Indian Journal of Clinical Anaesthesia 2022;9(4):461–466

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Clinical Anaesthesia

Journal homepage: www.ijca.in

Original Research Article

Effect of oral gabapentin as pre-emptive analgesia in total abdominal hysterectomy- A randomised prospective placebo controlled study

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ARTICLE INFO

Article history:
Received 18-07-2022
Accepted 08-08-2022
Available online 15-11-2022

Keywords:
Gabapentin
Post- operative pain
Analgesia
Visual analogue scale

ABSTRACT

Background: The postoperative period is an integral part of the surgical experience of the patient. Post-operative pain affects recovery from anaesthesia and surgery. Pre-emptive use of gabapentin speeds up recovery by decreasing post-operative pain.

Objectives: The objectives of the study were to evaluate the effect of oral gabapentin on post-operative pain scores, the request time for first analgesia and the total fentanyl requirement in 12 hours in patient undergoing total abdominal hysterectomy under epidural anaesthesia.

Materials and Methods: Eighty four patient of ASA grade I and II aged 40 to 60 years, scheduled for total abdominal hysterectomy under epidural anaesthesia were included in the study. Each patient was assigned into two groups (Gabapentin group, group G or Placebo group, group P) of 42 each. Participants in the study were administered 2 capsules (either gabapentin or placebo) one hour before surgery with sips of water. 15ml of Ropivacaine 0.75% was administered into epidural space through 20 gauge epidural catheter. Pain was evaluated post-operatively using visual analogue scale (VAS). Inj. Fentanyl 30 mcg was administered through epidural catheter as rescue analgesia when patients complained of pain.

Results: It was observed that Pain scores were notably lesser in group G as compared to group P at all time points (P<0.05). The first analgesic request time in the control group was significantly less compared to the study group (P<0.001). The amount of fentanyl required in the control group was more compared to study group (P<0.001).

Conclusions: We conclude that the pre-emptive administration of oral gabapentin 600mg significantly reduces pain scores, prolongs the time at which patient requires rescue analgesia and the amount of fentanyl needed was significantly reduced.

1. Introduction

Pain management is an essential component in the post-operative care of the surgical patient. There are various pharmacological methods to tackle post-operative pain which includes opioids, non-steroidal anti-inflammatory drugs (NSAIDS), injecting local anesthetics at the incisional site, adjuvants to spinal or epidural analgesia like clonidine and dexmedetomedine. These pharmacological methods have side effects. Opioids are inevitably associated with emesis and respiratory depression. NSAIDS have limitations such as renal, gastrointestinal and haemostatic adverse effects.[1–5]

The present day postoperative pain management targets at enhancing pain relief and decreasing opioid requirements by including two or more drugs that act by distinct mechanism for providing analgesia, so called multimodal analgesia.[6] Gabapentin has become an integral part of

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https://doi.org/10.18231/j.ijca.2022.093

present day multimodal analgesia along with opioids. Turan and colleagues proposed that gabapentin when added as an adjuvant to general anaesthesia can reduce post-operative pain and tramadol consumption after total abdominal hysterectomy.[7] Recently, many studies have compared oral gabapentin with a placebo to manage pain after abdominal surgeries.[8–10]

Despite using various analgesic techniques, pain relief and patient satisfaction remained inadequate in many patients in our institute. Further improvements in the post-operative pain management were warranted. So we selected gabapentin as an adjuvant to epidural analgesia in patient undergoing total abdominal hysterectomy.

2. Objectives

The objectives of the study were to evaluate the post-operative pain scores, the first analgesic requirement time and the total fentanyl requirement 12 hours post-operatively in patients undergoing total abdominal hysterectomy under epidural anaesthesia.

