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Oral gabapentin for postoperative pain relief after lower limb surgery – a randomized controlled trail

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Abstract

Introduction: In addition to anticonvulsant property of gabapentin, it was demonstrated that gabapentin also possesses analgesic property. In this randomized control trial the efficacy of gabapentin for postoperative pain relief was studied on 60 adult patients of either sex, belonging to ASA grade I or II, in the age range of 18-60 years posted for lower limb surgeries under spinal analgesia.

Methods: The patients were randomly divided into two groups of 30 patients each. Group A patients (n=30) received oral gabapentin 1200 mg 2 hours prior to scheduled surgery and the same dose was given at 9:00 am on the first and second postoperative days. Group B (n=30) served as control group received only placebo capsules. Subarachnoid block was established in both the groups by administering 4 ml of hyperbaric bupivacaine. Vital parameters such as heart rate, blood pressure respiratory rate along with pain assessment (VAS) were recorded at regular intervals in the postoperative period. Rescue analgesia was provided with intramuscular butorphanol.

Results: It was observed that patients in group A exhibited excellent quality of postoperative pain relief as compared to group B (*P<0.0001*). The requirement of opioids in the form of butorphanol was greatly reduced in group A as compared to group B (*P<0.0001*). Patient satisfaction using verbal rating scale was higher in Group A as compared to group B (*P<0.0001*). Minor side effects encountered were mild sedation, shivering, nausea, vomiting and dizziness which showed no significant difference between the groups.

Conclusion: Oral administration of gabapentin holds great promise for excellent postoperative pain relief and reduction in the overall requirement of opioids without producing significant side effects.

Keywords: Gabapentin, Butorphanol, Postoperative pain, Multimodal analgesia, Lower limb surgeries, Spinal analgesia

Introduction

Excellent pain relief administered to patients during intraoperative phase within the precincts of operation theatre unfortunately does not continue into the postoperative phase. In the postoperative period, when the effect of anaesthesia wears off, the tissue injury persists and the pain producing substances that are liberated during surgery greatly reduce the normal high threshold of nociceptors, so that innocuous stimulation produces great pain.[1] Pain in the postoperative period demands relief not only on humanitarian ground but also to reduce physical morbidity following the operation and to improve clinical outcome by reducing the incidence of postoperative pain. Various types of analgesics and techniques have been used alone or in combination for the management of postoperative pain. Keeping in mind the multiplicity of mechanism involved in the postoperative pain, it is possible to modify postoperative pain using multimodal analgesia techniques.

Gabapentin was first introduced for the treatment of epilepsy in early 1990.[2] It was later used for the patients of neuropathic pain,[3] bipolar disorders,[4] and migraine prophylaxis.[5] In addition, gabapentin is also effective in the treatment of acute post-operative pain.[6] Gabapentin acts supraspinally to activate the descending bulbospinal noradrenergic pathway in mice with peripheral nerve injury.[7]

This study is being under taken to assemble evidence base data of sufficient size and quality, to ascertain if, requirement of opioids used in the postoperative period is reduced or eliminated and to determine whether supplementing opioid analgesia with gabapentin can also alter postoperative pain score, patient satisfaction and side effects.

Material and Methods

After obtaining approval from Institutional ethical committee and written informed consent of the patients, this study was conducted on 60 adult patients of either sex, belonging to ASA grade I or II, in the age range of 18-60 years posted for lower limb surgeries. Only haemodynamically stable patients with normal laboratory investigations were included. Patients with known allergy to any of the study medications, central nervous system disease, renal insufficiency, peptic ulcer disease, uncontrolled diabetes and history of bleeding diathesis were excluded from the study. Patients with abnormal psychological profile or drug abuse and patients who are already on treatment with gabapentin also were not been included in the study. After obtaining written consent; initial preoperative counseling was done to gain confidence of the patient; thereby minimizing the emotional component of pain. The nature of the procedure was explained and the

patients were taught to assess the intensity of pain using Visual Analogue Scale.

The patients were randomly divided into two equal groups of 30 patients each. The patients were allotted to respective group by lottery method. Group A served as study group received oral gabapentin, while Group B served as control group received only placebo capsules of sugar. All the patients were kept fasting overnight, prior to the scheduled day of the operation. Group A patients received 1200 mg. oral gabapentin tablets 2 hours prior to the surgery and the same dose were given at 9:00 am on the first and second post-operative days. The same schedule was followed for placebo capsules in Group B.

