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Effect of Intravenous Acetaminophen on Postoperative Hypoxemia After Abdominal Surgery
The FACTOR Randomized Clinical Trial

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IMPORTANCE Opioid-induced ventilatory depression and hypoxemia is common, severe, and often unrecognized in postoperative patients. To the extent that nonopioid analgesics reduce opioid consumption, they may decrease postoperative hypoxemia.

OBJECTIVE To test the hypothesis that duration of hypoxemia is less in patients given intravenous acetaminophen than those given placebo.

DESIGN, SETTING, AND PARTICIPANTS Randomized, placebo-controlled, double-blind trial conducted at 2 US academic hospitals among 570 patients who were undergoing abdominal surgery, enrolled from February 2015 through October 2018 and followed up until February 2019.

INTERVENTIONS Participants were randomized to receive either intravenous acetaminophen, 1 g (n = 289), or normal saline placebo (n = 291) starting at the beginning of surgery and repeated every 6 hours until 48 postoperative hours or hospital discharge, whichever occurred first.

MAIN OUTCOMES AND MEASURES The primary outcome was the total duration of hypoxemia (hemoglobin oxygen saturation [Spo_2] <90%) per hour, with oxygen saturation measured continuously for 48 postoperative hours. Secondary outcomes were postoperative opioid consumption, pain (0- 10-point scale; 0: no pain; 10: the most pain imaginable), nausea and vomiting, sedation, minimal alveolar concentration of volatile anesthetic, fatigue, active time, and respiratory function.

RESULTS Among 580 patients randomized (mean age, 49 years; 48% women), 570 (98%) completed the trial. The primary outcome, median duration with Spo_2 of less than 90%, was 0.7 (interquartile range [IQR], 0.1-5.1) minutes per hour among patients in the acetaminophen group and 1.1 (IQR, 0.1-6.6) minutes per hour among patients in the placebo group (P = .29), with an estimated median difference of −0.04 (95% CI,−0.18 to 0.11) minutes per hour. None of the 8 secondary end points differed significantly between the acetaminophen and placebo groups. Mean pain scores within initial 48 postoperative hours were 4.2 (SD, 1.8) in the acetaminophen group and 4.4 (SD, 1.8) in the placebo group (difference, −0.28; 95% CI, −0.71 to 0.15); median opioid use in morphine equivalents was 50 mg (IQR, 18-122 mg) and 58 mg (IQR, 24-151 mg) , respectively, with a ratio of geometric means of 0.86 (95% CI, 0.61-1.21).

CONCLUSIONS AND RELEVANCE Among patients who underwent abdominal surgery, use of postoperative intravenous acetaminophen, compared with placebo, did not significantly reduce the duration of postoperative hypoxemia over 48 hours. The study findings do not support the use of intravenous acetaminophen for this purpose.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02156154

Visual Abstract

Supplemental content

CME Quiz at jamacmelookup.com and CME Questions page 387

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Opioids remain the primary and most commonly used postoperative analgesics. However, respiratory complications are common in postoperative patients and are probably often consequent to opioid-induced ventilatory depression.[1] Physicians therefore increasingly aim to reduce or even completely avoid giving opioids by substituting nonopioid analgesics.

Acetaminophen is among the oldest and most commonly used nonopioid analgesics and seems ideal for perioperative use because it does not promote bleeding or delay bone healing.[2] The intravenous formulation of acetaminophen, introduced in 2011 in the United States, avoids variable gastrointestinal absorption and quickly reaches peak central nervous system concentrations.[3]

There are nonetheless several concerns about perioperative use of acetaminophen. The first is that the intravenous preparation costs substantially more than oral acetaminophen in the United States, making it expensive compared with opioids—and compared with most nonopioid alternatives. The second is that its efficacy as an analgesic remains unclear. Several small trials and a large observational analysis suggest that acetaminophen provides relatively little opioid sparing, even by the limited standards of nonopioid analgesic adjuvants.[4-9] A consequence is that acetaminophen may not spare opioids sufficiently to reduce the risk of opioid-related respiratory depression. Previous studies did not demonstrate significant reductions in opioid-related adverse events, mostly because sample sizes were inadequate and complications were poorly monitored.

The objective of this randomized clinical trial was to evaluate whether postoperative intravenous acetaminophen, compared with placebo, reduces the duration of postoperative hypoxemia, defined as time with a hemoglobin oxygen saturation (Spo_2) of less than 90%. Secondary hypotheses were that intravenous acetaminophen decreases postoperative opioid consumption, pain, nausea and vomiting, sedation, minimal alveolar concentration of volatile anesthetic, and fatigue; and that intravenous acetaminophen improves activity and respiratory function.

Key Points

Question What is the effect of postoperative administration of intravenous acetaminophen, which is hypothesized to reduce opioid consumption, on postoperative hypoxemia after abdominal surgery?