3. Materials and Methods

After obtaining institutional ethical committee approval (No:SSMC/MED/IEC-12/Oct2018), 84 patients were included for the study. The present prospective randomized double-blind clinical study was conducted from January 2019 to January 2020. Informed written consent was obtained from each patient included in the study. Eighty four female patients belonging to the American society of Anaesthesiologist grade I and II status aged 40 to 60 years scheduled for total abdominal hysterectomy were included in the study. Patients having hypotension, sinus bradycardia, coagulational disorders, ischaemic heart disease, patients having complex pain syndrome, with previous pelvic surgeries and on anticonvulsant drugs were excluded from the study. Patients were divided into two groups Group G received gabapentin (cap neurontin 300mg, Pfizer, India) one hour before surgery and Group P received 2 capsules of 300mg similar to gabapentin capsule according to computer generated randomized table. The dosage were finalized by previous literature study and pilot study.

A thorough pre-anaesthetic evaluation was conducted a day before the surgery. The post-operative pain scores were recorded on a visual analogue scale. Patients were taught to read the visual analogue scale day before the surgery. A written informed consent was obtained from the patients and cap gabapentin 600mg was used for the study. A similar looking capsule filled with starch powder was prepared by hospital pharmacy. The capsules were enclosed in a sealed envelope. The selected patients were allotted either to group G or Group P as per computer generated randomization table prepared by the statistician. An Anaesthesiologist not involved in the administration of anaesthesia prepared and allocated gabapentin (300mg 2 capsules) and placebo (300mg 2 capsules with starch filled) to the patients 1 hour before the surgery. A different anaesthesiologist carried out epidural anaesthesia and collected the required data. The patient and anaesthesiologist, who collected the data in the postoperative period were blinded to the study design. Hence, the blinding was achieved throughout the procedure.

On arrival at the operation theatre, standard ASA monitors were connected. An eighteen gauge intravenous cannula was secured in the right hand under aseptic precaution. Ringers lactate solution, 10ml kg^{-1} was started. After attaching the monitors, non-invasive blood pressure, pulse oximeter probe and electrocardiogram, baseline vital signs were recorded. Patients of either group received epidural anaesthesia. In the operation theatre after attaching the above said monitors, patients were asked to lie in the left lateral position. Under strict aseptic precaution T_{10}-T_{11} interspace was located and skin infiltration with local anaesthetic 2% lignocaine was done. T_{10}-T_{11} epidural space located using 18G Tuohy needle with loss of resistance technique for air. After confirming the negative aspiration for blood or cerebrospinal fluid, an epidural catheter of 20 gauge was secured into the above said epidural space, 5cm of the catheter was left inside the epidural space and Tuohy needle was withdrawn. A test dose of 3ml containing 20mg/ml of lignocaine+5mcg/ml of adrenaline (1:200000) was injected into epidural space. The patient was monitored for 3 minutes for subarachnoid blockade and tachycardia. Each patient was administered 15ml of Ropivacaine 0.75%. Sensory and motor blockade were assessed every 5 minutes for 20 minutes. The most cephalad and the most caudal spread of anaesthesia was noted. The Bromage scale and Rectus abdominis test were used to assess the motor blockade. The degree of sensory blockade was assessed using pin prick method. Total abdominal hysterectomy with bilateral salphingo-ophorectomy was carried out. The hypotension (mean blood pressure <20%) below the baseline was treated with ephedrine 5mg and bradycardia (heart rate <50 beats/minute) was treated with I V atropine 0.6mg.

In the post-operative recovery unit, the pain was assessed using visual analogue scale at 1,2,4,8,12 hours. The anaesthesiologist assessed the intensity of pain. The time at which the patient complained of pain was recorded and if the post-operative pain score was >=4 on the visual analogue scale, the rescue analgesic in the form of fentanyl at a dose of 30mcg mixed with 10ml of normal saline through the epidural catheter was administered. This was recorded as first analgesic requirement time.

The post-operative pain scores for 12 hours were assessed and the first analgesic requirement time, the total fentanyl consumption for 12 hours were recorded in the gabapentin and placebo group. Infusion of fentanyl (1.5 – 2.5μg/kg/hour) was provided for both the groups.

