Impact of Intravenous Acetaminophen on Perioperative Opioid Utilization and Outcomes in Open Colectomies

A Claims Database Analysis

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ABSTRACT

Background: The value of intravenous acetaminophen in postoperative pain management remains debated. The authors tested the hypothesis that intravenous acetaminophen use, in isolation and in comparison to oral, would be associated with decreased opioid utilization (clinically significant reduction defined as 25%) and opioid-related adverse effects in open colectomy patients.

Methods: Using national claims data from open colectomy patients (Premier Healthcare Database, Premier Healthcare Solutions, Inc., USA; 2011 to 2016; n = 181,640; 602 hospitals), we separately categorized oral and intravenous acetaminophen use: 1 (1,000 mg) or more than 1 dose on the day of surgery, postoperative day 1, or later. Multilevel models measured associations between intravenous or oral acetaminophen and (1) opioid utilization and (2) opioid-related adverse effects. Percent change and multiplicity-adjusted 99.5% CI are reported.

Results: Overall, 25.1% of patients received intravenous acetaminophen, of whom 48.0% (n = 21,878) received 1 dose on the day of surgery. In adjusted analyses, particularly more than 1 dose of intravenous acetaminophen (*versus* nonuse) on postoperative day 1 was associated with a −12.4% (99.5% CI, −15.2 to −9.4%) change in opioid utilization. In comparison, a stronger reduction was seen in those receiving more than 1 oral acetaminophen dose: −22.6% (99.5% CI, −26.2 to −18.9%). Unadjusted group medians were 550 and 490 oral morphine equivalents, respectively. Intravenous *versus* oral differences were less pronounced among those receiving more than 1 acetaminophen dose on the day of surgery: −8.0% (99.5% CI, −11.0 to −4.9%) median 499 oral morphine equivalents *versus* −8.7% (99.5% CI, −14.4 to −2.7%) median 445 oral morphine equivalents, respectively; all statistically significant, but none clinically significant. Comparable outcome patterns existed for opioid-related adverse effects.

Conclusions: The demonstrated marginal effects do not support routine use of intravenous acetaminophen given alternative nonopioid analgesic options.

Visual Abstract: An online visual overview is available for this article at http://links.lww.com/ALN/B752. **(ANESTHESIOLOGY 2018; 129:77-88)**

DESPITE numerous advances in pain management, opioids remain the cornerstone of postoperative pain control.[1] However, increasing evidence supports a multimodal approach consisting of the simultaneous administration of two or more analgesic agents with different mechanisms of action, with the intent of reducing opioid utilization and opioid-related adverse effects.[2,3] To this end, enhanced recovery pathways have adopted multimodal analgesia as a means to faster recovery and a shorter length of hospital stay.[4]

Nonopioid alternatives include cyclooxygenase-2 inhibitors, other nonsteroidal antiinflammatory drugs (NSAIDs), and gabapentinoids, among others.[2] Approved for the U.S.

What We Already Know about This Topic

- Nonopioid analgesics are being used perioperatively with the goal of decreasing opioid utilization in patients undergoing colectomies
- It is unclear whether intravenous acetaminophen is associated with decreased opioid utilization or resource utilization in real-world practice

What This Article Tells Us That Is New

- A minority of open colectomy patients receive intravenous acetaminophen, which is mostly used as a single-dose administration on the day of surgery
- A variety of intravenous acetaminophen dosing regimens were not observed to decrease opioid utilization to a clinically significant threshold

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market in 2010, IV acetaminophen is one relatively new option in multimodal analgesia. Despite its approval, no clear indication exists for preferential prescribing of IV acetaminophen over the oral formulation among patients who can tolerate the oral medication.[5] Therefore, despite its rapid uptake into clinical practice, discussion remains on the value of IV acetaminophen in postoperative pain management, especially given its high price relative to the oral formulation, as well as to other nonopioid analgesics.[6] Moreover, small and controlled studies assessing the impact of IV acetaminophen (compared to either placebo or other analgesics) on postoperative pain management demonstrate equivocal results necessitating a large-scale, real-world assessment.[7–10] Open colectomies, with their high opioid use and the resulting emphasis on enhanced recovery pathways, provide a unique opportunity to examine the real-world impact of IV acetaminophen.[11] Therefore, using data from a large national claims database on open colectomy patients, we tested the hypothesis that IV acetaminophen use, in isolation and in comparison to oral, would be associated with decreased opioid utilization (clinically significant reduction defined as 25%) and opioid-related adverse effects. A threshold of 25% reduction in opioid utilization for clinical (not statistical) significance was based on the known dose–response relationship between morphine and opioid-related adverse effects.[12]

Materials and Methods

Data Source and Study Design

This retrospective cohort study was approved by the Mount Sinai Hospital Institutional Review Board (New York, New York; project No. 14-00647). We used data from the Premier Healthcare Database (Premier Healthcare Solutions, Inc., USA). This all-payer database contains data on nationwide hospitalizations including International Classification of Diseases, Ninth Revision, Clinical Modification codes, Current Procedural Terminology codes, as well as billed items.[13,14]

Study Sample

The study sample included patients from January 2011 to December 2016 who underwent an open colectomy, including a right or left hemicolectomy, resection of the transverse colon, a sigmoidectomy, or other, as indicated by International Classification of Diseases, Ninth Revision, Clinical Modification procedure codes 45.7X, 45.82, and 45.83, and received at least one of the seven most commonly prescribed opioids (fentanyl, hydrocodone, hydromorphone, meperidine, morphine, propoxyphene, and oxycodone).[15] Patients were excluded if they had an unknown sex or discharge status (n = 330), underwent a procedure not categorized as elective, urgent, or emergent (n = 2,837), were classified as outpatient (n = 255), had an opioid utilization greater than 95th percentile (to exclude outliers, n = 9,137), or were treated at a hospital performing less than 30 colectomies (to ensure sufficient sample size per cluster, n = 851).[16]

We did not perform an *a priori* sample-size calculation given the sheer size of the database. On the basis of an estimated opioid utilization of 500 oral morphine equivalents,[17] we had greater than 99% power to detect a 25% relative difference in opioid utilization between those that received IV acetaminophen and those that did not.

