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Retrospective Study

Oral Versus Intravenous Acetaminophen within an Enhanced Recovery after Surgery Protocol in Colorectal Surgery

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Background: Multimodal pain management within enhanced recovery after surgery (ERAS) protocols is designed to decrease opioid use, promote mobilization, and decrease postoperative complications.

Objectives: To evaluate the role of intravenous (IV) versus oral (PO) acetaminophen within an established ERAS protocol in colorectal surgery.

Study Design: This was a retrospective observational study.

Setting: This research took place within an established perioperative colorectal surgery protocol.

Methods: A total of 91 consecutive elective colorectal resections performed according to an ERAS protocol using only IV acetaminophen (IV group) were compared with 84 consecutive resections performed using one dose of IV acetaminophen followed by subsequent administration of oral acetaminophen (PO group). Our multimodal pain management strategy also included transverse abdominis plane blocks, celecoxib, and ketorolac medications for both groups. Opioid requirements, maximum and average daily pain scores by the Visual Analog Scale, and postoperative outcomes were compared between groups.

Results: There were no differences in maximum or average pain scores on postoperative days 0-3 or at time of discharge between IV and PO groups. Compared with the IV acetaminophen only group, the PO group received significantly more perioperative opioids through 72 hours postoperatively (68.8 oral morphine equivalents [OME] IV group vs. 93.7 OME PO group; $P < 0.0001$), were more likely to require opioid patient-controlled analgesia (8.9% IV group vs. 46.4% PO group; $P < 0.0001$), and were more likely to experience postoperative nausea and vomiting (33.0% IV group vs. 48.8% PO group; $P = 0.0449$).

Limitations: Significant limitations include the studies' retrospective nature and that it was performed at a single institution.

Conclusions: Restriction of IV acetaminophen within an ERAS protocol in colorectal surgery was associated with increased opioid use, greater need for opioid patient-controlled analgesia, and increased incidence of postoperative nausea and vomiting. IV acetaminophen may be superior to oral acetaminophen in the early postoperative setting.

Key words: Perioperative pain management, enhanced recovery after surgery, acetaminophen, multimodal pain control, nonopioid

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Opioid medications have traditionally been the backbone of postoperative pain control, but side effects such as sedation, nausea, ileus, respiratory depression, and the potential for addiction limit their use. Multimodal pain management strategies with enhanced recovery after surgery (ERAS) protocols are designed to minimize the effects of opioids, leading to earlier postoperative ambulation, return of normal

bowel function, and earlier postoperative discharge (1,2). According to the American Society of Enhanced Recovery, multimodal pain management strategies should include at least 2 nonopioid analgesics and an epidural or regional nerve block (3). Acetaminophen, available in oral, rectal, and intravenous (IV) formulations, is the most commonly used nonopioid analgesic in ERAS protocols (4).

The safety and efficacy of IV acetaminophen, first approved in the United States in 2010, has been demonstrated for a number of postoperative settings (5-12). Its clinical superiority over oral acetaminophen, however, has not yet been proven (13,14). Recently, several institutions have reported substantial cost-savings by restricting usage of perioperative IV acetaminophen (15-19).

Our institution recently changed from a postoperative pain management strategy protocol exclusively using IV acetaminophen to one that uses a single intraoperative dose of IV acetaminophen followed by subsequent administration of oral acetaminophen. We sought to evaluate the effect of our recent protocol change on pain scores, opioid requirements, postoperative nausea and vomiting, and other postoperative outcomes. We hypothesized that the change in postoperative pain management would result in no difference in postoperative pain, outcomes, or opioid use.

Methods

This research was approved by the Cooper Health System investigational review board (protocol #15-177).

Study Population

Patients were identified during their preoperative visit as candidates for the ERAS pathway. A total of 91 consecutive elective colorectal resection procedures performed with a perioperative multimodal pain management strategy using only IV acetaminophen (November 1, 2015 to September 30, 2016) were compared with 84 consecutive elective colorectal surgery cases performed with a multimodal strategy that used a single dose of IV acetaminophen followed by subsequent administration of oral acetaminophen (November 1, 2017 to October 31, 2017). The month of October 2016 was excluded as a wash-out period while the new protocol was implemented.

