

Gabapentin a pre-emptive analgesic in post-operative pain: a randomised double blind placebo controlled study

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Received: 28 April 2017

Accepted: 04 May 2017

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ABSTRACT

Background: Conventional analgesics, used in peri-operative period cause numerous adverse effects and are not free from interactions with co-administered drugs. Gabapentin has been shown to be effective in various types of neuropathic pain. The primary aim of this study was to evaluate gabapentin as a post-operative analgesic. The study also evaluates the analgesic requirement and safety of gabapentin in post-operative period.

Methods: Forty patients undergoing elective laparoscopic cholecystectomy were randomized to receive gabapentin or a matching placebo. The patients of group I received gabapentin 600mg orally 2 hrs before surgery and 12hrs after the first dose. The patients in group II received a matching placebo. Patients in both groups received diclofenac sodium 75mg i.m b.i.d for pain. Additional doses were given on demand and recorded.

Results: The present study found that gabapentin significantly reduced pain score and analgesic consumption as compared to a placebo for a period of 24 hours.

Conclusions: Gabapentin in the doses used was found to be effective in postoperative pain in patients undergoing planned laparoscopic cholecystectomy. It was found to be safe and no serious adverse events were reported.

Keywords: Cholecystectomy, Gabapentin, Postoperative pain

INTRODUCTION

International Association for the study of pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.¹ Post-operative pain (POP) is a psychological sensory experience caused by

various factors namely nociceptive, inflammatory and neuropathic.²

Nociceptive component of pain is the pain that results from activation of nociceptor neurons by intense mechanical, chemical, or thermal noxious stimuli like a scalpel blade cutting through skin. It signals the presence,

location, intensity and duration of a noxious stimulus and fades once the peripheral driving force is removed.²

Inflammatory component is due to the heightened pain sensitivity that occurs in response to tissue injury and inflammation. It results from the release of sensitising inflammatory mediators that lead to a reduction in the threshold of nociceptors that innervate the inflamed tissue. As a consequence of an increase in the excitability of neurons in the central nervous system (central sensitisation), inflammatory pain like the neuropathic pain is also associated with exaggerated response to normal sensory inputs (allodynia). These phenomena are evoked within a matter of minutes and outlast the precipitating tissue injury for several hours or days. However, the changes are generally reversible and normal sensitivity of the system is eventually restored. Inflammatory pain, even in the absence of any peripheral nerve damage, drives the acute postoperative pain until the surgical wound has healed. However, if the stimulus persists in the form of a mesh or clips, as is the case in laparoscopic cholecystectomy, the inflammatory pain is maintained.²

Neuropathic component of the pain arises after injury to nerves or to sensory transmitting systems in the spinal cord and brain. Nerve injury sets up reactive changes that spread centrally and produce abnormal neural function. Damage to the afferent transmission system causes partial or complete loss of sensory inputs. Neuropathic component of pain is characterised by the combination of sensory loss with paradoxical hypersensitivity. In addition to sensory loss, which results from nerve damage, some patients develop a "positive phenomena" which includes spontaneous pain, hypersensitivity, allodynia and hyperalgesia (exaggerated or amplified response to a noxious stimulus) and sympathetically mediated pain which arises due to expression of α_2 receptors on the regenerating neurons which causes pain on stimulation of sympathetic nervous system.³

Thus, both inflammatory and neuropathic pain mechanisms share the property of peripheral and central sensitization leading to development of hyperalgesia and allodynia. But the changes associated with inflammatory pain are usually reversible whereas those due to nerve injury are more prolonged or irreversible.