Findings In this randomized clinical trial that included 570 patients, the median duration of postoperative hypoxemia (defined as hemoglobin oxygen saturation <90%) was 0.7 minutes per hour in the acetaminophen group and 1.1 minutes per hour in the control group, a difference that was not statistically significant.

Meaning After abdominal surgery, intravenous acetaminophen did not significantly reduce the duration of postoperative hypoxemia over 48 hours.

Methods

This double-blind, randomized, placebo-controlled trial was conducted at the Cleveland Clinic Fairview and Main Campus hospitals between February 2015 and October 2018. The protocol was approved by the Cleveland Clinic institutional review board, and all patients provided written informed consent. There were no substantive changes to protocol after initiation of patient enrollment. The full trial protocol and statistical analysis plan are available in Supplement 1.

The study included patients who were aged 18 to 85 years, had an American Society of Anesthesiologists physical status of 1 to 3, were scheduled for elective open or laparoscopic abdominal or pelvic surgery (including colorectal, prostate, and hysterectomy procedures), and were expected to spend at least 2 nights in the hospital. Race was classified based on fixed categories and was self-identified; race data were collected because the response to the study drug may be influenced by race. Patients were excluded if they had acetaminophen allergy, liver disease, or kidney disease or were taking warfarin. We also excluded patients in whom epidural or regional blocks were planned.

Study Procedures

Patients were randomized in a 1:1 ratio to receive either acetaminophen or matching placebo using computer-generated codes with randomly sized block sizes of 2 and 4. Randomization was stratified based on long-term opioid use and trial site. Long-term opioid use was defined as more than 30 consecutive days at a daily dose of 15 mg or more of morphine or equivalent within the 3 months before surgery. The study intervention was prepared by the Cleveland Clinic research pharmacy; allocation was concealed from the investigators, patients, and surgeons. Acetaminophen and placebo were contained in identical intravenous infusion bags; the labels indicated that the bags contained either acetaminophen, 1 g, or normal saline placebo, but did not specify which.

Study drug or placebo infusion was initiated in the operating room at the beginning of surgery and repeated every 6 hours until 48 postoperative hours or hospital discharge, whichever came first. Anesthesia management was not controlled, but fentanyl was recommended for intraoperative use and hydromorphone for postoperative analgesia.

Patients were given intravenous boluses of hydromorphone (0.2-0.4 mg, intravenously) or fentanyl (25-50 µg, intravenously) every 10 minutes as needed in the postanesthesia recovery unit. Subsequently, patient-controlled analgesia was provided with standard clinical settings; additional fentanyl or hydromorphone was given for breakthrough pain. Patients were also given intravenous boluses of hydromorphone (0.2-0.4 mg) or fentanyl (25-50 µg) as needed. Clinicians who were blinded to intervention allocation adjusted opioid analgesia as necessary to target pain scores of less than 4 on a 0- to 10-point verbal response scale throughout hospitalization.

Other anti-inflammatory drugs were not used intraoperatively or for the initial 48 postoperative hours. A single dose of dexamethasone (4-8 mg) was permitted for postoperative nausea and vomiting prophylaxis, and inhaled steroids were

permitted as necessary to treat reactive airway disease. Patients were given prophylactic ondansetron intraoperatively based on risk assessment (Apfel simplified risk score)[10] for nausea and vomiting. Patients experiencing postoperative nausea and vomiting were given 4 mg of ondansetron intravenously. Open-label intravenous and/or oral acetaminophen was not permitted.

Outcomes

The original planned primary outcome was the total duration of hypoxemia (Spo_2 <90%). It was changed to minutes with hypoxemia (Spo_2 <90%) per hour of successful Spo_2 monitoring during the initial 48 hours of postoperative monitoring or for the duration of hospitalization, if shorter. It was calculated as (total minutes of Spo_2 <90%)/(total Spo_2 reading minutes − total gap), in which a gap was defined as any time interval longer than 1 minute between 2 consecutive Spo_2 measurements, from the monitoring data. This change to the protocol was made on January 21, 2014, before patients were enrolled and before the protocol was submitted to the institutional review board for approval. In 1 of 5 parts of the protocol, a single sentence was erroneously left unchanged.

The area under the curve for hypoxemia was calculated. As a sensitivity analysis, the total duration of hypoxemia over a 48-hour period (excluding gaps) was also calculated. The secondary outcomes included opioid consumption within 48 hours after the end of surgery, time-weighted mean pain scores within 48 hours, any postoperative nausea and vomiting within 48 hours after the end of surgery, the lowest Richmond Agitation-Sedation Scale (RASS) score[11] within 48 hours after the end of surgery, total volatile anesthetic dose (in minimal alveolar concentration hours) from intraoperative induction to extubation, fatigue score, active time (time spend sitting or in upright position), and respiratory function (including tidal volume, minute volume, and respiratory rate, and from which low respiratory function events were calculated) during the initial 48 hours of postoperative monitoring after the end of surgery or for the duration of hospitalization, if shorter.

