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Original Article

The Effects of Preoperative Pregabalin Administration on Postoperative Pain on Libyan Patients Undergoing Laparoscopic Cholecystectomy

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Abstract

Objective: The present prospective study was carried out in Surgical Department of Tripoli Central Hospital with the aim to evaluate the effect of preoperative single dose of 150 mg pregabalin in reducing postoperative pain and analgesic consumption after laparoscopic cholecystectomy. **Patients and Methods:** Sixty patients of both sexes in the age of 18–60 years undergoing laparoscopic cholecystectomy were randomly allocated into two equal groups of 30 patients each. The pregabalin group received 150 mg oral pregabalin 1 h before induction of anesthesia and a placebo group received a matching placebo orally. Variables measured included age, sex, body mass index (BMI), duration of surgery, time to first dose and total dose of meperidine after recovery, and the visual analog scale (VAS – static and dynamic). The occurrence of nausea and vomiting during the first 24 h postoperative was also recorded. **Results:** No significant difference was found between the meperidine and the placebo groups regarding age, sex, BMI, or duration of surgery. The time of first meperidine dose required to alleviate pain after surgery was significantly four times longer in the pregabalin group as compared to the placebo group. The total dose of meperidine required for pregabalin group was significantly lower than that required for placebo group. Moreover, VAS was significantly decreased in the pregabalin group compared to placebo group both at static and dynamic states only 1 h after recovery. **Conclusion:** This study validates the preoperative use of a single dose of pregabalin in attenuating pain intensity postoperatively and reducing total analgesic consumption.

Keywords: Laparoscopic cholecystectomy, placebo, postoperative pain, pregabalin

Introduction

Early postoperative pain is the most common complaint after laparoscopic cholecystectomy. It is also the most common cause of delayed discharge after the procedure.[1,2] Although it is generally less intense than after open cholecystectomy, it could be agonizing and viewed to be the cause of preventable distress.[2,3] The intensity of laparoscopic cholecystectomy pain usually peaks few hours after surgery and then declines over the following 2–3 days.

Postoperative pain relief following laparoscopic cholecystectomy remains controversial. Yet, being of multifactorial nature, a multimodal therapeutic approach may be necessary to optimize its relief.[4,5] Appropriate timing for the initiation of treatment could be started postoperatively, intraoperatively (with or without the use of adjuvant maneuvers), or even preoperatively in conjunction to postoperatively (preemptive analgesia).[6]

Pharmacotherapeutic management of postoperative pain could be achieved using opioids either alone or in conjunction with nonopioid analgesics or other pain controllers. Opioids usefulness is limited by side effects such as somnolence, nausea, vomiting, constipation, and respiratory depression. Nonopioids are safer but not all are as effective in control

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of visceral component of pain and usually are used in combination to others.[7-9] Other pain control therapies such as antiepileptics (as gabapentinoids) local anesthetics (as bupivacaine), N-methyl-D-aspartate receptor antagonists (as ketamine), and α_2-adrenergic agonist (as ziconotide) have all been assessed alone or in conjunction to analgesics.[10,11]

Other methods of administration have been reported by others including parenteral, intra/retroperitonal or a combination of both.[5,6,11,12]

Pregabalin and its developmental predecessor gabapentin are structural derivatives of the inhibitory neurotransmitter gamma-aminobutyric acid, their anticonvulsant, anxiolytic, and sleep-modulating utility permitted their use as adjuncts for the management of generalized or partial epileptic seizures resistant to conventional therapies.[13] Their therapeutic use was furthermore expanded over time to control chronic pain conditions (diabetic neuropathy, postherpetic neuralgia, central neuropathic pain, and fibromyalgia) as well as some acute pain conditions (inflammatory or incisional injuries [especially laparoscopic and day-care surgeries]).[14-16]

Therefore, this study was aimed to evaluate the effect of oral administration of a preoperative single dose of pregabalin on postoperative pain and analgesic consumption in Libyan patients undergoing laparoscopic cholecystectomy.

