Original Research Article

A randomised controlled trial evaluating the effect of Pre-operative oral gabapentin on post-operative pain relief and opioid consumption in patients undergoing modified radical mastectomy

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Abstract

Background: Postoperative pain is an acute pain which starts with surgical trauma and ends with tissue healing. The inadequate relief of postoperative pain has adverse physiological and psychological effects which result in delay of patient recovery and return to normal activities1.In addition, poorly controlled acute pain can result in changes in peripheral and central nervous system ***(neuronal plasticity***) that result in chronic pain2. Mastectomy is one such procedure, just like limb amputation, lateral thoracotomy etc., which has the propensity to result in chronic pain2. **Materials and Methods:** This prospective double blind randomized controlled study was done in patients who came to Tagore Medical College Hospital, planned for Modified Radical Mastectomy and fulfilled inclusion criteria. A total of 50 patients were selected for the study. They were randomized into two groups of 25 each namely, Group A: The Gabapentin group. Group B: The Placebo group .On the day prior to surgery, patients were assessed according to standard protocol and explained about the 0-10 VAS Scale. On the day of surgery patients received either two capsules of gabapentin or placebo two hours prior to surgery, given by an anesthesiologist who was otherwise not involved in the study. Anaesthesia and surgery proceeded as per standard protocol. No other sedative premedication or analgesic was administered. When the patients were shifted to postoperative ward, an anesthetist who was blind to the drug administered recorded the heart rate, blood pressure, SpO2, pain score (VAS) and sedation scores at 1st,2nd, 4th, 6th, 12th and 24 hour. **Result:** On conducting the analysis, the analgesic effect is more pronounced in the early postoperative period and group B has higher mean pain score (4.473) when compared to group A (2.820). **Conclusion:** The preoperative administration of oral gabapentin 600 mg two hours prior to surgery resulted in lesser pain scores and analgesic requirements during the 1st 24 hours.

Key Words: Analgesics, Gabapentin, Mastectomy, Postoperative, Pain, Mastectomy.

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INTRODUCTION

Pain has been a major concern of humankind since our beginning and it has been the object of ubiquitous efforts to understand and to control it. Postoperative pain is an acute pain which starts with surgical trauma and ends with tissue healing. Despite advances in the knowledge, skill and sophisticated technology, many patients continue to experience considerable discomfort during postoperative period. The inadequate relief of postoperative pain has adverse physiological and psychological effects which result in delay of patient recovery and return to normal

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activities[1]. In addition, poorly controlled acute pain can result in changes in peripheral and central nervous system (neuronal plasticity) that result in chronic pain2. The importance of pain control has been insisted by Joint Commission on Accredition of Health care Organizations by declaring it the "fifth vital sign".

Mastectomy is one such procedure, just like limb amputation, lateral thoracotomy etc., which has the propensity to result in chronic pain2.

There have been multiple methods to treat the post operative pain. They can be divided broadly into 2 groups.

1. Non pharmacological method
2. Pharmacological method.

Non pharmacologic measures include hypnosis, acupuncture, transcutaneous nerve stimulation etc.

Out of the pharmacologic methods, opioids, NSAIDS and local anesthetics are the commonly used drugs. Opioids, though offer analgesia, are inevitably associated with emesis and risk of respiratory depression. Local anesthetic techniques are often short lived or require interventional procedures, and the use of NSAIDS and COX-2 inhibitors are limited by renal, gastrointestinal and hemostatic effects. So, an adjuvant drug which could reduce the dose of other analgesics is useful in multimodal analgesia.

Treatment regimens could be used at different time periods relative to surgery to maximize the prevention of pain in response to different levels of sensory inputs.

Preemptive analgesia has been defined as treatment which

(1) is initiated before the application of the painful stimulus,

(2) prevents the establishment of central sensitization caused by incisional injury (covers only the period of surgery) and

(3) prevents the establishment of central sensitization caused by incisional and inflammatory injuries (covers the period of surgery and the initial post operative period)3.

Gabapentin introduced in 1993 as an anticonvulsant, has been found to have anti-nociceptive properties and is mainly attributed to the prevention of development of central neuronal sensitization4. There are reports which show gabapentin to have opioid sparing effect and to reduce the morphine consumption in healthy volunteers5. So, this study was undertaken to evaluate the efficacy of preoperative oral Gabapentin for relief of acute postoperative pain and reducing opioid requirement in postoperative period in patients undergoing Modified Radical Mastectomy.

