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To evaluate role of gabapentin as a preemptive analgesic in patients undergoing modified radical mastectomy

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Abstract

Introduction: Pre-emptive analgesia involves the introduction of an analgesic regimen before the onset of noxious stimuli, with the goal of preventing sensitization of the nervous system to subsequent stimuli that could amplify pain. We use Gabapentin as a preemptive analgesic and is more effective than conventional regimens in patients undergoing modified radical mastectomy.

Materials & Method: 50 adult female patients of ASA grade I and II were divided randomly in to 2 groups(n=25).Study Group: Group G received Tab. Gabapentin 600mg orally with sips of water 1 hour before surgery. Control Group: Group C Placebo group.

Observation result: Mean Duration of analgesia is statistically highly significant in Group G.($p < 0.0001$).Mean VAS was higher in Group C compared to Group G($p<0.0001$) statistically highly significant at 1, 2, 4hr post-operatively. Incidence of Sedation, Nausea and vomiting-Higher in Group G. In our study, further need of mean rescue analgesic doses during 24 hrs. In Group G is 1.44 doses and in Group C is 2.52 doses which statistically highly significant in Group C.($p < 0.0001$)

Conclusion: Preemptive Tab.Gabapentin 600mg. prolonges postoperative analgesia and reduces rescue analgesic requirement than control group but has more side effect like nausea and vomiting.

Keywords: Gabapentin, Modified Radical Mastectomy, Preemptive Analgesic

Introduction

Few sensations are as disturbing to the individual as that of pain. Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue* damage or described in terms of such damage" by the International Association for the study of pain (IASP).

The last 20 years have seen significant scientific advancement in our understanding of the psychology, pathophysiology and pharmacology of pain. In conjunction of this knowledge, there has been a resurgence of concept of pre-emptive analgesia and numerous studies have addressed the proposed benefits of this technique in surgical patient.

Pre-emptive analgesia, an evolving clinical concept, involves the introduction of an analgesic regimen before the onset of noxious stimuli, with the goal of preventing sensitization of the nervous system to subsequent stimuli that could amplify pain. Surgery offers the most promising setting for pre-emptive analgesia because the timing of noxious stimuli is known. Surgical trauma induces nociceptive sensitization leading to amplification and prolongation of post-operative pain.

When adequate drug doses are administered to appropriately selected patients before surgery, intravenous opiates, local anaesthetic infiltration, nerve block, subarachnoid block and epidural block offer benefits that can be observed as long as one year after surgery. The most effective pre-emptive analgesic regimens are those, which are capable of limiting sensitization of the nervous system throughout the entire peri-operative period. The only way to prevent sensitization of the nociceptive system might be to block completely any pain signal, originating from the surgical wound from the time of incision until final wound healing. Pharmacological interventions, including 'anti-hyperalgesic' drugs such as NMDA-receptor antagonists and gabapentin, may interfere with the induction and maintenance of sensitization.

Owing to this protective effect on nociceptive system, pre-emptive analgesia has the potential to be more effective than any analgesic treatment initiated after surgery. Theoretically immediate post-operative pain may be reduced, and development of chronic pain may be prevented. The concept is that, effect of pre-emptive analgesia is to reduce the development of any memory of pain stimulus in nervous system and that of lesser subsequent analgesic requirement. There are both, scientific and clinical interests in this effect.

Aims & Objectives

Our present study is undertaken to evaluate the role of **GABAPENTIN** as a pre-emptive analgesic in **Modified Radical Mastectomy** with following strategies:

1. Whether Gabapentin, a pre-emptive analgesic, is more effective than conventional regimens in managing acute post-operative pain following modified radical mastectomy.
2. Whether need of supplemental analgesic requirement following surgery is prolonged or not, when GABAPENTIN as a pre-emptive analgesic is given.
3. To study drug profile and adverse effect of GABAPENTIN.

Gabapentin

Gabapentin is described as 1-(aminomethyl) cyclohexane acetic acid with a molecular formula of C9H17NO2 and a molecular weight of 171.24.

Mechanism of action: Possible pharmacologic targets of Gabapentin are selective activation of the GABAB receptors, enhancement of N-methyl –D-aspartate(NMDA) currents, blocking AMPA receptor mediated transmission in the spinal cord. At clinically relevant concentration it reduces the membrane voltage gated Ca currents (VGCC channels) in dorsal horn ganglion neurons. ***I*** subunit of the pre-synaptic VGCC channels which inhibit calcium influx & subsequent release of excitatory neurotransmitters by sensory neurons. It increases serotonin concentration in brain.

