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) increased the incidence of nausea and vomiting (OR = 1.33, 95% CI: 1.03–1.72, p = 0.03); (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.

1. Introduction

Postoperative pain is the most common symptom after gastrointestinal surgery, and is associated with delay in postoperative recovery and prolonged hospitalization. Nonsteroidal anti-inflammatory 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% for postoperative analgesia and improve the recovery of intestinal function with reduced postoperative nausea and vomiting (the most common side effect).
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 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.

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%. For the safety of the patients and satisfactory postoperative recovery, the postoperative analgesia should be optimised.

In this study, our aim was to investigate the influence of COX-2 selective and nonselective NSAIDs on complications after gastrointestinal 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.

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). 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 a specific comparison across studies were not statistically significant, they were included into the meta-analysis; when statistical heterogeneity existed—in which case, the random effects model is used for the meta-analysis. 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, 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).
Figure 1. Flowchart of included articles.

Table 1
Quality evaluation for 12 studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Random distribution method</th>
<th>Distribution of hidden</th>
<th>blind method</th>
<th>Exit and lost</th>
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<td>STARSurg Collaborative</td>
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<td>No</td>
<td>Describe</td>
<td>3</td>
</tr>
<tr>
<td>Chen et al22</td>
<td>RCT</td>
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<td>Double blind</td>
<td>Describe</td>
<td>4</td>
</tr>
<tr>
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<td>RCT</td>
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<td>Double blind</td>
<td>Describe</td>
<td>5</td>
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<tr>
<td>Gorissen et al24</td>
<td>R</td>
<td>Yes</td>
<td>No</td>
<td>Describe</td>
<td>4</td>
</tr>
<tr>
<td>Holte et al25</td>
<td>R</td>
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<td>No</td>
<td>Describe</td>
<td>4</td>
</tr>
<tr>
<td>Klein et al26</td>
<td>R</td>
<td>Yes</td>
<td>No</td>
<td>Describe</td>
<td>4</td>
</tr>
<tr>
<td>Rosenberg and Harvald27</td>
<td>R</td>
<td>Yes</td>
<td>No</td>
<td>Describe</td>
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</tr>
<tr>
<td>Schlachta et al28</td>
<td>RCT</td>
<td>Yes</td>
<td>Double blind</td>
<td>Describe</td>
<td>5</td>
</tr>
<tr>
<td>Sim et al29</td>
<td>RCT</td>
<td>Yes</td>
<td>Double blind</td>
<td>Describe</td>
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<tr>
<td>Wattchow et al30</td>
<td>RCT</td>
<td>Yes</td>
<td>Double blind</td>
<td>Describe</td>
<td>5</td>
</tr>
<tr>
<td>Xu et al31</td>
<td>RCT</td>
<td>Yes</td>
<td>Double blind</td>
<td>Describe</td>
<td>5</td>
</tr>
<tr>
<td>Yang et al32</td>
<td>RCT</td>
<td>Yes</td>
<td>Double blind</td>
<td>Describe</td>
<td>5</td>
</tr>
</tbody>
</table>

R — random; RCT — randomized controlled trial.
3.2. Quality evaluation for studies included

We used the standard of the Jadad systematic review to assess the quality of the RCT literature (Table 1).

3.3. Meta-analysis for NSAIDs and anastomotic leak

There were 10 studies22–31 and 2236 patients included. There was no significant heterogeneity between the studies \( (p = 0.04, I^2 = 50\% \) when the fixed effects model was used for meta-analysis. The meta-analysis showed that there was a statistical difference for the incidence of anastomotic leak between the experimental group and the control group \((OR = 3.02, 95\% CI: 2.16–2.16, p = 0.00001)\). The result suggests that NSAIDs can increase the incidence of anastomotic leak (Figure 2).

