Egyptian Journal of Anaesthesia 32 (2016) 513–517

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Contents lists available at ScienceDirect

Egyptian Journal of Anaesthesia

journal homepage: www.sciencedirect.com

Research article

Analgesic efficacy and safety of peri-operative pregabalin following radical cystectomy: A dose grading study

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ARTICLE INFO

Article history:
Received 7 June 2016
Revised 18 September 2016
Accepted 8 October 2016
Available online 7 November 2016

Keywords:
Pregabalin
Postoperative analgesia
Radical cystectomy

ABSTRACT

Purpose: Adding novel drugs like pregabalin to analgesic regimens might reduce postoperative pain, total opioid consumption and side effects, this study compares multiple doses of pregabalin for postoperative analgesia following radical cystectomy.
Methods: This study is registered at www.clinicaltrials.gov at no.: NCT02724293. Sixty patients were randomized into 4 groups: Group I: control (placebo) group, Group II: received pregabalin 300 mg 2 h preoperatively, Group III: received pregabalin 300 mg 2 h preoperatively and 12 h thereafter, Group IV: received pregabalin 600 mg 2 h preoperatively. Postoperative pain, time to first request of analgesia, and total morphine consumption were recorded.
Results: VAS was significantly reduced in groups II, III, IV in comparison with group I immediately postoperative, and after 2 h ($P < 0.05$). Sedation score was significantly higher in groups II, III, IV compared to group I immediately postoperative ($P < 0.05$). First request of analgesia was significantly delayed in groups II, III, IV compared to control group ($P = 0.000$). Total analgesic consumption was significantly reduced in groups II, III, IV compared to group I ($P = 0.000$). Group IV showed a significantly higher incidence of dizziness compared to group I.
Conclusion: Peri-operative pregabalin at doses of 300 mg and 600 mg reduced postoperative opioid consumption and prolonged time to first request of analgesia in patients who underwent radical cystectomy, and a single preoperative dose of 600 mg is superior in analgesia to others, without serious side effects.

1. Introduction

Numerous studies have explored undesirable effects of unrelieved pain with maximum effects on different body systems. These effects include adrenal sympathetic hyperactivity, myocardial ischemia, deep venous thrombosis, difficulty of breathing, atelectasis, tachycardia, hypertension, and others [1].

Opioids represent the cornerstone in postoperative pain management despite serious side-effects [2] that might impair patient recovery after surgery [3].

Multimodal postoperative analgesic regimens may decrease the incidence of complications, shorten the requirement for hospitalization, and decrease recovery times and health costs [4].

Pregabalin is a structural analogue of the inhibitory neurotransmitter gaba-aminobutyric acid, with anticonvulsant, antihyperalgesic, and anxiolytic properties such as gabapentin, but with a more favorable pharmacokinetic profile [5,6]. There are several reports for the use of pregabalin in the management of postoperative pain with a positive result in a variety of surgical models [7–9].

Thus, using novel adjuvant drugs such as pregabalin, as a part of a multimodal analgesic regimen, might be reasonable for lowering postoperative pain scores, decreasing total opioid consumption, and hence, side effects [10,11].

Till now, there is no agreement upon the ideal dose of pregabalin when used as an adjuvant to a multimodal analgesic protocol for postoperative analgesia following major surgery. This randomized, double-blinded, controlled study was designed to examine the analgesic efficacy of three different pre/peri-operative doses of pregabalin following radical cystectomy and urinary diversion in comparison with placebo, in search of the ideal dosage.

2. Patients and methods

This prospective, randomized, double-blinded, controlled study was started after Institutional Ethics Committee approval (South

Peer review under responsibility of Egyptian Society of Anesthesiologists.
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http://dx.doi.org/10.1016/j.egja.2016.10.003
1110-1849/

Egypt Cancer Institute – Assiut University) and after obtaining written informed consent from all participating patients. It is registered at www.clinicaltrials.gov at no.: NCT02724293. The study was conducted according to the most recent version of the Declaration of Helsinki. Sixty patients between the ages of 18 and 60 years with ASA I-II physical status who underwent radical cystectomy under general anesthesia were enrolled in this study. Patients were randomized into 4 groups (15 patients in each):

Group I: control group (placebo group).
Group II: patients received pregabalin 300 mg 2 h preoperatively.
Group III: patients received pregabalin 300 mg 2 h preoperatively and 12 h after the preoperative dose.
Group IV: patients received pregabalin 600 mg 2 h preoperatively.

Randomization was done using lottery method. Pregabalin was given orally by a staff nurse who was not included in the study. Anesthesiologists and patients were blinded to the groups.

2.1. Exclusion criteria

Patients with a history of drug or alcohol abuse and patients with chronic pain or daily intake of analgesics, uncontrolled diabetes mellitus and/or hypertension, atherosclerotic heart disease, seizures, impaired kidney or liver functions, body mass index $\geqslant 35\ kg/m^2$, and who could not control a patient-controlled analgesia (PCA) device were excluded from the study.