Pain scores were evaluated on a visual analog scale of 0 to 10, with 0 being no pain and 10 the most pain imaginable. The RASS is scored from −5 to +4, with −5 being unarousable and +4 combative. The fatigue score ranged from 1 to 10, with 1 being no fatigue and 10 being the worst fatigue imaginable. Low respiratory function events were defined as episodes of less than 40% of predicted respiratory function for 2 minutes; this definition is routinely used by the monitoring system.[12]

Exploratory outcomes included the Quality of Recovery 15 score[13] administered on the second postoperative morning and the Brief Pain Inventory[14] and the 12-Item Short Form Health Survey[15] administered preoperatively and 90 days after surgery. Patients were queried about their satisfaction with analgesia management on the second postoperative morning in person if they remained in the hospital, or by phone if already discharged.

Analgesia satisfaction was rated on a 0- to 100-point scale, with 0 being worst. The Brief Pain Inventory pain severity score is scaled from 0 to 10, with 0 being no pain and 10 being worst pain. The Brief Pain Inventory interference score is a 0- to 10-point scale, with 0 indicating no interference and 10 indicating interferes completely. The 12-Item Short Form Health Survey is a scale of 0 to 100, with 0 indicating lowest health level. The Quality of Recovery 15 score ranges from 0 to 18, with 0 being worst.

Monitoring, Measurements, and Data Collection

Demographic and baseline comorbidity data were collected. All measurements were started at the time when patients were transferred to the recovery room. Mobile monitors (ViSi, Sotera Wireless Inc) cleared by the US Food and Drug Administration for continuous vital signs monitoring in hospitalized patients were used. The system is battery powered and communicates via wi-fi with the Cleveland Clinic's secure internal server system. Monitors were used for participating patients in the postanesthesia care unit and until 48 postoperative hours or hospital discharge. The monitors record various vital signs and patient activity, but the study's prespecified focus was oxygen saturation, respiratory rate, and patient position as a marker of activity. Clinicians were blinded to the information on the monitor. Clinical care was thus exclusively based on routine monitoring.

Respiratory volume monitors (ExSpiron, Respiratory Motion Inc) were used to estimate tidal volume, minute ventilation, and respiratory rate from chest wall impedence.[16]

Total opioid consumption over the initial 48 postoperative hours was extracted from patients' medical records and converted to intravenous morphine equivalents.[17] Pain was recorded at roughly 15-minute intervals in the postanesthesia care unit and at 4-hour intervals on surgical wards by nurses per clinical routine.

Patients were asked about postoperative nausea and vomiting in the postanesthesia care unit, at 4-hour intervals while awake through the remaining initial day of surgery, and on the first and second postoperative mornings. Fatigue was assessed on the first postoperative morning. Sedation was estimated by the RASS score[11] and recorded at 2-hour intervals by ward nurses per clinical routine during the initial 48 postoperative hours.

Active time was defined as time spent sitting or upright during the initial 48 postoperative hours, as determined by the monitoring system. Patients were queried about their satisfaction with analgesia management on the second postoperative morning in person if they remained in the hospital, or by phone if already discharged.

Statistical Analysis

For study planning purposes, amounts of hypoxemia were identified in 833 similar Cleveland Clinic patients. Based on the expected opioid-sparing effect of acetaminophen, the fraction of patients with no hypoxemia over 48 hours was anticipated to increase from 55% to 65%. The fraction of patients who had less than 1 cumulative hour of hypoxemia was similarly expected to change from 4% to 10%; the portion of patients who had between 1 and 2 cumulative hours of hypoxemia would change from 7% to 6%; the fraction of patients who had between 2 and 4 cumulative hours of hypoxemia would

decrease from 8% to 5%; the proportion of patients with 4 to 12 cumulative hours of hypoxemia would drop from 14% to 7%; and a decrease from 12% to 7% was expected in patients who experienced hypoxemia for more than 12 cumulative hours over the initial 48 postoperative hours.

This shift in the fraction of minutes of hypoxemia over 48 hours was deemed to be the clinically important outcome in the study design. Although minutes per hour of hypoxemia was considered in the final analysis, the estimated power remained unchanged because the randomized groups had approximately the same number of hours of observation.

It was expected that 528 patients would provide 90% power at α = .05 for identifying the expected group differences in minutes of hypoxemia over 48 hours with a Wilcoxon rank sum test. Accounting for 3 interim analyses, we planned to enroll a maximum of 580 patients.

All primary and secondary analyses were based on an a priori statistical plan that was included in our original institutional review board application. Baseline and procedural characteristics were summarized by standard descriptive statistics.

