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TO EVALUATE THE EFFECT OF PRE-OPERATIVE ORAL GABAPENTIN ON POSTOPERATIVE PAIN RELIEF AND TO EVALUATE THE ADVERSE EFFECTS.

Anesthesiology

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ABSTRACT

BACKGROUND: Gabapentin was introduced in 1980 as an adjuvant anti-convulsant drug for the treatment of refractory partial seizures. Subsequently, it was shown to be effective in treating a variety of chronic pain conditions, (Mao et al, 2000)1. In 2002, Gabapentin was approved by the US FDA for the treatment of post-herpetic neuralgia.

AIMS AND OBJECTIVE: Our study aims to evaluate the effect of preoperative oral Gabapentin on postoperative pain relief and also to evaluate the adverse effects of Gabapentin, if any.

MATERIALS AND METHODS: A prospective, randomized, placebo controlled, double blind clinical study was conducted on 60 normotensive patients (30 in each group), of either sex, undergoing elective upper abdominal surgeries under general anaesthesia. Patients were randomized to C or G group accordingly and received the respective capsules, that is, the Placebo Capsule B-Complex or Capsule Gabapentin 400 mg, 2 hours prior to surgery.

RESULTS: Visual analogue scale for postoperative pain was assessed in all patients. Patients who had received Gabapentin woke up with significantly less pain than control group; and also the patients in the Gabapentin group required rescue analgesic at a significantly later interval than the patients in the control group. Very few side effects were observed in both the groups.

CONCLUSION: Gabapentin (400 mg), when given orally two hours prior to surgery provides postoperative analgesia and extends the time required for first dose of rescue analgesic. There are only few side effects of oral Gabapentin (400 mg) in the form of sedation and dizziness which are tolerated well and require no further interventions.

KEYWORDS

Gabapentin, Analgesia, Intubation, Oral, Response.

I. INTRODUCTION

Gabapentin was introduced in 1980 as an adjuvant anti-convulsant drug for the treatment of refractory partial seizures. Subsequently, it was shown to be effective in treating a variety of chronic pain conditions, including post-herpetic neuralgia, diabetic neuropathy, complex regional pain syndrome, inflammatory pain, central pain, malignant pain, tri-geminal neuralgia, HIV-related neuropathy and headaches (Mao et al, 2000)[1]. In 2002, Gabapentin was approved by the US FDA for the treatment of post-herpetic neuralgia.

II. MATERIALS AND METHODS

A prospective, randomized, placebo controlled, double blind clinical study was conducted on 60 normotensive patients (30 in each group), of either sex, undergoing elective upper abdominal surgeries under general anaesthesia.

2.1 Inclusion criteria: Patients undergoing elective upper abdominal surgeries under general anaesthesia, ASA Grade I/II, Age between 20-40 years, Weight between 40-60 kg.

2.2 Exclusion criteria: Patient refusal, difficult intubation. (Malampatti Class III/IV, Restricted neck movements, Receding jaw, Oral masses, Cormack-Lehanne Grade>I) Drug or alcohol abuse, patients receiving sedatives, hypnotics and antidepressants, Cardiovascular and renal diseases, known allergy to gabapentin, patients suffering from any cardiovascular disorder, either controlled with drugs or uncontrolled (hypertension or ischemic heart disease or valvular heart disorders), history of acidity or gastro esophageal reflux. Study was carried out after getting approval from the Institutional Ethics Committee and informed consent was obtained for participation in the study from all patients. Tablet Alprazolam 0.5mg oral was given on the night prior to surgery; Patients were randomized to C or G group accordingly and received the respective capsules 2 hours prior to surgery with a sip of water. The capsule was given by an anaesthetist who was blinded for the study.

2.3 Study Medication:

G Group: Capsule Gabapentin 400 mg two hours prior to surgery.
Trade Name: GABANTIN400 (SUN PHARMACEUTICALS)
Generic name: 1-(amino methyl) cyclohexane acetic acid

C Group: Placebo Capsule B-Complex

In the pre-operative area, patient was monitored for vital parameters and level of sedation, before shifting to operation theatre.