MATERIALS AND METHODS

This prospective double blind randomized controlled study was conducted at Tagore Medical College Hospital, Chennai from January 2019 to January 2020 after obtaining the approval of Institute's ethical committee. A written informed consent was obtained from all patients. The study was done on all the patients who were planned for Modified Radical Mastectomy and fulfilled inclusion criteria. All patients in age group 30-70 years, belonging to ASA I-II and undergoing modified radical mastectomy were included for the study, whereas patients who are allergic to gabapentin, patients who are obese with a BMI > 30 Kg/m2, patients with renal or liver impairment, patients with chronic pain syndrome already taking analgesics for treatment were excluded from the study. After applying inclusion and exclusion criteria and getting a fully informed written consent, a total of 50 patients were selected for the study. They were randomized into two groups of 25 each namely,Group A: The Gabapentin group and Group B: The Placebo group. The allocation sequence was generated from a standard random number table by one of the investigators, not involved in the outcome assessment. Allocations were concealed using opaque sealed envelopes. The anesthesiologist involved in the intra-operative anesthetic management and performing the post-operative assessment were blind to the drug administered.The patients in gabapentin group were supposed to receive 600mg of gabapentin (2 capsules of 300 mg). The dose was based on a previous study byPandey *et al.*, demonstrating a ceiling effect of 600 mg of gabapentin in lumbar discectomy cases and no additional benefit at 900 mg or 1200 mg38. The placebo group received similar appearing capsules, which was prepared with the help of Hospital Pharmacy and contained B complex powder in it.On the day prior to surgery, after a detailed anesthesia workup for surgery, patients were explained about the 0-10 VAS Scale where 0 denotes "no pain" and 10 denotes "worst imaginable pain".On the day of surgery patients received either two capsules of gabapentin or placebo two hours prior to surgery, given by an anesthesiologist who was otherwise not involved in the study. No other sedative premedication or analgesic was administered. After the patients reached the operating room, monitors such as pulse oximeter, Noninvasive Blood Pressure monitor and ECG were connected and baseline values were recorded. A peripheral line was secured with an 18G IV cannula on the limb of non operative side and Ringer Lactate infusion was started. Anesthesia was induced with either Thiopentone sodium 3-5mg/kg or Propofol 1.5-2.5mg/kg whichever best suited the patient. Fentanyl 2µg/kg was the analgesic. Injection Xylocard 1.5mg/kg was used to obtund intubation response. Muscle relaxation was facilitated with Vecuronium bromide 0.1mg/kg and subsequent top ups were administered in a dose of 0.01mg/kg. Anesthesia was maintained with N2O:O2 and Sevoflurane 1 MAC. Intraoperative monitoring of pulse rate, blood pressure, SpO2 and EtCO2

was done. Any intraoperative increase in blood pressure or heart rate of >20% of baseline was treated with rescue analgesic Fentanyl 1µg/kg after ensuring adequate muscle relaxation. Intravenous Ondansetron 0.1mg/kg was given 30 min before the end of surgery. Injection fentanyl 1.5µg/kg was administered to the patient before wound closure, provided the patient didn't receive a repeat dose of analgesic after induction. At the end of surgery, neuromuscular blockade was antagonized with 0.05 mg/kg Neostigmine and 0.01 mg/kg Glycopyrrolate and after satisfactory regaining of muscle power, patients were extubated. The patients were shifted to postoperative ward and monitoring of their vitals was initiated. An anesthetist who was blind to the drug administered recorded the heart rate, blood pressure, SpO2, pain score (VAS) and sedation scores at first, second, fourth, sixth, twelfth and twenty fourth hour. The anesthesiologist collected data regarding analgesic requirement from the staff nurse who was blinded to the study. The staff nurse was advised not to give any other analgesics and use inj. Tramadol 1-2 mg/kg IV as the rescue analgesic, dose not exceeding 300 mg/day. Care was also taken to note down the time needed for first rescue analgesic. Side effects like nausea, vomiting, dizziness, urinary retention were recorded.

Drowsiness was recorded if either patient complained of it or if sedation scores were greater than or equal to 3 at more than two time intervals. Nausea, vomiting was treated with IV ondansetron 0.1 mg/kg.

STATISTICAL ANALYSIS

At the end of study all the data were unblinded and entered in windows excel sheet and analyzed using SPSS version 18 software. A p value of <0.05 was considered as statistically significant. Demographic variables, total tramadol consumption for 24 hours between groups and time for first rescue analgesia were compared using Independent t test. Variables such as pain scores, tramadol consumption at various time intervals were analyzed with Repeated Measures ANOVA and sedation scores were analyzed using a non-parametric test such as Friedman test and Mann and Whitney U test. Chi square test was used to compare incidence of side effects between the two groups. Mean and SD was calculated for all continuous variables.