Eight of these 10 studies22–24,26–28,30,31 used nonselective NSAIDs, and the result showed no statistical heterogeneity \( (p = 0.14, I^2 = 38\% \) \). Meta-analysis results showed that nonselective NSAIDs can significantly increase the incidence of postoperative anastomotic leak \((OR = 2.96, 95\% CI: 1.99–1.99, p = 0.00001; Figure 3)\). Four of these 10 studies24,25,29,30 used COX-2 selective NSAIDs; there was statistical heterogeneity between studies \( (p = 0.02, I^2 = 68\%; OR = 2.57, 95\% CI: 1.55–1.55, p = 0.00003)\). When the random effects model was used for meta-analysis, the results showed no statistical differences \((OR = 2.27, 95\% CI: 0.68–0.68, p = 0.18)\). Selective NSAIDs do not increase the incidence of anastomotic leak (Figure 4).

3.4. Meta-analysis for NSAIDs and cardiovascular events

There were three studies21,29,30 and 1784 patients included. There was no significant heterogeneity between the studies \( (p = 0.9, I^2 = 0) \) when the fixed effects model was used for meta-analysis. The result showed that there was no statistical difference for the incidence of cardiovascular events between the experimental group and the control group \((OR = 0.50, 95\% CI: 0.23–1.12, p = 0.09)\). Patients who were administered NSAIDs perioperatively did not show any increase in cardiovascular events after gastrointestinal surgery as compared with those who were given other analgesics (Figure 5).

3.5. Meta-analysis for NSAIDs and surgical site infection

There were five studies21–23,29,30 and 1973 patients included. There was no significant heterogeneity between the studies \( (p = 0.74, I^2 = 0) \) when the fixed effects model was used for meta-analysis. The result showed that there was no statistical difference for the incidence of surgical site infection between the experimental group and the control group \((OR = 0.77, 95\% CI: 0.52–1.15, p = 0.20)\). Patients who were administered NSAIDs perioperatively did not show any increase in surgical site infection after gastrointestinal surgery when compared with patients who were given other analgesics (Figure 6).

3.6. Meta-analysis for NSAIDs and nausea and vomiting

There were four studies22,23,30,32 and 489 patients included. There was no significant heterogeneity between the studies \( (p = 0.87, I^2 = 0) \) when the fixed effects model was used for meta-analysis. The result showed that there was statistical difference for the incidence of nausea and vomiting between the experimental group and the control group \((OR = 0.53, 95\% CI: 0.34–0.81, p = 0.003)\). Patients who were administered NSAIDs perioperatively showed a decreased risk of nausea and vomiting after gastrointestinal surgery as compared with patients who were given other analgesics (Figure 7).

3.7. Meta-analysis for NSAIDs and intestinal obstruction

There were two studies29,30 and 281 patients included. There was no significant heterogeneity between the studies \( (p = 0.65, I^2 = 0) \) when the fixed effects model was used for meta-analysis. The result showed that there was a statistically significant difference for the incidence of intestinal obstruction between the experimental group and the control group \((OR = 0.35, 95\% CI: 0.13–0.89, p = 0.03)\). Patients who were administered NSAIDs perioperatively showed less intestinal obstruction after gastrointestinal surgery as compared with those who were given other analgesics (Figure 8).

3.8. Publication bias and sensitivity analysis

In this meta-analysis, we produced a funnel plot for 10 public papers about anastomotic leak (Figure 9). The funnel chart shows that the trials were almost within 95% CI, and there was no significant publication bias. Results in this study were consistent with the articles included, and results from the random effects model and the fixed effects model were basically the same, confirming the stability of the current meta-analysis.

![Figure 2. Meta-analysis for NSAIDs and anastomotic leak. CI – confidence interval; M-H – Mantel-Haenszel test; NSAIDs – nonsteroidal anti-inflammatory drugs.](image-url)
### 4. Discussion