All the patients received Inj. Midazolam 0.02 mg/kg and Inj. Pentazocine 0.3 mg/kg I.V. as pre-medication; they were induced with Inj. Propofol 2-2.5mg/. Intubation was facilitated with Inj. Suxamethonium Hydrochloride 2 mg/kg. Patients were maintained on O_2 + N_2O (50% each) + Isoflurane (0.8%).Muscle relaxation was maintained using injection Vecuronium Bromide (0.1 mg/kg) after initiation of spontaneous respiration. $ETCO_2$ was also monitored during the study.

2.4 Parameters Measured:

Heart rate, Systolic, Diastolic and Mean arterial blood pressure were recorded before induction, Patient were observed for 8 hours in the post-operative period for side-effects like somnolence, nausea, vomiting, ataxia and dizziness and treated accordingly if needed. Incidences of all these parameters were recorded in both the group. Time when the first analgesic was demanded was noted. Patients were educated about Visual Analogue Scale (V.A.S.) for grading of postoperative pain. V.A.S. scale of pain was used where 10 cm scale marked with'0' at one end represented 'no pain' and marked '10' at other end represented 'worst possible pain'. When asked, patient was told to point out his assessment of pain at that time on the multiple points of this visual analogue scale. When V.A.S. score exceeded 4 or when patient requested pain relief, rescue analgesia was given with Inj. Tramadol 1 mg/kg.

III. Statistical analysis

Demographic parameters were analyzed by Student's t-test. Binary data like sex, ASA grade were analyzed by chi-square test. For finding statistical significance between the groups, unpaired t-test was applied to ascertain the pattern and magnitude of differences. A p value < 0.05 was considered as significant and p value < 0.01 was considered highly significant.

IV. RESULTS

Both the groups were comparable in terms of age, sex, weight and ASA

grade. Mallampatti grading, laryngoscopy and time required for intubation were comparable in both the groups. The duration of surgery was comparable in both the groups (P=0.7921). The data thus obtained was divided in the following two groups:

Gabapentin group ('G' group) -Patients receiving Capsule Gabapentin 400 mg orally with sips of water prior to surgery.

Control group ('C' group) -Patients receiving Capsule B-Complex as placebo with sips of water prior to surgery.

At the baseline, the time required for intubation, the heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure in both groups were comparable.

TABLE I - DEMOGRAPHIC DATA

PARAMETERS	'G'GROUP MEAN ± SD	'C'GROUP MEAN ± SD	'P' VALUE
AGE# (years)	33.57 ± 06.73	33.47 ± 6.65	0.954
WEIGHT# (kg)	52.83 ± 05.20	52.17 ± 6.39	0.659
SEX (M/F)	15/15	13/17	0.605
ASA GRADE (I /II)	28/02	27/03	0.647

- By unpaired Student's t-test
- By Chi-Square test

Both the groups were comparable in terms of age, sex, weight and ASA grade

TABLE II - DURATION OF SURGERY

	'G'GROUP MEAN ± SD (minutes)	'C'GROUP MEAN ± SD (minutes)
DURATION OF SURGERY	94.50 ± 17.14	93.33 ± 16.99

The duration of surgery was comparable in both the groups (P=0.7921).

TABLE III – COMPARISON OF POSTEXTUBATION VISUAL ANALOGUE SCALE (V.A.S.)

V.A.S. AT EXTUBATION	'G'GROUP MEAN ± S.D.	'C'GROUP MEAN ± S.D.	'P' VALUE
	1.80 ± 1.42	5.67 ± 1.94	< 0.001

After extubation when patients became awake and responded to verbal commands, visual analogue scale for postoperative pain was assessed in all patients. As shown, patients who had received Gabapentin woke up with significantly less pain than control group.

TABLE IV- TIME WHEN FIRST RESCUE ANALGESIC WAS DEMANDED

TIME WHEN FIRST RESCUE ANALGESIC WAS DEMANDED	'G'GROUP MEAN ± SD (hours)	'C'GROUP MEAN ± SD (hours)	'P' VALUE
	4.47 ± 2.19	0.23 ± 0.63	< 0.005

It was found that patients in the Gabapentin group required rescue analgesic at 4.47 hours whereas patients in the control group required the same within 0.23 hours. Thus, the patients in the Gabapentin group required rescue analgesic at a significantly later interval than the patients in the control group.

