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Efficacy of preoperative gabapentin in producing post-operative analgesia in patients undergoing elective surgery under general Anaesthesia: A randomized double blinded trial

B Sundari[1], S Baranidharan[2]
[1] Assistant Professor, Department of Anaesthesiology, Trichy SRM Medical College and Hospital, Irungalur, Trichy, Tamil Nadu, India
[2] Consultant in Apollo hospitals, Trichy, Tamil Nadu, India

Abstract
Background: Gabapentin is an adjuvant antiepileptic agent with analgesic properties used for the treatment of postoperative pain. The primary objective of this study is to assess and compare the analgesic effects of administering Gabapentin and Paracetamol pre-operatively, in patients undergoing elective surgery, under General Anesthesia.
Methods: The study was a single-center, randomized and double-blind trial.
A total of 60 patients of either sex, age > 18 yrs, with American Society of Anesthesiology (ASA) status I/II undergoing elective ENT surgery, under General Anaesthesia at a tertiary care hospital were included in this study. The patients were randomized into two groups. 30 patients were randomized to Group 1, who received oral Paracetamol, one hour prior to surgery. Group 2 had 30 patients who received oral Gabapentin, preoperatively. In this study, comparison of the duration of analgesia provided by a single dose of 600mg of Gabapentin over 650mg of Paracetamol, consumption of postoperative rescue analgesia and the incidence of side effects between both groups were assessed.
Results: The mean duration of analgesia produced by Paracetamol was 83 minutes, whereas the mean duration of analgesia produced by Gabapentin was 74.48 minutes(P=0.4413). The mean analgesic consumption of group 1 which received Paracetamol was 53.0 mg of Tramadol, whereas the mean analgesic consumption of group 2 which received Gabapentin was 51.66 mg of Tramadol (P=0.627). The incidence of adverse effects like nausea, vomiting, dizziness and headache were comparable but statistically not significant.
Conclusions: Both Paracetamol and Gabapentin were comparable in terms of potency as pre-emptive analgesic. The mean duration of analgesia produced by paracetamol and gabapentin were found to be in same range. This study has shown that the time to first rescue analgesia, total amount of rescue analgesia between the two groups in the first 6 hours following surgery were not statistically significant.

Keywords: analgesic effects, pre-emptive analgesic, rescue analgesia

Introduction
Inadequate pain relief in the post-operative phase is a well-known problem world-wide. The incidence of post-operative pain has been found to be between 25%-76% [1]. From review of literature it is seen that many patients still suffer from moderate to severe postoperative pain despite an increased focus on multimodal pain management [1]. Aside from the suffering caused by insufficient pain relief, this is an issue with potential adverse physiological and psychological consequences for patients [2]. Patients may anticipate future medical interventions with greater anxiety if pain has not been managed effectively in the past [3]. 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 post-operative period which were associated with various adverse effects [4]. Pre-emptive analgesia is a treatment that is initiated before and is operational during the surgical procedure in order to reduce the physiological consequences of nociceptive transmission provoked by the procedure. Owing to this protective effect on the nociceptive pathways, pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery [5]. Consequently, immediate postoperative pain may be reduced and the development of chronic pain may be prevented [6].
Gabapentin is an analogue of GABA (gamma amino butyric acid) which was initially used an anti-epileptic, and later it was tried out in diabetic neuropathy and chronic pain [7]. Of late there is increased evidence suggesting their efficacy as an anxiolytic, for attenuation of pressor response during laryngoscopy and intubation, postoperative analgesia, and for prevention of post-operative nausea and vomiting [8]. Paracetamol is a well-established analgesic agent used as breakthrough analgesic [9]. Various studies has been done regarding its potency as a pre-emptive analgesic. The purpose of our study was to analyze the pre-emptive analgesic efficacy of gabapentin compared to that of Paracetamol. Several dosage regime of gabapentin has been tried in different studies and found to be of varying effect in post-operative analgesia. We have compared the efficacy of 600mg of gabapentin with 650 mg of Paracetamol.

Aim
To assess the efficacy of preoperative gabapentin in providing

adequate postoperative analgesia compared to preoperative paracetamol.

Materials and Methods

This study is a randomized double-blind study, which was conducted at the department of anaesthesiology, Pondicherry Institute of Medical Sciences, Pondicherry. After the approval of Institutional Ethical Committee and obtaining informed consent, the study was conducted on 60 patients, divided into two groups of either sex, aged > 18 yrs, with Grading of American Society of Anesthesiology (ASA) status I/II undergoing elective ENT surgery under general anaesthesia, in this Institution were included in this study. The patients with ASA III, IV, V and emergency surgeries, renal dysfunction, known allergy and prior usage of Gabapentin were excluded from this study. The patients were randomized into two groups of 30 patients each by simple random sampling method. They were also explained about Visual Analogue Scale for the assessment of pain the day before the surgery.

