

# Effect of Intravenous Acetaminophen on Postoperative Opioid Use in Bariatric Surgery Patients

Shan Wang, PharmD, RPh; Ronik Saha, PharmD; Neal Shah, PharmD; Adel Hanna, MD; Jonas DeMuro, MD; Rose Calixte, PhD; and Collin Brathwaite, MD

## ABSTRACT

**Background:** The use of opioids to achieve adequate pain relief following surgery is a common clinical practice. Opioids, however, are associated with serious adverse effects, such as respiratory depression, excessive sedation, and prolonged ileus, as well as increased mortality. The administration of intravenous (IV) acetaminophen to control postoperative pain has been effective in reducing opioid consumption in various surgical populations, but no studies have been conducted in bariatric surgery patients. This investigation was performed to determine whether IV acetaminophen reduces opioid requirements after bariatric surgery.

**Methods:** IV acetaminophen was added to the Winthrop-University Hospital formulary in September 2012. We conducted a retrospective chart-review analysis of bariatric surgery patients who received at least four doses of IV acetaminophen (1 g every six hours) plus opioids from October 2012 to March 2013 (after IV acetaminophen was added to the hospital formulary), compared with bariatric surgery patients who received only opioids for postoperative pain control from January 2012 to June 2012 (before IV acetaminophen was added to the hospital formulary). The study's primary endpoint was the difference between the two groups in opioid consumption, expressed in oral morphine equivalents (OMEs). Secondary endpoints included the reduction in the baseline pain score; the total amount of each opioid used; and the average hospital length of stay (LOS).

**Results:** A total of 96 patients were identified for potential enrollment from January 2012 to March 2013. Eight patients, however, did not qualify for participation because they had received only one dose of IV acetaminophen. The remaining 88 patients comprised two study groups: IV acetaminophen plus opiates (n = 44) and IV opiates alone (n = 44). Paradoxically, the patients in the acetaminophen/opiates group required significantly more opiates (in OMEs) compared with the group that received opiates alone (median, 93.5 mg versus 63.0 mg, respectively;  $P = 0.017$ ). There were no significant differences between the two treatment groups in terms of

the median change from baseline in pain scores ( $-4$  versus  $-4$ ;  $P = 0.162$ ) or the median hospital LOS (two days versus two days;  $P = 0.704$ ).

**Conclusion:** IV acetaminophen did not reduce opioid use for postoperative pain management in bariatric surgery patients.

**Keywords:** intravenous acetaminophen, bariatric surgery, opioids, postoperative pain

## INTRODUCTION

Pain management is a key aspect of postoperative care. Insufficient pain control may be associated with increased complications (e.g., deep vein thrombosis), a longer hospital length of stay (LOS), and decreased patient satisfaction, especially in elderly patients and in patients following abdominal surgery because of a delay in the return of bowel functions.<sup>1</sup> Patients often inquire about the amount and types of pain they will experience after surgery.<sup>2</sup> Traditionally, postoperative pain has been managed with opioids, such as morphine, fentanyl, and hydromorphone, which can be associated with respiratory depression, excessive sedation, drowsiness, rash, nausea, vomiting, and severe constipation.<sup>3</sup> Studies have shown that a comprehensive, multimodal analgesic regimen in patients undergoing orthopedic surgeries can provide significant cost reductions.<sup>4</sup> Guidelines for the management of acute pain published by the American Society of Anesthesiologists recommend the use of multimodal pain management, including around-the-clock nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen in addition to opioids.<sup>5</sup>

The first IV formulation of acetaminophen (Ofirmev, Mallinckrodt Hospital Products Inc.) was approved by the Food and Drug Administration in 2010.<sup>6</sup> Several clinical studies have confirmed the efficacy and safety of IV acetaminophen in the management of mild-to-moderate pain as monotherapy as well as in the management of moderate-to-severe pain in conjunction with opioids. Sinatra and colleagues, for example, compared the analgesic efficacy of repeated doses of IV acetaminophen (1 g) or placebo administered every six hours for 24 hours in 101 patients with moderate-to-severe pain after total hip- or knee-replacement surgery. IV acetaminophen was significantly superior to placebo in reducing the intensity of pain over 24 hours. The authors also reported a decrease in opioid consumption.<sup>7</sup>

Wininger et al. evaluated the analgesic efficacy of repeated doses of IV acetaminophen (1 g every six hours or 650 mg every four hours) over a 24-hour period compared with placebo in the management of 244 patients with moderate-to-severe postoperative pain after abdominal laparoscopic surgery. Patients

