ORIGINAL ARTICLE

Does Gabapentin make any difference in Post-Operative Pain in Modified Radical Mastectomy patients?

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ABSTRACT

Background: Post-operative pain is one of the many distressing outcomes of breast surgery. It has been described that more than 50 % of the patients experience severe acute postoperative pain and about 8% of those suffer from chronic persistent pain. According to multiple studies, pain after modified radical mastectomy (MRM) is 23% to 40%. Pain causes significant emotional and physical discomfort, endocrine dysfunction, impairs wound healing, causes cardiopulmonary and thromboembolic complications.
Methods: This randomized control trial was conducted at the department of general surgery, Dow University Hospital Karachi. All females, ages ranged between 20 to 80 years and diagnosed with breast carcinoma stage II based on triple assessment were recruited in the study. Patients underwent modified radical mastectomy and assessed at 12 and 24 hours postoperatively, for pain scores at rest and arm mobilization using VAS pain score, a number of times rescue analgesia when VAS-score >3 by residents of surgery blinded to the study. Those patients, who experience pain (pain score >3) in spite of routine analgesics received injection ketorolac 30mg once, pain score between 3 to 6 received injection Kinz, pain score > 7 were given both analgesics single times, pain score > 8 will receive intravenous maximum thrice in 24 hours. Patients with pain scores 0-2 were not given any additional analgesics. The outcome variables of the study were age, pain score (VAS), and analgesic requirement.
Result: A total of 102 patients were recruited, 51 in each group. In our study, no group was found immune to pain. At initial 12 hours post operatively, in control group mean pain was 3.37±0.56, and pain was 3.02±0.14 in case group when arm was at rest. Increase in pain was observed in arm mobilization. Control and case group mean pain on ipsilateral arm mobilization was 3.72±0.49 versus 3.12±0.33 respectively. Additional analgesic requirement was also decreased from 93.8% in control group to 58.3 % in study group (p <0.001).
Conclusions: Gabapentin has shown to be effective in significant pain reduction.
Keywords: Carcinoma breast, Modified radical mastectomy, pain score, post-operative pain

INTRODUCTION

Carcinoma Breast is the second most common malignancy among women, secretarial for nearly 1 in 3 cancers diagnosed among women in the United States, and it is the subsequent leading cause of cancer related death among women[1]. About 60% of breast cancer patients are managed with primary tumor resection with axillary lymph node staging[2]. Postoperative pain is one of the many distressing outcomes of breast surgery[2,3,4,5]. It has been reported that more than 50% of the patients experience severe acute postoperative pain and about 8% of those suffer from chronic persistent pain[6]. According to multiple studies, pain after modified radical mastectomy (MRM) is 23% to 40%[7,8]. Pain causes significant emotional and physical discomfort, endocrine dysfunction, impairs wound healing, causes cardiopulmonary and thromboembolic complications.[5] Pain after MRM is multifactorial[2,5,9]. For decades, different analgesics with the various mechanisms of actions have been proposed as effective postoperative analgesia. They include non-opioid analgesics, opioid, non-steroidal anti-inflammatory drugs, local anesthetics, alpha-agonist, COX-2 inhibitors, epidural anesthesia, patient control anesthesia (PCA) brachial plexus block, and the local application of Nefopam and Memantine, but none of them is ideal analgesic[10,11]. Pre-emptive analgesia is a new emerging concept to introduce an analgesic regimen before contact with noxious stimuli[8,11]. It has the potential to be more effective than any analgesic regimen initiated after surgery[11]. Gabapentin is an anticonvulsant that is a structural analog to GABA pain receptors, which binds to GABA receptors and block the voltage-gated calcium current, and decreases the release of neurotransmitters by sensory neurons[4,11]. According to a study conducted by Pandey C K, gabapentin given 2 hours before surgery has no benefit over post-operative administration in terms of pain score[13,14]. Fassoulaki et al were unable to find any effect on reduction in post-operative pain after mastectomy[6]. There is also controversy regarding the dose and frequency of gabapentin as effective perioperative analgesia[2,3,5]. If this proves to be an effective analgesic, immediate postoperative pain can be decreased and the development of chronic pain can be prevented. The objective of this study was to evaluate the effect of gabapentin on acute post-operative pain following modified radical mastectomy.
Hypothesis: Preoperative single dose of Gabapentin is effective in reduction of pain following MRM.

