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Effect of two different dosages of pre-emptive pregabalin on the post-operative pain score after elective nasal surgeries: A prospective, randomised, double-blinded study

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Abstract

Good perioperative pain management is beneficial for both the patient and doctor. Poor pain management can lead to delayed patient mobility, increased hospital stay and chronic pain syndrome in susceptible patients. An important concept in pain management is the idea of pre-emptive analgesia. The recommendation is to administer analgesia prior to noxious stimulus to block peripheral as well as central nociception maintaining it throughout intra and post-operative period. One drug for such use is Pregabalin, which we used in our study on 62 patients undergoing elective nasal surgeries between 2017 and 2018 to assess analgesic efficacy of 75 mg vs 150 mg of pre-emptive Pregabalin. We observed that the mean Numerical Rating Scale (NRS) score was lower in patients receiving 150 mg Pregabalin compared to those receiving 75 mg at all times, with a p value of <0.05 . The former group also needed lower rescue analgesic dosage and a longer interval of first rescue analgesic dose time with comparable hemodynamic parameters in both groups.

Keywords: Pre-emptive pregabalin, post-operative pain, elective nasal surgeries, double-blinded study

Introduction

Perioperative pain management strategy constitutes comprehensive planning and execution, which is very procedure specific. Pain, considered the 5th vital sign, should be treated aggressively as it can trigger a sympathetic responses, emotional disturbances and pre-operative hemodynamic variations. Perioperative pain management is crucial with regards to patient satisfaction, early ambulation, improved patient outcome and cost-effectiveness. [1] The WHO, International Association for Study of Pain (IASP) and its European Federation declared that, 'Pain Management is a fundamental human right and the aim must be to turn it into a global reality. [2] An important concept in pain management is of pre-emptive analgesia. In early 20th century, Crile was the first person to formulate the idea of pre-emptive analgesia. [3] The idea is to give anaesthesia prior to tissue insult or injury. Pre-emptive analgesia is an anti-nociceptive treatment that prevents the establishment of altered processing of afferent input, which amplifies post-operative pain. The use of neuraxial blockade and regional nerve blocks with adjuvants have provided superior pain relief in the post-operative period and have a reduced need of post-operative analgesia as well as diminished opioid consumption. [4] Pregabalin, a lipophilic GABA analog with anticonvulsant, anxiolytic and sleep modulating properties have been extensively studied, with doses ranging from 75 mg to 1200 mg. [5] Even single doses of pre-emptive Pregabalin reduces the need for post-operative analgesia. Our study aimed to investigate 75 mg and 150 mg given as a single dose in patients undergoing nasal surgeries for their effect on post-operative pain scores and need for rescue analgesics

Material and Methods

The Study was done at Sri Ramchandra Institute of Higher Education (Deemed to be University), Chennai, India between 2017 to 2018 after approval of Ethics Committee.

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Study design

Prospective randomised double blinded trial

Sample size

62 patients, 31 in each group
 Group A-Pregabalin 75 mg
 Group B-Pregabalin 150 mg

Inclusion criteria

- ASA 1 and ASA 2 patients
- Ages 18-75 years, posted for elective nasal surgeries.

Exclusion criteria

- Patient refusal
- Patients on corticosteroids, benzodiazepines, tricyclic antidepressants in the preoperative period - Significant cardiac, renal, pulmonary and hepatic disease.
- History of allergy to Pregabalin.
- Patient with anticipated difficult airway.
- Body mass index more than 35 mg/kg square

Observations and Results

The patients were randomly assigned to the two groups. There was no statistically significant difference in the two groups in terms of age, gender, demographics & clinical characteristics. Also, the ASA physical status, quantity of local anaesthetic used, duration of surgery were all similar. Distribution of surgery in the two groups, was as follows, Septoplasty in Group A was 41.9% while it was 38.7% in Group B. Similarly, FESS was 58.1% in Group A while it was 59.7% in Group B.

