Effect of Preemptive Gabapentin on Postoperative Opioid Requirement in Patients Undergoing Abdominal Surgeries: A Placebo Controlled Study

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ABSTRACT

Introduction: Gabapentin a second generation anticonvulsant is known to be effective in treatment of chronic neuropathic pain. To study the effect of pre-emptive oral gabapentin on post-operative opioid requirements in patients undergoing abdominal surgeries.

Material and Methods: In a randomized double blind study, 60 patients were divided into two groups. Group G received 400 mg gabapentin and Group P oral placebo 1hour prior to surgery.After premedication with midazolam 0.03 mg/kg and fentanyl 2mcg/kg, anesthesia was induced with Propofol 2 mg/kg and Vecuronium 0.08 mg/kg and maintained with 50% N2O in O2 and sevoflurane. Epidural infusion of bupivacaine was started before abdominal incision and stopped at the onset of closure. Assessment of post-operative pain was made with the visual analogue scale and epidural tramadol given on patient demand or when the VAS>2. Rescue analgesia was given with i.v. Diclofenac 1.5 mg/kg. The total tramadol consumption and number of rescue analgesia doses in both the groups was noted. Haemodynamic variables and side-effects were studied.

Results: Immediately after surgery and at 24 hours postoperative period, VAS scores were higher in the placebo group but it was not significant (P=0.063), However from 1 hour to 20 hours postoperatively, significantly lower VAS scores were recorded in Group G. The mean time interval to the administration of the first dose of tramadol was longer in Group G (0.54±1.35 hr) as compared to Group P (0.03 ±0.18hr). The total tramadol consumption in the 24 hour post-operative period was 183.54± 76.19 mg in Group G as compared to 268±103.5 mg in Group P. On a weight per kg basis, Group G received a mean tramadol dosage of 3.16±1.16 mg/kg and Group P 4.44±1.6 mg/kg. The differences in both these doses were found to be significant with P<0.005. Group G required lesser doses of Diclofenac as rescue analgesic than Group P, however the variation was not significant. The Sedation Scores between the groups were comparable.

Conclusion: Oral Gabapentin (400 mg) given 1hour to abdominal surgeries reduces the post-operative opioid requirement without causing any side-effects.

Keywords: Preemptive Gabapentin, Opioid, Abdominal Surgeries

INTRODUCTION

There is evidence to suggest that perioperative administration of gabapentin is efficacious for postoperative analgesia, preoperative anxiolysis, preventing chronic post-surgical pain, postoperative nausea-vomiting, delirium and attenuation of hemodynamic response to laryngoscopy and intubation.[1] 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[2] Post-operative pain is not purely nociceptive in nature and may consist of inflammatory, neurogenic and visceral components. Since gabapentin has potent antihyperalgesic properties, it can be a useful component of multimodal analgesic therapy. Studies to determine the optimal pre-emptive drug dosage have used gabapentin in doses of 300 mg, 600 mg, 800 mg, 900 mg and 1200 mg.[3] The bioavailability of gabapentin is 60% and decreases with increasing doses, half life is 5-6 hours and no additional clinical benefit was found when given in doses of 1800 mg.[4] We used a smaller dose of 400 mg and sought to determine if it reduced post-operative pain and tramadol consumption in the initial 24 hr after abdominal surgeries. Our secondary objectives were to study the sedative and any other side effects exerted by gabapentin.

