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A Comparative Preemptive Use of Pregabalin With Placebo For Post-Operative Pain – A Randomized Double Blind Study

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ABSTRACT

Background and objectives

Pain is a personal, subjective experience that involvesensory, emotional and behavioral factors. Prevention and treatment of post-operative pain continues to be a major challenge in post–operative pain care. According to international association for the study of pain is defined as “pain is an unpleasant sensory and emotional experience associated with actual or potential damage. Good pain control after surgery is important to prevent negative outcomes such as hypertension, tachycardia, myocardial ischemia, decrease in alveolar entilation and poor wound healing. Although many analgesic drugs are used for post-operative pain, many patients still complain from suboptimal pain. Anti-hyperalgesic drugs can treat postoperative pain by preventing CNS pain hypersensitivity example of this drug is Pregabalin. Pregabalin is a potent ligand for alpha-2-delta subunit of voltage –gated calcium channels in the central nervous system, which exhibits potent anticonvulsant, analgesic and anxiolytic activity. Although it shows analgesic efficacy against neuropathic pain. The aim of this study is to evaluate the analgesic efficacy of preemptive use of oral pregabalin after maxillofacial surgery.

Material and Methods:

The study was conducted on 56 patients reporting to the Department of Oral & Maxillofacial Surgery at The Oxford Dental College & Hospital, Bangalore for maxillofacial surgery under general anaesthesia. Patients were selected on the basis of the inclusion criteria after obtaining the Informed consent.Patients were randomly divided into two groups, the experimental group and the control group. The following treatments were administered Tab.pregabalin 150mg orally for experimental group and placebo orally for control group. All the medication was administered 1 hour before the induction of anaesthesia with little sip of water by a staff nurse who will not involve in the study. Anaesthesia technique was standardized in both the groups. After connecting the standard monitors patients was induced with pentazocaine 30mg IV and propofol titrated 2mg/kg to loss of consciousness. Nasal or orotracheal intubation was facilitated by vecuronium 0.08mg/kg. Anaesthesia was maintained with nitrous oxide in oxygen and isoflurane maintained at end-tidal concentration of 1-1.5%. At the end of surgery residual neuromuscular paralysis was reversed with neostigmine 0.05mg/kg and glycopyrolate 0.01mg/kg. after satisfactory recovery, the patient was extubated and shifted to the post anaesthesia care unit(PACU). The side effects such as headache, sedation anddepression was noted. Baseline assessment of pain intensity using visual analogue scale (1-10 scale) was made before medication(time t-0), pain intensity and pain relief was assessed

at (0,4,8,12 &24 hours) after surgery, duration of pain relief and overall efficacy of drug

Results

A Comparative two group clinical study was carried out. A total of 56 patients who visited the Department of Oral and Maxillofacial Surgery, The Oxford Dental College and Hospital, Bangalore, for maxillofacial surgery under general anaesthesia were enrolled for the study. Randomization ensured that there were approximately 28 patients per treatment group. 36 patients were males (64.29%) and 20 females (35.71%) (Table & Graph 1). Samples are gender matched with P=0.78. Their age ranged from 18-40 years with mean age of 32.91±5.54. Samples were age matched with P=0.76. Majority of patients were in their third decade (Table & Graph 2). VAS scale for pain, pain relief, and duration of pain relief (Tables and Graphs 3-8), in the two treatment groups was statistically analysed and yielded a significant ($p \leq 0.001$) in this study. The overall assessment of analgesic efficacy compared between Group IV and Group OP showed a significance ($p \leq 0.001$) (Table & Graph 9). The results in this study showed that the analgesic efficacy of Tab.Pregabalin 150mg (Group PG) was superior to oral placebo (Group P).

Conclusion

In the current study we have confirmed our hypothesis that preemptive used of oral pregabalin 150mg are more reliably achieved superior analgesia than the oral placebo. We therefore suggest that oral preoperative single dose of pregabalin 150mg is an effective method for reducing post-operative pain and postoperative rescue analgesia requirement in patients undergoing maxillofacial surgery under general anaesthesia.

Keywords: *Maxillofacial Surgery, Preemptive, Oral Pregabalin, Oral Placebo, Postoperative Pain Control.*

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SUMMARY

This study was carried out at the Department of Oral and Maxillofacial Surgery, The Oxford Dental College and Hospital, Bangalore. The study sample included 56 patients who underwent maxillofacial surgery under general anaesthesia.

The study was conducted to compare the analgesic efficacy of preemptive use on oral administration of pregabalin 150mg with placebo for post-operative pain control after maxillofacial surgery.

Patients were divided into two equal groups.
Group A: Experimental group (PG)
(Patient who received Oral Tab.Pregabalin 150mg).
Group B: Control group (P)
(Patient who received oral placebo)

Pain was evaluated using standard visual analogue scale (VAS) immediately after procedure, 0h, 4h, 8h, 12h, 24h postoperatively.

Sedation was evaluated using ramsay sedation scale immediately after procedure 0h,4h,8h,12h, 24h postoperatively.
Total duration of pain relief is noted and the administration of rescue medicine before completion of duration (24 hour), if required.

Patients were requested to give an overall assessment of the analgesic efficacy of the tested medication (end of the 24-hour period) on a 5-point scale (none=0, poor=1, fair=2, good=3, very good=4).

In our study the results showed clearly that Tab.Pregabalin 150mg, has a longer duration of action, is more efficacious, the pain intensity difference score and the duration of pain relief were significantly ($P \leq 0.01$) superior to those of oral placebo.

1. INTRODUCTION

Pain is a personal, subjective experience that involve sensory, emotional and behavioral factor. Prevention and treatment of post-operative pain continue to be a major challenge in post-operative care.

According to international association for the study of pain is defined as “pain is an unpleasant sensory and emotional experience associated with actual or potential damage.1

Good pain control after surgery is important to prevent negative outcomes such as hypertension, tachycardia, myocardial ischemia, decrease in alveolar ventilation and poor wound healing. Although many analgesic drugs are used for post-operative pain, many patients still complain from suboptimal pain.2

In more than 50% of surgical procedure the most common and inadequately treated complaint is pain. After major surgical procedure this is the most important problem that affects patient recovery. Post operative pain response may be prevented or treated if planned early 3.

Advance in the knowledge of molecular mechanism have led to the development of multimodel analgesia and new pharmaceutical products to treat post-operative pain. opiods, NSAIDS and local anesthetics were the tools of doctors dealing with acute pain while tricyclic antidepressants and anticonvulsants were for the chronic pain.2

Considering that surgical stimulation with peripheral and central sensitization. Anti-hyperalgesic drugs can treat postoperative pain by preventing CNS pain hypersensitivity example of this drug are Pregabalin.4

Pregabalin (Lyrica ,Pfizer Inc) is an structural analog of γ- aminobutyric acid, which shows analgesic, anticonvulsant and anxiolytic effects. In many countries, it is approve for the treatment of neuropathic pain, the pharmacological basis of which is pre-synaptic binding to the α-2- subunit of voltage–dependent calcium channels that are widely distributed in the spinal cord and brain.