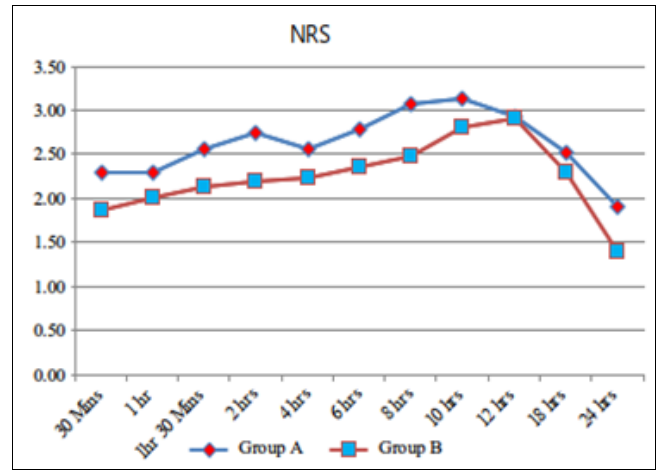


Fig 2: Mean NRS score of the two groups

The difference between mean time for administration of first rescue analgesic was compared for the two groups. It was 10.10 hours for Group A while it was 13.27 hours for Group B. P value of 0.001 which is statistically significant.

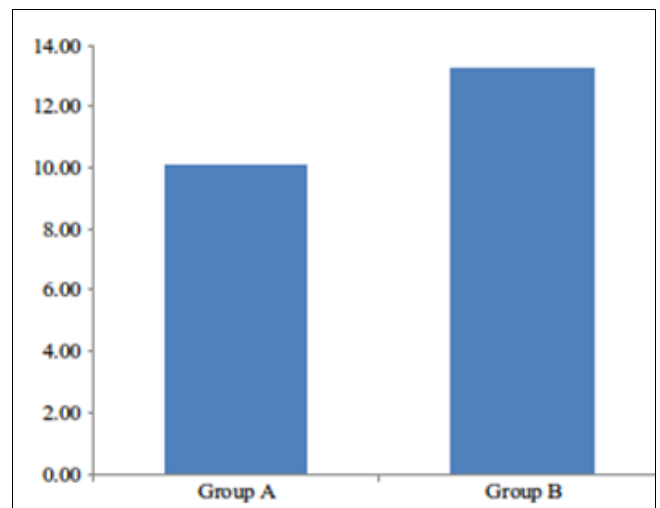


Fig 1: Distribution of surgery in two groups

Average NRS scores obtained in 24 hours were compared, NRS scores were compared using Mann-Whitney U test and Wilcoxon test, providing two tailed assessment for significance.

NRS scores were lower at 30 mins, 60 mins, 90 mins, 2 hours, 4 hours, 6 hours & 8 hours in group B than in A and was statistically significant. There was however no statistically significant difference between NRS of the two groups at 10, 12 and 18 hours respectively.

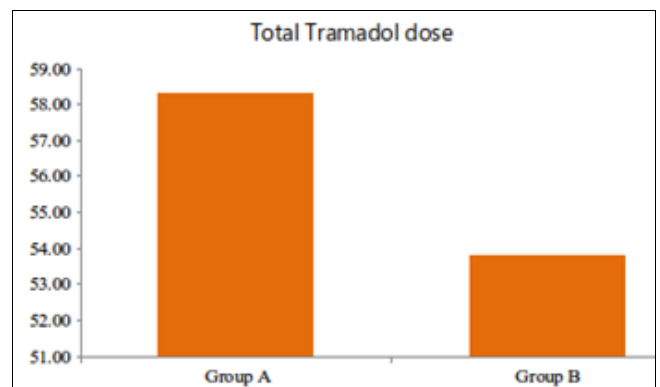


Fig 3: Mean time for 1st rescue analgesic

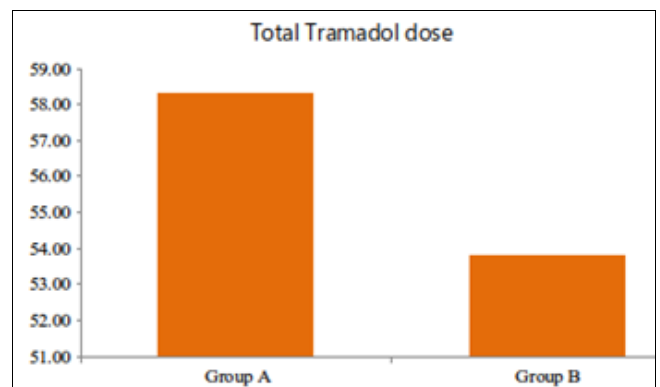


Fig 4: Mean Tramadol dose for the two groups

Need for rescue analgesics in the two groups was compared, 30 patients in group A, while 26 patients in group B needed rescue analgesics. Of the total study population, 7 patients had required a second dose of rescue analgesics out of which 5 belonged to Group A and 2 were from Group B.