3.1. Statistical analysis

Calculations were designed to detect a difference in mean opioid consumption in 12 hours between two groups with power of 80% and a significance level of 5%. Power analgesia was based on previous study.[9] Thus a sample size of 84 was reached. The data was entered in excel spread sheet. Data validation and data analysis was performed using SPPS package (version 20). Measured data were expressed as mean and standard deviation. The differences in variables like age, duration of surgery, duration of anaesthesia, BMI etc., between gabapentin and placebo groups were tested using independent sample t test. Repeated measure ANOVA was applied to test for differences in mean scores at successive interval of time. P value of <0.05 was taken as significant.

Sample size calculation

$$n = \frac{2*\{Z(1-\frac{\alpha}{2})+ Z(1-\beta))2 * \sigma 2}{d2}$$

1. Z value for 5% level of significance ($Z_{(1-\alpha\ /2)}$) (95% CI) = 1.96
2. Standard deviation (σ) = 27.20
3. Power (80%) = 0.84
4. Outcome variable = Total opioid requirement in 12hrs.
5. Effect size (d) = 16.67
6. Minimum Sample required is 42 in each group (Total = 84).
7. With 10% non-response 46 in each group (Total 92)

4. Results

Ninety-two patients were screened prior to eligibility. Eighty-four patients were divided into Group G and Group P (Figure 1). Eight patients were eliminated (four patients did not satisfy the inclusion criteria, four patients declined to participate). The study was completed with total of 84 patients. There were no significant differences between group P and group G observed in the demographic characteristics, duration of surgery and duration of anaesthesia (Table 1). We observed significant differences in VAS scores and these values were less in group G compared to group P (1^{ST} hour P<0.001, 2^{nd}hour P=0.039, 4^{th}hour, P=0.019, 8^{th} hour P=0.007, 12^{th}hour P=0.012 (Table 2). The time until the first analgesic requirement in the post-operative period was highly statistically significant and prolonged among the group G[P<0.001]. The mean time for first analgesic request for group G was 4.03±1.11SD hours while it was 1.72±0.52SD hours for group P (Table 3).The total amount of fentanyl consumption in group P was more with mean value 152±17.50SD as compared to group G with mean value of 87.50±14.31SD and it was found statistically significant P<0.001 (Table 3). Dizziness, sedation were the common side effects seen in patients and were statistically significant (P<0.05) (Table 4).