Contraindication: Gabapentin is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

Dosage and Administration: Gabapentin is given orally with or without food.

Dosage: Initially, 300 mg on the 1st day, 300 mg bid on the 2nd day and 300 mg tid on the 3rd day. Maintenance range: 0.9-3.6 g daily; daily dose to be taken in 3 equally divided doses and max dosing interval: 12 hr. Max: 4.8 g daily.

Adverse Reactions / Side Effects

- Somnolence, dizziness, ataxia, weakness, paraesthesia, fatigue, headache; nystagmus, diplopia; nausea, vomiting, wt gain, dyspepsia; rhinitis; tremor; leucopenia; altered LFTs; Stevens-Johnson syndrome.
- Severe allergic reactions; behaviour changes; confusion; difficult or painful urination; fever; memory problems; new or worsening mental or mood changes etc.

Material & Method

This study was conducted at our institute during the year 2010-2013 with the permission of **Institute Research Committee (IRC)** for guided research of hospital and after written informed consent of 50 adult female patients of ASA grade I and II have been diagnosed of Carcinoma Breast and posted for Modified Radical Mastectomy under general anesthesia.

Exclusion Criteria: Diabetes, Uncontrolled Hypertension, surgical duration more than 3 hours, Hypersensitivity reaction to any drug, patients with acute or chronic renal disease, patients taking antidepressant, sedative, hypnotics, drugs with effects on Central Nervous System.

Pre anaesthetic assessment: All patients were examined pre operatively and proper history including detailed personal history regarding drug allergy, surgical, medical as well as detailed history related to anaesthesia was obtained and noted. All routine investigations were done.

Group allocation: 50 patients were randomly allocated in 2 Groups (n=25).

- Study Group: Group G **received Tab. Gabapentin 600mg orally with sips of water 1 hour before surgery.**
- Control Group: Group C **did not receive any drug before surgery.**

Premedication: Tab Lorazepam 1 mg. at 10:00 pm previous night of surgery, Tab Diazepam 6 mg at 6:00 am on day of surgery.

Procedure: All the surgeries were done routine general anaesthesia with endotracheal intubation. All patients were given analgesia in form of Inj. Fentanyl 100mcg & Inj. Diclofenac Sodium 75mg IV intra-operatively.

Post-operative data: After completion of surgery and shifting the patient to post anaesthesia care unit, any other form of analgesia was also omitted. Patients were half hourly assessed for,

1. Pain scores on VAS and as they complain of pain 1sttime [VAS reaches 5 or more]
2. Duration for VAS to reach 5 or more
3. No. of doses Rescue analgeic (Inj.Tramadol 100 mg i.v.) when VAS 5 or more
4. Hemodynamics: pulse rate, BP (Systolic, Diastolic and Mean), Spo2
5. Side effects of drugs
6. Sedation score were observed thereafter and noted.

Sedation Score:

0: Alert
1: Sometimes Drowsy/ Easily Arouse
2: Often drowsy but easily aroused
3: Drowsy/ difficult to arouse
4: Asleep

Visual Analogue Scale:

0: No Pain 10: Severe Pain

Ondansetron 4 mg i.v was administered if patient experienced severe nausea or an episode of vomiting. After completion of study in 24 hrs, patients were shifted to their respective wards.

- Data calculation and p value calculation is done by ***unpaired t-test*** using online software graphpad.(**http://www.graphpad.com/quickcalcs/ttest1/?Format=SD).** p value <0.05 was considered statistically significant in all the comparisons.

Observation & Result

Table 1: Demographic Data: Age, Weight Distribution

	Group G	Group C	p Value	Significance
Age (yrs) M±SD	46.00±7.889	47.12±7.633	0.6116	NS
Wt (kgs) M±SD	52.48±8.317	52.80±7.052	0.3846	NS

(NS: not significant)

Mean Age (yr) and wt (kg) in both the groups are comparable and statistically not significant**(p value> 0.05)**

Table 2: Duration of surgery and Duration of post-operative analgesia

	Group G M ± SD	Group C M ± SD	p value	Significance
Duration of surgery (hrs.)	1.958±0.373	2.088±0.306	0.6067	NS
Duration of post op analgesia (hrs.)	5.36±0.52 *	1.54±0.5	<0.0001	HSS

(NS: not significant)(HSS: highly significant statistically)

- **mean surgical duration** in both groups is statistically not significant**(p>0.005)**
- ***mean Duration of analgesia** is statistically highly significant in Group G. **(p value is <0.0001).** Patients in Group G had prolonged analgesia in post-operative analgesia.

