THE EFFECT OF SINGLE DOSE ORAL GABAPENTIN AS PREEMPTIVE ANALGESIA FOR POSTOPERATIVE PAIN FOR ORTHOPEDIC SURGERIES DONE UNDER SPINAL ANAESTHESIA

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ABSTRACT

BACKGROUND

The concept of preemptive analgesia, which has been recently introduced is nothing but administering an analgesic drug prior to a noxious stimulus such as surgical skin incision. This analgesic administration is supposed to decrease surgical stress response as well as postoperative analgesic requirements. Gabapentin has demonstrated its utility in the treatment of chronic neuropathic pain. Gabapentin has been reported to possess antihyperalgesic and antiallodynia properties. Recently several reports have indicated that gabapentin may have a place in the treatment of postoperative pain. It has been shown in studies that there is lower pain score and significantly less requirements of opioids and related side effects postoperatively, when gabapentin is used as preemptive analgesia.

AIMS AND OBJECTIVES

This study is for comparison of preemptive analgesic efficacy of Gabapentin with placebo in post-operative period and to study any side effects associated with the drug.

MATERIALS AND METHODS

A prospective randomized study was carried out in the Department of Anaesthesia at Rajarajeswari Medical College and Hospital. Sixty normotensive patients of ASA grade 1 and ASA grade 2, in age group of 25 years to 65 years, posted for orthopedic surgeries under spinal anesthesia were selected for study. Patients were randomly divided into two groups of 30 each. Patients belonging to Group "A" - study group received oral Gabapentin 300mg 2 hours prior to surgery and patients in Group "B" - control group received Placebo 2 hours prior to surgery.

STATISTICAL ANALYSIS

Statistical analysis was done using student 't' test B, Chi square test, Fischer exact test. Statistical software used is SPSS 16. This was used for analysis and data. Microsoft Excel was used to generate graphs and tables. A value of $P<0.05$ was considered significant.

RESULTS

Based on our present comparative study, single oral dose of gabapentin given 2hrs before surgery provides better pain control as compared to the placebo.

CONCLUSION

We conclude that single oral dose of gabapentin given 2hrs before surgery provides better pain control as compared to the placebo.

KEYWORDS

Pain, Gabapentin, Spinal Anesthesia, Orthopedic Surgeries.

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INTRODUCTION

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or describe in terms of such damage. This definition of pain according to "International Association for Study of Pain" (IASP) by itself speaks so much about pain and how important it is to relieve pain of a person. Anaesthesia as a subject by itself originated in an endeavour to offer pain relief to the patient during surgical procedures.

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Over a period of years as the field of anaesthesia developed, efforts went on to invent better and better drugs to offer analgesia during and after surgery. Among the first to be introduced were opioids like morphine and local anaesthetics like cocaine. Later on many drugs were added to this armamentarium to offer good analgesia to the patients.

In the earlier periods, analgesia was restricted to surgical and postoperative period. However, this was associated with lots of morbidity to the patient in terms of surgical stress and increased requirements for analgesics in the postoperative period, which were associated with various adverse effects.

The concept of preemptive analgesia, which has been recently introduced is nothing but administering an analgesic drug prior to a noxious stimulus such as surgical skin incision. This analgesic administration is supposed to decrease surgical stress response as well as postoperative analgesic requirements.[1]

Various drugs like opioids, NSAIDs, antiepileptic drugs are being used for purpose of preemptive analgesia. Opioids act at peripheral, posterior horn of spinal cord as well as CNS

level to offer preemptive analgesia. NSAIDs preferentially act at peripheral site to offer preemptive analgesia. Antiepileptic drugs act at CNS level to offer preemptive analgesia.

Gabapentin is a structural analogue of gamma-aminobutyric acid, which was introduced in 1994 as an antiepileptic drug, particularly for partial seizures. Gabapentin has demonstrated its utility in the treatment of chronic neuropathic pain. Gabapentin has been reported to possess antihyperalgesic and antiallodynia properties.[2,3,4] Recently, several reports have indicated that gabapentin may have a place in the treatment of postoperative pain. It has been shown in studies that there is lower pain score and significantly less requirements of opioids and related side effects postoperatively when gabapentin is used as preemptive analgesia.[5,6]

The aim of the present study is to determine the efficacy of gabapentin in reducing acute postoperative pain in patients undergoing orthopedic surgeries under the title of "The effect of single dose oral gabapentin as preemptive analgesia for postoperative pain for orthopedic surgeries done under spinal anaesthesia."