For the primary outcome, patients were analyzed according to their randomized group, excluding patients who did not receive study intervention. We expected all patients to have at least some monitoring data available during the initial 48 hours and did not plan a prespecified multiple imputation analysis. However, because of unexpected technical problems, 28 patients (5%) did not have any data recorded. Missing primary outcome measurements were thus imputed by multivariable imputation using 5 imputation data sets. The imputation model included all of the baseline, intraoperative, surgical, and postanesthesia care unit variables listed in **Table 1** and all of the secondary outcomes. The secondary and exploratory outcomes were based on available data without imputation.

For the primary analysis, we tested the effect of acetaminophen vs placebo on minutes of hypoxemia per hour using a 2-sample Wilcoxon rank sum test, and we used the Hodges-Lehmann estimator of location shift to estimate median differences and confidence intervals. This method was appropriate because duration of hypoxemia exhibited a skewed distribution, with many patients not having any hypoxemia (counted as durations of 0). The significance level was $P < .044$ after adjustment for 3 interim analyses. A complete-case sensitivity analysis was performed on the subset of patients who had at least some oxygenation data available. We also conducted 2 sensitivity analyses by using the area under the hypoxemia threshold of Spo_2 less than 90% and the total duration of hypoxemia over the 48-hour period as outcomes.

In post hoc analyses we assessed the heterogeneity of the treatment effect (ie, the treatment group × covariate interaction) among subgroups of select baseline variables (age <60 vs ≥60 years, white vs other race, opioid use vs no opioid use, and laparoscopic vs open surgery) using a multivariable proportional odds model by categorizing the primary outcome into 4 ordinal groups (no hypoxemia and tertiles of hypoxemia with some amount below the threshold).

Table 1. Patient Characteristics

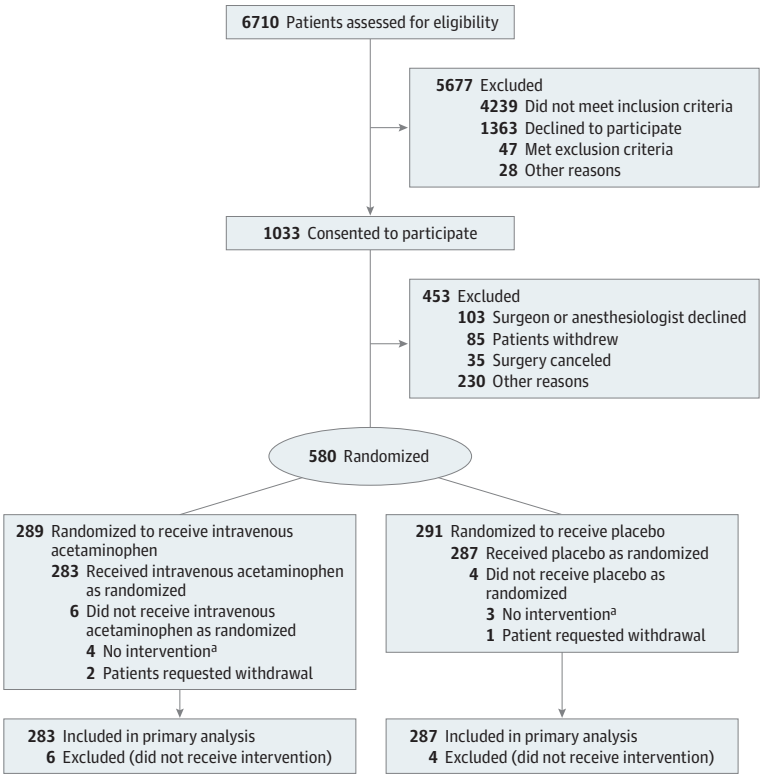
Characteristics	Intravenous acetaminophen (n = 283)	Placebo (n = 287)
Age, mean (SD), y	50.3 (15.3)	48.4 (15.1)
Sex, No. (%)		
Female	140 (49.5)	136 (47.4)
Male	143 (50.5)	151 (52.6)
Race, No. (%)[a]	n = 282	n = 286
White	261 (92.6)	265 (92.7)
Black	14 (5.0)	15 (5.2)
Other	7 (2.5)	6 (2.1)
Body mass index, mean (SD)[b]	26.7 (4.7)	26.7 (4.8)
ASA health status, No. (%)	n = 282	n = 286
1 (Healthy)	4 (1.4)	4 (1.4)
2 (Mild systemic illness)	124 (43.8)	128 (44.6)
3 (Severe systemic illness)	155 (54.8)	155 (54.0)
Social history, No. (%)	n = 282	n = 287
Current smoker	31 (11.0)	31 (10.8)
Current recreational drug user	15 (5.3)	14 (4.9)
Alcohol misuse	11 (3.9)	17 (5.9)
Medical history, No. (%)		
Cancer	80 (28.4)	88 (30.7)
Asthma	30 (10.6)	27 (9.4)
Chronic pain requiring opioid use	27 (9.6)	28 (9.8)
Diabetes mellitus	24 (8.5)	19 (6.6)
Obstructive sleep apnea	21 (7.4)	18 (6.3)
Neurologic diseases	11 (3.9)	15 (5.2)
Ischemic heart disease	10 (3.5)	9 (3.1)
Myocardial infarction	7 (2.5)	10 (3.5)
Chronic obstructive pulmonary disease	7 (2.5)	9 (3.1)
Pain management history, No. (%)		
Long-term opioid use	25 (8.8)	26 (9.1)
Nonopioid analgesic	37 (13.1)	49 (17.1)
Nonsteroidal anti-inflammatory drugs	17 (6.0)	22 (7.7)
Gabapentin	3 (1.1)	5 (1.7)
Amitriptyline/nortriptyline	0	2 (0.70)
Acetaminophen	17 (6.0)	18 (6.3)
Pregabalin	1 (0.35)	1 (0.35)
Other	3 (1.1)	3 (1.0)
Procedure characteristics		
Type of surgery, No. (%)	n = 283	n = 286
Colorectal	270 (95.4)	264 (92.3)
Gynecological	2 (0.71)	8 (2.8)
Urological	2 (0.71)	6 (2.1)
Bariatric	0	1 (0.35)
Other	9 (3.2)	7 (2.4)
Laparoscopic surgery, No. (%)	120 (42.4)	98 (34.1)
Duration of surgery, median (IQR), h	3.4 (2.1-4.6)	3.2 (2.0-4.7)
Intraoperative opioid use, intravenous morphine equivalents, median (IQR), mg	25.0 (19.3-32.5)	26.5 (17.7-35.7)