TABLE V - ADVERSE EFFECTS

ADVERSE EFFECTS	'G'GROUP	'C'GROUP
SEDATION	05 (16.67%)	00
DIZZINESS	02 (6.67%)	00
POSTOPERATIVE NAUSEA AND VOMITING	03 (10%)	03 (10%)

Very few side effects were observed in both the groups. Two patients receiving Gabapentin reported dizziness for 2 hours and required no intervention. Three patients in either group had post-operative vomiting which was treated with Inj. Ondensetron 0.08 mg/kg.

V. DISCUSSION

Gabapentin has more recently been used by Kong et al (2007)[2] for the management of more acute conditions, particularly in the peri-operative period viz, for post-operative analgesia, pre-operative anxiolysis, prevention of chronic post-surgical pain, prevention of post-operative nausea and vomiting and post-operative delirium. Hence, we planned to conduct a prospective, randomized, double blind, clinical study to assess effect of preoperative oral Gabapentin on post-operative analgesia and the requirement of first rescue analgesic.After extubation, when patients became awake and responded to verbal commands, visual analogue scale (VAS) for postoperative pain was assessed in all patients. Tramadol 1 mg/kg was given as rescue analgesic when VAS exceeded 4. In our study, 16.67% of the patients in the Gabapentin group and 86.67% of the patients in the control group required rescue analgesic immediately after extubation (Table *III*, IV). Patients who had received Gabapentin woke up with significantly less pain than control group. Koc et al (2007)[3], Pandey et al (2004)[4] and Menigaux et al (2005)[5] found similar results. Patients in the Gabapentin group in our study required rescue analgesic at 4.47 ± 2.19 hours whereas patients in the control group required the same within 0.23 ± 0.63 hours (TableIV). Thus, the patients in the Gabapentin group required rescue analgesic at a significantly later interval than the patients in the control group. Similar to our results, Menigaux et al (2005)[5] observed that the first rescue analgesic in the form of Morphine was requested at a later interval in the Gabapentin than in the control group. Koc et al (2007)[3] demonstrated that intraoperative total Remifentanil consumption and postoperative total Tenoxicam (rescue analgesic) consumption were lower in the Gabapentin and Dexamethasone group. This is the only study up till now which has studied the effect of preoperative Gabapentin on intraoperative opioid consumption which proved the opioid-sparing effect of Gabapentin and represents a good example of 'multimodal analgesia'.Inhibition of central neuronal sensitization by reducing hyper excitability of secondary nociceptive neuron in the dorsal horn, decrease in the glutaminergic transmission in the spinal cord induced by noxious stimulus and reduction of hypersensitivity associated with nerve injury, inflammation and pain after surgery (Cheong et al 2000[6] and Field et al 1997[7]) was proposed as the mechanism of postoperative analgesia by Feng et al (2003)[8],Menigaux et al (2005)[5], Turan et al (2004)[9] and Koc et al (2007)[3].

Thus, oral Gabapentin 400 mg given 2 hours prior to surgery
1. Decreases postoperative pain.
2. Has mild postoperative sedation without respiratory depression
3. Is cost effective, safe and acceptable to patients

VI. CONCLUSION

From our clinical study, it can be concluded that:
1. Gabapentin (400 mg), when given orally two hours prior to surgery provides postoperative analgesia and extends the time required for first dose of rescue analgesic.
2. There are only few side effects of oral Gabapentin (400 mg) in the form of sedation and dizziness which are tolerated well and require no further interventions.
3. Oral Gabapentin 400 mg is safe, acceptable and cost-effective compared to the drugs administered parenterally.

We recommend oral Gabapentin 400 mg two hours prior to surgery for post-operative analgesia in morbidly obese, elderly, chronic obstructive pulmonary disease patients where mild sedation without any fall in oxygen saturation is desirable.

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