Perioperative ERAS Protocol

All patients received preoperative outpatient counseling prior to surgery. Patients were instructed to eat a regular diet up until the night before surgery, and then were allowed only clear liquids until 2 hours prior to their operation. All patients additionally received oral antibiotic and mechanical bowel preparation on the night before surgery. Patients were started on a clear liquid diet immediately following surgery, and were advanced to a solid diet within 24 hours. IV fluids were discontinued within 24 hours following surgery. Patients were mobilized at least once on the day of surgery, and at least twice on subsequent days.

Perioperative multimodal pain management was provided with one dose of oral celecoxib 200 mg (held for Cr > 1.1 or glomerular filtration rate [GFR] < 60 or sulfa allergy), oral gabapentin 300 mg every 8 hours, IV ketorolac 30 mg every 6 hours (15 mg IV every 6 hours if age > 65, GFR < 60) and acetaminophen 1000 mg IV or 975 mg oral every 6 hours. Bilateral transverse abdominis plane nerve blocks with liposomal bupivacaine were administered to all patients.

Data Collection

All data were obtained through retrospective review of the electronic medical record. Patient demographic data, intraoperative data, and postoperative outcomes were recorded for the study and the control groups. Pain scores were taken every 8 hours according to the Visual Analog Scale (VAS). Doses of opioids and acetaminophen administered were recorded daily, summed, and averaged between groups. Opioid doses were converted to oral morphine equivalents (OME) using the ClinCalc.com "Equivalent Opioid Calculator" tool (20).

Statistical Analysis

Comparisons between the study and control groups were carried out using the Wilcoxon rank-sum test or analysis of variance for repeated measures on ranks to compare means of continuous variables, and the Fisher exact test to compare differences of categorical variables. All statistical analyses were carried out using SAS v9.4 (SAS Institute, Cary, NC). A 2-tailed *P* value of 0.05 was used to determine statistical significance.

Results

Group Comparison

The final study group included 91 patients managed with a pain management strategy using only IV acetaminophen "IV group," and 84 patients managed with a multimodal pain management strategy using one dose of intraoperative IV acetaminophen followed

by subsequent administration of oral acetaminophen "PO group." There were no differences in age, gender, body mass index, American Society of Anesthesiologists Physical Status Classification System score, procedure type, operative approach (laparoscopic vs. open procedure), preoperative diagnosis, procedure length, or intraoperative blood loss between the IV and PO groups (Table 1).

Pain Management

Pain management strategies are compared between IV and PO groups (Table 2). All patients received transverse abdominis plane nerve blocks and one dose of IV acetaminophen intraoperatively. The IV group received more doses of IV acetaminophen postoperatively (385 doses IV group vs. 0 doses PO group; $P < 0.0001$), and fewer doses of postoperative oral acetaminophen (95 doses IV group vs. 337 doses PO group; $P < 0.0001$).

Pain Scores

Pain scores are compared between the IV and PO groups in Table 3. There were no significant differences in daily maximum or average pain scores between groups through 72 hours postoperatively or at time of discharge.

Opioid Use

Intraoperative and postoperative daily opioid requirements are shown for PO and IV groups in OME in Table 4 and Fig. 1. There was no significant difference in intraoperative opioid requirements between groups. Through 72 hours postoperatively, average opioid use

Table 1. *Group comparison. Demographic and intraoperative characteristics are compared between IV and PO acetaminophen groups.*