In the immediate postoperative period, there is direct activation of nociceptors, inflammatory mediators and in some cases injury to nerves but the clinical picture is dominated by spontaneous resting pain referred to the site of surgery and the surrounding tissues. If nerves are injured during surgery, a neuropathic component of the pain might develop immediately and then persists in the absence of any peripheral noxious stimulus or ongoing peripheral inflammation. This pain, once established, is likely to be resistant to non-steroidal anti-inflammatory drugs (NSAIDs) and opioids.² Use of NSAIDs (whether cyclo-oxygenase non-selective or cyclo-oxygenase-2

selective) and opioids have well known limitations in the post-operative setting and this opens up an opportunity for other non-conventional drugs (like anti-epileptics) to be tried in such situations.²

Gabapentin use in various animal and human studies has shown promising results in post-operative pain. Pre-emptive analgesia with gabapentin has shown to prevent/decrease the development of hyperalgesia and tactile allodynia in an animal (rat) model of post-operative pain. Gabapentin provided pain relief for a period of 2 days if it was given before the injury and only for 3 hours when it was administered after the injury.⁴ Clinical studies using gabapentin as pre-emptive analgesic in different kinds of surgeries have shown efficacy in different doses and dosing schedules.

The site of action of gabapentin was considered to be central but in an animal study in which gabapentin was administered locally into the carrageenan/kaolin inflamed rat knee, showed dose dependent reduction in firing rates on applying torque to the knee, and demonstrated that gabapentin reduced sensitivity of the primary nerve fibres.⁴ Another study done on rats suggested that gabapentin presynaptically inhibited glutaminergic synaptic transmission in the superficial lamina. It also concluded that the antinociceptive effect of gabapentin may involve inhibition of release of excitatory amino acids from presynaptic terminals.⁵ In another study, gabapentin when administered by intra-planter injection, showed a reduction in flinching, lifting/licking behaviour during phase 2 of formalin induced pain in the lower doses. However, at a higher dose, it also blocked the phase 1 response suggesting a peripheral site of action.⁶

The most accepted mechanism for gabapentin is its binding to $\alpha_2\delta_1$ subunit of voltage gated calcium channels (VGCC). Leading to a reduction in neurotransmitter release and hence decreased neuronal excitability. Recent studies have demonstrated that the descending noradrenergic system and spinal α_2 adrenergic receptors and an intact spinobulbospinal circuit is crucial element, which influences analgesic effect of gabapentin in addition to $\alpha_2\delta_1$ interaction.⁷

More recently gabapentin use has been extended to management of more acute conditions, particularly in the perioperative period. A dose escalation study of gabapentin, used for pain relief in patients undergoing lumbar discectomy, found that at least 600 mg orally, given 2 hrs prior to operation, was the optimal dose for postoperative pain relief. The authors also concluded that increasing the dose from 600 mg to 1200 mg did not result in further fall in pain score.⁸ At the same time some studies did not find any benefit in using gabapentin in pain. A study done in patients undergoing laparoscopic cholecystectomy did not find 300 mg gabapentin given 1 hour before surgery to be useful in reducing pain.⁹ In another study done in patients undergoing breast surgery for cancer found that gabapentin 1200 mg/day in three

divided doses did not reduce pain scores and was not effective in reducing analgesic requirement in first 24 hours after surgery.¹⁰ Thus, the use of gabapentin for acute post-operative pain is still controversial and needs further evaluation. These contradicting results, prompted us to plan this study.

METHODS

This study was carried out jointly, in the departments of pharmacology, surgery and anesthesiology, Himalayan Institute of Medical Sciences, Dehradun. Approval from institutional ethics committee was obtained to conduct the study. Prior to initiation of study, written informed consent from the patient/legal guardian of the patient was obtained after full explanation of elements contained in the research protocol. A total of 40 patients were enrolled in the study.

Study design

It was a “randomized double-blind placebo- controlled parallel group study” done in patients undergoing elective laparoscopic cholecystectomy under general anesthesia with standardized premedication and anaesthetics.

Patients between 18-60 years of age and having American Society of Anesthesiologist (ASA) physical status I and II,¹¹ who were diagnosed on ultrasound of having uncomplicated gall stones were included in the study.

