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EFFECT OF ORAL PREGABALIN AS PRE MEDICATION IN REDUCING ACUTE POST-OPERATIVE PAIN IN HEAD AND NECK ONCOSURGICAL PATIENTS: A PROSPECTIVE, DOUBLE BLIND RANDOMIZED CONTROL STUDY.

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ABSTRACT

Aim: To evaluate the efficacy of oral pregabalin in decreasing acute postoperative pain and opioid requirement in head and neck oncosurgery patients. **Objectives:** The primary objectives were to evaluate the reduction in opioid consumption and pain score during immediate postoperative period. The incidence of sedation, nausea and vomiting as well as hemodynamic stability were documented as secondary objectives. **Background:** Head and Neck Cancer surgery results in considerable postoperative pain and opioids in large amounts are required to control pain postoperatively, which leads to reduction of immunity and progression of tumor. Addition of pregabalin as a premedication could reduce central sensitization, total opioid consumption and prevent development of Chronic Post Surgical Pain (CPSP). **Results:** The results from our study show that 150 mg Pregabalin night (HS) & 1h before surgery significantly reduces visual analogue scores(VAS) and total morphine consumption during the first 24h, postoperatively. The total morphine consumption over 24 h was significantly lower (P 0.000) in Pregabalin group with a mean +/- SD of 6.3 +/- 2.4 mg as compared to 12.2 +/- 4.9 mg in the control group. **Conclusion:** The results of the study confirms our hypothesis of pregabalin being an efficacious premedicant for reducing acute postoperative pain and opioid consumption in head and neck oncosurgery in the immediate postoperative period.

KEYWORDS: Acute pain, postoperative, pregabalin, oral premedication, prospective study.

KEYMESSAGE: Addition of pregabalin to multimodal analgesic regimens for head and neck oncosurgery, can be beneficial by reducing acute postoperative pain and opioid consumption.

INTRODUCTION

Head and Neck cancer is the most common cancer among males and the fifth most common cancer of females in India.[1] Post-treatment pain has been linked to recurrence and lower survival rate in head and neck cancer patients. Postoperative pain in head and neck surgery is usually treated with opioids and nonsteroidal anti-inflammatory drugs (NSAID). Major drawback of use of opioids are side effects and the fact that certain types of pain respond poorly to opioids. Monotherapy with opioid may result in inadequate analgesia. The use of NSAIDs are limited by well-known complications and concerns like gastric ulceration, renal dysfunction, bleeding and so on.

As multiple mechanisms are involved in pain generation and perception, using a combination or multimodal approach can ensure better pain relief and patient comfort. In a comparative study of postoperative pain after ear, nose and throat surgery, the risk of postoperative pain is 4 to 10 times higher in surgery of oropharynx, larynx and neck as compared to ear surgery alone.[2] Neck dissection pain was found strongly associated with neuropathic pain. Recently, a growing body of evidence has shown that pregabalin, a drug that is being used in the treatment of neuropathic pain, has a potential role in acute postoperative pain relief.[3]

The potential effect of pregabalin on acute postoperative pain following head and neck cancer surgery has not been evaluated in clinical practice. The present study aims to determine the efficacy of pregabalin in the management of acute postoperative pain in such a scenario. Our primary objective was to assess any reduction in opioid consumption and pain score over 24h postoperatively. Incidence of sedation and nausea and vomiting were also documented as secondary objectives. Hemodynamic variables like heart rate(HR), systolic blood pressure(SBP), diastolic blood pressure(DBP) and oxygen saturation(SpO_2) at baseline and at lh, 2h, 4h, 6h, 12h, 18h and 24h postop were recorded.

