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Research Article

Comparative study of single dose pre-emptive pregabalin vs. Placebo for post-operative pain relief in middle ear surgery

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Abstract

Objectives: The present study was designed to evaluate effect of Pregabalin on pain scores and analgesic requirements in middle ear surgeries.

Methods: ASA physical status I-III adults scheduled for elective middle ear surgery under general anesthesia were taken for study. Post-operative pain severity was assessed using VAS. Two study groups were designed. Group P (Study Group) received oral Pregabalin capsule (150 mg) while Group C (Control group) received oral placebo capsule one hour before surgery. The primary outcome was pain score in the recovery unit and patients were followed for 24 hours.

Results: Pain scores were significantly lower in pregabalin group as compared to placebo group especially after 1 and 4 hours. More number of patients was sedated in pregabalin group compared to placebo.

Conclusions: It can be concluded from our study that single dose preoperative pregabalin improves analgesia in early postoperative period and reduces analgesic consumption but with increased sedation without respiratory depression.

Keywords: Pregabalin, post-operative analgesia, ear surgery

1. Introduction

Pain has been found to be one of the three most common medical causes of delayed discharge after ambulatory surgery.Despite progress that has been made with regard to postoperative pain control and the development of new standards for pain control protocol; many patients continue to experience intense pain after surgery. Interest has been focused on the analgesic, sedative, anxiolytic and opioid sparing effects of pregabalin, a structural analogue of GABA and a derivative of gabapentin in various pain settings, including postoperative pain. Of a similar mechanism of action, it is thought to possess a superior pharmacokinetic profile than gabapentin.[1]

Pregabalin is a structural analog of γ-aminobutyric acid, which shows analgesic, anticonvulsant, and anxiolytic effects. In many countries, it is approved for the treatment of neuropathic pain, the pharmacological basis of which is presynaptic binding to the α 2-δ subunit of voltage-dependent calcium channels that are widely distributed in the spinal cord and brain[2]. Opioid sparing effects and improved pain scores have been seen after abdominal and pelvic surgery. Middle ear surgery involves bone drilling and extensive dissections. No studies are done with pregabalin for ear surgeries. So, we decided to investigate efficacy and safety of pregabalin for postoperative analgesia in ear surgeries.

2. Method

After Institutional Ethics committee`s approval, sixty American Society of Anesthesiologists (ASA) physical status I-III adults scheduled for elective middle ear surgery under general anesthesia were taken for study. In all patients, hospital stay was minimum 24 hours. Inclusion criteria were 18 Years of age or older, ASA status of I II, or III, undergoing elective ear surgery namely tympanoplasty or modified radical mastoidectomy. Exclusion Criteria were ASA IV or V, renal disease, bronchial asthma or acid-peptic disease contra-indicating use of diclofenec injections, history of obstructive sleep apnea, history of seizure or other neurologic disorders, currently taking gabapentin or pregabalin for other medical purposes, known allergic reaction to pregabalin from previous use, blood pressure less than 90 mm Hg, history of addiction, moderate to severe respiratory disorder. To detect a difference of VAS of 2 between the groups, with 80% power at an α of 0.05, a sample size of 27 per group was required allowing for 10% dropout rate, a total sample of 60 was recruited. All the patients were made familiar with a standard 10 cm visual analogue scale (VAS) on pre-operative visit. Two study groups were designed. Group P (Study Group) received oral Pregabalin capsule (150 mg) while Group C (Control group) received oral placebo capsule one hour before surgery. The placebo capsules were prepared by pharmacy into identical capsules to maintain blinding. They were packed in sequentially numbered packages which were given to recruited patient in random order by computer generated random numbers, by a person not involved in any other part of study.

All the patients were pre-medicated with injection Glycopyrolate intravenous (I.V.) 0.2 mg, injection Ranitidine 50 mg I.V. , injection Diclofenec sodium(1.5 mg/kg) I.V. and injection Ondensetron 4 mg I.V. before induction.