Abbreviations: ASA, American Society of Anesthesiologists; IQR, interquartile range.

[a] Race classification was identified by fixed categories; other races include Asian, Hispanic, and other races not listed. Ethnicity data were not collected.

[b] Calculated as weight in kilograms divided by height in meters squared.

Figure 1. Flow of Participants in the FACTOR Randomized Clinical Trial



The reasons for exclusion during the eligibility assessment were not collected.

[a] Reasons not known.

Opioid consumption, time-weighted mean pain scores, RASS scores, fatigue scores, and active time were analyzed using a 2-sample *t* test. Opioid consumption in morphine equivalent doses and active time outcomes were log-transformed to normalize the distributions in linear regression, with results reported as a ratio of 2 geometric means. We estimated the treatment effect on minimal alveolar concentration hours using a 2-sample Wilcoxon rank sum test and Hodges-Lehmann estimator of location shift. The incidence of postoperative nausea and vomiting and number of postoperative low respiratory function events were compared between the acetaminophen and placebo groups with a χ^2 test. Exploratory outcomes were reported descriptively only.

Three planned secondary outcomes were excluded because they proved to be insensitive measures of ventilation: tidal volume, minute ventilation, and respiratory rate. The remaining secondary outcomes were each compared at a significance criterion of .006 with 2-side testing instead of the planned .005, reflecting a Bonferroni correction for 8 simultaneous comparisons, to maintain an overall type I error rate of .05 (.05/8 = .006). Exploratory outcomes were reported descriptively only.

Three interim analyses and a final analysis were planned at each 25% increment of the maximum planned enrollment (n = 528) to assess for efficacy and futility. We used γ error spending functions with rate parameters of −4 for efficacy (maintaining type I error at .05 for the trial) and −2 for futility (maintaining type II error at .10 for the trial). The 3 interim analyses corresponded to patient enrollments of n = 145 on February 2016, n = 291 on January 2017, and n = 443 on December 2017. No efficacy or futility boundaries were crossed at the interim analyses. Critical *P* values for the primary outcome at the final analysis were $P < .044$ for efficacy and $P \geq .044$ for futility.

All testing was 2-sided, and SAS version 9.4 (SAS Institute Inc) was used for all analyses.

Results

A total of 580 patients were enrolled; 289 (50%) were randomized to receive intravenous acetaminophen and 291 (50%) were randomized to receive placebo. Ten patients were excluded from analyses because they asked to be excluded after randomization or because study intervention was not given for another reason. Thus, 570 patients were analyzed, with 283 (50%) given acetaminophen and 287 (50%) given placebo (**Figure 1**). However, because of unexpected technical problems, 14 patients (5%) did not have any data recorded. Baseline characteristics and procedural details are summarized in Table 1.

