ORIGINAL CLINICAL RESEARCH REPORT

Effect of Intravenous Acetaminophen on Mean Arterial Blood Pressure: A Post Hoc Analysis of the EFfect of Intravenous ACetaminophen on PosToperative HypOxemia After Abdominal SurgeRy Trial

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BACKGROUND: Acetaminophen is commonly used as part of multimodal analgesia for acute pain. The intravenous formulation offers a more predictable bioavailability compared to oral and rectal acetaminophen. There have been reports of hypotension with intravenous acetaminophen attributable to centrally mediated and vasodilatory effects. We tested the hypothesis that in adults having abdominal surgery the use of intravenous acetaminophen versus placebo for postoperative pain management is associated with a decrease in mean arterial pressure (MAP) after its administration.

METHODS: This is a substudy of eFfect of intravenous ACetaminophen on posToperative hypOxemia after abdominal surgeRy (FACTOR) trial (NCT02156154). FACTOR trial randomly assigned adults undergoing abdominal surgery to either 1 g of acetaminophen or placebo every 6 hours during the first postoperative 48 hours. Continuous monitoring of blood pressure was obtained by noninvasive ViSi Mobile device (Sotera Wireless, Inc, San Diego, CA) at 15-second intervals during initial 48 hours postoperatively. We excluded patients without continuous monitoring data available. The primary outcome was the MAP difference between MAP 5 minutes before study drug administration (baseline) and MAP 30 minutes poststudy drug administration initiation. We used a linear mixed effects model to assess the treatment effect on MAP change. The secondary outcome was MAP area under baseline (AUB) during the 30 minutes after treatment. In a sensitivity analysis of change in MAP from predrug to postdrug administration, we instead used postdrug MAP as the outcome adjusting for the baseline MAP in the model.

RESULTS: Among 358 patients analyzed, 182 received acetaminophen and 176 placebo. The mean (standard deviation [SD]) of average MAP change was −0.75 (5.9) mm Hg for the treatment and 0.32 (6.3) mm Hg for the placebo. Acetaminophen was found to decrease the MAP from baseline more than placebo after drug administration. The estimated difference in mean change of MAP was −1.03 (95% confidence interval [CI] −1.60 to −0.47) mm Hg; $P < .001$. The sensitivity analysis showed postoperative MAP in the acetaminophen group was 1.33 (95% CI, 0.76-1.90) mm Hg lower than in the placebo group ($P < .001$). The median of MAP AUB was 33 [Q1 = 3.3, Q3 = 109] mm Hg × minutes for the treatment and 23 [1.6, 79] mm Hg × minutes for the placebo. Acetaminophen was found to increase the AUB with an estimated median difference of 15 (95% CI, 5-25) mm Hg × minutes ($P = .003$).

CONCLUSIONS: Intravenous acetaminophen decreases MAP after its administration. However, this decrease does not appear to be clinically meaningful. Clinicians should not refrain to use intravenous acetaminophen for acute pain management because of worries of hypotension. (Anesth Analg 2021;133:1532–9)

KEY POINTS

- **Question:** Does intravenous acetaminophen induce hypotension?
- **Findings:** Intravenous acetaminophen induces blood pressure changes that are not clinically meaningful.
- **Meaning:** Clinicians should not refrain to use intravenous acetaminophen for acute pain management because of worries of hypotension

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Conflicts of Interest: See Disclosures at the end of the article.

GLOSSARY

ASA = American Society of Anesthesiologists; **ASD** = absolute standard difference; **AUB** = area under baseline; **BMI** = body mass index; **CI** = confidence interval; **FACTOR** = eFfect of intravenous ACetaminophen on posToperative hypOxemia after abdominal surgeRy; **IV** = intravenous; **MAP** = mean arterial pressure; **MINS** = myocardial injury after noncardiac surgery; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **PACU** = postanesthesia care unit; **RCT** = randomized controlled trial; **SD** = standard deviation; **STROBE** = Strengthening the Reporting of Observational Studies in Epidemiology; **TWA** = time-weighted average

