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PREOPERATIVE GABAPENTIN IN LAPAROSCOPIC CHOLECYSTECTOMY

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Abstract

Facts in gabapentin use are known about its effect on neuropathic pain management while its clinical significance as analgesic in laparoscopic cholecystectomy has not been studied much to clarify its importance and to know how and when it could be used or if this new analgesic strategy can be an alternative to others or be as a part of multimodal analgesic therapy in postoperative management. We conducted a prospective study to evaluate the significance of pre-emptive single dose gabapentin to reduce postoperative pain following laparoscopic cholecystectomy.

Study group of hundred patients were analyzed in prospective study; Fifty of them were gabapentin group and another fifty were placebo group. Age, sex, body mass index, operation time and length of hospital stay were comparable in both groups. Analgesic requirements were recorded and pain assessment using 100 visual analogue scale in both groups were studied at three times intervals of 8,12 and 24 hours after surgery. In addition we studied the incidence of certain postoperative side effects in both groups as nausea, vomiting and drowsiness.

Age, sex, body mass index, operation time and hospital stay were comparable in both groups. Opioid requirement two hours after surgery was significantly lower in gabapentin group than in placebo group ($p<0.05$). Also, significant difference was seen between gabapentin and placebo groups concerning the pain scores which were seen more in placebo as compared with gabapentin group in all study intervals ($p<0.05$). Significant difference between gabapentin and placebo groups was noticed regarding number of analgesic doses administered on the first 24 hours postoperatively which were more in placebo group ($p<0.05$). Insignificant difference was seen between gabapentin and placebo groups concerning certain postoperative side effects as nausea, vomiting and drowsiness ($p>0.05$).

In conclusion, our work shows that a single preoperative dose of gabapentin has a significant effect on postoperative pain after a laparoscopic cholecystectomy.

Introduction

The idea of pain prevention was first introduced into clinical practice by Crile in 1913[1], and further developed by Wall[2] and Woolf[3]. Based on a large body of experimental observations which suggested that analgesic interventions were more effective if they included the period of the noxious stimuli, and not just the post-injury stage, Woolf[3] suggested that "simple changes in the timing of treatment can have profound effects on postoperative pain". Postoperative pain has been evaluated thoroughly in different aspects concerning causes, pain degree and management ways to reach the best rationale to be documented in specific procedure. Type and duration of the operation, type of anaesthesia and analgesia used, and the patient's mental and emotional state are factors affect the postoperative pain degree[4]. If sufficient analgesia is provided, not only will the patient's comfort be increased but the duration of hospital stay will be shortened.

Of the many methods of postoperative pain relief, the oldest and most widely used is parenteral opioids[5].

Pre-emptive analgesia is a treatment that is initiated before and during the surgical procedure in order to reduce the physiological consequences of pain perception. 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. Consequently, immediate postoperative pain may be reduced and the development of chronic pain may be prevented[6].

Different analgesic strategies of different targets and mechanism of actions have been investigated for their influence on early pain after laparoscopic cholecystectomy.

Analgesic treatment after laparoscopic cholecystectomy carried many arguments where postoperative pain is reduced compared with open traditional cholecystectomy[7], but effective analgesic treatment after laparoscopic cholecystectomy has remained a clinical challange[8]. In 17–41% of the patients, pain is the main reason for staying overnight in the hospital on the day of surgery[9-13] in addition to be a primary reason for prolonged convalescence after laparoscopic cholecystectomy[8,14].

The fact that acute pain after laparoscopic cholecystectomy is complex in nature and does not resemble pain after other laparoscopic procedures[8,13,15] suggests that effective analgesic treatment should be multimodal. Therefore, detailed prospective studies in individual laparoscopic procedures such cholecystectomy, gynecologic procedures, hernia repair and fundoplication have shown procedure-related individual pain patterns requiring procedure-specific analgesic treatment regimens[13,16].

In laparoscopic cholecystectomy, overall pain is a conglomerate of three different and clinically separate components: incisional pain (somatic pain), visceral pain (deep intra-abdominal pain), and shoulder pain (presumably referred visceral pain)[13]. Characteristically, overall pain after laparoscopic cholecystectomy carries a high inter-individual variability in intensity and duration and is largely unpredictable[13]. Pain is most intense on the day of surgery and on the following day and subsequently declines to low levels within 3–4 days. However, pain may remain severe in approximately 13% of patients throughout the first week after laparoscopic cholecystectomy[13].

Introduced in 1994 as an anti-epileptic drug, Gabapentin, a new third-generation anti-epileptic drug, is a structural analogue of gamma-aminobutyric acid (GABA), an important neurotransmitter in the central nervous system[17]. Like other anti-epileptic drugs, gabapentin has been shown to be effective in the treatment of neuropathic and inflammatory pain after surgical operations.

Studies in recent years have particularly focused on the efficacy and safety of gabapentin in the treatment of postoperative pain[18,19].

Gabapentin does not interact with other commonly prescribed drugs. Its most frequent side-effects are drowsiness and fatigue[20], which are also common side-effects of widely used premedications. Because gabapentin seems to alleviate and prevent acute nociceptive and inflammatory pain and may reduce postoperative pain, we planned to study its use in patients undergoing laparoscopic cholecystectomy for symptomatic cholelithiasis.

