"EFFECT OF PRE-OPERATIVE GABAPENTIN ON EARLY POST OPERATIVE PAIN, NAUSEA, VOMITING AND ANALGESIC CONSUMPTION FOLLOWING HYSTERECTOMY IN A TERTIARY CARE TEACHING HOSPITAL: A RANDOMIZED CONTROLLED TRIAL"

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ABSTRACT

Introduction: *Gabapentin is not normally used for post-operative pain relief. Presently available data suggest that pre-operative Gabapentin may play role in the management of post operative pain but more work is necessary before recommending it for routine clinical use. So present study was taken up with the objective to evaluate the effects of pre operative Gabapentin on postoperative pain, nausea, vomiting and analgesic consumption.*

Methods: *A double blind, parallel group, placebo controlled randomized control trial was conducted among 60 patients (30 each in each group) undergoing abdominal hysterectomy to see the effect of 2 hour pre operative administration of single dose of Gabapentin (300 mg) on post operative pain and analgesic consumption. Severity of pain, nausea, vomiting and total analgesic consumption was compared between the two study groups at 4, 24 and 48 after operation.*

Results: *Statistically significant less median pain score in VAS were seen in Gabapentin group than in placebo group subjects at all time points. Post operatively at 4 hrs and 24 hrs the total dose of analgesic consumption were statistically lower in Gabapentin group ($p<0.5$) than placebo group. There was no statistically significant difference of nausea and vomiting at 4, 24 and 48 hours post operatively between Gabapentin and placebo group subjects. No patient in any group reported any adverse effects.*

Conclusions: *This study suggests that pre-operative gabapentin has clinical potential in management of early post operative pain. Low dose Gabapentin (300 mg) can be used as a preemptive analgesic before abdominal Hysterectomy.*

Keywords: *Gabapentin, Post-operative pain, VAS, Hysterectomy.*

INTRODUCTION

Post operative pain is the greatest fear of patients who undergo any surgical procedure. Prevention and treatment of post operative pain and complications such as post operative nausea and vomiting (PONV) continues to be a major challenge in post operative care and plays an important role in the early mobilization and well being of the surgical patients.[1]

The degree of postoperative pain, perceived by the patient, is multi factorial and depends on variables such as type and duration of the operation, type of anaesthesia and analgesia used, and the patient's mental and emotional state. If sufficient analgesia is provided, not only will the patient's comfort be increased but the duration of hospital stay will be shortened, reducing both treatment costs and the risk of hospital-acquired infections. Of the many methods of postoperative pain relief, the oldest and most widely used is parenteral opioids.[2]

Opioid analgesics are frequently used for postoperative analgesia, but their use is limited by their side effects. The mechanisms involved in pain suggest that a combination of non-opioid analgesics and opioids might enhance the quality of analgesia and reduce opioid requirements and side-effects. However, non-steroidal anti-inflammatory drugs, which would otherwise be ideal for administration in combination with opioids, have adverse effects on the gastro-intestinal and haematological systems as well as on renal function.[2]

Hysterectomy is one of the most common types of surgery. Hysterectomy is still the only definitive treatment of dysfunctional uterine bleeding (DUB) and, compared with most other alternative therapies, has acceptable satisfaction. In the majority of cases, hysterectomy is performed through the abdomen, although in many cases, vaginal surgery is considered less complicated than abdominal hysterectomy.[3]

Gabapentin, a structural analogue of gama-amino butyric acid, is used as an anticonvulsant drug. In addition, it has been effective in neuropathic pain, diabetic neuropathy, post herpetic neuralgia, and reflex sympathetic dystrophy. Pre-treatment with Gabapentin can block the development of hyperalgesia.[4]

Gabapentin does not interact with other commonly prescribed drugs. Its most frequent side-effects are somnolence, dizziness and fatigue, which are also common side-effects of widely used pre medications. In addition, the side-effects of Gabapentin are usually not severe.[2]