Acetaminophen is one of the most popular and frequently used medications around the world. First used clinically in the late 1800s, and introduced to the United States in 1955, the drug became widely accepted in the 1970s following several studies affirming its safety.[1,2] Acetaminophen, a derivative of p-aminophenol, inhibits prostaglandins via the cyclooxygenase pathway in the central nervous system by selective inhibition of cyclooxygenase-2-dependent prostaglandin E_2 formation.[1–3] The parenteral formulation of acetaminophen was approved by The US Food and Drug Administration agency in November 2010 for acute pain and fever and has been frequently used since, especially in the perioperative period.[3,4]

Manufacturer-listed adverse effects of intravenous acetaminophen report hypotension with an incidence of <1%.[5] However, several studies on critical care patients have demonstrated higher incidence of transient hypotension following acetaminophen administration.[4,6–11] The different definitions of hypotension and studies limitations make it difficult to establish the severity and clinical implications of these transitory hypotensive recorded events.[11] Hemodynamic changes associated with acetaminophen are not fully understood. These changes appear to be induced by reduction in systemic vascular resistance index mediated by the cyclooxygenase, and cardiac output, with this situation exacerbated in patients with low systemic vascular resistance states, for instance septic shock or postoperative inflammatory vasodilation.[7,10,12,13]

Hypotension during the intraoperative period and postoperative period is associated with increased risk of all-cause death, myocardial injury after noncardiac surgery (MINS), and stroke.[14,15] As acetaminophen is commonly used in the postoperative period and evidence suggests it induces transient hypotension, it is important to evaluate more clearly these hemodynamic effects in postoperative at-risk patients. We therefore aimed to assess the hemodynamic effects of intravenous acetaminophen on postoperative patients with continuous noninvasive blood pressure monitoring. We hypothesized that in adult patients undergoing elective open or laparoscopic abdominal surgery, the use of intravenous acetaminophen versus placebo for postoperative pain management is associated with decrease in mean arterial pressure (MAP) after its administration.

METHODS

This is a multicenter retrospective post hoc analysis of the eFfect of intravenous ACetaminophen on posToperative hypOxemia after abdominal surgeRy (FACTOR), a double-blind, placebo-controlled trial conducted at Cleveland Clinic Main Campus and Fairview hospitals from February 2015 to October 2018 (Clinical Trial NCT02156154).[16] The study was approved by the Institutional Review Board of the Cleveland Clinic Foundation with waived individual consent. Patients were randomly assigned to receive 1 g of acetaminophen or placebo every 6 hours during the first 48 postoperative hours following open or laparoscopic abdominal surgery. The continuous blood pressure measurements of participants were obtained using the noninvasive ViSi Mobile device (Sotera Wireless, Inc) which obtained measurements at 15-second intervals. The device is a small, relatively comfortable wearable battery-powered system. Blood pressure is continuously calculated using the "pulse arrival time" technology using data captured by a pulse oximeter and electrocardiograph electrodes and is calibrated to actual cuff measurements at least once every 24 h. We calibrated the system to oscillometric pressure twice a day, using the patients' own cuff, as selected by the ward nurses according to patients' habitus. We excluded patients who had <12 hours of continuous monitoring, monitoring gaps exceeding 4 hours, or an overall unrecorded duration exceeding 30% of the total monitoring period. This article adheres to the applicable Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

The primary outcome was the difference in MAP between MAP during 30 minutes poststudy drug administration and baseline (MAP_{30min} – baseline). The baseline was defined as the average MAP during the 5 minutes before study drug

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administration and MAP 30 minutes poststudy drug administration was the average MAP during 30 minutes after drug administration initiation. For the primary analysis, a linear mixed effects model assuming heterogeneous autoregressive correlation structure was used to assess the effect of acetaminophen versus placebo on MAP change after each drug administration adjusting for administration sequence number and the prespecified potential confounding variables of age, race, sex, body mass index (BMI), ischemic heart disease, myocardial infarction, smoking status, and surgery duration. We assessed the interaction between treatment and sequence of drug administration (1–8) on the MAP changes in an additional linear mixed effects model.

