Original Article

Comparative Study of Efficacy and Safety of Oral Gabapentin versus Placebo as a Pre-Emptive Analgesia in Total Abdominal Hysterectomy in a Tertiary Care Hospital of Eastern India

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ABSTRACT

Introduction: The postoperative treatment of the surgical patient must include pain control as a crucial aspect. Opioids, non-steroidal anti-inflammatory medications (NSAIDS), local anaesthetic injections at the point of the incision, and adjuvants to spinal or epidural analgesia such clonidine and dexmedetomidine are some of the medications used for post-operative pain. Vomiting and breathing problems are inextricably linked to opioids. NSAIDS include drawbacks like negative renal, digestive, and haemostatic consequences. It is necessary to make more advancements in the postoperative pain treatment

Aims/ objective: To assess the post-operative pain scores, the duration until an additional analgesic was needed, and the total amount of fentanyl used 12 hours after surgery in patients having a complete abdominal hysterectomy under epidural anaesthesia.

Materials and Method: Patients were divided into two groups: one hour prior to surgery with 46 patients in each group, the Gabapentin Group got gabapentin, while the Placebo Group received capsules of a similar 300mg dosage as the Gabapentin Group. At 1, 2, 4, 8, and 12 hours after surgery, the pain was measured in the recovery period following surgery using a visual analogue scale. The moment the patient first complained of pain was noted, and if the postoperative pain score was greater than or equal to 4 on the visual analogue scale, the rescue analgesic fentanyl was given via the epidural catheter at a dose of 30 microgram combined with 10ml of NS. This was noted as the first analgesic required time.

Results: Post-operative pain control was significantly better in gabapentin group than placebo group with respect to VAS score ($p<0.001$). There was significantly later requirement of analgesic in gabapentin group. Overall consumption of opioid was also significantly lesser in gabapentin group. The most frequent adverse effect associated with gabapentin was found to be dizziness followed by constipation, dry mouth, and tremors.

Conclusion: We draw the conclusion that gabapentin, when used in conjunction with epidural analgesia during complete abdominal hysterectomy, is a successful, non-invasive supplement. In general, gabapentin was found to be a well-tolerated, secure, and effective medication.

Keywords: Gabapentin, Pre-Emptive Analgesia, Pain, Abdominal Hysterectomy, Placebo.

INTRODUCTION

The postoperative treatment of the surgical patient must include pain control as a crucial aspect. Opioids, non-steroidal anti-inflammatory medications (NSAIDS), local anaesthetic injections at the point of the incision, and adjuvants to spinal or epidural analgesia such clonidine and dexmedetomidine are some of the medications used for post-operative pain. These therapeutic approaches come with drawbacks. Vomiting and breathing problems are inextricably linked to opioids. NSAIDS include drawbacks like negative renal, digestive, and hemostatic consequences. [1–5]

Today's treatment for postoperative pain aims to improve pain relief and reduce the need for opioids by combining two or more medications that work by different mechanisms to provide pain relief, or multimodal analgesia. [6]

Gabapentin reduces the hyperexcitability of posterior horn neurons, which is what causes central sensation and how it operates. [7] The postsynaptic attachment of gabapentin to the alpha2-delta subunit of the calcium channels that are voltage-dependent of the dorsal horn nerve cells may be the underlying cause of the anti-hyperalgesic activity, resulting in reduced entry of calcium into nerve terminals and consequently reduced discharge of neurotransmitters. The impact of gabapentin on NMDA receptors, sodium channels, mono-aminergic pathways, and the opioid system are additional potential biological processes. [8-11]

In the year 1994, gabapentin was first made available as an anti-epileptic drug (AED), mostly for partial seizures. After oral treatment, the anticonvulsant's adverse effects are tolerated well and well absorbed, with the maximum plasma concentration appearing around two hours to three hours later.[8, 12] Dizziness, somnolence, tiredness, ataxia, and peripheral oedema are some of the adverse effects of gabapentin that are most frequently observed.[10,13]

Today's multimodal analgesia includes gabapentin and opioids as essential elements. By adding gabapentin to general anaesthesia, Turan and colleagues hypothesised that full abdominal hysterectomy patients' post-operative

requirement for opioids could be reduced. [14] Recent studies have looked at oral gabapentin and a placebo to relieve pain following abdominal surgeries. [15–17]

Numerous patients at our institute experienced insufficient pain reduction and patient satisfaction in spite of the use of numerous analgesic methods. It was necessary to make more advancements in the postoperative pain treatment. As a result, we decided to provide gabapentin to patients who were having a total abdominal hysterectomy in addition to an epidural anaesthetic.