METHODOLOGY

After obtaining the institutional review board and ethics committee clearance (HEC No.12/2014), recruitment of patients started in February 2014 and study was completed in October 2014, in patients who underwent head and neck oncosurgery aged 20-60 years belonging to ASA I and II classes, during this period. The criteria for exclusion were patient refusal, inability to understand VAS scale preoperatively and drug allergy. After explaining the purpose and protocol, written informed consent was obtained. A visual analogue scale was used to teach patients to communicate their pain intensity nonverbally. Thus even if endotracheal tube was insitu, patients could communicate their pain. Patients were randomized using computer generated random numbers to receive two doses of oral pregabalin (150mg) HS and 1 hour before surgery in the study group (S) or placebo in control group (C). A total of fifty four opaque coded envelopes bearing serial numbers containing either oral pregabalin or identical placebo were prepared. Preparation of envelopes and group allocation were done by an anaesthesiologist who was not part of the study. The observer was also not aware of the drug administered.

All patients were premedicated with tablet Pantoprazole (40 mg) with l0 mg domperidone HS and morning of surgery along with tab pregabalin 150 mg HS and 1 hour before surgery orally with a sip of water in study group(S) and placebo in control group (C), by a nurse who was not part of the study. Both the groups were given oral alprazolam (0.5mg) HS and l hour before surgery. Inj. glycopyrrolate 0.2 mg and inj.midazolam 1 mg IV were given before induction of anesthesia. Baseline HR, BP and SpO_2 were recorded. General Anaesthesia(GA) was administered according to standard protocol in the institution, with nasal endotracheal intubation. Single dose Morphine (0.1 mg/kg) iv and Paracetamol (20mg/kg) iv were given immediately after intubation (If surgery was prolonged morphine repeated 4th h and paracetamol 8th h). Hypotension was treated with 3 mg of Ephedrine when mean arterial pressure was less than 20% of baseline for at least 60 sec and bradycardia when heart rate less than 50/minute with atropine (20 µg/kg). Continuous monitoring of ECG, HR, Respiratory rate, SpO_2, end tidal carbondioxide ($ETCO_2$) and NIBP with recordings at 5 minutes interval were made. Fluid and blood loss were replaced as per standard protocol. At the end of surgery muscle relaxant was reversed and patient shifted to ICU with endotracheal tube and monitored (HR, ECG, NIBP, SpO2, VAS). Pain score (0-10), which was the primary outcome measure was assessed at l^{st}, 2^{nd}, 4^{th}, 6^{th}, 12^{th}, 18^{th} and 24^{th} h. The VAS rating was interpreted as follows-