MATERIALS AND METHODS

After approval from the Institutional Ethical Committee and a written informed consent, this comparative study was carried out. The study conducted after informed written consent is taken from patients in both the groups. The study design is randomized and double blind. Patients randomly divided into 2 equal groups of 30 each. All study medications given orally with sips of water 2 hour preoperatively by a staff nurse who is not involved in the study.

Patients in study Group-A (Gabapentin) were received Cap. Gabapentin 300mg; whereas in study Group-B (Placebo) were received matching placebo. All patients were premedicated with ranitidine 150mg and alprazolam 0.5mg 12hr before surgery.

Routine monitoring with pulse oximetry, NIBP, ECG, temperature and urine output with an indwelling catheter were initiated in the operation theatre.

All patients were preloaded with 10ml/kg of lactated Ringers' solution and subarachanoid block performed at interspace L2-L3 or L3-L4 and 3.5ml of hyperbaric solution of 0.5% bupivaciane were given in the subarachnoid space.

After confirmation of the successful blockade and proper height of anaesthesia, all patients were sedated with IV midazolam 0.03mg/kg. After surgery patients shifted to recovery room and were given IV tramadol 1.5mg/kg as rescue analgesia for pain relief on demand.

Pain was assessed by VAS and if VAS >4 rescue analgesic were given. VAS scores was assessed by an independent person, who was not aware of the group allocation on a scale of 0-10 (0 mean no pain, 10 equals to worst imaginable pain) after 2, 4, 8, 12 and 24hrs after the surgery at the same time patients were asked for any complication suffered by them.

Total number of rescue analgesics received by each patient was noted. The mean ± SD from maximum pain scores for all patients in both groups at time intervals of 0–2, 2-4, 4-8, 8-12 and 12–24 hr was calculated.

A value of $P<0.05$ was considered significant. The total dose of Tramadol required as rescue analgesic in each group (mean ± SD) in 24 hr were compared using an unpaired 't' test. The data were analysed with the statistical software package SPSS 16.

STATISTICAL ANALYSIS: Study is randomized and double blinded statistical analysis was done using student 't' test B, Chi square test, Fischer exact test. Statistical software used is SPSS 16. This was used for analysis of data. Microsoft Excel was used to generate graphs and tables. A value of $P<0.05$ was considered significant.

Variable	Group-G (Gabapentin) (N=30)	Group-P (Placebo) (N=30)	P Value
Age(years)	41.73 ± 6.49 (39.31- 44.16)	43.13 ± 4.95 (41.28 - 44.98)	0.352
Weight(kg)	56.30 ± 4.22 (54.72-57.88)	56.83 ± 4.7 (55.08 - 58.59)	0.646
Duration of surgery(min)	90 ± 22.89 (81.45-98.55)	87.67 ± 18.51 (80.75 - 94.58)	0.666
ASA grade 1	26 (86.67%)	28 (93.33%)	0.566
ASA grade 2	4 (13.33%)	2 (6.67%)	
Total analgesic consumption	120 ± 43.43 (103.78-136.22)	255.17 ± 50.76 (236.21-274.12)	0.0001*

Table 1: Demographic Characteristics and Perioperative Data

- Values are shown as number of patients or mean ± SD. Values in brackets indicates 95% confidence interval. No significant differences were found between the groups except total analgesic consumption (P=0.0001) by using unpaired 't' test.
- Using Chi square, there was no statistical significant difference between gabapentin and placebo based on ASA grade 1 and 2.

Variable	Group-G (Gabapentin) (N=30)	Group-P (Placebo) (N=30)	P Value
0 min	80.47 ± 10.06	81.03 ± 9.87	0.826
30 min	79.03 ± 8.36	78.80 ± 8.49	0.915
60 min	79.37 ±8.76	81.67 ±9.34	0.329
120 min	81.27 ±8.42	83.90 ± 8.57	0.235

