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Comparison of Post-Operative Analgesic Effects of Pre-Operative Pregabalin with Diclofenac in Head and Neck Surgery

Medical Science

KEYWORDS : pre-emptive analgesia, diclofenac, pregabalin

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ABSTRACT

Background: Study conducted to compare effects of pre-emptive pregabalin with diclofenac on post-operative after head and neck surgery. Side effects assessed, and hemodynamics for 24 hrs post-operatively observed.
Methods: Prospective, randomized, placebo-controlled clinical study on 66 ASA 1 and 2 patients between 18-60 yrs posted for elective head and neck procedures. Patients were randomized in two groups. Pre-emptive analgesia was given 1 hr before surgery with
• 75 mg diclofenac orally
• 150 mg pregabalin orally
Primary outcomes were severity of postoperative pain, and postoperative analgesic requirement (IM diclofenac 75mg). Secondary outcomes were incidence and severity of side-effects.
Results: Patients in the pregabalin group: had less post-operative pain in the 12 - 24 hour period, were sedated more during the first 8 hrs, and less of them needed postoperative rescue analgesic, in lower doses.
Conclusion: Oral pregabalin 150 mg administered pre-operatively was more effective in reducing postoperative pain and rescue analgesic requirement in patients undergoing elective Head and Neck Surgeries compared to diclofenac.

INTRODUCTION

In more than 50% of surgical procedures, the most common and inadequately treated complaint is pain.[1] Post-operative pain responses may be prevented or treated if planned early. [2, 3, 4]

Pain is also the most common morbidity requiring prolonged and unplanned hospital stay in elective day case surgeries in a third of patients. 5, 6, 7 After major surgical procedures, this is the most important problem that affects patient recovery. 8, 9 It is now thought that intense acute post-operative pain might lead to chronic pain.10 Post-operative pain also remains under-treated even after the recent advances in the science of pain treatment. 11

Balanced analgesia has recently been introduced, to improve pain relief by using a combination of analgesics with complementary effects, with a view to avoid opioids with all their problems. 12 The different pathways of action and adverse effects should make pain treatment more safer and effective. However, this modality is still not fully utilized in clinical practice, even though the benefits in improving quality of life with less costs are of increasing importance in the present scenario of rising expectations from health care practice. 13, 14, 15

Gabapentin, and its successor pregabalin, were developed as anti-spasmodics and anti-epileptic drugs, but have been found effective to treat acute and chronic pain. [16,17] It acts by binding to the α2δ subunit site of neuronal voltage gated calcium channels, resulting in reduced depolarization-induced calcium influx at nerve terminals. It also reduces the release of specific neurotransmitters like glutamate, noradrenaline, CGRP and Substance P. These actions are related to its analgesic, anti-convulsant and anxiolytic properties. It has 6 to 7 times greater potency than gabapentin.

Gabapentin has been found to be useful for neuropathic pain[18] and postoperative pain after breast surgery,[19] spinal surgery, [20] and laparoscopic cholecystectomy. [21] Similarly, pregabalin has a proven role in treating neuropathic pain.[22] However, evidence supporting the postoperative analgesic efficacy of pregabalin is limited to randomized controlled trials in patients undergoing dental surgery,[23] spinal fusion surgery,[24] laparoscopic hysterectomy[25] day-case gynaecological laparoscopic surgery.[26] None of these trials has investigated the role of preoperative single-dose administration of pregabalin in attenuating postoperative pain after elective head and neck surgeries.

The present study was therefore designed to evaluate the role of preoperative single dose of pregabalin and compare it with diclofenac on post-operative pain and analgesic requirement following head and neck surgery. Any change in hemodynamics following surgery for 24 hrs post operatively and any side effects associated with pregabalin were also studied.

METHODOLOGY

This randomised double-blind controlled trial was conducted with 66 patients, between 18-60 yrs of age, of either sex, undergoing elective Head and Neck procedures lasting less than 2 hours, were divided into two groups of 33 patients each.

Patients with other co morbid illnesses like diabetes or hypertension, hepatic or renal derangements, on anti-epileptic treatment and already on chronic NSAID medication were excluded from the study.

The study protocol was approved by the institutional human ethics committee and written informed consent was obtained from all the patients.

All patients were given 5 mg oral diazepam on the night before the surgery and oral ranitidine 150mg on the morning of the surgery. The patients received either diclofenac 75 mg or pregabalin 150 mg orally on the morning of the surgery. All the medications were administered 1 h before the induction of anaesthesia with sips of water by a staff nurse who was not involved in the study.

