ORIGINAL ARTICLE

Effect of gabapentin on opioid requirements in patients undergoing total abdominal hysterectomy

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ABSTRACT

Introduction: Gabapentin possesses antihyperalgesic and antiallodynia properties and has a definite role in neuropathic pain relief. In this study, we tried to determine whether preemptive use of gabapentin can result in reduction of intra and postoperative pain and narcotic (nalbuphine) requirements in patients undergoing total abdominal hysterectomy (TAH).

Methods: In this randomized, double-blind controlled trial, 35 patients (study group) undergoing TAH received gabapentin 1200 mg and 35 patients (control group) received placebo orally two hours before induction of anesthesia. Intra-operatively, an increase in blood pressure and heart rate were taken as an indicator of pain during surgery and nalbuphine at 0.05-mg/kg body weight was administered as a rescue analgesia. Postoperatively, for the initial 24 hours, pain was assessed on a Visual Analogue Scale (VAS score 1-10, score 1-3 considered mild pain, 4-7 moderate pain & 8-10 as severe pain). If score was more than 3 a top up dose of nalbuphine 0.05 mg/kg was administered intravenously. Total nalbuphine consumption during the intraoperative period and initial 24 hours postoperative period was recorded for each patient.

Results: Thirty four patients in the gabapentin group (study group) and 35 patients in the Placebo group (control group) completed the study. Overall, pain scores in the gabapentin group were significantly lower as compared to the Placebo group. The total nalbuphine consumption was 13.2 ± 4.7 mg (mean ± SD) in the gabapentin group versus 24.3 ± 9.2 mg in the Placebo group ($P < 0.001$).

Conclusions: Preemptive use of gabapentin resulted in reduction of intra and postoperative narcotic (Nalbuphine) requirements in patients undergoing total abdominal hysterectomy.

Key Words: Gabapentin; Nalbuphine; Pain score; Total abdominal hysterectomy; Postoperative pain

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INTRODUCTION

Pain is always disturbing to the individuals and is accompanied by strong psychological and emotional components. Postoperative pain, a type of acute pain, is one of the disturbing conditions in surgical patients that almost always challenges the skills of anesthetist in managing such patients. A multimodal approach has been used and a variety of drugs have been tried to treat it. However, the basic drugs used for postoperative pain relief are still paracetamol, NSAIDS, local anesthetics and opioids. Most of these drugs have side effects that limit their use in clinical practice. Recent understanding of acute pain mechanisms particularly peripheral and central sensitization of dorsal horn neurons by surgical stimuli has led to the search for novel treatments.[1] Peripheral tissue injury provokes peripheral sensitization (a reduction in the threshold of nociceptor afferent peripheral terminals) and central sensitization (an activity dependent increase in the excitability of spinal neurons). These changes contribute to the post injury pain hypersensitivity state. The pre-emptive form of pain treatment (pain treatment before skin incision) prevents this state. This treatment can be directed at the periphery, at inputs along sensory axons, and at central neurons.

At the beginning of the last century, Crile was among the first to introduce the concept of preemptive analgesia.[2,3] The preemptive analgesia reduces the intra and postoperative requirements of analgesics. It is achieved

by modulation of central and peripheral sensitization processes, thereby attenuating or ideally preventing postoperative amplification of pain sensation.[4] Several drugs have been tried but the clinical utility has been limited by only moderate preemptive analgesic effect or significant side effects.[5,6]

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) and is an anti-epileptic drug introduced in 1993. It is reported to possess anti-hyperalgesic (hyperalgesia is an increased sensitivity to pain) and anti-allodynia (allodynia is a painful response to a normally innocuous stimulus) properties and the recent reports have suggested its place in the treatment of post-operative pain. Its analgesic actions are distinct from those of opioids in terms of mechanism and side effects. Antihyperalgesic action of gabapentin does not seem to be dependent on activation of opioid receptors, thus it does not reduce gut motility, which is the major side effect of opioids in postoperative patients.[7-15] The idea of using gabapentin as preemptive analgesic in this study was to determine whether it reduces intraoperative and postoperative opioids requirements. In different clinical trials, the gabapentin has been studied for pre-emptive analgesia with different dosages. The rationale of this study was to establish this effect with a maximum dose of gabapentin in elective total abdominal hysterectomy (TAH).

