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Review

Effect of pre-emptive pregabalin on pain management in patients undergoing laparoscopic cholecystectomy: A systematic review and meta-analysis

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HIGHLIGHTS

- We conducted a systematic review and meta-analysis to explore the effect of pregabalin on pain management of patients undergoing laparoscopic cholecystectomy.
- Our meta-analysis showed that there was no significant difference of nausea and vomiting, as well as headache between pregabalin group and control group.
- Pre-emptive pregabalin showed an important ability to reduce pain and improve sedation after laparoscopic cholecystectomy.
- Pre-emptive pregabalin was recommended to be administrated before laparoscopic cholecystectomy.

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ABSTRACT

Background: Pre-emptive pregabalin might be beneficial to the patients undergoing laparoscopic cholecystectomy. However, the results remained controversial. We conducted a systematic review and meta-analysis to explore the effect of pregabalin on pain management of patients undergoing laparoscopic cholecystectomy.

Methods: PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases were systematically searched. Randomized controlled trials (RCTs) assessing the effect of pregabalin versus placebo on laparoscopic cholecystectomy were included. Two investigators independently searched articles, extracted data, and assessed the quality of included studies. The primary outcome was pain scores Meta-analysis was performed using random-effect model.

Results: Six RCTs involving 434 patients were included in the meta-analysis. Overall, compared with control intervention, pregabalin intervention was found to significantly reduce the pain scores (Std. mean difference = −0.57; 95% CI = −0.85 to −0.29; $P < 0.0001$) and postoperative fentanyl consumption (Std. mean difference = −1.74; 95% CI = −2.31 to −1.16; $P < 0.00001$), improve Ramsay Sedation score (Std. mean difference = 1.03; 95% CI = 0.46 to 1.60; $P = 0.0004$), but demonstrated no influence on nausea and vomiting (RR = 0.82; 95% CI = 0.57 to 1.19; $P = 0.30$), as well as headache (RR = 0.95; 95% CI = 0.55 to 1.64; $P = 0.86$).

Conclusions: Compared to control intervention, pregabalin intervention was found to significantly reduce the pain scores and postoperative fentanyl consumption, and improve Ramsay Sedation score in patients undergoing laparoscopic cholecystectomy, but had no influence on nausea and vomiting, as well as headache.

1. Introduction

Early postoperative pain was known as a common complaint in patients undergoing laparoscopic cholecystectomy, and persistent acute postoperative pain had become the dominating complaint and resulted in prolonged hospital stay [1–5]. Currently, the main

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treatment of post-surgical pain was to use opioids. Non-opioid gradually became a trend as a part of multimodal analgesia in order to not only reduce the pain following many different surgical procedures but also to reduce the side effects concurrent with standard opioid therapy for improving postoperative recovery [6,7].

An ideal premedicant drug should be able to relieve anxiety, produce amnesia and sedation, decrease secretions, prevent nausea and vomiting, have dose-sparing effect on the anesthetic drugs and suppress pressor response to laryngoscopy and intubation [8,9]. Ggabapentinoids such as pregabalin showed some potential in the management of acute post-surgical pain as a part of multimodal analgesia due to the possible opioid sparing effects and prevention of chronic postsurgical pain [10,11]. Pregabalin was a structural analogue of the inhibitory neurotransmitterγ-aminobutyric acid and could reduce the release of several excitatory neurotransmitters (e.g. glutamate, noradrenaline, serotonin, dopamine, and substance P) through binding to the α-2-δ subunit of voltage-gated calcium channels [12,13]. In addition, it was able to block the development of hyperalgesia and central sensitization through interacting with neurons in the spino-bulbo-spinal loop in the superficial dorsal horn and brainstem, thereby causing 5-hydroxytryptamine 3 receptor-mediated facilitation [13,14]. Previous studies reported that pregabalin had anti-epileptic, anti-hyperalgesic, and anxiolytic properties similar to gabapentin, but it showed a more favorable pharmacokinetic profile including dose-independent absorption with fewer adverse effects [13–15]. Pre-emptive pregabalin was reported to alleviate pain, reduce postoperative fentanyl consumption and improve Ramsay Sedation score after laparoscopic cholecystectomy [16,17].

