

## Efficacy of Preemptive oral pregabalin for prolonging post-operative analgesia in modified radical mastectomies

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### Abstract

**Background:** The concept of preemptive analgesia had evolved in the recent years. Present days multimodal approach is the most preferred practice for perioperative pain relief, as no single agent is effective in inhibition of nociception without its side effects. Pregabalin originally a spasmolytic, now used as a newer anti-epileptic drug, in the management of generalized and partial epileptic seizures. Its use as a preemptive analgesic in many surgical procedures had proved promising results. Hence the aim of our study was to evaluate efficacy of preemptive pregabalin for prolonging post-operative analgesia, reducing post-operative opioid analgesic requirement and haemodynamic stability.

**Material and Methods:** 80 patients of ASA grade I and II physical status posted for elective modified radical mastectomy were divided into 2 groups of 40 each.

Group T –received pregabalin 150 mg orally 1 hour before general anaesthesia.

Group C – received identical empty capsules as placebo 1 hour before general anaesthesia.

**Results:** The postoperative VAS scores were significantly lower and duration of analgesia was longer in pregabalin group as to control group. The total analgesic consumption, PONV scores were also lower in pregabalin group. Ramsay sedation scores were slightly higher in pregabalin group but were acceptable clinically. The side effects were similar in both groups.

**Conclusion:** Preemptive 150mg oral pregabalin reduces post-operative pain scores(VAS)significantly, provides longer duration and better quality of post-operative analgesia, reduces opioid analgesic requirement and attenuates haemodynamic response to laryngoscopy, endotracheal intubation and also extubation without increase the side effects when used in optimal doses.

**Keywords:** Preemptive analgesia, Pregabalin, VAS scores, Hemodynamic stability, Modified radical mastectomies.

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### Introduction

Pre-emptive analgesia is the use of analgesic agents to prevent pain even before noxious painful stimulus is applied, compared to conventional analgesia which is used after painful stimulus. This was first introduced in animal studies by Wall in 1988<sup>(1)</sup> and Woolf in 1991 for post-operative analgesia<sup>(2)</sup>. Preemptive analgesia not only inhibits nociceptors and thus preventing the central alterations induced by afferent input after surgery but also reduces alterations in sensory central receptors responsible for central sensitization, neuropathic pain, and hyperalgesia and allodynia peri-operatively<sup>(3,4)</sup>.

Post-operative pain has been managed with a variety of drugs and techniques such as combination of opioids, non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol, small dose ketamine, infiltration of local anesthetics, interventional techniques like epidural and nerve blocks etc. which are associated with potential risks of serious complications. Thus, with the emerging

concepts of pre-emptive analgesia, a drug that has analgesic properties, opioid sparing effects, which possibly reduces opioid tolerance, relieves anxiety and is not associated with adverse effects typical for the traditional analgesic would be an attractive adjuvant for post-operative pain management<sup>(5)</sup>. In cancer patients, the effect of any medication on the disease course, adverse outcomes should also be considered. The technique of preemptive analgesia may restore the interleukin-2 levels to normal earlier, which plays a key role in T-cell mediated immune response in cancer. Immunosuppressive effects of opioids may have some tumor promoting effects in cancer patients<sup>(6,7)</sup>. Use of preemptive analgesics in cancer patients leads to reduced need for opioid analgesics peri-operatively, there by provides additional benefits. Gabapentin and pregabalin both have been used in the treatment of neuropathic pain as well as post-operative pain with good results.<sup>(8,9,10)</sup>

The major advantage of pregabalin in clinical use is that it has higher bioavailability when giving orally with linear pharmacokinetics property compared to gabapentin. It is rapidly and extensively absorbed after oral route in the fasting state with maximal plasma concentration occurring within 1 hour after single or multiple doses. In recent years, pregabalin has been introduced as an adjunct in multimodal management of postoperative analgesia in many studies because of its favorable pharmacokinetics<sup>(11-17)</sup>. This study has been designed to evaluate the role of single oral dose of 150

mg pregabalin compared to placebo in attenuating postoperative pain and analgesic consumption in adult patients undergoing modified radical mastectomy for breast cancer performed under general anaesthesia.

