Int J Clin Exp Med 2016;9(8):15157-15166
www.ijcem.com /ISSN:1940-5901/IJCEM0024040

Original Article

Efficacy of preemptive gabapentin for laparoscopic cholecystectomy: a meta-analysis of randomized controlled trials

Yan Sun, Yan Liu

Department of Anesthesiology, China-Japan Union Hospital, Jilin University, Changchun 130033, China

Received January 14, 2016; Accepted May 19, 2016; Epub August 15, 2016; Published August 30, 2016

Abstract: Purpose: Laparoscopic cholecystectomy (LC) is one of the most popular surgical procedures, while pain after this surgery still presents a major challenge mostly involving the responsible use of opioids. This meta-analysis was conducted to evaluate the efficacy of preemptive gabapentin for LC. Methods: Two researchers independently searched the following three main databases: PubMed, Embase and Cochrane Central Register of Controlled Trials for randomized controlled trials (RCTs). The data of these trials were analyzed using Review Manager. Results: Twelve RCTs with 1192 patients were included in this meta-analysis. Preemptive gabapentin decreased consumption of analgesic agent (standard mean difference (SMD) -1.68, 95% CI -2.81 to -0.56) and Visual Analogue Scale (SMD -0.63, 95% CI -1.27 to -0.00) compared with placebo. And we found significant decrease in postoperative nausea and vomiting (Risk Ratio (RR) 0.83, 95% CI 0.48 to 0.79) with not less than 600 mg gabapentin administrated, as well as the rescue antiemetic (RR 0.58, 95% CI 0.40 to 0.84). Furthermore, significant reductions in MAP at 15th minute post pneumoperitoneum (SMD -2.00, 95% CI -3.72 to -0.29) were also elicited. Conclusions: The current meta-analysis exhibits that oral administration of preemptive gabapentin is superiority to placebo in decreasing postoperative pain scores, analgesic consumption, and postoperative nausea and vomiting and can keep hemodynamic stability for LC.

Keywords: Gabapentin, laparoscopic cholecystectomy, meta-analysis

Introduction

Laparoscopic cholecystectomy (LC) is one of most popular surgical procedures, while pain after this surgery still presents a major challenge mostly involving the responsible use of opioid [1, 2]. And because of the related side effects, the use of these analgesics is limited. Given the significant shortcoming of opioids, a non-opioid analgesic as additional agent should be administrated for LC currently [3].

As a probably ancillary agent, gabapentin is an analogue of gamma-amino butyric acid (GABA). And it is a second generation antiepileptic agent used to treat neuropathic pain [4]. Meanwhile gabapentin with an opioid sparing action could prevent chronic postsurgical pain [5]. In addition, it has been found to decrease perioperative stress responses to noxious stimuli, provide preoperative anxiolysis and prevent postsurgical delirium [6].

In recent years, there have been several randomized controlled studies [7-18] evaluating the efficacy of preemptive gabapentin before surgical incision for LC as well as a combination preemptive and postoperative gabapentin. Therefore, we conducted this meta-analysis aiming to examine the evidence of prophylactic gabapentin in LC.

Methods

This meta-analysis aiming to assess the role of gabapentin in laparoscopic cholecystectomy was performed decently according to the recommendations of the PRISMA statement.

Search strategy

Two authors (L.Y. and S.Y.) systematically searched, PubMed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy comprised the following

key words: 'gabapentin' and 'laparoscopic cholecystectomy'. The literature search was updated to August fifth, 2015 without the limitation of language. The reference lists of the case reports, reviews and original reports (retrieved through the electronic searches) were checked to identify studies which had not been included in the computerized databases.

Study selection

The study selection criteria were pre-established. Inclusion criteria: (1) Randomized controlled trial; (2) The administration of gabapentin versus placebo. Exclusion criteria: (1) Duplications or abstracts only; (2) Missing data; (3) Patients with severe cerebrovascular disease or other contraindications of gabapentin; (4) Incorrect statistical analysis performed in the report; (5) Gabapentin versus other agent/agents.

Two authors (L.Y. and S.Y.) independently assessed the articles for compliance with the inclusion/exclusion criteria. Any of disputes about this meta-analysis was settled promptly by discussion among all of the authors. And data retrieval: name of the first author, year of publication, characteristic of patients, type of anesthesia, number of total patients, dose and timing of administration of gabapentin, pain assessment methods and scores, adverse effects, the analgesic and antiemetic consumption.

Pain assessment was documented in studies using the visual analog scale (VAS) or numerical rating scale (NRS). Pain was recorded on a scale of 0 (no pain) to 10 (maximum pain). Because different studies documented pain scores in different intervals, we selected pain scores at 24 hours postoperatively for our analysis. Cumulative analgesics consumption was reported in some trials, and we compared 24-hour cumulative analgesic doses between participants in the case group and those in the control group.

We also analyzed adverse outcomes including postoperative nausea and vomiting (PONV), pruritus, dizziness and sedation. The most commonly used time interval to measure the role of antiemetic is 24 hours [19], and when only longer or shorter time interval was reported, we used the time interval which was closest to the 24-hour interval. And dizziness is classified into three categories: vertigo, syncope, and non-vertigo non-syncope, which could be the standard to extract the data.

