Influence of pregabalin on post-operative pain after laparoscopic cholecystectomy: A meta-analysis of randomised controlled trials

Dan Zhang, Guangqiang You, Xiaoxiao Yao

Department of Hepatobiliary and Pancreatic Surgery, The Second Affiliated Hospital of Jilin University, Changchun, Jilin, China

Abstract

Background: Pregabalin may have some potential in reducing post-operative pain after laparoscopic cholecystectomy. However, the results remain controversial. We conduct a systematic review and meta-analysis to explore the influence of pregabalin on post-operative pain after laparoscopic cholecystectomy.

Materials and Methods: PubMed, Embase, Web of science, EBSCO and Cochrane Library databases have been systematically searched. Randomised controlled trials (RCTs) assessing the effect of pregabalin versus placebo on post-operative pain after laparoscopic cholecystectomy are included. The primary outcomes are pain scores at 8–12 h and 20–24 h. Secondary outcomes include sedation score, intraoperative fentanyl requirement, post-operative analgesic requirement, operative duration, post-operative nausea and vomiting, as well as respiratory depression. This meta-analysis is performed using the random-effect model.

Results: Eight RCTs involving 528 patients were included in the meta-analysis. Overall, compared with control intervention after laparoscopic cholecystectomy, pregabalin treatment is found to significantly reduce pain scores at 20–24 h (Standard Mean difference [Std. MD] = −0.46; 95% confidence interval [CI] = −0.82−−0.10), and post-operative analgesic requirement (Std. MD = −2.64; 95% CI = −3.94−−1.33), but cannot substantially decrease pain scores at 8–12 h (Std. MD = −0.71; 95% CI = −1.70−−0.27). In addition, pregabalin results in improved sedation score (Std. MD = 0.92; 95% CI = 0.55−1.29), but has no remarkable influence on intraoperative fentanyl requirement (Std. MD = 0.04; 95% CI = −0.30−0.39), operative duration (Std. MD = 0.34; 95% CI = −0.10−0.77), post-operative nausea and vomiting (Std. MD = 0.79; 95% CI = 0.59−1.11) as well as respiratory depression (Std. MD = 0.71; 95% CI = 0.17−3.02).

Conclusions: Compared to control intervention after laparoscopic cholecystectomy, pregabalin treatment can significantly decrease pain scores at 20–24 h and post-operative analgesic requirement, with no increase in adverse events.

Keywords: Laparoscopic cholecystectomy, meta-analysis, post-operative pain, pregabalin, randomised controlled trials

Address for correspondence: Dr. Xiaoxiao Yao, No. 218 Ziqiang Street, Nanguan, Changchun, Jilin 130041, China.
E-mail: yaoxx0710@163.com
Submitted: 12-Aug-2018, Accepted in Revised Form: 13-Oct-2018, Published: 11-Mar-2020

Access this article online

Website: www.journalofmas.com
DOI: 10.4103/jmas.JMAS_209_18

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Zhang D, You G, Yao X. Influence of pregabalin on post-operative pain after laparoscopic cholecystectomy: A meta-analysis of randomised controlled trials. J Min Access Surg 2020;16:99-105.
INTRODUCTION

Early post-operative pain is thought to be a common complaint after laparoscopic cholecystectomy, and persistent acute post-operative pain may result in a prolonged stay.[1,2] The use of opioids is the mainstay of treatment for post-surgical pain, and non-opioid medications can serve as a part of multimodal analgesia which is able not only to alleviate the pain following surgical procedures but also to reduce the side effects concurrent with standard opioid therapy. Gabapentinoids such as gabapentin and pregabalin have demonstrated some potential in reducing acute post-surgical pain as a part of multimodal analgesia due to their possible opioid-sparing effects and prevention of chronic post-surgical pain.[3] For instance, the combination of gabapentinoids and cyclooxygenase two inhibitors are reported to be effective for post-operative analgesia.[4-6]

Pregabalin is known as a structural analogue of the inhibitory neurotransmitter γ-aminobutyric acid.[7,8] Pregabalin is able to 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.[8,9] Pain reduction can also be achieved by interacting with neurons in the spino-bulbo-spinal loop in the superficial dorsal horn and brainstem and blocking the development of hyperalgesia and central sensitisation.[5,9] Numerous studies have reported the efficacy of pregabalin in reducing acute post-operative pain.[10,11]

