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COMPARISON BETWEEN PREGABALIN AND GABAPENTIN AS PREMEDICATION BEFORE SPINAL ANAESTHESIA IN LOWER ABDOMINAL SURGERY

Anaesthesiology

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ABSTRACT

Background: Adequate and satisfactory relief of postoperative pain continues to be a major challenge in the care of surgical patients. Several anticonvulsants have been tested as preemptive analgesic to prevent sensitisation of the nervous system before surgical stimulation and reduce postoperative pain. **Aims:** The aim of the study was comparative evaluation of analgesic efficacy of preemptive administration of pregabalin and gabapentin in patients undergoing lower abdominal surgery under spinal anaesthesia. The primary outcome was duration of postoperative analgesia and secondary outcome was total requirement of postoperative analgesics, any adverse effects attributable to study drugs, etc. **Materials & Methods:** Seventy eight patients belonging to ASA I & II were randomly allocated into two groups of thirty nine each. Patients in Group G received oral gabapentin 600mg and in Group P received oral pregabalin 150mg one hour before spinal anaesthesia. Postoperative pain was assessed by Visual Analogue Scale (VAS) at 6,12,18 and 24hours. At VAS score 4 or more, Diclofenac sodium 100mg intramuscular was administered as rescue analgesic. **Results:** The postoperative analgesic duration (time from spinal anaesthesia to first administration of rescue analgesic) was 197.65m in Gr G versus 325.83m in Gr P ($p < 0.001$). Mean dose of rescue analgesic required was higher in Gr G. **Conclusion:** Pregabalin premedication is more effective than gabapentin in prolonging postoperative analgesia after spinal anaesthesia with minimal side effects.

KEYWORDS

Pregabalin, gabapentin, preemptive analgesia, postoperative pain

INTRODUCTION

Delivery of adequate and satisfactory pain service in the postoperative period is a major challenge in the care of surgical patients. Effective postoperative analgesia confers many benefits like better patient satisfaction, improved cardiorespiratory function, lower incidence of deep vein thrombosis, earlier mobilisation, faster readiness for discharge, etc.[1]

Incision and tissue damage associated with surgery leads to sensitisation of dorsal horn neurones that may be associated with allodyna and augmentation of postoperative pain[2] especially movement related pain.

Preemptive analgesia, i.e. initiation of antinociceptive treatment before a noxious stimulus like surgical incision is made, can prevent sensitisation of the central nervous system and altered processing of subsequent afferent input resulting in dampening of amplification of postoperative pain. A wide variety of pharmacological interventions have been shown to have clinically significant preemptive analgesic effect. These include epidural analgesia, local anaesthetic infiltration, systemic administration of anti-inflammatory drugs, opioids, N-methyl D-aspartate antagonists, etc[3].

Neuropathic pain has been successfully treated with anticonvulsants, tricyclic antidepressants, etc. Gabapentin is a second generation antiepileptic that has been conventionally used in the treatment of partial seizures and chronic neuropathic pain states like diabetic neuropathy, postherpetic neuralgia, etc. Gabapentin is a structural analogue of Gamma Amino Butyric Acid (GABA) and acts by binding with alpha2 delta subunit of presynaptic voltage-gated calcium channels decreasing glutaminergic transmission in spinal cord[4]. Decrease of central sensory input processing leads to inhibition of central neuronal sensitisation and hyperalgesia. The preemptive analgesic effect of gabapentin administration resulting in reduced analgesic requirement in the postoperative period has been demonstrated in several clinical studies: abdominal hysterectomy[5], spinal surgery[3], laparoscopic cholecystectomy[6], radical mastectomy[7], etc.

Pregabalin is another structural analogue of GABA and its usefulness in the treatment of peripheral neuropathic pain states like painful diabetic neuropathy, postherpetic neuralgia, etc. is well established[8,9]. Its mechanism of action is similar to that of gabapentin but has a improved pharmacological profile[10]. It is claimed to be more effective in preventing neuropathic component of acute nociceptive pain of surgery. There is evidence that it may be as effective as gabapentin in relieving acute pain after surgery[11,12].

