Original Article: Investigating the Effectiveness of Ketorolac in Controlling Pain after Abdominal Surgeries

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ABSTRACT

Introduction: NSAIDs are widely used in the treatment of back pain as they avoid most of the side effects of opioids such as respiratory depression, sedation, hallucinations, euphoria, addiction, shortening of bowel movements, periods and constipation. They are mostly used for mild to moderate pain where patients can tolerate oral medications. Ketorolac trometamol is a parenteral NSAID, thus eliminating the need for patients to avoid entering the body, which is a problem immediately after abdominal surgery. Ketorolac inhibits prostaglandin synthesis by inhibiting the cyclooxygenase system. ***Material and Methods:*** At PACU, patients receive morphine at the discretion of the counseling program. All patients were given PCA morphine (1 mg bolus, 5 min lockout, 4-hour limit 30 mg) after discharge from the unit. Medicated analgesia is administered by the Pain Unit and stopped on the third postoperative day if the patient is urinating, has used less than 30 mg of morphine in the last 12 hours, and has less than 4/10 pain. During this time, all patients received 500 mg of BID oral naproxen supplemented with 1000 mg of oral acetaminophen every 6 hours.

Results: The ketorolac group held this drug until day 6, when all eight patients were hospitalized. Two patients in the ketorolac group developed anastomotic leakage early after surgery and their care was excluded from further analysis due to significant differences in the study. The first leak occurred 4 days later in a 37-year-old man who had undergone a sigmoidectomy for diverticulitis with peritonitis. ***Conclusion:*** The main effect of short hospital stay is uncertain, possibly due to insufficient power for early decision making. Anastomotic leakage rate was higher than normal, especially in the ketorolac group, but there is no example of this in other studies and we can only evaluate it as negative. The evidence here suggests that ketorolac should be part of the pain management regimen after laparoscopic surgery in patients without contraindications to NSAIDs.

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Introduction

In several randomized studies, laparoscopic colectomy has been associated with a shorter hospital stay than open colectomy [1-3]. However, these trials required an average hospital stay of 5 days or more, mainly due to the long time required for diabetic ileus and return to the stomach [4-6].

Some investigators have found that various strategies of early transplant, early feeding, reduction of opioid analgesia, and use of a thoracic epidural reduce length of hospital stay, but the results have not been replicated. In addition, there are some questions about the value of epidural analgesia compared to patient-controlled analgesia (PCA) in these patients [7].

The current standard for pain management after open colectomy is PCA. The optimal postoperative pain management protocol for laparoscopic colectomy has not been clarified. Dependence on opioids clearly demonstrates control of pain after open colectomy [8-10].

Despite advances in technology and surgical materials, cystoid macular edema (CME) is currently a common cause of vision loss after cataract surgery, with a rare outcome. Although the main definition is surgery to the intraocular tissue by inducing the release of inflammatory mediators, other mechanisms such as photoretinopathy or vitreous traction are also involved. Disruption of the blood-retina barrier leads to the release of prostaglandins and other inflammatory mediators into the vitreous space, resulting in a cascade of inflammatory events, followed by blood-retinal barrier disruptions and CME in some patients [11].

Post-operative treatment, usually with a variety of anti-inflammatory drugs, including non-steroidal anti-inflammatory drugs (NSAIDs) and steroids, to reduce postoperative complications, including CME [12].

However, the possibility of a synergistic effect makes it difficult to determine the efficacy of these two drug classes alone in preventing CME. NSAIDs inhibit the synthesis and release of prostaglandins by inhibiting the conversion of arachidonic acid to prostaglandins via cyclooxygenase. 5 NSAIDs inhibited motility and chemotaxis of polymorphonuclear cells, in addition to reducing cytokines and mast cell degranulation [13]. They also reduce the risk of iris damage and intraoperative complications by inhibiting intraoperative miosis during cataract surgery [14].

