.The number of ASA grade II patients in group PG were 22 and in group PA were 24. Both groups were comparable as far as the ASA grading was concerned as the p value is 0.707 (p value>0.05).

Figure 2 showing that mean visual analog score for group PG at 2, 4, 6, 12, and 24 hours after surgery was lower as compared to the corresponding rates for the group PA. This difference in VAS scores was significant for all times except at time 4 hrs and 6 hrs after surgery (p<0.05).

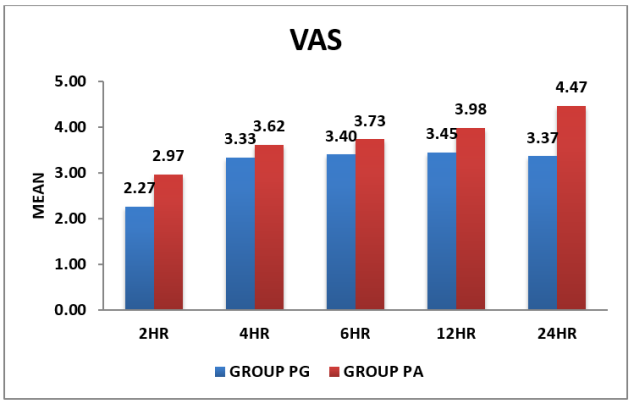

Fig. 2: Mean vas score between study group

Figure 3 shows that the mean time of 1st rescue analgesia for group PG was 4.3±1.2 Hrs and for group PA it was 3.3±1.1 Hrs. The time required for first rescue analgesia in group PA was early compared to group PG and which was statistically significant (p value less than <0.05).

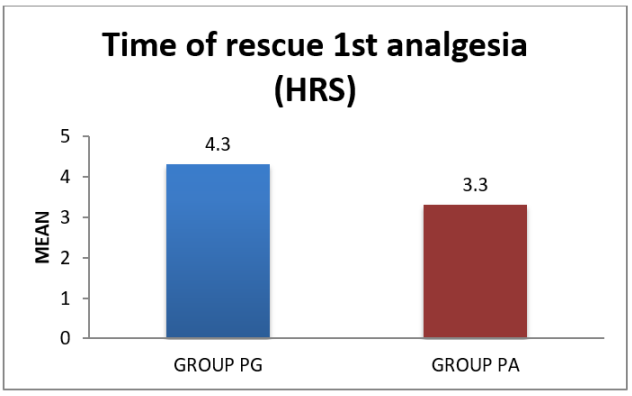

Fig. 3: Time of rescue 1st analgesia between study groups

Figure 4 showing the mean number of total rescue analgesia in 24 hrs for group PG was 1.6±0.6 and for group PA was 2.9±0.7. The total number of rescue analgesia requirement was more in group PA compared to group PG and which was statistically significant (p value less than <0.05).

Figure 5 showing group PG had higher episode of vomiting compared to group PA but was not statically significant as p value is 0.298.

6. Discussion

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[8] Pregabalin is a lipophilic GABA analogue approved by FDA for clinical use. It is superior to other routinely used analgesics in

Table 1: Demographic profile of both the groups

Demographic Profile	Group PG	Group PA	P Value	Significance
Age(Years)	41.70±13.96	40.23±12.62	0.547	NS
Gender(F:M)	09:51	13:47	0.345	NS
ASA Grades	38:22	36:24	0.707	NS