METHODOLOGY

This study, a double blind controlled trial with random allocation was done in the Anaesthesia Department of Fatima Memorial Hospital, Lahore from April, 2007 to January, 2008.

After approval from the hospital ethics committee, seventy patients ASA I & II aged 40-60 years undergoing TAH were included and divided into two equal groups, Group P (Preemptive, study group) and Group C (Control group), having 35 patients in each group. The patients having history of hypersensitivity to any drug, acid peptic disease, hypertension, ischemic heart disease, renal or hepatic insufficiency, coagulation disorders and patients on antidepressants or calcium channel blockers were excluded from the study.

These patients were randomly allocated to either of two groups after informed consent. A randomization list was generated by simple random allocation. Subsequently each patient was allocated a number according to randomization list. Each of the patients was shown the visual analogue scale preoperatively and was explained how to rate their severity of pain on the scale. The study drugs were prepared by the pharmacy into identical capsules using randomization list. They were packed in sequentially numbered packages which were given to the recruited patients in the same order by a trained nurse who was not involved in any other part of the study.

Group P (35 Patients) received oral gabapentin 1200 mg and Group C (35 Patients) received oral placebo capsules two hours before surgery. Surgery of one group P patient was postponed so this patient was excluded from the study.

Outcome Variables: Pain score measurement, intraoperative by assessing an increase in blood pressure and heart rate due to pain and postoperative, by visual analogue scale (VAS) were recorded by a person who was blinded of the study. Intraoperative and postoperative supplemental opioids (Nalbuphine) requirements were also recorded. Age and weight of patients were also noted.

Anesthetic technique was standardized for both the groups. General anesthesia was given to all patients. All patients received tablet midazolam 7.5 mg orally with a sip of water one hour before induction of anesthesia. Patients received thiopentone 5 mg/Kg, atracurium besylate 0.5 mg/kg and nalbuphine 0.15 mg/kg at induction. They were ventilated with 50% oxygen in nitrous oxide (N2O) with isoflurane 0.6% using circle system with a flow of 6 liters for 3 minutes. Patients were intubated using 7.5 mm ID endotracheal tube. Anesthesia was maintained using 40% oxygen in nitrous oxide and isoflurane 0.6 - 1.0 % reducing flows to 3-liters/ minute after 8 minutes. Muscle relaxation was maintained using atracurium besylate 10 mg on appearance of one twitch on train of four (TOF).

Patients received Ringer's lactate for deficit and maintenance according to body weight. Blood loss was replaced using three times the volume of Ringer`s lactate solution. Blood transfusion was given if estimated hemoglobin dropped below 8 g/dl.

Intraoperatively, if there was an increase in blood pressure or heart rate by more than 20% from the baseline, isoflurane was increased by 0.2%. If the changes persisted, rescue analgesia was given. All the additional doses and changes were noted.

On skin stitches, isoflurane was switched off. After return of two twitches on TOF, neostigmine 2.5 mg and glycopyrrolate 0.4 mg were administered intravenously. Nitrous oxide (N2O) was switched off after giving the reversal.

All patients were monitored using ECG, pulse oximetry, non invasive blood pressure, end tidal capnography and neuromuscular function monitor.

For postoperative analgesia, patients received nalbuphine 0.05 mg/kg IV every two hours by assessing VAS. The first post-operative dose of nalbuphine was given two hours after surgery. If pain relief was inadequate, rescue analgesia was given according to the protocol.

Postoperatively, patients were evaluated for pain scores using VAS score 1-10. (score 1-3 considered mild pain, 4-7 moderate pain and 8-10 as severe pain) on arrival to the

post anesthesia care unit (PACU), at 02 hours, 08 hours, 16 hours and at 24 hours. In case the pain score was more than 3 (moderate pain) a top up dose of nalbuphine 0.05 mg/kg was administered intravenously and was noted. The designated nurse who was blinded regarding the treatment groups collected the above information.

Statistical Analysis The data was entered on pre-coded forms and processed using SPSS version 12. Statistical analysis was done by applying Student's t-test for pain scores measurement and supplemental nalbuphine requirements. A p-value of < 0.05 was considered significant.