The study's goals were to assess the post-operative pain scores, the duration until an additional analgesic was needed, and the total amount of fentanyl used 12 hours after surgery in patients having a complete abdominal hysterectomy under epidural anaesthesia.

SUBJECTS AND METHODS

92 patients were enrolled in the study after receiving approval from the institutional ethical committee. Between January 2022 and January 2023, the current prospective randomised double-blind clinical study was carried out. Each patient enrolled in the trial provided signed informed consent.

Inclusion Criteria: The study comprised patients scheduled for complete abdominal hysterectomy between the ages of 40 and 60 who had American society of anesthesiologists grade I or II status.

Exclusion Criteria: Patients with complicated pain syndrome, hypotension, cardiac arrhythmia coagulation issues, ischemic heart disease, prior pelvic operations, and anticonvulsant use were excluded from the trial.

Patients were divided into two groups: one hour prior to surgery with 46 patients in each group, the Gabapentin Group got gabapentin (cap Neurontin 300mg, Pfizer, India), while the Placebo Group received capsules of a similar 300mg dosage as the Gabapentin Group. Web-generated random numbers were used for the randomization.

A full pre-anaesthetic assessment was performed the day before the procedure. A visual analogue scale was used to rate the pain following surgery. The day prior surgery, patients received instruction on how to interpret the visual analogue scale. The patients provided signed informed consent and cap gabapentin 600 mg was utilised in the trial. The institution's pharmacy created a capsule with a comparable appearance and a starch powder filling. A covered envelope contained the capsules. According to a digitally produced randomization table created by the statistician, the chosen patients were assigned to either to gabapentin group or placebo group.

One hour prior to surgery, an anaesthesiologist who was not involved in administering of anaesthesia had prepared and given gabapentin (300 mg/capsule) and placebo (300 mg/capsule with starch filled) to the participants. The necessary data was gathered while epidural anaesthesia was administered by a different anaesthesiologist. Data were gathered in the post-operative phase by an anaesthesiologist and participants who were unaware of the study's design. As a result, the treatment was completed with complete blinding.

Upon entering the operating room, typical ASA monitors were already attached. Under proper precaution, an 18-gauge IV cannula was positioned in the right hand. 10ml of Ringers lactate solution was begun per kilogramme. Initial vital signs were captured after the monitors, non-invasive blood pressure, pulse oximeter probe, and electrocardiogram were attached. Both groups' patients got epidural anaesthesia. Patients were given instructions to lie in the left lateral posture in the operating room after the monitors were attached. T10-T11 interspace was found under extreme aseptic precaution, and 2% lignocaine was injected into the skin. Using an 18G Tuohy needle and the loss of resistance approach for air, the epidural space between T10 and T11 had been found.

The epidural catheter of 20 gauge was inserted into the aforementioned epidural space, five centimetres of the catheter was left within the epidural space itself, and the Tuohy needle was taken out once it had been confirmed that there had been no aspirates of blood or CSF. The epidural space was injected with a trial dose of 3 ml that contained 20 mg/ml of lignocaine and 5 mcg/ml of epinephrine (1:200000). For three minutes, the patient was watched for tachycardia and subarachnoid blockage. Each patient received 15ml of ripivacaine 0.75 percent. For 20 minutes, motor and sensory blockage were evaluated each 5 minutes.