Rossetti et al 4 previously reported the clinical benefits of NSAIDs and corticosteroids in the prevention and treatment of CME in a meta-analysis [15]. A Cochrane review showed that ketorolac is effective in chronic CME. 8 In addition, several randomized controlled trials (RCTs) have shown that one of the NSAIDs, ketorolac tromethamine (Acular LS, Allergan Inc., Irvine, CA, USA) is less effective in the treatment of pseudophakic CME. The purpose of this review is to evaluate the efficacy of ketorolac versus ketorolac in the treatment of pseudophakic CMI requiring medical attention within 4 months of onset of CME [16].

colectomy reduces post-operative pain, presumably because it is done through a small incision that reduces overall injury. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of back pain as they avoid most of the side effects of opioids such as respiratory depression, sedation, hallucinations, euphoria, addiction, shortening of bowel movements, periods and constipation [17-19]. They are mostly used for mild to moderate pain where patients can tolerate oral medications. Ketorolac trometamol is a parenteral NSAID, thus eliminating the need for patients to avoid entering the body, which is a problem immediately after abdominal surgery. Ketorolac inhibits prostaglandin synthesis by inhibiting the cyclooxygenase system [20-22].

Material and Methods

Study Design: This study was designed to include all patients who were candidates for laparoscopic colectomy and had no contraindications to NSAIDs or morphine. Samples from all patients were sent to the Imam Reza Hospital (Tabriz, Iran).

Inclusion And Exclusion Criteria: Patients who met the inclusion and exclusion criteria were ready to participate in the study and informed consent was obtained. Exclusion criteria include other factors that can be expected to affect discharge.

Procedures*:* All patients, nurses, and researchers were blinded to the study group. The research group took 30 mg of ketorolac intravenously every 6 hours for 48 hours. The control group also received a saline placebo intravenously. The study drug was prepared by the pharmacy in the same sachet. The first dose is given in the operating room before being transferred to the post-anesthesia care unit (PACU).

At PACU, patients receive morphine at the discretion of the counseling program. All patients were given PCA morphine (1 mg bolus, 5 min lockout, 4 hour limit 30 mg) after discharge from the unit. Medicated analgesia is administered by the Pain Unit and stopped on the third postoperative day if the patient is urinating, has used less than 30 mg of morphine in the last 12 hours, and has less than 4/10 pain. During this time, all patients received 500 mg of BID oral naproxen supplemented with 1000 mg of oral acetaminophen every 6 hours. All patients got out of bed on the second day after surgery. Although surgical procedures vary according to the procedure performed, they are similar among surgeons. Gastrointestinal therapy, parenteral antibiotics and venous thromboprophylaxis were administered to all patients before surgery. Three surgeons (>100 patients each) experienced in laparoscopic colon surgery performed all procedures. For right resection, after laparoscopic lateral mobilization of the stomach, a small middle trocar incision was widened and the artery, intestine, and anastomosis were separated ex vivo. For left-sided resection, abdominal pain, distal resection and devascularization are performed laparoscopically.

Give dimenhydrinate for nausea or vomiting unless evaluation shows severe abdominal pain requiring nasogastric tube placement. All patients were evaluated daily by a blinded investigator and/or study coordinator. This evaluation includes routine post-operative evaluation (vital signs, fluid levels, etc.) in addition to postoperative data collection and management evaluation. Visual acuity (VAS) pain. Patients are discharged according to strict rules. It should be fever-free, should not experience any complications after surgery, completely avoid eating, avoid bloating, and be able to be transported. Pain should be controlled with oral medications.

Ethical considerations*:* This study is the result of a research project approved by the ethics committee of Tabriz University of Medical Sciences; Consent was obtained from all patients and after signing the consent, they entered the study; None of the participants were charged for participating in the study, and the project was conducted free of charge to manage their pain.

Statically Analysis: Statistical analysis for the primary outcome included Student's t-test for changes in length of stay. Student's t-test, rank sum test, chi-square test, and Fisher's exact test were used as appropriate for secondary outcomes. For all comparisons, a p-value of 0.05 was considered significant.

Results

During this time, 190 patients underwent laparoscopic colectomy and were evaluated for trial entry. Of these, 94 were approved and 80 (85%) accepted the study. Ten patients were found ineligible after consent and were excluded. Twenty patients were excluded from randomization, including 11 transplant patients (16%), 7 patients requiring stoma opening, and 2 patients who were administered ketorolac procedurally by the anesthesiologist at the start of anesthesia. 6 patients withdrew after randomization (2 patients did not receive study drug on the surgical ward, 1 patient was transferred after randomization, 1 patient went to the ICU after randomization, 2 patients spontaneously withdrawn after randomization - one patient was allergic to analgesics without blinding), completing the method trial .