However, the use of pregabalin for post-operative pain of laparoscopic cholecystectomy has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting.[10,12-14] Considering these inconsistent effects, we, therefore, conducted a systematic review and meta-analysis of randomised controlled trials (RCTs) to evaluate the influence of pregabalin on post-operative pain.[10,11]

Material and Methods

This systematic review and meta-analysis are conducted according to the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement[15] and the Cochrane Handbook for Systematic Reviews of Interventions.[16] No ethical approval and patient consent are required because all analyses are based on previously published studies.

Literature search and selection criteria

PubMed, Embase, Web of Science, EBSCO and the Cochrane library are systematically searched from inception to June 2018, with the following keywords: laparoscopic cholecystectomy and pregabalin. To include additional eligible studies, the reference lists of retrieved studies, relevant conference abstracts and reviews are also hand-searched, and the process above is performed repeatedly until no further article is identified.

Study eligibility criteria

Participants (P): Patients undergoing laparoscopic cholecystectomy.

Intervention (I): Intervention: pre-emptive pregabalin.

Control (Comparison) (C): Matched placebo.

Outcome (O). Primary outcomes: pain scores at 8–12 h and 20–24 h. Secondary outcomes: sedation score, intraoperative fentanyl requirement, post-operative analgesic requirement, operative duration, post-operative nausea and vomiting, as well as respiratory depression. The study design is RCT.

The exclusion criteria are as follows: impaired liver or kidney functions, chronic pain, a daily intake of analgesics or corticosteroid.

Data extraction and outcome measures

The following information is extracted for the included RCTs: First author, publication year, sample size, body weight, the American Society of Anesthesiology (ASA) and detailed methods of two groups. The author would be contacted to acquire the data when necessary.

Quality assessment in individual studies

The Jadad Scale is used to evaluate the methodological quality of each RCT included in this meta-analysis.[17] This scale consists of three evaluation elements: randomisation (0–2 points), blinding (0–2 points) and dropouts and withdrawals (0–1 points). One point would be allocated to each element if they have been mentioned in the article, and another one point would be given if the methods of randomisation and/or blinding have been appropriately described. If the methods of randomisation and/or blinding are inappropriate, or dropouts and withdrawals have not been recorded, then one point is deducted. The score of the Jadad Scale varies from 0 to 5 points. An article with Jadad score ≤2 is considered to be of low quality. If the Jadad score ≥3, the study is thought to be of high quality.[18]
**Statistical analysis**

Standard mean differences (Std. MDs) with 95% confidence intervals (CIs) for continuous outcomes (pain scores at 8–12 h and 20–24 h, sedation score, intraoperative fentanyl requirement, post-operative analgesic requirement and operative duration) and risk ratios with 95% CIs for dichotomous outcomes (post-operative nausea and vomiting, as well as respiratory depression) are used to estimate the pooled effects. The random-effects model is used for all the meta-analysis. An $F$ value >50% indicates significant heterogeneity. Sensitivity analysis is performed to detect the influence of a single study on the overall estimate through omitting one study in turn or undergo subgroup analysis when necessary. Owing to the limited number (<10) of included studies, publication bias is not assessed. $P < 0.05$ in two-tailed tests is considered statistically significant. All statistical analyses are performed with Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

**RESULTS**

**Literature search, study characteristics and quality assessment**

Figure 1 shows the diagram of meta-analysis search strategy and selection process. In all, 549 studies in the first search seem to be potentially relevant. One hundred and forty-two duplicates are removed. A total of 395 studies are excluded (irrelevant subjects) on the basis of initial screening of the titles and/or abstracts, and four studies are removed for not being RCTs. Ultimately, eight RCTs are included in the meta-analysis.[10,12-14,19-22]

The baseline characteristics of eight eligible RCTs in the meta-analysis are summarised in Table 1. The eight studies are published between 2008 and 2016, and sample sizes range from 34 to 120 with a total of 528. There are a similar age, male, body weight and ASA status between pregabalin group and control group at baseline. The doses of pregabalin vary from 150 mg to 600 mg preoperatively or in combination with post-operative use.