The motor blockage was evaluated using the Bromage scale and the Rectus abdominis test. Using the pin prick technique, the level of sensory blockage was determined. Bilateral salphingo-ophorectomy was performed along with a total abdominal hysterectomy. Ephedrine 5 mg was used to manage hypotension (mean blood pressure 20% below baseline), while intravenous atropine 0.6 mg was used to manage bradycardia (heart rate 50 beats per minute).

At 1, 2, 4, 8, and 12 hours after surgery, the pain was measured in the recovery period following surgery using a visual analogue scale. The anaesthesiologist evaluated the level of pain. The moment the patient first complained of pain was noted, and if the postoperative pain score was greater than or equal to 4 on the visual analogue scale, the rescue analgesic fentanyl was given via the epidural catheter at a dose of 30 microgram combined with 10ml of NS. This was noted as the first analgesic required time.

Statistical Analysis

Excel spread sheet was used to enter the data. Using the SPPS package (version 25), data evaluation and data verification were carried out. The mean and standard deviation were used to express the measured data. The independent sample t test was used to compare the

differences in age, operation duration, anaesthetic duration, BMI, and other factors between the gabapentin and placebo groups. P value less than 0.05 was used as the standard for determining significance. Evaluation of statistical significance of difference in VAS score at different phase within group was done using ANOVA.

RESULTS

100 patients were screened prior to eligibility. Eight patients were eliminated (four patients did not satisfy the inclusion criteria, four patients declined to participate). The study was completed with total of 92 patients with 46 patients in each group.

Table 1: Comparison of baseline demographic and clinical characteristics between gabapentin and placebo group

Variables	Gabapentin Group (n = 46)	Placebo Group (n = 46)	P-Value (Unpaired t test)
Age in years (mean ± SD)	46.15 ± 6.33	46.49 ± 6.09	0.79
Weight in Kg (mean ± SD)	56.94 ± 6.13	55.07 ± 6.29	0.15
Height in cm (mean ± SD)	158.18 ± 10.29	158.61 ± 9.84	0.74
Body Mass Index in kg/m^2 (mean ± SD)	22.68 ± 1.59	22.31 ± 1.32	0.23
Duration of Surgery in minutes (mean ± SD)	92.97 ± 4.26	92.79 ± 4.64	0.85
Duration of Anaesthesia in minutes (mean ± SD)	109.01 ± 5.13	107.42 ± 4.11	0.10

There were no statistically significant differences between two groups with respect to age, weight, BMI, duration of surgery or duration of anaesthesia (p>0.05). Thus, both the groups were comparable at baseline.

Table 2: Comparison of VAS scores between two groups

Time in Hours (Post-operative)	VAS Score in Gabapentin Group (mean ± SD)	VAS Score in Placebo Group (mean ± SD)	P-Value (Unpaired t test)
1	0.00 ± 0.00	1.59 ± 0.88	<0.001
2	0.93 ± 0.45	1.63 ± 0.77	<0.001
4	1.36 ± 0.83	2.29 ± 0.74	<0.001
8	2.03 ± 0.80	3.19 ± 0.73	<0.001
12	1.33 ± 0.61	2.18 ± 0.62	<0.001
P-Value (ANOVA)	<0.001	<0.001	

Post-operative pain control was significantly better in gabapentin group than placebo group with respect to VAS score (p<0.001).