There was no significant difference in the primary outcome of minutes per hour with an Spo_2 of less than 90%, with a median of 0.7 (interquartile range [IQR], 0.1-5.1) minutes per hour in the acetaminophen group and 1.1 (IQR, 0.1-6.6) minutes per hour in the placebo group ($P = .29$), corresponding to an estimated median difference of −0.04 (95% CI, −0.18 to 0.11) minutes per hour (**Table 2**; eFigure 1 in

Table 2. Effect of Acetaminophen on the Primary Outcome of Duration of Hypoxemia Per Hour of Spo_2 Monitoring[a]

	Intravenous acetaminophen (n = 283)[b]	Placebo (n = 287)[b]	Difference, median (95% CI)[c]	*P* value[d]
Hypoxemia, median (IQR), min/h	0.7 (0.1-5.1)	1.1 (0.1-6.6)	−0.04 (−0.18 to 0.11)	.29
Cumulative minutes of hypoxemia over 48 postoperative hours, median (IQR)	27 (3-194)	39 (2-260)	−0.6 (−4.9 to 3.7)	.45
Hypoxemia duration, No. (%)				
No hypoxemia	38 (14)	42 (15)		
≤1 h	119 (44)	109 (40)		
1.01 to 2 h	27 (10)	24 (9)		
2.01 to 4 h	31 (12)	24 (9)		
4.01 to 12 h	38 (14)	54 (20)		
>12 h	16 (6)	20 (7)		
Area under the hypoxemia threshold, median (IQR)[e]	52 (3-485)	68 (3-583)	−0.53 (−8.70 to 7.65)	.45

Abbreviation: IQR, interquartile range; Spo_2, hemoglobin oxygen saturation.

[a] Hypoxemia was defined as an Spo_2 of less than 90%.

[b] A total of 28 patients (5%) were missing monitoring data (14 patients in each group). Values for these patients were obtained using multivariable imputation with 5 imputation data sets. The imputation regression model included all of the baseline, intraoperative, surgical, and postanesthesia care unit variables listed in Table 1 and all of the secondary outcomes.

[c] Median differences for the acetaminophen vs placebo groups were estimated with the Hodges-Lehmann estimator of location shift between groups; the confidence interval is adjusted for 3 interim analyses to maintain an overall study α = .05; the treatment effect on the primary outcome was consistent across study sites (*P* = .99 for treatment × site).

[d] By Wilcoxon rank sum test, with a significance criterion of *P* < .044.

[e] The area under the hypoxemia threshold was calculated as the sum of the product of the duration of hypoxemia (in minutes) and its difference from an Spo_2 of 90% (ie, minutes × percentage). The minimum value is 0 (no Spo_2 <90%). For example, an area under the threshold value of 50 would result from 10 minutes at an Spo_2 of 85% (5% below 90%) or from 25 minutes at an Spo_2 of 88% (2% below 90%).

Supplement 2). The sensitivity analysis was restricted to complete cases (n = 542), that is, those without missing data, and the results were consistent with the primary analysis, with an estimated median difference of −0.04 (95% CI, −0.26 to 0.02) minutes per hour (*P* = .26). The treatment effect on the primary outcome did not vary across clinical sites (*P* = .99 for interaction) (eTable 1 in Supplement 2).

The summary of observed hypoxemia by study group is presented in Table 2 and in eFigure 2 in Supplement 2. For example, 7% of the acetaminophen group had at least 10 minutes per hour with an Spo_2 of less than 90% (or 8 cumulative hours of Spo_2 <90%) during the initial 48 postoperative hours, as did 9% of the placebo group (eFigure 2). The median cumulative minutes of hypoxemia (Spo_2 <90%) during the first 48 postoperative hours was 27 minutes in the acetaminophen group and 39 minutes in the placebo group. Twenty percent of the acetaminophen group and 27% of the placebo group experienced hypoxemia for more than 4 cumulative hours during the initial 48 postoperative hours (Table 2).

Neither the post hoc outcome of cumulative minutes nor the area under the hypoxemia threshold of an Spo_2 of less than 90% was significantly affected by acetaminophen use. The treatment effect did not vary significantly across levels of selected baseline variables (age, race, opioid use, and laparoscopic surgery), with *P* > .10 for all interactions (**Figure 2**).

There was no significant between-group difference for any of the secondary outcomes, with all *P* values exceeding the significance criterion of *P* = .006 (**Table 3**). Specifically, pain scores within the initial 48 postoperative hours had mean verbal response scores of 4.2 (SD, 1.8) for acetaminophen and 4.4 (SD, 1.8) for placebo (*P* = .07), and opioid use was not significantly different, with a ratio of geometric means of 0.86 (99.4% CI, 0.61-1.21; *P* = .22).

Descriptive data for the Quality of Recovery 15 score, analgesia satisfaction score, Brief Pain Inventory, and 12-Item Short Form Health Survey are presented in eTable 2 in Supplement 2. Patient postanesthesia care unit characteristics and supplemental oxygen use after postanesthesia care unit discharge are presented in eTable 3 in Supplement 2.

