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Review article

Influence of perioperative nonsteroidal anti-inflammatory drugs on complications after gastrointestinal surgery: A meta-analysis

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ABSTRACT

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are a key part of multimodal perioperative analgesia. This study aimed to evaluate the influence of perioperative NSAIDs application on complications after gastrointestinal surgery by using meta-analysis.

Methods: A systematic review of published literature was conducted by searching computerized databases including PubMed, CBM, Springer, Chinese Academic Journals, and China Info since the databases were published until June 2015. The articles and retrospective references regarding complications after gastrointestinal surgery were collected to compare postoperative complications associated with NSAIDs or other analgesics. After they were assessed by randomized controlled trials and extracted by the standard of the Jadad systematic review, the homogeneous studies were pooled using RevMan 5.3 software. The meta-analysis was performed on five postoperative complications: postoperative anastomotic leak, cardiovascular events, surgical site infection, nausea and vomiting, and intestinal obstruction. Results: Twelve randomized controlled trials involving 3829 patients met the inclusion criteria. The results of meta-analyses showed the following: (1) postoperative anastomotic leak: NSAIDs (including selective and nonselective NSAIDs) increased the incidence of anastomotic leak [odds ratio (OR) = 3.02, 95% confidence interval (CI): 2.16–4.23, p = 0.00001]. Further results showed that nonselective NSAIDs significantly increased the incidence of anastomotic leak (OR = 2.96, 95% CI: 1.99-4.42, p < 0.00001), and selective NSAIDs had no significant difference as compared with the control group using other analgesics (OR = 2.27, 95% CI: 0.68 - 7.56, p = 0.18); (2) postoperative cardiovascular events: NSAIDs (selective and nonselective NSAIDs) had no difference when compared with other analgesics (OR = 0.50, 95% CI: 0.23 -1.12, p = 0.09; (3) postoperative surgical site infection: NSAIDs (selective and nonselective NSAIDs) and other analgesics had no difference in surgical site infection (OR = 0.77, 95% CI: 0.52-1.15, p = 0.20); (4) postoperative nausea and vomiting: NSAIDs (selective and nonselective NSAIDs) decreased the incidence of nausea and vomiting (OR = 0.53, 95% CI: 0.34-0.81, p = 0.003); (5) postoperative intestinal obstruction: NSAIDs (selective and nonselective NSAIDs) decreased the incidence of intestinal obstruction (OR = 0.35, 95% CI: 0.13 - 0.89, p = 0.03).

Conclusions: The meta-analysis suggests that postoperative NSAIDs, especially nonselective NSAIDs, could increase the incidence of anastomotic leak. NSAIDs could decrease postoperative nausea and vomiting and intestinal obstruction, but showed no difference in cardiovascular events and surgical site infection as compared with other analgesics.

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1. Introduction

Postoperative pain is the most common symptom after gastrointestinal surgery, and is associated with delay in postoperative recovery and prolonged hospitalization.¹ Nonsteroidal antiinflammatory drugs (NSAIDs) are a key component of contemporary perioperative analgesia and work along with opioids to establish the multimodal perioperative analgesia treatment. It has been shown that NSAIDs can reduce the dosage of opioids by 30%² for postoperative analgesia and improve the recovery of intestinal function³ with reduced postoperative nausea and vomiting (the most common side effect⁴).

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However, NSAIDs have corresponding adverse reactions, mainly in the gastrointestinal tract (such as gastrointestinal bleeding, nausea and vomiting, and perforation), and cardiovascular events, liver and kidney injury, side effects of nerve and blood system, etc. A large number of studies have shown that NSAIDs can impair the healing of gastric ulcers, ^{5–7} and increase the risk of gastrointestinal bleeding. In addition, cyclooxygenase-2 (COX-2) selective NSAIDs can lead to thrombosis and increase the risk of postoperative cardiovascular events. ⁹

There has been one major concern in this area—to what extent might the side effects of NSAIDs used in postoperative analgesia exacerbate complications after gastrointestinal surgery? Common complications after gastrointestinal surgery include postoperative anastomotic leak, cardiovascular events, surgical site infection, nausea and vomiting, and intestinal obstruction. Among these five postoperative complications, anastomotic leak is the most severe, with a high morbidity and mortality. The incidence rate of anastomotic leak in patients with intestinal anastomosis is about 3–4% (up to 30%), and the mortality rate can be as high as 10–40%. ^{10–16} For the safety of the patients and satisfactory postoperative recovery, the postoperative analgesia should be optimised. ^{17–19}

In this study, our aim was to investigate the influence of COX-2 selective and nonselective NSAIDs on complications after gastro-intestinal surgery. We applied the principle and method of evidence-based medicine to collect clinical trial data in published studies including NSAIDs (including selective and nonselective NSAIDs) application and gastrointestinal surgery complications. The meta-analysis was performed to evaluate the influence of perioperative NSAIDs on complications after gastrointestinal surgery.