Study Variables

The main effect of interest was the use of IV acetaminophen, categorized into 1 (1,000 mg) or more than 1 dose. This was assessed separately on the day of surgery, postoperative day 1, or on postoperative day 2 or later, representing three separate variables. The same categorization was used for oral acetaminophen separately. The primary outcome of interest, specified *a priori*, was opioid utilization over the entire hospital stay. Secondary outcomes included adverse events generally associated with opioids (opioid-related adverse effects) and length and cost of hospitalization. Opioid utilization was based on billing (not administration) for opioids; all separate opioid orders for each hospitalization were summed and converted into oral morphine equivalents by the Lexicomp (USA) "opioid agonist conversion"[18] and the GlobalRPH "opioid analgesic converter."[19] Opioid-related adverse effects were categorized into respiratory, gastrointestinal (with ileus separated), central nervous system, genitourinary, and "other" (appendix 1 has a full list of International Classification of Diseases, Ninth Revision, codes).[15] In addition, we used billing for intravenous naloxone as a marker for an opioid-related complication.

Patient demographic variables included age, sex, and race or ethnicity (white, black, Hispanic, other). Healthcare-related variables were insurance type (commercial, Medicaid, Medicare, uninsured, other), hospital location (urban, rural), hospital size (less than 300, 300 to 499, greater than or equal to 500 beds), hospital teaching status, and the annual number of open colectomies performed per hospital. Procedure-related variables included the admission type (elective, urgent, or emergent), indication for surgery (neoplasm, diverticular disease, inflammatory bowel disease, other), type of surgery (right hemicolectomy, left hemicolectomy, resection of transverse colon, sigmoidectomy, other), and year of procedure. Anesthesia- or analgesia-related variables captured the use of general or general and neuraxial anesthesia, patient-controlled analgesia (defined by billing items), and nonopioid analgesics (IV and oral acetaminophen, gabapentin or pregabalin, NSAIDs, cyclooxygenase-2 inhibitors, and ketamine). Overall comorbidity burden was assessed with the Quan adaptation of the Charlson comorbidity index.[20] Considering their association with perioperative opioid utilization, we also included variables indicating substance use or abuse (including smoking), chronic pain conditions, psychiatric comorbidity variables, and preoperative opioid misuse defined by International Classification of Diseases, Ninth Revision, codes, as previously reported.[2,21]

Statistical Analysis

First, unadjusted associations between IV acetaminophen use and the study variables and outcomes were assessed with chi-square and Student's *t* tests for categorical and continuous

variables, respectively. In addition, annual patterns in unadjusted median per-patient opioid utilization were assessed before and after the introduction of IV acetaminophen to the U.S. market, as well as the interhospital variation in the utilization of IV acetaminophen. Multilevel, multivariable regression models measured associations between the use of IV acetaminophen and (1) opioid utilization, measured in oral morphine equivalents, as well as length and cost of hospital stay, and (2) opioid-related adverse effects. Effect estimates were then compared to those for the use of oral acetaminophen.

Models included a random intercept term that varies at the level of each hospital, accounting for correlation of patients within hospitals. Models were adjusted with all variables found statistically significant at the $P < 0.15$ level from the univariable tests and deemed clinically important. We report adjusted odds ratios and Bonferroni-adjusted CI (for 10 outcomes, 99.5% CI), recognizing an increased likelihood of type II errors.[22] Effect estimates for continuous outcomes are reported as percent change (compared to the reference). For all models we used the PROC GLIMMIX feature in SAS version 9.4 statistical software (SAS Institute, USA); for opioid utilization, cost of hospitalization, and length of hospital stay, the gamma distribution with a log link function was applied as these variables are skewed.[23,24]

Sensitivity Analyses

To assess robustness of our results, we performed two sensitivity analyses. In the first, we compared the effect estimates for IV acetaminophen use to estimates from a control nonopioid analgesic, NSAIDs, as we would theoretically expect both to be associated with decreased opioid utilization. The second sensitivity analysis addressed the potential for confounding by indication, *i.e.*, IV acetaminophen use in those patients with more pain, thus requiring more opioids. Here, we restricted our cohort to hospitals with IV acetaminophen used in at least 50% of patients, under the assumption that hospitals with a high IV acetaminophen use did so as part of standard postoperative pain protocols and, thus, would be less susceptible to indication bias.

A Priori versus Post Hoc

During the peer-review process the following adjustments were made to our initial analyses. Added to our cohort were patients without billing for opioids (n = 8,049) and patients undergoing open colectomies in 2015 or 2016 (n = 59,905; due to the availability of more recent data). Covariates added to the model included the use of oral acetaminophen and a variable indicating preoperative misuse of opioids, as previously defined.[21] These amendments did not change our main results.

Results

The final study cohort consisted of 181,640 patients undergoing an open colectomy at 602 hospitals between January 2011 and December 2016. Table 1 provides the breakdown of IV acetaminophen use by all covariates. Overall, 25.1% (n = 45,622) of patients received IV acetaminophen, of whom 48.0% (n = 21,878) received only 1 dose and 30.2% (n = 13,790) received more than 1 dose on the day of surgery, while 12.0% (n = 5,480) received 1 dose and 38.0% (n = 17,348) received more than 1 dose on postoperative day 1. On postoperative day 2 or later, 9.8% (n = 4,478) received only 1 dose while 33.5% (n = 15,283) received more than 1 dose. The majority of variables investigated were (statistically) significantly associated with IV acetaminophen utilization. Specifically, the use of IV acetaminophen was associated with higher use of other nonopioid analgesics. Moreover, patients receiving IV acetaminophen had a lower Charlson comorbidity index than patients not receiving IV acetaminophen.

Figure 1 shows substantial interhospital variation in IV acetaminophen utilization, with a median of 15.6% and interquartile range of 0.7 to 37.2% of colectomy patients receiving IV acetaminophen. Table 2 depicts unadjusted prevalence and median values of outcome variables by IV and oral acetaminophen use. Among patients receiving IV acetaminophen, the lowest unadjusted opioid utilization and hospitalization cost was seen in patients receiving more than 1 dose on the day of surgery: median 499 oral morphine equivalents over the entire hospitalization and $17,856, respectively; these unadjusted numbers were 488 oral morphine equivalents and $20,447, respectively, for patients that did not receive IV acetaminophen. This coincided with lower (compared to those not receiving IV acetaminophen) unadjusted prevalences of almost all opioid-related adverse effects, particularly among those receiving more than 1 IV acetaminophen dose on the day of surgery. Comparable patterns emerged for oral acetaminophen use categories.