>7	4 – 6	1-3	0
Severe pain	Moderate Pain	Mild Pain	No Pain

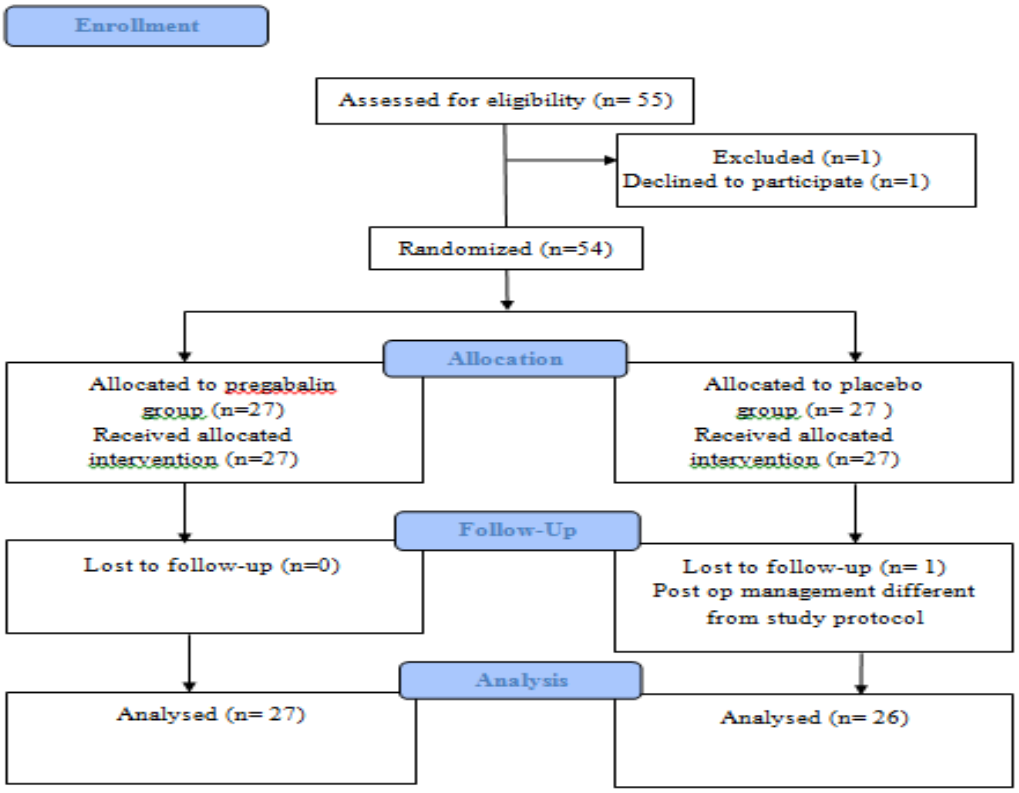
The interval between first and second morphine request were noted and cumulative dose of morphine at 24h calculated. Morphine was given (0.1mg/kg) on request and when VAS Score was above 3. Sedation was also rated on a 3 point scale as No sedation – 0, Easily arousable – grade 1, Deep sleep –grade 2. The presence or absence of nausea and vomiting were also noted. The ICU staff taking care of patients were also blinded about the study drug.

The sample size was calculated based on similar studies.[4-7] Considering postoperative pain at 8-12 h with alpha error at 5% and power 80% and effect size 0.6428, the sample size consisted of 27 patients per group. After completion of the study, data was unblinded, the mean and standard deviation (SD) for Pain Score (VAS) in both groups at lh to 24h calculated and compared using student's t test. P value of 0.05 or less was taken as significant. The VAS scores were asymptotically normally distributed and hence students t-test was used for comparing VAS score between control and study groups. The total opioid consumption was also calculated and compared between the study and control groups with student's t test. A P value <0.05 was taken as significant. The secondary outcomes such as sedation and PONV were analyzed using chi-square test and P values < 0.05 were taken as significant. Hemodynamic variables were analyzed using student t test. Statistical analysis was done with software SPSS Statistics for Windows, Version17.0.(Chicago: SPSS Inc.).

RESULTS

Fifty-five consecutive patients fulfilled the inclusion criteria in our study. One patient refused to participate. Fifty-four patients were enrolled and randomized into two groups of twenty seven each. Twenty-seven patients in the pregabalin group and twenty-seven patients in the placebo group completed the study. One patient in the control group was excluded as postoperative management differed from the study protocol. Patients in the pregabalin group (group S) received 150mg pregabalin HS &1 hour before surgery and patients in placebo group (group C) received a placebo HS and 1 hour before surgery. A flow chart of patient distribution is given in the following consort diagram.

CONSORT 2010 Flow Diagram



Demographic profile of all the patients is given in Table 1. Analysis of pain score in the severe category(VAS >7) shows a clear benefit to the study group in first hour, with only one patient complaining of severe pain requiring additional doses of morphine. Severe pain was experienced more often in the control group during all intervals of time. After 24 hrs, 10 out of 26 patients in control group had moderate pain while 16 had mild pain. At the same time all patients in the study group had only mild pain.(Table 2).

The statistical analysis of pain score in the two groups showed that the mean pain scores were significantly less in the study group during the first h and the consecutive time intervals also.(Table 3) Morphine requirement was more in the control group with a mean requirement of 12.2 mg cumulative dose against 6.2 mg in the study group.(Table 4) Following the first morphine dose analgesic benefit in study group was observed to last for a minimum of 12 hrs. This indicates both analgesic benefit as well as opioid sparing both of which are in agreement with previous studies.