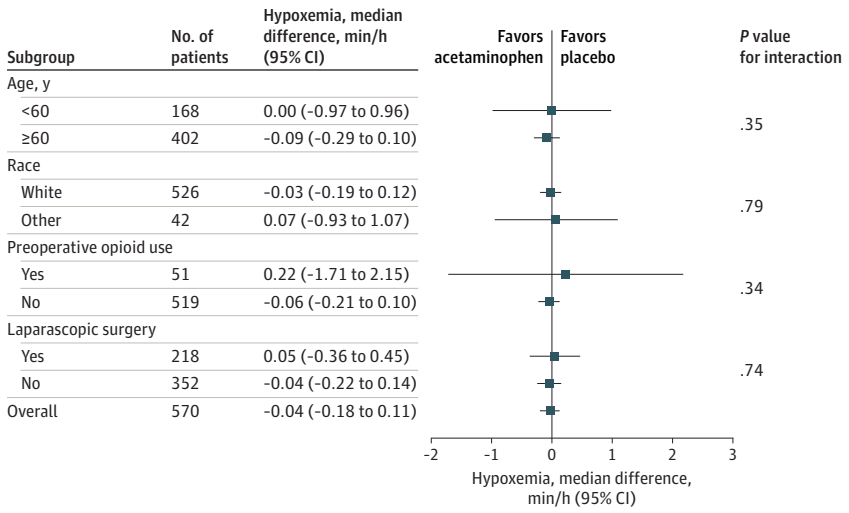
Monitoring Spo_2 Data Quality

Among the 542 patients with at least some available Spo_2 monitoring data, the median duration of Spo_2 monitoring was 48 hours including gaps and 40 hours without gaps in the acetaminophen group, and 48 hours with gaps and 41 hours without gaps in the placebo group. The median duration of the longest gap was 0.4 (IQR, 0.1-1.7) hours in the acetaminophen group and 0.3 (IQR, 0.1-1.0) hours in the placebo group, while the median cumulative duration of gaps was 4.2 (IQR, 1.8-7.8) hours in the acetaminophen group and 3.4 (IQR, 1.4-6.6) hours in the placebo group. In both groups, 69% of patients had Spo_2 monitoring for at least 90% of the planned follow-up time (from first reading to discharge or 48 hours after surgery, whichever came first). A summary of Spo_2 data quality by groups is presented in eTable 4 in Supplement 2.

Discussion

In this randomized clinical trial of patients who had abdominal surgery, intravenous acetaminophen, 1 g every 6 hours for 2 postoperative days, did not significantly reduce the amount of hypoxemia. The finding that there was no significant difference in the duration of hypoxemia between patients given acetaminophen vs placebo was presumably consequent to the fact that acetaminophen reduced opioid consumption by only

Figure 2. Assessment of Treatment Effect Heterogeneity for the Primary Outcome



The plot shows the median difference with 95% confidence interval for the primary outcome of minutes of hypoxemia per hour within levels of 4 post hoc baseline variables, as calculated using the Hodges-Lehmann estimator of location shift. The effect of acetaminophen (vs placebo) on the primary outcome did not significantly vary across levels of any of these factors ($P > .10$ for interaction for all covariates × treatment) using proportional odds logistic regression in a model testing all interactions simultaneously. Other race indicates Asian, Hispanic, and others not listed. Preoperative opioid use was defined as opioid use for more than 30 consecutive days during the last 3 months prior to surgery.

Table 3. Effect of Acetaminophen on Secondary Outcomes

Secondary outcomes	Intravenous acetaminophen (n = 283)	Placebo (n = 287)	Treatment effect, acetaminophen vs placebo (99.4% CI)[a]	*P* value
Time-weighted pain score during initial 48 postoperative hours, mean (SD)[b,c]	4.2 (1.8) [n = 276]	4.4 (1.8) [n = 282]	−0.28 (−0.71 to 0.15)	.07
Time-weighted pain score in postanesthesia care unit, mean (SD)[b,c]	4.3 (1.7) [n = 281]	4.4 (1.8) [n = 281]	−0.11 (−0.51 to 0.29)	.46
Fatigue score on morning of postoperative day 1, mean (SD)[b,d]	5.0 (2.6) [n = 271]	4.9 (2.7) [n = 272]	0.13 (−0.49 to 0.76)	.56
Lowest RASS score during initial 48 postoperative hours, mean (SD)[b,e]	−0.96 (0.75) [n = 192]	−0.89 (0.76) [n = 201]	−0.08 (−0.29 to 0.13)	.30
Opioid consumption during initial 48 postoperative hours, intravenous morphine equivalents, median (IQR), mg[f]	50 (18-122)	58 (24-151)	0.86 (0.61 to 1.21)	.22
Time spend in sitting or upright position during initial 48 postoperative hours, median (IQR), h[f]	2.2 (0.8-4.1) [n = 252]	2.2 (0.9-4.2) [n = 248]	0.94 (0.63 to 1.39)	.65
Total monitored patient active time, median (IQR), h	28 (19-39) [n = 252]	28 (21-38) [n = 248]		
Nausea and vomiting during initial 48 postoperative hours, No./total (%)[g]	140/280 (50)	124/280 (44)	1.13 (0.88 to 1.45)	.18
Low respiratory function event during initial 48 postoperative hours, No./total (%)[g,h]	52/188 (28)	50/163 (31)	0.90 (0.57 to 1.43)	.53
Total respiratory function monitoring time, median (IQR), h	45 (44-47) [n = 188]	47 (46-47) [n = 163]		
Total anesthetic dose from induction to extubation, median (IQR)[i]	2.9 (2.6-3.0) [n = 282]	2.9 (2.7-3.0) [n = 287]	0.0 (−0.39 to 0.36)	.99

Abbreviation: IQR, interquartile range.