In a sensitivity analysis to the primary analysis of change in MAP from predrug to postdrug administration we used postdrug MAP as the outcome, adjusting for the baseline MAP in the model. We further conducted 2 post hoc analyses. In the first we assessed whether factors such as age (being >60 years), race, sex, American Society of Anesthesiologists (ASA) physical status, opioid use, hypertension, and surgery type (open or laparoscopic) interact with the effect of acetaminophen on MAP change. In the second we assessed the treatment effect on whether or not a patient had at least 1 decrease of 10 mm Hg or more in MAP after drug administration with a Pearson χ^2 test.

The secondary outcome was MAP area under baseline (AUB) during the 30 minutes after each study drug administration. For the secondary analysis, we used a linear quantile mixed model assuming compound symmetric correlation structure to explore the effect of postoperative acetaminophen on MAP AUB during postoperative 30 minutes due to nonnormality of the outcome. Time-weighted average of MAP under baseline was used as an alternative secondary outcome for the sensitivity analysis, as this outcome directly adjusts the AUB for the time over which the outcome was measured. In the secondary analyses, we adjusted for the same confounders used in the primary analysis.

The significance criterion for primary and secondary analyses was 0.05. We used Statistical Analysis Software (version 9.4; SAS Institute, Inc., Cary, NC) for all analyses.

RESULTS

A total of 358 patients from FACTOR trial were included, 182 were assigned to acetaminophen and 176 to placebo, 212 patients were excluded due to unavailability of monitoring data and withdrawal (Figure 1). Baseline variables were balanced between

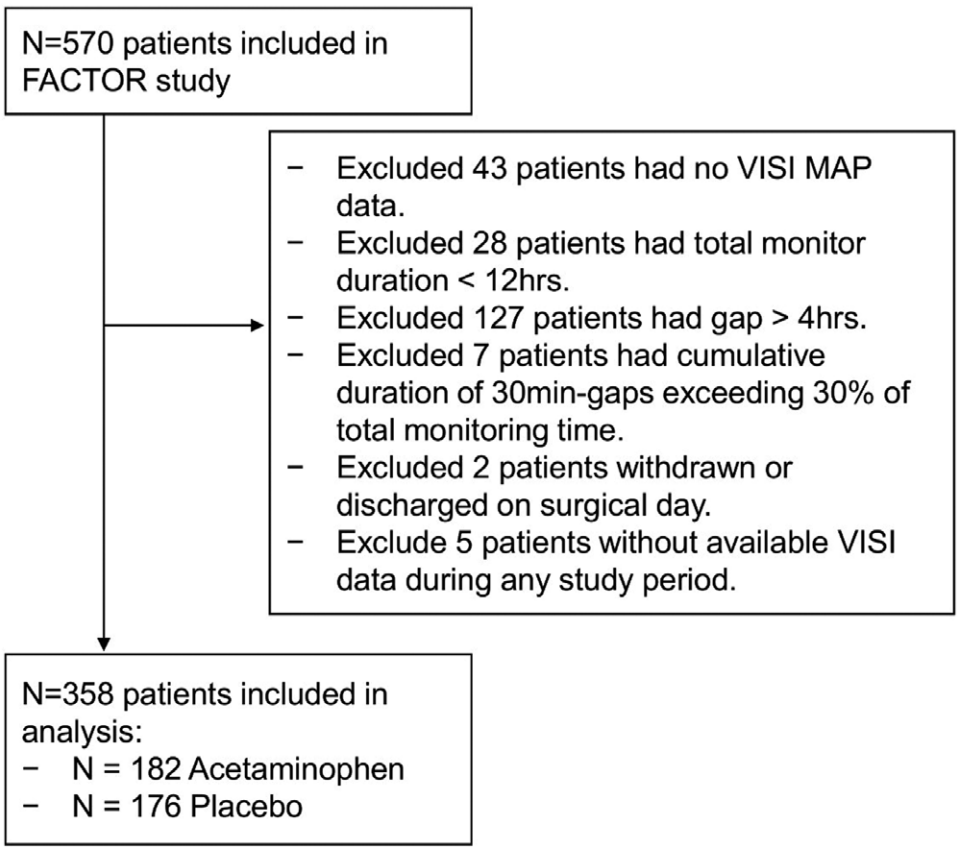

Figure 1. Study diagram. The plot shows the inclusion and exclusion criteria and sample size of the final analysis. FACTOR indicates eFfect of intravenous ACetaminophen on posToperative hypOxemia after abdominal surgeRy; MAP, mean arterial pressure.