Among the eight RCTs, four studies report pain scores at 8–12 h and 20–24 h,[10,12,20,21] three studies report sedation score,[12,14,21] three studies report intraoperative fentanyl requirement,[20-22] four studies report post-operative analgesic requirement,[12,14,20,21] six studies report operative duration,[10,12,14,19,21,22] five studies report post-operative nausea and vomiting,[10,12,14,20,21] as well as two studies report respiratory depression.[12,21] Jadad scores of the eight included studies vary from 3 to 5, and all eight studies are considered to be high-quality ones according to quality assessment.

**Primary outcomes: pain scores at 8–12 h and 20–24 h**

These two outcome data are analysed with the random-effects model, and the pooled estimate of four included RCTs suggested that compared to control group for laparoscopic cholecystectomy, pre-emptive pregabalin shows no substantial influence on pain scores at 8–12 h (Std. MD = −0.71; 95% CI = −1.70–0.27), with significant heterogeneity among the studies ($F = 93\%$, heterogeneity $P < 0.00001$) [Figure 2]. However, pregabalin intervention is associated with a significantly decreased pain scores at 20–24 h (Std. MD = −0.46; 95% CI = −0.82–−0.10), with significant heterogeneity among the studies ($F = 61\%$, heterogeneity $P = 0.08$) [Figure 3].

**Sensitivity analysis**

Significant heterogeneity is observed for pain scores at 8–12 h and 20–24 h. As shown in Figure 2, the study conducted by Agarwal et al. showed the results that are almost out of range of the others and probably contribute to the heterogeneity.[21] After excluding this study, the results suggest that pre-emptive pregabalin cannot reduce pain scores at 8–12 h (Std. MD = −0.09; 95% CI = −0.36–0.18), and there is no heterogeneity among the remaining RCTs ($F = 0\%$, heterogeneity $P = 0.65$).

As shown in Figure 4, we perform subgroup analysis of pain scores at 20–24 h between the pre-operative use and the pre- and post-operative combination use. No heterogeneity remains among the subgroup analysis ($F = 0\%$). Both methods of use are effective to reduce pain scores at 20–24 h and the pre-operative use may have better ability to alleviate post-operative pain after laparoscopic cholecystectomy.
Secondary outcomes

Compared with control intervention for laparoscopic cholecystectomy, pregabalin shows improved sedation score [Std. MD = 0.92; 95% CI = 0.55–1.29; Figure 5], but has no substantial impact on intraoperative fentanyl requirement [Std. MD = 0.04; 95% CI = −0.30–0.39; Figure 6]. Post-operative analgesic requirement in pregabalin group is significantly less than that in control group [Std. MD = −2.64; 95% CI = −3.94–−1.33; Figure 7]. In addition, in comparison with control intervention after laparoscopic cholecystectomy, pregabalin treatment shows no notable influence on operative duration [Std. MD = 0.34; Table 1].

### Table 1: Characteristics of included studies

| Author          | Pregabalin group | Control group | Methods |
|-----------------|------------------|---------------|---------|
| n               | Age (years)      | Male (n)      | Body weight (kg) | ASA status I/II (n) | n   | Age (years) | Male (n) | Body weight (kg) | ASA status I/II (n) | Methods |
| 1 Mishra 2016   | 30 35.8±8.43     | 14 59.2±6.44  | -         | 2 capsules of 75 mg pregabalin 1 h before induction of anesthesia | 30 35.67±8.59 | 9 57±6.9 | - | Matched placebo |
| 2 Gurunathan 2016 | 16 41.0±12.5 | 4 - | - | Pregabalin 150 mg approximately 1 h before surgery | 18 45.9±14.7 | 4 - | - | Matched placebo |
| 3 Bekawi 2014   | 30 37.6±6.9      | 5 77.9±10 24/6 | 150 mg pregabalin capsules 2 h pre-operative, 12 h post-operative and twice daily for 2 days | 30 37.6±7.9 | 3 73.5±7.4 25/5 | Matched placebo |
| 4 Sarakatsianou 2013 | 20 53 (18-72) | 12 - | 7/13 | 300 mg the night before surgery and 300 mg 1 h preoperatively | 20 53 (18-72) | 12 - | 11/9 | Matched placebo |
| 5 Balaban 2012  | 30 52.7±11.8     | 8 51.4±15.7 | - | 300 mg pregabalin orally 1 h before surgery | 30 51.4±15.7 | 6 74.9±13.7 | Matched placebo |
| 6 Gupta 2011    | 60 44.23±15.3    | 21 65.4±12.8 34/26 | 150 mg pregabalin orally 70–90 min before surgery | 60 48.46±16.4 | 22 63.6±11.2 36/24 | Matched placebo |
| 7 Peng 2010     | 48 43 (22-65)    | 20 - | - | 75 mg pregabalin orally 1 h before surgery, then every 12 h after operation for a total of three doses | 46 47 (21-65) | 13 - | - | Matched placebo |
| 8 Agarwal 2008  | 30 46.6 (25-76)  | 23 56.2±10.1 | - | 150 mg pregabalin orally 1 h before surgery | 30 44.6 (22-69) | 18 55.7±9.1 | - | Matched placebo |