Patients with history of smoking, alcohol or drug abuse, bleeding diathesis, analgesic or antacid use in recent past, impaired renal or hepatic function, motion sickness or taking anti-depressants or calcium channel blockers were excluded from the study. Pregnant and lactating females were also excluded.

Patients of both sexes, fulfilling the criteria given above, having normal investigations and scheduled for surgery were randomized into two groups: Group-I (The gabapentin group) and Group-II (The placebo group) with 20 patients in each group.

Randomization was done using table of random numbers with odd numbers assigned to gabapentin group and even numbers assigned to placebo group. The randomization schedule was maintained by a person not directly involved in observation of patients. The treatment was blinded by the use of placebo capsules which were identical to the gabapentin capsules in color, shape, size and weight. Neither the patient nor the prescriber knew about the treatment given. The patients of group I were administered gabapentin 600 mg orally 2 hrs before surgery and 12 hrs after the first dose i.e a total dose of 1200 mg on the day of surgery. The patients in group II were administered a matching placebo orally 2 hrs before surgery and 12 hrs after the first dose. The treatment was double blinded. Postoperatively, patients in both the

groups were given diclofenac sodium, 75 mg, intramuscularly, twice a day for pain relief and additional dose was given on demand.

Postoperative pain at 1, 4, 8, 12 and 24 hours post-surgery and at the time of discharge was assessed using the 100mm visual analogue scale (VAS).^{12,13} Analgesic requirement in 24 hours postoperative period was recorded and compared. Adverse events occurring during study were recorded. Secondly, time taken for bowel sounds to return, time taken to become ambulatory and duration of hospital stay were also recorded and compared in both the groups.

Statistical analysis

Statistical analysis of pain score was carried out using Mann Whitney test. The incidence of adverse effects observed was compared between the gabapentin and placebo groups using chi-square test. P value ≤ 0.05 was taken as significant. Analgesic consumption, between the two groups, in 24-hour post-operative period was compared using unpaired t-test. All results were expressed as Mean \pm S.E.

RESULTS

Forty patients completed the study and the data from all forty patients was analyzed. Both the groups were comparable in demographic profile i.e. age, sex, weight, height, and physical status (Table 1).

Table: 1 Demographic profile of patients in gabapentin and placebo groups.

Parameter	Gabapentin	Placebo
Age (years)	44.8 \pm 2.7	41 \pm 2.4
Male: Female ratio	7:13	1:2
Height (cm)	158.1 \pm 1.8	159.7 \pm 2.2
Weight (kg)	65.4 \pm 2.2	66.4 \pm 2.04
ASA Grade		
I	18(90%)	17(85%)
II	2(10%)	3(15%)

Pain scores at 1, 4, 8, 12 and 24 hours post operatively, and at the time of discharge in the gabapentin group were 28.1 \pm 6.28, 19.55 \pm 3.1, 16.6 \pm 1.98, 11.8 \pm 1.83, 7.75 \pm 1.17 and 7.75 \pm 1.17 mm respectively and the respective readings in the placebo group were 53.4 \pm 5.15, 31.3 \pm 2.79, 25.7 \pm 3.01, 19.3 \pm 2.18, 12 \pm 1.29 and 12 \pm 5.8 mm. The p values were 0.005, 0.008, 0.015, 0.012, 0.019 and 0.019 for inter group comparison between gabapentin and the placebo groups at corresponding time intervals respectively (Table 2). Pain scores at 1, 4, 8, 12 and 24 hours and at discharge were significantly lower in the gabapentin group as compared to the placebo group. Mean analgesic (diclofenac sodium, 75mg, i.m) consumption by the patients in group I (gabapentin) was 165 \pm 6.88 mg and in group II was 195 \pm 11.41 mg in the first 24 hours of post-operative period. The difference in

the analgesic consumption between the two groups was statistically significant (p value=0.03) (Table 3).

Table 2: Pain score (Mean±S.E) in group I (gabapentin) and group II (placebo).