Figure 1: Comparison of VAS Score Between Two Groups

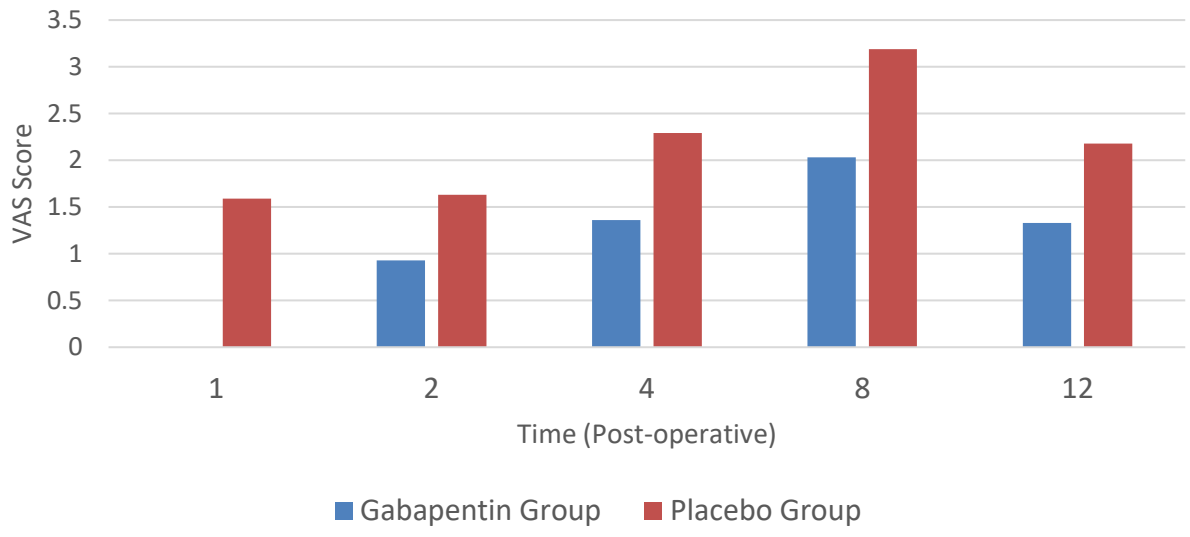

Table 3: Comparison of time of first analgesic requirement and fentanyl consumption between two groups

Variables	Gabapentin Group (n = 46)	Placebo Group (n = 46)	P-Value (Unpaired t test)
Time of first analgesic requirement in hours (mean ± SD)	3.99 ± 1.01	1.68 ± 0.43	<0.001
Fentanyl consumption in microgram (mean ± SD)	88.61 ± 13.42	151.97 ± 17.39	<0.001

There was significantly later requirement of analgesic in gabapentin group. Overall consumption of opioid was also significantly lesser in gabapentin group.

Table 4: Comparison of incidence of adverse drug reactions (ADRs) between two groups

ADRs	Gabapentin Group (n = 46)	Placebo Group (n = 46)	P-Value (Chi-square test)
Dizziness	9	2	0.864
Tremors	2	0	
Constipation	3	1	
Dry mouth	2	0	
Peripheral oedema	1	0	

The most frequent adverse effect associated with gabapentin was found to be dizziness followed by constipation, dry mouth, and tremors.

DISCUSSION

One of the frequently performed surgical procedures on older women is a total abdominal hysterectomy. It is accompanied by substantial postoperative pain, which if not managed properly, can lead to an extended hospital stay and a substantial rise in heart rate, blood pressure, and breathing difficulties. The exact duration of pain following surgery varies greatly from person to person and is influenced by a large range of interrelated factors. It is quite difficult to pinpoint specific elements that could affect how long pain following surgery lasts. The fact that pain is a multimodal sensation and difficult to measure adds to this challenge.

In our investigation, the visual analogue scale was utilised to assess the degree of pain. In our investigation, the initial hour of the experiment saw noticeably elevated mean pain scores in the placebo group. This can be attributed to the fact that the regional anaesthetic effect will be beginning to wane off at this point. Given that gabapentin has a 5-7 hour half-life, the patient in the gabapentin group would continue to be in a less painful state. In comparison to the placebo group, the gabapentin group's additional analgesic demand time was longer, and the total quantity of fentanyl administered was lower. The trial group's reduced fentanyl dosage helped to lessen opioid-related adverse effects such itching, nausea, and vomiting.

Voltage gated N-type calcium channels are a mechanism via which gabapentin lowers pain.18 Mean highest plasma concentrations are reached within two to three hours after the first dose. Therefore, the plasma level of gabapentin will be at its greatest during the first post-operative phase. The initial post-operative phase will typically experience more pain following the operation than the late post-operative phase, so gabapentin's early-phase effects on pain scores will be disproportionately great. This may be the cause of the usage of a single dosage of preventive gabapentin for a variety of procedures, despite the drug's 5–7-hour half-life.