	IV, n = 91	PO, n = 84	*P* value
Characteristic			
Age, mean, years ± SD	62.4 (±13.1)	58.9 (±11.9)	0.0672
Male gender, no. (%)	48 (52.7)	34 (40.5)	0.1296
Body mass index, average, no. ± SD	30.8 (±7.9)	30.1 (±7.4)	0.5632
American Society of Anesthesiologists Physical Status Classification System score			0.1378
1, no. (%)	0 (0.0)	1 (1.2)	
2, no. (%)	26 (28.6)	32 (38.1)	
3, no. (%)	65 (71.4)	50 (59.5)	
4, no. (%)	0 (0.00)	1 (1.2)	
Procedure type			0.8549
Right colectomy, no. (%)	33 (36.3)	33 (39.3)	
Left colectomy, no. (%)	24 (26.4)	26 (31.0)	
Low anterior resection, no. (%)	25 (27.5)	18 (21.4)	
Total abdominal colectomy, no. (%)	3 (3.3)	4 (4.8)	
Abdominal perineal resection, no. (%)	3 (3.3)	3 (3.6)	> 0.9999
Laparoscopic, no. (%)	61 (67.0)	60 (71.4)	0.5314
Preoperative diagnosis			0.8953
Cancer, no. (%)	59 (64.8)	46 (54.8)	
Diverticulitis, no. (%)	11 (12.1)	13 (15.5)	
Inflammatory bowel disease, no. (%)	8 (8.8)	9 (10.7)	
Benign disease, no. (%)	11 (12.1)	13 (15.5)	
Other, no. (%)	2 (2.2)	3 (3.6)	
Intraoperative factors			
Case length, min ± SD	296.2 (±120.0)	294.4 (±99.5)	0.9135
Estimated blood loss, mL ± SD	121.9 (±111.6)	138.6 (±117.4)	0.3367

Abbreviation: SD, standard deviation.

Table 2. *Pain management. Perioperative pain management strategies are compared between IV and PO acetaminophen groups.*

	IV, n = 91	PO, n = 84	*P* value
Transversus abdominus plane block, no. (%)	91 (100.0)	84 (100.0)	> 0.9999
Ketorolac, no. (%)	68 (74.7)	65 (77.4)	0.7254
Gabapentin, no. (%)	80 (87.9)	77 (91.7)	0.4635
IV acetaminophen intraoperative dose, no. (%)	91 (100.0)	84 (100.0)	> 0.9999
# of doses of postoperative IV acetaminophen	385	0	< 0.0001
# of doses of postoperative PO acetaminophen	95	337	< 0.0001

Table 3. *Pain scores. Maximum and average daily pain scores according to the VAS are compared between IV and PO acetaminophen groups.*

	IV, n = 91	PO, n = 84	*P* value
0-24 hours maximum pain score, VAS ± SD	4.49 (2.44)	5.11 (2.42)	0.0973
0-24 hours average pain score, VAS ± SD	2.87 (1.75)	3.39 (1.97)	0.0645
24-48 hours maximum pain score, VAS ± SD	5.70 (2.34	5.44 (2.10)	0.4339
24-48 hours average pain score, VAS ± SD	4.16 (2.16)	4.02 (1.81)	0.6499
48-72 hours maximum pain score, VAS ± SD	4.92 (2.21)	5.13 (2.04)	0.5357
48-72 hours average pain score, VAS ± SD	3.37 (1.85)	3.71 (1.73)	0.2222
Pain score at discharge, VAS ± SD	2.88 (1.98)	3.30 (1.71)	0.1305

Abbreviation: SD, standard deviation.

Table 4. *Opioid use. Intraoperative and daily opioid requirements through 72 hours are compared between IV and PO acetaminophen groups.*

	IV, n = 91	PO, n = 84	*P* value
Intraoperative opioids, OME ± SD	41.6 (16.8)	45.2 (12.5)	0.1102
0-24 hours, OME ± SD	12.5 (11.9)	21.9 (14.6)	1* < 0.0001
24-48 hours, OME ± SD	9.1 (10.0)	17.0 (11.6)	* < 0.0001
48-72 hours, OME ± SD	5.2 (5.8)	9.5 (10.1)	* 0.0008
Total opioid requirements through 72 hours, OME ± SD	68.5 (34.5)	93.7 (35.0)	* < 0.0001

Abbreviation: SD, standard deviation. *P value ≤ 0.05.

was higher in the PO group (68.8 OME IV group vs. 93.7 OME PO group; *P* < 0.0001). IV opioid patient-controlled analgesia was used in more patients in the PO group compared with the IV group (8.9% IV group vs. 46.4% PO group; *P* value < 0.0001).