Pneumoperitonium (PP) was created by insufflation with carbon dioxide and intraabdominal pressure was kept 12 mmHg during the surgery. The haemodynamics recorded at 15^{th} minute post PP were analyzed, because this time with maximal mean arterial blood pressure (MAP) of the placebo group might reflect the most serious effect of PP on patients [12, 14].

The five main outcome measures were total consumption of analgesics including morphine and fentanyl for the first 24 hours, VAS at 24 hours postoperatively, adverse effects, the antiemetic consumption and MAP at 15^{th} minute post PP. The data of the analgesics consumption performed by Quantitative analysis were presented as mean with standard deviation (SD).

Qualitative assessment

Two authors (L.Y. and S.Y.) evaluated the quality of the trials independently according to the guideline recommended by the Cochrane Collaboration [20]. Random sequence generation, blinding method, allocation concealment, incomplete outcome data, selective reporting and other bias were assessed with the first three categories considered as "key domains". And every category was divided into three levels including low risk, unclear risk and high risk. The risk of bias of the studies included were evaluated, according to the levels of the three key domains, as 'Low' (with low risk of bias for all key domains), 'Unclear' (with unclear risk of bias for one or more key domains) and 'High' (with high risk of bias for one or more key domains).

Statistical analysis

The efficacy of gabapentin on adverse outcomes in laparoscopic cholecystectomy, compared with placebo, was estimated by calculating pooled Risk Ratio (RR), and the total analgesic consumption, VAS and MAP at 15^{th} post PP was assessed by pooled Standard Mean Difference (SMD), with 95% confidence intervals (CI). Z test ($P < 0.05$ considered as statistical significance) was performed to determine the overall effect. A random effects model was adopted when $I^2 > 50\%$, otherwise a fixed effects model was used.

