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Effects of Gabapentin on Postoperative Pain and Total Analgesic Requirement After Laparoscopic Cholecystectomy

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The aim of this study is to determine the effect of preoperative use of gabapentin on postoperative pain in patients undergoing laparoscopic cholecystectomy. Sixty adult patients listed for laparoscopic cholecystectomy were randomly allocated to two groups of 30 each to receive gabapentin 600 mg p.o. or a matching placebo 2 hours before surgery. Postoperative pain was monitored using 100 mm visual analogue scale (0 for no pain and 100 for worst imaginable pain) at 1, 2,6,12 and 24 hours. Diclofenac 75 mg IM was used as rescue analgesic and total analgesic requirement (mg/24hr) in first 24 hours following surgery was recorded. Postoperative pain scores and total analgesic requirement was significantly less in gabapentin group compared to placebo group. A single 600 mg dose of gabapentin given preoperatively decreased postoperative pain and total analgesic requirement following laparoscopic cholecystectomy. Preemptive use of gabapentin can be used to treat postoperative pain caused by laparoscopic cholecystectomy.

Keywords: Gabapentin, postoperative pain, visual analogue scale.

Laparoscopic cholecystectomy is reported as one of the most common surgical procedures worldwide[1] and early postoperative pain is a common complaint of these patients.This pain is of lesser severity and duration than that of open cholecystectomy, nevertheless, it is still considerable[2] and it impedes quick postoperative recovery.

In laparoscopic cholecystectomy overall pain has three separate components: incisional pain (somatic pain at port site incision), visceral pain (deep intraabdominal pain) and shoulder pain (referred visceral pain) due to diaphragmatic irritation caused by Co_2 insufflation[3]. Shoulder and sub-diaphragmatic pain occur in 12 to 60 % of patients[4]. Severe acute pain after laparoscopic cholecystectomy might progress to chronic pain (postoperative cholecystectomy syndrome) [5].

Opioids are commonly used for postoperative pain management but they have a significant side effect profile including nausea, vomiting, constipation, urinary retention and allergic reactions. Nonsteroidal anti-inflammatory drugs (NSAIDS) can cause epigastric pain, gastric ulceration and bleeding, renal toxicity and fluid retention. Selective COX-2 inhibitors (coxibs) exert prothombotic properties and increase cardiovascular risk. Epidural analgesia is an invasive procedure with serious complications. A multimodal approach is advocated to manage

postoperative pain adequately with minimum risk of adverse effects to the patients. Gabapentin is an anti-seizure drug that has been shown effective in mitigation of pain associated with a variety of conditions. It is well-toleratedwith few drug interactions, does not induce hepatic enzymes, therefore, justifying its evaluation in postoperative context.

MATERIALS AND METHODS

This prospective, randomized, placebo-controlled study was conducted by the department of Pharmacology of Government Medical College, Srinagar in collaboration with the department of Surgery and Anesthesiology of SMHS hospital. The institutional ethical committee (IEC) approved the study protocol; informed consent was sought from each patient. Sixty adult patients, either sex, American Society of Anesthesiologists (ASA) physical status I & II with USG diagnosed cholelithiasis listed for laparoscopic cholecystectomy under general anesthesia were considered for the study. The exclusion criteria were patients with age < 18 or > 60 years; could not cooperate; patients having epilepsy; deranged kidney or liver functions; history of hypersensitivity to any drug; history of peptic ulcer disease; patients on psychotropic drugs, calcium channel blockers or antidepressants; if laparoscopic cholecystectomy got converted into open-cholecystectomy for any reason.

Patients were visited during preanesthetic assessment and those satisfying the inclusion criteria were asked about their medical history and demographic characteristics.The study protocol was explained and the participants were randomly assigned with the help of table of random numbers into the following groups of thirty patients each.

Table 1. Demographic and clinical features of the patients

Variable	Gabapentin group (n=30)	Placebo Group (n=30)
Age (yr,)	42.2±9.7	39.6±8.6
Weight (Kg)	58±7.7	60.3±8.6
Gender (M/F)	6/24	11/19
Duration of surgery (min)	63.0±16.1	65.6±10.7
Duration of anesthesia (min)76.0±16.0		79.4±11.5
ASA score 1/11	21/9	24/6
Co_2 insufflation time (min)	51.4±13.9	55.2±11.4

Values are shown as number (n) of patients or mean±SD. No significant differences were found between the two groups (P>0.05)

Table 2. Postoperative visual analogue scale (VAS) scores at 1, 2, 3, 6, 12, and 24 hours; and total analgesic consumption in first 24 hours

Variables	Gabapentin group (n=30)	Placebo group (n=30)
1 hr	57±1.7	8.5±0.6
2 hr	4.7±1.6	7.3±0.9
6 hr	3.3±1.4	4.7±1.3
12 hr	2.0±1.5	3.1±1.1
24 hr	1.4±0.9	2.4±0.7
Total diclofenac requirement (mg)	65±0.00	119.50±54.7

Values are presented as mean±SD. P value <0.05

Group G (gabapentin group, n=30): this group received 600mg gabapentin p.o.with sips of water2 hours before surgery. Dose of gabapentin was decided from previous available studies[6,7].