Several studies have been done about the possible effect of Gabapentin on postoperative pain.[3] Available data suggest that Gabapentin may indeed have a place in the management of post operative pain. However, considerably more work is required before recommending it for routine clinical use preoperatively for post operative pain relief. Considering the above facts present study was taken up with the Primary Objective to measure and compare the pain score by Visual analogue scale (VAS) at rest at 4, 24 & 48 hour postoperatively after hysterectomy under Spinal Anesthesia following single 2 hour pre-operative dose of 300 mg Gabapentin orally and Secondary Objectives were: i. To assess the total analgesic consumption in 4, 24 & 48 hours after hysterectomy following preoperative administration of Gabapentin, ii. To identify the time of patient's first request for supplemental analgesia after hysterectomy following preoperative administration of Gabapentin and iii. To evaluate the effects of preoperative administration of Gabapentin on postoperative nausea, vomiting, after hysterectomy on a 4 point verbal scale (Absent, mild, moderate and severe).

MATERIALS AND METHODS

1. **Trial Design:** This was a single centred, double blind, placebo controlled, parallel group, in 1:1 ratio, hospital based Randomized control trial (RCT) of pre-operative 300mg gabapentin orally compared with placebo in subjects undergoing elective abdominal hysterectomy operation for prevention of post operative pain, nausea and vomiting and analgesic consumption.
2. **Ethical Committee Approval:** Institutional ethical committee approval was taken.
3. **Trial Registration:** Trial was registered in Clinical Trial Registry of India (CTRI) vide **No. CTRI/2012/05/002700.**
4. Participants- **Inclusion Criteria:**

a. 18 yrs or older.
b. Patient with American Society of Anesthesiologists (ASA) classification grade I & Grade II will be included.
c. Undergoing elective abdominal hysterectomy under spinal anesthesia at tertiary care teaching hospital.

Exclusion Criteria:

a. Patients with present history of pregnancy.
b. Patients with history of epilepsy or chronic pain, or use of anti epileptic drugs or neuropathic analgesics.
c. Patient with American Society of Anesthesiologists (ASA) classification of 3 or greater.
d. Patients with a history of opioid or intravenous drug abuse.
e. Patients with known allergy to gabapenin.
f. Patients who have taken antacid medication in the previous 24 hrs.
g. Patients who refused spinal anaesthesia.

5. **Study Area:** Gynaecology ward and including preoperative and post operative care room of the Tertiary care Hospital.
6. **Interventions:** Patients were screened and satisfying inclusion criteria were recruited in the present study after written informed consent. A total of 60 patients of either sex were selected randomly by permuted variable block randomization, and assigned to receive either 300 mg of Gabapentin[5] or a matched placebo[6] (collected from KC Laboratories, Mumbai) in 1:1 ratio, orally 2 hr before spinal anaesthesia in a double blind manner. All the patients, both control and Gabapentin group were anesthetized under Spinal anaesthesia according to the standard institutional protocol after similar pre-medication. Single dose of 50 mg i.m injection Diclofanac sodium was provided in all subjects immediately after operation. All the subjects were assessed for pain at rest at 4, 24 & 48 hrs[7,8,9] post operatively by visual analogue scale score(VAS) (0 mm: no pain,100 mm: Worst pain imaginable).[2] They also were evaluated for nausea, vomiting, drowsiness, and pruritus and rated on a four point verbal scale (none, mild, moderate, severe) at 4, 24, 48 hrs.[2] Total rescue analgesic consumption also was assessed at 4, 24, 48 hrs post operatively. [2] The time of patient's first request for supplemental analgesia also was recorded. Injection Diclofanac sodium 50mg per dose i.m. was given as supplemental analgesic.

7. Outcome Variables:

a. **Primary Outcome Variable:** Pain score by 100 point visual analogue scale at 4, 24 and 48 hours post operatively.

b. Secondary Outcome Variable:

a) Total dose of analgesic consumption was measured at 4, 24 & 48 hours post operatively.
b) Request of 1st supplementary analgesia post operatively by the patient was recorded in terms of minutes.
c) Grading of nausea and vomiting post operatively at 4, 24 & 48 hours were measured using 4 point verbal scale. (None, mild, moderate, severe).
d) No changes in trial outcome were made after commencement of the trial.