RESULTS

All the fifty patients were included and randomized for study. The age distribution among groups was compared (Table 3 and Fig.5). The mean age in group A was 56.28±7.185 years and in group B was 56.68±6.731 years which was comparable. The p value was 0.840 which is not significant.

Table 1: Comparison of age between groups

	Group	N	Mean	SD	Independent t Test	P Value
Age (In years)	Group A	25	56.28	7.185	0.203	***0.840***
	Group B	25	56.68	6.731		

The weight between the groups were also comparable with group A patients having a mean of 61.44±5.546 kg while group B having a mean of 60.52±5.994 kg. p value was not significant (p>0.05) (Table 1)

Table 2: Weight distribution between groups

	Group	N	Mean	SD	Independent t Test	P Value
Weight (In kg)	Group A	25	61.44	5.546	0.563	***0.576***
	Group B	25	60.52	5.994		

The mean duration for which the surgery extended was 140.80±33.779 min in group A while it was 136.80±26.531 min for group B. They were comparable without much difference. p value was 0.644 which is not significant. (table 2)

Table 3: Comparison of duration of surgery

	Group	N	Mean	SD	Independent t Test	P Value
Duration In min	Group A	25	140.80	33.779	0.466	**0.644**
	Group B	25	136.80	26.531		

Table 4: ASA status comparison between groups

ASA class	Group A	Group B
ASA 1	3	3
ASA 2	22	22

Only ASA 1 and 2 patients were selected for the study. Both the groups contained equal distribution of ASA1/ASA2 patients with both group A and B having 3/22 patients.

On conducting the analysis, it is observed that there is statistical significance with respect to duration (F=28.823, p-value =0.000). Further, it is also noticed that there exists a statistical significance between two groups in terms of mean pain scores (F= 89.842, p value=0.000). This means that the analgesic effect is more pronounced in the early postoperative period and group B has higher mean pain score (4.473) when compared to group A (2.820).

Table 5: Pain scores at various time intervals

pain scores Time period	Group A		Group B	
	Mean	Std. Error of Mean	Mean	Std. Error of Mean
1 st hour	1.44	0.317	3.64	0.336
2 nd hour	2.08	0.288	4.56	0.295
4 th hour	2.56	0.217	4.04	0.268
6 th hour	3.40	0.200	4.20	0.238
12 th hour	3.56	0.174	4.24	0.194
24 th hour	3.88	0.176	6.16	0.149

The analgesic requirement analysis at first hour, from first to second hour, from second to fourth hour and so on up to first 24 hours was calculated. On conducting the analysis, it is noticed that there exists a statistical significance between two groups A and B (F= 384.000, p-value = 0.000). Here, group B has higher mean tramadol consumption (1.467 mg/Kg) when compared to group A (0.667 mg/Kg).

Table 6: Mean Tramadol Consumption

Tramadol Used Time	Group A (mg/Kg)		Group B (Mg/Kg)	
	Mean	SEM	Mean	SEM
1 st hour	0.12	0.066	0.60	0.129
2 nd hour	0.12	0.066	0.80	0.082
4 th hour	0.88	0.088	2.00	0.000
6 th hour	0.60	0.129	1.72	0.092
12 th hour	0.96	0.178	1.88	0.088
24 th hour	1.32	0.095	1.80	0.129

The total tramadol consumption over 24 hours was 3.96±0.841 in group A versus 6.56±1.294 mg/kg in group B. p value was found to be significant. (table 6)

Table 7: Comparison of total tramadol consumption

	Group	N	Mean	SD	Independent t Test	P Value
TRAM total (mg/kg)	Group A	25	3.96	0.841	8.427	0.0001
	Group B	25	6.56	1.294		

The mean time at which the patients requested analgesic was 172.60±41.486 min in group A, while it was 78.60±35.897 min in group B. p value was found to be significant ($p<0.05$)

Table 8: Comparison of first analgesic request time

	Group	N	Mean	SD	Independent t test	P Value
TIME In min	Control	25	78.60	35.897	10.150	0.0001
	Gabapentin	25	175.40	31.389		

The median values of sedation scores between the two groups over the six time periods were compared. It is observed that there exists a statistical significance between two groups (Z=4.857, pvalue=0.000) and that group A has higher sedation scores (2.13) when compared to group B (1.75) .

