DOES GABAPENTIN RELIEVE ACUTE PREOPERATIVE ANXIETY?

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ABSTRACT

INTRODUCTION: The role of Gabapentin in relieving chronic pain, chronic anxiety disorders and acute postoperative pain is well known by now. Trials done with the administration of Gabapentin to treat preoperative anxiety showed mixed results. So, this study was conducted to test the hypothesis that premedication with Gabapentin 1200 mg versus placebo would reduce preoperative anxiety in patients undergoing open cholecystectomy under general anesthesia.

MATERIAL AND METHODS: A prospective, randomized, double blind and placebo controlled study was carried out at Universal College of Medical Sciences & Teaching Hospital (UCMSTH) from August 2012 to Januray 2014. Total 160 adult patients of American Society of Anaesthesiologist **(**ASA**)** I and II were divided into 2 groups of 80 each. Patients in group 1 and group 2 received capsules Gabapentin (1200mg) or identical placebo capsules 2 hours prior to surgery respectively. Preoperative anxiety was assessed for three times using Anxiety Visual Analogue Scale (VAS) score. A uniform anesthetic technique was used in both groups. Parameters including preoperative and postoperative sedation scores and various side effects were also observed.

RESULTS: VAS anxiety scores after one hour of drug intake (47.19±17.37 versus 63.13±17.77) and just before induction of anaesthesia (43.81±17.72 versus 81.81±21.57) were significantly lower in Gabapentin group as compared to placebo group. No patient experienced any significant side effects or sedation in either group throughout the study period.

CONCLUSIONS: Premedication with 1200 mg Gabapentin in open cholecystectomy patients significantly reduced preoperative anxiety as evident by decrease in anxiety VAS scores without any significant side effects.

KEY WORDS: Acute anxiety, Gabapentin, Preemptive analgesia, Premedication

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INTRODUCTION

Does Gabapentin premedication relieve acute preoperative anxiety? Though it has been effectively used for chronic pain and anxiety disorders, its role in relieving acute anxiety has to be established.

Preoperative anxiety may be increased through ignorance of anesthetic and surgical procedures, given past experience and patient's psychological profile.[1] It also causes adverse physical response preoperatively by exerting significant haemo-dynamic stress response resulting in increased cardiac output and myocardial oxygen consumption. It adversely influences induction of anesthesia, postoperative anxiety and pain, length of hospital stay and patient recovery. It also makes pain control more difficult.[2] Prevention of anxiety is therefore a major issue during the perioperative care.

Literature search didn't reveal much information about its effectiveness in relieving acute preoperative anxiety. Thus, this study was carried out to evaluate the effect and safety of Gabapentin premedication on preoperative anxiety in patients undergoing elective open cholecystectomy.

MATERIAL AND METHODS

This was an open prospective, randomized, placebo controlled, double blind study. Study was conducted in UCMS TH, Bhairahawa, Nepal, over a period of 18 months. After taking approval of institutional ethics committee and written informed consent from patients, study was carried out in 160 adult patients (18-60 yrs) of ASA Grade I and II of both genders undergoing elective open cholecystectomy under general anaesthesia.

Exclusion criteria's were patients having body weight more than 20% of ideal body weight, history of chronic pain conditions, drug or alcohol abuse, Gabapentin hypersensitivity, administration of sedatives within 24 hours of scheduled surgery, systemic diseases like uncontrolled hypertension and diabetes mellitus, bronchial asthma, valvular heart diseases and coronary artery disease, renal and hepatic diseases, and neuromuscular or psychiatric disorder.

At the time of preanesthetic evaluation, patients were explained about 100mm VAS for anxiety that is Anxiety VAS (0=no anxiety to 100= worst imaginable anxiety) and were kept nil per oral after midnight before surgery.

On the day of surgery, patients were divided into 2 groups of 80 each and assigned randomly in a double blind fashion via random number table to receive either capsule Gabapentin 1200 mg (Group 1 or Gabapentin group) or an identical looking placebo (Group 2 or control group) orally 2 hours prior to surgery (n=40 per group). The study medication was prepared by the hospital pharmacy in identical appearing capsules and was put in 160 numbered envelopes containing 2 capsules each to maintain blinding. The capsules were kept in pharmacy and were taken only when required. No sedative premedication other than Gabapentin was used. The patients, attending anesthesiologists, persons involved in data collection and nurses involved in patient's care in the recovery room were all blinded to the content of the study medication.