On arrival at the operation theatre, baseline vital parameters like pulse rate, blood pressure and respiratory rate were recorded, intravenous line secured using 18G intravenous cannula and the patients were preloaded with lactate ringer solution 10 ml/kg body weight over 15-20 minutes. Spinal analgesia was given using 26 G Quincke's spinal needle under all aseptic precautions, with the patient in the sitting position. Midline approach was used. The interspace between lumbar vertebrae 3 and 4 (L3/4) or the interspace between lumbar vertebrae 2 and 3 (L2/3) was chosen. After the identification of clear, free flowing cerebrospinal fluid, subarachnoid block was established with the administration of 4 cc of 0.5% hyperbaric bupivacaine. Any change in the position required for the surgical procedure was given after the adequate level was achieved. The patients were not given head low position for 30 minutes following intrathecal administration of the drug. The level of block was assessed by pinprick method.

The surgeons were asked to proceed for surgery after the adequate level of block was achieved. Non Invasive blood pressure both systolic & diastolic along with pulse rate and respiratory rate were recorded at intervals of 10 minutes, 30 minutes 1 hour and 2 hours after spinal analgesia. Patients were closely monitored for pulse rate, BP, SPO_2, respiratory rate, ECG and blood loss. Any fall in blood pressure, greater than 20% decrease in mean arterial pressure or a systolic arterial pressure less than 90mmHg was treated with boluses of Injection mephentermine 6mg and fluids where appropriate. Bradycardia was treated with intravenous injection of atropine sulphate in a dose of 0.2-0.4mg. Any side effects such as sedation, dizziness, nausea, vomiting were noted and treated with appropriate drugs. Ringer lactate, dextrose normal saline solution and colloids, where appropriate, were used for intra venous infusion throughout the perioperative period.

After the surgery patients were shifted to postoperative room and were monitored for vital parameters like, pulse rate, blood pressure and respiratory rate. The assessment of postoperative pain was done using visual analogue scale (VAS) for 72 hours postoperatively. It involves use of a 10cm line on a piece of white paper and it represents patient's perception of the degree of pain. It was explained preoperatively to all the patients that, one end of the line depicts '0'whichrepresents no pain at all, while the other end depicts '10' which represents worst pain he/she has ever felt. The assessment was carried out by an anaesthesiologist who was blinded to the group to which the patient belonged.

Vital parameters such as heart rate, blood pressure both systolic and diastolic and respiratory rate along with pain assessment (VAS) were recorded at 1, 4, 8, 12, 24, 36, 48, 60, and 72 hours intervals. When the pain score reached 7 or on demand of the patient Inj. Butorphanol 1 mg was administered intramuscularly to relieve pain as rescue analgesic.

Patient satisfaction with their postoperative analgesia was assessed using a 101-point Verbal Rating Scale, with 0= highly dissatisfied to 100= completely satisfied, and recorded at 24, 48 and 72 hours. Patients were monitored for occurrence of any side effects such as nausea, vomiting and dizziness. Side effects were treated symptomatically. The total number of analgesic doses given to the patient in the 72 hours period postoperatively was recorded.

At the end of the study, results in both the groups were tabulated, statistically analyzed and compared to draw the conclusions.

Results

Both the groups were comparable with respect to age, weight, height, ASA status and duration of surgery. On comparison of vital parameters; the heart rate, systolic and diastolic blood pressure and respiratory rate, there were no significant difference between the groups at any of the measured time interval *(P>0.05).*

VAS score was compared at regular time intervals in the postoperative period and found that Group B patients perceived greater degree of pain as compared to Group A (Fig. 1). On statistical analysis this was found significant at 1 hour *(P <0.005)* and highly significant at 4, 8, 12, 24, 36, 48, 60, 72 hours *(P<0.0001).*

Satisfaction of patients with the pain management was compared between the groups and was higher in group A patients at all time intervals (Fig. 2). Statistically this is found to be highly significant *(P<0.0001).*

Total number of analgesic doses required for postoperative analgesia was compared and found that group A patients consumed significantly lower doses of butorphanol as compared to group B *(P<0.0001).* Group A (3.77 □ 0.94); Group B (4.67 □ 1.03) (Fig. 3).