Table 9: Comparison of sedation scores

Sedation score at	Group A	Group B
1 st hour	2.73	1.90
2 nd hour	2.42	1.70
4 th hour	2.09	1.83
6 th hour	1.88	1.74
12 th hour	1.88	1.84
24 th hour	1.80	1.71

The major side effects observed were postoperative nausea vomiting (PONV) and dizziness. There were no significant side effects in 76% of patients in group A and 72% of patients in group B. 4 out of 25(16%) patients had drowsiness in group A while it was in 2 patients of group B(8%). PONV was more in group B with5/25 patients having it (20%) while it was present in 2/25 patients of group A (8%) (table 8)

Table 10: Incidence of side effects

	SIDE EFFECTS							
	Nil		Drowsy		PONV		Total	
	N	%	N	%	N	%	N	%
Group A	19	76	4	16	2	8	25	100
Group B	18	72	2	8	5	20	25	100

DISCUSSION

Postoperative pain which is very unpleasant and physiologically stressful is a very common problem in postoperative period. The knowledge on mechanism of production of acute pain has advanced sufficiently over the past decade. So a rational, rather than empirically derived therapy could be used by aiming specifically at interrupting the mechanism responsible for the generation of clinical pain. This concept is more relevant in the management of surgical pain than in any other scenario.

Pain in the postoperative period does not bear a direct relationship with the surgical injury. Due to peripheral and central hypersensitivity or the wind up phenomenon post operative pain is always more severe for any surgical injury. Any therapeutic regimen that will prevent or modulate this sensitization should be helpful in the effective management of postoperative pain. Preemptive analgesia is one such intervention. The underlying principle is that the therapeutic intervention is made before the onset of pain rather than in reaction to it. Numerous antihyperalgesic methods and drugs have been evaluated in order to reduce the central neuronal hyperexcitability which amplifies the postoperative pain. Although gabapentin has been used in the treatment of neuropathic pain syndromes, it has also demonstrated potent antihyperalgesic properties in preclinical and clinical studies, without affecting acute nociception.

The present study was undertaken to evaluate the analgesic efficacy of gabapentin 600mg administered in a preemptive manner in patients undergoing Modified Radical Mastectomy in Southern Railway Headquarters Hospital. A total of fifty patients were selected for the study and randomized into two groups of 25 each.

All the patients selected were females and this avoided gender inequalities because, there have been studies to show females to have more pain intolerance and analgesic requirement40.

The age group of both the study population was supposed to be uniform. Age plays a role because the pharmacokinetics of drugs vary with different ages leading on to variation in elimination half life. In our study, the groups were comparable. The mean age in group A was 56.28 ± 7.185 years while it was 56.68 ± 6.731 years in group B. The p value was 0.840, which is not significant.

The weight of the patients also affects the outcome of the study because the volume of distribution of lipophilic drugs increases with increasing weight leading to prolonged duration of action. We excluded very obese women (BMI>30 kg/m2) from our study.

The mean weight of patients in group A was 61.44 ± 5.546 kg and in group B was 60.52 ± 5.994 kg which was almost equal. p value was not significant (p>0.05).

The risk stratification was equal between groups in that both had 3/22 number of ASA1/ASA2 patients.The duration of surgery also lasted for comparable period of time in both the groups. It was 140.80 ± 33.779 min in group A while it was 136.80 ± 26.531 min in group B.

The mean pain scores at various time intervals were noted and compared between the two groups. The mean pain scores at first, second, fourth, sixth, twelfth and twenty fourth hour were: 1.44±0.317 vs. 3.64±0.336, 2.08±0.228 vs. 4.56±0.295, 2.56±0.217 vs. 4.04±0.268, 3.40±0.200 vs. 4.20±0.238, 3.56±0.174 vs. 4.24±0.194, 3.88±0.176 vs. 6.16±0.149 respectively. Thus it was observed that the mean pain scores were less in gabapentin group compared to placebo group (p<0.001).

This was comparable to previous studies. In 2004, Turan et al, conducted a study on patients undergoing total abdominal hysterectomy under General anesthesia. The patients received either oral gabapentin 1200 mg or placebo 1 hour prior to surgery. The pain was assessed both in lying and sitting position. The mean pain scores were low throughout the study period (24hrs).At 1 h pain scores were 4.9±0.8 on lying position in placebo group while 1.9±2.5 in gabapentin group. Even at 24 hours scores were 1.6±1.2 in placebo group while it was 0.5±0.7 in gabapentin group26.

Similarly, a study conducted by Pandey *et al.*, comparing preemptive effects of gabapentin and tramadol in patients undergoing laparoscopic cholecystectomy found lower pain scores at all time intervals in gabapentin group than in tramadol and placebo group27.