8. **Sample Size & Sampling Unit:** A sample size of 30 in each group assumed to be sufficient to detect a clinically important difference of ($\mu_1 - \mu_2$) 20 points on the VAS scale of pain, assumed a standard deviation(σ) 20 with a power of 90% and a significance level of 1%. A total of 60 patients (30 placebo group and 30 Gabapentin group) who have undergone elective abdominal

hysterectomy operation under spinal anaesthesia (SA) were selected randomly from the gynaecology ward of the tertiary care Hospital. Sample size calculation done by the following formula.

$$n = \frac{2[(a+b)^2 \sigma^2}{(\mu_1-\mu_2)^2}$$

$$n = \frac{2[(2.58+1.28)^2 20^2}{(20)^2}$$ n = 30 (in each group) (Values are of VAS of pain)

9. **Randomization:**

a. **Sequence Generation:** Permuted variable block randomization.

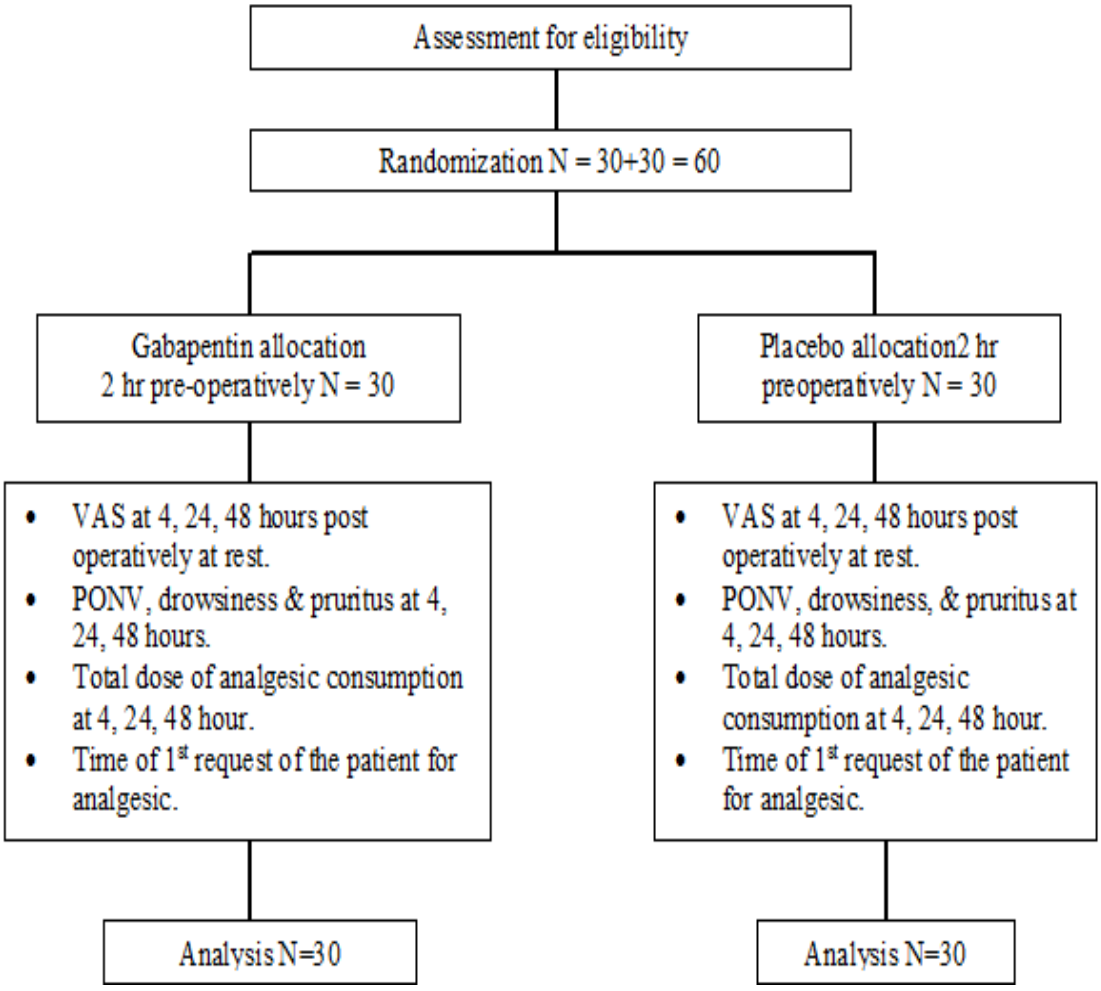
b. **Allocation Concealment Mechanism:** Sequentially numbered sealed opaque envelope.