RESULTS

Seventy patients were selected for the study on the basis of the inclusion criteria. One patient in the gabapentin group was withdrawn because surgery was postponed due to an allergic reaction a blood product transfusion. Thus, data from 69 patients, 34 out of 35 in the preemptive (gabapentin) group and 35 out of 35 in the control group, were included and analyzed. So there was 97.1% contribution from group P (Preemptive group) and 100% contribution from group C (control group) patients in this study (Table -1).

Table 1: Patients Distribution According To Groups

Group *	Frequency (n)	Valid Percentage	Cumulative Percentage
P	34	49.3	97.1
C	35	50.7	100
Total	69	100	

*P= Preemptive, C= Control

The ages of patients ranged between 40 and 57 years with mean of 43.9 ± 4.0 years and their weights ranged between 43 and 100 kgs with mean of 74.1 ± 9.0 kgs (Table-2).

Table 2: Patients Demographic Data

Parameter	Total Patients	Minimum Value	Maximum Value	Mean	SD
Age (years)	69	40	57	43.97	4.033
Weight (kg)	69	43	100	74.12	9.098

The hemodynamic values remained stable in two groups. None of the patients in either group required rescue analgesia intraoperatively. Postoperatively, the VAS scores recorded at zero, 2, 8, 16 and 24 hrs were significantly lower in the gabapentin as compared to pain scores of the control group. At zero hour, mean VAS scores in preemptive and control groups were 4.79±1.38 cms and 8.03±1.20 cms respectively. While at 24 hours, these were 0.852±0.74 cms in preemptive group and 2.428±1.11 cms in control group. The Student's t test was applied to VAS scores, which declared that the P-value was less than 0.001 and hence significant (Table-3).

Table 3: Postoperative VAS Pain Scores (In centimeters)

Time (Hours)	Group	Freq-uency	Mean± SD	Std. Error Mean	P-Value
TO	P	34	4.79±1.388	.238	0.000
(At zero Hr)	C	35	8.03±0.848	.203	
T2	P	34	4.352±0.779	.145	0.000
(At 2 Hrs)	C	35	6.971±1.200	.226	
T8	P	34	3.617±1.339	.133	0.000
(At 8 Hrs)	C	35	5.200±1.051	.177	
T16	P	34	2.088±0.865	.148	0.000
(At 16 Hrs)	C	35	4.028±1.175	.198	
T24	P	34	.852±0.743	.127	0.000
(At 24 Hrs)	C	35	2.428±1.118	.189	

SD= Standard deviation, Std= Standard, *P=Preemptive, C= Control, VAS= Visual analogue scale

The total nalbuphine consumption after surgery in the first 24 hr in preemptive group was significantly less than in the control group. Mean nalbuphine used was 13.2 ± 4.7 mg in preemptive group and 24.3 ± 9.2 mg in the control group. The Student`s t- test was applied and found the P-value to be less than 0.001 and thus significant (Table-4).

Table-4: Postoperative nalbuphine consumption (in milligrams)

Group	Frequency (No. of patients)	Mean±SD	Std. Error Mean	P-Value (Student's t- test)
P (Preemptive)	34	13.21±4.708	0.807	0.000
C (Control)	35	24.31±9.276	1.568	

DISCUSSION

The null hypothesis of this study was that there should be no difference in preemptive analgesic effect of gabapentin and placebo in reducing opioid requirements in patients undergoing TAH. The results were in contrary to our null hypothesis and showed that a single dose of 1200 mg of gabapentin given two hours before surgery significantly reduces the postoperative opioids requirements during the first 24 hours. Pain scores (VAS) recorded in gabapentin treated patients were reasonably lower than those of patients who received placebo.

Surgical pain results from traction of tissues during surgery, surgical wound and surgical drains.[16] The intensity of pain is greatest during the first postoperative day and requires efficient pain control. Different analgesic drugs

have been used for this purpose and combination of opioid and non-opioid analgesic drugs has shown a quality of postoperative pain control. Excessive use of opioids may result in side effects like respiratory depression, but preemptive use of gabapentin has shown to decrease the total dose of opioids required in surgical patients and thus lowers the chance for side effects. Gozal et al. reported marked reduced opioid requirements following local wound infiltration of bupivacaine 0.5% prior to skin closure in patients undergoing thyroidectomy.[17] In one study, Basto et al. found perioperative administration of ketoprofen and paracetamol was associated with a reduction in pain scores and morphine requirements after thyroid and parathyroid surgery.[18] In one study, preemptive analgesia with paracetamol has been tried with some success.[19] In another study, bilateral superficial blocks significantly reduced pain intensity in the postoperative period after thyroid surgery.[20] Aunac et al. demonstrated that the bilateral superficial and deep cervical blocks administered before thyroid surgery reduced the pain scores, and they also found a significant reduction of intraoperative requirements of anesthetics and analgesics.[21]

