The Meta analysis of postoperative nausea and vomiting after taking granisetron with hexadecadrol for laparoscopic cholecystemy

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Abstract: Objective: To evaluate systematically efficacy and side effects of postoperative nausea and vomiting (PONV) after taking granisetron with hexadecadrol for laparoscopic cholecystemy. **Methods:** We searched the Cochrane Library, PUBMED, EMBASE, CBM, CNKI and VIP by using computer retrieval, got randomized controlled trials (RCT) which related to postoperative nausea and vomiting after taking granisetron with hexadecadrol for laparoscopic cholecystemy. **Results:** The meta-analysis included 12 trials finally, a total of 956 patients were included in the analysis. Meta-analysis showed: there was significant difference in postoperative nausea and vomiting between two drugs taken and taking the only granisetron [RR=0.44,95%CI(0.31,0.61),P< 0.0001]. **Conclusion:** Taking granisetron with hexadecadrol for laparoscopic cholecystemy (LC) had a better effect in preventing postoperative nausea and vomiting than only granisetron taken.
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Key words: laparoscopic cholecystemy; nausea; vomit; granisetron, hexadecadrol; Meta-analysis

1. Introduction

Laparoscopic cholecystemy is widely used in clinical therapy because of its smaller trauma, less postoperative pain, fast recovery, no obvious scar leaving abdomen, and shorter hospitalization time and so on. But the rate of postoperative nausea and vomiting reach up from 53% to 72%(Erhan et al., 2008), therefore, negative influence, like misinhalation, water-electrolyte and acid-base imbalance, extend postoperative and hospital stays, increase hospital cost and so on(Ryu et al.,2010;Fujii et al., 2004).

Traditional anti-emetics drug includes cholinolytic, antihistamine, phenothiazine, butyrophenone and benzamide, yet, lots of untoward effects occurred after taking those drugs, like excessive calm, hypotension, thirsty, dysphoria, hallucination, and extrapyramidal symptoms. A experiment(Fujii et al.,2000) showed 5-TH3 receptor resistance granisetron, which had been widely used in clinical, had a better effect than traditional drugs, furthermore, it has no side effects above. Whether combining granisetron with hexadecadrol, which could also prevents postoperative nausea and vomiting after laparoscopic cholecystemy (LC) (Karanicolas et al., 2008) , has a better effect than taking only granisetron or not, still no system assessment about its effectiveness and safety. The study objectively evaluated the drugs' effects, which did on the basis of comprehensive literature retrieval and adopted Meta analysis, to provide reference for doctors in the future.

2. Materials and methods

2.1 Selection of studies

Two authors will take on the review. The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. Two authors will screen the search results and they will read the full text of eligible studies identified in this way. The two authors will decide on their suitability for inclusion in the review based on whether they meet the prespecified inclusion criteria. We will report disagreement and will resolve disagreement by a consensus procedure, if necessary, with a third review author.

2.2 Data extraction and management

Two review authors will extract the data independently to a self-developed data extraction form. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one trial exists, only the publication with the most complete data will be included. We will write to study authors for further information when necessary. Disagreements will be resolved by majority vote, if necessary, of a third review author. One author will enter data into Review Manager software(RevMan 5.0.20), and a second author will independently check the data entry(Higgins et al.,2008).

2.3 Assessment of risk of bias in included studies

Two authors will independently use the GRADE criteria to assess risk of bias for all included studies.

2.4 Measures of treatment effect

For dichotomous data, results will be summarised as risk ratios(RR), with 95% confidence intervals (CI). For continuous out-comes we will use

weighted mean difference (WMD) (when measures are in the same unit), or standardisedmean difference (SMD) (when different scales are used to evaluate the same outcome) with 95% CI as well.

2.5 Unit of analysis issues

Cross-over trials will not be included in this review. We will try to identify cluster-randomised trials; they will be included and analysed in accordance with section 16.3 of the Cochrane Handbook for Systematic Reviews of Interventions.