c. **Implementation:** Random allocation sequence was generated by a faculty member of the Dept. of Community Medicine independent to investigator. Participants were enrolled and assigned intervention by a particular investigator.

d. **Blinding:** Double blind (both patient and investigator) by matched placebo

10. **Statistical Methods:** Statistical analysis was done for significant difference for reduction of pain in VAS, nausea, vomiting and analgesic consumption post operatively between the control group and Gabapentin group population. Pain score (observed in VAS) was analyzed using Man-Whitney test. Total analgesic consumption and time of request of 1st supplementary analgesia were calculated of significance by Independent "t test". Nausea and Vomiting, being categorical variables were analyzed by Pearson Chi-square test.

11. Study overview & treatment arms:



No subjects were lost after randomization and all completed the study.

RESULTS

Total 60 patients, 30 of gabapentin and 30 of placebo group consented and participated and completed the study, conducted w.e.f. April 2013 to Sept 2013. To avoid the variability in the different surgical procedures of different indications, the patients who had undergone hysterectomy, done under spinal anaesthesia in our hospital had been considered for this study. There was no significant difference in the demographic data like age and also in the clinical data like ASA classification, duration of anaesthesia, types of operation. (Table -1)

Table 1: Demographic and pre operative data in the two study groups

Variables	Gabapentin N=30	Placebo N=30
Age(Mean + SD)	43.13 ± 11.27	44.10 ± 10.76
ASA1:ASA2	20:10	18:12
Types of operation.	Hysterectomy	Hysterectomy
Duration of anaesthesia in terms of hrs. (Mean ±SD)	2.86 ± 0.80	2.76 ± 0.98

*** ASA 1 & 2=American society of Anesthesiologists classification grade 1 and 2.**

Table 2: Pain score in VAS after preoperative Gabapentin at 4, 24, 48 hrs post operatively.

Trial Medication	Gabapentin (N =30)			Placebo (N=30)		
Pain scores at;	Mean ± SD	Median	Percentile (25, 75)	Mean± SD	Median	Percentile (25, 75)
4 hrs *	56.16±14.24	57.50	50, 62.50	77.0±12.90	80	70,90
24 hrs *	37.00±12.56	40.00	30, 50	54.66±15.5	60	40, 66.25
48 hrs **	18.33±13.21	20.00	10, 30	22.83±20.6	20	10, 30

*** p< 0.001 (Gabapentin vs Placebo) & ** p=0.672 (Gabapentin vs Placebo) (As per Man Whitney test).**

Table 2 shows that after hysterectomy at 4, & 24 hours post operatively there were statistically significant less pain score in Gabapentin group than in placebo group subjects.

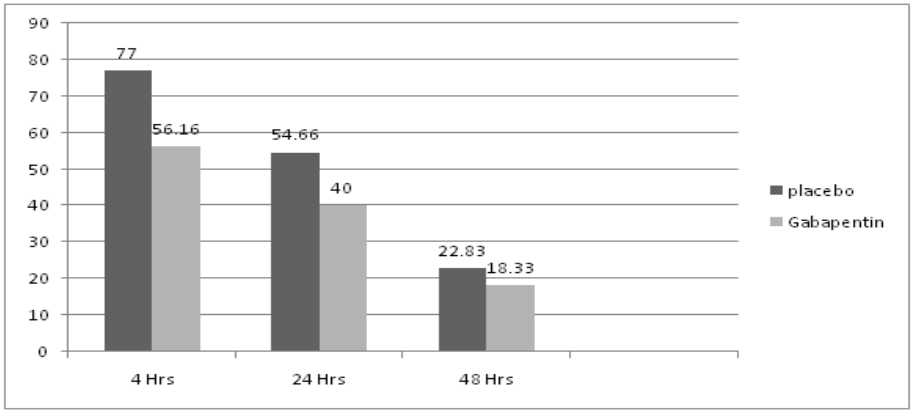


Fig. 1: Pain score in VAS at 4, 24, 48 hours post operatively following hysterectomy in preoperative Gabapentin and placebo group subjects.