Analysis of sedation scores revealed that the study group had higher scores compared with the control group at all points of time. (Table 5) The hemodynamic parameters (HR, BP) were significantly lower in the study group as compared to control group at all points of time. There was no statistically significant difference between the two groups in terms of occurrence of PONV although the meaningful interpretation of the same was masked by the contemporaneous use of antiemetics. (Table 6).

Table 1: Demographic profile of patients.

Variables	Study group	Control group
Age (years)		
<40 (n/ %)	7 (25.9)	7(25.9)
40-49 (n/%)	10(37)	8(29.6)
50-59 (n/%)	8(29.6)	6(22.2)
>60 (n/%)	2(7.4)	5(19.23)
Weight Kg (mean+/-SD)	61.6+/-10.9	59.6+/-12.2
Gender		
Males (n/%)	24(88.9)	17(63)
Females (n/%)	3(11.1)	9(34.6)
n- no of participants, kg- kilograms, SD- standard deviation		

Table 2: Distribution of pain between the study and control groups.

Time intervals	Group	VAS scores			
		Nil	Mild	Moderate	Severe
1h	Control	0(0)	3.7(1)	69.2(18)	25.9(7)
	Study	0(0)	18.5(5)	77.8(21)	3.7(1)
2h	Control	0(0)	88.4(23)	11.1(3)	0(0)
	Study	0(0)	74.1(20)	25.9(7)	0(0)
4h	Control	0(0)	84.6(22)	11.1(3)	3.7(1)
	Study	3.7(1)	96.3(26)	0(0)	0(0)
6h	Control	0(0)	14.8(4)	76.9(20)	7.4(2)
	Study	3.7(1)	51.8(14)	44.4(12)	0(0)
12h	Control	0(0)	44.4(12)	46.1(12)	7.4(2)
	Study	3.7(1)	92.6(25)	3.7(1)	0(0)
18h	Control	0(0)	76.9(20)	22.2(6)	0(0)
	Study	0(0)	66.7(18)	33.3(9)	0(0)
24h	Control	0(0)	61.5(16)	37(10)	0(0)
	Study	0(0)	100(27)	0(0)	0(0)

VAS score was used to assess pain in the two groups. VAS- Visual analogue scale. VAS >7 severe, 4-6 moderate, 1-3 mild, 0 no pain. The values are given as percentages and frequencies.

Table 3: Analysis of pain scores in the study and control groups.

Time intervals	VAS score in control group			VAS score in study group			t	P
	Mean	SD	N	Mean	SD	N		
1h	5.9	1.1	26	4.6	1.2	27	4.32	0.000
2h	2.5	1.1	26	2.6	1.3	27	0.23	0.820
4h	2.6	1.3	26	1.6	0.6	27	3.31	0.002
6h	5.0	1.7	26	3.2	1.9	27	3.6	0.001
12h	3.9	1.7	26	1.9	1.0	27	5.18	0.000
18h	2.9	1.4	26	2.7	2.0	27	0.4	0.694
24h	3.2	1.0	26	1.4	0.6	27	8.01	0.000

The VAS scores were asymptotically normally distributed and student's t test was used for analysis. VAS- Visual Analogue Scale, SD- standard deviation, N- no. of participants.

Table 4: Comparison of morphine requirement based on groups.

Group	Cumulative morphine requirement over 24 h			t	P
	Mean	SD	N		
Control	12.2	4.9	26	5.63	0.000
Study	6.3	2.4	27		

SD- standard deviation, N- number of participants, t-student's t test.

Table 5: Sedation scores in study and control groups.

Sedation Scores	Study group		Control group		χ^2	P
	Count	Percentage	Count	Percentage		
No Sedation	1	3.7	14	51.9	20.07	0.000
Grade I	18	66.7	12	46.15		
Grade II	8	29.6	0	0		

χ^2 – Chi square, Easily arousable- grade I, Deep sleep- grade II

Table 6: Comparison of nausea based on groups.