#### 4.1. Results analysis

This systematic review and meta-analysis includes all available data on perioperative NSAID therapy in gastrointestinal surgery, enabling us to evaluate the effect of postoperative NSAIDs on common complications after gastrointestinal surgery. According to the results and pharmacological effects of NSAIDs, we conclude that postoperative NSAIDs could increase the incidence of anastomotic leaks, but could decrease postoperative nausea and vomiting and intestinal obstruction.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Non-selective NSAIDs</th>
<th>No NSAIDs</th>
<th>Weight</th>
<th>Odds ratio M.H. fixed, 95% CI</th>
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<tr>
<td>Chen 2005^22</td>
<td>2</td>
<td>39</td>
<td>12.7</td>
<td>1.90 (0.17, 21.82)</td>
</tr>
<tr>
<td>Chen 2009^23</td>
<td>3</td>
<td>15</td>
<td>8.3</td>
<td>3.12 (0.31, 30.92)</td>
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<tr>
<td>Gorissen 2012^24</td>
<td>29</td>
<td>204</td>
<td>60.5</td>
<td>2.04 (0.21, 3.43)</td>
</tr>
<tr>
<td>Klein 2009^26</td>
<td>7</td>
<td>33</td>
<td>2.4</td>
<td>11.04 (1.28, 94.97)</td>
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<tr>
<td>Roszenberg 2007^27</td>
<td>16</td>
<td>18</td>
<td>0.9</td>
<td>8.29 (3.27, 21.06)</td>
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<tr>
<td>Schlichta 2007^28</td>
<td>4</td>
<td>22</td>
<td>1.1</td>
<td>4.67 (0.48, 45.62)</td>
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<tr>
<td>Wattchow 2009^30</td>
<td>2</td>
<td>5</td>
<td>0.2</td>
<td>0.97 (0.13, 7.09)</td>
</tr>
</tbody>
</table>

**Figure 3.** Meta-analysis for NSAIDs and anastomotic leak. CI – confidence interval; M-H – Mantel-Haenszel test; NSAIDs – nonsteroidal anti-inflammatory drugs.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Selective NSAIDs</th>
<th>No NSAIDs</th>
<th>Weight</th>
<th>Odds ratio M.H. Random, 95% CI</th>
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<tr>
<td>Gorissen 2012^24</td>
<td>7</td>
<td>39</td>
<td>12.7</td>
<td>1.17 (0.50, 2.74)</td>
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<tr>
<td>Hoite 2009^25</td>
<td>18</td>
<td>119</td>
<td>35.3</td>
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<tr>
<td>Sim 2007^26</td>
<td>1</td>
<td>36</td>
<td>10.4</td>
<td>3.00 (0.12, 78.16)</td>
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<tr>
<td>Wattchow 2009^30</td>
<td>2</td>
<td>74</td>
<td>18.5</td>
<td>0.90 (0.12, 8.59)</td>
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</table>

**Figure 4.** Meta-analysis for selective NSAIDs and anastomotic leak (random-effects model). CI – confidence interval; M-H – Mantel-Haenszel test; NSAIDs – nonsteroidal anti-inflammatory drugs.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>NSAIDs</th>
<th>No NSAIDs</th>
<th>Weight</th>
<th>Odds ratio M.H. fixed, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Bhangu 2014^21</td>
<td>5</td>
<td>242</td>
<td>78.7</td>
<td>0.49 (0.18, 1.24)</td>
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<tr>
<td>Sim 2007^29</td>
<td>0</td>
<td>36</td>
<td>7.3</td>
<td>0.32 (0.01, 8.00)</td>
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<tr>
<td>Wattchow 2009^30</td>
<td>3</td>
<td>143</td>
<td>13.0</td>
<td>0.70 (0.11, 4.27)</td>
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</table>

**Figure 5.** Meta-analysis for NSAIDs and cardiovascular events. CI – confidence interval; M-H – Mantel-Haenszel test; NSAIDs – nonsteroidal anti-inflammatory drugs.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>NSAIDs</th>
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<th>Weight</th>
<th>Odds ratio M.H. fixed, 95% CI</th>
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<td>Bhangu 2014^21</td>
<td>28</td>
<td>242</td>
<td>96.7</td>
<td>0.91 (0.52, 1.23)</td>
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<td>Chen 2005^22</td>
<td>0</td>
<td>41</td>
<td>2.7</td>
<td>0.30 (0.01, 7.62)</td>
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<tr>
<td>Chen 2009^23</td>
<td>0</td>
<td>55</td>
<td>4.3</td>
<td>0.19 (0.01, 4.11)</td>
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<tr>
<td>Sim 2007^29</td>
<td>2</td>
<td>36</td>
<td>1.7</td>
<td>2.00 (0.17, 23.11)</td>
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<tr>
<td>Wattchow 2009^30</td>
<td>2</td>
<td>143</td>
<td>4.6</td>
<td>0.46 (0.06, 3.35)</td>
</tr>
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</table>