We did not discriminate by gender, age, weight or body mass, or time of surgery. Before day 3, none of the patients in both groups underwent a discharge procedure. While 5 patients from the ketorolac group were discharged on the 3rd day, the patients from the open group were not discharged. This is a significant difference in the number of patients in hospital at day 3 ($p = 0.024$, Fisher's exact test). The ketorolac group held this drug until day 6, when all eight patients were hospitalized. Two patients in the ketorolac group developed anastomotic leakage early after surgery and their care was excluded from further analysis due to significant differences in the study. The first leak occurred 4 days later in a 37-year-old man who had undergone a sigmoidectomy for diverticulitis with peritonitis. Anastomotic lesion was confirmed on computed tomography and the patient was reoperated due to failure. 11 more days to release(Figure 1)

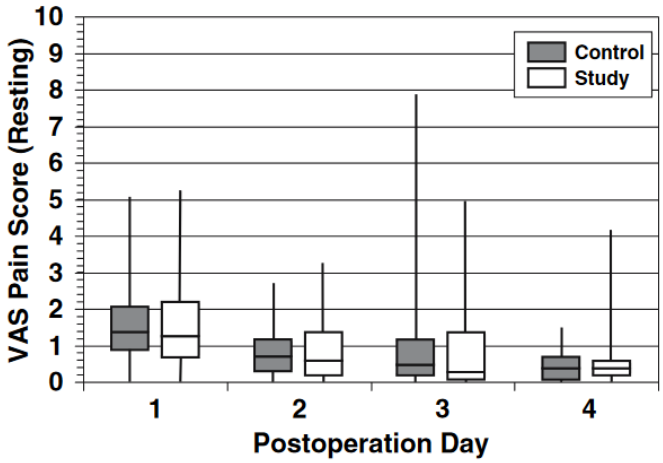

Figure 1: Post operation Day between tow groups

The second air leak was a 60-year-old male patient with abdominal pain, fever, and leukocytosis 3 days after delayed right colectomy for transverse colon cancer. Computed tomography confirmed some leakage, and the patient was treated with intestinal obstruction and antibiotics. 9 more days to release. The mean hospital stay for the entire study was 4.0 days, and there was a positive correlation between mg morphine ingested and time before exhalation ($r = 0.422$, $p = 0.005$), food intake ($r = 0.522$, $p < 0.001$) and excretion ($r = 0.437$, $p = 0$). The reduction in hospital stay was not significant. Pain control was significantly better in the Ketorolac group. Patients in the ketorolac group reported less

pain when walking and overall better pain control (Figure 1).6) Days 1 to 3 were significantly better than the placebo control group. Ketorolac patients also reported greater satisfaction with pain control in the first 48 hours. Patients taking ketorolac for 4 days reported more coughing than those taking placebo(Figure 2).

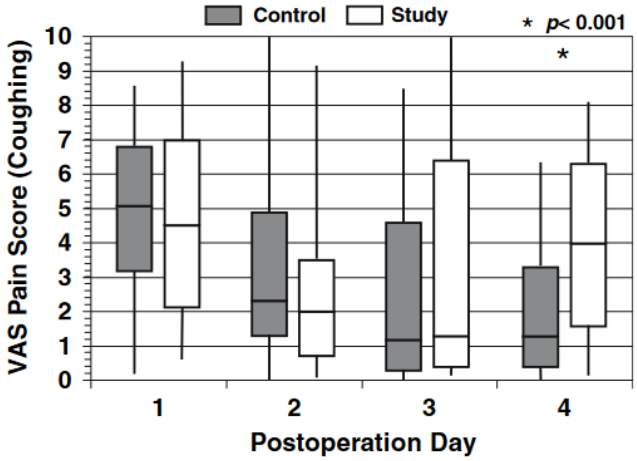

Figure 2: Pain severity between tow groups

Three patients had to be re-hospitalized due to anastomotic leakage.In the ketorolac group, a 50-year-old man was discharged 4 days after policy colectomy for polyps and a 68-year-old woman was discharged 3 days after policy colectomy for cancer, both with pain, fever, and leukocytosis within the same 5 days. And come back. Computed tomography confirmed the presence of partial leak, and two patients were hospitalized with 4 and 8 days of bowel movements and antibiotics, respectively. In the placebo group, an 82-year-old woman was discharged with colon cancer 4 days after sigmoidectomy and re-hospitalized 3 days later with peritonitis and disability. He was discharged from the hospital 24 days later. A total of 5 anastomotic leaks were recorded (4 in the ketorolac group and 1 in the placebo group, p=0.15), both need to be reworked. The leak had nothing to do with the surgeon's job. Other complications that occurred in included 1 case of deep vein thrombosis (read required), 1 case of pneumonia, 1 case of supraventricular tachycardia, and 1 case of throat swelling and shortness of breath that returned to the room for emergency treatment but did not read the patient without death.