MATERIAL AND METHODS

After approval from the institutional ethics committee and written informed consent 60 patients were recruited for the study during the year 2007-2008 at BYLNair Charitable Hospital, Mumbai. Patients enrolled included both male and female aged 18-60 years, ASA physical status I and II, weighing 40-75 kgs posted for elective abdominal surgery under general anaesthesia. Exclusion criteria was allergy to any of the drugs intended to be used, peptic ulcer disease, bleeding disorders, alcohol/drug abuse and chronic analgesic consumption. Patients were randomly assigned to one of the groups using computer generated table. Patients in Group P received oral placebo capsule and Group G received 400 mg of capsule gabapentin one hour prior to surgery. Upon arrival in the operating room, baseline pulse, mean arterial pressure and peripheral oxygen saturation were recorded. Crystalloid infusion was started at 6-8ml/kg/hr. Epidural space was located by midline approach, catheter secured after confirming negative aspiration for blood and CSF and ruling out intravascular placement with a test dose of 1:200,000 adrenalised lignocaine. All patients were premedicated with i.v. glycopyrrolate 0.004 mg/kg, midazolam 0.03 mg/kg and fentanyl 2 mcg/kg. Anaesthesia was induced with propofol 2 mg/kg and vecuronium bromide 80mcg/kg to facilitate orotracheal intubation and maintained with sevoflurane 2% at a fresh gas flow rate of 2 litre/min in combination

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How to cite this article: Sarita Fernandes, Tapas Mandal. Effect of preemptive gabapentin on postoperative opioid requirement in patients undergoing abdominal surgeries: a placebo controlled study. International Journal of Contemporary Medical Research 2016;3(7):1939-1942.

with nitrous oxide 50% in oxygen, An epidural infusion of bupivacaine 0.125% was started before the surgical incision and stopped at the beginning of closure. Patients were mechanically ventilated to maintain end expiratory carbon dsioxide tension between 30-40mmHg. At the end of the surgery, neuromuscular block was antagonised with neostigmine 0.05 mg/kg and glycopyrrolate 0.008 mg/kg. After extubation the patient was monitored in the recovery room. Pain scores were recorded using the Visual Analogue Scale (VAS) at 0, 1,4,8,12,16,20 and 24 hours where 0 was no pain and 10 corresponded to worst imaginable pain. The patient was given epidural tramadol (1 mg/kg) on patients demand or when VAS score was greater than 2 along with ondansetron 0.08 mg/kg. If pain persisted the epidural tramadol (1 mg/kg) was repeated. Inspite this if there was no pain relief, i.v. diclofenac was given as the rescue analgesic. The time from the end of surgery to the first demand for analgesia, the 24 hour total tramadol consumption and the number of patients requiring Diclofenac was documented. The Ramsay sedation scale[5] (1-anxious, agitated or restless. 2-co-operative, oriented, tranquil. 3-responds to commands 4-asleep but has a brisk response to light glabellar tap or loud auditory stimulus 5-asleep but has a sluggish response to a light glabellar tap or a loud auditory stimulus 6- asleep, no response) was used to record the sedation score. Side effects such as nausea, vomiting, respiratory depression, dizziness and somnolence were recorded. The anaesthetists who collected the data in the peri-operative period were blinded to group assignment.

STATISTICAL ANALYSIS

Sample size was calculated as 25 considering a previous study,[6] difference of 25 mg in total post-operative morphine consumption with standard deviation of 10units in each group to detect a considerable difference in epidural analgesic consumption with a power of 80% and significance level of 5%. In order to make good for dropouts a total number of 30 patients in each group were included in the study. Data was analysed using SPSS.11. Descriptive statistics are expressed as Mean(standard deviation). Student's *t* test was used for comparison of the means of continuous variables and normally distributed data. Mann- Whitney *U* –test was used otherwise. Two-way analysis of variance(ANOVA) was used for variable differences in groups. Categorical data were analysed using chi-square test analysis. Statistical significance was considered as $P<.05$

RESULTS

The 2 groups were comparable with respect to age, gender, weight, height and duration of surgery, There was a significant difference in the pulse rate and systolic blood pressure between the two groups during the 24hr post-operative period with maximum variation in the first 4 hours Table-1 and 2. The difference in diastolic blood pressure, respiratory rate and oxygen saturation was not significant. The Ramsay Sedation Scores between the groups were comparable.

Immediately after surgery and at 24 hours postoperative period, VAS scores were higher in the placebo group but it was not significant, P=0.063. However from 1 hour to 20 hours postoperatively, significantly lower VAS scores were recorded in the gabapentin group Table-3.