Few studies have compared preemptive gabapentin versus pregabalin for postoperative pain relief[13,14]. The aim of the present study was to evaluate the postoperative analgesic benefit of gabapentin and pregabalin administered as premedication for surgery under spinal anaesthesia. The duration of analgesia, total postoperative requirement of analgesics, any systemic side effects attributable to the study drugs were assessed.

MATERIALS AND METHODS

This prospective, randomised, double blinded, parallel group study was conducted on seventy eight adults patients, of either sex, aged 18 to 60 years, belonging to ASA PS I and II posted for elective lower abdominal surgery under spinal anaesthesia.

Sample size of the study was estimated based on duration of analgesia (time to rescue analgesia following completion of surgery}. It was calculated that 35 subjects would be required in each group in order to detect a difference in 20 minutes with 80% power and 5% probability of Type I error. This calculation assumes a standard deviation of 30 minutes for the time to first administration of rescue analgesic and two sided testing, keeping 10% allowance in drop out. Thus the target was set at 39 subjects in each group. Sample size calculation was done by nMaster 2.0 (Dept of Biostatistics, Christian Medical College, Vellore, 2011) software.

The exclusion criteria for the study were as follows: significant systemic disease, allergy to study drugs, pregnancy, lactation, any contraindication to spinal anaesthesia, etc. After obtaining Institutional Ethics Committee clearance, patients were assessed and written informed consent was taken. Patients were randomly allocated into two equal groups of 39 each by sealed opaque envelope technique. Group G patients received oral gabapentin 600mg and Group P patients received oral pregabalin 150mg administered one hour before spinal anaesthesia. The drugs were administered by a nursing personnel not involved in the study.

After following proper fasting guidelines, the patients were brought to the operating room, a 18G intravenous cannula was inserted and fluid

infusion started with Ringer Lactate solution. Standard monitors were attached and baseline parameters (heart rate, blood pressure, SpO2, ECG) were recorded. The patient was then put in the sitting position and after antiseptic dressing and draping, intrathecal puncture was done with 25G Quincke's needle at L3-4/L4-5 interspace. After confirming free flow of CSF, 3.5ml of 0.5% heavy bupivacaine and 25ug preservative free fentanyl was injected through the spinal needle. The patient was then made supine and after confirming satisfactory height of block surgery was allowed to begin. Oxygen at 2L/min by nasal cannula was administered continuously throughout surgery.

In case of failure of spinal anaesthesia, general anaesthesia was administered and the patient was excluded from the study. Intraoperatively, events like hypotension, bradycardia, nausea, vomiting etc. were managed appropriately.

Postoperative pain was recorded by Visual Analogue Scale (VAS) immediately after surgery and every 6hours for 24hours. Rescue analgesic was administered as diclofenac sodium 1mg/kg intramuscular whenever VAS was equal or greater than 4 or patient complained of pain. Time to first administration and total dose of rescue analgesic administered in 24hours was recorded.

Sedation was assessed by Ramsay Sedation Scale immediately after surgery and then 6hourly for 24hours. Other complications like nausea, vomiting, hypotension, dizziness, somnolence etc were recorded and treated accordingly. The same anaesthesiologist performed the spinal anaesthesia for all the study patients not knowing to which group the patient belonged. All intraoperative and postoperative data collection was done by an anaesthesiologist who was not aware to which group the patient belonged. A p value of <0.05 was considered as significant.

At the end of surgery, the patients were shifted to Recovery Room for clinical monitoring of vital signs, appropriate fluid therapy, etc. For first 24hours postoperative period, the defined parameters were evaluated in each patient and the findings were recorded. The principal investigator, who was blinded to the study drugs, performed statistical analysis of collected data.

RESULTS

Seventyeight adult patients, aged 18-60years, belonging to ASA PS I & II, posted for elective lower abdominal surgery under spinal anaesthesia were included in this study. The patients were randomly allocated into two groups, Group P(n=39) and Group G(n=39). The demographic variables such as age, weight, sex, ASA status and types of surgeries were comparable between the two groups (Table 1 and Figure 3).