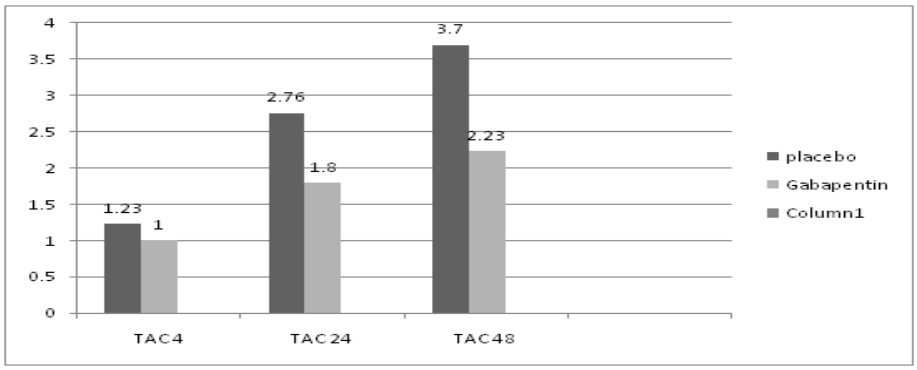


Fig. 2: Total analgesic (TAC) consumption post operatively following hysterectomy in preoperative Gabapentin and placebo group subjects.

Table 3: Total number of dose of analgesic consumption & time of the request for 1st supplementary analgesia post operatively following hysterectomy in preoperative Gabapentin & Placebo group subjects.

Variables	Gabapentin (Mean±SD)	Placebo (Mean±SD)
Total dose of analgesic consumption		
At 4 hrs *	1.00±0.00	1.23±0.43
At24 hrs **	1.80±0.55	2.76±0.67
At 48 hrs **	2.23±0.93	3.70±0.98
Request for 1st supplementary analgesia after operation in minutes**	188.66± 56.79	122.00±53.13

***p<0.01, (Gabapentin vs Placebo), **p < 0.001, (Gabapentin vs Placebo), (Gabapentin vs Placebo), **p< 0.001, (Gabapentin vs Placebo), As per Independent "t test".**

Table 3 shows that at 4, 24 & 48 hrs post operatively, total dose of analgesic consumption in Gabapentin group was significantly less in comparison to analgesic consumption by placebo group subjects. Post operatively, the mean time interval for the first request for supplementary analgesia by subjects in Gabapentin group was at 188.66 ± 56.79 minutes which is significantly less ($p< 0.01$), than that of placebo group subjects.

There were no statistically significant difference of nausea and vomiting at 4, 24 & 48 hrs (p value >0.05) postoperatively between Gabapentin and placebo group subjects.

No patient in any group reported any adverse effect like somnolence, ataxia, light headedness, dizziness, pruritus or visual disturbances. Only in 2 patients in each group there was complain of drowsiness which disappeared with continued therapy.

DISCUSSION

Gabapentin is not normally used to treat pain due to injury after an operation. Studies in recent years have particularly focused on the efficacy and safety of Gabapentin in the treatment of post operative pain. Gabapentin does not interact with other commonly prescribed drugs. Available data suggest that it may have a place in the management of post operative pain. However experience with Gabapentin as a pre-emptive analgesic in acute post operative pain is limited and more work is required before recommending it for routine clinical use [2]. So present study has been taken up to validate the effect of pre operative low dose gabapentin in post operative pain management.