Table 1. Baseline Characteristics

	Acetaminophen (N = 182)	Placebo (N = 176)	ASD
Factor			
Number of drug doses	6 [4, 7]	6 [5, 7]	0.17
Demographic			
Age (y)	51 ± 15	48 ± 15	0.19
Sex (%)			0.04
Female	85 (47)	86 (49)	
Male	97 (53)	90 (51)	
Race[a]			0.26
White	167 (92)	165 (94)	
Non-White	15 (8)	11 (6)	
BMI (kg/m^2)	27 ± 4.7	26 ± 4.6	0.06
ASA physical status (%)			0.08
I	3 (1.6)	4 (2.3)	
II	87 (48)	77 (44)	
III	92 (51)	95 (54)	
Social history			
Current smoker (%)	23 (13)	18 (10)	0.08
Current recreational drug user (%)	10 (5.5)	6 (3.4)	0.10
Alcohol abuse (%)	8 (4.4)	8 (4.5)	0.01
Medical history			
Asthma (%)	20 (11)	18 (10)	0.03
Chronic pulmonary disease (%)	6 (3.3)	7 (4.0)	0.04
Obstructive sleep apnea (%)	11 (6.1)	13 (7.4)	0.05
Diabetes mellitus (%)	14 (7.7)	11 (6.3)	0.06
Myocardial infarction (%)	5 (2.8)	4 (2.3)	0.03
Ischemic heart disease (%)	6 (3.3)	5 (2.8)	0.03
Neurologic diseases (%)	4 (2.2)	8 (4.5)	0.13
Chronic pain requiring opioid (%)	15 (8.3)	14 (8.0)	0.01
Cancer	52 (29)	53 (30)	0.03
Chronic opioid usage (%)	16 (8.8)	13 (7.4)	0.05
Nonopioid analgesic use (%)	19 (10)	31 (18)	0.21
NSAIDs (%)	8 (4.4)	12 (6.8)	
Gabapentin (%)	3 (1.6)	3 (1.7)	
Amitriptyline/Nortriptyline (%)	0 (0.0)	2 (1.1)	
Acetaminophen (%)	7 (3.8)	12 (6.8)	
Pregabalin (%)	1 (0.6)	1 (0.6)	
Other (%)	1 (0.6)	3 (1.7)	
Procedure characteristics			
Duration of surgery (h)	3.4 [2.1, 4.6]	3.2 [2.0, 4.5]	0.10
PACU stay (h)	2.6 [2.0, 3.6]	2.6 [2.0, 3.4]	0.05
Type of surgery			0.08
Colorectal	173 (95.1)	164 (93.2)	
Others	9 (4.9)	12 (6.8)	
Intraoperative opioid use (mg as IV morphine equivalent)	25 [20, 34]	27 [20, 36]	0.07

Statistics are presented as mean ± SD, median [Q1, Q3], median (min, max), or N (column %). ASD is calculated as the difference in mean values or proportions divided by the pooled SD. [a]Factors with ASD > 0.21 were considered as imbalanced.Abbreviations: ASA, American Society of Anesthesiologists; ASD, absolute standard difference; BMI, body mass index; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; PACU, postanesthesia care unit; SD, standard deviation.

both groups (Table 1). Number of treatments with the study drug per patient was a median [Q1, Q3] of 6 [4, 7] for acetaminophen and 6 [5, 7] for placebo (Supplemental Digital Content, Figure 1, http://links.lww.com/AA/D400).