By altering calcium currents, pregabalin reduces or modulates the release of several excitatory neurotransmitters, including glutamate nor-epinephrine substance p and calcium gene related peptide, producing inhibitory modulation of over-excited neurons and returning them to a normal state.

Pregabalin is several times more potent than the similar drug gabapentin. It is rapidly absorbed orally with more than 90% bioavailability achive peak plasma levels within 30min to 2hr and shows linear pharmacokinetic with low inter subject variability. The side effects profile is good with the most common adverse events being dizziness and somnolence and pregabalin has no effect on arterial blood pressure or heart rate.5

The European Commission, granted Pfizer approved for pregabalin (lyrica, Pfizer , new york) in july 2004 in all European union members states for the treatment of peripheral neuropathic pain and as an adjunctive therapy for partial seizure in patients with epilepsy. the approval was based on results from 10 trials studying more than 9000 patients.

In December 2004, the food and drug administration approved pregabalin for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN), under the trade name of lyrica.6

Pre-emptive used of pregabalin has been claimed to be more effective in preventing neuropathic component of acute nociceptive pain of surgery. Pre-emptive analgesia is an antinociceptive treatment that prevents establishment of altered processing of afferent input.1

Recently it has been introduced as an adjunct in the multimodel management of postoperative analgesia. The role as an oral pre-emptive analgesia of pregabalin for post-operative pain relief has been review with the concept of pre-emptive analgesia for control of postoperative pain.7

Several studies have been conducted to evaluate effects of preemptive analgesia pregabalin in orthopedic surgery, laparoscopic cholecystectomy surgery, postherpetic neuralgia, tonsillectomy surgery, gynaecological surgery, fibromylgia syndrome, chronic low back pain. But not many studies have been conducted in maxillofacial surgery. So, we decided to conduct a study to evaluate and compared the efficacy use of oral Pregabalin after maxillofacial surgery.

Our hypothesis in the current study is to prove that preemptive use of oral Pregabalin 150mg is more reliably achives superior analgesia than the oral placebo. The aim of this randomized clinical trial was to evaluate postoperative analgesia benefit in patient administered Tab Pregabalin 150mg or Placebo one hour before surgery as oral pre-medication for maxillofacial surgery under general anaesthesia and to study its post-operative efficacy with respect to duration of analgesia, side effect or any haemodynamic changes following surgery for 24 hours post-operatively.

Aims

The aim of the study is to evaluate the analgesic efficacy of preemptive use of oral

pregabalin after maxillofacial surgery.

Objectives

The objective is to compare the analgesic efficacy of pre-emptive use on oral administration of pregabalin with placebo for post-operative pain control after maxillofacial surgery.

2. METHODOLOGY

The present study was conducted in the department of oral and maxillofacial surgery, The Oxford Dental College and hospital, Bangalore, after obtaining ethical clearance. This study included both male and female patients who were referred to the department of oral and maxillofacial surgery for maxillofacial surgery which is carried under general anaesthesia.

Inclusion Criteria

- In the age group of 18-40 years.
- Gender- both male and female.
- Patient who required maxillofacial surgical procedure.
- Patients who give written informed consent for the study.
- Duration of surgery less than 4 hours.

Exclusion Criteria

- Pregnant or breast-feeding women.
- Alcohol or drug abuse, psychiatric or medical disorder able to modify patient compliance.
- Patients on long term analgesic due to chronic conditions like arthritis.
- Patient with history of cardiovascular metabolic, respiratory, renal disease or coagulation abnormalities.
- History with seizures.
- Patient with phenylketonuria.

Patients are divided into two groups
Group A: Experimental group (IP)
(Patient who received oral tab. Pregabalin 150mg).
Group B: Control group (OP)
(Patient who received oral placebo).

Blinding procedure

The concealed allocation was performed using a set of random number obtained from randomization chart placed in sealed opaque envelope to blind the patient and evaluator. The pre-emptive oral tab.pregabalin or placebo will be administered 1 hour prior to surgery by the post-graduate student on anaesthesia duty. The post-operative principal evaluation was done by the blinded examiner. The patients were unaware of the group to which they are allocated.
Materials used in the study
1. Stop watch
2. Tab. pregablin 150mg
3. Placebo

Fig:1

Procedure

After explaining the entire procedure, a detailed written informed consent on his/her vernacular language was obtained from the patient. Patients were randomly divided into two groups, the experimental group and the control group. The following treatments were administered tab.pregabalin 150mg orally for experimental group and placebo orally for control group. All the medication was administered 1 hour before the induction of anaesthesia with little sip of water by a staff

nurse who will not involve in the study(fig.2). Anaesthesia technique was standardized in both the groups. After connecting the standard monitors patients was induced with pentazocaine 30mg IV and propofol titrated 2mg/kg to loss of consciousness. Nasal or orotracheal intubation was facilitated by vecuronium 0.08mg/kg. Anaesthesia was maintained with nitrous oxide in oxygen and isoflurane maintained at end-tidal concentrationof 1-1.5%. At the end of surgery residual neuromuscular paralysis was reversed with neostigmine 0.05mg/kg and glycopyrolate 0.01mg/kg. after satisfactory recovery, the patient was extubated and shifted to the post anaesthesia care unit(PACU). The side effects such as headache, sedation and depression was noted.

Baseline assessment of pain intensity using visual analog scale (1-10 scale) was made before medication(time t-0), pain intensity and pain relief was assessed at (0,4,8,12 &24 hours) after surgery, duration of pain relief and overall efficacy of drug(fig.3).

FIG 2

FIG 3

Evaluation Criteria:

The following parameters were measured: pain intensity, pain relief, duration of pain relief , haemodynamic changes , sedation scale and overall efficacy of drug as follows.

Pain was evaluated using standard visual analogue scale (VAS) immidietly after procedure 0hr, 4hr, 8hr, 12hr& 24 hr

postoperatively.

1 division=10mm

0 1 2 3 4 5 6 7 8 9 10

0: None
1: No distress
2-3: Annoying
4-5: Uncomfortable
6-7: Dreadful
8: Horrible
9: Unbearable stress
10: Agonizing

Pain relief (PR):

Pain relief (PR) was evaluated on a five-point categorical scale (none=4; a little=3; moderate=2; a lot=1; complete=0) at each evaluation time from T15 min to T6 h. PR was expressed by the following derived scores: maximum PR (MaxPR), time of maximum PR (tMaxPR) and a weighted sum of PR (TOTPAR) (T0 hour–T24 h).

Haemodynamic changes:

Any changes hypotension, bradycardia, respiratory depression, vomiting, dizziness changes was recorded.

Sedation scale:

The ramsay sedation scale was used to asses the sedation. patient with sedation scale greater than 4 were considered as sedated.

Overall assessment of the analgesic efficacy:

Patients were requested to give an overall assessment of the analgesic efficacy of the tested medication (end of the 24-hour period) on a 5-point scale (none=0, poor=1, fair=2, good=3, very good=4).

Need for rescue medicine:

If any need for recue medicine before completion of duration (24hour), were noted.