*Dr. Wang and Dr. Saha are Critical Care Pharmacists in the Department of Pharmacy at Winthrop-University Hospital in Mineola, New York. Dr. Shah is a third-year Medical Doctor/Doctor of Philosophy student at the West Virginia University School of Medicine in Morgantown, West Virginia. Dr. Hanna is a Critical Care Attending Physician in the Department of Surgery at Winthrop-University Hospital. Dr. DeMuro is a Critical Care Attending Physician in the Department of Surgery at Good Samaritan Medical Center in West Islip, New York. Dr. Calixte is a Biostatistician in the Department of Biostatistics at Winthrop-University Hospital. Dr. Brathwaite is a Surgical Attending Physician in the Department of Surgery at Winthrop-University Hospital.*

**Disclosure:** The authors report no commercial or financial interests in regard to this article.

# Effect of IV Acetaminophen on Postoperative Opioid Use in Bariatric Surgery Patients

receiving IV acetaminophen experienced a significantly greater reduction in pain intensity compared with those given placebo.<sup>8</sup>

In another study, Cakan and colleagues found that IV acetaminophen improved the quality of postoperative analgesia but did not reduce the use of narcotics in patients undergoing lumbar laminectomy and discectomy.<sup>9</sup>

Because of their long-term efficacy in maintaining weight loss, bariatric surgical procedures are becoming increasingly more common as the incidence of morbid obesity increases in the U.S.<sup>10</sup> Despite data that support the use of multimodal pain management in reducing opioid consumption in patients undergoing bariatric surgery, no studies have been performed to examine the effect of IV acetaminophen on opioid use in these patients.<sup>11</sup>

## METHODS

The present study was approved by our center's institutional review board. Data were retrospectively collected on patients who underwent bariatric surgical procedures between January 2012 and March 2013.

Before the introduction of IV acetaminophen at our center in September 2012, the standard pain-management protocol for patients undergoing bariatric surgery was IV morphine (2 mg or 4 mg every four hours) or IV hydromorphone (1 mg or 2 mg every three hours), plus ketorolac (30 mg IV every six hours) as needed. Once patients tolerated oral medications, oxycodone tablets were started.

In our study, three opiate medications were ordered after bariatric surgery: IV morphine, IV hydromorphone, and oral oxycodone. The study's primary objective was to evaluate postoperative opioid consumption in bariatric surgery patients who received IV acetaminophen (1 g every six hours for at least four doses) plus opioids from October 2012 to March 2014 (after IV acetaminophen was added to our hospital's formulary) compared with a historical control of bariatric surgery patients who received only opioids postoperatively between January 2012 and June 2012 (when IV acetaminophen was not available at our hospital). The amount of IV acetaminophen examined in this study was the standardized dose administered to all bariatric surgery patients at our institution.

To quantify the amounts of opioid that were consumed, each drug was converted to an oral morphine equivalent (OME) on an opioid conversion table used at our institution (Table 1).<sup>12</sup> Patients who did not receive IV acetaminophen served as the control group.

Secondary endpoints included the average change in pain from baseline according to a numerical scale from 0 to 10, with 0 representing "no pain" and 10 representing "worst pain

**Table 2 Baseline Demographic Characteristics**

Characteristics	All Patients (N = 88)	IV Acetaminophen (1 g)		P Value
		Yes (n = 44)	No (n = 44)	
Mean age (years) <sup>a</sup>	41.85 ± 10.35	43.73 ± 11	39.98 ± 9.4	0.089
Gender, n (%)				0.792
Male	18 (20.4)	8 (18.2)	10 (22.7)	
Female	70 (79.6)	36 (81.8)	34 (77.3)	
Mean BMI (kg/m <sup>2</sup> ) <sup>a</sup>	45.03 ± 6.3	46.39 ± 6.26	43.68 ± 6.12	0.043 <sup>b</sup>

<sup>a</sup> Plus or minus standard deviation  
<sup>b</sup> Statistically significant  
 BMI = body mass index; IV = intravenous

imaginable;" the average hospital LOS; and the differences in the total amount of opioid administered in the two treatment groups for the duration of the patients' LOS. Although the 0-to-10 pain scale is necessarily a subjective tool because of the varying pain tolerances among patients, it is recognized by the Joint Commission and is widely used for pain assessment. We ascertained the average pain score over 48 hours, the baseline pain score, and the change in the pain score.