Patients and Methods

Patients

This study was approved by the Ethical Committee of Tripoli Central Hospital on August 2014. Patients who met the inclusion criteria and assessed for eligibility from September 2014 to March 2015 received a detailed information about the study, and a written informed consent was given by each.

Patients with uncontrolled medical disease (hypertension and diabetes mellitus), a history of drug or alcohol abuse, problems in the kidney or liver functions, and a history of intake of nonsteroidal anti-inflammatory drugs within 24 h before surgery were excluded from the study.

Patients were randomly allocated into two equal groups (30 patients each) using the double-blind technique. Pregabalin group received 150 mg of pregabalin-containing capsules orally (Lyrica®, Pfizer), while a matching placebo group received an empty capsule filled with starch orally 1 h before the induction of anesthesia with sips of water. Treatment is done under double-blind techniques.

Methods

Visual analog scale (VAS) is an international classification measure used for the assessment of acute pain intensity after surgery.[17] Pain is classified into mild (1–3): patients feel pain and discomfort but can complete most activities; moderate (4–6): pain makes patient difficult to concentrate and may interfere with his normal activities; and severe (7–10): intense pain, patient limits physical activity and cannot concentrate on anything else except the pain. Patients were instructed in the day before operation how to use the VAS. Postoperative pain assessment was recorded at rest (static) and during coughing (dynamic).

Assessment of pain began in the recovery room (0 h) and then 1, 2, and 3 h after the arrival of patient to the ward. Accordingly, patients received 1 mg/kg intramuscular meperidine whenever postoperative pain (static or dynamic) as measured by VAS ≥4. The time needed for the initiation of the first dose of meperidine during the postoperative period and the total administered doses of meperidine required to prevent pain score from exceeding VAS ≥4 throughout the 3 h period were calculated.

Patients were observed for any nausea and vomiting during the first three postoperative hours.

Statistical analysis

SPSS software package version 16 was used for the statistical analysis of the data. Chi-square test was used for comparison between quantitative data and Mann–Whitney test was used for qualitative data. A difference was considered statistically significant when $P < 0.05$. Results are presented as a mean ± standard error of the mean.

Results

There were no significant differences between the pregabalin and placebo groups in terms of age, gender, body mass index (BMI), or mean duration of surgery [Table 1].

The assessment of intraoperative meperidine consumption (dose given during the induction of anesthesia) showed that there were no significant differences between the pregabalin and placebo groups [Table 2]. On the other hand, the time of first meperidine dose required to alleviate pain after surgery was significantly longer in the pregabalin group as compared to the placebo group [Table 2]. Moreover, the total dose of meperidine required for pregabalin group was significantly lower than that required for the placebo group [Table 2].

VAS was significantly decreased in the pregabalin group compared to placebo group both at static and dynamic states at time (0) when patients were in the recovery room [Figures 1 and 2]. The value of VAS score remained

Table 1: Demographic data

Variables	Groups Mean±SE		*P*
	Placebo (*n*=30)	Pregabalin (*n*=30)	
Age (year)	37.1±1.7 (20-54)	35.8±1.5 (19-53)	0.646
Sex (male/female)	5/25	11/19	0.143
BMI	27.5±0.6	27.7±0.7	0.853
Duration of surgery (min)	63.2±1.4	66.2±1.9	0.323

BMI: Body mass index, SE: Standard error

significantly lower in the pregabalin groups as compared to the placebo groups in the 1st h following the operation. However, at the 2nd and 3rd h after surgery, the difference between pregabalin and placebo groups was insignificant [Figures 1 and 2].

Nausea occurred in eight people (26.7%) and vomiting in one (3.3%) of the placebo group. In the pregabalin group, only three patients (10%) had nausea, and no one suffered a vomiting episode. No statistically significant differences were noted between the two groups [Table 3].