Statistical Analysis:

Descriptive and inferential statistical analysis has been carried out in the present study. The results were analysed by using SPSS version 18 (IBM Corporation, SPSS Inc., Chicago, IL, USA). Microsoft word and Excel was used to generate graphs, tables etc. Results on continuous measurements were presented on Mean SD (Min-Max) and results on categorical measurements were presented in Number (%). Significance was assessed at 5 % level of significance. Student t test, Fisher extract test, Chi-square test were used to find the significance of study parameters between the two groups.

3. RESULT

A Comparative two group clinical study was carried out. A total of 56 patients who visited the Department of Oral and Maxillofacial Surgery, The Oxford Dental College and Hospital, Bangalore, for maxillofacial surgery under general anaesthesia were enrolled for the study. Randomization ensured that there were approximately 28 patients per treatment group. 36 patients were males (64.29%) and 20 females (35.71%) (Table & Graph 1). Samples are gender matched with P=0.78. Their age ranged from 18-40 years with mean age of 32.91±5.54. Samples were age matched with P=0.76. Majority of patients were in their third decade (Table & Graph 2).

VAS scale for pain, pain relief, and duration of pain relief (Tables and Graphs 3-8), in the two treatment groups was statistically analysed and yielded a significant ($p \leq 0.001$) in this study. The overall assessment of analgesic efficacy compared between Group IV and Group OP showed a significance ($p \leq 0.001$) (Table & Graph 9).

The results in this study showed that the analgesic efficacy of tab.pregabalin 150mg (Group PG) was superior to oral placebo (Group P).

Table 1: Gender distribution of study participants

Gender	PREGABALIN	PLACEBO	Total
Female	11(39.30%)	09(32.10%)	20(35.71%)
Male	17(60.70%)	19(67.90%)	36(64.29%)
Total	28(100%)	28(100%)	56(100%)

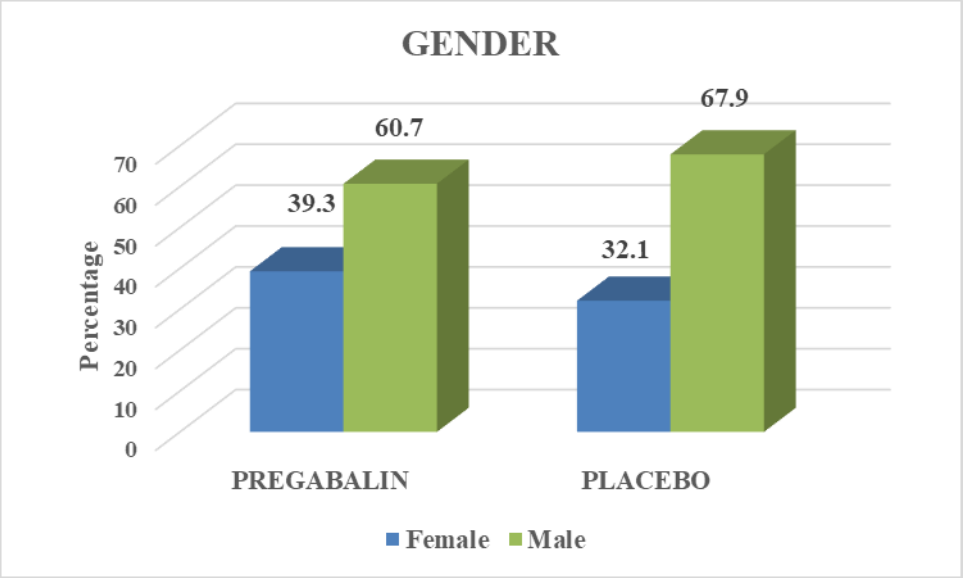


Table 2: Age distribution of study participants

Samples are age matched with P=0.76

Age in years	PREGABALIN	PLACEBO	Total
<20	0(0)	0(0)	0(0)
21-30	08(28.57%)	08(28.57%)	16(%)
31-40	20(71.43%)	20(71.43%)	40(%)
Total	28(100%)	28(100%)	56(100%)
Mean ± SD	32.61±5.79	33.21±5.37	32.91±5.54