[a] Confidence intervals were adjusted for 8 comparisons using Bonferroni correction (.05/8 = .006), for a significance criterion of $P < .006$.

[b] Treatment effect data are reported as differences in means between the study groups, assessed using a 2-sample *t* test.

[c] Pain scores were calculated on a visual analog scale of 0 to 10, with 0 being no pain and 10 being the most pain imaginable; time-weighted mean was calculated as the area under the curve of the pain score measurements divided by total measurement time.

[d] Fatigue scores were calculated on a scale of 1 to 10, with 1 being no fatigue and 10 being the worst fatigue imaginable.

[e] The Richmond Agitation-Sedation Scale (RASS) is scored from −5 to +4, with −5 being unarousable, 0 being alert and calm, and +4 being combative.

[f] Treatment effect data are reported as ratios of geometric means, assessed using a 2-sample *t* test after logarithmic transformation of outcomes.

[g] Treatment effect data are reported as relative risks, assessed using a χ^2 test; ordinal variables were analyzed with the Wilcoxon rank sum test.

[h] A low respiratory function event was defined as an episode of less than 40% of predicted minute ventilation for 2 minutes.

[i] Total anesthetic dose is measured in minimal alveolar concentration hours. Treatment effect is reported as median difference, estimated using the Hodges-Lehmann estimator of location shift.

14% (by a total of 8 mg, or 4 mg/d), an amount that was neither statistically significant nor clinically important. As might be expected from nonsignificantly different opioid consumption in each group, acetaminophen did not significantly reduce postoperative pain. Given that opioid use was not significantly different in the acetaminophen and placebo groups, it is expected that secondary outcomes did not differ significantly, including nausea and vomiting, sedation, fatigue, active time, and respiratory function.

Uncertainty remains regarding the opioid-sparing efficacy of intravenous acetaminophen. Previous studies that evaluated the effects of intravenous acetaminophen on postoperative pain and opioid consumption reported mixed results. Some studies have reported that intravenous acetaminophen spares opioid use and reduces postoperative pain.[6,18-20] A recent study in elderly patients recovering from cardiac surgery reported that intravenous acetaminophen decreased opioid consumption and reduced delirium.[21]

But most of the studies are limited by inclusion of only a small number of patients, retrospective study designs, and/or dosing issues. In contrast, many trials have showed little or no reduction in opioid use and pain, including trials in patients having hysterectomies (n = 183),[8] pelvic organ prolapse repair (n = 101),[22] cesarean deliveries (n = 100),[23] vaginal reconstruction (n = 100),[24] and robotic-assisted laparoscopic prostatectomy (n = 86).[9] Each of these trials was limited to just 1 or 2 doses of intravenous acetaminophen, but their results are similar to those in current study patients who were given 1 g of intravenous acetaminophen every 6 hours for 2 days. Furthermore, 3 recent studies based on a national claims database evaluated the effects of intravenous acetaminophen on opioid consumption and opioid-related outcomes in open colectomies, orthopedic surgery, and spine surgery.[5,25,26] Both of the national registry analyses of patients who had colorectal and spine surgery reported limited opioid sparing with intravenous acetaminophen, while in shoulder arthroplasty, there was no apparent benefit.

Limitations

This study has several limitations. First, enrollment was restricted to 2 hospitals, both belonging to the Cleveland Clinic. Current results thus reflect the clinical practices of the institution, which may limit its generalizability. Second, only abdominal procedures were included because they are painful and usually require considerable opioid use, averaging more than 50 mg of morphine equivalent per patient. While restricting enrollment to high-pain procedures enhanced the ability to identify clinically important opioid sparing, it remains possible that intravenous acetaminophen is more effective for less painful procedures. Third, although concurrent nonopioid medication use was limited, about 15% of patients used concurrent analgesics, although the amounts were similar in each treatment group. Fourth, there was a substantial amount of missing data due to unexpected technical problems.

Conclusions

Among patients who underwent abdominal surgery, use of postoperative intravenous acetaminophen, compared with placebo, did not significantly reduce the duration of postoperative hypoxemia over 48 hours. The study findings do not support the use of intravenous acetaminophen for this purpose.

ARTICLE INFORMATION

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