Hypotensive Response to IV Acetaminophen in Pediatric Cardiac Patients*

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Objectives: Acetaminophen is ubiquitously used as antipyretic/analgesic administered IV to patients undergoing surgery and to critically ill patients when enteral routes are not possible. Widely believed to be safe and free of adverse side effects, concerns have developed in adult literature regarding the association of IV acetaminophen and transient hypotension. We hypothesize that there are hemodynamic effects after IV acetaminophen in the PICU and assess the prevalence of such in a large pediatric cardiovascular ICU population using high-fidelity data.

Design: Observational study analyzing an enormous set of continuous physiologic data including millions of beat to beat blood pressures surrounding medication administration.

Setting: Quaternary pediatric cardiovascular ICU between January 1, 2013, and November 13, 2017.

Patients: All patients less than or equal to 18 years old who received IV acetaminophen. Mechanical support devices excluded.

Interventions: None.

Measurements and Main Results: Physiologic vital sign data were analyzed in 5-minute intervals starting 60 minutes before through 180 minutes after completion. Hypotension defined as mean arterial pressure −15% from baseline and relative hypotension defined −10%. Only doses where patients received no other medications, including vasopressors, within the previous hour were included. *t* test and a correlation matrix were used to eliminate correlated factors before a logistic regression analysis was performed. Six-hundred eight patients received 777 IV acetaminophen doses. Median age was 8.8 months (interquartile range, 2–62 mo) with a dose of 12.5 mg/kg (interquartile range, 10–15 mg/kg). Data were normalized for age and reference values. One in 20 doses (5%) were associated with hypotension, and one in five (20%) associated with relative hypotension. Univariate analysis revealed hypotension associated with age, baseline mean arterial pressure, and skin temperature ($p = 0.05$, 0.01, and 0.09). Logistic regression revealed mean arterial pressure ($p = 0.01$) and age ($p = 0.05$) remained predictive for hypotension.

Conclusions: In isolation of other medication, a hemodynamic response to IV acetaminophen has a higher prevalence in critically ill children with cardiac disease than previously thought and justifies controlled studies in the perioperative and critical care setting. The added impact on individual patient hemodynamics and physiologic instability will require further study. (*Pediatr Crit Care Med* 2019; 20:527–533)

Key Words: congenital heart defects; critical care; drug-related side effects and adverse reactions; hemodynamics; patient generated clinical data; pediatric

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Acetaminophen is ubiquitously used as an antipyretic and as part of a multimodal analgesic regimen in many postsurgical care units (1, 2). After the parenteral formulation gained approval by the U.S. Food and Drug Administration in November 2010 for the treatment of acute pain and fever in children and adults, it has been frequently administered IV to patients undergoing major surgery and to critically ill patients in whom enteral routes may not be possible (3–5). Although widely believed to be safe and free of adverse effects, the hemodynamic effects of this formulation are largely understudied especially in pediatric patients. There is a growing body of literature in adult critical care settings raising concern regarding the association of IV formulations of acetaminophen and transient hypotension, especially significant decrease in systolic and/or mean arterial pressure (MAP), and all agree that such effects are underreported (6–14). This may be

most relevant to certain patient subgroups, for example, postoperative cardiac surgical patients, in whom maintenance of hemodynamic stability is important to improved recovery. We hypothesize that there are significant hemodynamic effects, including hypotension, after IV acetaminophen administration in the critically ill pediatric patient population. Our primary objective was to assess the prevalence of significant hemodynamic effects following IV acetaminophen administration in a large pediatric cardiovascular ICU (CVICU) population using high-fidelity continuous vital sign collection.

MATERIALS AND METHODS

This study was conducted under an Institutional Review Board protocol approved by Baylor College of Medicine, and the need for written consent was waived. Retrospective electronic medical records were obtained for all patients who received at least one dose of IV acetaminophen while admitted to the CVICU of Texas Children's Hospital from January 1, 2013, to November 13, 2017, between birth and 18 years old regardless of diagnosis. Patients supported on mechanical support devices were excluded including extracorporeal membrane oxygenation, ventricular assist devices, or continuous renal replacement.

Vital signs were measured using standard ICU bedside monitors (GE B850). The Sickbay platform (Medical Informatics Corp, Houston, TX) was used to "continuously" capture data from all the bedside patient monitors in the unit over the course of the study. Captured vital signs included heart rate (HR), respiratory rate (RR), systolic blood pressure, temperature, and oxygen saturation. All vital signs were sampled at 0.5 Hz (every 2 s) and stored on the Sickbay system located in the data center of the institution. Data analysis was completed using Matlab (The Mathworks, Natick, MA). This methodology has been used in previously published reports comparing continuous hemodynamic data with events such as medication administration with validated results as described below (15). The vital signs were collected and analyzed for a window of time from 60 minutes before the start of dose to 180 minutes after the start of the dose infusion to account for the medication half-life, time to onset, and to also include an extended block of vital sign analysis after any possible interventions. For notational convenience, the infusion starting time is the origin (0 min) of the time axis. The time window was broken into the baseline interval which covers from –60 to –10 minutes. The last 10 minutes prior to the start of infusion were discarded from the analysis for any inaccuracies in the documentation of the start time as inputted by the bedside nurse via manual entry. This is acceptable protocol envelope for documentation of which our nursing policy dictates no further allowance than 30 minutes. During the time study specified, our institution was using only one preparation of acetaminophen for injection, Ofirmev (Mallinckrodt Pharmaceuticals, Staines, United Kingdom) (16), and was dosed by protocol in a routine scheduled manner for postsurgical patients for the first 48–72 hours. Following recommended prescribing information, the IV acetaminophen dose was administered over 15 minutes, vital signs were continuously collected after the start of the infusion. A 5-minute nonoverlapping moving average was applied to filter noise and other high-frequency components that are not of interest for this study.