Acetaminophen Use

Intraoperative and postoperative acetaminophen use through 72 hours of admission is shown in Table 5 and Fig. 2. All patients received identical amounts of IV acetaminophen intraoperatively. As expected, the IV group received significantly more doses of IV acetaminophen (5.2 doses IV group vs. 1 dose PO group; *P* < 0.0001) and fewer doses of oral acetaminophen (1.0 dose IV group vs. 4.0 doses PO group; *P* < 0.0001) through 72 hours of admission compared with the PO group. Total acetaminophen use was higher in the IV group compared with the PO group (6280.8 mg IV group vs. 4907.4 mg PO group, *P* = 0.0002). The largest difference in acetaminophen use between groups was seen in the time period 0 to 24 hours from surgery (2424.2 mg IV group vs. 1655.7 mg PO group; *P* < 0.0001).

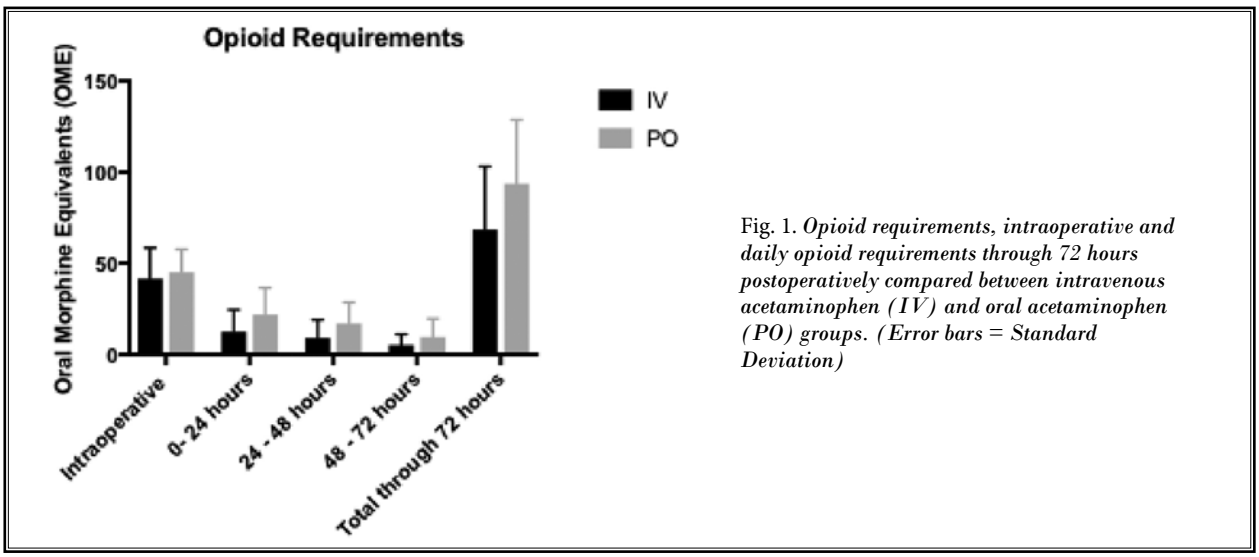

Fig. 1. *Opioid requirements, intraoperative and daily opioid requirements through 72 hours postoperatively compared between intravenous acetaminophen (IV) and oral acetaminophen (PO) groups. (Error bars = Standard Deviation)*

Table 5. *Acetaminophen use. Average intraoperative and daily acetaminophen use through 72 hours are compared between IV and PO acetaminophen groups.*

	IV, n = 91	PO, n = 84	*P* value
Intraoperative acetaminophen, mg ± SD	1000 (0.0)	1000 (0.0)	1.0000
0-24 hours, mg ± SD	2424.2 (773.8)	1655.7 (1049.6)	1* < 0.0001
24-48 hours, mg ± SD	1585.2 (1150.2)	1230.4 (1173.5)	* 0.0452
48-72 hours, mg ± SD	1271.4 (1175.4)	1021.4 (1161.6)	0.1591
Total doses IV acetaminophen, no. ± SD	5.2 (1.8)	1.0 (0.0)	* < 0.0001
Total doses oral acetaminophen, no. ± SD	1.0 (1.0)	4.0 (2.7)	* < 0.0001
Total acetaminophen use through 72 hours, mg ± SD	6280.8 (2159.1)	4907.4 (2681.6)	* 0.0002

Abbreviation: SD, standard deviation. *P value ≤ 0.05

Postoperative Outcomes

Selected postoperative outcomes are shown in Table 6. There were no differences in length of postoperative stay, overall complication rates, or hospital readmission rates between groups. The rate of postoperative nausea and vomiting was significantly higher in the PO group compared with the IV group (33.0% IV group vs. 48.8% PO group; *P* = 0.0449).