Table 3: VAS (Visual Analogue score)

Time	Group G (M±SD)	Group C (M±SD)	p value	Significance
5 min	0.40±0.80	1.08±0.99	0.0103	NS
1/2 hr.	0.48±0.91*	2.68±0.94	<0.0001	HSS
1 hr.	0.68±1.14*	5.08±1.46**	<0.0001	HSS
2 hr.	1.56±1.52*	4.50±0.67	<0.0001	HSS
4 hr.	2.52±1.53*	4.10±0.80	<0.0001	HSS
6 hr.	4.41±1.70	4.62±0.92	0.9836	NS
8 hr.	5.94±0.74	6.20±1.04	0.8761	NS

- ***mean VAS** was higher in Group C compared to Group G (**p<0.0001**) statistically highly significant, at 1, 2,4hr post-operatively.*** We give rescue analgesic Inj. TRAMADOL 100MG IV in Group C.

Table 4: Sedation Score

Time	Group G (M±SD)	Group C (M±SD)	p value	Significance
5 min	2±0*	0.44±0.50	<0.0001	HSS
1/2 hr.	2±0*	0.40±0.50	<0.0001	HSS
1 hr.	2±0*	0.08±0.27	<0.0001	HSS
2 hr.	1.68±0.47*	0.06±0.19	<0.0001	HSS
4 hr.	1±0.40*	0.02±0.05	<0.0001	HSS
6 hr.	0.52±0.50	0±0	----	
8 hr.	0.20±0.35	0±0	----	

- ***mean sedation score** is statistically highly significant in Group G. **(p value is <0.0001).**

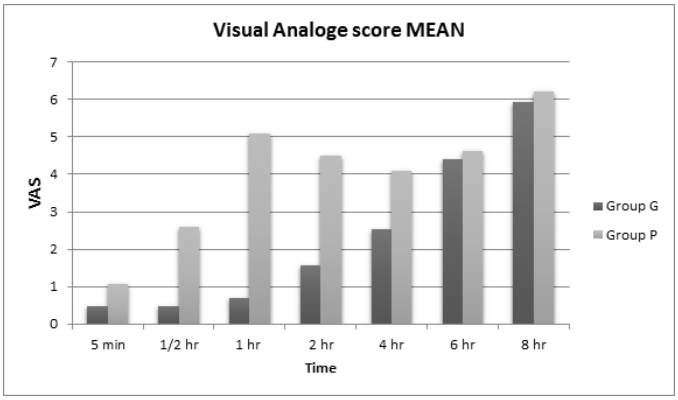

Fig. 1: Visual Analogue score (VAS)

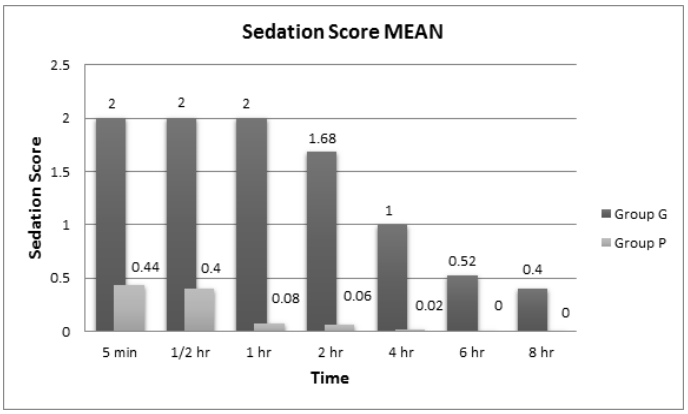

Fig. 2: Sedation Score

Table 5: Number of Rescue analgesic dose

No. of Rescue analgesic dose in 24 hors	Group G	Group C	p value	Significance
1	15	00	---	---
2	10	12	---	---
3	00	13	---	---
(M±SD)	1.44±0.50	2.52±0.63	<0.0001	HSS

- Further need of rescue analgesic doses during 24 hrs in Group G is 1.44 doses and in Group C is 2.52 doses which is statistically highly significant in Group C.**(p value is <0.0001)**

