

Research Article

Evaluation of Gabapentin in Breast Surgery (Our Experience of 60 Cases)

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Abstract: Successful acute pain management after breast surgery remains challenging, and if not achieved, may increase the likelihood of subsequent chronic pain. Many options are available for the treatment of postoperative pain after breast surgery, including opioids(oral/parenteral), nonopioids (NSAIDS), local anesthetics' infiltration or instillation and regional (paravertebral blocks) analgesic techniques. In this study we evaluated the effect of gabapentin as a component of multimodal analgesia comprising local anesthetics instilled through surgical drain, for acute pain and analgesic requirement in patients undergoing modified radical mastectomy. Sixty ASA Class I and II adult patients between 18 to 60 years of age, undergoing elective surgery were included in the study. After randomization to Group C or G, patients were treated as follows: Group C received placebo capsules identical to capsules of gabapentin, every 6 hours, starting the evening before surgery and continued until fourth postoperative day. Patients of Group G received 300mg of gabapentin with the same time points and of the same duration as the control group. In our study we included the patients undergoing breast surgery for breast cancer and failure to adequately treat acute pain well into the postoperative period may lead to the persistence of nociceptive pathways and the development of chronic pain (Post mastectomy pain syndrome). Most of studies have shown that either single preoperative or repeated doses of gabapentin, continued for up to a few days after surgery, decrease acute postoperative pain and/or need for postoperative opioids. . Our results support the use of gabapentin in the acute postoperative period. But further trials are needed to delineate the optimal dose, timing and duration of gabapentin use following surgery.

Keywords: Breast surgery, post mastectomy pain, gabapentin

INTRODUCTION

Pain relief in an acute pain situation, besides having a human value, has an important bearing in the well-being of an individual. The tissue damage produced by surgery is similar to that of acute injury. It causes local and systemic noxious stimuli that initiate nociceptive impulses, relays, and reflexes throughout the nervous system. The nociceptor information is transmitted to the cord via the A-delta (myelinated) fibres and the C (unmyelinated) fibres. When peripheral sensitization occurs, painful information can also be carried by A-alpha and A-beta fibres. This is manifested by allodynia, a pain state where non-noxious stimuli are transformed and expressed as painful. Signals entering the central nervous system from the periphery will be increased in amplitude and duration ("wind up" or central sensitization.) [1]. Effective analgesic techniques need to counteract these activation of nociceptors at the periphery as well as centrally, thus the need for preemptive analgesia along with multimodal or "balanced" analgesia [2] to ensure

patient comfort, to improve early mobilization, and reduce acute postoperative pain/hyperalgesia and chronic pain after surgery[3]. Successful acute pain management after breast surgery remains challenging, and if not achieved, may increase the likelihood of subsequent chronic pain. Many options are available for the treatment of postoperative pain after breast surgery, including opioids(oral/parenteral), nonopioids (NSAIDS), local anesthetics' infiltration or instillation and regional (paravertebral blocks) analgesic techniques. In 2002, gabapentin was approved by US Food and Drug Administration for the treatment of post herpetic neuralgia. Gabapentin has antiallodynic and antihyperalgesic properties useful for treating neuropathic pain. [4] These properties may also be beneficial in acute post operative pain. In this study we evaluated the effect of gabapentin as a component of multimodal analgesia comprising local anesthetics instilled through surgical drain, for acute pain and analgesic requirement in patients undergoing modified radical mastectomy.

MATERIAL AND METHODS-

After ethics committee approval, this study was conducted in the department of anesthesiology Sixty ASA Class I and II adult patients between 18 to 60 years of age, undergoing elective surgery were included in the study. Written informed consent was obtained from all patients [Patients undergoing radical modified mastectomy (MRM) or lumpectomy with axillary lymph node dissection). Patients were randomly assigned to receive either of placebo capsules or gabapentin capsules. Randomization was done using sealed envelope technique into two groups.

Group C-Control group treated with placebo capsules (identical to gabapentin capsules) and bupivacaine instillation.

Group G-Study group treated with gabapentin and bupivacaine instillation.

Visual analogue scale (VAS) and patient controlled analgesia (PCA) was explained during pre anesthetic evaluation. The study was conducted in a double blind manner. Placebo capsules were identical in appearance with the gabapentin capsules. The same number of capsules were packaged in group specific bottles and coded as bottle C and bottle G for the control and study group, respectively.

An independent anesthesiologist, who did not participate in the study or data collection, read the number contained in the envelope and made group assignments. After randomization to Group C or G, patients were treated as follows:

Group C received placebo capsules identical to capsules of gabapentin, every 6 hours, starting the evening before surgery and continued until fourth postoperative day.

Patients of Group G received 300mg of gabapentin with the same time points and of the same duration as the control group.