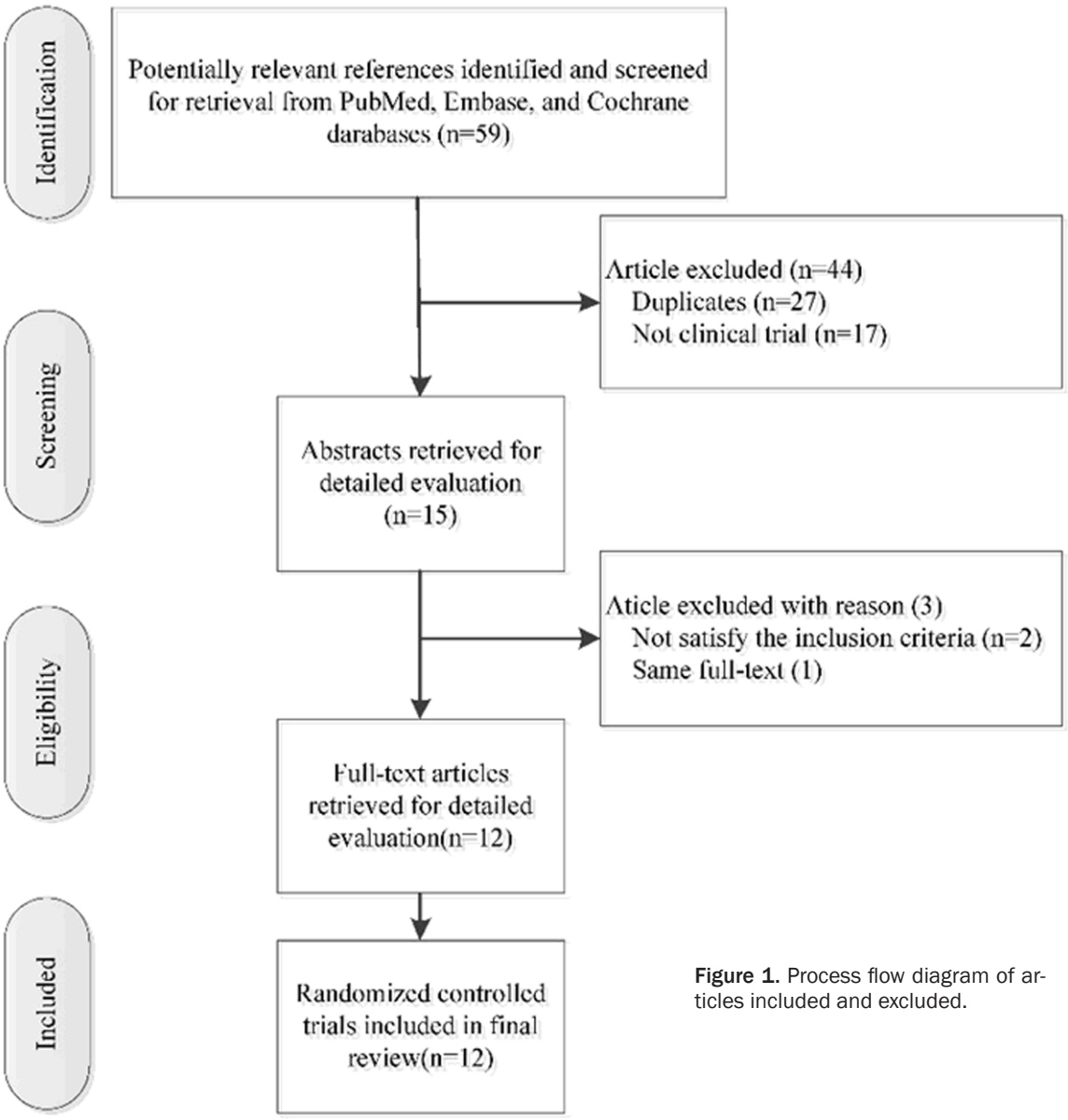

Figure 1. Process flow diagram of articles included and excluded.

We tested the robustness of these results by reanalyzing the data of low-risk and unclear-risk studies. Subgroup analyses were based on the dose of gabapentin administrated orally. And Review Manager 5.2 and Stata 12.0 were adopted to analyze the data of the included trials.

Results

Study selection

As shown in the flow diagram (**Figure 1**), the search of PubMed, Embase, CENTRAL and reference lists yielded 59 articles. Initially, 44 trials were discarded because they were duplicates and not controlled trials by reading the titles. Then, two were excluded for not relevant to our study by reviewing the abstracts. In addition, we found one paper published in two different journals [7, 21], so one [21] of the two was excluded. Twelve papers were carefully read, and then included in the meta-analysis because they met the selection criteria.

Study characteristic

The included articles were published between the years of 2004 between 2015. Each study consisted of between 48 and 306 patients. And the pooled data included 596 cases in the gabapentin group and the control group respectively. Of all the included studies, in ten trials [8, 10-18], gabapentin was administrated preop-

Table 1. Characteristics of the included trials

Author	Year	Patients	Type of anesthesia	Numbers gabapentin/placebo	Dose	Timing	Pain scores (P)	Analgesic consumption (P)
Kotsovolis	2015	adults	GA	24/24	600 mg	4 hours before surgery and 24 hours after surgery	> 0.05	0.01
Aggarwal	2015	adults	GA	30/30	300 mg	night before surgery and 300 mg at 6:00 AM on the day of surgery	-	-
Bekawi	2014	adults	GA	30/30	1200 mg	2 hours before surgery and 12 hours after surgery and 400 mg 3 times daily for 2 days	0.051	-
Semira	2013	adults	GA	30/30	600 mg	2 hours before surgery	-	-
Maleh	2013	adults	GA	40/40	600 mg	1.5 hours before surgery	> 0.05	> 0.05
Shrestha	2012	adults	GA	24/24	600 mg	1 hour before surgery	-	-
Pandey	2012	adults	GA	35/35	600 mg	2 hours before surgery	-	< 0.05
Neogi	2012	adults	GA	30/30	900 mg	2 hours before surgery	-	-
Abasivash	2010	adults	GA	25/25	1200 mg	3 hours before surgery	-	-
Bashir	2009	adults	GA	50/50	600 mg	2 hours before surgery	-	-
Pandey	2006	adults	GA	125/125	600 mg	2 hours before surgery	-	0.01
Pandey	2004	adults	GA	153/153	300 mg	2 hours before surgery	< 0.05	< 0.05

GA: general anesthesia, -: not mentioned.

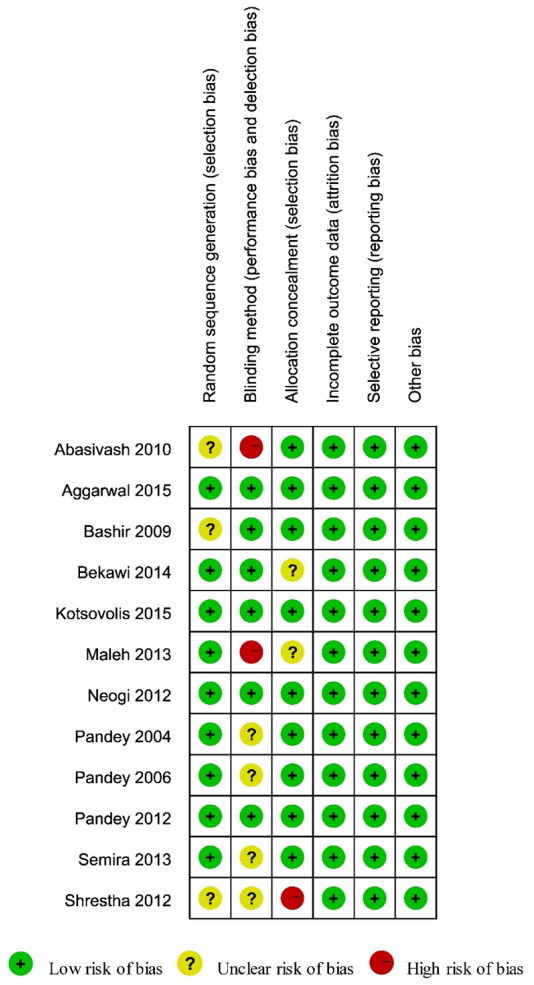

Figure 2. Summary of risk of bias about the included articles.

eratively, whereas in the other two trials [7, 9], gabapentin was given preoperatively and postoperatively. All operative interventions were performed under general anesthesia (**Table 1**).