Table 2: A comparison of first analgesic requirement times since patient's recovery and total analgesic consumption during 24 h

Variables	Groups Mean±SE		*P*
	Placebo (*n*=30)	Pregabalin (*n*=30)	
Timing of 1st meperidine dose after recovery (min)	91.1±6.3	375.0±31.9	0.001**
Total dose of meperidine given (mg) 24 h	160.0±9.1	115.4±6.7	0.001**
Total intraoperative meperidine consumption (µg)	148.3±2.9	141.7±5.9	0.256

***P* value was calculated using Mann-Whitney test. SE: Standard error

Table 3: Incidence of postoperative nausea and vomiting

Variables	Groups		*P**
	Placebo group (*n*=30)	Pregabalin group (*n*=30)	
Nausea	8 (26.7%)	1 (10.0%)	0.15
Vomiting	1 (3.3%)	0 (0.0%)	
Vomiting and nausea (v/n)	3.3%	0.0%	

**P* value was calculated using Chi-square test

Discussion

Pain is one of the primary concerns of the surgeon because of its close ties with clinical outcome and acute postoperative patient well-being.[18] The role of pregabalin in controlling acute pain, especially acute postoperative pain, was assessed in several randomized controlled trials of surgeries performed under general anesthesia, spinal anesthesia, or day-care surgery in doses varying from 50 to 600 mg/day.[19] Within those aforementioned surgeries, some approved and others denied pregabalin utility in controlling acute postoperative pain evoked by laparoscopic cholecystectomy. When contrasting between those reports, the doses of pregabalin used, the quality of pain assessed, the methodology by which pain was scored, the type of rescue analgesic added, and the conclusion that was drawn were all different.[20-23]

Therefore, this study aimed to evaluate the preemptive analgesic properties of pregabalin on acute postoperative pain, and how this drug can modify meperidine consumption in patients undergoing laparoscopic cholecystectomy.

In this study, the patients were observed for 24 h after recovery; however, patient self-assessment of pain intensity was done only for 3 h after recovery from surgery. The results of the present work showed no differences among the studied groups regarding age, sex, BMI, and duration of surgery, which indicates the homogeneity between the two groups.

Single-dose pregabalin was effective in prolonging the timing of first meperidine dose and reducing the total dose of meperidine given during 24 h after recovery. On the other hand, the reduction of postoperative pain as reported by the patients in VAS was significant only 1 h after recovery. The results regarding VAS measures were not in agreement with those reported by Agarwal *et al*., who using the same dose of pregabalin, reported a significant reduction in postoperative pain intensity till the end of 24th h;[24] this could be attributed

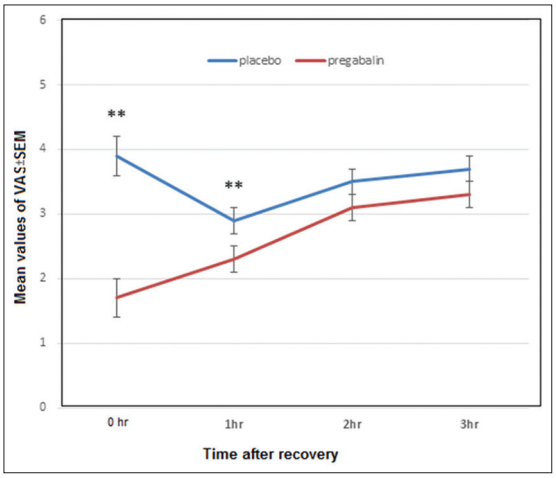

Figure 1: Distribution of visual analog scale (Static) in patients of pregabalin and placebo groups during the follow-up after the operation. Data are expressed as a mean ± standard error of the mean, ***P* < 0.005 using Mann–Whitney test

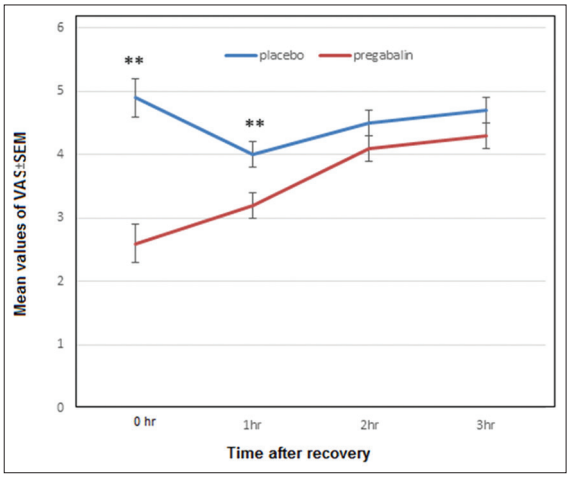

Figure 2: Distribution of visual analog scale (Dynamic) in patients of pregabalin and placebo groups during the follow-up after the operation. Data are expressed as a mean ± standard error of the mean, ***P* < 0.005 using Mann–Whitney test