The side effects observed during postoperative period were dizziness mild sedation, nausea and headache. The incidence of dizziness was greater in group A, however statistically this was not significant *(P>0.05).*

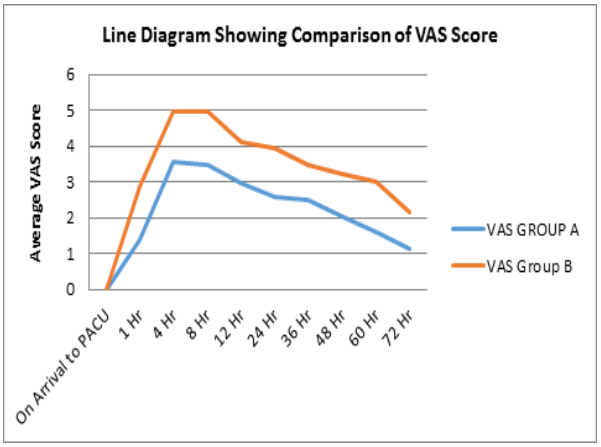

Fig. 1: Comparison of pain score between the groups. Group A patients who received gabapentin had felt lesser amount of post-operative pain than Group B patients who received only placebo capsules

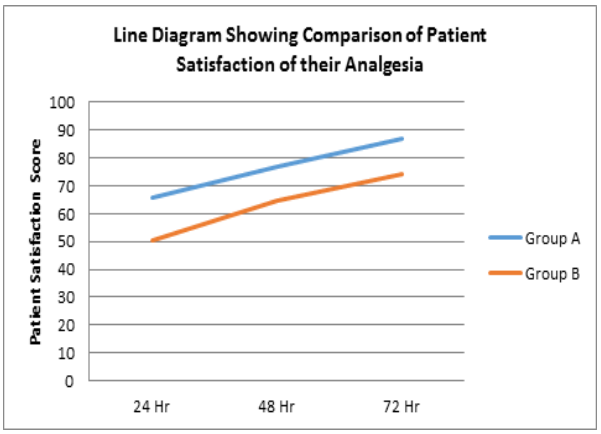

Fig. 2: Comparison of patient satisfaction regarding the quality of analgesia during the postoperative period. Group A patients who received gabapentin had higher level of satisfaction

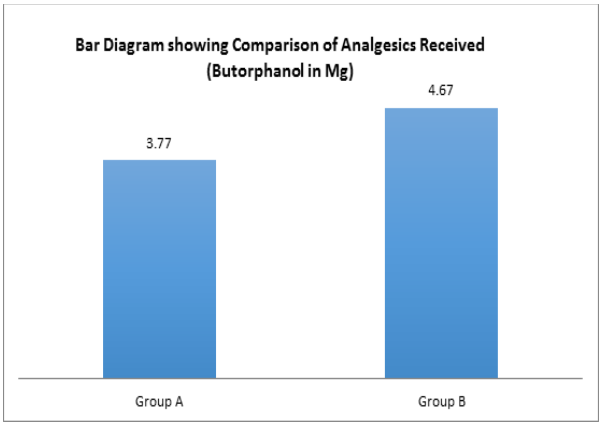

Fig. 3: Comparison of amount of post-operative analgesics received between the groups. Group A patients who received gabapentin consumed lesser amount of analgesics than Group B patients who received only placebo capsules

Discussion

Although the pathophysiology of postoperative pain and neuropathic pain are considered as separate and distinct, there is significant overlap in between. Allodynia and hyperalgesia are cardinal signs and symptoms of neuropathic pain, but they are also often present after trauma and surgery. Various nociceptive mechanisms are involved in postoperative pain, including sensitization of peripheral nociceptive nerve terminals and central neurons.[8]