The methodological quality of the included studies

Nine trials [7-11, 13, 14, 17, 18] provided a detailed description of randomization. Ten studies [7-10, 12-14, 16-18] were double-blinded; 11 trials [7-11, 13-18] reported allocation concealment. All the studies had no incomplete outcome (attrition bias) and all the studies reported all the end points mentioned in the Methods section (reporting bias). Other bias might not exist in all trials included with detailed description on surgery and anesthesia. An overview of the risk of bias is summarized in **Figure 2**.

Results of meta-analysis

Consumption of analgesic agent

Administration of gabapentin decreased the total consumption of analgesic, morphine or fentanyl as the only analgesic agent intravenously (pooled SMD of five trails [7, 11, 13, 17, 18] including 754 patients: -1.68, 95% CI -2.81 to -0.56) compared with placebo. In subgroup analysis, the morphine consumption could be reduced, whereas the difference was not statistically significant, but oral gabapentin administrated preemptively could decrease the consumption of fentanyl significantly (**Figure 3**).

A sensitivity analysis to remove a high-risk study [11] showed a similar result favoring gabapentin (SMD -2.10, 95% CI -2.98 to -1.23), but only decrease total heterogeneity slightly, I^2 from 97% to 94% (**Figure 3**), whereas the consumption of morphine (SMD -0.86, 95% CI -1.46 to -0.27) infused intravenously was decreased statistically significantly.

Begg's (P = 0.462) and Egger's (P = 0.366) Test suggested that no significant publication bias existed in the comparisons of analgesic consumption between gabapentin and placebo (**Figure 4**).

Pain score

Two trials [9, 18] comprising 366 patients measured the available pain scores using VAS. The result showed a reduction in the pain score (SMD -0.63, 95% CI -1.27 to -0.00, I^2 81%) in gabapentin group compared with placebo (**Figure 5**).

Adverse effects

PONV: Five trials [9, 10, 16-18], comprising 776 patients, researched the efficacy of gabapentin on postoperative PONV, The incidence of PONV (RR 0.83, 95% CI 0.48 to 0.79; I^2 88%) in the gabapentin group was lower than the placebo group (**Figure 6**).

Subgroup analysis showed that, in gabapentin group the incidence of PONV after gabapentin administrated preoperatively was statistically significant decreased with the not less than 600 mg dose (600 mg and 1200 mg), while when 300 mg dose was adopted orally, PONV could not be arrested significantly (**Figure 6**).

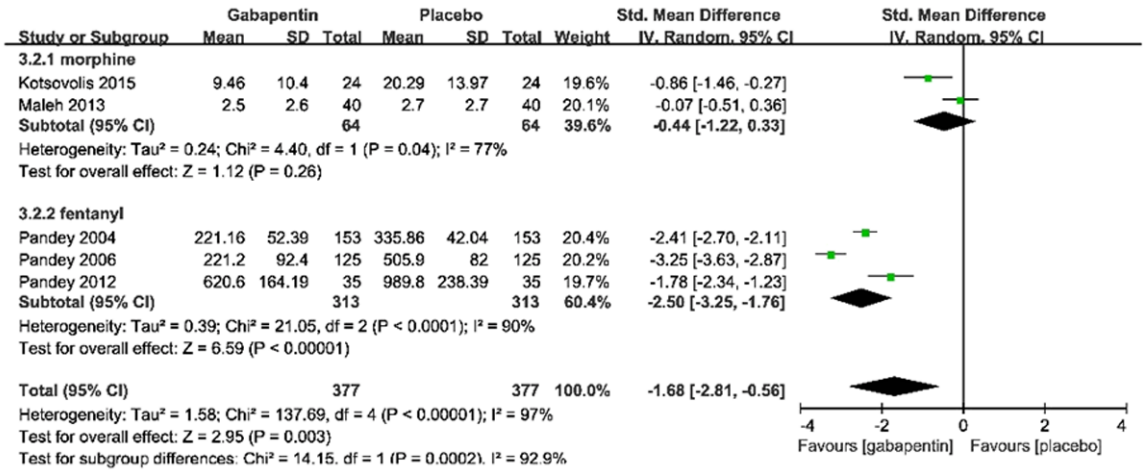

Figure 3. Result of SMD for consumption of analgesic agent comparing gabapentin with placebo.