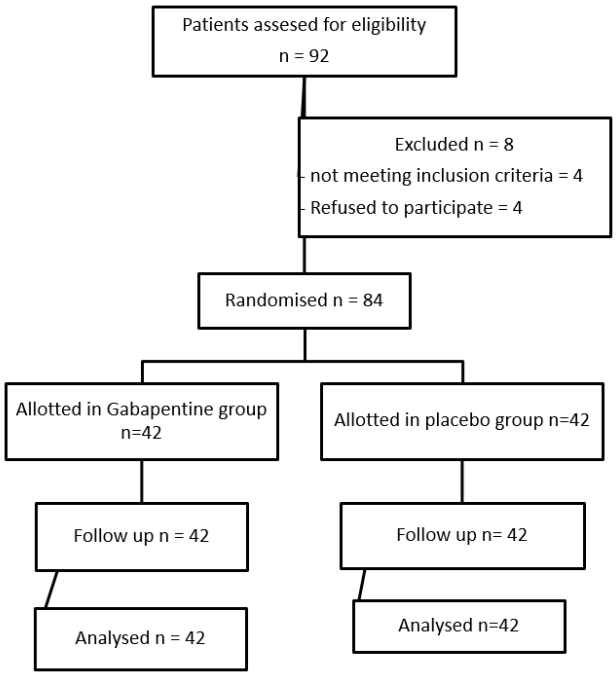

Fig. 1: Consort diagram for the randomized controlled trial

5. Discussion

Total abdominal hysterectomy is one of the common surgical intervention performed in elderly females. It is associated with significant postoperative pain which if left untreated can cause significant increase in heart rate, blood pressure, respiratory difficulty and thus prolonged hospital stay. The precise duration of post-operative pain differs widely among individuals and is effected by a multitude of inter connected factors. It is rather impossible to isolate individual factors that may influence the duration of post-operative pain. Compounded on this difficulty is the fact that pain being a multi-dimensional sensation is not ease to quantify. The visual analogue scale was used in our study to determine the intensity of pain. In our study, the mean pain scores were notably high in the placebo group during first hour of the study. This can be explained on the fact that at this time, the local anaesthetic action will be starting to wear off. The patient in gabapentin group would be still experiencing the less pain, as the half-life of gabapentin is 5-7 hours. The first analgesic request time was prolonged in gabapentin group as compared to placebo and total amount of fentanyl consumed was less in gabapentin as compared to placebo. The lower requirement of fentanyl in the study group was helpful in reducing the opioid related side effects like pruritus, nausea, vomiting.

Gabapentin is a structural analogue of gamma amino butyric acid. Gabapentin reduces pain by involving voltage gated N-type calcium channels.[11] After a single dose, mean maximum plasma concentrations are attained in two

Table 1: Demographic characteristics, duration of surgery and duration of anesthesia

Characteristics	Group G		Group P		t-value	P-value ű
	Mean	S.D	Mean	S.D		
Age (in years)	47.32	6.65	47.98	6.17	-0.464	0.643
Weight (Kgs)	55.97	6.26	55.13	5.58	0.544	0.588
Height (cms)	157.07	6.18	157.50	5.95	-0.276	0.782
BMI	22.49	1.61	22.22	1.28	0.707	0.481
Duration of Surgery (Minutes)	91.88	4.15	91.88	4.55	0.000	1.00
Duration of Anesthesia (Minutes)	108.10	5.00	106.51	3.88	1.603	0.112

S.D:Standard Deviation; ŰIndependent samplet-test;

Table 2: Comparison of VAS scores between gabapentin and placebo group

Time Interval (in hours)	Group G		Group P		t-value	P-value ű
	Mean	Standard Deviation	Mean	Standard Deviation		
1	0.00	0.00	1.63	1.96	-4.573	0.000
2	0.97	0.89	1.67	1.45	-2.258	0.039
4	1.40	1.65	2.33	1.49	-2.331	0.019
8	2.07	1.60	3.23	1.48	-2.295	0.007
12	1.37	1.22	2.23	1.25	-2.722	0.012
F-value		6.187		3.028		
P-value		<0.001		0.005		

Independent sample t-test; Repeated measure ANOVA;

Table 3: Comparison of first analgesic request time and fentanyl consumption between gabapentin and placebo group

Parameter	Group G		Group P		t-value	P-value ű
	Mean	Standard Deviation	Mean	Standard Deviation		
First analgesic request time (hours)	4.03	1.11	1.72	0.52	10.383	<0.001
Fentanyl consumed (mcg)	87.50	14.31	152.00	17.50	15.629	<0.001

Independent sample t-test

Table 4: Side effects

Side Effects	Group G	Group P	Total	Chi-Square, P-value
Dizziness	26 (52.0%)	14 (28.0%)	40 (43.0%)	3.389, 0.048
Sedation	26 (52.0%)	13 (26.0%)	43 (43.0%)	3.407, 0.034