The mean time interval to the administration of the first dose of tramadol was longer in Group G(0.54±1.35 hr) as compared to Group P (0.03 ±0.18hr). The total tramadol consumption in the 24 hour post-operative period was 183.54± 76.19 mg in the gabapentin group as compared to 268±103.5 mg in the placebo group. On a weight per kg basis, Group G received a mean tramadol dosage of 3.16±1.16 mg/kg and Group P 4.44±1.6 mg/kg. The differences in both these doses were found to be significant with $P<0.005$. Group G required lesser doses of Diclofenac as rescue analgesic than Group P, however the variation was not significant Table-4.

Pulse Rate	Gabapentin(Mean±SD)	Placebo(Mean±SD)	P value	Significance
Baseline	73.57±12.24	68.83±10.13	0.108	Not significant
0 hr post-op	79.70±13.23	86.90±12.65	0.035	Significant
1hr post-op	75.97±12.62	85.60±10.59	0.002	Significant
4hr post-op	77.07±9.14	82.30±10.06	0.039	Significant
8hr post-op	77.03±8.95	79.27±9.37	0.349	Not significant
12hr post-op	74.87±7.85	76.57±8.17	0.414	Not significant
16hr post-op	74.07±7.84	77.10±7.07	0.121	Not significant
20hr post-op	72.83±6.48	74.27±7.96	0.447	Not significant
24hr post-op	72.07±6.33	72.37±8.21	0.875	Not significant

Table-1: Comparison of the pulse rate between the patients receiving gabapentin and placebo

Systolic BP	Gabapentin(Mean±SD)	Placebo(Mean±SD)	P value	Significance
Baseline	122.87±11.69	126.43±13.14	0.271	Not significant
0 hr post-op	125.80 ±10.05	132.93 ±12.08	0.016	Significant
1hr post-op	124.87±9.78	132±10.85	0.010	Significant
4hr post-op	125.40±9.64	129.33±11.31	0.020	Significant
8hr post-op	124.17±9.37	128.60±11.12	0.100	Not significant
12hr post-op	124.07±10.25	128.53±11.41	0.116	Not significant
16hr post-op	122.87±8.80	127.00±11.27	0.119	Not significant
20hr post-op	122.40±7.85	126.23±11.57	0.139	Not significant
24hr post-op	121.93±8.13	126.10±11.15	0.104	Not significant

Table-2: Comparison of systolic blood pressure between patients receiving gabapenin and placebo

VAS	Gabapentin(Mean±SD)	Placebo(Mean±SD)	P value	Significance
0 hr post-op	3.97 ±1.90	5.10 ±1.63	0.063	Not Significant
1hr post-op	3.40 ±1.45	4.47±1.22	0.010	Significant
4hr post-op	3.10 ±1.42	3.73 ±1.28	0.019	Significant
8hr post-op	2.73 ±1.44	3.47 ±1.20	0.006	Significant
12hr post-op	2.20 ±1.19	2.67 ±0.96	0.013	Significant
16hr post-op	2.10 ±0.84	2.70±0.92	0.004	Significant
20hr post-op	1.83±0.75	2.30 ±0.75	0.007	Significant
24hr post-op	1.70 ±0.53	1.97 ±0.67	0.120	Not significant

Table-3: Comparison of VAS scores

	Gabapentin	Placebo	P value	Significance
Interval to first tramadol dose	0.54±1.35	0.03±0.18	0.046	Significant
Total tramadol consumption(mg)	183.54±76.19	268±103.50	0.002	Significant
Tramadol consumption (mg/kg)	3.16±1.16	4.44±1.60	0.002	Significant
Diclofenac(mg)	75±0.00	112.50±54.77	0.088	Not Significant

Table-4: Comparison of the analgesic consumption between the 2 groups

DISCUSSION

The optimal form of analgesic treatment during surgery is that given pre, intra and post-operatively to preempt the establishment of pain hypersensitivity. The preemptive treatment could be directed at the periphery, at inputs along sensory axons and at central neurons. Gabapentin, a structural analogue of gamma aminobutyric acid acts at the alpha 2 delta 1 subunits of voltage-dependent calcium channels. It can act via primary afferent neurons, dorsal root ganglia, dorsal horn neurons and surpaspinal sites.[7]