The dose of gabapentin in our study (1200 mg) was within the limits of a single daily dose as the dosage for the treatment of neuropathic pain is 300 to 1200 mg three times a day.[22] In this study, gabapentin was administered orally two hours before the surgery on the basis of findings in laboratory animals that preemptive treatment with gabapentin is more effective and longer lasting than the post-treatment. Preemptive treatment with a single dose of gabapentin blocked the development of hyperalgesia for two days in a rat model of postoperative pain, while gabapentin one hour after intervention reduced symptoms for only three hours.[23] Previous clinical studies involving gabapentin for postoperative pain relief have shown favorable results. Gabapentin 1200 mg administered orally one hour before surgery decreased pain scores and postoperative morphine consumption in the early postoperative period in patients undergoing spinal surgery, thereby decreasing morphine-related side effects like nausea and vomiting.[24] In an another study, gabapentin 3000 mg administered before and during the first 24 hrs after total abdominal hysterectomy caused reduced morphine consumption by 32%, without significant effects on pain scores at rest or during mobilization.[25] Rorarius et al. demonstrated that a single dose of 1200 mg gabapentin given 2 to 2.5 hr before induction of anesthesia reduced the need for additional postoperative pain treatment by 40% during the first 20 postoperative hours in patients undergoing vaginal hysterectomy.[26] This study is comparable with our study which shows 47% reduction in dose of narcotics in postoperative period. Pain scores (VAS) and postoperative nalbuphine consumption in our study were significantly lower in gabapentin-treated patients undergoing TAH. Despite differences in surgical procedures and different doses of gabapentin used, a significant effect on postoperative analgesic requirements was observed in most of the above studies. In addition, gynecological surgery carries a major risk of nausea and vomiting and this risk is increased if opioids are used excessively in the immediate postoperative period. So gabapentin, by decreasing the opioids requirements during postoperative period causes a reduction in the incidence of these side effects. Oral administration of gabapentin approximately two hours before surgery appears rationale in order to attain a maximum plasma concentration at the time of surgical stimuli. Gabapentin, being a highly lipophilic drug, is absorbed from gut and crosses the blood-brain barrier rapidly and consequently, its concentration in brain tissue, where it exhibits its effects, is nearly as high as in blood.[27] Dierking et al. found a significant inverse relationship between plasma levels of gabapentin two hours postoperatively, thus indicating a dose response effect. Gabapentin has been reported as an anxiolytic drug in previous studies.[28] By causing preoperative anxiolysis, gabapentin may have positive effect on postoperative pain relief and thereby reduced opioid requirements, as there is a possible association between preoperative anxiety and postoperative pain.[29] In addition, studies have shown a synergistic effect of opioid and gabapentin in both animal experiments and humans.[30] In rats, gabapentin prevents the development of morphine tolerance and partially reverses established tolerance.[31] It is suggested that central sensitization plays an important role not only in chronic pain states, but also in postoperative pain. The relative contribution of various pain mechanisms to postoperative pain has not been established.[32] Numerous anti-hyperalgesic methods and drugs have been evaluated in order to reduce the central neuronal hyperexcitability which, theoretically, may amplify postoperative pain. Although gabapentin has been used in the treatment of neuropathic pain syndromes, it has also demonstrated potent anti-hyperalgesic proprieties in preclinical and clinical studies.[33] Gabapentin was well tolerated by the patients in our study and no significant side effects were observed with oral gabapentin during the perioperative period. Our results are similar to other published studies.

CONCLUSION

The results of our study clearly show that the preemptive use of gabapentin significantly reduces intra and postoperative pain and hence narcotic/opioid requirements in patients undergoing TAH, thereby minimizing the side effects of narcotics. Thus gabapentin may be used as a preemptive analgesic or as an adjunct therapy to reduce the requirements of narcotics during the intra and postoperative period in patients undergoing TAH.

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