2.6Dealing with missing data

The authors of papers withmissing data will be contacted. We will make a note of all trials that do not use intention-to-treat (ITT)analysis; we will make every attempt to analysis our data by this principal.

2.7 Assessment of heterogeneity

I^2 will be used to assess heterogeneity among studies. I^2 > 50% will be considered considerable heterogeneity.

2.8 Assessment of reporting biases

We will assess reporting bias by funnel plots. We will search multiple databases, contact authors, utilize clinical practice guidelines and systematic reviews, to minimize reporting and publicationbias.

2.9 Data synthesis and Sensitivity analysis

A ï¬xed-effects model will be used unless significant heterogeneity with I^2> 50% among studies. In that case a random-effects model will be used.

Subgroup analysis will be used to explore possible sources of heterogeneity. Heterogeneity among studies will be estimated by the I^2 statistic. Typically, values above 50% are deemed to suggest significant heterogeneity. Values of 25% to 50% are deemed to show modest heterogeneity, and values below 25% are deemed to represent low heterogeneity.

We will perform a sensitivity analysis if we find significant heterogeneity (I^2> 50%).

3.Result

3.1 Search Result

Firstly, retrieved 125 related literatures, which including 62 Chinese articles and 63 foreign articles respectively. 104 articles with headline and summary, which had excluded reviews, articles included repeatability from different databases, and non-clinical research literature. Read further article, literatures inconsistent with the inclusion criteria and about non-randomized control trial were excluded, totally 8 literatures were abandoned. Besides, one foreign article(Biswas and Rudra 2003) was listed as evaluating literature for not searching out the whole test. Finally, 12 randomized controlled trials were included, 4 English articles and 8 Chinese articles(Zhen et al., 2003;Chen 2009;Li 2006;Wang et al., 2008; Pu et al., 2008; Kuan et al.,2005; Lie et al., 2005; Chen et al., 2006;), a total of 956 patients, 487 experimental groups and 478 control groups. 8 research locations were distributed in china, 2 in Japan (Yoshitaka et al.,2006; Fujii et al.,2000) and India (Biswas et al.,2003; Khan et al.,2006) respectively.

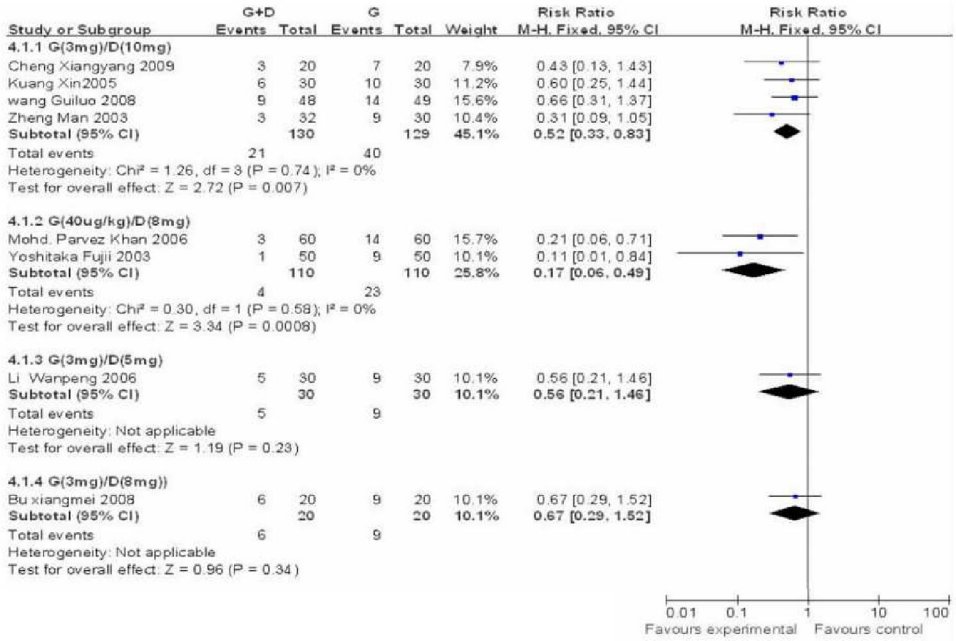

Fig 1. The rates of postoperative nausea and vomiting in 24 hours.