Group P (placebo group, n=30): this group was give placebo p.o. 2 hours before surgery.

Anesthesia was induced usingpropofol 2 mg/kg. Intubation of trachea was done with suxamethonium2mg/kg. Anesthesia was maintained with N_2O:O_2: isoflurane. Intraoperative muscle relaxation was facilitated by injection of atracurium besylate 0.5mg initially. After intubation a nasogastric tube was inserted which was removed at the end of the surgery before

extubation. During the surgery patient was kept in reverse trendelenburg positionwith right side of the table elevated. The abdomen was insufflated with carbon dioxide (CO_2) to an intra-abdominal pressure of 10-14mmHg. Duration of anesthesia, surgery and CO_2 insufflation was also recorded in each patient as per the proforma. After completion of the surgery, neuromuscular blockade was reversed with a standard mixture of neostigmine and atropine (2.5mg: 1.2mg) and patients were extubated and when adequate spontaneous ventilation was established, patients were shifted to recovery. While in the recovery, postoperative data was collected at 1, 2, 6, 12 and 24 hours.

Postoperative wound pain at rest was assessed at 1, 2, 6, 12 and 24 hours with a 10cm Visual Analog Scale (VAS: 0=no pain; 10 = most severe pain) score in each arm. Diclofenac (IM 75 mg) was used as rescue analgesic in both the groups depending on VAS scores. Total analgesic requirement (mg/24 hr) between the two arms was recorded. Data was expressed as mean ± standard deviation (SD) or number (n) as appropriate. VAS scores and total analgesic consumption in first 24 hours was compared using an unpaired t-test. Chi-square test was used for comparison of proportions. A value of $P < 0.05$ was considered statistically significant. The software used was Statistical Package for Social Sciences (SPSS) and Microsoft Excel.

RESULTS

There was no difference between the two groups with respect to age, weight, gender, ASA score, duration of anesthesia, duration of surgery and Co_2 insufflation time (table 1).

VAS score (mean ± SD) at 1,2,6,12 and 24 hours were significantly lower in group G than in group P at all time points ($P < 0.05$) (table 2).

Total analgesic requirement (mean±SD) in first 24 hours was 65±0.05 in group G and 119±54.7 in group P ($P < 0.05$) (table 2).

DISCUSSION

In our study 600 mg of gabapentin decreased postoperative pain and total analgesic requirement after laparoscopic cholecystectomy.

Gabapentin was designed as a hydrophobic analogue of inhibitory neurotransmitter, gamma amino butyric acid (GABA) thatwas able to cross blood brain barrier. It was approved by USFDA for epilepsy in December 1993 and for postherpetic neuralgia in 2002; and now it is widely recommended as first line agent in neuropathic pain. Gabapentin enacarbil extended-release tablet formulation was approved for treatment of moderate to severe restless leg syndrome in adults in April 2011. The bioavailability of gabapentin is 35 to 60%; peak plasma concentration is attained in less than 2 hours and its elimination half-life is between 4.8 and 8.7 hours.

Although a GABA analogue with anticonvulsant properties, it does not bind to GABA receptors or transporters. Instead it binds to á$_2$ä-1, an auxiliary subunit of voltage gated calcium channels. á$_2$ä-1 is present in numerous tissues and is richly expressed on various CNS neurons: within spinal cord it is present presynaptically in the dorsal horn and postsynaptically on deeper neurons[8, 9]; moderate to high expression has been found in nociception processing areas of brain like dorsal raphe, periaqueductal gray, locus coeruleus, and amygdala[10, 11]. Molecular and transgenic studies suggest á$_2$ä-1 as the therapeutic target of gabapentinoids[12, 13].Experiments done on mice and cell culture suggest that gabapentin is a powerful inhibitor of thrombospondin/astrocyte stimulated synapse formation claiming that inhibition of excitatory synapse formation is an important mechanism of its therapeutic role in pain and epilepsy[14]. The exact cellular and molecular mechanism by which gabapentin acts is debatable; additional molecular targets and other mechanisms of action cannot be ruled out.

Gabapentin has been shown to reduce postoperative acute pain by reducing central sensitization[15]. Recent meta-analyses indicate that gabapentin can decrease the amount of opioid analgesics after abdominal hysterectomy, spinal surgery and orthopedic surgeries[16-18]. Gabapentin has been evaluated in other acute perioperative conditions including postoperative nausea vomiting (PONV)[19-21], postoperative delirium[22], pressor response to direct laryngoscopy, tracheal intubation[23] and postoperative anxiety[24]. Future research is essential to gain further insight into the pharmacology of this novel multimodal drug to facilitate fast postoperative rehabilitation

after laparoscopic cholecystectomy. Limitations of our study include absence of dose-response relationship exploration and we did not evaluate the effects of continuation of therapy beyond a single dose.

CONCLUSION

In conclusion, preemptive use of 600 mg of gabapentin is effective in reducing postoperative pain and total analgesic requirement in patients undergoing laparoscopic cholecystectomy. The drug may be safe and well tolerated treatment modality to improve several parameters following laparoscopic cholecystectomy allowing fast postoperative rehabilitation of these patients. However, the optimal dose and duration of treatment needs to be established.

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