Patients were monitored with ECG, noninvasive blood pressure and pulse oximetry (SpO_2). Pre-oxygenation with 100% O_2 was done for 3 minutes. A standard balanced general anesthesia technique was used in all patients. Induction was done with injection Thiopentone Sodium 5-7 mg/kg till loss of eyelash reflex. Endotracheal intubation was facilitated with injection Succinylcholine 1.5 mg I.V.

Appropriate size cuffed Endotracheal tube was inserted and the anesthesia was maintained with Isoflurane with 50% N2O & 50% 02. Neuromuscular blockade was maintained with Vecuronium Bromide. Intra-operative monitoring included ECG, NIBP, HR and SPO2.At the end of surgery residual neuromuscular black was antagonized with injection Glycopyrolate 0.08 mg/kg and Neostignine 0.05 mg/kg I.V.

After Tracheal extubation, patients were transferred to post-anesthesia care unit. Post-operative pain severity was assessed using VAS. Assessment of VAS pain score were made at 1, 2, 4, 6, 12, 24 hours in post-operative period. Assessment of sedation scores were also made at 1, 2, 4, 6, 12, 24 hrs. Inj. Diclofenac sodium intravenous bolus 1.5mg/kg was given I.V. if VAS was three or more. Inj. Tramadol 50 mg intravenous bolus was given if no pain relief occurred after 10 minutes.

The primary end points were the pain scores during first 24 hours post operatively. Other end points include total diclofenac dose and adverse events.

3. Observation and Results

Table – 1: Age Distribution

Age (Years)	No. of patients Pregabalin	No. of patients (Placebo)
20 – 30	15 (50%)	17 (56%)
31 – 40	8 (27%)	8 (27%)
41 – 50	7 (23%)	5 (17%)

Table – 2: Sex Distribution

Sex	No. of patients Pregabalin	No. of patients (Placebo)
Male	13 (44%)	17 (56%)
Female	17 (56%)	13 (44%)
Total	30	30

Table – 3: Post – operative pain score in pregabalin and placebo groups

Variable (Time)	Pregablin (n = 30) VAS mean +/- SD	Placebo (n = 30) VAS mean +/- SD	P Value
1 hr.	3.78±0.92	6.13±1.74	<0.0001
4 hrs.	3.36±0.54	3.86±0.46	0.0001
8 hrs.	3.26±0.48	3.82±0.42	<0.0001
12 hrs.	3.23±0.43	3.73±0.53	0.0005
18 hrs.	3.20±0.41	3.56±0.52	<0.0001
24 hrs.	2.78±0.39	3.46±0.48	<0.0001

Figure 1: Post – operative pain score in pregabalin Vs placebo groups

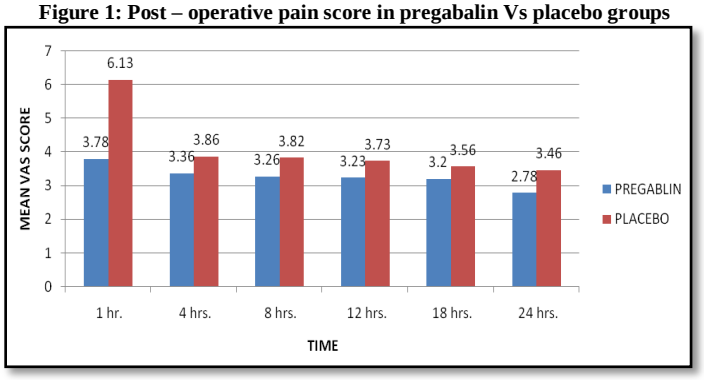

Table 4: Number of patients requiring injection Diclofenac sodium

VAS	Pregablin (n = 30) No. of patients receiving diclofenac	Placebo (n = 30) No. of patients receiving diclofenac	p-value*
1 hr.	10	25	0.0002
4 hrs	1	4	0.0009
8 hrs.	0	1	-
12 hrs.	0	0	-
18 hrs.	0	0	-
24 hrs.	0	0	-

* Fischer's exact test

In our study it was observed that patients in pregabalin group had significantly lower pain scores at all-time interval in comparison to placebo group, particularly in the early four hours of the post-operative period.