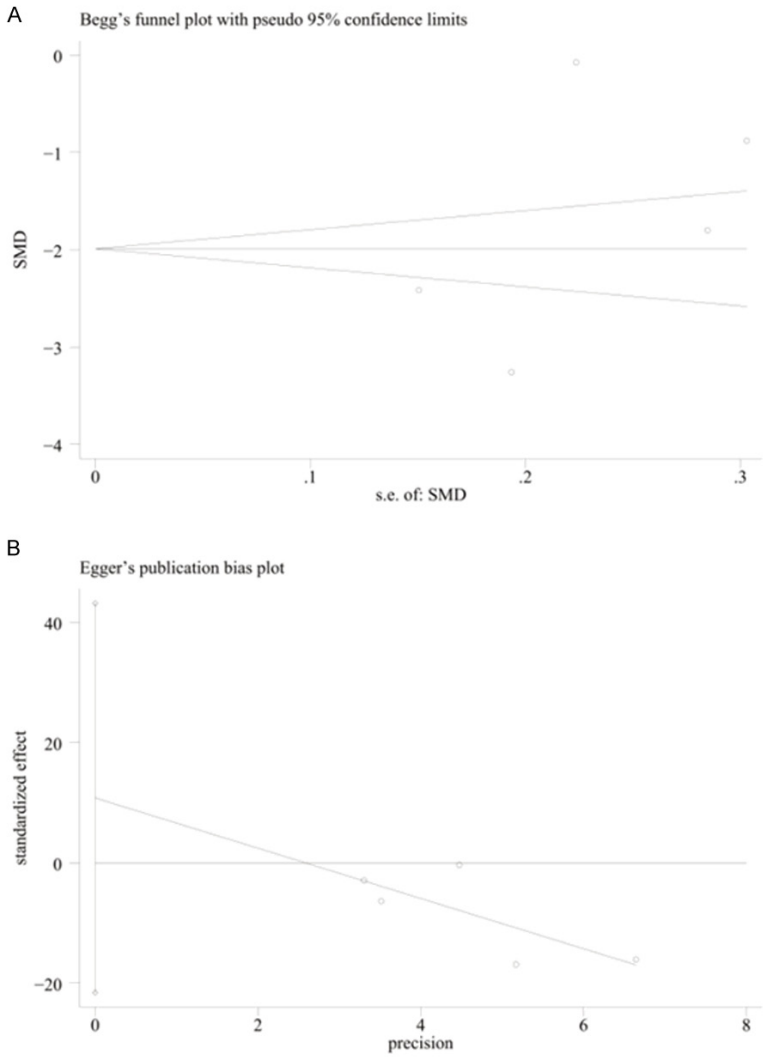

Figure 4. Publication bias analysis. A. Result of Begg's Test (P = 0.462); B. result of Egger's Test (P = 0.366).

Pruritus: Two studies [7, 17] assessed postoperative pruritus. The pooled analysis showed a non-statistically significant decrease (RR 0.33, 95% CI 0.04 to 3.16) in this side effect in gabapentin group (**Table 2**).

Dizziness: There were four trials [9, 14, 17, 18] reporting postoperative dizziness. Compared with placebo, a reduction in dizziness without statistical significance (RR 0.72, 95% CI 0.21 to 2.43; I^2 56%) was exposed in patients receiving gabapentin (**Table 2**).

Sedation: Postoperative sedation was involved in two studies [7, 18], the pooled estimate did not excluded a statistical reduction in sedation (RR 2.99, 95% CI 0.23 to 39.33; I^2 93%) in patients receiving gabapentin compared with placebo (**Table 2**).

Postoperative rescue antiemetic

Two studies [10, 16] reported the need for postoperative rescue antiemetic including ondansetron and granisetron. The pooled analysis

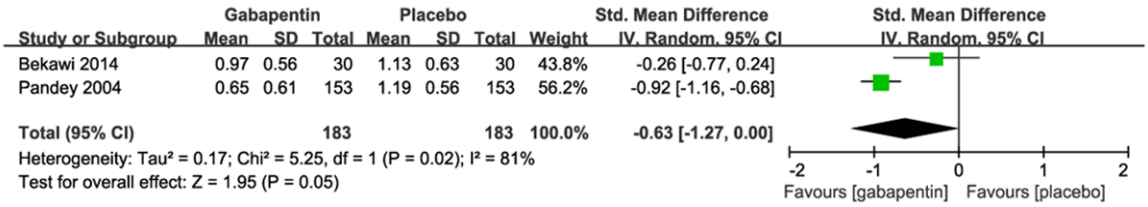

Figure 5. Result of SMD for pain scores comparing gabapentin with placebo.