Blinding

The study medications were numbered according to random number table method. Participants was also assigned numbers according to random number table method and added to their group. One group was given Tab. Gabapentin 600mg 1 hr before surgery and the other group was given Tab. Paracetamol 650mg 1hr before surgery. All patients were premedicated with lorazepam 1mg on the night before and morning of surgery. On table they were medicated with Inj. Fentanyl 1.5mcg/kg, inj. Glycopyrolate 10mcg/kg and induced with inj. Thiopental 3-5mg/kg iv and inj. Vecuromium 0.1 mg/kg iv, and maintained with O2, N2O and volatile anaesthetics and Vecuronium. About 20 mins prior to extubation inj. Ondansetron 4mg iv was given. After the surgery they were reversed with inj. Neostigmine 60mcg/kg iv and Inj. Glycopyrolate 10mcg/kg iv. The patients were then shifted to recovery room.

Parameters studied

Post operatively the patients were examined at half hourly interval for first 6 hrs for the presence of pain and pain was graded using visual analogue scale. If pain grading > 4 or if moderate, inj. Tramadol 1mg/kg IV was given as rescue analgesic and noted. Any adverse effect such as dizziness, vomiting, nausea was also noted at half hourly interval for fist six hours following surgery. Total dosage and frequency of tramadol in the 6-hour period was also calculated. Use of anti-emetics was noted.

Results and Observation

In our study we have compared the postoperative analgesic efficacy of 300mg of oral gabapentin given one hour prior to surgery compared with 650mg of oral paracetamol given one hour prior to surgery. Study population consists of 60 patients who underwent surgery under general anaesthesia. Group 1 had 30 patients who were given oral Paracetamol one hour prior to surgery. Group 2 had 30 patients who were given oral gabapentin one hour prior to surgery.

Patient characteristics were age, sex, weight and ASA grade.

Preoperatively patient's heart rate and blood pressure were recorded. In the postoperative period these patients were examined at half hourly interval for first six hours for pain, nausea, vomiting, headache and dizziness. Pain was graded with VAS and if more than or equal to 4, rescue analgesia was given. In case of nausea and vomiting, Ondansetron 4mg was given intravenously. The following observations were made from the study.

Table 1: Mean demographic data in both groups

Characteristics	Group 1 Paracetamol N=30 (Mean± SD)	Group 2 Gabapentin N=30 (Mean± SD)	P value
Age (years)	40.533(15.45)	36.2(14.99)	0.95
Weight (Kgs)	56.06(7.43)	54.93(8.13)	0.56
Duration of surgery	148.5 (31.02)	154.8(35.87)	0.321

The mean age, weight and duration of surgery of both the groups were in the same range and found to be statistically insignificant.

Table 2: Sex distribution between both the groups

			Drug group		Total
			Paracetamol	Gabapentin	
Sex	Female	Count	13	13	26
		% within drug group	43.3%	43.3%	43.3%
	Male	Count	17	17	34
		% within drug group	56.7%	56.7%	56.7%
Total		Count	30	30	60
		% within drug group	100.0%	100.0%	100.0%

The sex distribution between both the groups were equal.

Table 3: Comparison of types of surgery between two groups

	Group 1 Paracetamol	Group 2 Gabapentin	p value
Plastic Surgery	8(26.7%)	6(20%)	0.536
General Surgery	14(46.7%)	11(36.7%)	
Urology	1(3.3%)	3(10%)	
ENT	7(23.3%)	10(33.3%)	

The comparison of types of surgery between two groups were statistically not significant.

Table 4: Comparison of the mean duration of surgery between both the groups

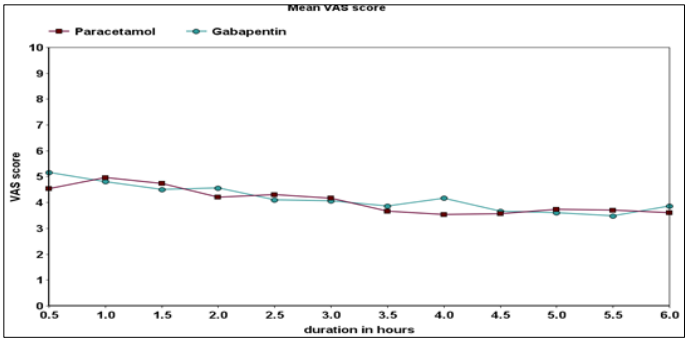
	Mean duration of surgery (minutes)	P value
Group 1 Paracetamol	148.5 (31.02)	0.3211
Group 2 Gabapenitn	154.8 (35.87)	

The mean duration of surgery between two groups were comparable. And the P value is statistically insignificant.

Table 5: Comparison of the mean duration of analgesia between both the groups

	Duration of analgesia (minutes) Mean ± SD	P value
Group 1 Paracetamol	83 (43.64)	0.4413
Group 2 Gabapenitn	74.48(46.69)	

The mean duration of analgesia produced by paracetamol and gabapentin were found to be in same range, and the P value is statistically insignificant.



Post-operative VAS between both the groups were comparable during the first 6 hours.