Anaesthesia technique was standardized in all the groups. After connecting the standard monitors patients were induced with fentanyl 2μg.kg^{-1} and propofol titrated to loss of consciousness; orotracheal intubation was facilitated by vecuronium 0.08

μg.kg^{-1}. Anaesthesia was maintained with 50% nitrous oxide in oxygen and isoflurane maintained at an end-tidal concentration of 1-1.5%.All the patients included in the study group had their operating times less than 2 hrs. At the end of surgery, residual neuromuscular paralysis was antagonized with neostigmine 0.05 mg kg^{-1} and glycopyrrolate 0.01 mg kg^{-1}. After satisfactory recovery, the patients were extubated and shifted to the post-anaesthesia care unit (PACU).

In the post anaesthesia care unit (PACU), patients received intramuscular diclofenac 75 mg as and when they complained of pain with the intention to treat principle or when they had VAS pain scores of 4 or more. Primary outcomes noted were severity of postoperative pain and postoperative analgesic requirement. Secondary outcomes noted were incidence and severity of side-effects such as headache, sedation, and respiratory depression if any. Both these outcomes were assessed by an independent anaesthesia registrar blinded to group allocation.

Assessment of pain was done using a 100 mm visual analogue scale (VAS) where 0, no pain and 100, worst imaginable pain. Assessment of pain was done on arrival of patient to the PACU (0 hrs) and then every hour till the end of the study, that is, 24 h after operation. From these data, the maximum pain scores at different time intervals (0, 0–4, 4–8, 8–12, and 12–24 h) for each patient were considered for statistical analysis.

The Ramsay sedation scale was used to assess the sedation; patients with a sedation scale of $\geq$4 were considered as sedated.

Calculation of sample size was based on the presumption that postoperative VAS scores after preoperative administration of pregabalin 150 mg would be 30 mm when compared with 45 mm in the placebo group with a standard deviation of 20 mm at all time points. For the results to be of statistical significance with α=0.05 and β=0.90, we needed to recruit 33 patients in each group. The method of analysis was decided prospectively and incorporated the intention-to-treat principle. Patient characteristic data were analysed with one-way ANOVA for continuous variables and χ2 test for categorical variables. Postoperative diclofenac consumption was analysed with student's *t*-test. The VAS pain scores were analysed with Mann–Whitney *U*-test; the package SPSS 14.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. *P*<0.05 was considered significant.

RESULTS

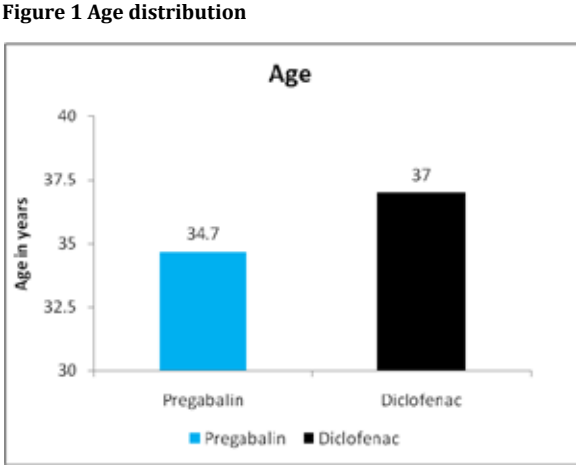
AGE DISTRIBUTION

The mean age in both the groups was comparable.

Table 1. Age distribution

	GROUP	N	Mean	Std. Deviation	T
Age	Prgb	33	34.69	13.294	.696
	Diclo	33	37.00	13.475	P=.489 NS

Figure 1 Age distribution



p=0.489 NOT SIGNIFICANT

SEX DISTRIBUTION

Age and sex distribution in both the groups did not differ significantly.