Group	1Hour	4Hours	8Hours	12Hours	24Hours	Discharge
I (n=20)	28.1±6.28**	19.55±3.1**	16.6±1.98*	11.8± 1.83*	7.75± 1.17*	7.75± 1.17*
II (n=20)	53.4± 5.15	31.3±2.79	25.7±3.01	19.3± 2.18	12± 1.29	12± 5.8

* P < 0.05; ** P < 0.01; versus corresponding values in placebo group.

Table 3: Analgesic consumption (Mean±S.E) in 24-hour postoperative period in group I (gabapentin) and group II (placebo).

Group	Analgesic consumed (diclofenac sodium, i.m) (mg)
I (gabapentin) (n=20)	165±6.88*
II (placebo) (n=20)	195±11.42

* P < 0.05 versus corresponding values in placebo group

Adverse events in gabapentin and placebo groups were assessed over a period of 24 hours. The observed adverse effects were mild and showed comparable incidence between the two groups (Table 4). On follow up, 6 Patients in the gabapentin group and 8 in the placebo group reported itching at the site of surgery. 5 patients in the gabapentin and 7 in the placebo group reported dullness in the right hypochondrium. The difference in incidence of the complaints between the groups was not statistically significant (Table 5).

Table 4: Incidence of adverse drug events occurring during 24-hour post-operative period in group I (gabapentin) and group II (placebo).

Group	Adverse drug events				
	Pruritus	Dryness of mouth	Weakness	Dyspepsia	Sedation
I (Gabapentin) (n=20)	1	2	3	2	4
II (Placebo) (n=20)	1	1	1	1	3

Table 5: Incidence of adverse drug events on follow up in group I (gabapentin) and group II (placebo).

Group	Itching at the operation site	Right hypochondrium dullness after meals
I (gabapentin) (n=20)	6	5
II (placebo) (n=20)	8	7

Time taken for return of bowel sounds, to become ambulatory and duration of hospital stay between the two groups did not show any statistical significant difference.

DISCUSSION

In the present study gabapentin was effective in reducing post-operative pain score and analgesic consumption up to a period of 24 hours post-operatively. The readings were highly significant (p value <0.01) at 1 and 4 hours post-operatively (that is 3-6 hours of oral intake of gabapentin). The inter-group difference in pain scores at the time of discharge remained significant and the readings were similar to the 24-hour readings as most of the patients were discharged after an average of 26 to 29 hours after surgery in both the groups. There was marked

reduction in pain score up to 8 hours after surgery i.e up to 10 hours after the oral intake of 600 mg gabapentin. This finding is in conformity with an earlier study done in patients undergoing laparoscopic cholecystectomy who received a single dose of 300 mg gabapentin, 2 hours before surgery. In the above mentioned study gabapentin 300 mg, given 2 hours before surgery was found to be better than tramadol (100mg, 2 hours before surgery), signifying strong postoperative analgesic effect of gabapentin.¹⁴ The average maximum pain score recorded during 0-6 hours in the above said study was similar to that recorded in the present study in both gabapentin as well as placebo group but the results in the present study were more pronounced than the above said study probably due to the higher dose used in the present study(600mg). Gabapentin use in above study reduced fentanyl consumption in the patients similar to the present study where analgesic (diclofenac sodium, i.m) consumption was reduced during the first 24 hours postoperatively. In another study, use of 600 mg gabapentin, 2 hours before laparoscopic cholecystectomy showed a significant reduction in fentanyl consumption.¹⁵ In the present study fentanyl was not administered through patient controlled analgesia (PCA) because of the higher cost of fentanyl and non-availability of PCA in the present set up. In another study with gabapentin 300 mg, given 1 hour before laparoscopic cholecystectomy did not

show any benefit in reduction of pain within 6 hours postoperatively.⁹ This may be due to a lower dose of gabapentin used. Gabapentin in the above cited study was given 1 hour before surgery and the peak concentration is achieved in 2-3 hours; more over the pain scores in their study were recorded for 6 hours.