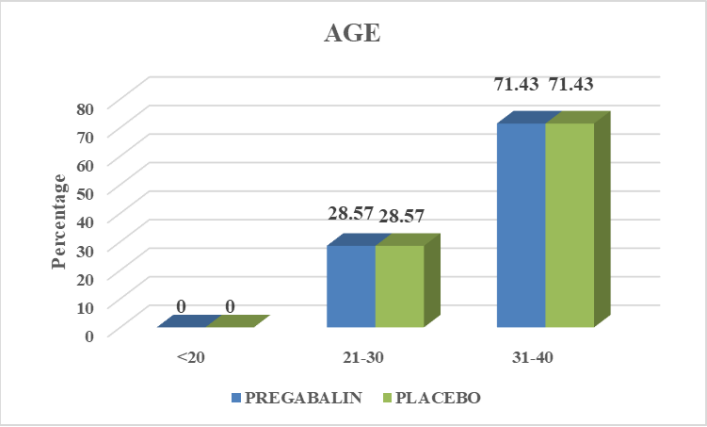
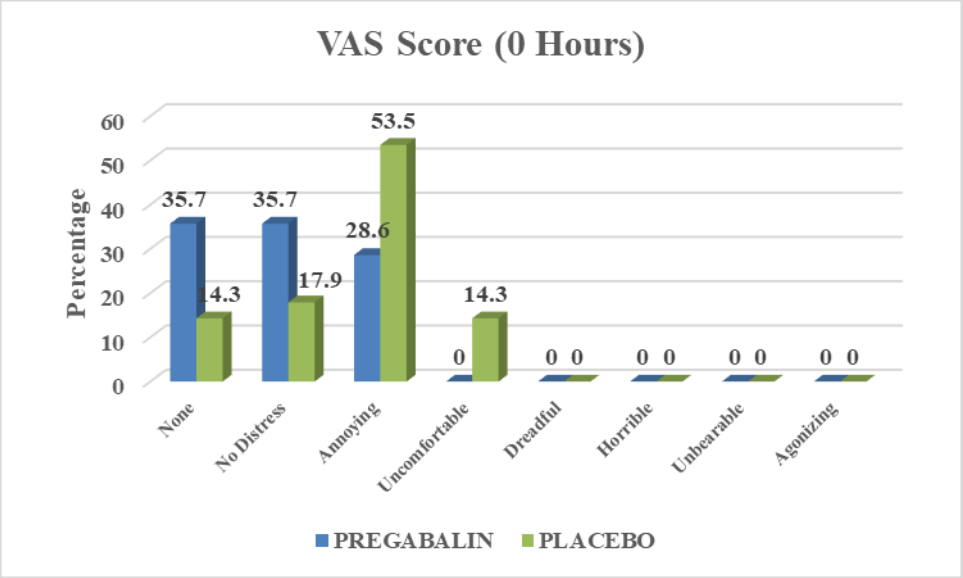
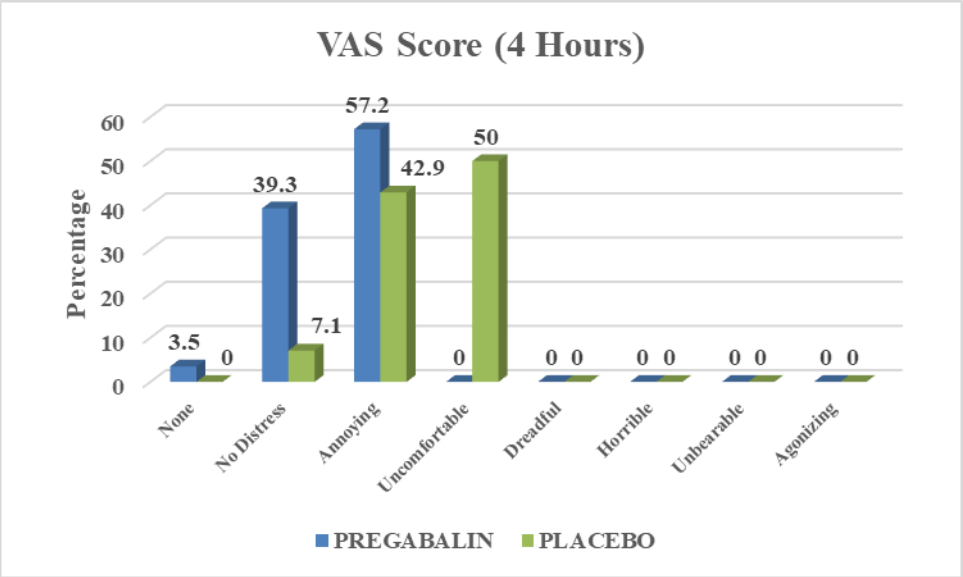
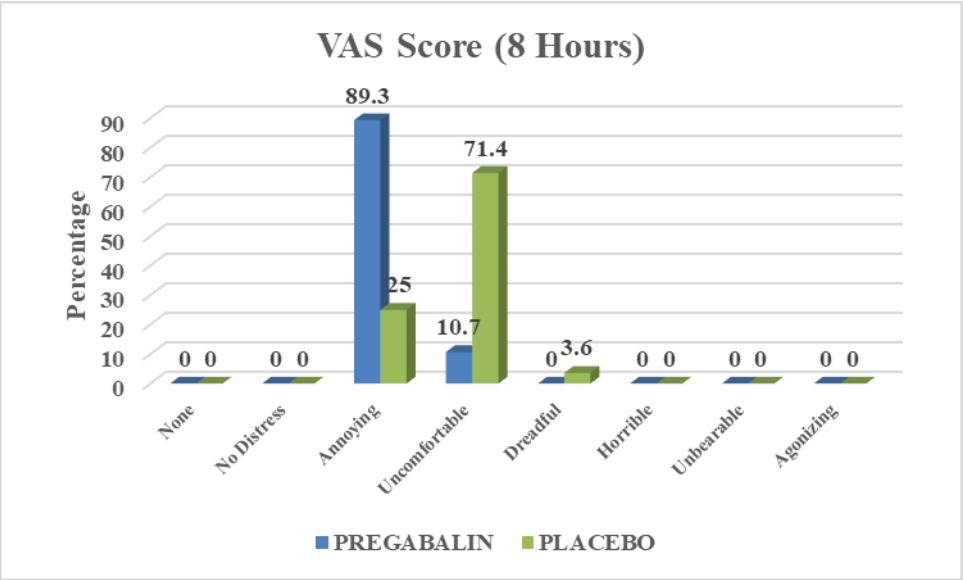


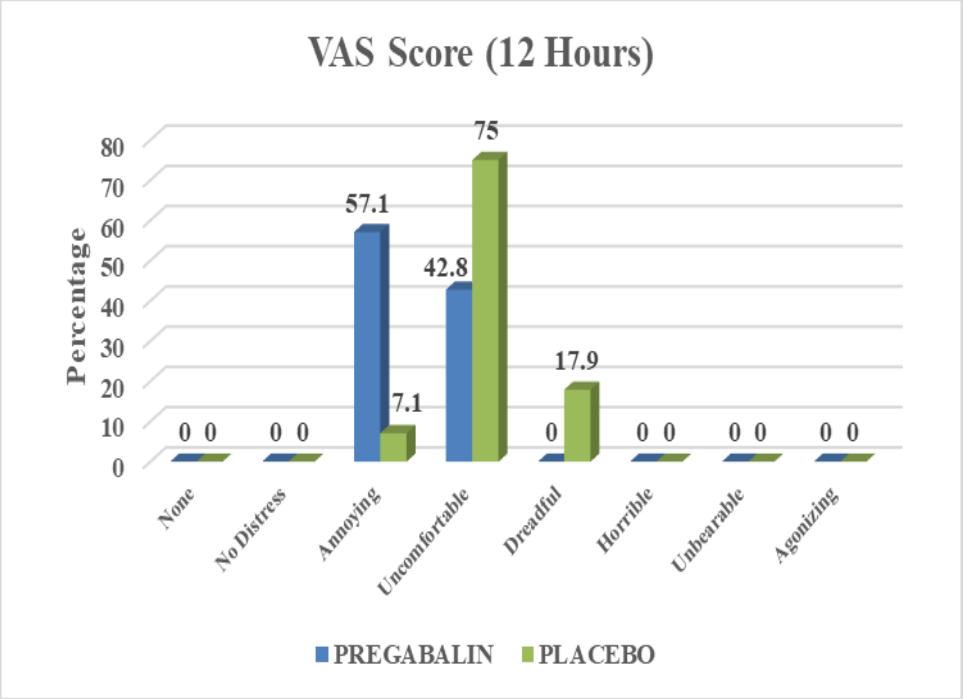
Table 3: Table for VAS Score

VAS Score	CRITERIA	PREGABALIN	PLACEBO	Total (n=120)	P value
0 hours					
0	None	10(35.7%)	04(14.3%)	14(25%)	**0.015**
1	No Distress	10(35.7%)	05(17.9%)	15(26.79%)	
2-3	Annoying	08(28.6%)	15(53.5%)	23(41.07%)	
4-5	Uncomfortable	0(0%)	04(14.3%)	04(7.14%)	
6-7	Dreadful	0(0%)	0(0%)	0(0%)	
8	Horrible	0(0%)	0(0%)	0(0%)	
9	Unbearable	0(0%)	0(0%)	0(0%)	
10	Agonizing	0(0%)	0(0%)	0(0%)	
4 hours					
0	None	01(3.5%)	0(0%)	1(100%)	**<0.001**
1	No Distress	11(39.3%)	02(7.1%)	13(0%)	
2-3	Annoying	16(57.2%)	12(42.9%)	28(0%)	
4-5	Uncomfortable	0(0%)	14(50.0%)	14(0%)	
6-7	Dreadful	0(0%)	0(0%)	0(0%)	
8	Horrible	0(0%)	0(0%)	0(0%)	
9	Unbearable	0(0%)	0(0%)	0(0%)	
10	Agonizing	0(0%)	0(0%)	0(0%)	
8 hours					
0	None	0(0%)	0(0%)	0(0%)	**<0.001**
1	No Distress	0(0%)	0(0%)	0(0%)	
2-3	Annoying	25(89.3%)	7(25.0%)	32(0%)	
4-5	Uncomfortable	03(10.7%)	20(71.4%)	23(0%)	
6-7	Dreadful	0(0%)	01(3.6%)	01(0%)	
8	Horrible	0(0%)	0(0%)	0(0%)	
9	Unbearable	0(0%)	0(0%)	0(0%)	
10	Agonizing	0(0%)	0(0%)	0(0%)	
12 hours					
0	None	0(0%)	0(0%)	0(0%)	**<0.001**