3.2 The results of Meta analysis

The 9 researches compared postoperative nausea and vomiting number of patients taking granisetron and hexadecadrol with only taking granisetron for laparoscopic cholecystemy. No statistical heterogeneity existed among studies, and fixed effect model was adopted to analyze heterogeneity. The results of Meta analysis showed that there was significant difference between two groups for the rate of postoperative nausea and vomiting, the RR was equal to 0.44, 95%CI (0.31, 0.61), P< .0001, and combination drug therapy was superior to taking only granisetron (the first chart). One Chinese article only appeared number of nausea and vomiting respectively to prompt that the rate of combination drug therapy was lower than control group. Two English articles gave the frequency of postoperative nausea and vomiting in different periods. It prompted that experimental group was superior to control group, too.

4. Discussion

12 studies were included and methodological qualities of studies were inconsistent. Random methods of 8 articles were confirmed by contacting with authors, double blind were adopted in 9 researches, single blind were adopted in 3 studies, and all literatures did not describe allocation concealment but did not make intentional analysis, and one literature lost to follow up. Therefore, all included studies existed selection bias, performance bias, and the possibility of measurement bias at moderate or high degree. Included Chinese and English articles had the possibility of language bias. In addition, the accuracy of the results was influenced by one literature which partly appeared.

The results of evaluation showed that taking granisetron with hexadecadrol was superior to only granisetron for laparoscopic cholecystemy (LC) in preventing postoperative nausea and vomiting, though the difference between two groups in adverse reaction of drugs had no statistical significance. Laparoscopic cholecystemy (LC) is widely used in clinic because of its small trauma, light postoperative pain and fast recovery. But the high rate of postoperative nausea and vomiting severely affect patients' recovery and rest. Granisetron is 5-TH3 receptor antagonist with high selectivity, it control nausea and vomiting by chemoreceptor trigger zone of antagonism centrum and 5-TH3 receptor of peripheral nerve endings. Headache, dizziness, constipation and increase of momentary transaminase are its main adverse reactions. Studies in recent year showed that hexadecadrol had an effect in preventing postoperative nausea and vomiting of LC, moreover, high dosage of hexadecadrol (8-16mg) has a better effect than low dosage (2-5mg). The mechanism of hexadecadrol, which might related to restraining prostaglandin synthesis and the 5-TH3 produced and released, is still not clear yet. Hexadecadrol also has many adverse reactions like increase the chances of infection, adrenal suppression, and delay healing wound, etc. Drug combination effectively indicated the possibility of multiple factors involved and multi mechanism, it also prompted that 5-TH3 was not the only mechanism. Furthermore, combing granisetron with long half-life hexadecadrol could increase balancing antemetic, and hexadecadrol could also make up the short action time of granisetron. Dosage of administration of two drugs in studies included was different, and there was a large difference in drugs administration time. The study did not explore the optimal timing and dosage of administration for the limited sample size of subgroup of studies included. Articles refer to occurrence of adverse reactions about the two drugs, like headache, dizziness and constipation etc. The results of Meta analysis showed that the difference between two groups had no statistical significance, in other words, hexadecadrol increased anti-emetic properties of granisetron, but no other adverse reactions increased. Still the rate of adverse reactions and other unknown ADRs remain to be observed in future studies.

A systematic evaluation published by Lai et al.(2009) showed that Ondansetron Hydrochloride Tablets, which is alternative of granisetron, could reach efficacy of granisetron with hexadecadrol. Results of this study(Moussa et al.,2007) showed that drug combination was superior than taking only granisetron. The limitations of quantity and quality of studies included and the limitation of drug dosage in the former might lead to inconsistent conclusions. The exact mechanism of drug combination and timing and dosage of administration are still need to be explored.

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