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Non-Steroidal Anti-Inflammatory Medication Administered in a Pre-Scheduled Manner Reduces Opioid Consumption after Laparoscopic Appendectomy and Cholecystectomy

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Abstract

Background: Improving postoperative outcomes by achieving adequate pain relief and increasing utilization of non-opioid analgesics is essential in reducing adverse outcomes associated with opioid use. The purpose of this study was to evaluate the difference in opioid requirements for patients utilizing scheduled non-steroidal anti-inflammatory drugs after laparoscopic appendectomy or cholecystectomy versus routine care in postoperative analgesia.

Methods: This was a single-center, retrospective observational study evaluating analgesia regimens of patients who underwent laparoscopic appendectomy or cholecystectomy. Consecutive, eligible patients between January 2019 and December 2023 who underwent laparoscopic cholecystectomy or appendectomy were identified for study inclusion and data collection. Patients received scheduled non-steroidal anti-inflammatory drugs after surgery and had as needed opioids available for additional pain relief (non-steroidal anti-inflammatory drug group) or received routine care postoperative analgesia, including as needed opioids, acetaminophen, or non-steroidal anti-inflammatory drugs (routine care group). The difference in morphine milligram equivalence up to 48 hours post-procedure in each group was evaluated.

Results: The total morphine milligram equivalents of opioids utilized post-procedure was significantly lower in the scheduled non-steroidal anti-inflammatory drugs group (mean: 26.3; 95% CI: 19.8-32.8) than in the routine care group (mean: 44.2; 95% CI: 35.3-53.2; (difference = 17.9, p = 0.002)).

Conclusion: The use of scheduled non-steroidal anti-inflammatory drugs decreased the amount and number of opioids utilized to control pain after laparoscopic appendectomy or cholecystectomy. Reducing opioid use may improve long-term patient outcomes and decrease adverse effects from opioid use.

Introduction

The multimodal approach to pain control in the acute pain setting is a standard practice, recommended to adequately achieve safe and effective analgesia [1]. Multimodal analgesia is defined as the use of a variety of analgesic medications and techniques targeting different mechanisms of action in the peripheral and/or central nervous system. The American Pain Society Guidelines on the Management of Postoperative Pain recommends clinicians offer multimodal analgesia for the treatment of postoperative pain. Utilization of multiple analgesic agents of varying mechanisms may have additive or synergistic effects, resulting in more adequate analgesia than use of a single agent [1]. The multimodal approach involves the use of at least 2 pharmacologic agents from the following classes: Acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), gabapentin/pregabalin, topical anesthetics, regional anesthetics, and opioids [1,2].

Opioid analgesics are a routine care in managing pain after surgical procedures and can provide adequate acute pain control based on postoperative pain scores [1]. Opioids come with numerous adverse effects and concerns with use [1,2]. Constipation is a common adverse effect of opioid use and may manifest regardless of a patient's tolerance to opioid therapy. Opioids may also cause nausea, vomiting, sedation, and pruritus after administration. Especially concerning are the effects of opioids on the respiratory drive, which may result in respiratory depression, and the risk of dependence and/or misuse with continued use. Due to these unwanted effects, the Centers of Disease Control (CDC) recommends maximizing non-opioid therapies for pain to reduce opioid consumption for pain control [2]. As part of a multimodal pain regimen, the addition of non-opioid pain management strategies can be incorporated for superior control of postoperative pain and to reduce overall opioid utilization [1,2].

NSAIDs are another class of analgesics that are effective in managing both pain and inflammation. Through the inhibition of cyclooxygensase-1 and 2

(COX-1 and 2) enzymes, NSAIDs produce antipyretic, analgesic, and anti-inflammatory effects. NSAIDs may be used in a multimodal approach to managing postoperative pain. There is evidence to show that the postoperative use in pain management could reduce opioid utilization [3-5]. The CDC and the American College of Surgeons guidelines discuss that NSAIDs alone or in combination with opioids can greatly decrease opioid requirements for pain control [2,3]. The American Pain Society Guidelines on Postoperative Pain recommend preoperative NSAIDs, namely the COX-2-selective NSAID, celecoxib. A preoperative dose of oral celecoxib is associated with reduced opioid requirements after major surgery [1].