In our trial, a single 600 mg dosage of preventive gabapentin was given. In comparison to the placebo group, the quantity of opioids consumed by the patients in gabapentin group was much lower. Our findings are in line with the analysis done by Clivatti J. According to their research, 82.4 percent of patients who got a single dose of gabapentin before surgery and 77.8 percent of patients who received pre- and post-operative doses of gabapentin saw decreased opioid usage.[19]

Previous research by Pandey CK et al examined the effectiveness of various gabapentin doses in patients scheduled for lumbar discectomy (300 mg, 600 mg, 900 mg, and 1200 mg). individuals who got 600 mg, 900 mg, or 1200 mg of gabapentin had lower VAS scores than individuals who received 300 mg of gabapentin at any given time. They found that increasing the gabapentin dosage from 600 mg to 1200 mg had no effect on the VAS ratings. They also discovered that raising the gabapentin dosage had no appreciable impact on fentanyl usage. As a result, they came to the conclusion that gabapentin 600 mg is the recommended dosage for post-operative pain management following a single level lumbar discectomy. [20]

In our trial, we discovered that gabapentin 600 mg was beneficial in lowering VAS scores, lengthening the period during which rescue analgesics were needed, and minimising fentanyl usage. In a double-blind, randomised trial, 60 patients receiving spinal anaesthesia for

procedures were compared to oral gabapentin 600 mg and a control group receiving vitamin B complex. It's interesting to note that compared to vitamin B complex, gabapentin improved post-operative pain management and decreased overall opioid intake.[21]

In a different trial, Devon E. Anderson et al. assessed the therapeutic effects of gabapentin (15 mg/kg) given to adolescents undergoing posterior spinal fusion before surgery. They showed that gabapentin significantly decreased opioid consumption and visual analogue pain scores when combined with an opioid strategy. They noted that at each point, patients using gabapentin in the post-operative period required much fewer opioids than those taking a placebo.[22] According to Harshel G. Parikh, gabapentin 600mg decreased the VAS scores at 0, 2, 4, 6, and 12 hours following abdominal procedures as compared to a placebo. They discovered that in the gabapentin and placebo groups, respectively, there were considerably fewer patients who required emergency diclofenac analgesia (3 vs 14). [17]

Laparoscopic cholecystectomy patients were the subject of a research trial. Two hours prior to surgery, patients received either 300 mg of gabapentin or 100 mg of tablet tramadol. The authors noted that gabapentin had a substantial analgesic effect following surgery. 23 With tramadol as a backup analgesic, Srivastava et al. investigated the effectiveness of pre-emptive gabapentin on postoperative pain following minilap open cholecystectomy. They claimed that the control group had a noticeably increased requirement for rescue analgesia. 24 Our results are consistent with this research.

The most frequent adverse effect associated with gabapentin was found to be dizziness followed by constipation, dry mouth, and tremors. Rapchuk et al.'s study found no clinically significant side effects of gabapentin, such as drowsiness and vertigo. 25

Information on the dosage response properties of gabapentin is scarce. Nevertheless, we opted for the greatest acceptable dose to avoid conducting a much larger trial that would have had unfavourable results. Another drawback is that gabapentin may have had a diminishing effect over time if it was taken as a single dose. The gabapentin half-life is 5-7 hours, and more research including divided doses is required.

CONCLUSION

Oral gabapentin 600 mg was pre-emptively administered, and it dramatically decreased post-operative pain levels, lengthened the period when the patient has no requirement rescue analgesia, and decreased the amount of opioid needed. So, we draw the conclusion that gabapentin, when used in conjunction with epidural analgesia during complete abdominal hysterectomy, is a successful, non-invasive supplement. However, it has been demonstrated that gabapentin considerably lowers the incidence of post-operative nausea and vomiting. In general, gabapentin has been described as a well-tolerated, secure, and effective medication.

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Presentation at a meeting: Nil

Conflicting Interest: Nil

Ethical clearance: Institutional Ethics Committee of Darbhanga Medical College and Hospital, Lehariasarai, Bihar, India.

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