When study drug was administered, the mean (standard deviation [SD]) across patients (ie, across multiple dose administrations) patient decrease from baseline in MAP during the 30 minutes after administration was 0.75 (5.9) mm Hg for acetaminophen and 0.32 (6.3) mm Hg for placebo. Acetaminophen was found to decrease MAP from baseline values after each administration more than placebo in a linear mixed effects model, with an estimated difference in mean change of −1.03 (95% confidence interval [CI], −1.60 to −0.47) mm Hg, $P <$ .001 (Table 2; Figures 2 and 3). The interaction between acetaminophen (versus placebo) and the sequence of drug administration on the change in MAP change was not significant ($P = .51$), suggesting homogeneity of the drug effect over time (among first to eighth administration). Sensitivity analysis showed that the postdrug administration MAP of patients receiving acetaminophen was an estimated 1.33 (95% CI, 0.76-1.90) mm Hg lower than patients who were given placebo ($P < .001$) (Table 2; Figure 3). The post hoc analyses did not find that any of the factors of age, race, sex, ASA physical status, hypertension, surgery type, or opioid use had an interaction with the effect of acetaminophen on MAP change (Figure 4). However, we found that acetaminophen patients were more likely to have at least one decrease of 10 mm Hg or more in MAP after drug administration compared to the placebo group, (26% vs 15%, $P = .007$).

In the secondary analysis, we quantified the amount of MAP reduction as AUB of MAP during the 30 minutes after study drug administration. The median [Q1, Q3] was 33 [3.3, 109] mm Hg × minutes for acetaminophen and 23 [1.6, 79] mm Hg × minutes for placebo. Acetaminophen was associated with a higher amount of MAP below the patient baseline level, with an estimated median difference in AUB of 15 (95% CI, 5-25; $P = .003$) mm Hg × minutes. As a sensitivity analysis, we used the AUB of MAP divided by the duration of blood pressure measurements after removing gaps in measurement as an alternative way to quantify MAP reduction. Patients given acetaminophen had a larger amount of MAP reduction per minute, with an estimated median difference of 0.50 (95% CI, 0.14-0.87; $P = .007$) mm Hg (Table 2; Figure 3).

DISCUSSION

In this post hoc analysis, we assessed the difference in MAP between the MAP 30 minutes following its administration and baseline, defined as 5 minutes before 1 g of intravenous acetaminophen or placebo administration. Although our results demonstrated that in the acetaminophen group, the MAP from the baseline value after administration decreased more than in the placebo group, with an estimated difference in mean change of −1.03 (−1.60 to −0.47) mm Hg, these changes were not clinically meaningful.

Previous studies have demonstrated transient hypotension after acetaminophen administration, however different hypotension definitions and limitations for continuous blood pressure monitoring have made difficult to evaluate the incidence and

Table 2. Primary and Secondary Analysis Result

	Acetaminophen (N = 182)	Placebo (N = 176)	Effect estimate	*P* value
Primary analysis			Mean difference of change (95% CI)	
Change of MAP (mm Hg)[a]	−0.75 ± 5.9[b]	0.32 ± 6.3[b]	−1.03 (−1.60 to −0.47)	<.001[c]
Sensitivity analysis				
Postdrug MAP (mm Hg)	93 ± 14[b]	96 ± 15[b]	−1.33 (−1.90 to −0.76)	<.001[c,d]
Secondary analysis			Median difference of AUB (95% CI)	
MAP AUB (mm Hg × min)	33 [3.3, 109]	23 [1.6, 79]	15 (5-25)	.003[e]
Sensitivity analysis			Median difference of TWA (95% CI)	
TWA under baseline (mm Hg)	1.3 [0.1, 3.9]	0.9 [0.1, 2.9]	0.50 (0.14-0.87)	.007[e]

[a]Change of MAP was defined as MAP mean during 30 min after the drug administration minus MAP mean during 5 min before the drug administration.[b]Data are presented as mean ± standard deviation of the average value across all doses of drug administration for each patient.[c]*P* values were obtained from linear mixed effects model assuming heterogeneous autoregressive correlation structure adjusting for age, race, sex, BMI, ischemic heart disease, myocardial infarction, smoking status, and surgery duration.[d]Besides confounders adjusted in the primary analysis, baseline MAP was also adjusted for in the model.[e]*P* values were obtained from linear mixed effects quantile regression model adjusting for confounders in the primary analysis. Abbreviations: AUB, area under baseline; BMI, body mass index; CI, confidence interval; MAP, mean arterial pressure; TWA, time-weighted average.