Figure 2 tracks patterns of unadjusted annual per-patient median opioid utilization (in oral morphine equivalents) while stratifying by IV acetaminophen dose and day of utilization after its introduction to the U.S. market; only the line representing more than 1 dose IV acetaminophen use on the day of surgery mostly stays at or below the "no IV acetaminophen" line, suggesting that, without any adjustment for covariates (which could reverse the direction of effects based on covariate distributions), these patients receive the least amount of opioids (among those receiving IV acetaminophen), reflecting the findings from table 2.

Table 3 shows outcomes from the multivariable models separating out effect estimates for IV and oral acetaminophen utilization categories. Full *P* values and effect estimates for all covariates in the multivariable models are provided in the Supplemental Digital Content (tables A and B, respectively; http://links.lww.com/ALN/B694). None of the adjusted effects for opioid utilization crossed the −25% threshold we prespecified as indicative of clinical significance. For IV acetaminophen use, the strongest adjusted reductions in opioid utilization (compared to no IV acetaminophen use) were seen with use of more than 1 dose of IV acetaminophen on

Table 1. Patient Demographics and Healthcare-related, Procedure-related, Anesthesia- or Analgesia-related, and Comorbidity Variables by IV Acetaminophen Use

	Use of IV Acetaminophen				
	Yes (n = 45,622)		No (n = 136,018)		
	n	%	n	%	*P* Value**
Patient demographics					
Age*	64	53–74	66	55–76	< 0.0001
Sex					0.6385
Female	24,810	54.4	74,141	54.5	
Male	20,812	45.6	61,877	45.5	
Race					< 0.0001
White	35,287	77.3	101,889	74.9	
Black	4,350	9.5	14,593	10.7	
Hispanic	6	0.0	347	0.3	
Other	5,979	13.1	19,189	14.1	
Healthcare-related variables					
Insurance type					< 0.0001
Commercial	16,192	35.5	40,466	29.8	
Medicaid	3,640	8.0	10,922	8.0	
Medicare	22,970	50.3	75,232	55.3	
Uninsured	1,748	3.8	5,656	4.2	
Other	1,072	2.4	3,742	2.8	
Hospital location					< 0.0001
Rural	4,441	9.7	16,843	12.4	
Urban	41,181	90.3	119,175	87.6	
Hospital size					< 0.0001
Small (< 300 beds)	13,666	30.0	53,545	39.4	
Medium (300–499 beds)	15,487	33.9	46,028	33.8	
Large (≥ 500 beds)	16,469	36.1	36,445	26.8	
Hospital teaching status					< 0.0001
Nonteaching	23,342	51.2	82,877	60.9	
Teaching	22,280	48.8	53,141	39.1	
Annual no. of colectomies per hospital*	105	69–152	89	55–131	< 0.0001
Procedure-related variables					
Admission type					< 0.0001
Elective	22,443	49.2	78,032	57.4	
Urgent or emergency	23,179	50.8	57,986	42.6	
Indication for colectomy***					
Neoplasm	12,140	26.6	35,885	26.4	0.3405
Diverticular disease	11,790	25.8	33,705	24.8	< 0.0001
Inflammatory bowel disease	13,852	30.4	38,216	28.1	< 0.0001
Other	19,977	43.8	63,023	46.3	< 0.0001
Type of procedure***					
Right hemicolectomy	13,718	30.1	42,885	31.5	< 0.0001
Left hemicolectomy	4,564	10.0	15,407	11.3	< 0.0001
Resection of transverse colon	2,361	5.2	7,590	5.6	0.0010
Sigmoidectomy	14,757	32.3	44,171	32.5	0.6129
Other	11,532	25.3	30,014	22.1	< 0.0001
Year of procedure					< 0.0001
2011	1,099	2.4	28,771	21.2	
2012	4,751	10.4	26,294	19.3	
2013	8,684	19.0	22,055	16.2	
2014	9,928	21.8	20,153	14.8	
2015	10,128	22.2	20,379	15.0	
2016	11,032	24.2	18,366	13.5	

(*Continued*)

Table 1. Continued

	Use of IV Acetaminophen				
	Yes (n = 45,622)		No (n = 136,018)		
	n	%	n	%	*P* Value**
Anesthesia and analgesia					
Type of anesthesia					< 0.0001
General	38,088	83.5	112,133	82.4	
General and neuraxial	1,319	2.9	3,664	2.7	
Unknown or other	6,215	13.6	20,221	14.9	
Use of patient-controlled analgesia	11,547	25.3	26,659	19.6	< 0.0001
IV acetaminophen administration, day and doses***					
Day of surgery, 1 dose	21,878	48.0	—	—	
Day of surgery, > 1 dose	13,790	30.2	—	—	
Postoperative day 1, 1 dose	5,480	12.0	—	—	
Postoperative day 1, > 1 dose	17,348	38.0	—	—	
Postoperative day 1+, 1 dose	4,478	9.8	—	—	
Postoperative day 1+, > 1 dose	15,283	33.5	—	—	
Oral acetaminophen administration, day and doses***					
Day of surgery, 1 dose	1,746	3.8	6,123	4.5	< 0.0001
Day of surgery, > 1 dose	411	0.9	1,971	1.4	
Postoperative day 1, 1 dose	1,713	3.8	6,034	4.4	< 0.0001
Postoperative day 1, > 1 dose	1,263	2.8	3,648	2.7	
Postoperative day ≥ 2, 1 dose	4,116	9.0	13,218	9.7	< 0.0001
Postoperative day ≥ 2, > 1 dose	8,122	17.8	19,115	14.1	
Gabapentin or pregabalin					
Day of surgery	2,283	5.0	4,495	3.3	< 0.0001
Postoperative day 1 and ≥ 2	3,210	7.0	6,952	5.1	< 0.0001
NSAIDs					
Day of surgery	10,598	23.2	21,637	15.9	< 0.0001
Postoperative day 1 and ≥ 2	15,744	34.5	33,359	24.5	< 0.0001
Cyclooxygenase-2 inhibitors					
Day of surgery	616	1.4	970	0.7	< 0.0001
Postoperative day 1 and ≥ 2	360	0.8	805	0.6	< 0.0001
Ketamine					
Day of surgery	2,158	4.7	3,511	2.6	< 0.0001
Postoperative day 1 and ≥ 2	536	1.2	1,037	0.8	< 0.0001
Comorbidities					
Charlson comorbidity index					< 0.0001
0	19,215	42.1	51,572	37.9	
1	5,232	11.5	17,066	12.5	
2	9,096	19.9	25,797	19.0	
≥ 2	12,079	26.5	41,583	30.6	
History of substance use or abuse	7,829	17.2	25,609	18.8	< 0.0001
Chronic pain conditions	20,556	45.1	59,589	43.8	< 0.0001
Psychiatric comorbidities	9,230	20.2	28,390	20.9	0.0035
Opioid use disorder	254	0.6	741	0.5	0.7644

*Continuous variable median and interquartile range instead of n and %, respectively. **Chi-square test for categorical variables; Student's *t* test for continuous variables. ***Overlap between categories.