NSAID use has been evaluated in both the pre- and post-operative setting and has been shown to reduce opioid utilization and overall postoperative pain [4-6]. Most of the previous studies investigate orthopedic surgery specifically or combine a wide range of procedures. Scheduled intravenous ibuprofen was shown in one such study to reduce opioid utilization by 22% [4]. There is limited data in the setting of intra-abdominal procedures, particularly in cases of appendectomy and cholecystectomy [4-7]. M Ekinci, et al. evaluated ibuprofen, acetaminophen, or no additional treatment to evaluate pain scores and opioid utilization after laparoscopic cholecystectomy [6]. Patients received either ibuprofen 800 mg IV every 8 hours, acetaminophen 1000 mg IV every 8 hours or no additional treatment for a 24 hour course. Both non-opioid treatment groups showed reduced pain scores and lower opioid use than the opioid monotherapy group, and the ibuprofen group showed additional reductions compared to the acetaminophen group. Considering previous findings of reduced pain scores and opioid use when NSAIDs are used in a multimodal approach to pain after abdominal procedures, additional data in the setting of appendectomy and cholecystectomy is warranted. The goal of this study was to evaluate opioid utilization and pain control post laparoscopic appendectomy and cholecystectomy in patients utilizing both opioids and NSAIDs versus the routine care in postoperative pain treatment.

Methods

Study design

This was a single-center, retrospective observational study that focused on postoperative pain management in two groups: patients receiving scheduled NSAIDs and as needed opioids or routine care, which included as needed NSAIDs, acetaminophen, and opioids. Data was collected between January 2019 and December 2023 on consecutive patients using the Cerner computer system and patient electronic medical records. The study's design and data collection methods were approved by the hospital's Institutional Review Board (IRB) prior to initiation.

Participants

Patients who underwent laparoscopic appendectomy or cholecystectomy at the institution were screened for inclusion. Patients had to be at least 18-years-old and have opioids and/or NSAIDs prescribed after surgery. Patients requiring more complicated procedures such as exploratory or laparoscopic converted to exploratory procedures, procedures performed in addition to the study procedures, or procedures requiring additional interventions due to surgical complications, or were pregnant were excluded from the study. Patients who were opioid tolerant (defined as 60 mg of oral morphine or another opioid with an equal or greater morphine milligram equivalence (MME) for at least 7 days prior to surgery) or known to use NSAIDs prior to surgery through review of home medication lists, as preoperative NSAID use could affect postoperative pain control, were also excluded.

Outcomes

The primary objective of this study was to determine the difference in opioid utilization (expressed as MME) in patients taking scheduled postoperative NSAIDs compared to patients not taking scheduled postoperative NSAIDs as a part of multimodal analgesia. Scheduled NSAIDs were defined as two or more doses of IV or oral NSAIDs ordered following completion of surgery and administered within 6 to 12 hour intervals. Pain scores were evaluated as a secondary outcome at postoperative hours 1, 2, 4, 8, 12, 24, and 48. Pain scores ranged from 0 to 10, with 0 indicating no pain and 10 indicating most intense pain per patient report. The time interval for MME and pain score data collection was the immediate postoperative period until 48 hours after the procedure or until discharge if discharge occurred before 48 hours. Other secondary outcomes included incidence of bleeding events in each group based on International Society on Thrombosis and Haemostasis (ISTH) major bleeding criteria, which is defined as fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin levels of 2 g/dL or greater, or transfusion of 2 units or more of whole blood or red cells, and episodes of acute kidney injury (AKI) defined by KDIGO (Kidney Disease Improving Global Outcomes) as an absolute increase in serum creatinine of at least 0.3 mg/dL within 48 hours or by a 50% increase from baseline within 7 days, or a urine volume of less than 0.5 ml/kg/hr for at least 6 hours [8,9]. The incidences of respiratory depression requiring naloxone, nausea and/or vomiting requiring antiemetics,

constipation requiring unscheduled laxatives and/or stimulants, and the use of rescue (as needed) non-opioid pain medications including acetaminophen and NSAIDs not meeting the scheduled NSAIDs criteria in each group were evaluated.

Statistical Analysis

To detect a difference in opioid utilization between the two groups, a sample size of 208 patients (104 patients in each treatment arm) to meet 80% power was determined based on results from previous studies of NSAID use with opioids and the overall decrease of MME by 22% [4]. A t-test was used to assess the difference in MME and pain scores in each group throughout the study duration. Secondary endpoints and baseline characteristics including age and sex were assessed using t-test or Chi-square test depending on the endpoint. The Type I error (α) probability was 0.05. A p-value of 0.05 or less was considered statistically significant for all statistical tests performed on study data. All statistical analysis were completed using the statistical software program, STATA version 14.2.

Results

A total of 212 patients who underwent laparoscopic cholecystectomy or appendectomy and met inclusion criteria were consecutively identified over the course of the study period. There were a total of 106 patients included in the scheduled NSAID group and 106 patients in the routine care group. The mean age in the scheduled NSAID group was 48.3 years versus 68.7 years in the routine care group (95% CI: 44.9-51.7 vs. 65.1-71.8; difference = 20.5, p < 0.001). Overall, 131 (62%) patients were female and 81 (38%) patients were male, with no difference between groups (p = 0.672) (Table 1). There were not any patients noted to have a history of kidney injury or kidney failure in either group.