Table – 6 Incidence of side effects

Side Effects	Pregabalin	Placebo	p-value*
Sedation	12	3	0.015
Dizziness	2	0	0.493
Nausea	0	2	0.493
Vomiting	2	5	0.424
Pruritus	0	0	-
Urinary retention	0	0	-
Visual disturbances	0	0	-

* Fischer's exact test

4. Discussion

Pain during and after surgery can lead to sensitization and consequently over-sensitivity to pain, it can also transform post-operative acute pain into chronic pain. Relieving pain during an operation by administering opioids is a common practice, which can also result in undesirable side effects. In order to scale down these side effects, other non-opioid drugs can be utilized. Pregabalin is an analogue of gammaaminobutyric acid (GABA) which can be effective in dealing with post-operative pain. Studies also suggest that gabapentin[3] has a satisfactory effect in alleviating post-operative pain. Pregabalin has been introduced as the new gabapentinoid with a higher efficacy and more desirable pharmacological profile than gabapentin. Therefore, it seems that pregabalin could be a better choice in alleviating post-operative pain.

4.1 Dose

In a review done by Zhang *et al*; five trials with six treatment arms used a perioperative pregabalin dose of less than 300 mg/ day and combined data showed a statistically significant opioid-sparing effect of pregabalin.[1] Paech *et al*[2] did not observe any reduction in analgesic requirement after 100 mg pregabalin after gynec surgeries. The dose was lower compare to other studies which resulted in no effect of pregabalin on analgesia. Agrawal *et al*[4] gave patients a 150 mg dose of pregabalin, before a laparoscopic cholecystectomy under general anesthesia to relieve pain. The pain intensity was significantly lower in the group receiving pregabalin, than in the control group. We used same dose of 150 mg pregabalin as routinely surgeons at our institute infiltrate the operating site with xylocaine adrenaline, so less analgesia is needed.

4.2 Visual analogue scale

Balaban *et al*[5] studied randomized placebo controlled trial of pregabalin on post-operative pain intensity after laparoscopic cholecystectomy. They concluded that post-operative pain scores were significantly lower in pregabalin group as compared to placebo group.

Chang *et al* administrated pregabalin 150 mg 1 hr before and 12 hrs after an operation, but they did not find statistically significant differences in post-operative pain scores in these two groups.

Mathieson *et al*[8] studied effect of oral pregabalin 300 mg one hour before surgery. They studied effects of pregabalin in two different painful surgeries like hip arthroplasty and abdominal hysterectomy. No statistically significant difference was found in both groups of pregabalin and placebo.

Ghai *et al*[6] studied randomized controlled trial to study effect of pregabalin and gabapentin on post-operative pain after abdominal hysterectomy. They concluded that post-operative pain scores were decreased with single pre-operative dose of both pregabalin and gabapentin after initial hour of recovery which was consistent with our study. There was no difference after initial hour. They concluded that it may be due to the fact that both drugs have a relatively shorter half-life and given as single dose pre-operatively.

Kim *et al*[7] studied effect of pregabalin on post-operative pain after mastectomy. Assessment of pain scores were done in both pregabalin and placebo group 1, 6, 24 and 48 hours after surgery. VAS scores were significantly lower in pregabalin group as compared to placebo group in initial 8 hours.

In our study patients were given oral pregabalin 150 mg 1 hr before surgery. Post-operative pain was assessed in the recovery room with the help of visual analogue scale (VAS) 0,1,2,4,8,12 and 24 hrs post-operatively. Pain scores were significantly lower in pregabalin group as compared to placebo group especially after one and four hrs which is concurrent with the many of the studies stated above.