The use of gabapentin for relief of pain has also been extended to other surgical procedures and has been found to be useful. In patients undergoing abdominal hysterectomy, single dose of gabapentin 1200 mg, given 1 hour before surgery produced marked analgesic effect and a reduction in tramadol use in 24 hour postoperative period.¹⁶ In a comparative study of rofecoxib (50mg), gabapentin (1200mg), combination (rofecoxib 50mg+ gabapentin 1200mg) and a placebo, a reduction in fentanyl and acetaminophen consumption was found in the gabapentin group as compared to a placebo.¹⁷ From this study it was concluded that gabapentin 1200 mg/day was similar to rofecoxib (50mg/day) in improving pain control and decreasing opioid consumption.¹⁷ Remarkable effects on improvement of pain were obtained in another study done in patients undergoing thyroid surgery with the same dose of gabapentin.¹⁸ Although 1200 mg of gabapentin was used in other surgeries, the present surgery used 600 mg, 2 hours before surgery based on the results of a dose escalation study (300 to 1200mg) done in patients undergoing lumbar discectomy where the authors have concluded that 600 mg of gabapentin given 2 hours before surgery is the optimal dose in that surgery.⁸ All the above studies have found single dose of gabapentin given pre-operatively to be effective in controlling post-operative pain up to a period of 24 hours, irrespective of its half-life which is approximately 8 hours. This finding has also been substantiated in the animal studies where gabapentin given before the injury, prevented development of hyperalgesia and tactile allodynia in a rat model of post-operative pain for a period of 2 days. Whereas gabapentin when given after insult showed analgesic effect only for 3 hours.¹⁹ From the above studies it is evident that analgesic effect of gabapentin is at least equivalent to or better than cyclooxygenase-2 inhibitors as well as tramadol or fentanyl. Gabapentin use prior to surgery as pre-emptive analgesic, is better than using gabapentin during or after surgery.

In the present study, no serious side effects were found with gabapentin use. Sedation was the most common adverse effect and the others being weakness, dyspepsia, dryness of mouth and pruritus in decreasing order of their occurrence. All these adverse effects were mild and were comparable to that of placebo group as well as to those reported in other studies.^{14-16,20} These adverse effects are well documented in literature to occur at this dose.²¹ Itching, observed on follow up may be a sign of healing and dullness in right hypochondrium is a well-known complication of gall bladder surgery. Gabapentin is increasingly being used in peri-operative setting for control of pressor response to endotracheal intubation,

post-operative nausea vomiting apart from pain. So, gabapentin makes a strong case for itself to be used as pre-emptive analgesic with added benefits.^{22,23}

CONCLUSION

To conclude, gabapentin in the doses used was found to reduce postoperative pain up to 24 hours in patients undergoing elective laparoscopic cholecystectomy with standardized pre anaesthetic and anaesthetic medication. Moreover, gabapentin was found to be safe and no serious adverse events were reported in the present study.

The present study has a few limitations. Since it was a time bound study the number of patients enrolled was limited. A study on large number of patients undergoing different kinds of surgical procedures of varying duration would better bring out the actual role of gabapentin in postoperative setting and be able to bring out significant difference in secondary outcomes i.e. time taken for return of bowel sounds, to become ambulatory and duration of hospital stay. The present study did not use fentanyl with or without PCA as done by the other studies. Keeping these limitations in view caution is to be exercised while interpreting the results of this study.

ACKNOWLEDGMENTS

Authors would like to thank the participation and cooperation of the patients enrolled for the study.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Bhandari V, Sharma G, Dhasmana DC, Gupta M, Sharma JP, Chaturvedi A. Gabapentin a pre-emptive analgesic in post-operative pain: a randomised double blind placebo controlled study. *Int J Basic Clin Pharmacol* 2017;6:1317-22.