Nausea	Study group		Control group		χ^2	P
	Count	Percentage	Count	Percentage		
Absent	20	74.1	19	73.07	-	-
Present	7	25.9	7	25.9		

χ^2 – Chi square

DISCUSSION

The results from our study show that 150 mg Pregabalin HS & 1 hour before surgery significantly reduces total postoperative morphine requirement during the first 24 hours (Table 4). VAS scores at different points in time postoperatively were also lower in the study group. (Table 2).

Prevention of pain is not only humane, but also a way to reduce postoperative morbidity and mortality. Joseph Scharpf and colleagues reported that head and neck cancer patients experiencing higher level of post-treatment pain had lower survival rates.[8] Patient perception regarding pain, especially in oral and maxillofacial surgery can be difficult for the surgical team to overcome. Pain following head and neck cancer surgery results from surgical dissection, intra-op cervical hyperextension causing postoperative cervical muscular pain, irritation and laryngeal discomfort from frequent tracheal stimulation and movements of endotracheal tube during surgical stimulation and during the postoperative period if extubation is delayed and the endotracheal tube retained for a time-period postoperatively (as in the case of our patients) and from presence of surgical drains.

Pregabalin with its antiallodynic and anti hyperalgesic property, has been reported to be effective in reducing acute pain after thyroidectomy and tonsillectomy, in preventing the development of CPSP and also to attenuate the response to endotracheal intubation.[9,10] Head and neck surgery, malignancy and CPSP, all have both inflammatory and neuropathic components and are associated with up-regulation of α2δ subunit of voltage gated calcium channels (VGCC's), which is a binding site for pregabalin.[11,12] Our study shows that pregabalin is effective in reducing acute pain score in first 24 h after head and neck cancer surgery. There was significant reduction in the pain scores (P value < 0.001) at lh, 4 h, 6h, 12h and 24 h postoperatively (Table 3).

Patients with high catastrophizing scores have a high risk of experiencing pain longer after surgery.[13,14] Pregabalin has been shown to provide anxiolysis when given preoperatively.[14] Pregabalin has an onset of action of half to 1 h and bioavailability of 90%. In our study, therefore, we timed the dosage of pregabalin 1hour before surgery. Larger doses were found to be associated with side-effects like sedation, dizziness and delayed extubation.[13]

The total morphine consumption over 24 h was significantly lower(P 0.000) in Pregabalin group with a mean +/- SD of 6.3 +/- 2.4mg as compared to 12.2 +/- 4.9 mg in the control group. (Table 4) Pregabalin has opioid sparing effect thereby reducing side-effects like nausea, vomiting, pruritus, sedation and respiratory depression. Pain was assessed using the Visual Analogue Scale (0-10cm). VAS is the most commonly used scale for measuring postoperative pain.[15] The mean VAS scores (Table 2) were significantly lower at lh; mean +/- SD of 4.6+/- 1.2 in group S vs.5.9 +/- 1.1 in group C(P 0.000). In group S, 77.8% patients reported moderate pain and 3.7% reported severe pain at 1 h. In group C, 69.2% experienced moderate pain and 25.9% severe pain at 1 h. Although both groups had pain at 1 h and required rescue analgesia, the intensity of pain was less in the pregabalin group. Further, the second dose of rescue analgesic was not required or duration of first rescue dose lasted more in the study group. Therefore, group S had less opioid consumption. This is in accordance with the previous studies.