Turan A et al noted a total morphine consumption of 16.3± 8.9 mg versus 42.8± 10.9 mg in placebo patients. Guignard et al also had similar findings where the gabapentin group consumed less morphine (29±22 mg) than the control (69±40 mg) with $P<0.001$. In the study by Pandey CK et al who used fentanyl as rescue analgesic, patients who received gabapentin at 300 mg, 600 mg, 900 mg and 1200 mg recorded a fentanyl consumption of 987.5 mcg, 702.5 mcg, 635 mcg and 626.5 mcg respectively. Absorption kinetics of gabapentin are dose dependent, possibly due to a saturable transport system[4]

We observed that the total tramadol consumption in the 24 hour post-operative period was 183.54± 76.19 mg in the gabapentin group as compared to 268±103.5 mg in the placebo group. On a weight per kg basis, Group G received a mean of 3.16±1.16 mg/kg and Group P 4.44±1.6 mg/kg. The differences in both these doses were found to be significant with $P<0.005$. Post-operatively the time to first demand for analgesia was longer in Group G(0.54±1.35hr) as compared to Group P(0.03±0.18hr). ($P=0.046$)

Turan et al in their study of gabapentin in spine surgeries and Pandey CK et al in lumbar diskectomy recorded lower pulse rates and systolic blood pressures at 0,1 and 4 hr post-operatively. They concluded that these variables correlated with the lower VAS pain scores and thereby reduced sympathetic stimulation. We too found a significant difference in hemodynamic parameters between the two groups. Karamanlioglu B, Turan A et al extensively studied the effect of gabapentin on postoperative epidural analgesia in lower limb surgeries. They found the respiratory rate to be less in the gabapentin as compared to the placebo group. This they co-related with better patient satisfaction in the recovery period.[6]

Dirks et al found a substantial reduction in post-operative morphine consumption without significant side-effects when given one hour before the surgical stimulus. This lower incidence of side-effects despite a larger dose may be explained by the fact that patients were assessed in the immediate post-operative period from zero to four hours after surgery when anesthetics may have masked the side effects of gabapentin.[8]

Pandey et al compared the analgesic effect of gabapentin with tramadol and reported a fall in oxygen saturation values below 90% which they attributed to respiratory depression.We did not observe any fall in sPo2 in patients of either group. All the patients in our study had a sedation score of 2 to 3 as per Ramsay Scoring system. Studies[9] on safety issues have demonstrated adverse effects like dizziness, confusion, headache, somnolence, nausea, ataxia and weight gain. However these studies were usually performed in patients with long term gabapentin use. In our study we used only a single oral dose and observed no significant adverse effects.

A Gabapentin dose of 1.2grams per day 1hour before surgery and for two days after CABG surgery showed that post-operative pain scores at 1,2 and 3 days as well as the consumption of tramadol given as rescue analgesia were significantly lower in the gabapentin group when compared to placebo group.[10] Although not statistically significant, Group G received a mean Diclofenac dose of 75 mg while the placebo group got a mean of 112.5±54.77 mg. Dosing of gabapentin is critical and can be the cause for varied results in different studies. Concentration of gabapentin reaches peak levels 2-3hrs after oral administration and crosses the blood brain barrier rapidly. At dose of 400 mg as in our study, the serum concentration of gabapentin might have been too low to cause side effects such as somnolence, nausea and vomiting as seen with other studies but enough for prevention of central neuronal sensitisation. In our study we observed that patients who received Gabapentin had a better haemodynamic profile, lower pain scores and reduced requirements of post operative analgesia in comparison to those who received placebo. A limitation of our study is the usage of only one dose: further investigation for determining various dose-response relationship is desirable.

CONCLUSION

We conclude that pre-emptive oral gabapentin helps reduce the post-operative analgesic requirements and has an important role in multimodal analgesia.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 15-05-2016; **Published online**: 17-06-2016