An 18 or 20 gauge i.v. cannula was inserted and inj. Ringer lactate started. Each patient was pre-oxygenating for three minutes. Inj. Ondansetron 4.0mg was given intravenously.

Anesthesia was induced with i.v. fentanyl 2µg/Kg and propofol 2mg/kg. Intubation of trachea was facilitated with i.v. vecuronium 0.08mg/kg and anesthesia was maintained with 0.6-0.8% isoflurane and

70% nitrous oxide in oxygen. At the end of surgery neuromuscular block was antagonized with i.v. neostigmine (.05mg / kg) and i.v. glycopyrolate (.01mg/kg) and trachea was extubated. After extubation chest and axillary drains were instilled with 10-10ml of 0.4% bupivacaine under all aseptic precaution and drains were clamped for 20 minutes in both groups, and patients were transferred to the post anesthesia care unit (PACU).

All patients remained in the PACU for 24 hours. Those who complained of pain in PACU till 6 hours received i.v. paracetamol 300mg.

Acute post operative pain at rest and after movement (movement is described by sitting up in bed and moving arm of operative side) was assessed using the VAS by an Anesthesiologist blinded to group assignment. Pain was recorded and graded as:-

Visual analogue scale (VAS) 0-10 [5].

0 - Representing no pain.

10 - Representing worst possible pain.

Pulse, blood pressure, SPO₂, sedation, nausea/vomiting ,rescue analgesic and pain at rest and movement on VAS were recorded at time 0 (arrival to PACU), 30 minutes, 3, 6, 9, 12, 18, 24 hours after surgery and each morning from first to fourth post operative day.

Statistical analysis was performed using Primer software. Demographic data were compared with Chi-square test. Hemodynamic parameters and pain scores were analyzed by t-test. Analgesic consumption and nausea/ vomiting and sedation were analyzed by Chi-square test.

OBSERVATION AND RESULTS

The two groups were comparable with respect to age and did not differ statistically. The study groups were statistically similar with respect to ASA grade. Heart rate, systolic and diastolic blood pressure were comparable in both group (Table1 and 2). Mean VAS at rest and movement was significantly lower in group G at all point of evaluation.(Table 3,4,5 and 6). In early postoperative period i.e. up to six hours analgesic consumption was low in group G but that was not statistically significant (Table 7). Total analgesics consumption was significantly low in group G.(Table 8).

Table No. 1 Mean Heart Rate ± Sd

	0 MIN.	30 MIN	3 HR	6 HR	9 HR	12 HR	18 HR	24 HR
CONTROL	74.2± 9.618	71.17± 9.12	72.67± 9.546	73.33± 9.342	74.77± 8.468	75± 9.233	75.63± 9.053	76.53± 8.153
GABAPENTIN	71.33± 8.872	71.07± 8.562	75.63± 9	77.1± 10.64	78.47± 10.26	79± 9.695	80.53± 9.741	80.5± 7.615
'P'VALUE	0.235	0.965	0.221	0.150	0.133	0.107	0.048	0.056
	NS	NS	NS	NS	NS	NS	S	NS

Table No. 2 Mean Sbp ± Sd

	0 MIN	30 MIN	3 HR	6 HR	9 HR	12 HR	18 HR	24 HR
CONTROL	126.1± 12.3	124± 11.46	123.1± 13.45	119.9± 12.69	117.8± 9.669	120.3± 8.15	119.7± 9.169	120.7± 9.827
GABAPENTIN	124.1± 11.91	122.3± 11.4	120.4± 11	121.5± 9.328	119.6± 11.24	121.3± 10.07	120.4± 10.56	119.8± 8.998
'P'VALUE	0.525	0.575	0.392	0.572	0.493	0.684	0.795	0.733
	NS	NS	NS	NS	NS	NS	NS	NS

Table No. 3 Pain Score (Vas) At Rest

	0 MIN	30 MIN	3 HR	6 HR	9 HR	12 HR	18 HR	24 HR
CONTROL	1.533± 1.408	1.833± 1.367	2.067± 1.172	2.133± 0.8996	2.033± 0.8899	2.467± 1.042	2.633± 1.098	2.7± 1.055
GABAPENTIN	0.5± 0.9377	1.033± 0.9643	1.567± 0.9714	1.467± 0.9732	1.3± 0.6513	1.4± 0.8137	1.533± 1.008	1.433± 1.04
'P'VALUE	<0.001	<0.05	>0.05	<0.01	<0.001	<0.001	<0.001	<0.001
	HS	HS	NS	HS	HS	HS	HS	HS