In the operation room, routine monitoring including electrocardiography (ECG), non invasive blood pressure (NIBP) and pulse oximeter (SpO_2) was applied and preoperative baseline vitals were recorded. The level of anxiety was assessed first at the time of drug intake (Anxiety VAS-1), then one hour after the drug intake in pre-anesthesia preparation room (Anxiety VAS-2) and lastly, just before induction inside the operating room (Anxiety VAS-3). Preoperative sedation scores were also recorded for three times along with VAS. Uniform anaesthetic technique was used in all groups. Anesthesia was induced with intravenous (i.v) Propofol 2 mg/kg followed by Vecuronium 0.1 mg/kg to facilitate orotracheal intubation. Intravenous Morphine 0.1mg/kg bolus was given for intraoperative analgesia. Anaesthesia was maintained with Oxygen, Isoflurane 2 volume % and intermittent 1 mg bolus of Vecuronium. All patients received intramuscular Diclofenac 75mg and intravenous Ondansetron 4mg after removal of gall bladder. Isoflurane was discontinued at the beginning of skin closure. At the end of surgery and after initiation of spontaneous respiration, reversal of neuromusmular blockade was done with intravenous Neostigmine 0.05 mg/kg and Glycopyrrolate 0.01 mg/ kg. After patient started obeying commands, trachea was extubated. Throughout intraoperative periods vitals monitoring of all patients were done and were within normal ranges. Then, patients were shifted to post anesthesia care unit (PACU) for observation for 12 hours. Intravenous Paracetamol 1 gram was given slowly as a drip over an hour for postoperative pain in PACU. Side effects like nausea, vomiting, retching, dizziness, vertigo, sedation, visual disturbance, headache and respiratory depression (Respiratory rate<8/min and Oxygen saturation, SpO2 <90% without oxygen supplement) were also observed and recorded for 12 postoperative hours and were treated whenever indicated like respiratory depression or SpO_2 <90 % was treated with oxygen supplementation, ≥2 episodes of vomiting was treated with Ondansetron 4 mg intravenously.

Both pre and postoperative sedation was measured on a 4-point categorical scale derived from the Ramsay Score as

follows:
0 = alert, aware.
1 = somnolent, arousable by verbal contact.
2 = somnolent, arousable by tactile stimulation.
3 = asleep, arousable by painful stimulation.

Statistical Analysis-.Morphometric and demographic characteristics of patients, clinical variables and preoperative anxiety in both Gabapentin and control groups were compared with student's t-test. Results are expressed as mean ± SD. $P < 0.05$ was considered statistically significant.

RESULTS

The two groups were comparable with respect to demographic characteristics, preoperative vitals and length of anesthesia. (Table 1)

Table1: Patient characteristics and preoperative data

Parameters	Group 1 (n=80)	Group2 (n=80)	P value
Age(years)	39.28±12.24	40.44±12.55	0.554
Wt (kg)	53.89±7.85	54.43±8.29	0.674
L-Anesthesia (min)	58.23±6.98	58.21±7.78	0.991
Heart Rate (beats/min)	81.41±13.36	82.33±13.30	0.666
Systolic BP (mmHg)	124.21±10.33	126.24±10.72	0.226
Diastolic BP (mmHg)	77.20±7.21	75.97±6.76	0.270
RR (breaths/min)	12.38±1.42	12.60±1.49	0.332
SPO_2(%)	99.68±0.49	99.59±0.56	0.301

All the values are in mean (±) SD.

Preoperative VAS anxiety scores at the time of drug administration were similar in both the groups but VAS anxiety scores after one hour of drug intake and just before induction were significantly lower in Gabapentin group than in control group. (Table 2)

Table 2: Preoperative anxiety VAS scores

	Group 1(n=80)	Group 2 (n=80)	P value
Anxiety VAS 1	77.31±19.02	70.00±21.88	0.25
Anxiety VAS 2	47.19±17.37	63.13±17.77	0.000
Anxiety VAS 3	43.81±17.72	81.81±21.57	0.000

All the values are in mean (±) SD.

Preoperatively, all patients had sedation score of zero in either group. Postoperative sedation scores were also observed. It was recorded at the time of admission in PACU, then every 15 minutes for the first 1 hour and hourly for remaining 11 hours. Maximum sedation score observed throughout the study period was 1.

Table 3: Postoperative sedation scores

Sedation Scores	Groups	PACU admission	15 minutes	30 minutes	45 minutes
0	Group 1	6	71	78	80
	Group 2	9	72	77	80
1	Group 1	74	9	2	-
	Group 2	71	8	3	-

As shown in Table 3, at the time of admission in PACU, only 15 patients were awake and alert having the sedation score of zero whereas 145 patients had sedation score of 1. But, at 45 minutes of admission in PACU, all the patients of either group had sedation score of Zero. Thereafter, they all were awake and alert throughout the study period.