DISTRIBUTION OF CASES IN THE STUDY

Operation

			GROUP		Total
			Prgb	Diclo	
	Excision	Count	2	1	3
		%	6.3%	3.0%	4.6%
	Hemi-Thyroidectomy	Count	4	4	8
		%	12.5%	12.1%	12.3%
	Mastoidectomy	Count	4	6	10
		%	12.5%	18.2%	15.4%
	Mastoidectomy and Myringoplasty	Count	0	1	1
		%	.0%	3.0%	1.5%
	Myringoplasty	Count	1	0	1
		%	3.1%	.0%	1.5%
	ORIF	Count	5	2	7
		%	15.6%	6.1%	10.8%
	Osteoplasty	Count	0	1	1
		%	.0%	3.0%	1.5%
	RT SMG excision	Count	1	0	1
		%	3.1%	.0%	1.5%
	Septoplasty	Count	2	0	2
		%	6.3%	.0%	3.1%
	Septoplasty, FESS	Count	8	10	18
		%	25.0%	30.3%	27.7%
	Septorhinoplasty	Count	1	0	1
		%	3.1%	.0%	1.5%
	Thyroidectomy	Count	1	3	4
		%	3.1%	9.1%	6.1%
	Tonsillectomy	Count	3	5	8
		%	9.4%	15.2%	12.3%
Total		Count	33	33	66
		%	100.0%	100.0%	100.0%

Table 2 Distribution of surgical procedures taken up for the study

VISUAL ANALOG SCALE PAIN SCORES

VAS

	GROUP	N	Mean	Std. Deviation	t
0 hrs	Pregabalin	33	2.1563	1.11034	.49700
	Diclo	33	2.3030	1.26206	p=.621 ns
4 hrs	Pregabalin	33	2.2188	1.03906	2.55600
	Diclo	33	2.9394	1.22320	p=.013 sig
8 hrs	Pregabalin	33	2.2500	1.16398	2.31800
	Diclo	33	2.8485	.90558	p=.024 sig
12 hrs	Pregabalin	33	2.0938	1.44480	2.03400
	Diclo	33	2.7273	1.03901	p=.046 sig
16 hrs	Pregabalin	33	1.5000	.71842	4.67600
	Diclo	33	2.5152	1.00378	P<0.001 yes
20 hrs	Pregabalin	33	1.3438	1.00352	2.77200
	Diclo	33	1.9697	.80951	p=.007 hs
24 hrs	Pregabalin	33	1.1875	.64440	2.58900
	Diclo	33	1.6061	.65857	p=.012 sig

VAS scores in the pregabalin group were lower throughout the study period but significantly lower in the 12 to 24 hour period as compared to the diclofenac group.

Table 3 Visual Analog Pain Scale scores

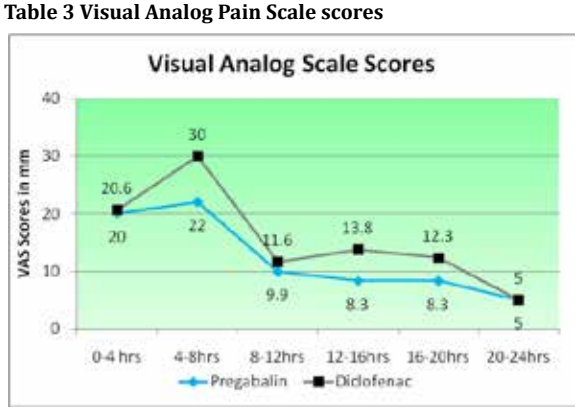


Figure 2 VAS scores

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RAMSAY SEDATION SCALE SCORESTable 4 Ramsay Sedation Scores

RSS

	GROUP	N	Mean	Std. Deviation	T
0 hrs	Pregabalin	33	3.6250	.55358	3.68100
	Diclo	33	3.0000	.79057	p<0.001 VHS
4 hrs	Pregabalin	33	3.3438	.48256	6.22900
	Diclo	33	2.4848	.61853	p<0.001 VHS
8 hrs	Pregabalin	33	2.7500	.62217	2.78900
	Diclo	33	2.3636	.48850	P=.007 HS
12 hrs	Pregabalin	33	2.7188	.68318	.46500
	Diclo	33	2.6364	.74239	P=.643 NS
16 hrs	Pregabalin	33	2.7500	.80322	.79100
	Diclo	33	2.6061	.65857	P=.432 NS
20 hrs	Pregabalin	33	2.4688	.62136	1.69400
	Diclo	33	2.2121	.50087	P=.0.006 NS
24 hrs	Pregabalin	33	2.3125	.47053	1.55600
	Diclo	33	2.1515	.36411	P=.0.127 NS

Table 4 Ramsay Sedation Scores

Patients in the pregabalin group were sedated more during the first 8 hrs as compared to those who received diclofenac.