**Figure 6.** Meta-analysis for NSAIDs and surgical site infection. CI – confidence interval; M-H – Mantel-Haenszel test; NSAIDs – nonsteroidal anti-inflammatory drugs.
Anastomotic leak has the highest morbidity and mortality among gastrointestinal complications, and the relationship between NSAIDs and anastomotic leak is an important part of this meta-analysis. Results showed that NSAIDs might increase the incidence of anastomotic leak, which is consistent with some published reports. According to this study, the incidence of anastomotic leak in the NSAIDs group was 0.21.2% versus 0.7.6% in the control group. Among the 10 studies about anastomotic leak, eight were related to nonselective NSAIDs, suggesting that nonselective NSAIDs could significantly increase the incidence of anastomotic leak. There were four research studies related to selective NSAIDs, and results showed that, compared with other analgesics, selective NSAIDs had no significant difference in terms of impact on the incidence of anastomotic leak. The incidence of anastomotic leak was 2.7–15.1% in the selective NSAIDs group and 0–7.6% in the control group. The results of the fixed effects model were consistent with those of the random effects model, but had a larger heterogeneity ($I^2 = 69\%$). However, Holte et al. reported that selective NSAIDs could increase the incidence of anastomotic leak, and the incidence rates in the NSAIDs and control groups were 15.1% and 2.6%, respectively. Meta-analysis from animal experiments provides strong evidence that NSAIDs could increase the risk of anastomotic leak. To sum up, we conclude that NSAIDs (especially nonselective NSAIDs) could increase the incidence of anastomotic leak.

The primary causes of postoperative anastomotic leak include a large anastomotic tension, bad involution of intestinal tube, complicated with pelvic infection, inadequate preoperative bowel preparation, age (>65 years), and malnutrition. In contrast to the mechanism of NSAIDs action, nonselective NSAIDs block prostaglandin biosynthesis, thereby changing the balance between the mucous membrane and mucosal reconstruction. NSAIDs contain acidic groups that cause gastrointestinal damage, whereas COX-2 selective NSAIDs do not exhibit direct damage to the gastrointestinal tract because they do not have these acidic groups.

Studies have found that COX-2 selective NSAIDs might increase the risk of cardiovascular events, mainly presenting a higher mean arterial pressure. However, the underlying mechanism of elevated blood pressure is not clear, and may be related to the inhibition of prostaglandin synthesis, inhibiting urinary sodium excretion, diastoling partial renal tubular, and increasing the plasma aldosterone levels, sodium retention, and edema. Nonselective NSAIDs cause postoperative bleeding and disturb platelet aggregation function. COX-2 selective NSAIDs do not inhibit platelet aggregation, but the destruction of the COX-1/COX-2 balance will also lead to cardiovascular events. This meta-analysis concluded that NSAIDs as compared with other analgesics used perioperatively showed no significant differences in cardiovascular events. Long-term use of NSAIDs is likely to result in cardiovascular events, but short-term perioperative use seems to make this less likely. Given the lack of appropriate experiments, this meta-analysis does not include enough data and the sample size is insufficient. Therefore, selective

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**Figure 7.** Meta-analysis for NSAIDs and nausea and vomiting. CI = confidence interval; M-H = Mantel-Haenszel test; NSAIDs = nonsteroidal anti-inflammatory drugs.

**Figure 8.** Meta-analysis for NSAIDs and intestinal obstruction. CI = confidence interval; M-H = Mantel-Haenszel test; NSAIDs = nonsteroidal anti-inflammatory drugs.