ASA: American Society of Anesthesiology

**Figure 2:** Forest plot for the meta-analysis of pain scores at 8–12 h

**Figure 3:** Forest plot for the meta-analysis of pain scores at 20–24 h
Zhang, et al.: Pregabalin on pain after laparoscopic cholecystectomy

DISCUSSION

Pregabalin is known as a structural analogue of gamma-aminobutyric acid with antinociceptive and antihyperalgesic properties and is effective to alleviate peripheral neuropathic pain, prevent neuropathic component of the acute nociceptive pain of surgery, produce a more opioid-sparing effect and the amelioration of perioperative anxiety. The action mechanism of pregabalin is probably the same as gabapentin but with a superior pharmacokinetic profile. Several clinical trials have revealed the efficacy of pregabalin for treating symptoms of generalised anxiety disorder.

A single pre-operative dose of pregabalin is found to significantly attenuate postoperatively static (at rest) and dynamic pain and opioid consumption. However, in a randomised placebo-controlled trial, a single pre-operative dose of 100 mg pregabalin is ineffective to reduce acute post-operative pain or to improve recovery after minor surgery involving only the uterus, possibly because a smaller dose (100 mg) is lower than the recommended starting dose.

95% CI = −0.10–0.77; Figure 8. Post-operative nausea and vomiting [Std. MD = 0.79; 95% CI = 0.59–1.11; Figure 9], as well as respiratory depression [Std. MD = 0.71; 95% CI = 0.17–3.02; Figure 10] in pregabalin group seem to be lower than that in control group, but with no significant difference.

Figure 4: Forest plot for the subgroup-analysis of pain scores at 20–24 h

Figure 5: Forest plot for the meta-analysis of sedation score

Figure 6: Forest plot for the meta-analysis of intraoperative fentanyl requirement (µg)

Figure 7: Forest plot for the meta-analysis of post-operative analgesic requirement
groups. In addition, pregabalin (64.67 ± 16.69 mg) group has consumed significantly less tramadol as compared to the gabapentin (116.13 ± 14.08 mg) and placebo (169.87 ± 20.32 mg) group.\[12\]

Our meta-analysis suggests that pregabalin treatment is associated with significantly reduced pain scores at 20–24 h and post-operative analgesic requirement, but showed no substantial influence on pain scores at 8–12 h, intraoperative fentanyl requirement and operative duration after laparoscopic cholecystectomy. Pre-operative pregabalin administration (oral 75–300 mg) is reported to increase perioperative sedation in a dose-related fashion, and pregabalin 300 mg may lead to more severity of sedation than that of pregabalin 150 mg.\[32\] When comparing the analgesic efficacy of gabapentin and pregabalin in surgery under spinal anaesthesia, total post-operative analgesic time is significantly more in pregabalin (14.17 h) as compared to gabapentin (8.98 h) group.\[33\] Improved sedation score is observed after pregabalin use for laparoscopic cholecystectomy in our meta-analysis, and pregabalin reduces on average nausea, vomiting and respiratory depression, but there is no sufficient evidence to support this observation. Regarding the sensitivity analysis, different doses and the time of pregabalin use may account for the heterogeneity.