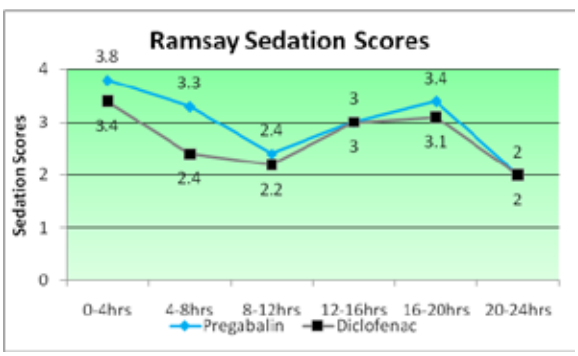

Figure 3 Ramsay Sedation Scores

DIASTOLIC BP RECORDINGS

DBP

	GROUP	N	Mean	Std. Deviation	t
0 hrs	Pregabalin	33	73.4063	5.91804	.17100
	Diclo	33	73.1515	6.07825	p=.865 ns
4 hrs	Pregabalin	33	74.7188	5.89278	.71600
	Diclo	33	73.7576	4.89279	p=.476 ns
8 hrs	Pregabalin	33	72.6250	5.35061	.93000
	Diclo	33	71.4242	5.06230	p=.356 ns
12 hrs	Pregabalin	33	71.0625	6.01041	.78500
	Diclo	33	70.0303	4.50337	p=.435 ns
16 hrs	Pregabalin	33	71.4688	4.04797	.95200
	Diclo	33	70.4848	4.28020	p=.345 ns
20 hrs	Pregabalin	33	70.0625	4.61371	.47200
	Diclo	33	69.5455	4.20633	p=.638 ns
24 hrs	Pregabalin	33	69.1250	5.10376	.07800
	Diclo	33	69.0303	4.72020	p=.938 ns

Table 5 Diastolic Blood Pressure Recordings

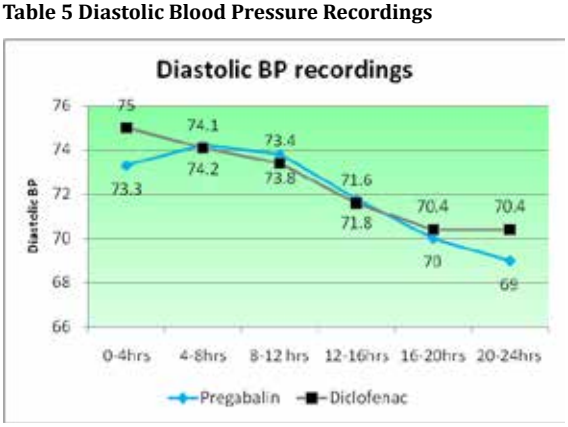

Figure 6 Diastolic Blood Pressure recordings

SYSTOLIC BP RECORDINGS

SBP

	GROUP	N	Mean	Std. Deviation	t
0 hrs	Pregabalin	33	119.6250	12.94388	.06400
	Diclo	33	121.3939	8.19275	p=.509 ns
4 hrs	Pregabalin	33	113.5625	9.26644	.44300
	Diclo	33	114.4848	7.43354	p=.659 ns
8 hrs	Pregabalin	33	114.7500	8.28134	.31300
	Diclo	33	115.3333	6.62697	p=.756 ns
12 hrs	Pregabalin	33	113.0625	6.48541	.87700
	Diclo	33	114.4242	6.03651	p=.384 ns
16 hrs	Pregabalin	33	112.2500	6.15394	1.19900
	Diclo	33	114.0000	5.61249	p=.235 ns
20 hrs	Pregabalin	33	110.9375	5.10496	1.20500
	Diclo	33	112.5455	5.59626	p=.236 ns
24 hrs	Pregabalin	33	112.3125	5.46273	1.16800
	Diclo	33	113.8788	5.40693	p=.247ns