Table No. 4 Pain Score (Vas) At Movement

	0 MIN	30 MIN	3 HR	6 HR	9 HR	12 HR	18 HR	24 HR
CONTROL	3.033± 2.042	3.8± 1.54	3.7± 1.442	4.1± 1.062	3.967± 1.098	4.433± 1.305	4.433± 1.305	4.533± 1.074
GABAPENTIN	1.533± 1.332	2.333± 1.241	2.9± 1.296	2.967± 1.129	2.633± 0.8087	2.667± 1.028	2.867± 1.252	2.8± 1.27
'P'VALUE	<0.001	<0.001	<0.05	<0.01	<0.001	<0.001	<0.001	<0.001
	HS	HS	S	HS	HS	HS	HS	HS

Table 5: Vas at Rest

	48 HR	72 HR	96 HR
CONTROL	2.667±0.8442	2.467±0.7761	2.233±0.6261
GABAPENTIN	1.333±0.8023	1.267±0.7397	1.033±0.7184
'P'VALUE	<0.001	<0.001	<0.001
	HS	HS	HS

Table No 6: Vas at Movement

	48 HR	72 HR	96 HR
CONTROL	4.367±0.8087	4.233±1.006	3.933±0.7849
GABAPENTIN	2.833±0.9499	2.533±1.008	2.3±1.022
'P'VALUE	<0.001	<0.001	<0.001
	HS	HS	HS

Table No.7 Analgesics Consumption

TIME ELAPSED	GROUP		'P' VALUE
	CONTROL	GABAPENTIN	
0 MIN. (I.FIBRINIL)	9	2	P <0.05
30 MIN. (I.FIBRINIL)	5	2	P >0.05
3 HRS. (I.FIBRINIL)	3	2	P >0.05
6 HRS. (I.FIBRINIL)	1	1	P >0.05
6 HRS. (T.ULTRACET)	8	2	P >0.05

Table No. 8 Total Analgesics Consumed

TIME ELAPSED	GROUP		'P' VALUE
	CONTROL	GABAPENTIN	
I.FIBRINIL	18	7	P >0.05
T.ULTRACET	103	28	P <0.001
TOTAL	121	35	P <0.001

DISSCUTION

Pain is a multifaceted and highly personal experience, as McCaffery described "pain is whatever the experiencing person says it is and exists whenever he/she says it does" [6]. It causes significant distress to patients and has adverse effects on the endocrine and immune function,[7] which can affect wound healing [8] and cardiopulmonary and thromboembolic complication [9,10,11]. Postoperative pain is one of the most frequently reported postoperative symptoms [12]. Despite recent advances in our understanding of the physiology of acute pain, the development of new opioids and nonopioids analgesics and novel methods of drug delivery, and more widespread use of pain-reducing minimally invasive surgical techniques, pain after surgical procedures remains a challenge for many practitioners [13]. The concept of multimodal "opioids-sparing" analgesic techniques (so-called balanced analgesia) was introduced more than 15 yr ago,[14] with the aim of improving analgesia by combining analgesics with additive or synergistic effects. Theoretically, the use of a combination of analgesics from different pharmacologic drug classes for managing perioperative pain should improve the safety and efficacy of pain therapy due to the differing mechanisms of action and the side-effect profiles of the individual drugs. Despite available evidence showing the benefits of multimodal analgesic techniques, [14, 15, 16] major surveys have reported that these techniques are underused in clinical practice. We need to improve the perioperative pain management and to implement the existing evidence-based recommendations regarding the use of individual nonopioids analgesics (namely, NSAIDs, cyclooxygenase-2 inhibitors, acetaminophen, gabapentanoids, ketamine, and local and regional anesthetic techniques) supplemented by opioids analgesics on an as needed basis.[17].

Gabapentin and pre-emptive & multimodal analgesia

Dirks J *et al.*; & Pandey CK *et al.*; demonstrated that gabapentin alleviates and/or prevents acute nociceptive and inflammatory pain both in animals and in volunteers, especially when given before surgical stimulus [18-21] and an advantage of preincision (pre-emptive) administration of gabapentin could be demonstrated in their study.

Woolf and Chong [1] suggested the use of antihyperalgesic drugs to improve postoperative pain treatment. Antihyperalgesic drugs prevent the development of central excitability and therefore elicit analgesic effects that extend beyond their pharmacological actions

Hussain Al - Mujadi *et al.*; [22] in a prospective randomized double blind clinical trial, gave gabapentin 1200mg or placebo two hours prior to induction of anesthesia to patients undergoing elective thyroidectomy. Pain scores at rest and during swallowing in the gabapentin group were significantly lower when compared with the placebo group

In our study patients were evaluated for up to 96 hrs postoperatively. VAS pain score at rest in gabapentin group at 0, 30 min, 6,9,12,18,24,48,72,96 hrs was significantly lower than control group. At 3hr postoperative period VAS pain score was lower but it was not statistically significant. VAS pain score after movement was significantly lower at all point of evaluation

Peng PW *et al.*; [23] reviewed in a meta analysis that gabapentin caused a 35% reduction in total opioids consumption over the first 24 hours of surgery and a significant reduction in postoperative pain at rest and with movement, reduction of vomiting and pruritis. It was associated with a significant increase in dizziness and sedation.