For the primary outcome (Table 2) the total MME of opioids utilized post-procedure was lower in the scheduled NSAID group (26.3; 95% CI: 19.8-32.8) than in the routine care group (44.2; 95% CI: 35.3-53.2; p = 0.002). This significant difference in MME was consistent on both days 1 and 2 after surgery as shown in Table 2. There were 29 (27%) patients in the scheduled NSAID group and 10 (9%) patients in the routine care group that did not receive any opioids in the 48 hour period after surgery (p = 0.001).

Regarding pain scores after surgery, the 1, 2, 8, 12, and 48 hour pain scores were not shown to be different between groups. The pain scores at 4 hours and 24 hours were lower in the scheduled NSAID group (p = 0.004 and p = 0.041, respectively). The pain scores for all time intervals for each group can be found in Table 3. The prescribing and usage of as needed or one-time NSAIDs in each group was also assessed. In the scheduled NSAID group, 41 (39%) patients had as needed NSAIDs ordered. In the routine care group, 29 (27%) patients had as needed NSAIDs ordered, and 5 (5%) patients utilized as needed NSAID orders but not to a degree to meet scheduled NSAID criteria.

The rate of nausea and/or vomiting requiring antiemetic use was significantly lower in the scheduled NSAID group (24 vs. 40; p = 0.017). Constipation requiring scheduled laxatives and/or stimulants was not shown to be different between the two groups (14 in the scheduled NSAID group vs. 24 in the routine care group, p = 0.073). No patients in either group required the administration of naloxone for reversal of opioid induced respiratory depression, although there was one patient in the NSAID group and five patients in the routine care group with a reported respiratory rate less than 12, respectively (p = 0.098). There were no noted incidences of AKI or major bleeding in either group. The

Table 1: Baseline characteristics.

Outcome	NSAID Group (N = 106)	Routine Care Group (N = 106)	p-value
Age, mean, (range), yrs	48.3 (44.9-51.7)	68.7 (65.7 -71.8)	< 0.001
Male, no. (%)	42 (40)	39 (37)	0.672
Female, no. (%)	64 (60)	67 (63)	

NSAID: Non-Steroidal Anti-Inflammatory Drug

Table 2: Primary outcome.

Outcome, Mean (95% CI)	NSAID Group (N = 106)	Routine Care Group (N = 106)	Difference	p-value
Total MME	26.3 (19.8-32.8)	44.2 (35.3-53.2)	17.9 (6.9-28.9)	0.002
Day 1 MME	19.4 (15.1-23.8)	30.3 (24.5-36.1)	10.9 (3.6-18.1)	0.003
Day 2 MME	6.9 (3.8-10.0)	13.9 (9.2-18.7)	7.0 (1.4-12.7)	0.015

MME: Morphine Milligram Equivalent; NSAID: Non-Steroidal Anti-Inflammatory Drug

Table 3: Pain scores.

Hours, Mean (95% CI)	NSAID Group (N = 106)	Routine Care Group (N = 106)	p-value
Hour 1	3.0 (2.5-3.5)	3.5 (2.9-4.0)	0.271
Hour 2	3.6 (2.9-3.0)	4.5 (3.8-5.1)	0.062
Hour 4	3.4 (2.8-4.0)	4.6 (4.0-5.1)	0.004
Hour 8	3.5 (2.9-4.0)	3.7 (3.1-4.4)	0.524
Hour 12	3.0 (2.5-3.6)	3.6 (3.0-4.2)	0.147
Hour 24	2.9 (2.4-3.4)	3.7 (3.2-4.1)	0.041
Hour 48	2.9 (2.1-3.8)	3.2 (2.6-3.8)	0.649

NSAID: Non-Steroidal Anti-Inflammatory Drug

Table 4: Other secondary outcomes.

Outcome	NSAID Group (N = 106)	Routine Care Group (N = 106)	p-value
No Opioids Given, N (%)	29 (27)	10 (10)	0.001
Respiratory Rate < 12, N (%)	1 (1)	5 (5)	0.098
Naloxone Given, N (%)	0 (0)	0 (0)	N/A
Antiemetic Use, N (%)	24 (23)	40 (38)	0.017
Laxatives Given, N (%)	14 (13)	24 (23)	0.073
BUN, mean (95% CI), mg/dL	12.7 (11.5-13.8)	15.3 (13.4-17.1)	0.026
Serum Creatinine, mean (95% CI), mg/dL	0.8 (0.76-0.84)	0.9 (0.82-0.97)	0.028
Hemoglobin, mean (95% CI), g/dL	12.2 (11.9-12.5)	11.8 (11.5-12.1)	0.074
Hematocrit, mean (95% CI), %	36.7 (35.8-37.5)	35.7 (34.9-36.6)	0.129
PACU Ketorolac, N (%)	22 (21)	16 (15)	0.283
PRN NSAID Use, N (%)	35 (33)	5 (5)	< 0.001
PRN NSAID Ordered, N (%)	41 (39)	29 (27)	N/A
PRN Acetaminophen Use, N (%)	76 (72)	91 (86)	0.012