VAS Score (0 Hours)
Percentage
60
50
40
30
20
10
0
35.7
14.3
35.7
17.9
28.6
53.5
0
14.3
0 0
0 0
0 0
0 0
None
No Distress
Annoying
Uncomfortable
Dreadful
Horrible
Unbearable
Agonizing
PREGABALIN
PLACEBO


VAS Score (4 Hours)
Percentage
60
50
40
30
20
10
0
3.5
0
39.3
7.1
57.2
42.9
0
50
0 0
0 0
0 0
0 0
None
No Distress
Annoying
Uncomfortable
Dreadful
Horrible
Unbearable
Agonizing
PREGABALIN
PLACEBO


VAS Score (8 Hours)
Percentage
90
80
70
60
50
40
30
20
10
0
0 0
0 0
89.3
25
10.7
71.4
0
3.6
0 0
0 0
0 0
None
No Distress
Annoying
Uncomfortable
Dreadful
Horrible
Unbearable
Agonizing
PREGABALIN
PLACEBO


VAS Score (12 Hours)
Percentage
80
70
60
50
40
30
20
10
0
0 0
0 0
57.1
7.1
42.8
75
0
17.9
0 0
0 0
0 0
None
No Distress
Annoying
Uncomfortable
Dreadful
Horrible
Unbearable
Agonizing
PREGABALIN
PLACEBO

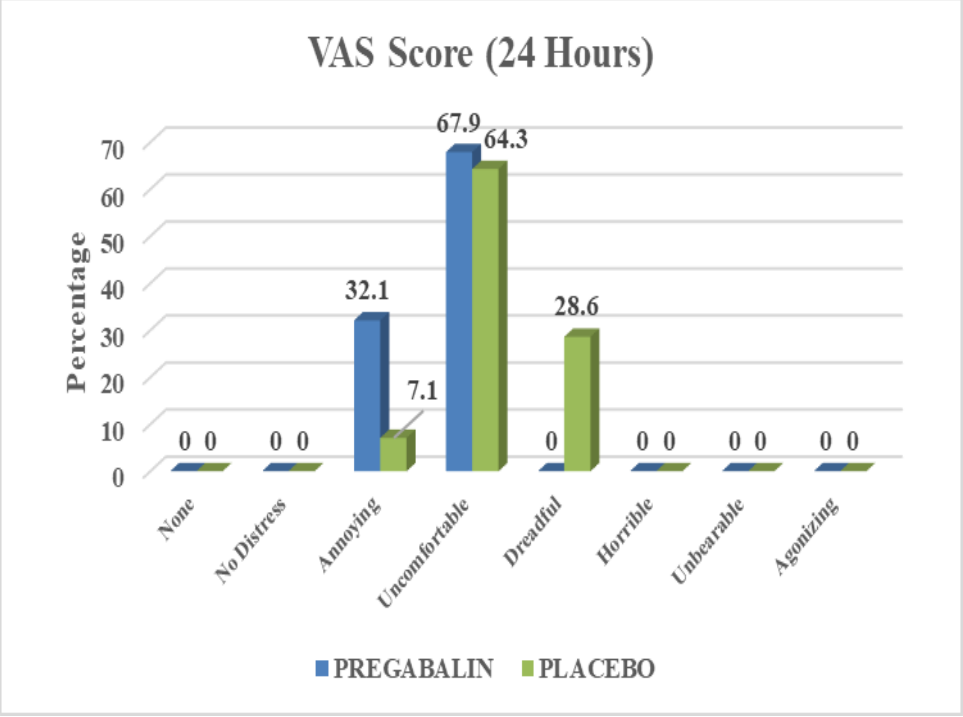
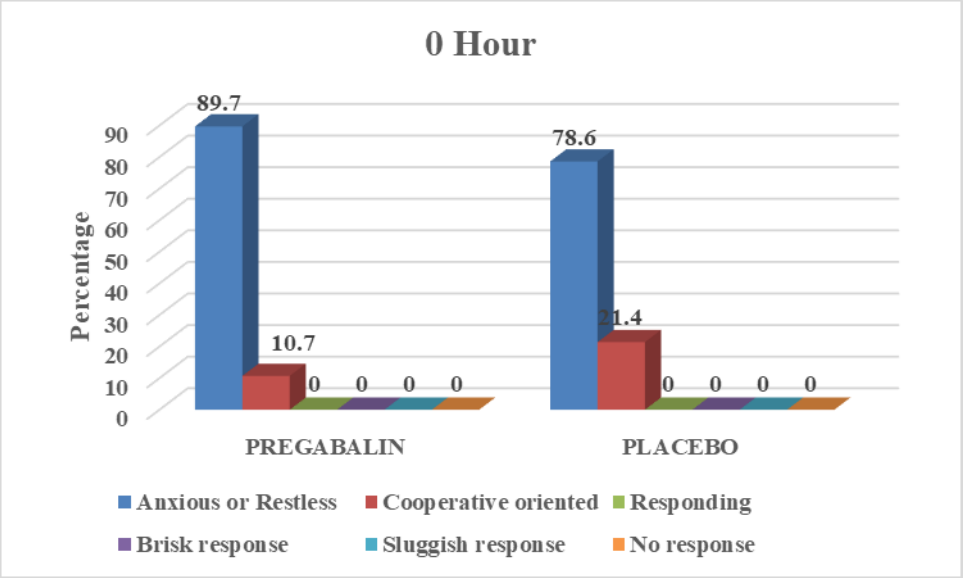
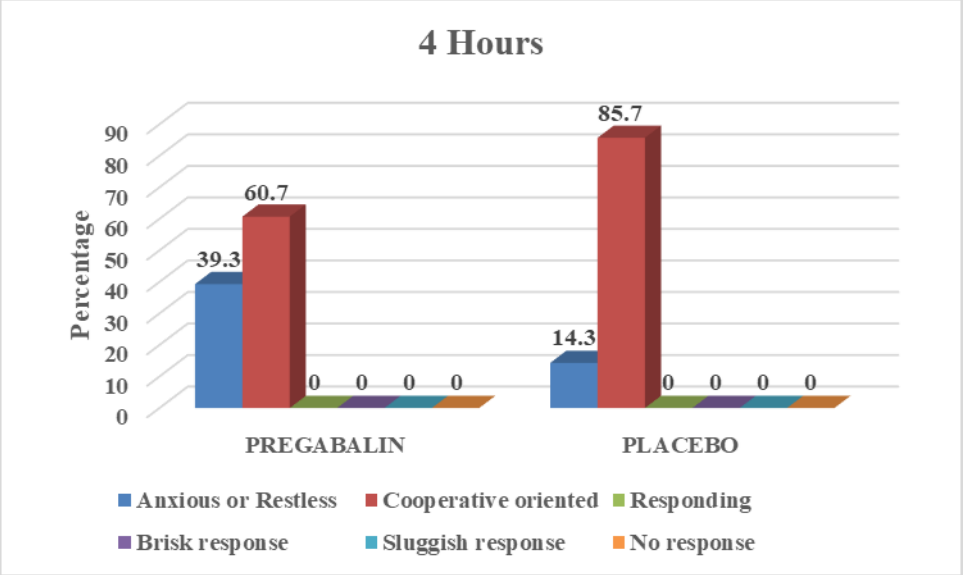
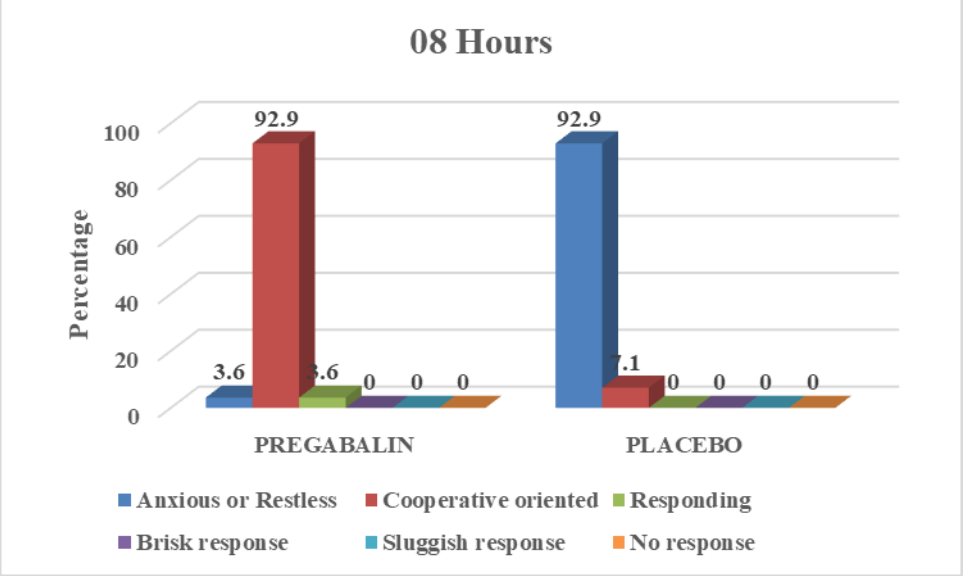