IV = intravenous; NSAID = nonsteroidal antiinflammatory drug.

the day of surgery (–8.0%; 99.5% CI, –11.0 to –4.9%) and postoperative day 1 (–12.4%; 99.5% CI, –15.2 to –9.4%), both $P < 0.0001$. This coincided with statistically significant reductions in length and cost of hospitalization, while odds for some opioid-related adverse effects were particularly decreased among patients receiving more than 1 dose of IV acetaminophen on postoperative day 1. However, effect estimates for oral acetaminophen (table 3, *lower half*) showed stronger reductions in outcomes, particularly in those using more than 1 dose on postoperative day 1 (–22.6% change

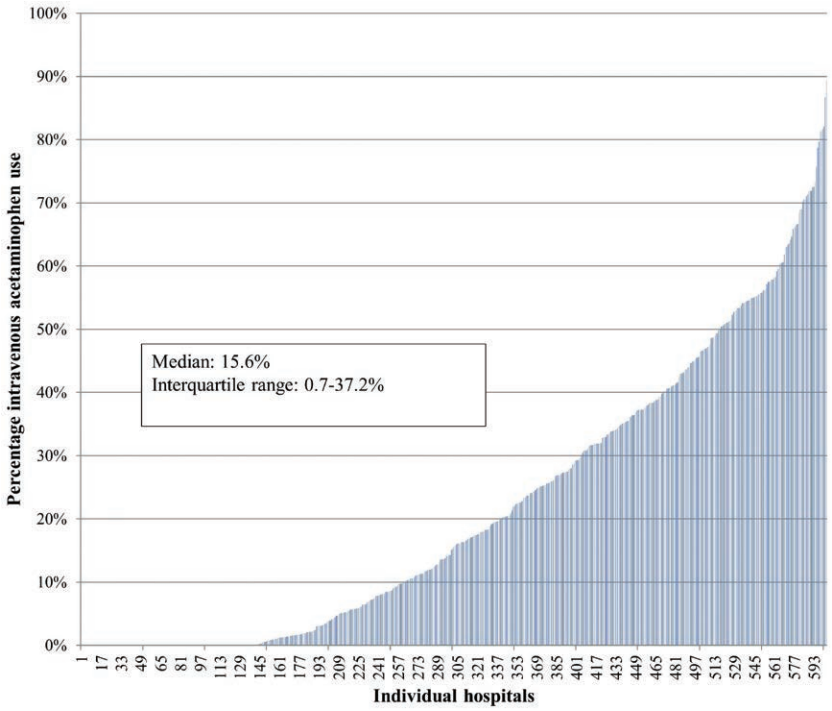

Fig. 1. Hospital variation in intravenous acetaminophen utilization among patients undergoing open colectomies.

in opioid utilization; 99.5% CI, −26.2 to −18.9%), while a more equivalent pattern was seen for oral acetaminophen use on the day of surgery (−8.7% change in opioid utilization; 99.5% CI, −14.4 to −2.7%); all $P < 0.0001$. Similar patterns extended to opioid-related adverse effects.

Interestingly, IV and oral acetaminophen use on postoperative day 2 or later was associated with up to +33.7% (99.5% CI, +29.8 to +37.7%; $P < 0.0001$) change in opioid utilization with higher statistically significant odds for opioid-related adverse effects, suggesting that IV and oral acetaminophen beyond postoperative day 1 may be selectively used in some patients with more pain, thus requiring more opioids.

Table 4 describes the association between a control nonopioid analgesic (NSAIDs) and outcomes. Compared to IV acetaminophen, the use of NSAIDs on the day of surgery showed a more consistent pattern of reduced opioid utilization paired with lower odds for opioid-related adverse effects. NSAID use beyond the day of surgery was associated with 5.4% increased opioid utilization with mainly higher odds for opioid-related adverse effects.

In the second sensitivity analysis (appendix 2), we restricted the cohort to only hospitals with at least 50% IV acetaminophen use (cohort size n = 32,855; 82 hospitals). For opioid utilization, the same pattern emerged, with more than 1 dose of IV acetaminophen on the day of surgery and postoperative day 1 associated with −10.1% (99.5% CI, −13.1 to −7.0%) and −10.8% (99.5% CI, −13.8 to −7.8%) opioid utilization, respectively, while IV acetaminophen use beyond postoperative day 1 was associated with up to +38.3% (99.5% CI, +34.2 to +42.6%) change in opioid utilization; all $P < 0.0001$. For oral acetaminophen, however, stronger effects were seen for use of more than 1 dose on postoperative day 1: −26.4% (99.5% CI, −33.7 to −18.3%), $P < 0.0001$.

Discussion

Our data from 181,640 patients undergoing open colectomies revealed that IV acetaminophen was used in a minority (25.1%) of patients, of which nearly half (48.0%, n = 21,878) received only 1 dose on the day of surgery. In addition, IV acetaminophen use was not associated with clinically significant reductions in opioid utilization, prespecified as a minimum reduction of 25%.[12] However, it did coincide with reductions in length and cost of hospitalization along with some reduction in opioid-related adverse effects. Crucially, oral acetaminophen demonstrated more pronounced reductions in opioid utilization than IV acetaminophen in those using more than 1 dose of acetaminophen on postoperative day 1. Oral acetaminophen was associated with a 22.6% decrease while IV acetaminophen only demonstrated a 12.4% decrease. Day of surgery use of more than 1 dose of oral acetaminophen (8.7% decrease) was clinically and statistically indistinguishable from IV acetaminophen (8.0% decrease). Thus, while IV acetaminophen may be beneficial in some patients on the day of surgery, oral acetaminophen showed clear superiority over IV acetaminophen when used on postoperative day 1. Use of IV and oral acetaminophen beyond postoperative day 1 was associated with increased opioid utilization and opioid-related adverse effects, possibly reflecting a group of patients with more pain who required more opioids in addition to IV acetaminophen. The main findings persisted in sensitivity analyses.