### Material and Methods

The present prospective, randomized, double-blind, placebo controlled clinical study includes 80 adult patients (16–60 yr) of either sex, American Society of Anaesthesiologists (ASA) physical status I and II, posted for modified radical mastectomy under general anaesthesia. The study protocol was approved from the institutional ethical committee and written informed consent was obtained from all the patients. Patients with history of documented hypersensitivity to pregabalin, impaired renal & liver functions, history of chronic pain and on medications for the same, uncontrolled medical disease (cardiac, pulmonary, endocrine, neurological, diabetes, hypertension etc.) history of intake of non-steroidal anti-inflammatory drugs within 24 h before surgery, were excluded from the study. Patients meeting the inclusion criteria during the preanaesthetic evaluation were educated regarding post-operative pain assessment and randomly assigned into two groups of 40 each with the help of a computer generated table of random numbers, to receive either oral pregabalin 150mg capsule with sips of water - Group T (n=40) or an identical empty capsule (Placebo) - Group C (n=40), with sips of water 1 hour prior to induction of general anaesthesia by a staff nurse who was not involved in the study. All the patients were pre-medicated with oral tab. alprazolam 0.5mg and tab. ranitidine 150mg on the night before the surgery. On arrival to Operation Theater anaesthesia technique was standardized in all the groups. Patients were pre-medicated with. Inj.ondansetron 4mg, Inj.midazolam 0.03mg/kg, Inj.fentanyl 1ug/kg IV. After 3 min of pre oxygenation, anaesthesia was induced with Inj.thiopentone 5mg/kg, laryngoscopy and intubation was facilitated by Inj.succinylcholine 1.5mg/kg. Patients were monitored using multiparameter monitor. Maintenance of anaesthesia was done with oxygen 33%, nitrous oxide 66%, Isoflurane (0.4%-1%), neuromuscular blockade was maintained with inj.vecuronium. At the end of surgery, residual neuromuscular blockade was antagonized with neostigmine 0.05 mg/ kg and glycopyrrolate 0.01 mg/ kg. After satisfactory recovery, the patients were extubated and shifted to the post-anaesthesia care unit (PACU). The primary outcomes were severity of postoperative pain and postoperative opioid requirement. Secondary outcomes were incidence and severity of side-effects such as postoperative nausea and vomiting (PONV), sedation, and respiratory depression if any. Both these outcomes were assessed by an independent anaesthesiologist blinded to group allocation.

Following parameters were noted in Post Anaesthesia Care Unit:

- Assessment of pain at rest (static) was done using 10 mm visual analogue scale (VAS). 0 = no pain, 10 = worst pain on arrival to Post-anaesthesia Care Unit and then every 2 hours till first 12 hours postoperatively. Rescue analgesic was given only if VAS score is  $\geq 4$  mm at any point of time during assessment. Slow intravenous inj.tramadol 1mg/kg was used as rescue analgesic. The time duration of rescue analgesic requirement, also the total dose of rescue analgesic given was noted.
- Heart rate, Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Pressure were noted before induction, immediately after laryngoscopy & intubation, at 1, 3, 5, 10 minutes and at extubation.
- The severity of Post-operative nausea vomiting was graded on a four point ordinal scale.  
0 – no PONV, 1 – mild nausea, 2 – moderate nausea, 3 – severe. Inj.ondansetron 4mg slow IV was given to all patients with grade  $\geq 2$  of PONV as rescue anti-emetic.
- Ramsay sedation score was determined with patient's response to "glabellar tap" or "loud auditory stimulus".  
1 = anxious, restless/agitated or both.  
2 = oriented, co-operative & tranquil.  
3 = responds to stimulus.  
4 = brisk response to stimulus.  
5 = sluggish response to stimulus.  
6 = no response to stimulus.  
Patients with grade  $\geq 4$  were considered sedated.
- Respiratory depression was considered/defined as
  - Ventilatory frequency  $\leq 8$ /minute.
  - Oxygen saturation  $< 90\%$  without oxygen supplementation.