The time to first administration of rescue analgesia following end of surgery was compared between the two groups. In Group P it was 325.83 (S.D. 73.11)min and in Group D it was 197.65(S.D. 14.47)min. This difference was highly significant (p= 0.0004), Table 2.

The total dose of rescue analgesic administered in first 24hours after surgery was compared between the two groups. In Group P it was 71.15(S.D. 48.51)mg and in Group G it was 105.77(61.36)mg. This difference was highly significant (p=0.0168), Table 2.

Figure 1 shows the distribution of VAS score among the two groups in the first 24hurs after surgery. Group P patients reported significantly lower VAS score at the 6th postoperative period compared to Group G. During rest of the study period, there was no significant difference in VAS score between the two groups.

Figure 2 shows the distribution of sedation score among the two groups in the first 24hours after surgery. Group P patients reported a significantly lower sedation score at the 6th postoperative period compared to Group G. During rest of the study period, there was no significant difference in sedation score between the two groups.

Figure 4 shows the incidence of complications in the two groups of patients. Nausea was the commonest complication and was reported in a higher proportion of patients in Group G. Other complications like dizziness, nausea, headache, somnolence, etc were minor and self limiting and patients improved with simple assurance. Perioperative haemodynamic changes were similar in both groups.

Figure 1:

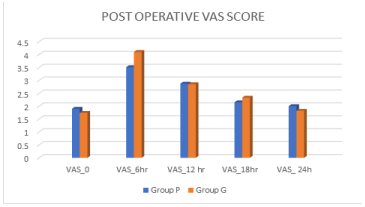

Figure 2:

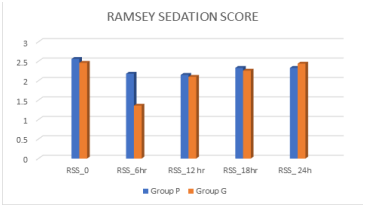

Figure 3: Types of surgeries between two groups

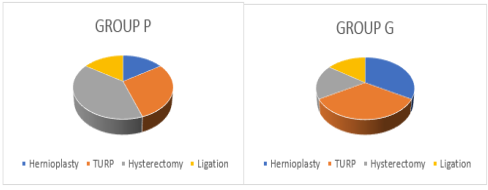

Figure 4: Incidence of complications:

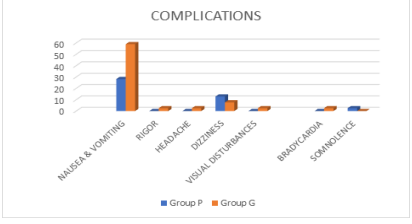

Table 1: Demographic Profile

	Group P (Mean ±SD)	Group G (Mean ±SD)	Level of Significance
Age (in yrs)	52.89 ±14.08	53.07 ± 13.74	0.954
Weight (in Kgs)	63.77 ±13	62.97 ± 11.32	0.7742
Sex Ratio (Male : Female)	6:7	6:7	
ASA Ratio (I : II)	25/14	23/16	

Table 2: Outcome Variables:

	Group P (Mean ±SD)	Group G (Mean ±SD)	Level of Significance
Time for first analgesia dose (minutes after completion of surgery)	325.83 ± 73.11	197.65 ± 14.467	0.0004
Requirement of total analgesia (in mg)	71.15 ± 48.51	105.77 ± 61.36	0.0168

DISCUSSION

This study shows that single dose oral pregabalin 150mg significantly prolonged postoperative analgesia and reduced the required dosage of rescue analgesic compared to single dose of oral gabapentin 600mg in patients undergoing lower abdominal surgery under spinal anaesthesia. The utility of spinal anaesthesia is restricted by the limited duration of sensory block. Various pharmacological agents like opioids, alpha2 adrenergic agonists, etc have been added to local anaesthetics in an effort to prolong the duration of sensory block and provide extended postoperative analgesia.

Pre-emptive or pre-incisional analgesia is capable of limiting postoperative pain by guarding the central nervous system from harmful effects of noxious stimuli that result in allodyna and

hyperalgesia. The known antiallodynic and antihyperalgesic properties of pregabalin and gabapentin that is utilised in treatment of neuropathic pain may also beneficial in acute postoperative pain as central neuronal sensitisation contributes to postoperative pain14—17. This study was planned to assess the comparative efficacy of pre-emptive doses of pregabalin and gabapentin to reduce postoperative pain and provide extended analgesia following spinal anaesthesia.