However study by Fassoulaki *et al.*, showed no significant difference among gabapentin 400 mg, mexilitine 200mg or placebo in VAS scores till first 24 hours of the postoperative period. But still they noticed reduction in the pain scores in gabapentin group starting from the third day and also a significant reduction in analgesic requirement24.

The time taken for the first request of analgesia was compared between groups. There are previous studies which evaluated the time required for first rescue analgesia.

In 2004, Turan *et al.*, conducted a study to evaluate efficacy of gabapentin in rhinoplasty and endoscopic sinus surgery, conducted under TIVA and monitored anesthesia care.

The patients were given either placebo or gabapentin 1200mg one hour prior to surgery. IM diclofenac 75 mg was the rescue analgesic. The time for first analgesic request was significantly prolonged in gabapentin group 18±9 hrs versus 9±7 hrs in placebo group ($p<0.001$)29.

In another study done by Dr. Subhendru sarkar *et al.*, on effect of gabapentin premedication on postoperative opioid consumption following spinal decompression surgery, the time to rescue analgesia was significantly prolonged in gabapentin group
(120 ± 60 min vs. 240 ± 60 min)41.

Our study correlated with the above findings. In our study the request for first analgesic request was 172.60 ± 41.486 min in gabapentin group while it was 78.60 ± 35.897 min in placebo group ($p<0.001$).

The consumption of tramadol at various time intervals and the total tramadol used over 24 hours were studied between groups. The patients in gabapentin group required less tramadol boluses as compared to the placebo group at all time intervals. The effect was more pronounced during early post operative hours ($F= 384.000$, P value <0.001). The total tramadol consumption over 24 hours was 3.96±0.841 mg/kg in gabapentin group when compared to 6.56±1.294 mg/kg in the placebo group.This was in concordance with previous studies. Dirks et al, demonstrated a reduction in total morphine consumption from a median of 29 mg to 15 mg after administration of 1200mg gabapentin 1 hour prior to surgery in patients undergoing Modified Radical Mastectomy25.

Pandey et al, also demonstrated a reduction in total fentanyl consumption in the first 24 hours after administration of 300mg of gabapentin in patients undergoing lumbar discectomy. It was 223.5±141.9 µg in gabapentin group when compared to 359.6±104.1 µg in placebo group28.

Turan *et al.*, used same rescue analgesic as that of our study, IV tramadol and demonstrated a reduction of tramadol consumption at 12,16,24 hours and a overall reduction in consumption over 24 hours(270.4±144.4 vs. 419.6±83.6), after administration of 1200mg gabapentin, 1 hour prior to patients undergoing Total Abdominal Hysterectomy under general anesthesia26.

A recent study on administration of gabapentin as prophylactic anticonvulsant for patients undergoing craniotomy for supratentorial tumor resection, also revealed analgesic properties of gabapentin and reduction in total morphine consumption when compared to phenytoin group(24±19 mg vs. 33±17 mg, $p=0.01$)42.

The incidence of side effects was compared between the groups. The sedation scores were high in gabapentin group as compared to placebo. Patients who complained of sedation or whose sedation scores were greater than 3 at more than two points of time, were about 16% in gabapentin group while it was 8% in control group. Majority of the patients, about 76% in gabapentin group and 72% in placebo group, complained no side effects. PONV was more in placebo group (20%) as compared to the gabapentin group (8%).

Literatures have shown similar results in the past. A study conducted by Turan *et al.*, on pre operative administration of gabapentin in patients undergoing rhinoplasty or endoscopic sinus surgeries under Monitored Anesthesia Care revealed that sedation is a significant side effect in gabapentin group limiting its use in ambulatory surgeries (24% vs. 8%)29.

In 2004, a study conducted by Turan *et al.*, on preoperative gabapentin in patients undergoing Total Abdominal Hysterectomy demonstrated no significant side effects between the two groups. PONV was less in gabapentin group compared to placebo group (5% vs. 7%) ,but it was not statistically significant26.

Similarly, a study done by Pandey *et al.*, to evaluate efficacy of gabapentin for relief of post operative nausea and vomiting in cases of laparoscopic cholecystectomy revealed lesser incidence of PONV in gabapentin group as compared to placebo (37.8% vs 60%)43.

CONCLUSION

Based on the observations, we conclude that the preoperative administration of oral gabapentin 600 mg two hours prior to surgery resulted in lesser pain scores and analgesic requirements during the first 24 hours. The time for first analgesic request was also significantly prolonged. There was a higher incidence of sedation in gabapentin group when compared to placebo but the incidence of vomiting was lower in gabapentin group.

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