No significant difference was observed in the pain scores at 2h, 4h and 18 h. The pain scores were mainly in mild category at these time-periods. This can be explained based on the duration of analgesic action of morphine administered in the control group. The control group received morphine at 12 h accounting for the lesser pain at 18 h compared to the study group. There was significant difference in pain score at 6h, 3.2 +/- 1.9 in group S vs. 5.1 +/- 11.7 in group C (P 0.000), with 76.2% patients in group C reporting moderate pain and 7.4% reporting severe pain requiring morphine. This peak in requirement of analgesic can be explained by the fact that the duration of action of morphine is about 4h. Significant difference in pain score was also noted at 12h, 3.9+/- 1.7 in group C vs.1.9 +/- 1.0 in group S (P<0.01) with 46.1% in group C reporting moderate pain and 7.4% reporting severe pain. Only 3.7% in pregabalin group had moderate pain and none had severe pain. The morphine consumption showed similar peaks. There was no significant difference in pain score at 18 h postoperative. Although there was significant difference in pain score at 24 h, 61.5% in group C and 100% in group S had only mild pain. At 24 h postoperative the pain scores were mild in both groups. This is in accordance with previous studies that no residual effect of pregabalin was observed after 24 h when using a single dose. A meta-analysis conducted by Zhang, Ho and Wang in 2010 identified valid RCT's that used pregabalin for acute postoperative pain and reported a reduction in cumulative opioid consumption.[3] In our study, the cumulative 24h morphine requirement for the control group was 12.2mg+/-4.9 where as in the study group it was 6.3+/-2.4; which shows a significantly lower consumption of morphine in the study group (P 0.000). The primary objectives of our study showed the opioid sparing effects of pregabalin as well as reduction in pain scores as reported by other investigators in various previous studies.

The sedative side effect of pregabalin reported by other investigators is confirmed in our study also, but patients were easily arousable in our study.[16] Anxiety levels need further evaluation. In our study we didn't find any difference of basal heart rates between the two groups. Other measures to evaluate anxiety levels were not employed in the present study. Head and neck cancer surgery produces high levels of anxiety as it affects the physical appearance of patients. The use of different

anxiolytics needs to be evaluated separately, which is outside the scope of the present study. The present study did not identify the other side effects of pregabalin which are described in literature during the first 24 h postoperatively.[17-20] There was no statistically significant difference between the study and control groups for postoperative nausea, which is in accordance with previous studies showing no benefit for pregabalin alone in terms of PONV. The use of antiemetics concurrently could also be a confounding factor. As with the previous studies, there was significant reduction in opioid consumption over 24h and lower pain score at 24h postoperatively. Adding pregabalin as preemptive analgesic in head and neck cancer surgery is overall safe and apparently advantageous.

CONCLUSION

The aim of the study was to determine the efficacy of oral pregabalin as premedication in reducing acute postoperative pain in head and neck oncosurgical patients.

The following conclusions were arrived at.

Preemptive Pregabalin usage resulted in

1. Statistically significant opioid sparing effect in the immediate postoperative period (up to 24h).
2. Statistically significant pain control in the immediate postoperative period.
3. Better preoperative sedation, good perioperative heamodynamics and postoperative endotracheal tube tolerance. Minimal side effects such as nausea and vomiting and sedation were noted. Anxiolysis needs further evaluation.

The results of the study confirm our hypothesis of pregabalin being an efficacious premedicant for reducing acute postoperative pain. The dosing of pregabalin in most studies comprised of a single dose of 300mg before surgery. This dosing seems to have contributed to some of the clinically significant side effects. In our study a reduced dose of 300mg divided into two doses achieved significant pain control and opioid sparing with minimal side effects. We are thus able to substantiate the fact that pregabalin adverse effects are dose dependent. Inspite of the mixed results of efficacy of preemptive analgesia the results of our study suggest that preemptive analgesia is a clinically relevant phenomenon especially when employed as an adjunct in a multimodal analgesia regimen.

LIMITATIONS

The limitation of the study design is that pregabalin is used only as premedication. The half-life of the drug is 5-7 h and conclusions about the optimal dose and duration of treatment cannot be made.

Long-term benefits of such a therapy, like prevention of chronic postoperative pain and improvement in recovery, morbidity after head and neck cancer surgery, needs further studies and are beyond the scope of this study.

Sedation, which is the side-effect of pregabalin can be a confounding factor when assessing pain.

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