Table 2: Heart Rate Intraoperative

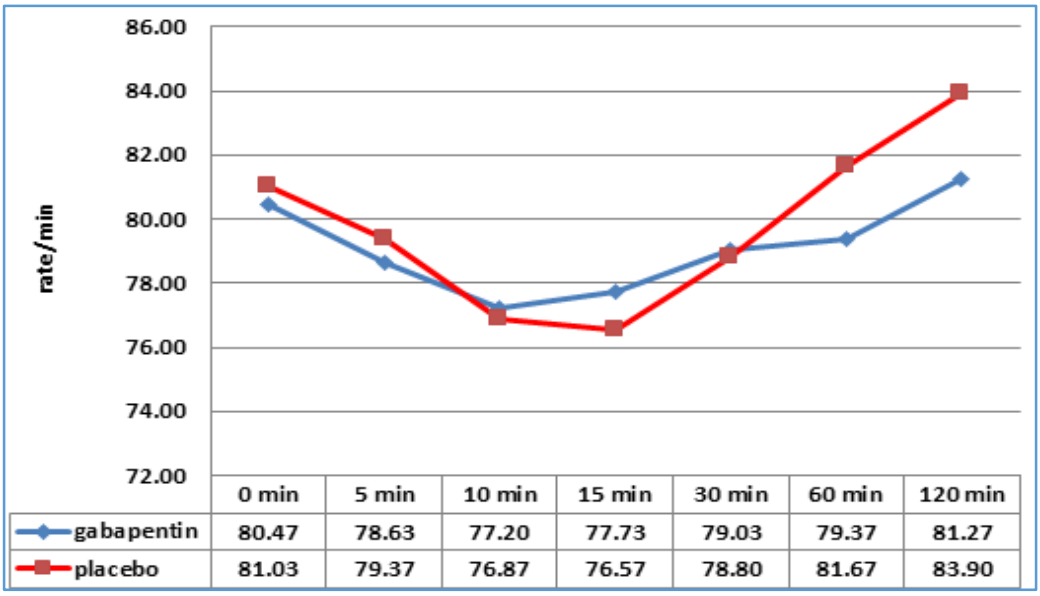

Fig. 1: Effect on Heart Rate

- No significant differences were found between the groups in heart rate intraoperatively.

Variable	Group-G (Gabapentin) (N=30)	Group-P (placebo) (N=30)	P Value
0 min	120.27 ± 10.70	122.43 ±10.59	0.434
30 min	111.73 ± 9.98	111.10 ± 12.39	0.828
60 min	116.23 ± 11.03	117.20 ± 10.04	0.724
120 min	119.77 ± 10.93	120.73 ± 9.27	0.713

Table 3: Systolic BP Intraoperative

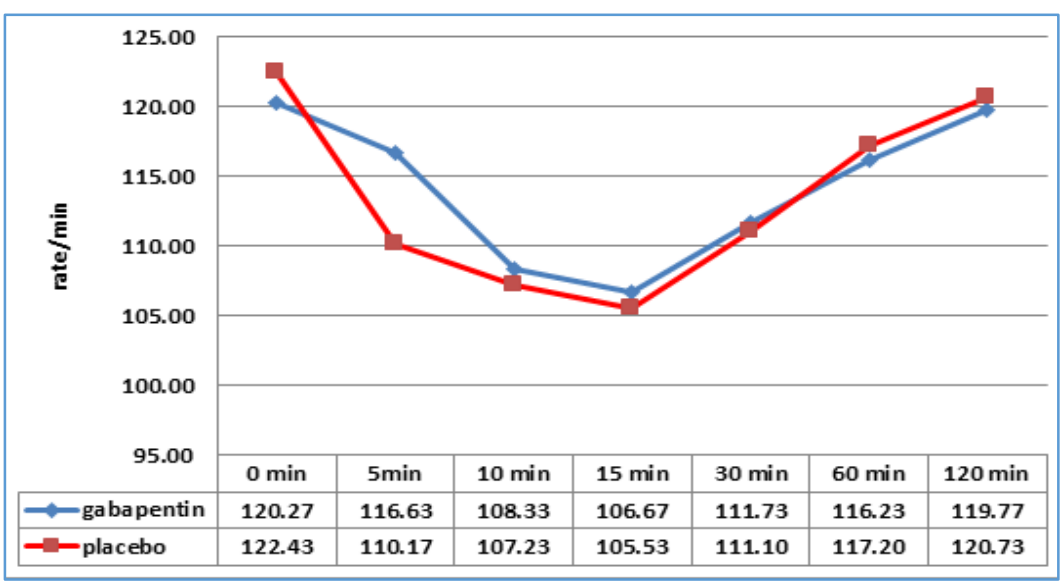

Fig. 2: Effect of Systolic BP

- No significant differences were found between the groups in systolic BP intraoperatively.