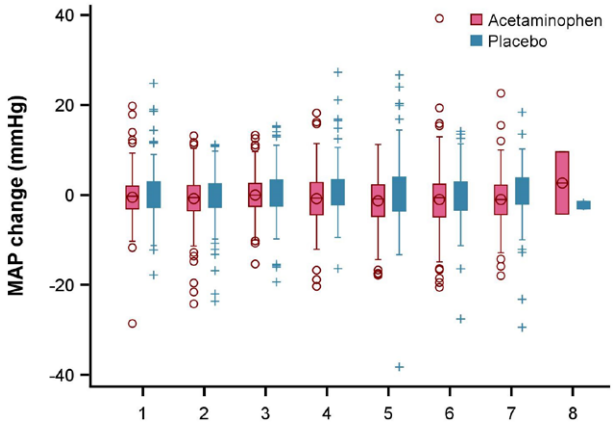

Figure 2. Change of MAP by treatment. This figure shows the boxplot of MAP change between 30 min after the administration and baseline at each drug administration time. The blue group was acetaminophen and red was placebo. MAP indicates mean arterial pressure.

duration of blood pressure changes associated with acetaminophen administration. Some investigators have considered changes in systolic blood pressure with a variation from 7% to 25% from the baseline, while others have chosen variation in the MAP with different thresholds.[4–11,13,17–20]

On the severity of changes associated between intravenous acetaminophen administration and blood pressures values, Cantais et al[11] showed acetaminophen-induced hypotension defined as a MAP decrease of 15% or more in 51.9% of their 160 study patients. Kelly et al[18] in their randomized controlled trial (RCT) found a decrease in systolic blood pressure from baseline systolic blood pressure immediately after acetaminophen administration >20% in 8.2% of critically ill patients following acetaminophen administration. Similar to Chiam et al,[13] our study objectively evaluates the association between acetaminophen administration and blood pressure changes. We analyzed the data of 358 patients included in FACTOR trial where continuous arterial pressure was monitored and recorded with ViSi monitor, and our sample size added strength to our results. This continuous monitoring allowed us to calculate the change from the baseline MAP, defined as the average MAP during the 5 minutes before study drug was given, and the MAP 30 minutes after its administration for every patient. We also found a decrease in MAP associated with intravenous acetaminophen administration.[13] However, opposite to the majority of previous literature, our results show no clinically significant differences in MAP after acetaminophen administration.[4,8,20] These differences can be explained because our study population, patients having elective colorectal surgery, differed from previous studies, mostly done in critically ill patients. The noncritically ill patients remain a vulnerable group to develop hypotension events during the postoperative period. Unfortunately, these events are commonly missed as a result of inadequate routine monitoring on the wards leading to poor postoperative outcomes.[21]

Given that blood pressure changes were not clinically significant, it is expected that the secondary outcome of MAP AUB during the 30 minutes after study drug administration did not show clinically significant difference either. To our knowledge, this is the first study assessing MAP AUB after acetaminophen administration.

The mechanism of hypotension associated with acetaminophen administration remains unclear. Krajčová et al[8] in their prospective study, explained the effect of acetaminophen on cardiac output and peripheral vascular resistance, suggesting the reduction in both as the etiology associated with the related-blood pressures changes following intravenous acetaminophen administration, especially in the critically ill patient. Even though we did not directly measure cardiac output or peripheral vascular resistance, the subtle hemodynamic changes observed in our study after acetaminophen administration made cardiac output and peripheral vascular resistance changes very unlikely in the noncritically ill patient.