Discussion

The precise etiology of postoperative ileus is unclear, but it is generally believed to result from sympathetic nerve reflex inhibition of intestinal peristalsis secondary to surgery [23-25]. Less surgery is needed to reduce bowel movements. This has been observed in many laparoscopic versus open colectomy studies [26]. However, ileus and thus delayed bowel movements have also been attributed to opioid use [27-29]. Therefore, reducing opioid use should have a positive effect on the duration of postoperative ileus [30-32].

Laparoscopic surgery has been shown to reduce opioid use due to the overall reduction associated with this surgical procedure. However, opioid administration remains the mainstay of pain management after most central colectomy procedures [33-35].

Kehlet and Wilmore presented a brief clinical presentation of various modalities for open and

laparoscopic colon resection [36]. They even provide some evidence that laparoscopy has a negative effect on reducing ileus if more aggressive methods are used in colon surgery [37]. However, in their study, there were concerns about the high readmission and death rate in the open surgery group [38-40].

This study is a very simple model to evaluate the distinction between the use of NSAIDs (especially ketorolac) to supplement (or replace) PCA morphine [41]. This work ran into several problems that hindered its success: it was interrupted twice by the SARS epidemic, which slowed production in Toronto; In addition, when we were worried that there would be more leakage than normal in this study, the patients voluntarily stopped when the announcement came [42-44]. The independent safety committee reviewed the results at the time. This time alone, 19 patients were missing. The committee allowed the proceedings to continue, but was concerned enough to request a second review of 60 cases [45-47]. This goal was never achieved because all surgeons participating in this single study dropped out of college [48-50].

When the test was created, it was estimated that over 80% of referrals met the inclusion criteria, but only 44% met the criteria. Most exceptions are to avoid confusion caused by conditions that may delay discharge (ICU admission, ostomy instruction, social environment), but do not use NSAIDs. Only 17% of our study population had such contraindications [51-53]. Fifteen of them had a history of peptic ulcer disease. We accept this diagnosis without the recommendation of endoscopy or barium swallow [54-56].

The findings in this study of ileus reduction, as measured by the number of first bowel movements and time to complete a meal, are consistent with previous data in colon surgery described above [57-59]. The overall mean hospital stay was only 4 days, which is lower than most large studies, and there were fewer patients in the hospital at day 3 in the ketorolac group. This benefit disappeared in the following days, and the overall reduction in hospital stay was not significant. We think this was most likely due to the premature termination of the trial and the unfortunate lack of analysis. One might wonder what to expect from the 120 patients as planned.

Pain control (walking and pleasure) was best in the ketorolac group for the first 3 days, a finding previously observed. It is not clear why the placebo group should have reported better pain control (noos) on day 4, only 50% of the ketorolac group stayed in hospital at day 4 and may represent patients with difficulties in recovery.

The occurrence of anastomotic leakage in this study is of concern. Total leakage was 11% (18% in the ketorolac group). This is more than previously reported by the authors.In a previous series of 750 laparoscopic collectomies performed by the same surgeon, the leak rate was 2.5%, well within the margin. Therefore, we think that this finding is unlikely to be due to a surgical error. Four of these leaks occurred in the ketorolac group, but there was no evidence in other colon studies that ketorolac affected wound healing or anastomotic leak. Therefore, this finding is unlikely to demonstrate the previously underappreciated role of ketorolac in anastomotic healing. The leak makes the data difficult to interpret. We believe that this result can only represent the lack of talent of a weak study group. Evaluation of the validity of the method can be seen by excluding these problems as variables.

Conclusion

This prospective, double-blind, placebo-controlled, randomized clinical trial compared ketorolac with placebo for the treatment of postoperative pain in patients undergoing laparoscopic segmental colectomy with PCA

morphine analgesia and showed that Ketorolac reduced the need for postoperative ileus and morphine. The main effect of short hospital stay is uncertain, possibly due to insufficient power for early decision making. Anastomotic leakage rate was higher than normal, especially in the ketorolac group, but there is no example of this in other studies and we can only evaluate it as negative. The evidence here suggests that ketorolac should be part of the pain management regimen after laparoscopic surgery in patients without contraindications to NSAIDs.

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