2.2. Anesthetic management and operation

One day before surgery, patients were trained on how to use the PCA pump that when they feel pain, a push to the button will relieve it, but they cannot push the button frequently to avoid overdose (lock out period). They were also taught how to express the level of pain they experience using an 11-point Visual Analogue Scale (VAS), with 0 indicating no pain and 10 indicating the worst imaginable pain. On arrival to the operating room, an intravenous line was inserted. Patients were pre-medicated with 0.25 mg/kg intravenous ranitidine. Monitoring included electrocardiography, noninvasive blood pressure (NIBP), O_2 saturation, and temperature. Anesthesia was induced for all participating patients with 1.5–2 μg/kg fentanyl, 1–2.5 mg/kg propofol, and 1.5 mg/kg lidocaine. Endotracheal intubation was facilitated by 0.15 mg/kg cis-atracurium. Anesthesia and muscle relaxation were maintained by 1–1.5 MAC isoflurane in 50% oxygen/air mixture and 0.03 mg/kg cisatracurium, respectively, and mechanical ventilation was maintained in parameters that keep ETCo2 in the range of 35–40 mmHg. Intravenous crystalloid solution was infused at a rate of 8 mL/kg/h to correct for third space loss apart from added losses, and blood transfusion was allowed when hemoglobin is <10 g/dl, or when hematocrit value is <30%.

2.3. Patient controlled analgesia and pain scores

At the end of surgery, residual neuromuscular paralysis was antagonized with neostigmine 0.04 mg/kg and atropine 0.02 mg/kg. The patients were connected to a morphine patient controlled analgesia (PCA) pump (Perfusor® Space PCA Infusion Pump System, B. Braun, USA) on arrival at the PACU. The PCA pump was set to deliver a loading dose of 2.5 mg and an incremental dose of 2.5 mg at a lockout interval of eight minutes and a four-hour limit of 50 mg. Sedation level was evaluated using a 4-point sedation scale where 0 = awake, 1 = easily aroused, 2 = awakens after tactile stimulation, 3 = awakens after verbal stimulation, and 4 = not arousable [12]. Vital signs, visual analogue scale (VAS), total morphine consumption and adverse effects such as nausea, vomiting, pruritus, headache, dizziness, and visual abnormalities (double or blurred) were recorded.

Our primary outcome measure was the efficacy of the studied doses in reducing postoperative total analgesic consumption. Secondary outcome measures included reduction of postoperative pain scores, time to first request of rescue analgesia, and the tolerability of the used doses represented by the side effects during the follow-up period of 24 h.

3. Statistical analysis

3.1. Power of the study

The primary end point was the total dose of intravenous PCA morphine consumption in the first 24 h postoperatively. Secondary endpoints were the safety profile of the studied doses in terms of predefined adverse events, nausea, vomiting, and level of sedation during the study period. A calculated sample size of 12 patients in each group would have an 80% power of detecting a difference of 20% decrease in intravenous PCA morphine consumption at a 0.05 level of significance using a confidence interval of 95%. We enrolled 15 patients in each group to compensate for possible dropouts.

3.2. Data analysis

Analysis was performed using statistical package for the Social Sciences software, ver. 20 (SPSS Inc., Chicago IL, USA). Data were presented as mean ± SD, numbers, and percentages. Mann-Whitney was used to compare between each two groups. Chi-square test was used for comparison between percentages and frequencies. $P < 0.05$ was considered significant.

4. Results

This study was conducted on 60 patients who underwent radical cystectomy for management of urinary bladder cancer. Patients were given different doses of perioperative pregabalin in order to investigate its analgesic efficacy and safety.

Regarding the demographic and clinical data of the participating patients, there was no significant difference between group I (control group) and the study groups II, III, IV Table 1.

Looking into the hemodynamic changes and changes in arterial oxygen concentration in the intra-, and post-operative periods, there was no significant difference between study groups II, III, IV, and the control group I Figs. 1–4.

VAS showed a significant reduction in groups II, III, IV in comparison with control group I immediately postoperative, and after 2 h ($P < 0.05$). After that time, VAS values did not significantly differ between the four study groups till the end of the 24 h of observation Fig. 5.

Sedation score was significantly higher in groups II, III, IV in comparison with the control group I immediately postoperative ($P < 0.05$). Two hours postoperatively, only group IV (600 mg pregabalin) continued to show significantly higher sedation score compared to control group I ($P = 0.005$). After 12 h postoperatively, only group III (300 mg pregabalin twice) showed a significantly higher sedation score compared to control group ($P = 0.028$). Fig. 6.

First request of rescue analgesic was significantly delayed in groups II, III, IV in comparison with control group ($P = 0.000$) Table 2. First request of analgesia was also significantly delayed in groups III and IV compared to group II, and in group IV compared to group III ($P = 0.000$).