Gabapentin is structurally related to the major inhibitory transmitter, γ - aminobutyric acid (GABA). It is derived by addition of cyclohexyl group to the carbon backbone of GABA. It's molecular formula is $C_9H_{17}NO_2$ described as 1 - (aminomethyl) cyclohexaneacetic acid with a molecular weight of 171.24. Gabapentin is a white to off-white crystalline solid with a pK_{a1} of 3.7 and a pK_{a2} of 10.7. Melting point is 164º – 167º C. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is –1.25. Gabapentin is rapidly absorbed after oral administration in part by the L-amino acid transport system, which is a carrier mediated, saturable transport system. Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses, respectively. Peak plasma concentrations are reached within 2 to 3 hours after administration. Absorption is unaffected by food and plasma protein binding is very low. Absolute bioavailability of 300 mg and 400 mg gabapentin capsules is approximately 55%.Less than 3% of gabapentin circulates bound to plasma protein. Gabapentin has an apparent volume of distribution of approximately 50 to 60 L.[9]

The mechanisms underlying the therapeutic actions of gabapentin remain poorly understood. The chemical structure and behavioral properties of gabapentin strongly suggest actions on inhibitory neurotransmission mediated by γ-aminobutyric acid (GABA); however, gabapentin does not directly modulate $GABA_A$ or $GABA_B$. A high-affinity gabapentin binding site has been unequivocally identified in animal brain membranes as the auxiliary α_2 δ subunit of voltage activated calcium channels.[10,11] Inhibition of voltage gated calcium channels by gabapentin is thought to reduce the release of an excitatory neurotransmitter associated with the central sensitization that occurs in neuropathic pain.[12] Hayashida KI and colleagues suggested that gabapentin activates the descending noradrenergic system and induces spinal norepinephrine release, which produces analgesia via spinal α_2-adrenoceptor stimulation, followed by activation of G protein-coupled inwardly rectifying potassium channels.[13]

Quite a few studies have been conducted to evaluate the analgesic property of gabapentin. However our study is the first to evaluate the postoperative opioid sparing effect of oral gabapentin, where opioids were administered intramuscularly.

In the present study visual analogue pain score were recorded at 1, 4, 8, 12, 24, 36, 48, 60, and 72 hours intervals in the postoperative period. When the pain score reached 7, butorphanol 1 mg was administered intramuscularly to relieve pain as rescue analgesic. On comparison of VAS between the groups, it was observed that pain score was always greater in group B as compared to group A. Statistical analysis showed that, this difference is significant at 1 hour ($P<0.005$) and highly significant at 4, 8, 12, 24, 36, 48, 60 and 72 hours intervals ($P<0.0001$).

In addition, in both the groups pain score were gradually increased in the postoperative period till 4 hours. Thereafter, it was observed that VAS score gradually decreased throughout the study period. Hence it is clear that the peak of pain (maximum pain) was at 4 hours in both the groups. Group A 3.58 ± 0.59 (4 hr) Group B 4.95 ± 0.81 (4 hr).

Patient Satisfaction with the pain management was assessed and compared between the groups, at 24, 48 and 72 hours in the postoperative phase. Patient satisfaction was higher in group A when compared to group B and this was found highly significant throughout the study ($P<0.0001$). Reducing preoperative anxiety and thus increasing patient satisfaction with the pain management using gabapentin, may have contributed to the improved postoperative pain and to the reduced analgesic consumption because there is a possible association between preoperative anxiety and postoperative pain.[14]

Postoperative side effects observed were mild sedation, dizziness, nausea and headache. In Group A: 16% patients had mild sedation, 16% complained of dizziness, 6% had nausea and none had head ache. 66% patients were free from any side effects in group A. While in Group B: only 6% of patients elicited mild sedation, merely 3% had dizziness, 10% had nausea and 3% had head ache. 76% patients had not shown any side effects in group B. Nausea was treated with oral ondansetron 4 mg. Headache was not severe, and did not require any specific treatment, while simple reassurance was enough for dizziness.

It was observed that, the incidence of dizziness and sedation was higher in patients treated with gabapentin. However this was found to be insignificant statistically. It is perhaps the central action of gabapentin that accounts for these side effects. Gabapentin may act on vestibular nucleus in the brain stem to produce dizziness.

Conclusion

Oral gabapentin administered prior to surgery and for two days after surgery, holds great promise for excellent postoperative pain relief and reduction in the overall requirement of opioids, without producing any significant side effects. Hence it is concluded that gabapentin will form an important adjuvant for relief of postoperative pain in the armamentarium of the anaesthesiologists.

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