Table 7 Systolic Blood Pressure Recordings

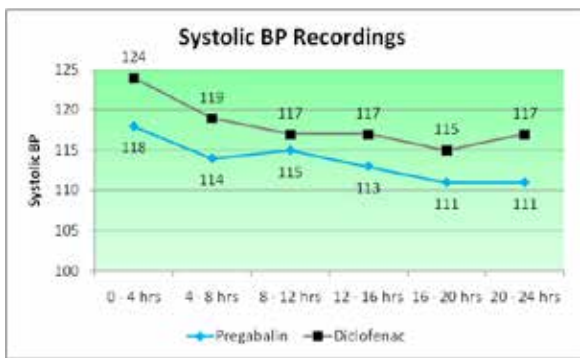

Figure 8 Systolic Blood Pressure Recordings

PULSE RATE RECORDINGS

PR

	GROUP	N	Mean	Std. Deviation	t
0 hrs	Pregabalin	33	77.0313	7.29332	1.10300
	Diclo	33	75.5697	6.07607	p=.274 ns
4 hrs	Pregabalin	33	73.7188	5.76549	.01300
	Diclo	33	73.6970	7.57250	p=.990 ns
8 hrs	Pregabalin	33	73.4375	5.90755	.33900
	Diclo	33	74.0000	7.36546	p=.736 ns
12 hrs	Pregabalin	33	72.9063	6.37211	.70800
	Diclo	33	71.9091	4.91403	p=.482 ns
16 hrs	Pregabalin	33	68.9375	4.31754	.69900
	Diclo	33	69.7879	5.40693	p=.487 ns
20 hrs	Pregabalin	33	69.7500	5.10925	.31100
	Diclo	33	70.1515	5.19688	p=.757ns
24 hrs	Pregabalin	33	69.9375	5.29112	.43200
	Diclo	33	70.4848	4.92520	p=.667 ns

Table 8 Pulse Rate Recordings

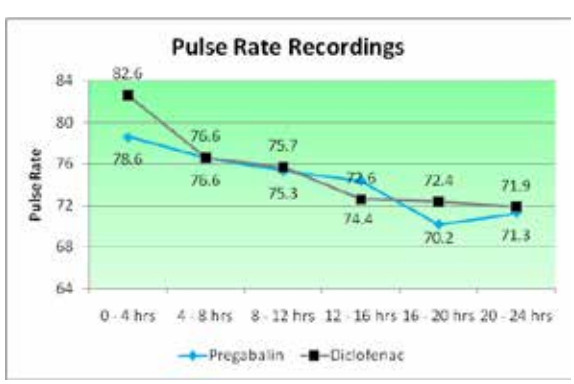

Figure 9 Pulse rate Recordings

There were no significant differences in the systolic and diastolic Blood pressure recordings or in the pulse rate amongst those who received either pregabalin or diclofenac.

TOTAL RESCUE ANALGESIC NEEDED

			GROUP		
			Pregabalin	Diclo	Total
Rescue Analgesic	0	Count	18	14	32
		%	56.3%	42.4%	49.2%
	75 mg	Count	13	10	23
		%	40.6%	30.3%	35.4%
	150 mg	Count	1	9	10
		%	3.1%	27.3%	15.4%
Total		Count	32	33	65
		%	100.0%	100.0%	100.0%

a. x2=7.278 P=.026 SIG

Table 9 rescue analgesics needed

Lesser number of patients in the pregabalin group needed post-operative rescue analgesic as compared to those who received diclofenac preoperatively also patients in the pregabalin needed lesser total dose of rescue analgesic.

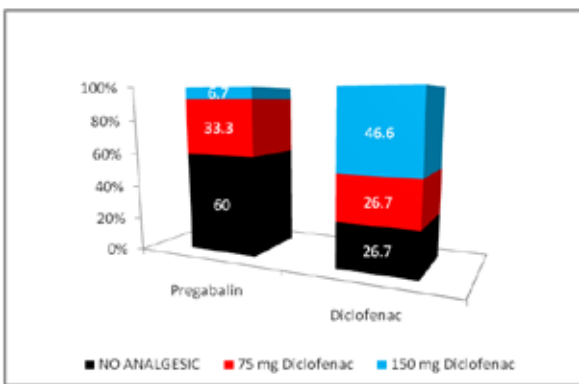

Figure 10 Total Rescue analgesics needed

DISCUSSION

The effects of pre-operative pregabalin and diclofenac on post-operative pain, the need for rescue analgesics and any side-effects associated with these drugs were analysed in this study.

We found that pregabalin reduced post-operative pain significantly, mainly in the 12 – 24 hr period post-operatively, and reduced the overall consumption of rescue analgesics needed. There were no significant differences in relation to variations in heart rate, systolic or diastolic blood pressure although the patients in the pregabalin group were sedated for a longer period than those in the diclofenac group post-operatively.

It was also noted that there were no differences in other side effects as respiratory depression, dizziness or vomiting in either of the groups.

CONCLUSION

Oral pregabalin 150 mg administered before operation was effective in reducing postoperative pain and postoperative rescue analgesic requirement in patients undergoing elective head and neck surgeries. The side-effect profiles were similar in both the groups. We therefore suggest that oral preoperative single dose of pregabalin 150 mg is an effective method for reducing post-operative pain and postoperative rescue analgesic requirement in patients undergoing these procedures.

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