Various side effects mentioned above were observed and recorded for 12 postoperative hours. Only one episode of nausea was present in 3 patients of Group 1 and in 2 patients of Group 2. Except nausea, no other side effects were seen in any patient in either group.

DISCUSSION

Gabapentin is an inhibitory neurotransmitter. The mechanisms of action is mediated via GABA B receptor, enhancement of N methyl D-aspartate current at GABAergic interneurons, blockade of AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors in the spinal cord and activation of ATP (adenosine triphosphate) sensitive potassium channels leading to hyperpolarization. Also, its binding in a state dependent manner to the alpha-2 delta subunit of voltage gated Ca channels in overexcited presynaptic neurons reduce release of excitatory neurotransmitters and thereby reducing levels of anxiety and pain.[3]

Gabapentin has known antinociceptive, antihyperalgesic and anxiolytic properties. Studies have found that pre-emptive use of gabapentin before surgery is better than postoperative administration due to its antihyperalgesic properties.[4-6]

Pretreatment with a single dose gabapentin blocked the development of hyperalgesia and tactile allodynia for upto 2 days in a rat model of postoperative pain, while gabapentin 1

hour after intervention reduced symptoms for only three hours.[7] Gabapentin crosses blood brain barrier rapidly and its concentration in brain tissue is nearly as high as in blood when administered approximately 2 hours before surgical stimuli.[8] So in this study, Gabapentin was used preemptively 2 hours prior to induction.

Few studies have been done till date regarding its use for acute anxiety relief and is still a controversial issue. Common drug used to reduce preoperative anxiety is Benzodiazepines. But unlike Benzodiazepines, Gabapentin has anxiolytic effect at low dose with lack of amnesic effect, cognition deficits and drug interaction. It does not need plasma monitoring and has less dependence or abuse liability.[9]

Reduced anxiety level without any adverse effect of gabapentin on memory was initially found in rat models.[10] Similar finding was found in another study suggesting its potential advantage over the existing anxiolytics that causes amnesia at doses used for the treatment of anxiety disorders.[9] Its effectiveness in co-morbid anxiety, social phobia and panic disorder is well known.[11-14] De Paris et al again investigated the effects of 400mg and 800mg gabapentin on anxiety induced by simulated public speaking that resembles preoperative anxiety state. It showed attenuated anxiety in subjects with decrease in Visual Analogue Mood Scale and Profile of Mood State scores[15]. Premedication with 900 mg gabapentin and 300 mg pregabalin decreases preoperative anxiety and improves sedation without producing significant side effects in patients undergoing elective abdominal hysterectomy under general anaesthesia.[16] But, Clarke H et al.[17] did not show any beneficial effect with 600mg gabapentin premedication in patients undergoing total hip arthroplasty but in his another study done with 1200mg dose, preoperative anxiety and pain scores were reduced and sedation was increased prior to entering the operating room suggesting that 1200mg gabapentin may be a treatment option for patients who exhibit high levels of preoperative anxiety.[18] Use of single 1200mg dose of gabapentin premedication was very effective not only in reducing postoperative pain but also in reducing preoperative anxiety without causing amnesia, sedation and other side effects in patients undergoing various surgical procedures.[4,5,19-27] This present study also showed that 1200 mg gabapentin premedication significantly reduced preoperative anxiety scores 1 hour after the drug intake and just before induction of anesthesia. Recent study have also found that oral Gabapentin premedication reduced intraoperative anxiety, sedation and intraocular pressure with improved postoperative recovery in elderly patients undergoing elective intraocular surgery.[28]

Studies on safety issues were performed in chronic pain patients on long term Gabapentin therapy and have demonstrated adverse effects like dizziness, somnolence, confusion, headache, nausea, ataxia and weight gain.[29,30] In our study, we used only a single 1200 mg dose and observed no significant side effects. Our findings are consistent with the findings in many single dose studies related to postoperative pain where no significant side effects were observed. Neither a single patient experienced serious side effects nor any patient received treatment for it in either group throughout the study period. Postoperatively, sedation was present for half an hour after PACU admission and was mild. All patients were awake and alert at 45minutes of PACU admission and thereafter.

The result of our study demonstrated that preemptive use of single 1200mg dose gabapentin significantly decreased preoperative anxiety in patients undergoing elective open cholecystectomy with very negligible side effects.

CONCLUSION

Our findings suggest that Gabapentin should be considered a potentially useful premedicant drug in relieving preoperative anxiety.

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