Variable	Group-G (Gabapentin) (N=30)	Group-P (Placebo) (N=30)	P Value
0 min	73.57 ± 7.46	75.93 ± 7.61	0.229
30 min	68.93 ± 8.36	71.23 ± 8.10	0.283
60 min	71.50 ± 6.97	74.23 ± 7.58	0.151
120 min	73.43 ± 7.47	75.53 ± 7.66	0.287

Table 4: Diastolic BP Intraoperative

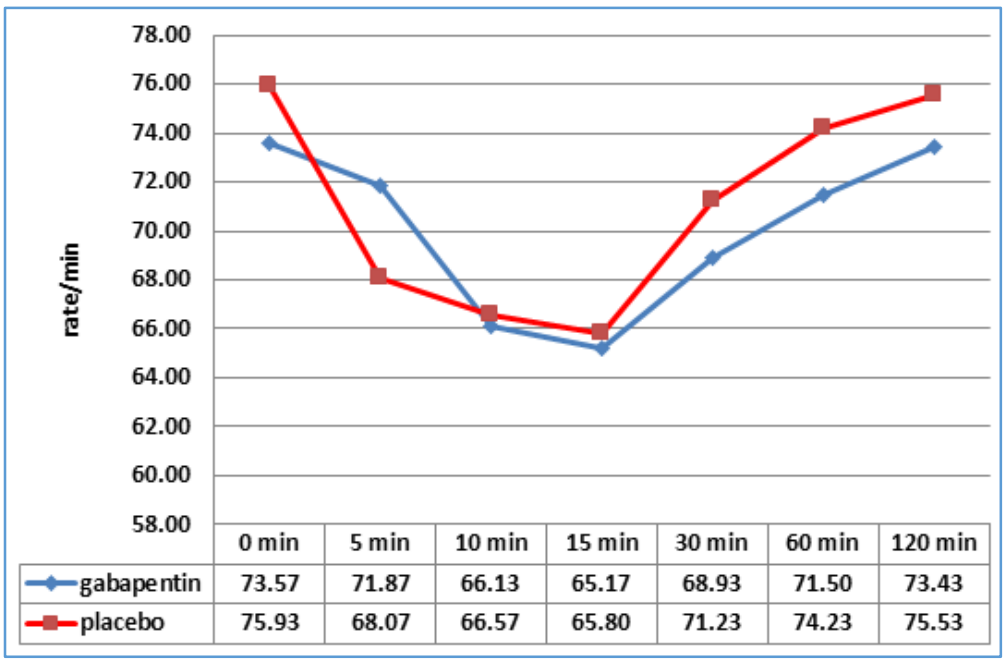

Fig. 3: Effect on Diastolic BP

- No significant differences were found between the groups in diastolic BP intraoperatively.

Variable	Group-G (Gabapentin) (N=30)	Group-P (Placebo) (N=30)	P Value
0 min	14.63 ± 1.19	15.10 ± 1.58	0.262
30 min	14.00 ±1.08	14.13 ± 1.53	0.698
60 min	14.57 ± 0.94	14.83 ± 1.51	0.414
120 min	14.77 ± 0.82	14.87 ± 1.63	0.765

Table 5: Respiratory Rate Intraoperative

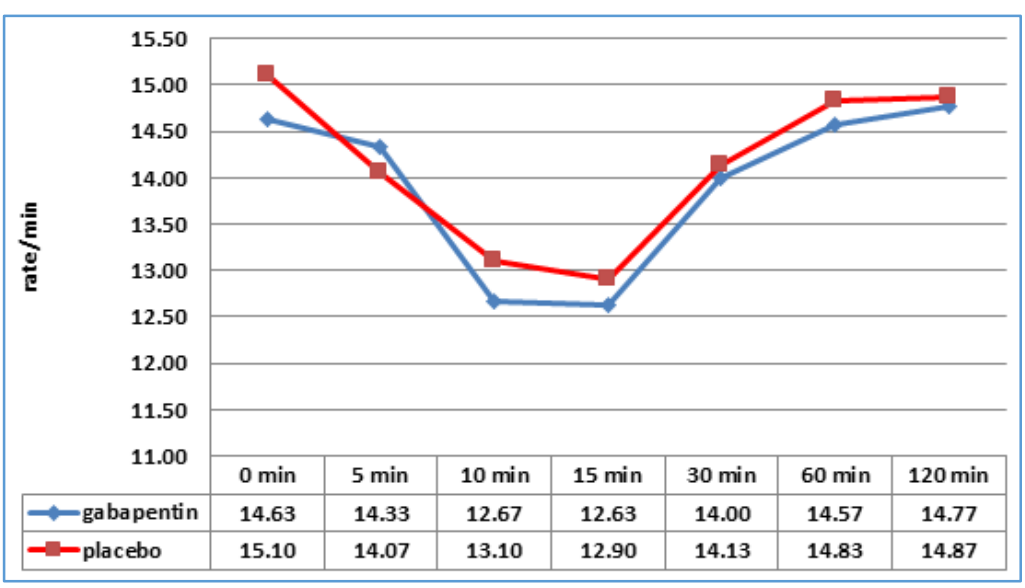

Fig. 4: Effect on Respiratory Rate

- No significant differences were found between the groups in respiratory rate intraoperatively.