Table 2. Unadjusted Outcomes by IV Acetaminophen (Upper) or Oral Acetaminophen (Lower) Use

	No IV Acetaminophen	Day of Surgery		Postoperative Day 1		Postoperative Day ≥ 2	
		1 Dose	> 1 Dose	1 Dose	> 1 Dose	1 Dose	> 1 Dose
Use of IV acetaminophen							
Continuous outcomes, median (interquartile range)							
Oral morphine equivalents	488 (210–1030)	543 (270–1067)	499 (243–1038)	510 (240–1115)	550 (263–1117)	620 (278–1305)	706 (325–1430)
Length of hospital stay	8 (5–13)	7 (5–11)	7 (4–10)	7 (5–12)	7 (5–11)	9 (6–15)	9 (6–15)
Cost of hospitalization	$20,447 ($13,650–$33,520)	$18,460 ($13,061–$27,696)	$17,856 ($12,925–$26,742)	$19,936 ($13,495–$32,474)	$19,503 ($13,963–$29,374)	$23,329 ($15,172–$39,354)	$24,243 ($16,106–$39,901)
Opioid-related adverse effects, n (%)							
Respiratory	15,411 (11.3)	1,404 (6.4)	772 (5.6)	552 (10.1)	1,096 (6.3)	560 (12.5)	1,655 (10.8)
Gastrointestinal (excluding ileus)	2,302 (1.7)	366 (1.7)	222 (1.6)	96 (1.8)	319 (1.8)	75 (1.7)	352 (2.3)
Ileus	27,139 (20.0)	4,046 (18.5)	2,305 (16.7)	964 (17.6)	3,111 (17.9)	928 (20.7)	3,620 (23.7)
Central nervous system	3,426 (2.5)	387 (1.8)	251 (1.8)	139 (2.5)	376 (2.2)	148 (3.3)	535 (3.5)
Genitourinary	5,006 (3.7)	788 (3.6)	560 (4.1)	217 (4.0)	742 (4.3)	182 (4.1)	725 (4.7)
Other*	3,235 (2.4)	385 (1.8)	238 (1.7)	94 (1.7)	341 (2.0)	109 (2.4)	396 (2.6)
Naloxone	4,074 (3.0)	570 (2.6)	418 (3.0)	176 (3.2)	480 (2.8)	136 (3.0)	476 (3.1)
Use of oral acetaminophen							
Continuous outcomes, median (interquartile range)							
Oral morphine equivalents	475 (210–992)	563 (240–1159)	445 (172–1030)	520 (235–1070)	490 (203–1045)	575 (263–1176)	638 (282–1315)
Length of hospital stay	7 (5–12)	8 (5–14)	7 (4–12)	8 (5–13)	6 (4–10)	10 (6–16)	11 (7–19)
Cost of hospitalization	$19,187 ($13,199–$30,054)	$20,723 ($13,787–$34,134)	$17,362 ($12,236–$29,432)	$19,219 ($13,033–$32,018)	$16,208 ($11,537–$24,628)	$23,508 ($15,104–$39,400)	$26,527 ($16,346–$47,994)
Opioid-related adverse effects, n (%)							
Respiratory	6,661 (12.8)	842 (10.7)	175 (7.4)	751 (9.7)	273 (5.6)	2,186 (12.6)	3,794 (13.9)
Gastrointestinal (excluding ileus)	1,075 (2.1)	132 (1.7)	42 (1.8)	131 (1.7)	81 (1.7)	361 (2.1)	589 (2.2)
Ileus	12,003 (23.0)	1,640 (20.8)	457 (19.2)	1,529 (19.7)	942 (19.2)	3,838 (22.1)	6,817 (25.0)
Central nervous system	1,771 (3.4)	185 (2.4)	43 (1.8)	190 (2.5)	72 (1.5)	501 (2.9)	1,143 (4.2)
Genitourinary	2,371 (4.6)	319 (4.1)	94 (4.0)	306 (4.0)	176 (3.6)	764 (4.4)	1,351 (5.0)
Other*	1,364 (2.6)	187 (2.4)	42 (1.8)	157 (2.0)	84 (1.7)	457 (2.6)	751 (2.8)
Use of naloxone	1,939 (3.7)	218 (2.8)	108 (4.5)	264 (3.4)	140 (2.9)	622 (3.6)	1,088 (4.0)

Oral morphine equivalents represent opioid utilization over the entire hospitalization.

*"Other" includes postoperative bradycardia, rash or itching, fall from bed, or "drugs causing adverse effects with therapeutic use."

IV = intravenous.

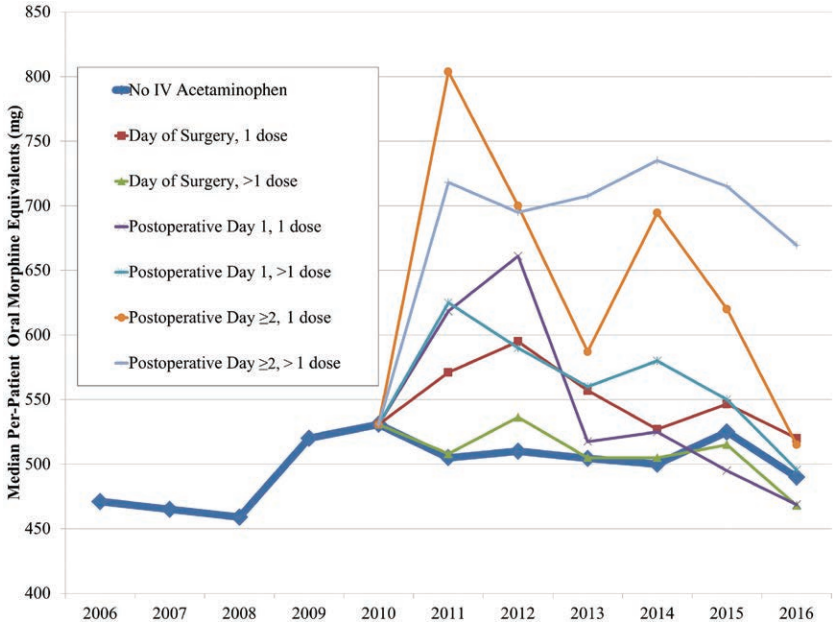

Fig. 2. Patterns in unadjusted median per-patient opioid utilization (in oral morphine equivalents), stratified by intravenous (IV) acetaminophen use based on dose and day of use.