Note: * significant at 5% level of significance ($p<0.05$)
NS - Not Significant

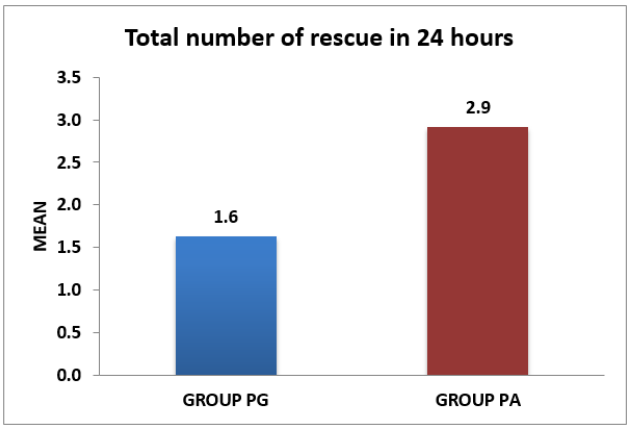

Fig. 4: Total number of rescue analgesia in 24 hours between study groups

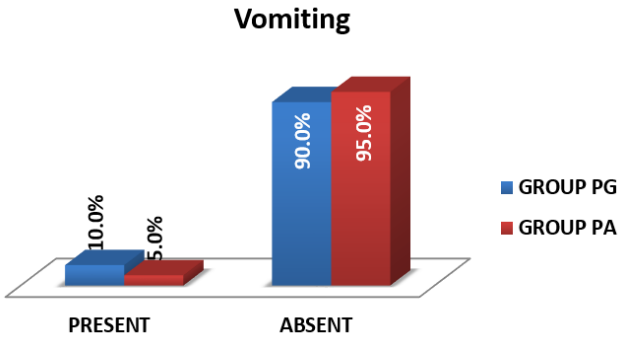

Fig. 5: Comparison of vomiting between study groups

that it reduces the anxiousness of the patient, is effective against neuropathic component of pain and is available at a reasonable cost. "Pregabalin binds to the $\alpha 2$-δ sub unit of voltage-gated calcium channels and modulate the release of several excitatory neurotransmitters such as glutamate, norepinephrine and substance P. Few authors have noticed increased incidence of adverse effects when used in higher doses. Hence we limited the dose of pregabalin to 150 mg in our study. Hence pregabalin reduces the hyperexcitability of the dorsal horn neurons of spinal cord that is induced by tissue damage and thereby decreases perception of acute postoperative pain". [9]

Paracetamol is often included with non-steroidal anti-inflammatory drugs in classifications of analgesics, even though it has differences in both action and side effect profile. It was proposed that paracetamol exerted its analgesic action by inhibition of centrally situated isoforms of the cyclo-oxygenase enzyme". [10] More recently, other central mechanisms of action have been proposed.

In this study, Demographic data like age, gender, male to female ratio and ASA status was taken into consideration. In our study mean age distribution in group PG was 41.70±13.96 and in group PA 40.23±12.62. The age distribution was higher in group PG compared to group PA but was statistically not significant. The groups were comparable. Comparison of gender distribution among the two groups shows that males were higher in both the groups when compared to the female, which was statistically not significant. (Male: Female -85%:15% and 78.3%:21.7% in group PG and group PA respectively). ASA status in both groups were comparable.

These findings were similar to the study by Bon Sebastian et al., (2016)who had 90 patients aged between 18 and 60 years old of both sex of American Society of Anaesthesiologists (ASA) physical status I and II undergoing lower limb orthopedic surgeries under spinal anaesthesia. Results of the their study too, did not show significant difference in the demographic data of the groups of patients as regard age, male to female ratio, ASA physical status. [11]

Group PG has significantly less VAS score then group PA for 24 hours of Post operative period**.** The mean visual analog score for group PG at 2, 4, 6, 12, and 24 hours after surgery was lower as compared to the corresponding rates for the group PA. This difference in VAS scores was significant for all times except at time 4 hrs and 6 hrs after surgery ($p<0.05$).

Similarly in the study by Mohamed Ommid et al.,(2015) "who found that there was no difference observed in the first analgesic requirement time values between the two groups ($p>0.05$). A statistically significant decrease was observed in the VAS scores of the Pregabalin group at 1, 4, 12 and 24 hours after surgery ($p<0.005$). Total morphine consumption in the Pregabalin group was statistically significantly lower than in the control group at 8, 12 and 24 hours after surgery ($p<0.005$). No significant difference was observed between the two groups regarding side effects during the first postoperative 24 hours ($p>0.05$)". [12]

Time requirement of first rescue analgesia with group PG mean duration was of 4.3±1.2 hrs and group PA

mean duration 3.3±1.1 hrs and p values < 0.001which statistically significant. It shows Pregabalin has better post-operative analgesia compared to Paracetamol. Total number of rescue analgesia with group PG was 1.6±0.6 and compared to group PA which was 2.9±0.7, which is statistically significant with p values <0.01. It shows that requirement of total dose of rescue analgesia is less with Pregabalin group compared to Paracetamol group.

This finding was similar to the study by Esmat et al., (2015) who found that first rescue analgesia requirement in Paracetamol group was 27.5min and for Pregabalin 150mg and Pregabalin 300mg group it was 164 min and 166 min respectively. [13]

In our study incidence of post-operative nausea and vomiting was not significant in either group, but in comparison to group PG (6 patients) has higher incidence of vomiting compared to group PA (3 patients). Group PG had higher episode of vomiting compared to group PA but was not statically significant as p value is 0.298.

According to Joon Ho Kim et al., (2014), "study the incidences of PONV were similar in both groups (P=0.666), and the incidence of sedation was higher in the placebo group (P=0.022). Multivariate analysis on sedation scores could not be performed to correct for the use of additional analgesics because no patient complained about sedation in the Pregabalin group. The incidence of PONV was low, and there were no sedation scores of 2 and 3 in either group". [14]

Our study found that the Pre-emptive administration of Pregabalin and Paracetamol has better post-operative analgesia and of longer duration, reduces the requirement of rescue analgesia.

The main findings of our study were in accordance with the studies done by Ibrahim M et al., Jon Ho Kim et al., Mohammed Hamid et al., Prashanth Gotham RJ SK et al.,Anitha Kumari et al,.who found that administration of pre-emptive Pregabalin and Paracetamol improves the post-operative analgesia.

7. Conclusion

Based on the finding of the study, we can conclude that pre-operative administration of oral Pregabalin 150mg was an effective and a safe adjuvant for acute pain after surgery compared to oral Paracetamol 1000 mg. Pregabalin reduces the postoperative pain score and total analgesic consumption and there were no other significant side effects in the postoperative period.

8. Source of Funding

None.

9. Conflict of Interest

None.

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