Pregabalin and gabapentin, despite being derivatives of GABA, do not interact with GABAA or GABAB receptors. They bind with the alpha2 delta subunit of voltage dependent calcium channels in peripheral and central nervous system which inhibits calcium influx and blocks release of excitatory neurotransmitters in the pain pathways.

What is the optimum dose of pregabalin as pre-emptive analgesic? Anand et al18 in a study on patients undergoing hysterectomy under spinal anaesthesia used two different doses of pregabalin, 225mg and 150mg pre-emptively,. It was found that patients receiving higher dose of pregabalin had significantly prolonged duration of spinal anaesthesia and significantly lower postoperative tramadol consumption but had higher incidence of side effects like dizziness, sedation etc. They suggested that pre-emptive oral 150mg pregabalin is very effective in providing good postoperative analgesia with better patient satisfaction. In a similar study, Kohli et al19 compared two doses of pregabalin, 300mg and 150mg administered as oral premedication. While patients receiving the higher dose had significantly prolonged duration of spinal anaesthesia but also complained of higher incidence of sedation and dizziness. Level of overall satisfaction was nearly the same in both groups. The authors suggested pregabalin 150mg is the optimal pre-emptive dose for hysterectomy under spinal anaesthesia. Hence, we chose pregabalin in a dose 150mg for our study. Agarwal et al20 also showed that a single dose of 150mg pregabalin was effective in reducing pain after laparoscopic cholecystectomy and had no significant complication compared to placebo.

What is the optimum dose of gabapentin as pre-emptive analgesic? Based on rat model of neuropathic pain, it is predicted that doses of pregabalin that are effective as antihyperalgesic are generally half to one-fourth that of gabapentin20,21. Authors have used pre-emptive doses of gabapentin ranging from 600mg to 1200mg and even higher. Turan et al5 administered 1200mg gabapentin 1hour before surgery in patients undergoing hysterectomy under general anaesthesia and found that postoperative pain scores and tramadol consumption without significant sedation. Saraswat et al23 compared 1200mg gabapentin with 300mg pregabalin 1hour prior to spinal anaesthesia, Khetarpal et al24 compared 1200mg gabapentin with 300mg pregabalin 1.5hours before spinal anaesthesia, Pal et al25administered 1200mg gabapentin and 300mg pregabalin before spinal anaesthesia, Gilron et al26used gabapentin 1800mg with or without rofecoxib perioperatively in abdominal hysterectomy, etc. Other authors have used dose of 600mg. Trivedi et al27 compared 600mg pregabalin with 150mg pregabalin 1hour before spinal anaesthesia in hysterectomy, Gogna et al28 tested 600mg oral gabapentin 2hours before spinal anaesthesia, etc.

The rationale of choosing a lower dose(600mg) of gabapentin for the present study was to find out whether this lower dose would be effective without adverse effects like somnolence, dizziness, ataxia, etc. The absorption of gabapentin is limited by saturable l-amino acid transport mechanism in the gastrointestinal tract. As this transport mechanism is saturable, on increasing the dose the bioavailability of gabapentin remains nonlinear and varies inversely as the dose29. The bioavailability of 600mg dose is 60% whereas that of 1200mg is 40%. Gastrointestinal absorption is variable and peak blood level is attained after 3hours30. Pregabalin is absorbed from the small intestine and demonstrates linear uptake without transporter saturation[31].