To be included in our study, patients had to be 18 years of age or older and had to have undergone a bariatric surgical procedure (i.e., gastric bypass, sleeve gastrectomy, or laparoscopic partial gastrectomy). Patients were excluded if they were less than 18 years of age; had a documented allergy to acetaminophen or opioids; and had received fewer than four doses of IV acetaminophen. Demographic information included age, gender, and body mass index (BMI) (Table 2).

## STATISTICAL ANALYSIS

We used the Wilcoxon rank sum test to compare the primary and secondary outcomes between the two groups. We also used the two-sample *t*-test to compare between-group ages and BMIs, and the exact Pearson's *chi*-square to compare gender distribution. *P* values of less than 0.05 were considered to be statistically significant. All analyses were performed using SAS 9.2.

## RESULTS

### Demographic Characteristics

Of the 88 patients in this study, 70 (79.6%) were female (Table 2). The patients' mean age was 41.9 years, and there was no age difference between the two acetaminophen groups (*P* = 0.0893). Likewise, the age difference between genders was not significant (*P* = 0.189).

The mean BMI of all 88 patients was 45.03 kg/m<sup>2</sup> (Table 2). The acetaminophen-treated group had a significantly higher mean BMI than the untreated group (*P* = 0.043).

### Treatments

Of the 88 patients, 44 received IV acetaminophen (1 g) after bariatric surgery and 44 did not. A total of 24 patients were treated with IV hydromorphone alone; 21 patients received IV morphine alone; and two received oral oxycodone alone (Figure 1). In addition, 18 patients received IV morphine and oral oxycodone; 10 patients received IV hydromorphone and oral oxycodone; four patients received IV morphine and IV

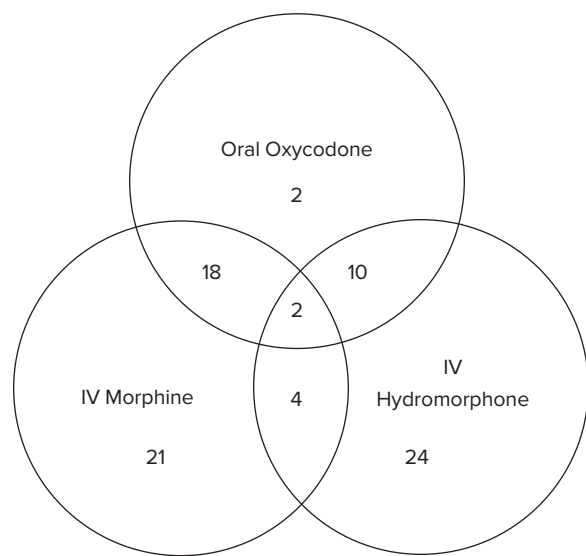
**Table 1 Conversion of Opioids To Oral Morphine Equivalents**

Opioid	Oral Route	Parenteral Route (SC/IV)
Hydromorphone	7.5 mg	1.5 mg
Morphine	30 mg	10 mg
Oxycodone	20 mg	NA

IV = intravenous; NA = not applicable; SC = subcutaneous

# Effect of IV Acetaminophen on Postoperative Opioid Use in Bariatric Surgery Patients

**Figure 1 Distribution of Patients Among Narcotic Classes (n = 81)\***



\* Seven of the 88 patients received no narcotic.

hydromorphone; and two patients received all three narcotics. Twenty-one patients (48%) in the acetaminophen/opioid group were treated with provisional ketorolac, an NSAID, compared with 20 patients (45%) in the opioid group.

## Opioid Consumption

Forty-five patients received IV morphine at a mean dose of 15.04 mg per patient; 40 received IV hydromorphone at a mean dose of 5.51 mg; and 32 received oral oxycodone at a mean

dose of 24.38 mg. Converting these opioid doses to OMEs, all 88 patients received an estimated mean total of 7.66 g of oral morphine.

Among all patients, the median OME was 80 mg (interquartile range [IQR], 39.5–115.5) (Table 3). The median OME was significantly greater among the patients who received IV acetaminophen (1 g) with opioids than among those who received opioids alone (93.5 mg [IQR, 51.5–121.5] versus 63.0 mg [IQR, 36–90], respectively;  $P = 0.017$ ). There was no difference in the use of OMEs between the two genders ( $P = 0.675$ ).

Of the 45 patients receiving IV morphine, eight were in the IV acetaminophen treatment group, and 37 were in the nontreatment group. Patients in the nontreatment group received significantly ( $P = 0.049$ ) more IV morphine compared with those in the acetaminophen group (Table 4). There was no gender difference in the use of IV morphine ( $P = 0.121$ ), although men tended to receive less of the drug ( $P = 0.061$ ).