Gabapentin, a new third-generation anti-epileptic drug, is a structural analogue of gamma-amino butyric acid (GABA), an important neurotransmitter in the central nervous system[6]. It affects the nociceptive process by binding to the $\alpha_2\delta$ subunit of voltage dependent calcium channel and blocks the development of hyperalgesia and central sensitization [1, 5]. Like other anti-epileptic drugs, Gabapentin has been shown to be effective in the treatment of neuropathic and inflammatory pain after surgical operations. Studies in recent years have particularly focused on the efficacy and safety of Gabapentin in the treatment of postoperative pain [2].

Peripheral tissue injury such as that caused by surgery provokes two kinds of modifications in the responsiveness of the nervous system: peripheral sensitization which causes a reduction in the threshold of nociceptor afferent terminals, and central sensitization which causes activity dependent increase in the excitability of the spinal neurons. Together these changes contribute to a hypersensitivity state which manifest as an increase in the response to noxious stimuli and decrease in the threshold at the site of injury and the surrounding tissue. The rationale for preemptive analogue is to prevent this hypersensitisation by blocking the initial nociceptive input to the spinal cord. Gabapentin does not affect the nociceptive threshold; rather it is effective in reducing allodyna and hyperalgesia, suggesting that it has a selective effect on the nociceptive process that is involved in central sensitization. [10]

In this study all the study population has under gone abdominal hysterectomy and there was no difference of operating procedures and duration of anaesthesia in the two study groups. The duration of surgery in this Elective abdominal hysterectomy performed, was not so long and comparable in both study groups.

After a single oral dose of 300 gabapentin, mean maximum plasma concentrations attains in 2-3 hours. Bioavailability of single dose of 300 mg oral dose is 60% and decreases with increasing dose. The pre emptive administration of gabapentin approximately 2 hr before surgery appears optimal and rational in order to attain maximal plasma concentration at the time of surgical stimuli**.** So in this study 300 mg of Gabapentin was used, as earlier clinical trials had shown that similar dose of Gabapentin given 2 hr before surgery remained safe and effective [1, 7, 11, 12].

Measurement of pain by visual analogue scale (VAS) is a widely used[2, 7] dependable method hence it is used in the present study. Evaluation of nausea, vomiting, drowsiness and pruritus was rated

in this study on a 4 point verbal scale, as described by the earlier investigators. [2, 7, 9]

In this randomized placebo controlled study it has been found that oral administration of 300 mg Gabapentin as pre medication 2 hours before surgery decreased post operative pain, total analgesic consumption. The present study demonstrated that pre operative administration of Gabapentin significantly reduced the pain score in VAS postoperatively,($P < 0.001$) at 4 & 24 hrs and it is comparable with the findings of Sekhavat L et al. 2009, Chowdhuri L et al. 2012, Montazeri K et al. 2007 and Pandey CK et al. 2004 [1, 2, 10 - 12].

In accordance with the findings of previous workers, Montazeri K et al.2007, Sekhavat L et al. 2009 and Pandey CK et al. 2004 [2, 11, 12] in the present study total dose of analgesic consumption was also significantly less in all time intervals i.e. at 4, 24 & 48 hrs post operatively. The first request for supplementary analgesics were also significantly ($p<0.01$) delayed in Gabapentin group [2, 11].

In the current study there was no significant difference in nausea and vomiting in both the study groups at different time intervals and this is probably because of low dose of Gabapentin. It is likely to be high dose Gabapentin that has anti-emetic effects. [2] Our findings regarding the incidence of nausea and vomiting at different time intervals are similar to those reported previously by Behdad S et al.2012, Turan A et al. 2009Dauri M et al. 2009 and Khademi S et al. 2010 [3, 4, 13, 14].As reported by the other workers in the present study also no significant adverse effect like drowsiness, pruritus, dizziness, somnolence, ataxia was recorded by the use of Gabapentin pre operatively [2, 7, 10].

This study had the limitations of being conducted in single center, low study populations and less frequent pain score assessment in VAS at 4, 24 and 48 hours post operatively.

To conclude, this study showed that pre operative administration of low dose Gabapentin 300 mg 2 hrs before abdominal hysterectomy decreased post operative pain and total analgesic consumption and delayed the need of supplementary analgesics, suggesting that Gabapentin has clinical potential in the treatment of post operative pain without significant side effects.

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