VAS Score (24 Hours)
Percentage
70
60
50
40
30
20
10
0
0 0
0 0
32.1
7.1
67.9
64.3
0
28.6
0 0
0 0
0 0
None
No Distress
Annoying
Uncomfortable
Dreadful
Horrible
Unbearable
Agonizing
PREGABALIN
PLACEBO

Table 4: Table for Ramsay Sedation Score

VAS Score	Criteria	PREGABALIN	PLACEBO	Total (n=120)	P value
0 hours					
1	Anxious or Restless or both	25(89.7%)	22(78.6%)	47(%)	
2	Cooperative oriented and tranquil	03(10.7%)	06(21.4%)	09(0%)	
3	Responding to commands	0(0%)	0(0%)	0(0%)	**0.47**
4	Brisk response to stimulus	0(0%)	0(0%)	0(0%)	
5	Sluggish response to stimulus	0(0%)	0(0%)	0(0%)	
6	No response to stimulus	0(0%)	0(0%)	0(0%)	
4 hours					
1	Anxious or Restless or both	11(39.3%)	04(14.3%)	15(%)	
2	Cooperative oriented and tranquil	17(60.7%)	24(85.7%)	41(0%)	
3	Responding to commands	0(0%)	0(0%)	0(0%)	
4	Brisk response to stimulus	0(0%)	0(0%)	0(0%)	**0.07**
5	Sluggish response to stimulus	0(0%)	0(0%)	0(0%)	
6	No response to stimulus	0(0%)	0(0%)	0(0%)	
8 hours					
1	Anxious or Restless or both	01(3.6%)	26(92.9%)	27(100%)	
2	Cooperative oriented and tranquil	26(92.9%)	02(7.1%)	28(0%)	
3	Responding to commands	01(3.6%)	0(0%)	01(0%)	
4	Brisk response to stimulus	0(0%)	0(0%)	0(0%)	**<0.001**
5	Sluggish response to stimulus	0(0%)	0(0%)	0(0%)	
6	No response to stimulus	0(0%)	0(0%)	0(0%)	
12 hours					
1	Anxious or Restless or both	02(7.1%)	21(75.0%)	23(%)	
2	Cooperative oriented and tranquil	23(82.1%)	07(25.0%)	30(0%)	
3	Responding to commands	03(10.7%)	0(0%)	03(0%)	
4	Brisk response to stimulus	0(0%)	0(0%)	0(0%)	**<0.001**
5	Sluggish response to stimulus	0(0%)	0(0%)	0(0%)	
6	No response to stimulus	0(0%)	0(0%)	0(0%)	
24 hours					


0 Hour
Percentage
89.7
10.7
0
0
0
0
78.6
21.4
0
0
0
0
PREGABALIN
PLACEBO
Anxious or Restless
Cooperative oriented
Responding
Brisk response
Sluggish response
No response


4 Hours
Percentage
39.3
60.7
0
0
0
0
14.3
85.7
0
0
0
0
PREGABALIN
PLACEBO
Anxious or Restless
Cooperative oriented
Responding
Brisk response
Sluggish response
No response


08 Hours
Percentage
3.6
92.9
3.6
0
0
0
92.9
7.1
0
0
0
0
PREGABALIN
PLACEBO
Anxious or Restless
Cooperative oriented
Responding
Brisk response
Sluggish response
No response