### Statistical Methods

For the results to be statistically significant with  $\alpha=0.05$  and power of the study 80%, 35 patients are needed in each group. Considering any dropouts, we had enrolled 40 patients in each group. Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean $\pm$ SD (Minimum–Maximum) and results on categorical measurements are presented in number as percentage. Significance is assessed at 5% (level of significance). Chi square test for categorical variables and Students' 't' test for continuous variables were used to compare the data.

### Results

Both groups were comparable with respect to the demographic data. No significant differences were found between the groups with respect to age, sex, and weight [Table 1]. Haemodynamic parameters are shown in graphs [1-4]. HR, SBP, DBP, MAP at different intervals were significantly lower in test group ( $p < 0.05$ ). Post-operative VAS scores shown in graph 5 at 0, 2 and 8

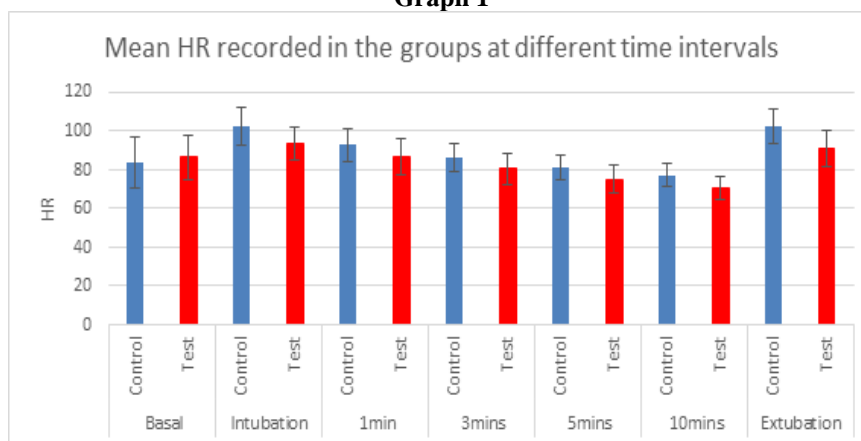
hours were significantly lower in test group as compared to control group ( $0.70 \pm 0.46$  v/s  $1.35 \pm 0.62$ )  $p < 0.001$ , ( $1.7 \pm 0.65$  v/s  $3.25 \pm 0.78$ )  $p < 0.001$ , ( $2.25 \pm 0.74$  v/s  $3.13 \pm 0.91$ )  $p < 0.001$  respectively. Total rescue analgesic requirement were also lower in test group as compared to control group ( $93.13 \pm 25.81$  v/s  $134.63 \pm 27.63$ ) ( $p < 0.001$ ) as shown in Table 2. Ramsay sedation score were

lower in control group as compared with test group (0.001) (Table 3). PONV scores were significantly lower in test group as compared to control group ( $p = 0.021$ ) (Table 4). Side effects like headache, dizziness, and light headedness were similar and comparable between the two groups.

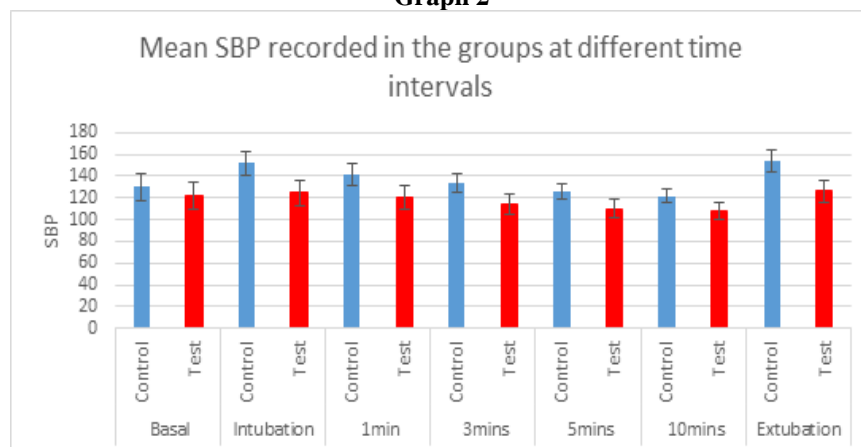
**Table 1: Demographic distribution of the study population**