Graph 1: Comparison of mean VAS scores between two groups

Table 6: Comparison of analgesic consumption between both the groups

	Analgesic consumption(mg) Tramadol IV Mean ± SD	P value
Group 1 Paracetamol	53.00(7.02)	0.627
Group 2 Gabapenitn	51.66 (7.46)	

The analgesic consumption between paracetamol and gabapentin were found to be in similar range and not statistically significant

Table 7: Adverse effects between the groups.

Adverse effects	Group 1 Paracetamol	Group 2 Gabapentin	P value
Headache	1	4	0.161
Dizziness	1	4	0.085
Nausea	8	7	0.76
Vomiting	3	2	0.64

There is no statistically significant difference in the adverse effects between both group.

Table 8: Comparison of Ondansetron consumption between both groups

Drug group	Ondansetron		P value
	Yes	No	
Group 1 Paracetamol	8	22	0.76
Group 2 Gabapenitn	7	23	

The antiemetic consumption were compared between the groups but statistically insignificant.

Discussion

Post-operative pain is a major cause of morbidity in the postoperative period. Pain control in the post-operative period is essential for improving gastrointestinal, respiratory function, psychological outcome of a patient and also patient's anticipation of future surgeries (3). Preemptive analgesia helps to prevent the sensitization of neurons both peripherally and centrally. This not only helps in better analgesia but also helps to prevent unwanted adverse effects associated with commonly used breakthrough analgesics such as opioids and NSAIDs. Post-operative pain increases stress hormone release and cause negative nitrogen balance which eventually weakens the immune system (6).

This study was designed with the aim of assessing the preemptive analgesic efficacy of oral gabapentin in post-operative period compared with Paracetamol which is an established preemptive and breakthrough analgesic. We also studied the adverse effects of both groups. Opioids form the mainstay of post-operative pain management, but they have adverse effects like respiratory depression, pruritis, nausea, vomiting, constipation, tolerance.

Gabapentin is a GABA analogue earlier used as an antiepileptic, later found to be beneficial in neuropathic pain. Despite its functional similarities with GABA, they don't act via mechanisms related to GABA. Their exact mechanism of action is not understood. Proposed mechanisms include ability to increase concentration and rate of synthesis of GABA in brain, binding with high affinity to alpha binding site in brain tissues associated with voltage sensitive calcium channels. It has antihyperalgesic and antiallodynia properties (10). Paracetamol is a centrally acting inhibitor of COX. The drug was first found to be associated with suppression of prostaglandin synthesis through inhibition of cyclooxygenase enzyme. Along with this, it also inhibits the descending seratonergic pain pathway (11).

Duration of analgesia

The mean duration of analgesia produced by paracetamol was 83 minutes; whereas the mean duration of analgesia produced by gabapentin was 74.48 minutes. This was not found to be statistically significant between the groups. The duration of first breakthrough analgesia for preoperative gabapentin in a study by syal *et al* where 1200mg of gabapentin was used was 332 minutes. The duration of analgesia has not been studied previously with 600mg any trial. The duration of analgesia produced by preoperative Paracetamol was consistent with the duration of action of Paracetamol and with the duration of analgesia in the study by syal *et al*. (12)

Mean analgesic consumption

The mean analgesic consumption of group 1 which received Paracetamol was 53.0 mg of tramadol, whereas the mean analgesic consumption of group 2 which received gabapentin was 51.66 mg of Tramadol. This finding is not consistent with the previous studies comparing the analgesic consumption between Gabapentin and Paracetamol.

Incidence of adverse effects

The incidence of headache in Paracetamol group is 1 among 30 patients which is negligible. And the incidence of headache in gabapentin group is 4 among 30. This effect has not been studied in the previous studies. The incidence of dizziness among patients who received Paracetamol is 1 out of 30 and incidence among patients who received gabapentin is 5 out of 30. There is a mildly significant difference in the incidence of dizziness which is comparable with the study by Dirks *et al* where 1200mg of gabapentin was given one hour prior to surgery and the incidence of dizziness was 6 among 25 patients. The incidence of nausea in Paracetamol group is 8 among 30 and incidence in gabapentin group is 7 among 30. This result was consistent with the study by Dirks *et al* where the incidence was 5 among 25 patients who received 1200mg of gabapentin one hour prior to surgery. The incidence of vomiting in Paracetamol group is 2 among 30 patients and in gabapentin group is 3 among 30 patients. This result is comparable to the study by Turan *et al* where the incidence of vomiting was 1 among 25 pateints who received 1200mg of gabapentin one hour prior to surgery. The incidence of antiemetic use in Paracetamol group is 8 among 30 and with gabapentin group is 7 among 30. There hasn't been much

difference between between the groups in our study which is comparable with the study by Turan *et al* which had an incidence of 9 among 25 patients.

Conclusion

Both Paracetamol and Gabapentin had comparable potency as pre-emptive analgesic. Our study has shown that the time to first rescue analgesia, total amount of rescue analgesia between the two groups in the first 6 hours following surgery were not statistically significant. Moreover, the incidence of adverse effects like nausea, vomiting, dizziness and headache were comparable also comparable between two groups.

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