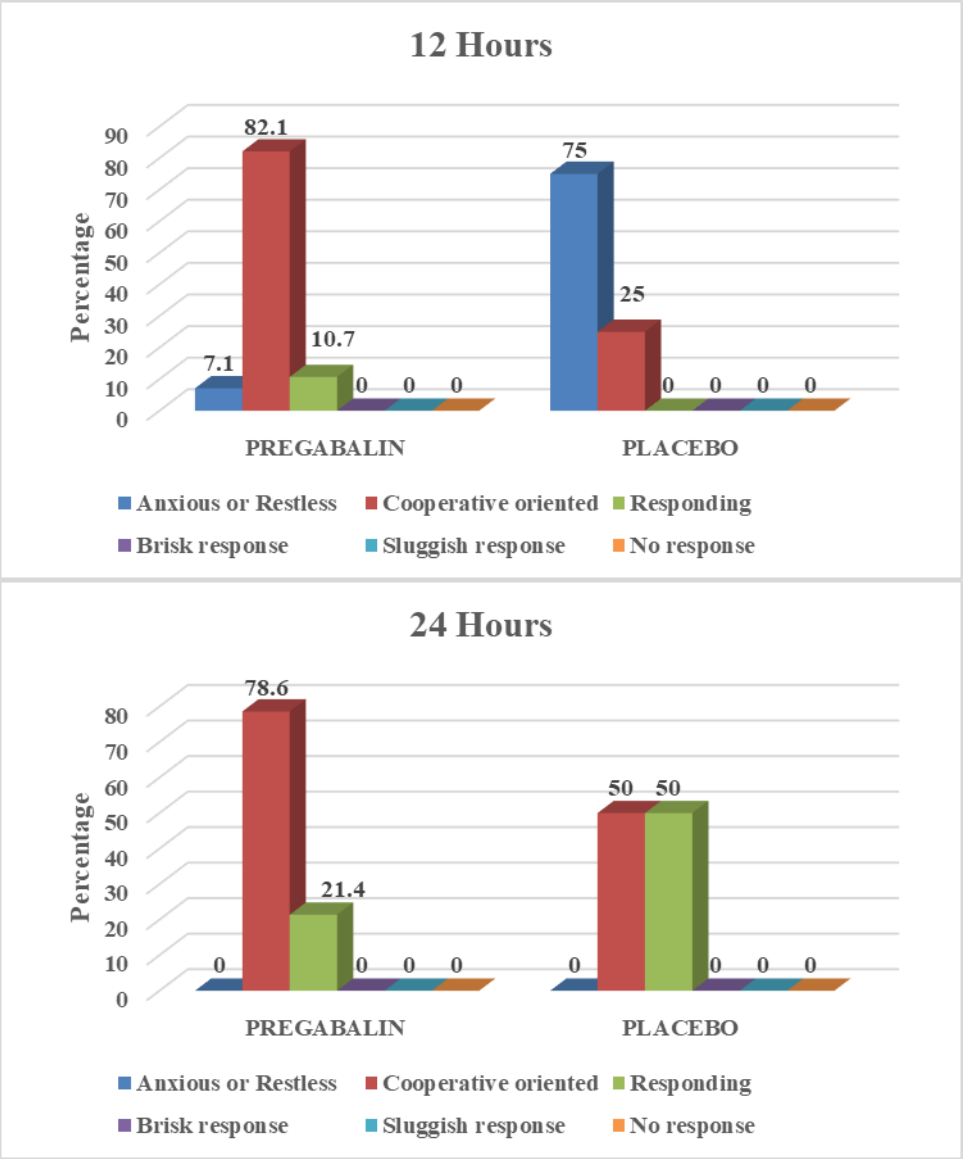


Table 5: Visual Analgue Scale (VAS)

Hours	PREGABALIN	PLACEBO	Total	P value
0	0.96±0.88	2.14±1.29	1.55±1.25	**<0.001**
4	1.71±0.81	3.29±1.05	2.50±1.22	**<0.001**
8	2.79±0.63	4.07±0.81	3.43±0.97	**<0.001**
12	3.43±0.74	4.79±0.83	4.11±1.04	**<0.001**
24	3.86±0.71	4.93±0.90	4.39±0.97	**<0.001**

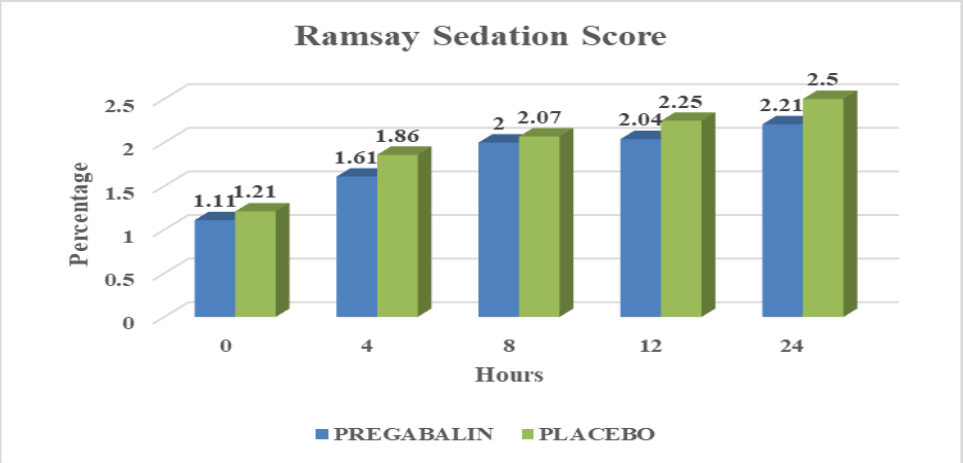
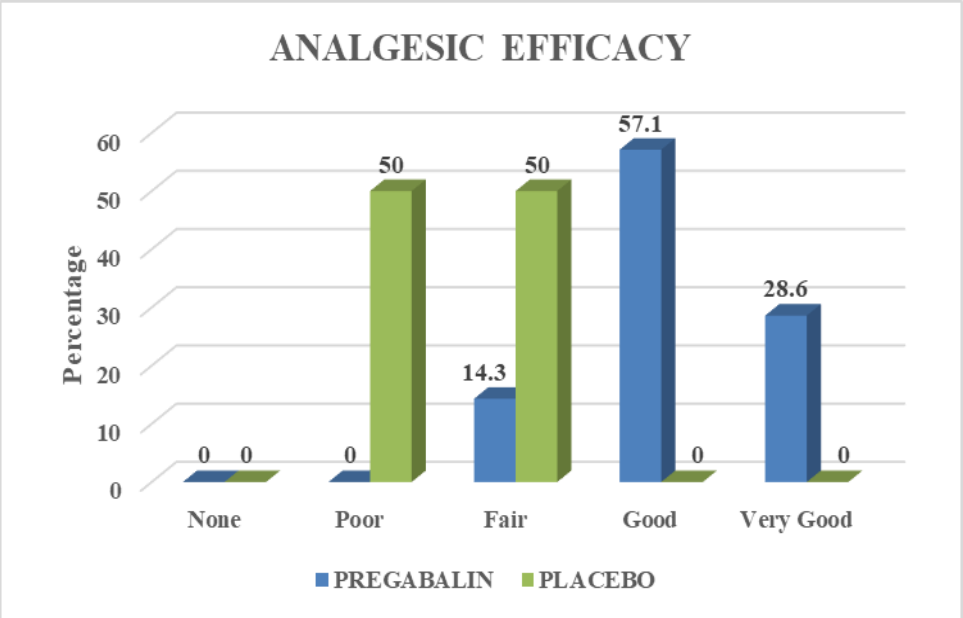


Table 7: Overall assessment of analgesic efficacy

Score	Overall assessment of analgesic efficacy	PREGABALIN	PLACEBO	Total
0	None	0(0%)	0(0%)	0(0%)
1	Poor	0(0%)	14(50.0%)	14(25%)
2	Fair	04(14.3%)	14(50.0%)	18(32.14%)
3	Good	16(57.1%)	0(0%)	16(28.58%)
4	Very Good	08(28.6%)	0(0%)	08(14.28%)
	Total	28(100%)	28(100%)	56(100%)

P<0.001**



4. 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" 1. Postoperative pain is a severe nociceptive stimulus associated hyperalgesia and allodynia which can exacerbate the existing pain by wind up phenomenon in dorsal column of spinal cord.