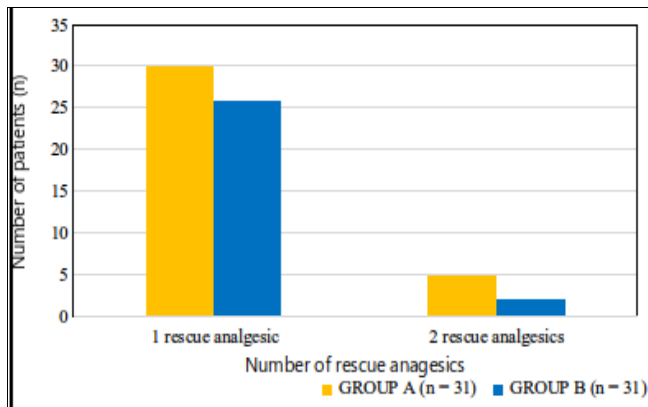


Fig 5: Need for rescue analgesic in two groups

Ramsay Sedation Scores for two groups was compared at different time intervals.

Sedation scores were analysed using Mann Whitney U test. Mean sedation scores at times T0, T1, T2, T3, T4 were higher in Group B than in Group A. The difference was statistically significant, with a p value of <0.001. None of the patients in both groups had sedation score of >4.

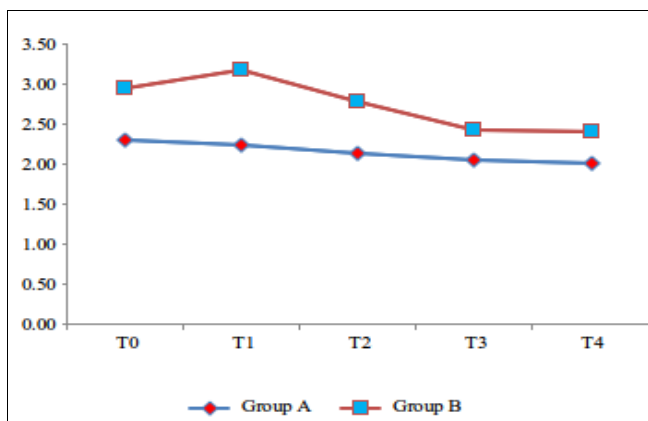


Fig 6: Sedation scores of the two groups

No patient had delayed emergence from anaesthesia or delayed discharge from PACU. Hemodynamic parameters in both the groups were comparable throughout the peri operative period with no statistically significant difference.

Discussion

Suboptimal pain management leads to significant discomfort and morbidity in the immediate post-operative period. Multimodal analgesia constitutes current practice strategy in acute pain management. [6] Pregabalin has been investigated for the same across various surgical specialties with doses ranging from 75 mg to 1200 mg. Pregabalin is a lipophilic GABA analogue. Gabapentin and Pregabalin have proven efficacy in chronic neuropathic pain, for example diabetic neuropathy, post herpetic neuralgia, spinal cord injury & phantom limb pain, to name a few. [7] There are two hypotheses suggesting two different mechanisms of action of gabapentinoids. One suggests action via voltage dependent Calcium channels. [8] Here it modulates the

release of several excitatory neurotransmitters like glutamate, nor epinephrine and substance P. Alternatively, another hypothesis postulates anti nociceptive mechanism that may arise through activation of nor adrenergic pain inhibiting pathways in spinal cord in brain [9]. ENT surgeons employ various techniques in nasal surgeries, such as stripping of inflamed mucosa, turbinate dissection & placement of pack in situ, all of which contribute to varying degrees of pain & discomfort in the post-operative period [10-12].