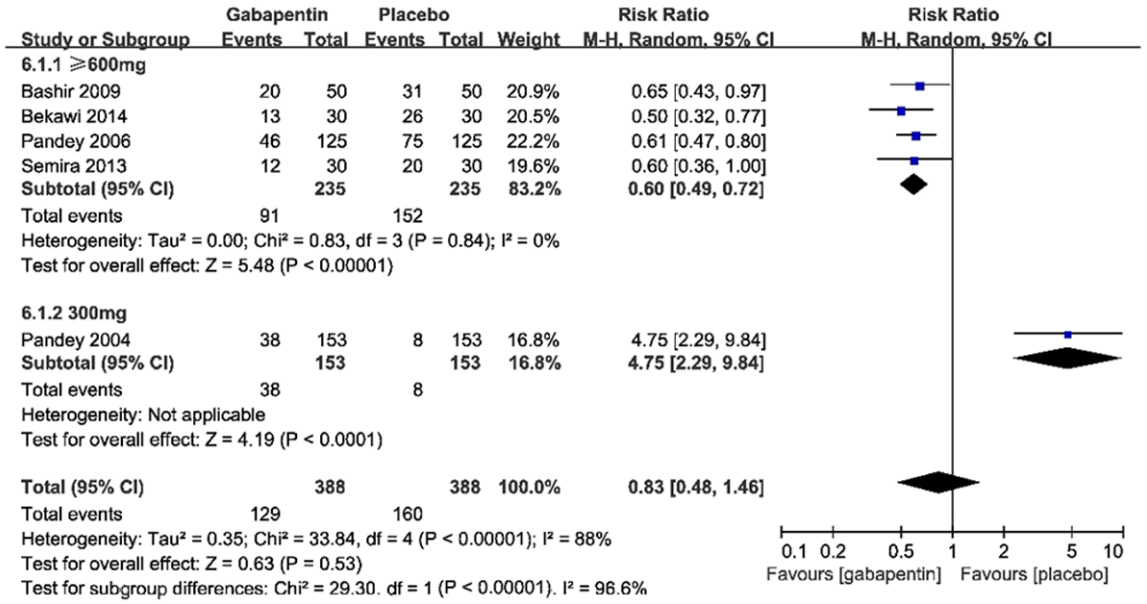

Figure 6. Result of RR for PONV comparing gabapentin with placebo.

showed a statistic diminution in the need for rescue antiemetic (RR 0.58, 95% CI 0.40 to 0.84, I^2 0%) (**Figure 7**).

MAP at 15th minute post PP

Two trials [12, 14] consisting of 108 patients explore the intraoperative MAP post PP, the pooled analysis showed the statistically lower MAP at 15th minute post PP (SMD -2.00, 95% CI -3.72 to -0.29, I^2 92%) using gabapentin compared with placebo (**Figure 8**).

Sensitivity analysis

Upon the studies with high risk were excluded by sensitivity analysis, there was no significant difference in results from overall pooled estimates across all outcomes above.

Discussion

Pain after LC as a long-standing problem, is most intense on the day and the follow day of this operation [22]. Despite numerous studies have been designed and executed during the past few decades, pain after LC and the responsible use of opioids still could result in serious consequences (postlaparoscopic cholecystectomy syndrome, PONV, etc.) [23]. Therefore, a more effective way to decrease pain is still needed urgently.

This meta-analysis undertaken to evaluate the effect of gabapentin in LC include four main findings: (1) Preemptive use of gabapentin could significantly reduce the consumption of opioids and pain score compared with placebo. (2) The need for rescue antiemetic could be reduced with the oral administration of gabapentin, and preemptive 600 mg and 1200 mg gabapentin show superiority to placebo in prevention of PONV, interestingly 300 mg does not.(3) Using of Gabapentin could non-statistically significantly decrease the incidence of pruritus and dizziness, meanwhile did not

Table 2. Incidence of side effects with gabapentin compared with placebo

Side effects	Number of studies	Number with side effects/total number of patients		RR (95% CI)	References
		Gabapentin	Placebo		
Pruritus	2	1/149	3/149	0.33 (0.04 to 3.16)	[7, 17]
Dizziness	4	23/338	37/338	0.72 (0.21 to 2.43)	[9, 14, 17, 18]
Sedation	3	57/177	11/177	0.29 (0.23 to 39.33)	[7, 18]

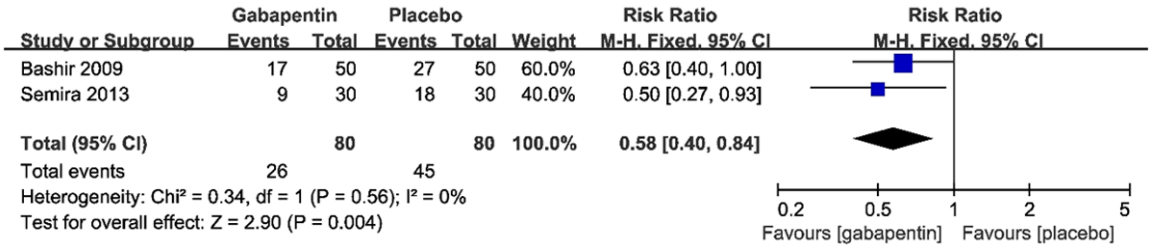

Figure 7. Result of RR for postoperative rescue antiemetic comparing gabapentin with placebo.