**Figure 9.** Funnel plot for NSAIDs and anastomotic leak (10 trails). NSAIDs = nonsteroidal anti-inflammatory drugs; OR = odds ratio.
and nonselective NSAIDs cannot be separated to make relevant conclusions. NSAIDs can excite the medulla oblongata vomiting center to induce postoperative nausea and vomiting.37 Opioids can inhibit gastric peristalsis, result in muscle relaxation of lower esophagus (smooth muscle), and increase the sensitivity of ear vestibular.38 Studies show that about 19% of patients with a long-term use of NSAIDs can have some gastrointestinal reactions including abdominal discomfort, nausea, vomiting, and epigastric full bilge.39 There are still no relevant experiments to prove the influence of using NSAIDs for a short term on postoperative nausea and vomiting. This meta-analysis leads to a conclusion that, as compared with other analgesics, perioperative use of NSAIDs can reduce the occurrence of postoperative nausea and vomiting. This might be attributable to the reduced opioids dosage when combined with NSAIDs. Postoperative intestinal obstruction, also a common complication, is mainly attributed to the following: changes in nerve and body fluids by surgical stimulation,40 effects of drugs used during perioperation, and surgery inflammation.41 Some animal experiments have shown that, to promote the recovery of gastrointestinal function, COX-2 selective NSAIDs have a more obvious effect than COX-1 selective NSAIDs.42 Perioperative use of NSAIDs could reduce the occurrence of postoperative ileus. This may be attributable to the reduced dosage of opioids and alleviated inhibitory effect on intestinal peristalsis. NSAIDs can replace opioids partially, reduce the inhibitory effects of bowel movement, and promote the recovery of gastrointestinal function.43 In addition, intestinal obstruction as part of the inflammation reaction caused by surgery could be inhibited by NSAIDs as they have anti-inflammatory effects.44,45

To sum up, this meta-analysis has shown that perioperative use of NSAIDs (especially nonselective NSAIDs) could increase the incidence of anastomotic leak. In the occurrence of cardiovascular events and surgical site infection, NSAIDs has no significant effects. Furthermore, NSAIDs can reduce the incidence of postoperative nausea and vomiting, and intestinal obstruction.

4.2. Limitations and enlightenment

Meta-analysis gets through analysis and summarizes test results. Therefore, we can increase the sample size to improve the credibility of the results; however, bias from the original literature will also increase. Moreover, inaccuracy of experiment and test results, as well as loss of information could influence the final results. By analyzing all the literatures included, we still noted several points of concern in the quality of tests and design of experiments: some experiments were not RCTs, not all complications were included as compared between different types of NSAIDs, and the group divisible design in some experiments was not particularly reasonable. Major concerns include literature quantity, the sample size, specific allocation and hiding schemes, concrete operation methods, specific drug dosage and dosing time (such as preoperative, after incision, or postoperative), and the effects of risk factors for complications—all of which are likely to affect the results. Therefore, we need more strict quality tests to reduce the bias and increase the credibility of meta-analysis. In the section of cardiovascular events, there were no available experiments to demonstrate that NSAIDs can increase the risk of cardiovascular events after gastrointestinal surgery, although we know that COX-2 selective NSAIDs can promote cardiovascular risk. Gastrointestinal bleeding is usually observed during long-term use of NSAIDs but is not commonly seen with NSAID treatment after gastrointestinal surgery. Therefore, we did not include gastrointestinal bleeding in this meta-analysis.

The analgesics we used have their own advantages and disadvantages. With the development and improvement of basic and clinical experiments, we will be able to make more specific conclusions. Further research should focus on the definite classification of NSAIDs in order to compare the specific application of one drug with balanced drug combination on postoperative complications.

5. Conclusion

This meta-analysis investigated the association of NSAIDs and common gastrointestinal complications after surgery, including postoperative anastomotic leak, cardiovascular events, surgical site infection, nausea and vomiting, and intestinal obstruction. NSAIDs can decrease the risk of postoperative nausea and vomiting, and intestinal obstruction, but did not show a statistically significant change in the risk of cardiovascular events and surgical site infection. Meanwhile, we conclude that postoperative NSAIDs could increase the incidence of anastomotic leak.

Conflicts of interest

None.

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