In contrast to this promising finding, however, some relevant RCTs showed that pre-emptive pregabalin had no influence on pain control in patients undergoing laparoscopic cholecystectomy [18]. Considering these inconsistent effects, we therefore conducted a systematic review and meta-analysis of RCTs to evaluate the effectiveness of pre-emptive pregabalin intervention on pain management in patients undergoing laparoscopic cholecystectomy.

2. Materials and methods

This systematic review and meta-analysis were conducted according to the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement [19] and the *Cochrane Handbook for Systematic Reviews of Interventions* [20]. All analyses were based on previous published studies, thus no ethical approval and patient consent were required.

3. Literature search and selection criteria

PubMed, EMbase, Web of science, EBSCO, and the Cochrane library were systematically searched from inception to March 2017, with the following keywords: pregabalin, and laparoscopic cholecystectomy. No limitation was enhanced. To include additional eligible studies, the reference lists of retrieved studies and relevant reviews were also hand-searched and the process above was performed repeatedly until no further article was identified. Conference abstracts meeting the inclusion criteria were also included.

The inclusion criteria were as follows: study population, patients undergoing laparoscopic cholecystectomy; intervention, pre-emptive pregabalin intervention; control, placebo; outcome measure, pain score; and study design, RCT.

4. Data extraction and outcome measures

The following information was extracted for the included RCTs: first author, publication year, sample size, baseline characteristics of patients, pre-emptive pregabalin, control, study design, pain score, postoperative fentanyl consumption, Ramsay Sedation score, nausea and vomiting, as well as headache. The author would be contacted to acquire the data when necessary.

The primary outcome was pain score. Secondary outcomes included postoperative fentanyl consumption, Ramsay Sedation score, nausea and vomiting, as well as headache.

5. Quality assessment in individual studies

The Jadad Scale was used to evaluate the methodological quality of each RCT included in this meta-analysis [21]. This scale consisted of three evaluation elements: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points). One point would be allocated to each element if they have been mentioned in article, and another one point would be given if the methods of randomization and/or blinding had been detailedly and appropriately described. If methods of randomization and/or blinding were inappropriate, or dropouts and withdrawals had not been recorded, then one point was deducted. The score of Jadad Scale varied from 0 to 5 points. An article with Jadad score≤2 was considered to be of low quality. If the Jadad score≥3, the study was thought to be of high quality [22].

6. Statistical analysis

Standard Mean differences (Std. MDs) with 95% confidence intervals (CIs) for continuous outcomes (pain score, postoperative fentanyl consumption, and Ramsay Sedation score), and risk ratios (RRs) with 95% CIs for dichotomous outcomes (nausea and vomiting, as well as headache) were used to estimate the pooled effects. All meta-analyses were performed using random-effects models with DerSimonian and Laird weights. Heterogeneity was tested using the Cochran Q statistic ($p < 0.1$) and quantified with the I^2 statistic, which described the variation of effect size that was attributable to heterogeneity across studies. An I^2 value greater than 50% indicated significant heterogeneity. Sensitivity analysis was performed to detect the influence of a single study on the overall estimate via omitting one study in turn when necessary. Owing to the limited number (<10) of included studies, publication bias was not assessed. $P < 0.05$ in two-tailed tests was considered statistically significant. All statistical analyses were performed with Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

7. Results

7.1. Literature search, study characteristics and quality assessment

The flow chart for the selection process and detailed identification was presented in Fig. 1. 479 publications were identified through the initial search of databases. Ultimately, six RCTs were included in the meta-analysis [16–18,23–25].

The baseline characteristics of the six eligible RCTs in the meta-analysis were summarized in Table 1. The six studies were published between 2008 and 2014, and sample sizes ranged from 40 to 120 with a total of 434. There were no significant difference of age, BMI (or body mass), and surgery duration between pregabalin group and control group at baseline. The doses and methods of pregabalin were different. Four included RCTs reported pregabalin only before surgery [16,23–25], and the remaining two included RCTs reported pregabalin before and after surgery [17,18]. The pregabalin doses before surgery varied from 75 mg to 600 mg.

Among the six RCTs, three studies reported the pain score [16,18,24], three studies reported the postoperative fentanyl