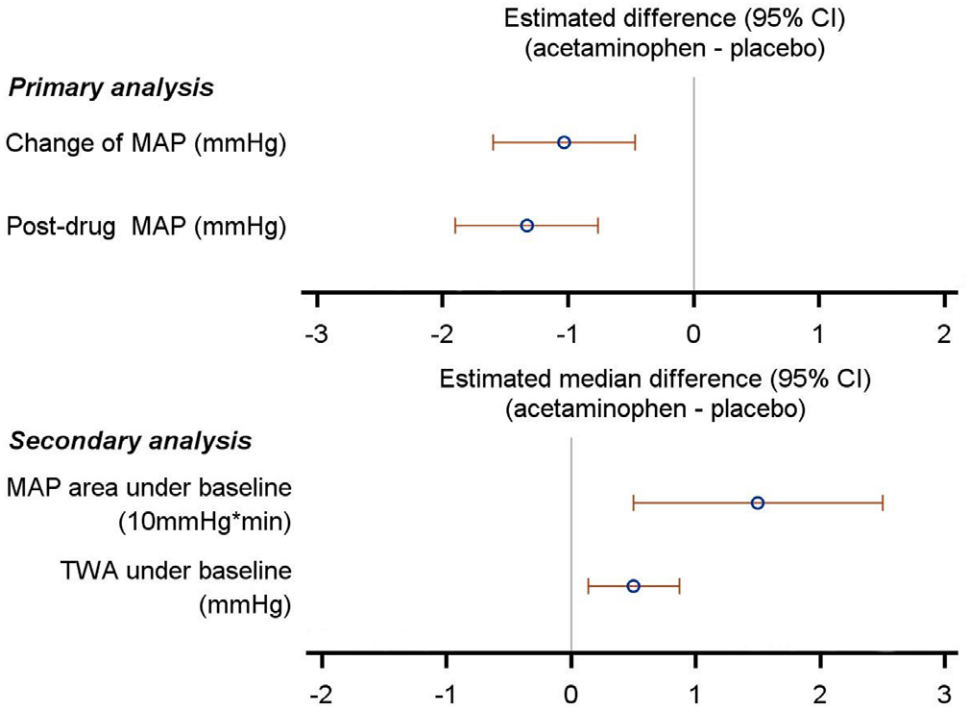

Figure 3. Forest plot of primary and secondary analyses. The plot shows the acetaminophen effect on blood pressure with 95% CI. Acetaminophen group had larger decrease from baseline compared to placebo group. The sensitivity analysis showed similar result with smaller postdrug MAP in acetaminophen group. The MAP area under baseline of acetaminophen was also larger than that of placebo in the secondary analysis. CI indicates confidence interval; MAP, mean arterial pressure; TWA, time-weighted average.