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MATERIAL AND METHODS

This Randomized control trial was conducted at the department of general surgery, Dow University Hospital Karachi from September 2017 to September 2018 after taking

permission from institutional review board. (IRB # 2017/169). Females, age ranged between 20 to 80 years and diagnosed with breast carcinoma stage-II were included in the study. Patients who refused to participate in the study, allergic to gabapentin on the basis of history, previous treatment with Gabapentin in the previous 8 weeks, chronic pain syndrome, substance abuse, sedatives, hypnotics, or antidepressants, analgesic intake within 48 hours before surgery. Patients with diabetes mellitus, hypertension, and renal failure, and inability to understand VAS pain scores were excluded from the study. The sample size was calculated by the Open Epi calculator. The mean pain score difference at rest between two groups was taken as 0.7 (placebo: mean±SD=2.9±1.2 and Gabapentin: mean±SD=2.2±1.3.5 With 80% power, and 95% confidence level, the total sample size came out to be 102, 51 patients in each group. Consecutive sampling was used to achieve the desired sample. Patients fulfilling inclusion criteria were randomly enrolled in either of the 2 groups by sealed opaque envelop method bearing cards, which will be picked by the staff nurses. The intervention group was labeled as group A and the control group as group B. Patients in the intervention group received a single dose of 1200 mg of gabapentin 2 hours before surgery. All procedures were performed under general anesthesia. Postoperative analgesic injection ketorolac 30 mg thrice a day and injection paracetamol 1 gram intravenous thrice a day was advised. Patients were assessed at 12 and 24 hours post-operatively for pain scores at rest and arm mobilization using VAS pain score, a number of times rescue analgesia when VAS score > 3 by residents of surgery blinded to the study. Those patients, who experience pain (pain score > 3) in spite of routine analgesics received injection ketorolac 30 mg once, pain score between 3 to 6 received injection Kinz, pain score > 7 were given both analgesics single times, pain score > 8 were given intravenous analgesics thrice in 24 hours. Patients with pain scores 0-2 were not given any additional analgesic All patients will receive an antiemetic injection of metoclopramide 10 mg I.V in case of nausea and vomiting. All demographics and outcome variables were added to the proforma. The outcome variables of the study were age, pain score (VAS), and analgesic requirement.

RESULT

A total of 102 patients were recruited, 51 in each group. Three patients from the control group were excluded due to the inability to understand the pain scoring system. Three patients from the case group were excluded due to early discharge on request. After the collection of data SPSS version 16 was used for analysis. Mean and the standard deviation was calculated for age, BMI, and duration of surgery as shown in table 1. Pain score was calculated for an ipsilateral arm at rest and on movement at 12 and 24 hours post-operatively as shown in table 2a. The pain was further categorized into mild, moderate, and severe in both groups as shown in table 2b. Patients were given analgesics according to the pain score shown in table 3. P-value <0.05 was taken as significant.

Table 1: Demographics and duration of surgery (n=96)

Variables	Controls	Cases	p-value
Age in years			
mean ± SD	53.47 ± 13.0	50.62 ± 10.9	0.248
BMI			
mean ± SD	35.77 ± 5.75	32.51 ± 8.29	0.028
Duration			
mean ± SD	136.0 ± 23.4	136.4 ± 26.3	0.935

Table 2A: Vas pain score with study groups (n=96)

	Controls	Cases	p-value
VAS-12 hours			
At rest			
mean ± SD	3.37 ± 0.56	3.02 ± 0.14	<0.001
At arm mobilization			
mean ± SD	3.72 ± 0.49	3.12 ± 0.33	<0.001
VAS-24 hours			
At rest			
mean ± SD	2.83 ± 0.47	1.83 ± 0.63	<0.001
At arm mobilization			
mean ± SD	3.35 ± 0.72	2.27 ± 0.49	<0.001

Table 2B: Vas pain score in categories with study groups

	Controls	Cases	p-value
VAS-12 hours			
At rest			
1-3 Mild	2 (4.2)	-	<0.001
4-6 Moderate	26 (54.2)	47 (97.9)	
7-10 Severe	20 (41.7)	1 (2.1)	
At arm mobilization			
1-3 Mild	1 (2.1)	-	<0.001
4-6 Moderate	11 (22.9)	42 (87.5)	
7-10 Severe	36 (75.0)	6 (12.5)	
VAS-24 hours			
At rest			
No Pain	2 (4.2)	14 (29.2)	<0.001
1-3 Mild	4 (8.3)	28 (58.3)	
4-6 Moderate	42 (87.5)	6 (12.5)	
At arm mobilization			
No Pain	2 (4.2)	-	<0.001
1-3 Mild	1 (2.1)	36 (75.0)	
4-6 Moderate	23 (47.9)	11 (22.9)	
7-10 Severe	22 (45.8)	1 (2.1)	