Several limitations should be taken into account. First, our analysis was based on only eight RCTs and seven of them have a relatively small sample size (n < 100). Overestimation of the treatment effect is more likely in smaller trials compared with larger samples. Next, different doses and methods of pregabalin treatment in each included RCTs may result in the heterogeneity. Finally, some unpublished and missing data might lead to bias to the pooled effect.

CONCLUSIONS

Pregabalin treatment is effective to alleviate post-operative pain after laparoscopic cholecystectomy and is recommended to be administered in clinical work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Gurusamy KS, Vaughan J, Toon CD, Davidson BR. Pharmacological interventions for prevention or treatment of postoperative pain in people undergoing laparoscopic cholecystectomy. Cochrane Database Syst Rev 2014;CD008261.
2. Jiménez Fuertes M, Costa Navarro D. Outpatient laparoscopic

Figure 8: Forest plot for the meta-analysis of operative duration (min)

Figure 9: Forest plot for the meta-analysis of post-operative nausea and vomiting

Figure 10: Forest plot for the meta-analysis of respiratory depression
cholecystectomy and pain control: A series of 100 cases. Cir Esp 2015;93:181-6.

3. Durkin B, Page C, Glass P. Pregabalin for the treatment of postsurgical pain. Expert Opin Pharmacother 2010;11:2751-8.

4. Carmichael NM, Katz J, Clarke H, Kennedy D, Kreder HJ, Gollish J, et al. An intensive perioperative regimen of pregabalin and celexcoxib reduces pain and improves physical function scores six weeks after total hip arthroplasty: A prospective randomized controlled trial. Pain Res Manag 2013;18:127-32.

5. Gilron I, Orr E, Tu D, Mercer CD, Bond D. A randomized, double-blind, controlled trial of perioperative administration of gabapentin, meloxicam and their combination for spontaneous and movement-evoked pain after ambulatory laparoscopic cholecystectomy. Anesth Analg 2009;108:623-30.

6. Parsa AA, Sprouse-Blum AS, Jackowe DJ, Lee M, Oyama J, Parsa FD. Combined preoperative use of celexcoxib and gabapentin in the management of postoperative pain. Aesthetic Plast Surg 2009;33:98-103.

7. Schmidt PC, Ruehelli G, Mackey SC, Carroll IR. Perioperative gabapentinoids: Choice of agent, dose, timing, and effects on chronic postsurgical pain. Anesthesiology 2013;119:1215-21.

8. Martinotti G, Lupi M, Sarchione F, Santacroce R, Salone A, De Berardis D, et al. The potential of pregabalin in neurology, psychiatry and addiction: A qualitative overview. Curr Pharm Des 2013;19:6367-74.

9. Stahl SM, Porrca F, Taylor CP, Cheung R, Thorpe AJ, Clair A. The diverse therapeutic actions of pregabalin: Is a single mechanism responsible for several pharmacological activities? Trends Pharmacol Sci 2013;34:332-9.

10. Bekawi MS, El Wakeel LM, AlTaher WM, Mageed WM. Clinical study evaluating pregabalin efficacy and tolerability for pain management in patients undergoing laparoscopic cholecystectomy. Clin J Pain 2014;30:944-52.

11. Kim JH, Seo MY, Hong SD, Lee J, Chung SK, Kim HY, et al. The efficacy of preemptive analgesia with pregabalin in septicplasty. Clin Exp Otorhinolaryngol 2014;7:102-5.

12. Mishra R, Tripathi M, Chandola HC. Comparative clinical study of gabapentin and pregabalin for postoperative analgesia in laparoscopic cholecystectomy. Anesth Essays Res 2016;10:201-6.

13. Sarakatsianou C, Thodorou E, Georgopoulou S, Stamatiou G, Tzovaras G. Effect of pre-emptive pregabalin on pain intensity and postoperative morphine consumption after laparoscopic cholecystectomy. Surg Endosc 2013;27:2504-11.

14. Balaban F, Yagär S, Özyök A, Koş M, Güllapoglu H. A randomized, placebo-controlled study of pregabalin for postoperative pain intensity after laparoscopic cholecystectomy. J Clin Anesth 2012;24:175-8.

15. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ 2009;339:b2535.

16. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Ver. 5.1.0. The Cochrane Collaboration; 2011. Available from: http://www.cochrane-handbook.org. [Last updated on 2011 Mar 21].

17. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996;17:1-2.