2. Materials and methods

According to the contents of the literature included and the reference document number for complications, we selected five complications for meta-analysis: (1) postoperative anastomotic leak; (2) cardiovascular events; (3) surgical site infection; (4) nausea and vomiting; and (5) intestinal obstruction. This meta-analysis was performed according to the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.²⁰

2.1. Inclusion and exclusion criteria

Randomized controlled trials (RCTs), prospective observational studies, or retrospective cohort studies were selected, in which NSAIDs were administered during the perioperative period of gastrointestinal surgery. The following inclusion criteria were applied: (1) studies that compared patients receiving NSAIDs with a control group using other analgesics; (2) studies that compared patients receiving selective NSAIDs with a control group using other analgesics; (3) studies that compared patients receiving nonselective NSAIDs to a control group using other analgesics. A small sample size, incomplete data, or case reports were excluded from this study. The postoperative complications include postoperative anastomotic leak, cardiovascular events, surgical site infection, nausea and vomiting, and intestinal obstruction.

2.2. Search strategy

A systematic review of published literature was conducted by searching computerized databases including PubMed, CBM, Springer, Chinese Academic Journals, and China Info since the databases was established until 2015. The articles and retrospective

references regarding complications after gastrointestinal surgery were collected to compare postoperative complications associated with NSAIDs or other analgesics. After they were assessed by RCTs and extracted by the standard of Jadad systematic review, the homogeneous studies were pooled using RevMan 5.3 software (Australasian Cochrane Centre). The meta-analysis was performed on five postoperative complications: postoperative anastomotic leak, cardiovascular events, surgical site infection, nausea and vomiting, and intestinal obstruction. The following keywords were used: NSAIDs, gastrointestinal surgery, anastomotic leakage, and postoperative complications.

2.3. Study selection and data extraction

After excluding the articles whose titles and abstracts were not in accordance with the inclusion criteria, we then proceeded to read the full-text version of the papers that met the specific inclusion criteria. To completely document the literature, we used a unified form of information extraction with contents including: (1) general situation: title, author's name, publication date, and sources of literature; (2) the characteristics: general situation and intervention measures for the objectives of study; (3) observation indexes: the incidence of various common postoperative complications.

2.4. Quality evaluation

The standard of the Jadad systematic review was used to assess the quality of the RCT literature: (1) the randomized methods used, whether or not the methods are correct (0-2 points); (2) whether the study conducted allocation concealment, the methods are correct or not (0-2 points); (3) whether the study used blinding method, the method is correct or not (0-2 points); (4) whether loss to follow-up existed and the reasons for this (0-1 point).

2.5. Data statistical analysis

The meta-analysis using RevMan 5.3 software was applied to analyze the data. First, we checked out the research on heterogeneity test, then merged the odds ratio (OR) and calculated the 95% confidence interval (CI). When heterogeneity test results for p > 0.1 or $I^2 \le 50\%$, indicating no statistical heterogeneity, results can be analyzed using the fixed effects model; otherwise, heterogeneity exists—in which case, the random effects model is used for the metaanalysis. Using OR and 95% CI for data statistics, when p < 0.05, the results were statistically significant. When the document number incorporated into the meta-analysis is more than five, the potential publication bias cannot be ignored; we then need to use a funnel graph for description and analysis. The following methods were used to judge the results of meta-analysis: (1) compare the results of the fixed effects model and the random effects model; (2) when the number of trials involved is larger than five, use a funnel graph for the analysis; eliminate the tests that obviously declined from 95% CI, then perform the meta-analysis again, and compare the two results.

3. Results

3.1. Literature screening results

During the database search, after reading the titles, abstracts, and full-text versions, 12 articles were considered to have met the standard of RCTs, including 11 in English and one in Chinese, ^{21–32} and were incorporated into this system for evaluation. A total of 3829 cases from these studies were included, and all the trials were RCTs (Figure 1).

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