The aim of the study is to determine the effect of pre-emptive single dose gabapentin in comparison with placebo on postoperative pain in laparoscopic cholecystectomy.

Patients and methods

This prospective randomized clinical double-blind study was carried out in Basrah General Hospital, Department of Surgery between December 2010 and July

2011 for patients with symptomatic cholelithiasis.

Patient demographics, past history, recent history, drug history and accompanying systemic diseases were evaluated. The experimental protocol was approved by the hospital research and ethics committee. All patients gave informed consent and were interviewed individually by the researcher.

The exclusion criteria were a known allergy to gabapentin, epilepsy, previous treatment with gabapentin, a chronic pain syndrome, history of cardiovascular, respiratory, renal or hepatic disease, psychiatric disorders, and substance abuse. Patients who regularly used opioids, or who had used drugs with known analgesic properties within 24 hours before surgery, were also excluded.

During period of the study, one hundred patients were scheduled for laparoscopic cholecystectomy and were randomly allocated to either the gabapentin group (50 patients) or the placebo group (50 patients). Randomization was determined by the drawing of a sealed envelope to determine group. The patients in the gabapentin group received single dose 600 mg orally two hours before surgery, while those in placebo group received placebo which was vitamin B complex where shape and size of capsule resemble that of gabapentin capsule.

All patients received one gram ceftriaxone intravenously at the induction of anesthesia and some received four thousands units low molecular weight heparin (LMW heparin) given two hours before the operation.

Two anesthesiologists were responsible for the general anesthesia, using endotracheal intubation and a standard anaesthetic approach intra operatively (general anesthesia with endotracheal intubation) and analgesic technique in recovery room (3 mg i.v morphine) were applied.

Laparoscopic cholecystectomy was performed by two surgeons, using the standard four-port technique; the pneumo-peritoneum was created by the closed method, dissection of Calot's triangle was done by grip and strip blunt method using dissecting forceps "Maryland", or by electrocautery using surgical hock. Dissection of gall bladder was performed using electrocautery with energized hock "monopolar". The cystic artery and duct were ligated with titanium medium-large sized "9 mm"clips. The gall bladder was removed through the epigastric port.

Pain was self-assessed by the patients on a validated 100 mm visual analogue scale (VAS), as instructed by surgical resident who was not enrolled in categorization method. This pain scale provides a validated and minimally intrusive measure of pain intensity, and ranges from 'No pain' (0) to 'The worst pain imaginable' (100). Patients were instructed to place a mark on the line that indicated the level of pain experienced. The distance in millimeters from the low end of the scale and the patient's mark was used as a numerical index of pain intensity.

Questionnaires were filled out for each patient at the beginning of the study and after the operation. During the first 24 hours postoperatively pain intensity was evaluated at 8, 12, and 24 hours. Analgesia was given when VAS was 30 and more.

Postoperatively, all patients transferred to surgical ward where pain assessment was started and resumed oral intake after few hours.

Visual analogue scale was assessed at the second hour after surgery and narcotic analgesia was administered (50 mg intravenous pethidine) accordingly. After that, analgesic requirement was given as NSAIDs (Diclofenac sodium 75 mg intra muscular injection) at 8, 12 and 24 hours intervals and according to VAS record.

Data were analyzed using SPSS 15.0 software, with the chi-square test, t-test and Mann-Whitney test, as appropriate; $p<0.05$ was considered to be statistically significant.

Results

A total of hundred patients entered the study and randomly divided into gabapentin group (n=50) and placebo group (n=50). There was no significant difference between these groups of patients with respect of age, sex, body mass index, operation time and length of hospital stay as shown in table I. (p>0.05).

Opioid requirements were studied two hours after surgery in both groups where fifteen patients out of fifty (30%) required opioid in gabapentin group as compared to twenty seven patients out of fifty (54%) in placebo group as shown in table II. (p<0.05).

Table III showed the pain assessment scores in both groups at three time intervals (8, 12 and 24 hours) postoperatively in addition to the assessment of number of analgesic requirements on the first 24 hours postoperatively.

Significant difference was seen between gabapentin and placebo groups regarding the pain scores which were seen more in placebo as contrasted with gabapentin group in all study intervals(p<0.05).

Also significant relationship between gabapentin and placebo concerning the number of analgesic doses of all types administered on the first 24 hours postoperatively as shown in table III (p<0.05).

Insignificant difference was found between gabapentin and placebo groups concerning certain side effects such as nausea, vomiting and drowsiness as shown in table IV. (p>0.05).