While the use of IV acetaminophen appears to be increasing over time, a distinct minority of patients in our cohort received any IV acetaminophen. This may be explained, in part, by the vast interhospital variability of use of any multimodal analgesia therapy, which is also supported by figure 1. Furthermore, Ladha *et al.* showed that utilization of postsurgical multimodal therapy ranged from 43 to 99%, even after adjustment for relevant characteristics.[2] They concluded that the use of multimodal therapy is mainly based on nonmedical and institution-specific factors, including local hospital culture and individual physician preference, independent of patient or hospital characteristics. Indeed, our results demonstrate that among patients who received IV acetaminophen, 48.0% received only 1 dose on the day of surgery. While this may be due to institutional protocols, 1 dose of IV acetaminophen is not likely to result in a clinically relevant reduction of opioid utilization in patients undergoing open colectomies.

In this study we were able to indirectly compare IV to oral acetaminophen and found stronger improvements in outcomes for oral acetaminophen. These results do not directly support routine use of IV (over oral) acetaminophen and will add to the current discussion on the value of the intravenous over the oral formulation, especially given the substantial difference in average wholesale price ($45.02 per IV acetaminophen vial compared to well below $1 for oral acetaminophen[25]), even with existing hospital-specific rebates. In addition to the pricing discussion, a variety of studies have assessed the value of IV acetaminophen; however, studies greatly differ regarding choice of control groups, which vary from placebo to oral acetaminophen and other (nonopioid) analgesics.[5,8] Some small studies have indeed shown the effectiveness of IV acetaminophen in controlling postsurgical pain in various surgical settings; however, the ability of IV acetaminophen to reduce opioid utilization remains unclear.[9,10] A 2016 Cochrane review of 75 studies comparing single-dose IV acetaminophen to a placebo found a 26% reduction in opioid utilization over 4 h (and 16% reduction over 6 h); however, this did not translate into a clinically meaningful reduction in opioid-related adverse effects.[8]

While IV acetaminophen is relatively new in the U.S. setting, a large number of studies have been conducted in Europe, where IV acetaminophen has been available since the early 2000s.[26] However, these are largely controlled trials, which may not adequately capture the effects of IV acetaminophen in a real-world setting, where multiple analgesic options are available and those patients most likely to benefit from IV acetaminophen may not be the ones receiving it. Because our data do not evaluate any specific patient subgroups, we cannot exclude the possibility that some patients may benefit from IV acetaminophen given the challenges in postoperative oral tolerance. Future studies should focus on identifying those patients that may benefit the most.

We—counterintuitively—found that the use of IV and oral acetaminophen beyond postoperative day 1 was associated with increased opioid utilization. It is unlikely that increased opioid utilization is caused by oral or IV acetaminophen. A more likely explanation is that these effect estimates are driven by a group of patients that receive these drugs after postoperative day 1 in response to more pain, thus requiring more opioids. This group may easily skew effect estimates for opioid utilization for the postoperative day 2 or later group toward increased opioid utilization,

Table 3. Adjusted Association between IV Acetaminophen (Upper) or Oral Acetaminophen (Lower) and Outcomes

	Day of Surgery		Postoperative Day 1		Postoperative Day ≥ 2	
	1 Dose	> 1 Dose	1 Dose	> 1 Dose	1 Dose	> 1 Dose
Use of IV acetaminophen						
Continuous outcomes						
Oral morphine equivalents	−3.2% (−5.4 to −1.0%)*	−8.0% (−11.0 to −4.9%)*	−4.4% (−8.2 to −0.4%)*	−12.4% (−15.2 to −9.4%)*	23.1% (17.9 to 28.6%)*	33.7% (29.8 to 37.7%)*
Length of hospital stay	−7.8% (−9.2 to −6.3%)*	−10.4% (−12.5 to −8.2%)*	−7.5% (−10.1 to −4.7%)*	−15.1% (−17.1 to −13.1%)*	20.3% (16.7 to 24.1%)*	36.4% (33.5 to 39.3%)*
Cost of hospitalization	−10.6% (−12.3 to −8.9%)*	−10.0% (−12.5 to −7.4%)*	−3.6% (−6.9 to −0.2%)*	−14.4% (−16.8 to −12.0%)*	25.4% (20.9 to 30.1%)*	37.8% (34.4 to 41.3%)*
Opioid-related adverse events						
Respiratory	0.67 (0.61, 0.74)*	0.66 (0.57, 0.76)*	1.08 (0.93, 1.25)	0.68 (0.60, 0.78)*	1.61 (1.39, 1.87)*	1.66 (1.50, 1.84)*
Gastrointestinal (excluding ileus)	0.96 (0.80, 1.15)	0.89 (0.68, 1.15)	1.00 (0.73, 1.39)	0.98 (0.75, 1.26)	0.98 (0.69, 1.39)	1.39 (1.12, 1.72)*
Ileus	0.99 (0.93, 1.05)	0.93 (0.85, 1.02)	0.83 (0.74, 0.93)*	0.76 (0.69, 0.83)*	1.33 (1.18, 1.49)*	1.71 (1.58, 1.84)*
Central nervous system	0.81 (0.69, 0.97)*	0.83 (0.65, 1.06)	1.06 (0.80, 1.39)	0.78 (0.62, 0.98)*	1.55 (1.19, 2.01)*	1.75 (1.47, 2.09)*
Genitourinary	0.95 (0.84, 1.08)	1.04 (0.87, 1.24)	0.99 (0.79, 1.23)	1.01 (0.85, 1.20)	1.07 (0.85, 1.35)	1.24 (1.07, 1.44)*
Other**	0.85 (0.71, 1.01)	0.85 (0.66, 1.10)	0.82 (0.59, 1.13)	0.85 (0.66, 1.09)	1.35 (1.00, 1.82)	1.48 (1.21, 1.81)*
Use of naloxone	0.91 (0.78, 1.06)	0.95 (0.77, 1.17)	1.12 (0.87, 1.44)	0.91 (0.73, 1.12)	1.17 (0.89, 1.54)	1.23 (1.03, 1.48)*
Use of oral acetaminophen						
Continuous outcomes						
Oral morphine equivalents	1.4% (−1.9 to 4.9%)	−8.7% (−14.4 to −2.7%)*	−10.8% (−13.7 to −7.8%)*	−22.6% (−26.2 to −18.9%)*	12.6% (10.1 to 15.2%)*	22.7% (20.3 to 25.2%)*
Length of hospital stay	2.5% (0.0 to 5.0%)*	−4.1% (−8.3 to 0.4%)	−12.2% (−14.3 to −10.1%)*	−28.4% (−30.8 to −26.0%)*	25.3% (23.3 to 27.4%)*	57.6% (55.4 to 59.9%)*
Cost of hospitalization	4.3% (1.4 to 7.4%)*	0.1% (−5.1 to 5.7%)	−11.4% (−13.8 to −8.8%)*	−26.4% (−29.3 to −23.4%)*	24.7% (22.3 to 27.2%)*	52.8% (50.2 to 55.5%)*
Opioid-related adverse events						
Respiratory	1.10 (0.98, 1.23)	0.96 (0.75, 1.24)	0.85 (0.76, 0.96)*	0.55 (0.45, 0.67)*	1.30 (1.20, 1.40)*	1.58 (1.48, 1.69)*
Gastrointestinal (excluding ileus)	0.98 (0.75, 1.28)	1.12 (0.68, 1.84)	0.90 (0.69, 1.18)	0.78 (0.53, 1.15)	1.24 (1.05, 1.48)*	1.29 (1.11, 1.50)*
Ileus	1.09 (0.99, 1.19)	1.00 (0.84, 1.18)	0.89 (0.82, 0.98)*	0.73 (0.65, 0.84)*	1.28 (1.20, 1.36)*	1.56 (1.48, 1.64)*
Central nervous system	0.96 (0.76, 1.20)	0.86 (0.53, 1.38)	0.87 (0.69, 1.09)	0.48 (0.33, 0.70)*	1.32 (1.14, 1.52)*	1.88 (1.68, 2.11)*
Genitourinary	1.06 (0.88, 1.26)	1.02 (0.73, 1.44)	1.00 (0.83, 1.19)	0.77 (0.59, 1.00)*	1.31 (1.17, 1.48)*	1.44 (1.30, 1.60)*
Other**	1.23 (0.98, 1.54)	1.08 (0.67, 1.73)	0.88 (0.69, 1.12)	0.74 (0.51, 1.07)	1.21 (1.04, 1.41)*	1.29 (1.13, 1.46)*
Use of naloxone	0.96 (0.77, 1.19)	1.64 (1.17, 2.30)*	0.99 (0.81, 1.21)	0.70 (0.51, 0.95)*	1.33 (1.16, 1.52)*	1.54 (1.37, 1.72)*