Groups	2 hr	4hr	8hr	12hr	24hr
Gabapentin (Gp-G)	0.27 ± 0.67	2.73 ± 1.04	4.13 ± 1.69	3.4 ± 1.81	2.87 ± 1.04
Placebo (Gp-P)	2.47 ± 1.47	4.43± 2.07	3.27 ± 1.48	3.63 ± 1.54	5.03 ± 0.99
P value	0.0001*	0.0001*	0.040*	0.593	0.0001*

Table 6 : Visual Analogue Scores at various time intervals postoperatively (mean±SD) Groups 2hr. 4hr. 8hr. 12hr. 24hr.

- Unpaired 't' test between the two groups at 2, 4, 8 and 24 hours is significant. P value <0.05. VAS score is less in Gabapentin group at 2, 4, 12 and 24 hours compared to placebo. VAS score is higher in 8 hr in Gabapentin group compare to placebo(4.13 Vs 3.27), that is because at this hour most of the cases in Gabapentin group received first rescue analgesic.

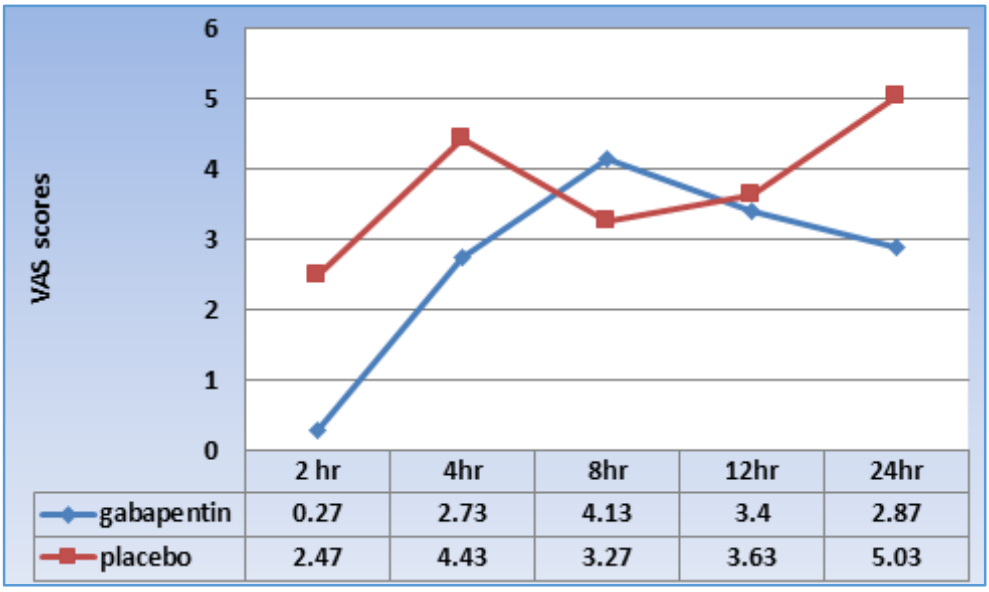

Fig. 5: Visual Analogue Scores at various time intervals postoperatively

- Patients in the Group-G (Gabapentin) had lower VAS scores at 2, 4, 12 and 24hrs than those in the Group-P (Placebo) (Table 7 and Fig 17). At 8hr VAS score in Group-P is less compared to Group-G. Unpaired 't' test between the two groups at 2, 4, 8 and 24 hours is significant. P value <0.05.