P-value calculated using Chi-square and Fisher Exact tes

Table 3: Additional analgesic dose

AT 12 Hours:	Controls	Cases	P-value
Additional Analgesic Required			
Yes	46 (95.8)	48 (100)	0.247
No	2 (4.2)	-	
Additional Analgesic Name (n=94)			
Toradol	2 (4.3)	37 (77.1)	<0.001
Kingz	22 (47.8)	10 (20.8)	
Both	22 (47.8)	1 (2.1)	
Additional Analgesic Frequency (n=94)			
Once	24 (52.2)	47 (97.9)	<0.001
Multiple	22 (47.8)	1 (2.1)	
At 24 hours			
Additional Analgesic Required			
Yes	45 (93.8)	28 (58.3)	<0.001
No	3 (6.2)	20 (41.7)	
Additional Analgesic Name (n=73)			
Toradol	10 (22.2)	16 (57.1)	<0.001
Kingz	13 (28.9)	12 (42.9)	
Both	22 (48.9)	-	
Additional Analgesic Frequency (n=73)			
Once	42 (93.3)	28 (100)	0.228
Multiple	3 (6.7)	-	

P value calculated using Chi-square and Fisher Exact test

DISCUSSION

Gabapentin is an anticonvulsant and structural analog of gamma-aminobutyric acid (GABA) that has been known to reduce post-operative pain by various mechanisms. In our study, no age group was found to be immune to post-operative ipsilateral arm pain but it was observed that overall women in age ranged between 41 to 60 years have more pain at rest in the initial 12 hours of surgery. No possible cause can be ruled

out. In our study, no group was found immune to pain. At the initial 12 hours post-operatively, in the control group mean the pain was 3.37±0.56 and pain was 3.02±0.14 when the arm was at rest. An increase in pain was observed in arm mobilization. Control and case group mean pain on ipsilateral arm mobilization was 3.72±0.49 versus 3.12±0.33 respectively. On the contrary, at 24 hours after surgery, the pain was significantly reduced in both of the groups, 2.83±0.47 versus 1.83±0.63 at rest 3.35±0.72 and versus 2.27±0.49 at arm mobilization. In contrast to our study, pain at rest in the placebo group to the gabapentin group at 2 and 4 hours postoperatively were not statistically significant (p-value=0.094 and p-value=0.084 respectively). Whereas pain during movement was significantly reduced at 2 hours postoperatively (p-value=0.0001) but no significant difference was observed at 4 hours postoperatively (p-value=0.018)[1]. Pain was further categorized into no pain, mild-moderate and severe on the basis of VAS score. After an exhaustive literature search, no study was found that has compared the VAS score in terms of mild-moderate and severe pain. In a study conducted by Kim et al in 2011, postoperative pain score at 2 hours was 2.6±1.4 in the control group whereas 2.06±1.2 in the case group. It was not statistically significant most likely due to the low dose of gabapentin 75 mg in spite of being in 2 doses, pre and post-operatively[12]. Turan A, Memis et al in 2006 using gabapentin 1200mg 1 hour prior to surgery in patients undergoing ambulatory rhinoplasty or endoscopic sinus surgery showed an analgesic efficacy of gabapentin similar to our findings.18 95.8% of the case group and 100% of the control group required some level of additional analgesia which was statistically not significant (p-value=0.427). Dirks J et al concluded that total morphine consumption was reduced from 29 mg in the placebo group to 15 mg in the gabapentin group (p-value=0.0001)[1]. Similar results were observed in another study in which 26% of the cases and 60% in the placebo group required analgesia[19]. Trials on multiple doses and timings of Gabapentin has been studied. In our study, a single dose of 1200mg of gabapentin was given 2 hours preoperatively. The same dose was followed in a study done by Dirks J et al. but gabapentin was given in the immediate postoperative and found a statistically significant reduction in morphine requirement from 29mg in placebo to 15 mg in the case group[1]. However, a single dose of 600 mg was given 1 hour preoperatively in another study, and it was found that the analgesic requirement was 48 % less than in the control group[2]. In a meta-analysis of 8 studies, lower doses of gabapentin resulted in more analgesic consumption but otherwise, there were no appreciable differences in results based upon dosing. [17] So It can be concluded that there is definitely a decrease in analgesic requirement but the correct dose and timings of these drugs are still not been standardized. It is worthwhile noting that gabapentin is currently not available parenterally, which may limit its utility among those for whom the oral route is not an option.

CONCLUSION

Gabapentin has shown to be effective in significant pain reduction and is a requirement of post-operative analgesia**.**
Limitation: It's a solitary center study with minor sample size. A multicenter authentication study is required to endorse our results and second our conclusion.

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