Table 6: Side Effect

Complication	Group G (no.pt)	Group C (no.pt)
Nausea/ Vomiting	36% (9/25)	16% (4/25)
Diarrhoea	nil	nil
Pruritus	nil	nil
Urinary Retention	nil	nil
Constipation	nil	nil
Headache	nil	nil

- Nausea/ Vomiting is 2.25% higher in Group G **[36%pt]** than Group C**[16%pt]**

Discussion

Pre-emptive analgesia, an evolving clinical concept, involves the introduction of an analgesic regimen before the onset of noxious stimuli, with the goal of preventing sensitization of the nervous system to subsequent stimuli that could amplify pain. Surgery offers the most promising setting for pre-emptive analgesia because the timing of noxious stimuli is known. Surgical trauma induces nociceptive sensitization leading to amplification and prolongation of post-operative pain. Pharmacological interventions, including 'anti-hyperalgesic drugs such as NMDA-receptor antagonists and Gabapentin, may interfere with the induction and maintenance of sensitization.

Elina M. Tiippana, MD, Katri Hamunen, MD, PhD, Vesa K. Kontinen, MD, PhD et al(2007)in their study, Do Surgical Patients Benefit from Perioperative Gabapentin/Pregabalin? A Systematic Review of Efficacy and Safety concluded Gabapentinoids

effectively reduce postoperative pain, opioid consumption, and opioid-related adverse effects after surgery.

VK Grover, PJ Mathew, S Yaddanapudi, S Sehgal et al (2009) in their study A single dose of preoperative gabapentin for pain reduction and requirement of morphine after total mastectomy and axillary dissection: Randomized placebo-controlled double-blind trial study concluded, single low dose of 600 mg gabapentin administered 1 h prior to surgery produced effective and significant postoperative analgesia after total mastectomy and axillary dissection without significant side effects.

Dirks, Jesper M.D.; Fredensborg, Birgitte B. M.D.; Christensen, Dennis M.D., Ph.D et al (2002) in their study A Randomized Study of the Effects of Single-dose Gabapentin versus Placebo on Postoperative Pain and Morphine Consumption after Mastectomy concluded single dose of 1,200 mg oral gabapentin resulted in a substantial reduction in postoperative morphine consumption and movement-related pain after radical mastectomy, without significant side effects.

Current study "To evaluate role of Gabapentin as a preemptive analgesic in patients undergoing modified radical mastectomy" is such an attempt to evaluate effect of GABAPENTIN in terms of prolongation of analgesic duration post-operatively and to study its side effects.

Dosage: In our study we decided to give Tab. Gabapentin 600mg orally 1 hr. pre-operatively.

VK Grover, PJ Mathew, S Yaddanapudi, S Sehgal et al (2009) in their study A single dose of preoperative gabapentin for pain reduction and requirement of morphine after total mastectomy and axillary dissection: Randomized placebo-controlled double-blind trial study concluded single low dose of 600 mg gabapentin administered 1 h prior to surgery produced effective and significant postoperative analgesia after total mastectomy and axillary dissection without significant side effects.

Pandey, Chandra Kant MD; Navkar, Deepa Vishwas MD; Giri, Pramod Janardan MS et al (2005) in their study Evaluation of the Optimal Preemptive Dose of Gabapentin for Postoperative Pain Relief After Lumbar Diskectomy: A Randomized, Double-Blind, Placebo-Controlled Study concluded, gabapentin 600 mg is the optimal dose for postoperative pain relief following lumbar diskectomy.

- ❖ Thus as per our study pre-emptive Tab.Gabapentin 600mg. prolongs postoperative analgesia up to 4 hours, reduces rescue analgesic requirement than control group but has more side effect like nausea and vomiting.

Then after further comparisons with previous works of different authors in the similar or nearly similar direction, we are able to conclude that:

- Duration of post-operative analgesia (VAS reduction up to 4 hours) and need of first rescue analgesic is prolonged in Gabapentin group than control group.
- No. of rescue analgesic requirements is significantly reduced in Gabapentin group than control group.
- Gabapentin provided better hemodynamic stability post operatively than control group.
- Gabapentin was associated with higher incidences of PONV and sedation was the main side effect noted in Gabapentin Group; however none of the patients showed significant respiratory depression.

Thus, we can use Gabapentin as a preemptive analgesia.

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