Odds ratios for binary variables; for continuous outcomes, exponentiated coefficients from the log model depicting percent change compared to reference (= no intravenous [IV] or oral acetaminophen use). Oral morphine equivalents represent opioid utilization over the entire hospitalization. Models adjusted for age, sex, race or ethnicity, insurance type, hospital location, bed size and teaching status, hospital-specific open colectomy volume, elective or emergent procedure, indication for colectomy and procedure type, year of procedure, anesthesia type, patient-controlled analgesia, gabapentin or pregabalin, nonsteroidal antiinflammatory drug, cyclooxygenase-2 inhibitor and ketamine use, Charlson comorbidities, history of substance use or abuse, chronic pain conditions, psychiatric comorbidities, or opioid use disorder.

*$P < 0.05$. **"Other" includes postoperative bradycardia, rash or itching, fall from bed, or "drugs causing adverse effects with therapeutic use."

Table 4. Adjusted Association between NSAIDs and Outcomes

	Use of NSAIDs			
	Day of Surgery	*P* Value	Postoperative Day 1 and ≥ 2	*P* Value
Continous outcomes				
Oral morphine equivalents	−11.1% (−12.8 to −9.3%)	< 0.0001	5.4% (3.6 to 7.2%)	< 0.0001
Length of hospital stay	−13.3% (−14.6 to −12.1%)	< 0.0001	−0.5% (−1.7 to 0.7%)	> 0.999
Cost of hospitalization	−14.5% (−15.9 to −13.0%)	< 0.0001	−4.8% (−6.2 to −3.4%)	< 0.0001
Opioid-related adverse effects				
Respiratory	0.59 (0.53, 0.64)	< 0.0001	0.75 (0.70, 0.80)	< 0.0001
Gastrointestinal (excluding ileus)	0.86 (0.73, 1.01)	0.0780	1.28 (1.12, 1.46)	< 0.0001
Ileus	0.88 (0.83, 0.93)	< 0.0001	1.20 (1.15, 1.26)	< 0.0001
Central nervous system	0.60 (0.50, 0.73)	< 0.0001	0.99 (0.87, 1.12)	> 0.999
Genitourinary	0.93 (0.83, 1.05)	0.9150	1.10 (1.00, 1.22)	0.0380
Other*	0.77 (0.66, 0.90)	< 0.0001	0.98 (0.87, 1.11)	> 0.999
Use of naloxone	1.00 (0.89, 1.14)	> 0.999	1.07 (0.96, 1.19)	0.9440

Odds ratios for binary variables; for continuous outcomes exponentiated coefficients from the log model depicting percent change compared to reference (= no use of NSAIDs). Oral morphine equivalents represent opioid utilization over the entire hospitalization. Models adjusted for age, sex, race/ethnicity, insurance type, hospital location, bed size and teaching status, hospital-specific open colectomy volume, elective or emergent procedure, indication for colectomy and procedure type, year of procedure, anesthesia type, patient-controlled analgesia, IV or oral acetaminophen, gabapentin or pregabalin, cyclooxygenase-2 inhibitor and ketamine use, and Charlson comorbidities, history of substance use or abuse, chronic pain conditions, psychiatric comorbidities, or opioid use disorder.

*"Other" includes postoperative bradycardia, rash or itching, fall from bed, or "drugs causing adverse effects with therapeutic use."