Proper pain relief is a major concern and area of focus. One of the most common questions asked preoperatively is about the amount of pain after the surgery. Pain is one of the most common three causes of delayed discharge after one day surgery, the other two are nausea and vomiting and drowsiness . Unfortunately prevention and treatment of postoperative pain continues to be a major challenge in postoperative period [2].

There has been increasing awareness among the clinicians that postoperative pain has also a hyperalgesic component which has prompted many authors to study the effect of neuropathic pain drugs used as preemptive analgesics for management of acute postoperative pain.

In our study we compared the anxiolytic and analgesic effects provided by single dose pregabalin 150 mg given 2 hours preoperatively versus placebo, against control group, in patients undergoing maxillofacial surgery under general anaesthesia.

Pregabalin is a lipophilic GABA analogue approved by FDA for clinical use. It is superior to other routinely used analgesics in 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 α2-δ subunit of voltage-gated calcium channels and modulate the release of several excitatory neurotransmitters such as glutamate, norepinephrine and substance P. Hencepregabalin 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. Preemptive use of pregabalin helps in the control of postoperative pain by its anti allodynic and antihyperalgesic activity.

Pregabalin is being used for neuropathic pain conditions such as postherpetic neuralgia, painful diabetic neuropathy, central neuropathic pain and fibromyalgia. It has an additional use in partial seizures of temporal lobe epilepsy and generalized anxiety disorders in doses ranging from 75mg – 300 mg . 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. The effects of pre-operative and placebo on post-operative pain control, need for rescue analgesic and side effects associated with these drugs were analysed in this study.

Usha Bafna et al., did a study to compare the effect of oral gabapentin 600mg and pregabalin 150mg with control group for postoperative analgesia in patients undergoing elective gynecological surgeries. They concluded that preemptive use of gabapentin and pregabalin significantly reduces the postoperative rescue analgesic requirement with pregabalin being superior to gabapentin. They noted some adverse effects like nausea, hypotension and bradycardia associated with the drugs . Our results were correlating with the above study in terms of reduced rescue analgesic requirement. The adverse effects noted were much less in our study.

Few authors compared pregabalin in a dose of 150mg and 225 mg for finding the optimal dose for patients undergoing abdominal hysterectomy. They found that though both were effective in prolonging postoperative analgesia. Pregabalin 225mg was associated with more adverse effects like dizziness. They arrived at a conclusion that pregabalin 150mg would be a better choice [8].

Few studies showed that a single preoperative oral dose of pregabalin 150mg is an effective method for reducing postoperative pain, opioid and NSAIDs consumption in patients undergoing orthopedic and abdominal hysterectomy surgeries [12-14]. These studies concentrated only on quantitative reduction of postoperative analgesic drugs. In our study extra effort was taken to assess the satisfaction of the patient as a whole which is of immense value to the anaesthetists in assessing the actual utility of such drugs in perioperative period.

Few authors studied pregabalin in various doses for gynaec laproscopic surgeries and laparoscopic cholecystectomy and found that preemptive oral pregabalin significantly decreases the postoperative pain as well as reduces analgesic requirement [15-17].

Another randomized study evaluating single preoperative dose of 100mg pregabalin concluded that it does not reduce acute pain nor improve recovery after minor surgery involving the uterus [18]. This showed that a preemptive oral pregabalin 100mg is insufficient in offering postoperative analgesia. In our study we used a dose of 150mg and it was effective in

offering good postoperative analgesia.

Two comparative studies (gabapentin v/s pregabalin) using single oral pre-emptive drug for infraumbilical surgeries under SAB, for evaluation of their comparative efficacy in terms of a cute postoperative analgesic benefits with rescue analgesic as diclofenac have shown similar results to our study. V. Saraswat et al,10 concluded that the total postoperative analgesic time was 8.98hrs in gabapentin group though less than pregabalin group (14.17hrs), both being effective in prolongation of post-spinal analgesia. Vishal Arora et al,19 reported that the total postoperative analgesic duration was 6.14 ± 2.07hrs in gabapentin group,7.31 ± 1.43hrs in pregabalin group and 4.13 ± 1.00hrs in placebo group,($p<0.001$ in both the studies) with reduced rescue analgesic requirements.[7]

Sahu S. etal9 concluded that a 300mg dose of pregabalin in two divided doses before below umbilical surgeries under spinal anaesthesia, provides better pain control than placebo and reduces demand for rescue analgesics, since, the time of first analgesic requirement was 4.0±0.0 hrs in placebo & 7.60±0.95 hrs in pregabalin group which was definitely more than duration of spinal anesthesia suggesting prolongation of spinal anesthesia.

Kohli Met al15 observed that time required for first rescue analgesia was 131.38±5.15 minutes in control gr, 176.38±4.80 minutes in pregabalin 150 gm gr and 202.42±6.77 minutes in pregabalin 300 gm gr (p-value <0.05) in hysterectomy under spinal anaesthesia and hence they concluded that oral pregabalin is useful in immediate postoperative analgesia.

However, we specifically assessed movement pain by asking them to move from lying to sitting, which should limit the amount of bias secondary to this side effect. Nausea and vomiting in control group could be because of more number of NSAIDs (I.V. Diclofenac) required in this group. Various studies have successfully demonstrated the efficacy of pregabalin in reducing acute postsurgical pain. Ruben et al20 observed that pre-emptive pregabalin significantly reduced postoperative VAS scores and rescue analgesic requirements in patients undergoing posterior spinal fusion surgery with no adverse effects on heart rate, blood pressure and respiration.

Mathiesen et al16observed 50% reduction in postoperative pain scores and no negative hemodynamic effects with single dose pregabalin administration 1 hr preoperatively in total hip arthrtoplasty cases. Agarwal et al11 used single dose 150 mg 0f pregabalin one hr preoperatively in laparoscopic cholecystectomy, also observed reduced rescue analgesic consumption postoperatively with stable hemodynamics.

Our study was correlating with the above studies in that pregabalin increases the time for rescue analgesia and reduces the total dose of analgesic requirement with better patient satisfaction and comfort. These study results suggest that pregabalin reduced post-operative pain significantly, mainly 24hours period post-operatively and reduced the overall consumption of rescue analgesics needed. There were no significant difference in relation to variations in heart rate, systolic or diastolic blood pressure.

It was also noted that there were no difference in other side effects as respiratory depression, dizziness or vomiting in either of the groups.
This study design, has certain limitations, in that, single dose of pregabalin has been used. The half-life of pregabalin is 9-12hrs which may have resulted with decreased effect over time and conclusion about the optimal dose and duration of the treatment cannot be made for these particular types of surgeries. Another limitation is that we could not detect difference as regard to adverse but more studies are required to assess adverse effects with low incidences.

5. CONCLUSION

Preemptive used of Oral pregabalin is effective in reducing postoperative pain and it is also effective in reducing the requirement of post-operative analgesic drugs in patient undergoing maxillofacial surgery. In the current study we have confirmed our hypothesis that preemptive used of Oral Pregabalin 150mg achieved superior analgesia than the oral placebo. We therefore suggest that oral preemptive single dose of Tab.pregabalin 150mg is an effective method for reducing post-operative pain and also reducing requirement of postoperative analgesic drugs in patients undergoing maxillofacial surgery under general anaesthesia.

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