to race difference in pain perception among patients of the two studies.[23] However, we have to point out that pregabalin half-life time is estimated to be around 6 h. A meta-analysis has shown that the dose and number of doses of pregabalin can affect pain scores following laparoscopic cholecystectomy, where, for example, a significant reduction in pain intensity with lower pain scores was observed at rest in the pregabalin 75 mg group in the first 90 min after surgery; while in the pregabalin 50 mg group, the reduction in pain intensity was more transient and lasted for 45 min compared to placebo group.[25] The perioperative administration of pregabalin was reported to reduce the consumption of opioids in other surgeries such as gynecological laparoscopic hysterectomy,[26] laparoscopic sleeve gastrectomy,[27] and transperitoneal nephrectomy.[28] The pretreatment with pregabalin in this study has resulted in no increase in nausea and vomiting after recovery from surgery.

Conclusion

This study has confirmed that oral administration of a preoperative single dose of 150 mg pregabalin has resulted in lower postoperative pain and meperidine consumption in Libyan patients undergoing laparoscopic cholecystectomy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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ملخص المقال باللغة العربية

آثار استعمال بريجابيلين ما قبل الجراحة على آلام ما بعد الجراحة للمرضى الليبيين تعرضوا لاستئصال المرارة بالمنظار

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الهدف: أجريت الدراسة المستقبلية في قسم الجراحة بمستشفى طرابلس المركزي بهدف تقييم تأثير الجرعة الواحدة من البريجابلين (150 ملي جرام) تعطي للمريض قبل العملية في تقليل الألم واستهلاك المسكن بعد العملية الجراحية لاستئصال المرارة بالمنظار.

المرضي والطرق: تم توزيع 60 مريضا من الجنسين (عمر 18-60 سنة) على إجراء استئصال المرارة بالمنظار بشكل عشوائي إلى مجموعتين متساويتين. تلقت المجموعة الأولي البريجابلين (150 ملي جرام) عن طريق الفم ساعة قبل تحريض التخدير. المجموعة الثانية تناولت نفس الكبسولة ولكن غير محتوية على الدواء. شملت المتغيرات المقاسة العمر والجنس ومؤشر كتلة الجسم، مدة الجراحة، الوقت للجرعة الأولى والجرعة الكلية من الميبريدين بعد انتهاء أثر التبنيج، والمقياس التناظري البصري. تم تسجيل حدوث الغثيان والقيء خلال 24 ساعة بعد العملية الجراحية أيضا.

النتائج: لم يتم العثور على اختلاف كبير بين المجموعتين الأولي والثانية فيما يتعلق بالعمر أو الجنس أو مؤشر كتلة الجسم أو مدة الجراحة. كان وقت جرعة الميبريدين الأولى المطلوبة لتخفيف الألم بعد الجراحة بشكل ملحوظ أربع مرات أطول في المجموعة الأولي بالمقارنة مع المجموعة الثانية. كانت الجرعة الكلية من الميبريدين المطلوبة للمجموعة الأولي أقل بكثير من تلك المطلوبة لمجموعة الثانية. علاوة على ذلك، انخفض المقياس التناظري البصري بشكل ملحوظ في المجموعة الأولي مقارنة مع المجموعة الثانية ساعة واحدة بعد الاستفاقة من البنج.

الاستنتاج: هذه الدراسة تحققت من فاعلية استخدام جرعة واحدة من البريجابلين في تخفيف الألم بعد العمل الجراحي وتقليل الاستهلاك الكلي للمسكن.

الكلمات المفتاحية: استئصال المرارة بالمنظار، آلام ما بعد الجراحة، البريجابلين. طرابلس.