Table I: General criteria of both groups

	Gabapentin	Placebo	P value
Sex M/F	7/43	10/40	0.05
Age (years) Mean (S.D)	17 – 80 40.3(17.43)	18 – 70 40(17.08)	0.05
Body Mass Index (BMI) Mean (S.D)	22.6 – 34.8 26.5(2.9)	19.8 – 36 26.7(3.7)	0.05
Duration of surgery (minutes) Mean	16 -75 38.8	18 -70 37.4	0.05
Length of hospital stay (hours)	24	24	0.05

The P value by Pearson Chi-Square is > 0.05, the differences between two groups are insignificant
"S.D = Standard deviation"

Table II: Opioid requirements of both groups

	Gabapentin	Placebo	Total
Needed opioid	15 (30 %)	27 (54%)	42
Didn't Need opioid	35 (70 %)	23 (46%)	58
	50	50	100

The P value by Chi square test = 0.015 which is less than 0.05 so is significant

Table III: Analgesic requirements in study groups

	Gabapentin (N=50)	Placebo (N=50)	P value
Pain scores = Mean (SD):- 8 hour after surgery 12 hour after surgery 24 hour after surgery	33.8 (15.9) 31.5 (16.6) 28.2(16.2)	60.8 (18.5) 58.8 (16.7) 56.6 (13.9)	< 0.05 < 0.05 < 0.05
Number of analgesic doses on the first day = Mean(SD)	1.5 (0.8)	2.4 (1.1)	< 0.05

Table IV: Number and percentage of patients experiencing side effects in the first 24 hours postoperatively

Side effects	Gabapentin	Placebo	P value
Nausea	33 (66%)	36 (72%)	0.05
Vomiting	18 (36%)	20 (40%)	0.05
Drowsiness	26 (52%)	24 (48%)	0.05

Discussion

Gabapentin has been reported as an anxiolytic drug in previous studies[21,22] which could be attributed to the improved postoperative analgesia and to reduce other analgesic requirements because there is a possible association between preoperative anxiety and postoperative pain[24].

A number of hypotheses explaining gabapentin-opioid interactions have been proposed, including gabapentin inhibition of glutamate release, nitric oxide synthetase activation, dynorphin-induced allodynia, or postsynaptic calcium entry[23]. However, the real challenge in the clinical setting is not simply to minimize the dose of analgesic drug, but to minimize long-term complications and occurrence of chronic pain syndromes within weeks or months after surgery.

Oral administration of gabapentin approximately two hours before surgery appears rational in order to attain maximal plasma concentration at the time of surgical stimuli. Gabapentin crosses rapidly the blood-brain barrier and consequently, its concentration in brain tissue, where it exhibits its effect, is nearly as high as in blood[24,25]. The dose of gabapentin did not appear to have any overall bearing on the outcome and it ranged from 300 mg to 1200 mg preoperatively. The studies which evaluated the lowest doses yielded the least impressive reductions in analgesic consumption[26-28], but otherwise there were no appreciable differences in results based upon dosing. It is worthwhile noting that gabapentin is currently not available parenterally, which may limit its utility among those for whom the oral route is not an option.

The current study shows that single dose gabapentin had a significant and beneficial effect on pain perceived by patients during the first 24 hours after laparoscopic cholecystectomy. During this period, average pain intensities in the gabapentin group were lower than 40 mm, while those in the placebo group were higher than 50 mm. This is of importance; because pain scores of 5-44 mm are considered to indicate mild pain and those of 45 - 74 mm moderate pain[29].

Our findings are similar to those reported previously, but in our study the patients received single dose gabapentin compared with placebo.

Durmus et al[5] compared the effects of a combination of gabapentin and paracetamol with gabapentin alone and placebo on postoperative pain and morphine consumption in abdominal hystrectomy and reported that a single dose of gabapentin as well as a combination of gabapentin and paracetamol decreased postoperative opioid requirements and increased patient satisfaction.

In contrast, Fassoulaki et al[30]. reported that gabapentin had no effect on pain and morphine consumption immediately after abdominal hysterectomy but decreased pain one month postoperatively.

In a recent large-scale of Pandy et al, double-blind, randomized trial of 459 patients undergoing laparoscopic cholecystectomy, the analgesic effects of a very low dose of 300 mg oral gabapentin 2 hours before operation was compared

with 100 mg oral tramadol or placebo[26]. Gabapentin significantly decreased total opioid consumption by 17% versus tramadol and by 37% versus placebo. Also, there was a significant decrease in visual analog scale pain scores compared with placebo and tramadol treatment[26].

The effect of timing of administration of gabapentin has not been studied in laparoscopic cholecystectomy.

Pain complexity after laparoscopic cholecystectomy has urged surgeons and anesthesiologists to perform different high quality, large scale trials to provide a good evidence for optimal analgesic intervention in laparoscopic chole-cystectomy.

The hypothesis that severe acute pain after laparoscopic cholecystectomy predicts development of chronic pain (such as post–laparoscopic cholecystectomy syndrome)[15] should be investigated thoroughly in future by well defined, prospective, large-scale studies and whether optimized perioperative analgesic treatment reduces risk of chronic pain after laparoscopic cholecystectomy is a question that needs to be answered.

Clinical awareness is the master of knowledge to advocate proper analgesic strategy at appropriate time and circumstance to yield appropriate results in certain procedures like laparoscopic cholecystectomy.

Conclusion

Our work shows that a single preoperative dose of gabapentin has a significant effect on postoperative pain after a laparoscopic cholecystectomy.

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