Many authors have compared the efficacy of pre-emptive doses of pregabalin and gabapentin in relieving postoperative pain and reducing dosage of rescue analgesic. Saraswat et al13 compared 300mg of oral pregabalin with 1200mg oral gabapentin administered 1hour before spinal anaesthesia for infraumbilical surgery. They found that the pregabalin group had a significantly prolonged duration of total postoperative analgesia compared with gabapentin (14.17hours vs 8.98hours). In our study oral pregabalin 150mg was compared with oral 600mg gabapentin administered 1hour before spinal anaesthesia for lower abdominal surgery. The results of our study are also similar. The pregabalin group reported a significantly greater time to first administration of rescue analgesic (325.83min vs 197.65min) and the required dose of rescue analgesic in first 24hours postoperative period was also significantly lower in pregabalin group (71.15mg vs 105.77mg). Saraswat et al used a higher dose of pregabalin compared to our study (300mg vs 150mg) and this probably explains the longer duration of postoperative analgesia noted in their study. Unlike gabapentin, increasing the dose of pregabalin is associated with linear increase in bioavailability and greater analgesic effect.

Pal et al25 compared 300mg pregabalin with 1200mg gabapentin administered pre-emptively 1hour before spinal anaesthesia in infraumbilical surgeries. In pregabalin group rescue analgesic was required after 15.38hours and in gabapentin group after 9.41hours.

Similar to our study, Trivedi et al27 compared the proanalgesic effects of oral 150mg pregabalin and 600mg gabapentin administered 1hour prior to spinal anaesthesia for abdominal hysterectomy. Patients in pregabalin group reported a significantly greater analgesic duration (6.26 vs 4.54hours). This is in agreement with the findings of our study. In their study, the dose of rescue analgesics was significantly lower in pregabalin group which also matches with results of our study.

Kalu et al32 compared the postoperative analgesic effect of pregabalin 150mg and gabapentin 300mg administered 1hour before surgery in patients posted for lower limb orthopaedic surgery. The mean duration of analgesia was significantly prolonged in pregabalin group compared to gabapentin group, 422min vs 272min. This is in agreement with the results of our study as well as that of Saraswat et al23, Pal et al25, Trivedi et al[27].

Pregabalin is rapidly absorbed after oral administration, peak blood level is attained within 1hour of oral dosage and its bioavailability exceeds 90%33. Gabapentin is absorbed more slowly, peak blood level is attained 3-3.2hours after oral dose, has shorter elimination half life and its bioavailability decreases with higher dosage30. The superior pharmacokinetic profile of pregabalin is likely the reason for its more potent attenuation of postoperative pain after both regional and general anaesthesia as borne out by various studies23,25,27,32 including our study.

In our study the total dose of diclofenac as rescue analgesic required was significantly lower in the pregabalin group compared to gabapentin, 71.15mg vs 105.77mg respectively. This finding is in agreement with results obtained by other authors23-27,32. Rescue analgesia was not required in 9 patients(23.07%) in pregabalin group and in 5 patients(12.82%) in gabapentin group.

In our study, the postoperative VAS score at 6hours was significantly lower in the pregabalin group compared to gabapentin group. The VAS score immediately after surgery and at 0,12,18 and 24 hours after surgery were comparable among the two groups. Usama et al34, Trivedi et al27 likewise found that there was no significant difference between pregabalin and gabapentin groups in postoperative pain scores. On the contrary, other authors24,25,32 have detected significant difference in postoperative pain scores in favour of pregabalin.

The main side effects of pregabalin and gabapentin are sedation, dizziness, ataxia, etc. In our study side effects like nausea, rigor, etc were higher in pregabalin group. Pregabalin treated patients reported a higher incidence of dizziness(12.8% vs 7.7%) and 2.6% incidence of somnolence. But these problems were mild in intensity, selflimiting and did not result in delay in transfer from OR to Recovery Room. Haemodynamic changes in both groups were unremarkable and comparable in the study period.

The major limitation of the present study is that the chosen doses of pregabalin and gabapentin are in the lower ranges and have not been compared with higher doses eg 300mg pregabalin or 1200mg gabapentin. Higher doses may provide longer duration of postoperative analgesia but at cost of increased incidence and severity of side effects and decreased patient satisfaction19,20. Due to the short study period of 24hours, incidence of chronic postsurgical pain developing in the study population could not be assessed.

CONCLUSION

This study showed that pre-emptive administration of single oral dose

of 150mg pregabalin before spinal anaesthesia in lower abdominal surgery significantly prolongs duration of post surgical analgesia and reduces requirement of postoperative parenteral diclofenac when compared with single oral dose of 600mg gabapentin with minimum side effect.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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