IV = intravenous; NSAID = nonsteroidal antiinflammatory drug.

which may lead to "confounding by indication." Interestingly, however, this phenomenon persisted when analyzing only hospitals with an IV acetaminophen utilization rate of 50% or higher, where we expected IV acetaminophen to be part of standard postoperative pain protocols and, thus, less susceptible to indication bias. Moreover, these results further question the optimal utilization of IV acetaminophen in these patients, as patients might have tolerated oral acetaminophen beyond postoperative day 1.[27]

The sensitivity analysis examining the effect of NSAIDs compared to IV acetaminophen revealed similar direction of effects with, however, more consistent opioid-sparing effects and lower odds for opioid-related adverse effects for NSAIDs. As NSAIDs represent another commonly used medication category in multimodal analgesia, this finding suggests that IV acetaminophen may not be the most effective tool to reduce opioid utilization or that patients most likely to benefit from IV acetaminophen are not the ones receiving it. Indeed, the McNicol *et al.* Cochrane review demonstrated the statistical superiority of NSAIDs over IV acetaminophen in terms of pain control, which, however, may be clinically nonsignificant.[8]

Our study has several limitations. First, the lack of clinical details in our administrative dataset means there was no information on pain scores, which may have influenced both the use of IV acetaminophen as well as the amount of opioids consumed. However, we were able to adjust for the use of nonopioid analgesics, as well as other anesthesia- or analgesia-related variables, that are associated with pain scores. Additionally, we did not have information on single-shot or continuous neuraxial analgesia utilization and preoperative opioid use, a potential confounder in perioperative opioid utilization. We attempted to minimize this limitation by adjusting our models for substance use or abuse, chronic pain conditions, psychiatric conditions, and preoperative opioid misuse, all of which are associated with opioid utilization.[2,21] As we do not have information on local postoperative pain protocols or reasons behind IV acetaminophen use, we cannot exclude the possibility that patients with higher pain scores received IV acetaminophen for that reason, leading to the observed increase in opioid utilization among patients receiving IV acetaminophen beyond postoperative day 1. However, our sensitivity analysis, in which we restricted the cohort to hospitals where IV acetaminophen was assumed to be part of an established protocol, showed no change in our main results. Finally, as with any billing dataset, what is actually billed may not adequately reflect what is administered to the patient. This potential overestimation refers to both opioids and naloxone and should apply equally to IV acetaminophen utilization groups; it is unlikely to lead to any significant bias.

In conclusion, in this large nationwide study assessing the use of IV acetaminophen in patients undergoing open colectomies in 602 hospitals, we found that IV acetaminophen was used in a minority (25.1%) of cases. Moreover, IV acetaminophen use was not associated with clinically significant reductions in opioid utilization, prespecified as a minimum reduction of 25%. When used on the day of surgery, oral and IV acetaminophen appeared equivalent in associations with reduced opioid utilization, while oral acetaminophen appeared superior when using more than 1 dose on postoperative day 1. Interestingly, among patients receiving IV acetaminophen, almost half received just 1 dose on the day of surgery, further calling into question the current IV acetaminophen utilization patterns. Important next steps include validation of these results with alternative data and identifying patients and administration schedules (*e.g.*,

routine IV acetaminophen every 6 h, dosing for 48 h) most likely to result in benefit.

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Competing Interests

The authors declare no competing interests.

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Appendix 1. Opioid-related Adverse Effects[15]

Adverse Event	Diagnosis Code, International Classification of Diseases, Ninth Revision
Respiratory	
Bradypnea	786.09 acute
Pulmonary insufficiency after surgery and trauma	518.5 acute
Respiratory complications	997.3 acute
Asphyxia	799.01
Hypoxemia	799.02
Gastrointestinal (excluding ileus)	
Constipation	564.09
Constipation, narcotic induced	E937.9 acute
Dizziness or vertigo	386.2 acute
Dry mouth	527.7 acute
Nausea or vomiting	787.01 acute
Nausea or vomiting after gastrointestinal surgery	564.3 acute
Ileus	
Ileus, postoperative	997.4 acute
Paralytic ileus	560.1
Central nervous system	
Cerebral hypoxia	997.01
Nervousness	799.2 chronic or acute
Delirium	780.09 acute
Confusion, postoperative	293.9 acute
Confusion classified otherwise	293 acute
Altered mental status	780.97 acute
Genitourinary system	
Urinary retention	788.2 acute
Oliguria	997.5 acute or relatedness
Other	
Bradycardia, postoperative	997.1 acute or relatedness
Rash or itching	698.9 acute or relatedness
Drugs causing adverse effects with therapeutic use	E935.2 acute or relatedness
Fall from bed	E884.4

Appendix 2. Sensitivity Analysis Restricting the Cohort to Only Hospitals with at Least 50% IV Acetaminophen Use (Cohort Size n = 32,855; 82 Hospitals); Outcome Is Opioid Utilization in Oral Morphine Equivalents; Exponentiated Coefficients from the Log Model Depicting Percent Change Compared to Reference (= No IV or Oral Acetaminophen Use)

	Opioid Utilization	*P* Value
Use of IV acetaminophen		
Day of surgery		
1 dose	−5.1% (−7.6 to −2.6%)	< 0.0001
> 1 dose	−10.1% (−13.1 to −7.0%)	< 0.0001
Postoperative day 1		
1 dose	−4.6% (−8.5 to −0.4%)	0.0114
> 1 dose	−10.8% (−13.8 to −7.8%)	< 0.0001
Postoperative day ≥ 2		
1 dose	20.8% (15.6 to 26.3%)	< 0.0001
> 1 dose	38.3% (34.2 to 42.6%)	< 0.0001
Use of oral acetaminophen		
Day of surgery		
1 dose	4.7% (−2.8 to 12.6%)	0.6150
> 1 dose	−8.1% (−21.4 to 7.5%)	0.9384
Postoperative day 1		
1 dose	−8.8% (−15.2 to −1.9%)	0.0054
> 1 dose	−26.4% (−33.7 to −18.3%)	< 0.0001
Postoperative day ≥ 2		
1 dose	9.6% (4.5 to 14.9%)	< 0.0001
> 1 dose	16.8% (12.1 to 21.7%)	< 0.0001

Models adjusted for age, sex, race or ethnicity, insurance type, hospital location, bed size and teaching status, hospital-specific open colectomy volume, elective or emergent procedure, indication for colectomy and procedure type, year of procedure, anesthesia type, patient-controlled analgesia, gabapentin or pregabalin, nonsteroidal antiinflammatory drug, cyclooxygenase-2 inhibitor and ketamine use, Charlson comorbidities, history of substance use or abuse, chronic pain conditions, psychiatric comorbidities, or opioid use disorder.

IV = intravenous.

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