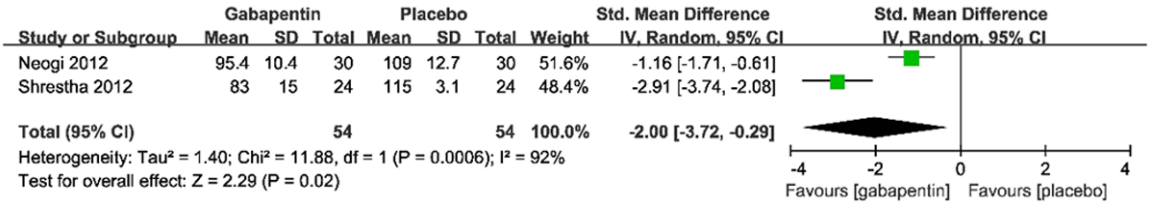

Figure 8. Result of SMD for MAP at 15th minute post PP comparing gabapentin with placebo.

increase the incidence of sedation. (4) Preemptive gabapentin administration could reduce intraoperative MAP post PP to keep hemodynamic stability.

Gabapentin have a high binding affinity for the α2δ subunit of the presynaptic voltage gated calcium channels [24], which may inhibit calcium influx to keep hemodynamic stability, in addition decrease the subsequent release of glutamate, norepinephrine, substance P that could reduce the intraoperative and postoperative pain [25]. Therefore it decreases the release of several excitatory neurotransmitters including tachykinin, and this modulation of tachykinin release probably contributes to the antiemetic effects of gabapentin [26, 27].

To the best of our knowledge, there was no meta-analysis about gabapentin premedication for LC specifically before, and this may be the first time to shed light on the efficacy of preemptive gabapentin for LC from a variety of aspects, by a meta-analysis of RCTs. The majority of included trials were well designed and assessed as "Low". Moreover, we directly compared gabapentin with placebo, meanwhile eliminated studies with high risk by sensitivity analysis. All of these strategies were administrated to come up with a solid conclusion.

Interestingly, besides decreased postoperative pain and consumption of total analgesic agents, we newly found that preemptive 600 mg and 1200 mg of gabapentin administrated orally were sufficiently effective to prevent PONV, however 300 mg gabapentin did not reduces the occurrence of PONV in this meta-analysis. We speculate that low plasma concentrations of gabapentin may be responsible. After a single oral dose of 300 mg administrated [18] the mean maximum plasma concentrations of gabapentin are attained in about 2-3 hours. Meanwhile the oral bioavailability of a single 300 mg dose is only 60%, and varies inversely with dose which could not ensure the efficacy of binding to plasma proteins [28], therefore it cannot be metabolized significantly in humans

[10]. In addition, as an adverse result of PP, hemodynamic alteration could be harmful to patients with compromised cardiac function especially [29]. While we have demonstrated that preemptive 600 mg or 900 mg gabapentin can keep hemodynamic stability, this cause may be that gabapentin could inhibit membrane voltage gated calcium channels [30].

Still, there are several limitations in this meta-analysis. First, the total number of trails included is significant relatively, but with minor amounts in subgroups. In addition, the significant heterogeneity in several groups, due to the administration of general anesthesia probably, still exists after lots of efforts. Therefore, more RCTs, including kinds of patients and various dosage regimens should be designed reasonably to detect the efficacy of gabapentin for LC.

In conclusion, our meta-analysis demonstrated that the preemptive use of not less than 600 mg of oral gabapentin may reduce postoperative pain, PONV and keep hemodynamic stability in LC. As results, except its routine usage for anticonvulsant, the clinical value of gabapentin may be expanded with this new evidence.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yan Liu, Department of Anesthesiology, China-Japan Union Hospital, Jilin University, Changchun 130033, China. Tel: +86-431-89876666; Fax: +86-431-89876666; E-mail: yanliu_doctor@163.com

References

[1] Niranjan B, Chumber S and Kriplani AK. Symptomatic outcome after laparoscopic cholecystectomy. Trop Gastroenterol 2000; 21: 144-148.

[2] Gurusamy KS, Vaughan J, Toon CD and Davidson BR. Pharmacological interventions for prevention or treatment of postoperative pain in people undergoing laparoscopic cholecystectomy. Cochrane Database Syst Rev 2014; 3: CD008261.

[3] Tocher J, Rodgers S, Smith MA, Watt D and Dickson L. Pain management and satisfaction in postsurgical patients. J Clin Nurs 2012; 21: 3361-3371.

[4] Wolkerstorfer A, Handler N and Buschmann H. New approaches to treating pain. Bioorg Med Chem Lett 2016; 26: 1103-1119.

[5] Sills GJ. The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol 2006; 6: 108-113.

[6] Kong VK and Irwin MG. Gabapentin: a multimodal perioperative drug? Br J Anaesth 2007; 99: 775-786.

[7] Kotsovolis G, Karakoulas K, Grosomanidis V and Tziris N. Comparison between the combination of gabapentin, ketamine, lornoxicam, and local ropivacaine and each of these drugs alone for pain after laparoscopic cholecystectomy: A randomized trial. Pain Pract 2015; 15: 355-363.

[8] Aggarwal S, Baduni N and Jain A. Attenuation of pressor response to laryngoscopy and intubation-A comparative study between two doses of gabapentin in patients undergoing laparoscopic cholecystectomy. Anaesthesia Pain Intens Care 2015; 19: 33-36.

[9] Bekawi MS, El Wakeel LM, Al Taher WM and Mageed WM. Clinical study evaluating pregabalin efficacy and tolerability for pain management in patients undergoing laparoscopic cholecystectomy. Clin J Pain 2014; 30: 944-952.