Discussion

In our study, we report an increase in opioid requirements following a change to restrict the use of IV acetaminophen within our ERAS protocol. We observed an elevated requirement for IV opioid patient-controlled analgesia, an increased incidence of the opioid-related outcome postoperative nausea and vomiting, as well as nonsignificant uptrends in other opioid-related adverse events such as ileus, length of stay, and time to return of bowel function. When used as part of multimodal pain management strategies, the use of IV acetaminophen has been associated with decreased opioid use (8,21), decreased incidence of nausea and vomiting (22), decreased ileus (5), and improved pain control (12,23) compared with placebo. Its superiority to oral acetaminophen, however, is still in question. Our study, with well-matched groups using near equivalent pain management strategies, demonstrates a benefit when using IV acetaminophen over oral

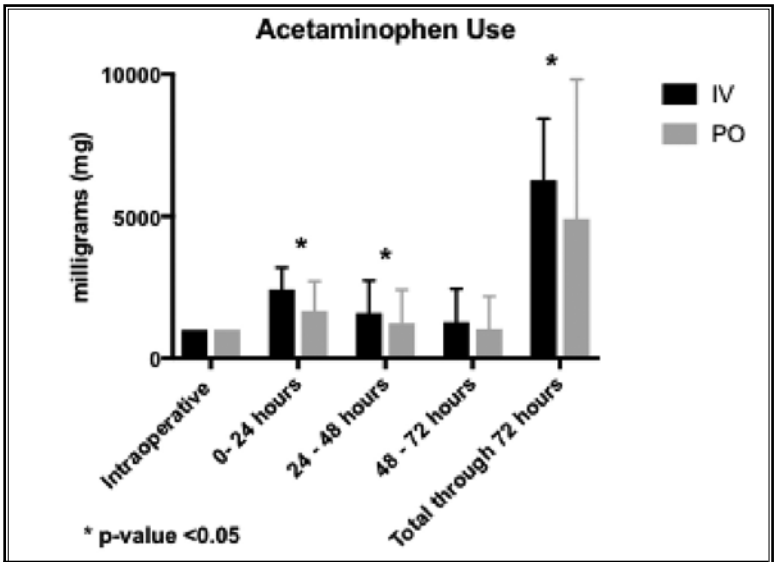

Fig. 1. *Acetaminophen requirements, intraoperative and daily acetaminophen use through 72 hours postoperatively compared between intravenous acetaminophen (IV) and oral acetaminophen (PO) groups. (Error bars = Standard Deviation)*

Table 6. *Postoperative outcomes. Length of stay, readmission rates, and complication rates are compared between IV and PO acetaminophen groups.*

	IV, n = 91	PO, n = 84	*P* value
Length of postoperative stay, days ± SD	5.88	6.04	0.8038
Return of bowel function, days ± SD	2.47	2.84	0.1331
30 day reoperations, no. (%)	5 (5.5)	4 (4.8)	1.0000
30 day readmissions, no. (%)	8 (8.8)	9 (10.7)	0.7997
Any complications, no. (%)	15 (16.4)	17 (20.2)	0.5612
Ileus, no. (%)	10 (11.0)	12 (14.3)	0.6490
Postoperative nausea and vomiting, no. (%)	30 (33.0)	41 (48.8)	1*0.0449
Pneumonia, no. (%)	1 (1.1)	0 (0.0)	> 0.9999
Deep vein thrombosis, no. (%)	1 (1.1)	2 (2.4)	0.6082
Pulmonary embolism, no. (%)	0 (0.0)	0 (0.0)	> 0.9999

Abbreviation: SD, standard deviation. *P value ≤ 0.05

acetaminophen in the early postoperative setting. We observed no differences in pain scores between groups, however, a finding we believe is because of the substantially increased opioid use in the PO group.