Demographic data	Group C	Group T	P value
Mean age	$43.3 \pm 10.74$	$43.85 \pm 9.85$	0.812
Mean weight	$54.83 \pm 6.21$	$52.75 \pm 4.3$	0.085
Mean height	$155.20 \pm 3.70$	$157.38 \pm 5.08$	0.032

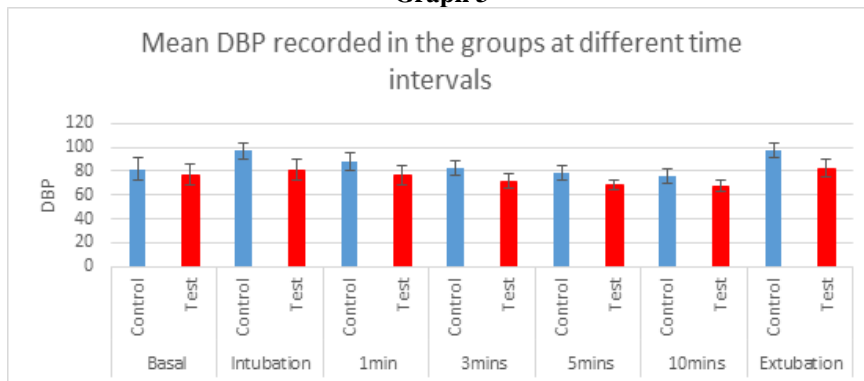
**Graph 1**



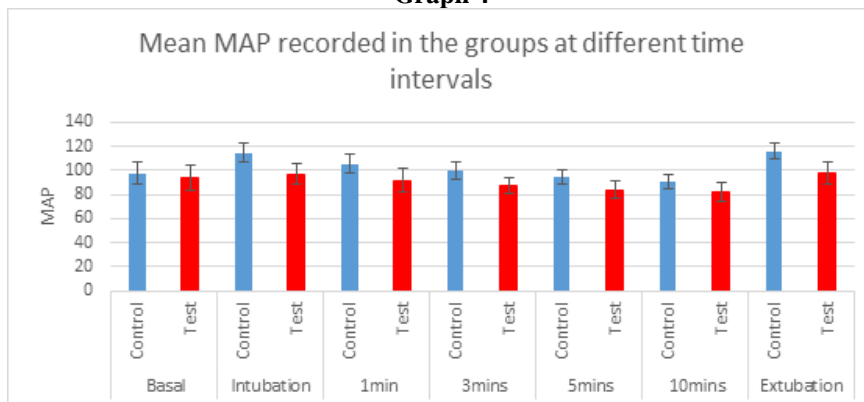
**Graph 2**



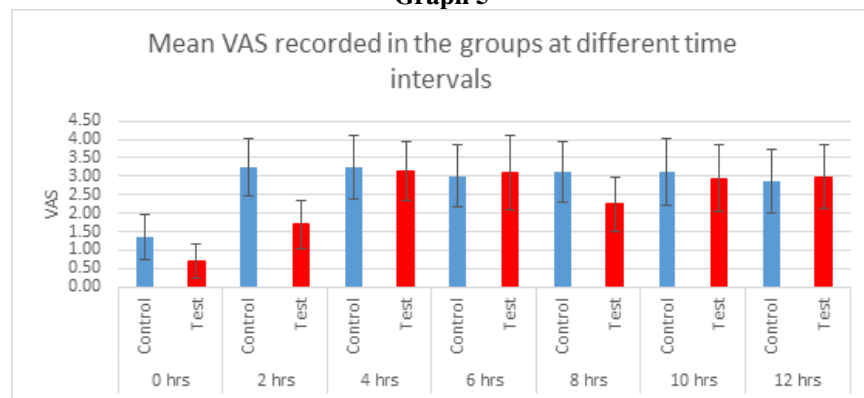
**Graph 3**



**Graph 4**



**Graph 5**



**Table 2: Comparison of mean rescue analgesia between the two groups**

Rescue Analgesic (mg)	Mean	Std Dev	SE of Mean	Mean Difference	t	P-Value
Control	134.63	27.63	4.37	41.500	6.942	<0.001*
Test	93.13	25.81	4.08			