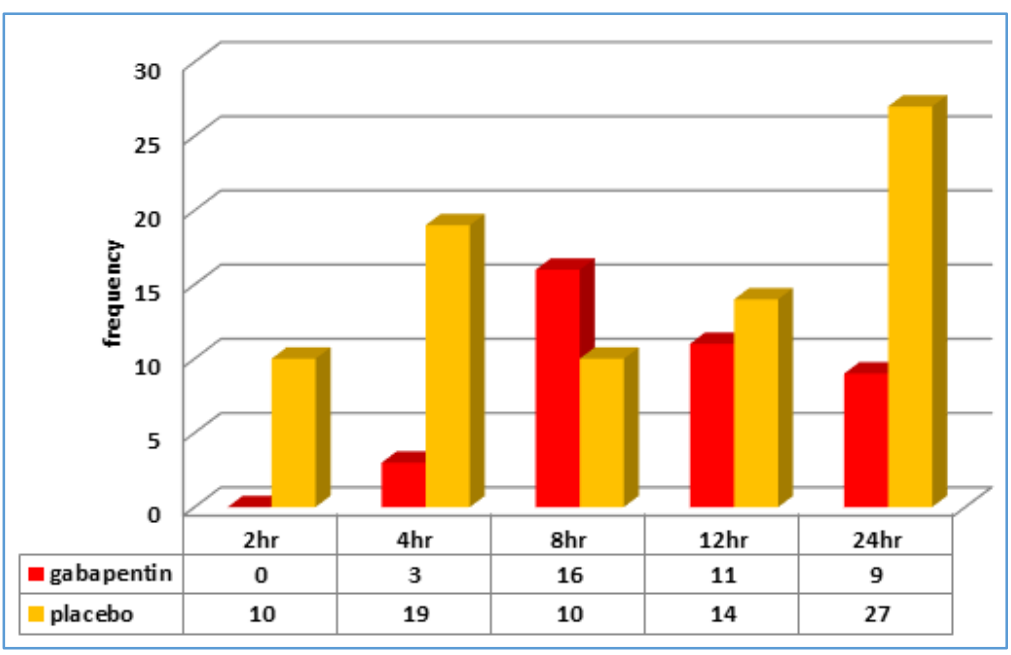

Fig. 6 : No. of patients received Tramadol at 2, 4, 8, 12 & 21 Hour in both groups

- No. of patients received tramadol at various time interval in Gabapentin vs Placebo group at 2 hr (0 vs 10), 4 hr (3 vs 19), 8 hr (16 vs 10), 12 hr (11 vs 14) and 24 hr (9 vs 27).
- From the above figure, it is clear that time to first rescue analgesia was longer in gabapentin group compared to placebo group, i.e., most of the patients in gabapentin group received rescue analgesic at 8 hour post-operatively.

Variable	Group-G (Gabapentin) (N=30)	Group-P (Placebo) (N=30)	P Value
Total Tramadol consumption (in mg)	120 ± 43.43 (103.78-136.22)	255.17 ± 50.76 (236.21-274.12)	0.0001*

Table 7: Total amount of Tramadol consumed

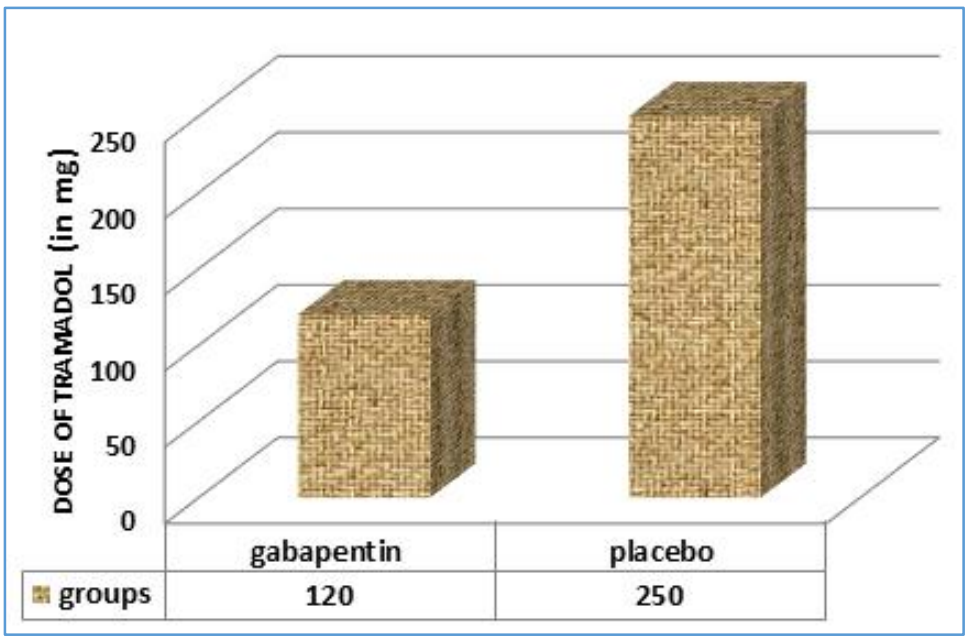

Fig. 7: Total amount of Tramadol consumed

- The total amount of tramadol demanded after surgery in the first 24 hr in the Group-G (Gabapentin) (120 ± 43.43, mean ± SD) was significantly less than in the Group-P (Placebo) (255.17 ± 50.76, mean ± SD).