The difference in results may be due to variation in the pain depending on surgery and whether it is visceral or somatic. In our study for ear surgery, pregabalin was effective in reducing VAS scores.

4.3 Post-operative Diclofenac requirement

Patients with pain scores of 3 or more were given inj. diclofenac sodium 75 mg. Number of diclofenac doses required were calculated and total analgesic consumption were recorded in 24 hrs. It was observed that total numbers of patients requiring diclofenac were significantly lower in pregabalin group as compared to placebo group.

Several studies have been done on pre-operative pregabalin use and post-operative analgesic consumption which have similar results as compared to our study.

Gilron I[10] *et al* concluded that Pregabalin reduced movement evoked pain with additional lower analgesic consumption and this lead to enhanced functional recovery post-operatively.

Zhang *et al*[1] in their study reported that there was statistically significant difference in opioid consumption during first 24 hours after surgery. They concluded that pregabalin had opioid sparing effect in first 24 hours. Reduction in the opioid requirement resulted in decreased incidence of post-operative nausea and vomiting.

Jokela *et al*[11,12] did two different studies on pregabalin. In first study they gave 300 mg oral pregabalin pre-operatively in patients undergoing laparoscopic hysterectomy. They concluded that pre-emptive pregabalin reduced post-operative oxycodone consumption with improved analgesia. In second study they gave 150 mg pre-emptive pregabalin in patients undergoing minor gynaecological surgery. They concluded that there was no difference in the amount of post-operative analgesics required.

Ghai *et al*[11] concluded that time to first analgesic requirement was longest in pregabalin group as compared to gabapentin group which may be due to quicker onset and better analgesia due to pregabalin.

4.4 Side effects

In our study, only side effect that was statistically significant in pregabalin group was sedation. Patients of pregabalin group had sedation in early post-operative periods. These patients had complained of mild sleepiness but patient responded normally to verbal commands. No respiratory depression was seen. Other side effects that were seen with pregabalin group were vomiting and dizziness.

Ghai *et al*[6] concluded that incidence of side effects did not differ in both groups except sedation and somnolence that were significant in pregabalin group.

Zhang *et al*[1] concluded that the incidence of postoperative vomiting was significantly lower with the use of pregabalin. This might be related to the decreased use of opioids after surgery and the consequent decrease in opioid-related adverse effects. The incidence of visual disturbance, however, was significantly higher in the pregabalin group. There were also more patients with sedation, dizziness, and headache in the pregabalin group, although no statistically significant differences were observed. These side-effects are well known and have been reported in various chronic pain trials. Therefore, pregabalin should be used with caution in ambulatory surgery. Side-effects may also influence the use of opioids. It is possible that over the more sedated patients in the pregabalin group will use less opioid. They reported that incidence of visual disturbances was high in pregabalin group.

Sharaswat *et al*[13] in their study concluded that most common side effects that were seen with pregabalin were sedation and somnolence in the early post-operative period that subsided over 2-3 hours.

Alimian *et al*[14] in their study concluded that apart from sedation, nausea and vomiting were also seen in pregabalin group but much less than in the control group. So, it was not statistically significant. Other side effects that were commonly seen with pregabalin group like dizziness and visual disorder were not seen in any of our patients.

Few limitations of our study were that we did not observe long term effect on chronic pain as gabapentinoids are known to reduced hyper sensitization to surgical pain; they may have effect on chronic pain. Our sample size is small. We did not analyze data on first demand of analgesic.

5. Conclusion

Our clinical study demonstrated that pre-emptive oral pregabalin reduces diclofenac requirement post-operatively which was significantly lower as compared to placebo group. Only side effect that was statistically significant was sedation which was higher in pregabalin group as compared to placebo group. So, it can be concluded from our study that single dose preoperative pregabalin improves analgesia in early postoperative period and reduces analgesic consumption but with increased sedation without respiratory depression.

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