**Table 3: Association between Ramsay score and the groups: (Chi-squared test)**

Ramsay Score	Control		Test		$\chi^2$	P-Value
	N	%	n	%		
Score 1	22	55%	8	20%	0.056	0.813
Score 2	18	45%	32	80%		
Total	40	100%	40	100%		

**Table 4: Association between PONV grade and the groups: (Chi-squared test)**

PONV	Control		Test		$\chi^2$	P-Value
	n	%	n	%		
Grade 0	20	50%	31	78%	7.716	0.021*
Grade 1	11	28%	7	18%		
Grade 2	9	23%	2	5%		
Total	40	100%	40	100%		

## Discussion

In this present study we observed that preemptive single oral dose of pregabalin 150 mg was effective in reducing the postoperative pain along with postoperative opioid consumption in patients undergoing modified radical mastectomy. VAS scores were the primary outcome variables to measure the quality of analgesia. Being aware that VAS scores have subjective variations, the other outcome variables like time of demand for rescue analgesic and the total number of patients requiring rescue analgesic and the total dose required were also recorded and compared between 2 groups. In our study, the VAS scores in test group were significantly very lower as compared to control group (<0.001) at 0, 2 and 8 hr post operatively. This finding of pregabalin groups having significant lower VAS score as compared with the control are in agreement with the studies conducted by Agarwal A et al and others<sup>[13,14,15,16]</sup>. On the contrary, the published article by Paech and colleagues<sup>(17)</sup> reported that a single preoperative dose of 100 mg pregabalin was ineffective in reducing acute postoperative pain or improving recovery after minor surgery involving only the uterus. The difference in the results from our study could possibly be because Paech and colleagues administered a smaller dose (100 mg) against the recommended starting dose of 150 mg<sup>(18)</sup> or because of the difference in the nature of surgery.

The pharmacological effects of pregabalin are believed to be results from its action as a ligand at the alpha-2-delta binding site, which is associated with the voltage-gated calcium channels in the central nervous system. Potent binding of pregabalin at alpha-2-delta site has been shown to reduce the depolarization-induced calcium influx at nerve terminals with a consequential reduction in the release of several excitatory neurotransmitters, including glutamate, norepinephrine, substance P, and CGRP<sup>(19-22)</sup>. It is probable that this modulation of neurotransmitter release by pregabalin contributes to the anticonvulsant, analgesic and anxiolytic effects.

In our study, the 150 mg oral pregabalin had effectively attenuated the laryngoscopy and intubation induced haemodynamic pressor response with perioperative haemodynamic stability when compared to control group. These findings and results were similar and supported the observations made in our study by Gupta K et al and others<sup>[23-25]</sup>.

We analyzed the Ramsay sedation score which were higher in test group as compared to control group (Table

11), with statistically significant difference (p 0.001) but was clinically acceptable. Even though, the mean sedation score of 2 was recorded in pregabalin 150mg group as compared with the significant mean score of 1 in the control group, it did not produce clinical sedation, as also reported by Kim SY et al and many other authors<sup>[15,19,20,21]</sup>.

The incidence of side effects such as nausea and vomiting were higher in control group hence required more rescue antiemetic. The increased incidence of PONV in control group was due to increased requirement of rescue analgesic in the form of inj.tramadol 1mg/Kg. Tramadol, being a weak opioid is not devoid of side effects, most commonly PONV. Pregabalin reduced rescue analgesic requirement in test group, hence rescue analgesic (opioid) related side effects. These results were comparable with results of many studies.<sup>(13,15,26,27)</sup>

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