[10] Semira, Abbas Z, Tandon VR, Bashir A and Kour K. A prospective, randomized, placebo-controlled, trial comparing the effectiveness of gabapentin, ondansetron & dexamethasone in prevention of nausea & vomiting after laparoscopic cholecystectomy. JK Sci 2013; 15: 117-121.

[11] Maleh PA, Alijanpour E, Nickbakhsh N, Modarress R, Naghshineh A and Esmaeili M. Effects of gabapentin on postoperative pain following laparoscopic cholecystectomy. J Maz Uni Med Sci 2013; 23: 29-32.

[12] Shrestha BR, Gautam B, Shrestha S and Maharjan SK. Study of haemodynamic and endocrine stress responses following carbon dioxide pneumoperitonium. J Nepal Health Res Counc 2012; 10: 41-46.

[13] Pandey CK, Tripathi M, Joshi G, Karna ST, Singh N and Singh PK. Prophylactic use of gabapentin for prevention of succinylcholine-induced fasciculation and myalgia: a randomized, double-blinded, placebo-controlled study. J Postgrad Med 2012; 58: 19-22.

[14] Neogi M, Basak S, Ghosh D, Mukherjee S, Dawn S and Bhattacharjee DP. A randomized double-blind placebo-controlled clinical study on the effects of gabapentin premedication on hemodynamic stability during laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol 2012; 28: 456-459.

[15] Abasivash R, Heshmati F, Noroozinia H, Poorghasem J and Ghazi SF. The effect of a single dose of gabapentin on the rate of consumption of propofol and remifentanil during total intravenous anesthesia. Sci J Kurdistan Uni Med Sci 2010; 15: 40-48.

[16] Bashir F, Mohammad Bhat K, Qazi S and Hashia AM. A randomized, double blind, placebo controlled study evaluating preventive role of gabapentin for PONV in patients undergoing laparascopic cholecystectomy. JK Sci 2009; 11: 190-193.
[17] Pandey CK, Priye S, Ambesh SP, Singh S, Singh U and Singh PK. Prophylactic gabapentin for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: a randomized, double-blind, placebo-controlled study. J Postgrad Med 2006; 52: 97-100.
[18] Pandey CK, Priye S, Singh S, Singh U, Singh RB and Singh PK. Preemptive use of gabapentin significantly decreases postoperative pain and rescue analgesic requirements in laparoscopic cholecystectomy. Can J Anaesth 2004; 51: 358-363.
[19] Apfel CC, Roewer N and Korttila K. How to study postoperative nausea and vomiting. Acta Anaesth Scand 2002; 46: 921-928.
[20] Higgins JPT, Green S; Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions. Chichester, England; Hoboken, NJ: Wiley-Blackwell; 2008. pp. 649.
[21] Kotsovolis G, Karakoulas K and Grosomanidis V. Comparison between the combination of gabapentin, ketamine, lornoxicam and local ropivacaine and each of these drugs alone for pain after laparoscopic cholecystectomy: A randomized trial. Eur J Anaesth 2014; 31: 214-215.
[22] Bisgaard T, Klarskov B, Rosenberg J and Kehlet H. Characteristics and prediction of early pain after laparoscopic cholecystectomy. Pain 2001; 90: 261-269.
[23] Bisgaard T, Rosenberg J and Kehlet H. From acute to chronic pain after laparoscopic cholecystectomy: a prospective follow-up analysis. Scand J Gastroentero 2005; 40: 1358-1364.
[24] Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 2004; 45 Suppl 6: 13-18.
[25] Sarzi-Puttini P, Atzeni F, Salaffi F, Cazzola M, Benucci M and Mease PJ. Multidisciplinary approach to fibromyalgia: what is the teaching? Best Pract Res Clin Rheumatol 2011; 25: 311-319.
[26] Bryans JS and Wustrow DJ. 3-substituted GABA analogs with central nervous system activity: a review. Med Res Rev 1999; 19: 149-177.
[27] Belliotti TR, Capiris T, Ekhato IV, Kinsora JJ, Field MJ, Heffner TG, Meltzer LT, Schwarz JB, Taylor CP, Thorpe AJ, Vartanian MG, Wise LD, Zhi-Su T, Weber ML and Wustrow DJ. Structure-activity relationships of pregabalin and analogues that target the alpha(2)-delta protein. J Med Chem 2005; 48: 2294-2307.
[28] Vollmer KO, von Hodenberg A and Kolle EU. Pharmacokinetics and metabolism of gabapentin in rat, dog and man. Arzneimittelforschung 1986; 36: 830-839.
[29] Gurusamy KS, Koti R and Davidson BR. Abdominal lift for laparoscopic cholecystectomy. Cochrane Database Syst Rev 2013; 8: CD006574.
[30] Sarantopoulos C, McCallum JB, Kwok WM and Hogan Q. Gabapentin decreases membrane calcium currents in injured as well as in control mammalian primary afferent neurons. Reg Anesth Pain Med 2002; 27: 47-57