Compared with oral acetaminophen, IV acetaminophen has a faster onset and time to peak effect (24), reaches higher mean cerebrospinal fluid concentrations (25), experiences less first pass effect (26), and may have better bioavailability in the setting of postoperative ileus (27). In clinical studies for postoperative pain control, however, the results have been indeterminate, showing no benefit or only moderate benefits for IV acetaminophen (28-30). A recent systematic review of randomized-controlled trials has also concluded that there is no evidence to support IV acetaminophen for patients who can tolerate oral formulations of the drug (13). Although the quality of these studies is generally high, few studies have been performed with abdominal surgery, and treatment periods in these studies have often been limited to as little as one dose. Extrapolating these results to the field of colorectal surgery is difficult as this group of patients often require pain medications for several days postoperatively. In a recent data claims analysis in colorectal surgical patients within an ERAS pathway, IV acetaminophen use was not associated with a clinically significant decrease in opioid use or in opioid-related side effects compared with oral acetaminophen (14). In that study, the majority of patients who received IV acetaminophen received only a single dose during their admission. In contrast, the patients in our study received an average of 6 doses of acetaminophen in the IV group and 5 doses of acetaminophen in the PO group within 72 hours of surgery, a dosing regimen much more typical for a postoperative clinical setting.

In our study, restriction of IV acetaminophen use led to decreased overall use of total acetaminophen in the PO group, an effect that is likely at least partially explained by the increased opioid use in the PO group. The unequal doses of acetaminophen between groups (1000 mg/dose IV group vs. 975 mg/dose PO group) also may have played a small role. When acetaminophen use in the PO and IV groups was compared by postoperative day, the effect was most marked in the first 24 hours following surgery (Fig. 2), suggesting that oral acetaminophen may be poorly tolerated during this time. Adding several additional doses of IV acetaminophen postoperatively until oral acetaminophen is tolerated may be a simple way to improve pain control in our patients, and would only result in a modest increase in the number of IV acetaminophen doses required.

Behind the drive to restrict the use of IV acetaminophen is its cost: approximately $35 per 1 g dose for IV acetaminophen compared with $0.03 for an equivalent dose of oral acetaminophen (31). Institutions have reported cost savings as high as $400,000 per year with restriction of perioperative IV acetaminophen (16). During our study, the average cost of acetaminophen per patient through 72 hours of admission was calculated as $182.00 per patient in our IV group compared with $35.00 per patient in our PO group, a cost that was not meaningfully compensated by the increased use of opioids in the PO group (cost of opioids through 72 hours: $5.50 per patient in IV group vs. $7.33 per patient in PO group). Although the difference in cost may at first appear substantial, it is unlikely to be significant when taken into account for the typical $9,000 to $20,000 expected costs of hospitalization within a typical admission following colorectal surgery (32). Additionally, we did not consider the possible cost savings experienced in our IV group secondary to the decreased incidence of nausea and vomiting, such as decreased need for perioperative antiemetic use. Decreased nausea and vomiting could also provide potential clinical benefit from a decreased incidence of dehydration, perioperative aspiration, and wound dehiscence. Although this study was not adequately powered to detect an increase in time to return to bowel function, a higher opioid use within our PO group certainly has the potential to lead to this unwanted opioid-related side effect.

We recognize the limitations of this study. This was a retrospective, nonrandomized study performed at a single institution with a relatively small sample size. As this was an observational study, we could not account for differences in management strategies between providers. In addition, it is possible that patients and providers were influenced by their preconceived notions regarding the efficacy of IV versus oral formulations of acetaminophen. Despite our limitations, our populations were homogenous, the pain-control strategies used were similar between groups, and the study was conducted in a typical postoperative setting.

Our study highlights not only the possible clinical benefits of IV acetaminophen, but also the importance of monitoring ERAS protocols closely after implementation. One relatively small change in our protocol led to a significant change in outcome, which may have gone unnoticed without careful attention. Future work should be undertaken with larger sample sizes to compare and clarify the benefit of IV acetaminophen

over the oral formulation, and to determine which specific populations may benefit from use of IV acetaminophen. Ideally, this would be accomplished through a multicenter randomized control trial, the findings of which would be used to update current evidence-based guidelines for perioperative pain control in colorectal enhanced recovery protocols.

Conclusions

Restriction of IV acetaminophen within an ERAS protocol in colorectal surgery was associated with increased opioid use, greater need for opioid patient-controlled analgesia, and increased incidence of postoperative nausea and vomiting. IV acetaminophen may be superior to oral acetaminophen in the early postoperative setting.

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