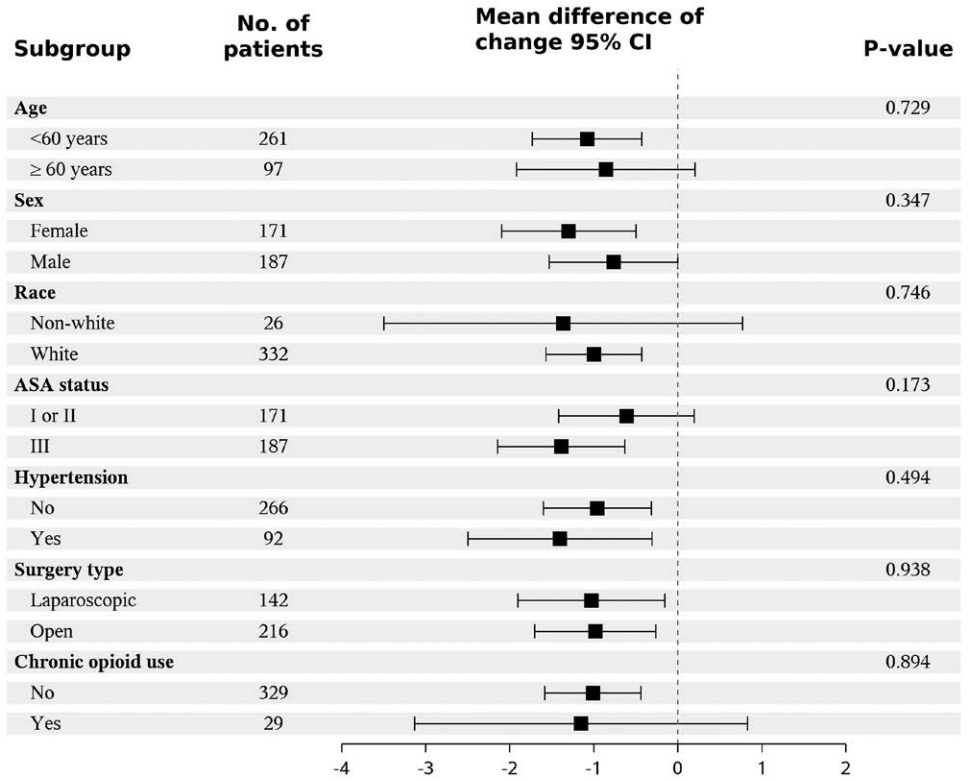

Figure 4. Assessing treatment effect heterogeneity of the effect of acetaminophen on change of MAP after drug administration. The forest plot shows the results of post hoc subgroup analyses for the primary analysis. None of age, sex, race, ASA status, hypertension, surgery type, or chronic opioid use was found to modify the treatment effect on MAP change from baseline to 30 min after drug administration ($P > .1$ for all interaction terms). ASA indicates American Society of Anesthesiologists; CI, confidence interval; MAP, mean arterial pressure.

We observed the maximal effect on blood pressure changes occurred at 15–30 minutes after infusion initiation and ultimately resolving within an hour after administration, which is in concordance with the pharmacokinetics of intravenous acetaminophen that reaches its maximum concentration (C max) at the end of a 15-minute infusion.[3,17,22,23]

However, while we did not find clinically important differences in the mean MAP from predrug to postdrug administration, we found that patients receiving acetaminophen were more likely to have at least one decrease of 10 mm Hg or more in MAP after study drug administration. Interestingly, in our study, these episodes happened more often in male patients, which is in concordance with the previous finding from Lee et al.[24] Further research is necessary to evaluate whether a reduction in MAP is associated with intravenous acetaminophen depending on patients' characteristics. Our findings should encourage blood pressure monitoring carefully in patients receiving intravenous acetaminophen as has been previously reported in the literature.[5,11,24]

Continuous noninvasive monitoring has been emerging as a possible pathway to address the lack of vital signs monitoring problem on the regular nursing floor, especially in the postoperative period. The ViSi Mobile device is a validated Food and Drug Administration–approved system intended for continuous monitoring of patients on hospital wards. The continuous blood pressure feature is accurate within 5 mm Hg to radial intraarterial pressure measurements.[20]

LIMITATIONS

FACTOR trial only included colorectal procedures. Thus, our results reflect the effect of intravenous acetaminophen just in this population, which may limit its generalizability to other surgical procedures where hemodynamic changes could be more accentuated and, therefore, more likely to develop hypotension after acetaminophen administration. Besides, since the MAP was not the primary outcome in the FACTOR trial, there was a substantial amount of nonavailable data because of technical problems with the devices, which restricted our analysis to fewer patients. However, missing data happened randomly, having little consequence on our outcome.

In summary, intravenous acetaminophen decreases mean arterial blood pressure after its administration. However, this decrease does not appear to be clinically meaningful. Clinicians should not refrain to use intravenous acetaminophen for acute pain management because of worry of hypotension especially when oral route is not available and opioid use is not desired.

DISCLOSURES

Name: Mauro Bravo, MD.
Contribution: This author helped conceive and design the study, analyze and interpret the data, and write and critically revise the manuscript.
Conflicts of Interest: None.
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Contribution: This author helped design the study, analyze and interpret the data, and write and critically revise the manuscript.
Conflicts of Interest: None.
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Contribution: This author helped conceive and design the study, analyze and interpret the data, and write and critically revise the manuscript.
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