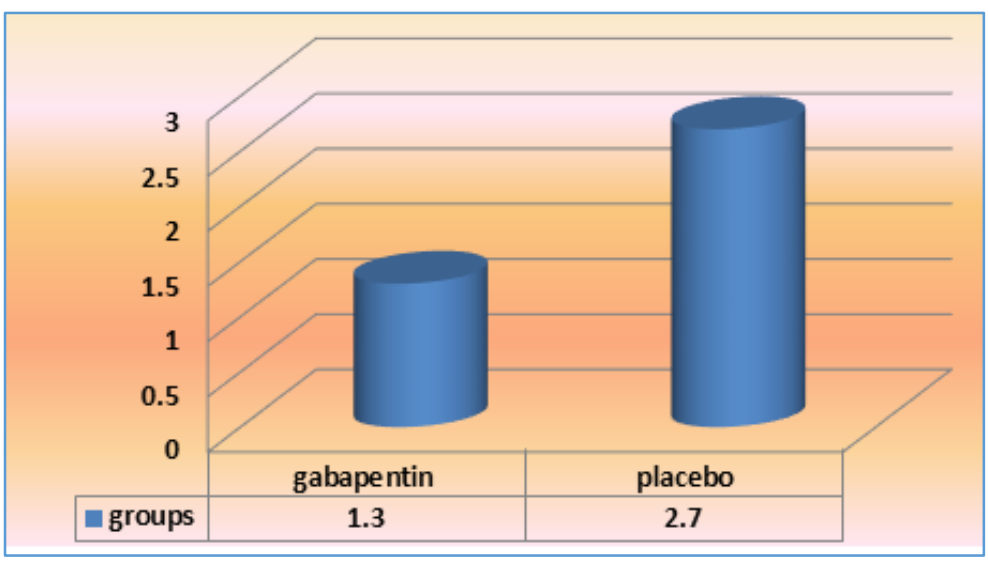

Fig. 8: Mean number of top ups (Tramadol) required

- The mean number of top ups (Tramadol) requirements in Gabapentin group is significantly less compared to Placebo group (1.3 Vs 2.7).

	Gabapentin	Placebo	P VALUE
Nausea	1	15	0.0001 *
Vomiting	0	15	0.0001*
Dizziness	1	0	-
Light headedness	0	0	-

Table 8: Side Effects

*P<0.05 significant

- Nausea and vomiting is significantly less in gabapentin group compared to placebo.
- The incidence of dizziness and light headedness was not significant in both the group.

RESULTS

Based on our present comparative study and after analysing all the graphs and charts the following conclusions were drawn:

1. Single oral dose of gabapentin given 2hrs before surgery provides better pain control as compared to the placebo.
2. The time to first rescue analgesia was longer in gabapentin group compared to placebo group.
3. Gabapentin also reduces the requirement of postoperative analgesia (Tramadol) significantly in patients undergoing orthopaedic surgeries under spinal anesthesia.
4. There were not any significant side effects associated with a single oral dose of gabapentin.
5. Nausea and vomiting is significantly less in gabapentin group compared to placebo.

DISCUSSION

Postoperative analgesia can be provided by pharmacological and non-pharmacological methods.[7] Pharmacological methods commonly employed are:

- Opioids (Morphine, fentanyl, pethidine).
- Local anesthetic agents (Epidural, intrathecal, nerve block).
- Non-steroidal anti-inflammatory agents.

The pharmacological methods employing opioids continue to be a cornerstone in postoperative pain control. Testing new analgesics as well as combinations of analgesics in order to reduce the need for opioids is a key area in acute pain research.

The concept of preemptive analgesia, which has been recently introduced is nothing but administering an analgesic drug prior to a noxious stimulus such as surgical skin incision. This analgesic administration is supposed to decrease surgical stress response as well as postoperative analgesic requirements.[1]

Gabapentin is a structural analogue of gamma-amino butyric acid, which was introduced in 1994 as an antiepileptic drug, particularly for partial seizures. Gabapentin has demonstrated its utility in the treatment of chronic neuropathic pain. Gabapentin does not bind with plasma protein and is not metabolized in humans. Despite its structural similarity to GABA, it does not act via mechanisms related to GABA.[2] Though the exact mechanism of action of gabapentin is not known, the proposed mechanisms are its ability to increase the concentration and the rate of synthesis of GABA in brain, binding with high affinity to α-binding sites in brain tissues that are associated with an auxiliary subunit of voltage-sensitive calcium channels ($\alpha_2\delta$ subunits), reducing the release of monoamine neurotransmitters, inhibiting voltage activated sodium channels and increasing serotonin concentrations in human blood.[2,3,4] Gabapentin has been reported to possess antihyperalgesic and antiallodynia properties.

Recently several reports have indicated that gabapentin may have a place in the treatment of postoperative pain. It has been shown in studies that there is lower pain score and significantly less requirements of opioids and related side effects postoperatively, when gabapentin is used as preemptive analgesia.[5,6] Preincisional analgesia has been shown to be more effective in control of postoperative pain by protecting the central nervous system from deleterious effects of noxious stimuli and resulting allodynia and increased pain. We choose to administer gabapentin before the start of the surgical trauma on the basis of the findings in laboratory animals that pretreatment with gabapentin is substantially more effective and longer-lasting than post-treatment.