BUN: Blood Urea Nitrogen; NSAID: Non-Steroidal Anti-Inflammatory Drug; PACU: Post-Anesthesia Care Unit; PRN: As needed

mean serum creatinine was noted to be significantly lower in the scheduled NSAID arm (mean: 0.8; CI: 0.76-0.84) compared the routine care arm (mean: 0.9; CI: 0.82-0.97; p = 0.028). Additionally, the use of PRN acetaminophen was noted to be significantly lower in the scheduled NSAID arm compared to the routine care arm (76 in scheduled NSAID arm vs. 91 in routine care arm; p = 0.012). A full list of secondary outcomes assessed is shown in Table 4.

Discussion

The results of this study demonstrated a reduction in opioid requirements after laparoscopic appendectomy or cholecystectomy when scheduled NSAIDs were utilized as a part of multimodal analgesia. There was also a significant portion (27% of patients in the scheduled NSAID arm) of patients receiving scheduled NSAIDs that did not require any opioids after surgery compared to the routine care group (10% of patients in the arm). There was a significant difference in average patient age in each group; the scheduled NSAID group was significantly younger. The difference in age between groups reflects common prescribing practices of NSAIDs at this institution with more reserved usage in elderly patients. Another aspect to consider is the effect of age on pain sensitivity. Previous studies have shown that pain sensitivity decreases with aging, which may strengthen the overall results in this study as a higher opioid and acetaminophen utilization was seen in the routine care group despite being an older population [10]. A possible area of improvement would be to educate nurses and providers administering as needed pain medications. Ensuring that as needed NSAIDs are at least offered first before utilizing opioids may further increase the routine use of multimodal analgesia.

The lack of a difference in overall pain scores is likely due to both groups utilizing opioids to achieve adequate analgesia. However, there was a statistical difference in pain scores at the 4 hour and 24 hour intervals after surgery. The 4 hour pain scores were possibly significantly lower in the scheduled NSAID group because opioids used during surgery or in PACU

such as morphine, hydromorphone, or fentanyl reached the end of expected effectiveness, while NSAIDs given in that period likely had longer lasting effects. Although the pain scores at 24 hours favored the scheduled NSAID arm, the clinical relevance of this finding is limited as the majority of pain scores did not show a statistical difference. Another significant difference was the use of antiemetics to treat nausea and/or vomiting. Antiemetic use was lower in the scheduled NSAID group, likely due to the lower overall opioid utilization. As constipation may occur regardless of the opioid dose or patient tolerance, the lack of the difference in scheduled laxatives in each group is expected despite the difference in opioid utilization between groups. As this was a secondary outcome, the study was not powered to find a difference for this outcome.

Although not statistically significant, five patients in the routine care group and one patient in the scheduled NSAID group experienced a respiratory rate less than 12 breaths per minute at some point after surgery. However, no patient in either group had naloxone given. There was a statistically significant difference in BUN and serum creatinine in favor of the scheduled NSAID group. Although there was a statistical difference, the clinical relevance of this difference is limited as both BUN and serum creatinine were found to be within a normal range in each group. Two patients in the routine care group had a hemoglobin less than 9.0 g/dL versus one patient in the NSAID group, but there were no noted episodes of AKI or major bleeding noted in the 48 hours after surgery.

Limitations

This was a single-center study focusing on laparoscopic appendectomy and cholecystectomy at a community teaching hospital, which limits the overall external validity. Another limitation is the use of NSAIDs by patients in the routine care group. As shown in Table 4, 16 patients in the routine care group received a one-time dose (not part of a PRN order) of IV ketorolac while in PACU. Along with the infrequent use of as needed NSAIDs by some patients in this group, this weakens the overall difference between groups. Despite this, a difference in MME was still found between the two groups. The use of a single postoperative NSAID dose more accurately reflects the routine care per guidelines and at this facility and may strengthen applicability to real-world practice.

Conclusion

Overall, the use of scheduled NSAIDs was shown to decrease the amount of opioids utilized to control pain after laparoscopic appendectomy or cholecystectomy at this community teaching hospital. These results support the scheduled use of NSAIDs as part of a multimodal approach to managing pain after surgery and to reduce overall opioid use and minimize opioid adverse effects. Future prospective studies may be needed to evaluate a specific NSAID dose regimen and apply these results to a variety of patient populations.

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