Ho KY, Gan TJ *et al.*; [24] included randomized controlled trials (RCTs) comparing gabapentin with inactive controls in surgical patients. Sixteen valid RCTs were included. Weighted mean difference (WMD) for postoperative pain intensity (0-100 mm visual analogue scale) was -16.55 mm at 6 h and -10.87 mm at 24 h for treatment with a single preoperative dose of gabapentin 1200 mg. Cumulative opioids consumption at 24 h was also significantly decreased with gabapentin (WMD, -27.90 mg). When gabapentin was administered at doses less than 1200 mg, pain intensity was also lower at 6 h (WMD, -22.43 mm) and 24 h (WMD, -13.18 mm). Cumulative 24 h opioids consumption was also lower (WMD, -7.25 mg). Gabapentin was associated with an increased risk of sedation (OR 3.86; 95% CI 2.50-5.94) but less opioids-related side effects such as vomiting (OR 0.58; 95% CI 0.39-0.86) and pruritus (OR 0.27; 95% CI 0.10-0.74). They concluded that gabapentin has an analgesic and opioids-sparing effect in acute postoperative pain management when used in conjunction with opioids

In our study in the first 6 hrs, analgesic consumption was lower in G group compared with group C but this difference was not statistically significant. This lowered consumption reached level of statistical significance at 9, 18, and 24 hrs ($p < 0.05$, $p < 0.01$, $p < 0.001$ respectively). Total analgesic consumption was significantly lower in G group.

Gabapentin and breast surgery-

In our study we included the patients undergoing breast surgery for breast cancer and failure to adequately treat acute pain well into the postoperative period may lead to the persistence of nociceptive pathways and the development of chronic pain (Post mastectomy pain syndrome). This syndrome consists of persistent pain in the anterior chest, axilla, medial and posterior parts of the arm following breast surgery. The exact mechanism producing PMPS is unclear, but is believed to be due to surgical injury to the intercostobrachial nerve [25]. A variety of perioperative analgesics have been administered for mastectomy surgery in an attempt to "preempt" the process of central sensitization and thus the incidence of pain.

Most of studies have shown that either single preoperative or repeated doses of gabapentin, continued for up to a few days after surgery, decrease acute postoperative pain and/or need for postoperative opioids. Reduced opioids consumption may translate into fewer opioids related unwanted effects with an impact on postoperative recovery.

Fassoulaki *et al.*; [26] investigated the effect of regional brachial plexus block, oral mexiletine, and the

combination of both on acute and chronic pain following breast cancer surgery. They found regional block reduced the analgesic requirements in the early postoperative period, while mexiletine combined with regional block reduced the total analgesic requirements during the next 5 postoperative days. Although chronic pain was not affected by these treatments late-abnormal sensation may be diminished by combination of these treatments.

Fassoulaki *et al.*; [27] were unable to demonstrate a reduction in the incidence of chronic pain following mastectomy surgery with the perioperative administration of gabapentin 1,200 mg/day for 10 postoperative days.

Fassoulaki *et al.*; [27] evaluated the effect of utilizing multiple analgesics including gabapentin, local anesthetic infiltration, and EMLA cream on acute and chronic pain following breast cancer surgery. Their study demonstrated a significant reduction in acute and chronic pain following surgery with this multimodal regimen.

Eckhardt K *et al.*; [28] found that gabapentin enhanced the analgesic effects of morphine in healthy volunteers.

In conclusion, perioperative use of oral gabapentin (300mg), has been found to be safe in providing analgesia in early postoperative period (up to 96 hrs) in breast surgery. Analgesic consumption was significantly low up to 24 hrs in patients taking gabapentin, however there was no significant difference in analgesic consumption after 24 hrs.

More studies are needed to determine the optimal dose and duration of administration for different types of surgery, especially considering the capacity of prolonged administration of gabapentin postoperatively, to prevent the development of chronic pain.

In our study, the perioperative use of 300 mg gabapentin in patients undergoing radical breast surgery, as a component of a multimodal regime with local anesthetics and oral PCA resulted in effective and safe postoperative analgesia.

Gabapentin and side effect (nausea, vomiting & sedation)- In our randomized study nausea and vomiting was less in G group compared with C group and sedation was less in C group, although that was not statistically significant

CONCLUSION

Gabapentin is a safe and effective component of multimodal therapy comprising local anesthetics, paracetamol and tramadol for acute post-mastectomy pain. Our results support the use of gabapentin in the acute postoperative period. But further trials are needed to delineate the optimal dose, timing and duration of gabapentin use following surgery.

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