Pain management has been advocated by use of NSAIDs, opioids, nerve blocks among others [13]. Pregabalin used pre-emptively has been shown to decrease analgesic requirement over a wide range of doses. In our study the mean NRS scores were lower in the patients belonging to the group that had received 150 mg Pregabalin (Group B) than those in patients who had received 75 mg of Pregabalin (Group A). The NRS score at all times from NRS 30 (30 minutes post-surgery) to NRS 8 (8 hours post-surgery) was lower, with statistically significant P-value <0.05. We observed a decrease in the NRS scores in the early post-operative period (first 8 hours after surgery) which correlates with the pharmacokinetic profile of Pregabalin, with an elimination half-life of 4.6-6.8 hours [14] Kim *et al*, reported reduction in the pain score for 12 hours post operatively after septoplasty, where the patients had received pregabalin prior to induction and 12 hours after the first dose. The VNRS scores were significantly lower only till the first 12 hours post-operatively, in their study. But we observed lower NRS scores for 8 hours following surgery, with a single pre-emptive dose of 150 mg pregabalin in our study. Kim *et al*, however, acknowledged the possible confounding effect of dexamethasone on postoperative analgesia. Hence, in our study, we avoided the use of glucocorticoids so as to try and isolate the beneficial effect, of pregabalin. [15]

Jokela *et al*, reported a decrease in early post-operative VAS scores in patients undergoing day-care laparoscopic gynaecological procedures after 150 mg T. pregabalin compared to 75 mg of Pregabalin. This correlates with our finding of early post-operative pain relief evidenced by lower NRS scores with a single dose of 150 mg of pregabalin [16]. Demirhan *et al*, in his study, reported a median dose of tramadol requirement as 20 mg (PCA) in the first 12 hours and 60 mg in the first 24 hours following septoplasty in patients who had received 150 mg of pregabalin [17]. Sagit *et al*, found no difference in post-operative analgesic consumption between patients who had received pregabalin 75 mg and 150 mg ($p > 0.05$). Our study arrived at a similar conclusion, where the two groups did not show any significant difference with respect to their 2-hour tramadol consumption. The difference between our study and the one conducted by Sagit *et al*, was the omission of glucocorticoids which allowed us to assess the effect of Pregabalin alone, without any confounding elements. There was no statistically significant difference in the tramadol consumption in our two groups. All patients were prescribed T. Acetaminophen 650 mg to be given 8th hourly as a standard analgesic regimen which possibly contributed the decreased Tramadol consumption [18]. In our study, the mean sedation scores were higher at extubation and for the first 2 hours in the PACU in patients who received 150 mgs of pregabalin (Group B) with $p \leq 0.01$. However, none of the patients had any delayed emergence from anaesthesia nor any delayed discharge from the Post-anaesthesia Care Unit (which was defined as PACU stay > 2 hours). Hence, we concluded that despite the statistical difference between the two groups, with respect to the sedation scores, there was no

clinical significance in our population. White PF *et al.*, concluded that single dose pre-emptive pregabalin produces sedation in a dose-dependent manner.^[19] They had assessed sedation levels with pregabalin 75 mg, 150 mg and 300 mg against a control group and the highest sedation scores had been reported with Pregabalin 300 mg ($p < 0.05$).

Jadeja *et al.*, in their study, found the sedation scores to be higher in patients who were given pregabalin 150 mg in middle ear surgery^[20]. Demirhan *et al.*, found no effect on intra operative haemodynamics in patients undergoing rhinoplasty and septoplasty after preoperative pregabalin 150 mg. Similarly, our patients had similar intra operative hemodynamic parameters in both the groups.

Conclusion

In our study, comparing 2 doses (75 mg versus 150 mg) of single dose of Pregabalin given preoperatively, in patients undergoing elective nasal surgeries, we found that, A- The analgesic efficacy was superior with 150 mgs of Pregabalin, for the first hours in the post-operative period B- The NRS scores were lower along with the reduction in the number of rescue analgesic doses with 150 mgs of Pregabalin C- The time of rescue was prolonged and the sedation score was relatively higher with 150 mgs of pregabalin.

Limitations

Sample size and limited to only nasal surgeries

Abbreviations

NRS- numerical rating scale, mg- milligrams, WHO- World Health Organisation, GABA- Gamma-aminobutyric acid, kg- kilograms, ASA- American Society of Anaesthesiologists score, FESS- Functional endoscopic sinus surgery, ENT- Ear, nose and throat, NSAIDs- non-steroidal anti-inflammatory drugs, PCA- patient controlled analgesia, PACU- post anaesthesia care unit.

Conflict of Interest

Not available

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