Pretreatment with a single dose of gabapentin blocked dose-dependently the development of hyperalgesia (which is NMDA-mediated) and tactile allodynia (Which is AMPA and metabotropic receptor-mediated) for up to two days in a rat model of postoperative pain, while giving gabapentin one hour after intervention reduced symptoms for only 3 hr (Field et al., 1997b).[7,8] This finding was recently confirmed by the Yaksh group, which found that intrathecal gabapentin attenuated the pain behaviour when given prior to the injection of formalin into the rat hind paw, but not when given after formalin (Yoon and Yaksh, 1999b).[9,10] Similar comparative studies on the effect of pre- versus post-trauma given gabapentin in humans (Volunteers or patients) are lacking so far.

There are however some studies on patients, which demonstrate that pretreatment with gabapentin is effective in reducing neuronal sensitisation as expressed in reduced primary mechanical allodynia in acute inflammation and in reducing the need for postoperative pain treatment with morphine after mastectomy (Dirks et al. 2002).[11]

Among the most frequent complaints of postoperative pain treatment is opioid-induced nausea and vomiting. Therefore, one of the main reasons for the search for new agents or adjuvants for postoperative pain treatment is to avoid or minimise the typical side effects of opioids by reducing the overall demand for such additional treatment. Though we did not power our investigation for a possible reduction of postoperatively opioid-induced side effects, there was a clear trend ($P<0.05$) in lower nausea scores during the 24 postoperative hours. This result is underlined by a significantly lower cumulative incidence of postoperative vomiting/retching in the gabapentin-treated group compared to control group from 24 hr postoperatively onwards ($P<0.001$).

The underlying mechanisms of our finding might be two-fold: (a) By reducing the cumulative amount of tramadol doses, the nausea inducing effect of our pain treatment was reduced; and (b) Gabapentin might exhibit a preventive anti-emetic effect as demonstrated in a recent open-label, not placebo-controlled study on chemotherapy induced nausea in patients with breast cancer (Guttuso et al. 2003).[12] One supposed mechanism of action of gabapentin is via the modulation of neurokinin primed NMDA receptor (Nicholson, 2000).[13] Tachykinins like substance P trigger the release of intracellular Ca^{2+}, which leads to an unplugging of the magnesium ion on the NMDA receptor allowing Ca^{2+} influx into the cell resulting in an activation of the NMDA receptor.

Gabapentin has a high affinity to the $\alpha_2\delta$-1 subunit of voltage-dependent Ca^{2+} channels, whose expression is increased in the spinal cord and dorsal root ganglia after a peripheral nerve trauma (Luo et al. 2001).[14] resulting in blocking of these channels. Tachykinins like substance P are emetogenic when applied into cells of the brain stem (Saria 1999).[15] By the above-mentioned mechanism gabapentin blocks the neurokinin-1 receptor, through which the tachykinins exhibit their actions. This action might inhibit the development of neuronal sensitisation and also of tachykinin-induced nausea. The anti-emetic effect of gabapentin, however, has to be verified in further studies.

In present study, we have demonstrated that 300mg of gabapentin taken 2hrs before surgery results in significant reduction in pain and requirement of the tramadol in patients undergoing orthopaedic surgeries done under spinal anesthesia and that gabapentin was not associated with more side effects when compared with placebo. Pain scores at rest were significantly higher in the control group compared to the gabapentin-treated patients during the 24 postoperative hours. Additionally, pretreatment with gabapentin reduced the incidence and degree of postoperative nausea and vomiting possibly induced by the side effects of postoperative pain treatment with tramadol compared to the active placebo group. No preoperative differences between the two groups were encountered with respect to side effects of the premedication.

Although postoperative analgesic consumption is primary outcome in many studies, time to first rescue analgesia is another useful outcome. We measured the time to first rescue analgesia, which was longer in gabapentin group compared to placebo group.

CONCLUSION

Hence from our clinical comparative study we conclude that single oral dose of gabapentin given 2hrs before surgery provides better pain control as compared to the placebo. VAS score was significantly lower in gabapentin group at 2, 4, 12, and 24 hrs compared to placebo group. The time to first rescue analgesia was longer in gabapentin group compared to

placebo group. Gabapentin also reduces the requirement of tramadol consumption (120mg vs 250mg) significantly in patients undergoing orthopaedic surgeries under spinal anesthesia without any side effects.

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