Of the 40 patients who were treated with IV hydromorphone, 34 were in the IV acetaminophen group, and six were in the nontreatment group. There was no difference in the amounts of hydromorphone given to these two cohorts ( $P = 0.348$ ) (Table 4). Among those who received IV acetaminophen plus IV hydromorphone, men were given significantly less hydromorphone ( $P = 0.033$ ).

Of the 32 patients receiving oral oxycodone, 12 were in the IV acetaminophen treatment group and 20 were in the nontreatment group. Again, there was no difference in the amounts of oxycodone given to these two groups ( $P = 0.626$ ). Men used significantly more oxycodone than women ( $P = 0.017$ ).

Age was not a significant predictor of the use of oral morphine ( $P = 0.229$ ), IV hydromorphone ( $P = 0.851$ ), IV morphine ( $P = 0.723$ ), or oral oxycodone ( $P = 0.385$ ). Likewise, the BMI was not a significant predictor of OMEs ( $P = 0.180$ ), IV

**Table 3 Comparisons of Opioid Consumption**

Opioid Use	All Patients		IV Acetaminophen (1 g)				P Value
			Yes		No		
	N	Median (IQR)	n	Median (IQR)	n	Median (IQR)	
OME (mg)	88	80 (39.5–115.5)	44	93.5 (51.5–121.5)	44	63 (36–90)	0.017*
Hydromorphone, IV (mg)	40	5 (4–8)	34	4.5 (4–8)	6	7.75 (5–8)	0.348
Morphine, IV (mg)	45	16 (8–20)	8	8 (5–16)	37	16 (12–20)	0.049*
Oxycodone, oral (mg)	32	20 (10–35)	12	25 (10–35)	20	20 (10–35)	0.626

\* Statistically significant

IQR = interquartile range; IV = intravenous; OME = oral morphine equivalent

**Table 4 Comparisons of Pain Scores**

Variables	All Patients (N = 88) Median (IQR)	IV Acetaminophen (1 g)		P Value
		Yes (n = 44) Median (IQR)	No (n = 44) Median (IQR)	
Baseline pain score (0 to 10)	6 (6–8)	6 (6–8)	6 (6–8)	0.983
Pain score after analgesic use (0 to 10)	3 (2–4)	3 (2.0–3.5)	3 (2–4)	0.173
Change in pain score	4 (3–5)	4 (3–5)	4 (3–4)	0.162

IQR = interquartile range; IV = intravenous

# Effect of IV Acetaminophen on Postoperative Opioid Use in Bariatric Surgery Patients

hydromorphone ( $P = 0.827$ ), IV morphine ( $P = 0.991$ ), or oral oxycodone ( $P = 0.851$ ).

## Pain Scores

The median baseline pain score in both groups was 6 on a scale of 0 to 10 ( $P = 0.983$ ), and the median post-medication pain score was 3 ( $P = 0.173$ ) (Table 4). There was no gender difference in baseline pain scores ( $P = 0.409$ ).

After opioid treatment, patients in both groups had a median pain score of 3 ( $P = 0.173$ ), and in both groups the median change in the pain score was 4 ( $P = 0.162$ ). Overall, gender had no influence on post-medication pain scores ( $P = 0.154$ ) or on the changes in those scores ( $P = 0.616$ ).

## Other Key Findings

Both groups had a median LOS of two days ( $P = 0.704$ ), and there was no significant difference in LOS between genders ( $P = 0.480$ ). In addition, there was no significant difference in the rates of provisional use of ketorolac between the two groups: 48% for treated patients and 45% for untreated patients.

## DISCUSSION

Although acetaminophen is a key component of many pain-management approaches because of its analgesic and opioid-sparing effects, this retrospective chart-review study found that IV acetaminophen was ineffective in reducing opioid consumption in bariatric surgery patients.

A previous study of the pharmacokinetics of IV acetaminophen in patients undergoing major surgery showed that advanced age and renal function could significantly alter the formation and elimination of acetaminophen metabolites.<sup>13,14</sup> That was the first study to look at IV acetaminophen in a surgical population. Until the present report, IV acetaminophen had not been investigated in bariatric surgery patients.

Previously, the study with the most relevance to the bariatric setting looked at the pharmacokinetic properties of IV acetaminophen and its metabolites in 20 patients who had undergone abdominal surgery.<sup>15</sup> This study found no evidence of metabolite formation or clearance difficulties, thus supporting the safety of IV acetaminophen in surgery patients.