to three hours. So in the early postoperative phase the plasma level of gabapentin will be the highest. Generally the postoperative pain will be higher in the early postoperative phase than in the late postoperative phase and so any effect on pain score produced by gabapentin will be considerably large in the early phase. This might be the reason behind the use of single dose of preemptive gabapentin for various surgeries despite the half-life of gabapentin being 5-7 hours. In our study we administered single dose of preemptive gabapentin 600mg. The opioid consumption was significantly reduced in our patients as compared to control group. Our results are in consistent with the review conducted by Clivatti J. In their review they reported that opioid consumption was reduced in 82.4% of patients receiving single preoperative dose of gabapentin, and in 77.8% of patients who received pre and postoperative doses of gabapentin.[12] In another study conducted by Pandey CK et al explored the efficacy of four different doses of gabapentin (300mg, 600mg, 900mg, 1200mg) in patients posted for lumbar discectomy. The VAS scores of patients who received gabapentin 600mg, 900mg, 1200mg were less as compared to patients who were administered 300mg of gabapentin at any point of time. They revealed escalating the dose of gabapentin from 600mg to 1200mg did not reduce the VAS scores. They also found that increasing the dose of gabapentin did not remarkably decrease fentanyl consumption. Thus they concluded that gabapentin 600mg is the ideal dose for post-operative pain relief after single level lumbar discectomy. In our study we used gabapentin 600mg and found it effective in reducing

VAS scores, increased the time for rescue analgesic requirement and decreased fentanyl consumption.[13] Roshan et al. performed a randomised, double-blind study on 60 patients undergoing surgeries under spinal anaesthesia and evaluated oral gabapentin 600mg vs vitamin B complex used as placebo. Interestingly, gabapentin provided better pain control and reduced the total opioid consumption in the post-operative period than placebo.[14] In another study, Devon E Anderson et al performed the study to evaluate the effects of gabapentin (15mg/kg) perioperatively in adolescent patients undergoing posterior spinal fusion. They demonstrated that gabapentin in combination with opioid protocol significantly reduced the opioid use and visual analogue pain scores. They registered that the patients who received gabapentin in the post-operative period requested significantly less opioid than the placebo group at every time point.[15] Harshel G Parikh reported gabapentin 600mg in comparison with placebo in abdominal surgeries reduced the VAS scores at 0, 2, 4, 6, 12, 24 hours. They found that the number of patients in need of rescue analgesia with diclofenac were significantly less (3 vs 14) in gabapentin and placebo group respectively.[10]

A study was conducted in patient undergoing laparoscopic cholecystectomy. Patients were administered either gabapentin 300mg or tab tramadol 100mg two hours before surgery. The authors noticed that gabapentin provided a strong postoperative analgesic effect.[16] Srivastava et al. explored the efficacy of preemptive gabapentin on postoperative pain after minilap open cholecystectomy using tramadol as rescue analgesia. They reported that the need for rescue analgesia was significantly higher in the control group.[17] Our findings are in conformity with this study.

Fewer patients complained of dizziness and somnolence in the gabapentin group than in the placebo group in our study and this was statistically significant. A study conducted by Rapchuk et al., did not report any clinically limiting side effects ie, sedation and dizziness with gabapentin.[18]

6. Limitation

There is a limited data concerning dose response characteristics of gabapentin. Nevertheless, we chose the highest reasonable dose to avoid considerably larger study with a potentially negative outcome. Another pitfall might be that gabapentin administered as a solitary dose might have resulted with a decreased effect over time. The half-life of gabapentin is 5-7 hours and further studies with divided doses are needed.

7. Conclusion

The pre-emptive administration of oral gabapentin 600mg significantly reduced post-operative pain scores, prolonged the time at which patient required rescue analgesia and the amount of fentanyl needed was significantly reduced. Thus, we conclude that gabapentin is an effective, non-invasive adjuvant to epidural analgesia in total abdominal hysterectomy.

8. Source of Funding

None.

9. Conflict of Interest

None.

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Cite this article: Sujay J. N, Prakash B.C, Kalaburgi RA. Effect of oral gabapentin as pre-emptive analgesia in total abdominal hysterectomy- A randomised prospective placebo controlled study. *Indian J Clin Anaesth* 2022;9(4):461-466.