In the present investigation, the median OME was statistically higher in the acetaminophen-treated group compared with the untreated group (median, 93.5 mg versus 63.0 mg, respectively;  $P = 0.017$ ). Surprisingly, IV acetaminophen increased opioid consumption in this patient population. The higher OME in the acetaminophen group may have been due to higher prescribing of IV hydromorphone (a potent narcotic) in those patients.

The limitations of this study include its retrospective nature, its small sample size, the differences in opioid use between the two acetaminophen groups, and the significant difference in BMIs between those groups. In the future, a prospective study design may help address some of these limitations.

## CONCLUSION

Our retrospective chart-review analysis indicates that IV acetaminophen is ineffective in reducing opioid consumption in bariatric surgery patients. In fact, the OME was significantly higher in IV acetaminophen-treated patients than in untreated

patients. We suggest that a prospective, randomized, double-blind study be conducted to validate our findings.

## ACKNOWLEDGMENT

The authors gratefully acknowledge the assistance of Jamie Huang, 2016 Doctor of Pharmacy candidate, in the preparation of this manuscript.

## REFERENCES

1. Morrison RS, Magaziner J, McLaughlin MA, et al. The impact of post-operative pain on outcomes following hip fracture. *Pain* 2003;103:303-311.
2. Vadivelu N, Mitra S, Narayan D. Recent advances in postoperative pain management. *Yale J Biol Med* 2010;83:11-25.
3. Viscusi ER, Singla N, Gonzalez A, et al. *Special Report: IV Acetaminophen Improves Pain Management and Reduces Opioid Requirements in Surgical Patients: A Review of the Clinical Data and Case-based Presentations*. New York, New York: McMahon Publishing; April 2012 [monograph]. Available at: [http://www.anesthesiologynews.com/download/SR122\\_WM.pdf](http://www.anesthesiologynews.com/download/SR122_WM.pdf). Accessed September 22, 2015.
4. Duncan CM, Hall Long K, Warner DO, Hebl JR. The economic implications of a multimodal analgesic regimen for patients undergoing major orthopedic surgery: a comparative study of direct costs. *Reg Anesth Pain Med* 2009;34:301-307.
5. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2012;116:248-273.
6. Ofirmev (acetaminophen injection) prescribing information. Hazelwood, Missouri: Mallinckrodt Hospital Products Inc.; December 2014. Available at: <http://www.ofirmev.com/Prescribing-Information.aspx>. Accessed September 22, 2015.
7. Sinatra RS, Jahr JS, Reynolds L, et al. Efficacy and safety of single and repeated administration of 1 gram IV acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. *Anesthesiology* 2005;102:822-831.
8. Winger SJ, Miller H, Minkowitz HS, et al. A randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of two IV acetaminophen dosing regimens for the treatment of pain after abdominal laparoscopic surgery. *Clin Ther* 2010;32:2348-2369.
9. Cakan T, Inan N, Culhaoglu S, et al. IV paracetamol improves the quality of postoperative analgesia but does not decrease narcotic requirements. *J Neurosurg Anesthesiol* 2008;20:169-173.
10. Gilbert EW, Wolfe BM. Bariatric surgery for the management of obesity: state of the field. *Plast Reconstr Surg* 2012;130:948-954.
11. Ziemann-Gimmel P, Hensel P, Koppman J, Marema R. Multimodal analgesia reduces narcotic requirements and antiemetic rescue medication in laparoscopic Roux-en-Y gastric bypass surgery. *Surg Obes Relat Dis* 2013;9:975-980.
12. Gammaitoni AR, Fine P, Alvarez N, et al. Clinical application of opioid equianalgesic data. *Clin J Pain* 2003;19:286-297.
13. Owens KH, Murphy PG, Medicott NJ, et al. Population pharmacokinetics of IV acetaminophen and its metabolites in major surgical patients. *J Pharmacokinet Pharmacodyn* 2014;41:211-221.
14. Owens KH, Medicott NJ, Zacharias M, et al. The pharmacokinetic profile of IV paracetamol in adult patients undergoing major abdominal surgery. *Ther Drug Monit* 2012;34:713-721.
15. Lewis AN. IV acetaminophen (Ofirmev). *Pharmacy Times*, January 25, 2012. Available at: <http://www.pharmacytimes.com/publications/health-system-edition/2012/jan-2012/iv-acetaminophen-ofirmev>. Accessed September 22, 2015. ■