To allow for comparison with previous reports in the literature, a hypotensive reaction to the IV acetaminophen infusion was defined as a decrease in MAP of at least 15% from patient baseline (20) within the first 60 minutes as described by the published maximal effect (C_{max}) (17). Due to the fact that clinically important decreases in MAP in this patient cohort could also include those with greater than or equal to 10% drop from baseline, we have included those defined as "relative" hypotensive events.

To account for the heterogeneity of the study population (age 0 to ≤ 18 yr old), age was log-transformed prior to analysis and acetaminophen dose was normalized by weight. Additionally, measurements of weight, MAP, HR, and RR were controlled for age by subtracting the median value of the measure obtained from healthy age-matched population shown with a solid line in **Figure 1** created from normal values for reference (18, 19). These steps allowed the separation of the natural confounding effects of age on these data.

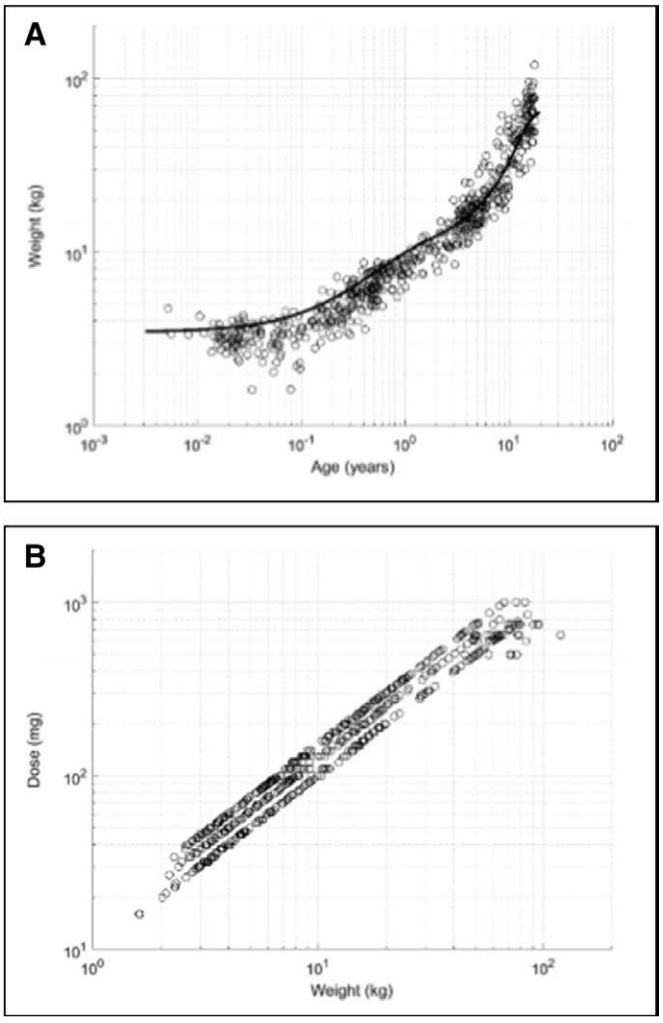

Figure 1. The distributions of age (**A**) and weight (**B**) versus dose of acetaminophen which reveal high correlation between these three variables.

TABLE 1. Characteristics of 608 Patients

Variable	f (%); Median (IQR)
Post surgical	571 (94)
Male	359 (59)
Race	
White	463 (77)
African American	76 (11)
Asian	29 (2.5)
Other/not noted	40 (9.5)
Age (mo)	8.8 (2–62)
Average dose (mg/kg)	12.5 (10–15)

IQR = interquartile range.

A control dataset was identified for each patient which consisted of 60 minutes of continuous physiologic measurements recorded at least 6 hours prior to the study dose. To avoid confounders, data were filtered to only include those IV acetaminophen doses where patients received no other medications including vasoactive medications 1 hour before or 1 hour after administration. Medications given in the operative suite were excluded from both the study and control data. The difference in hemodynamics observed in the control and study data was then quantified, with each subject serving as their own control. Since hemodynamic perturbations can occur spontaneously, we compare the baseline vital sign distribution observed in the control data with the vital sign distribution observed in the time period adjacent to the documented acetaminophen dose. Nonphysiologic changes in systolic blood pressure, that is, due to the flushing of arterial catheters, were filtered out prior to data analysis.

RESULTS

Overall, 1,676 patients received 9,298 doses of IV acetaminophen in the time period studied. After filtering for any other medications including vasoactive medications 1 hour before or after acetaminophen doses, 608 patients received a total of 777 doses of IV acetaminophen and had continuous and uncorrupted vital sign data for evaluation. Characteristics of the patient cohort are found in **Table 1**. Ninety-four percent of the cohort received IV acetaminophen following a surgical procedure. Median age was 8.8 months (interquartile range [IQR], 2–62 mo) with a median dose 12.5 mg/kg (IQR, 10–15 mg/kg). Distributions of age, weight, and dose are illustrated in Figure 1 which also reveal the high correlation between these three variables. The distributions of weight, MAP, rather, and RR versus age are shown in **Figure 2**. These vital signs are the respective averages of the raw signals measured during the baseline interval of time. To differentiate any difference in response to the first dose of IV acetaminophen exposure versus subsequent doses, those doses were analyzed separately. With the exclusion

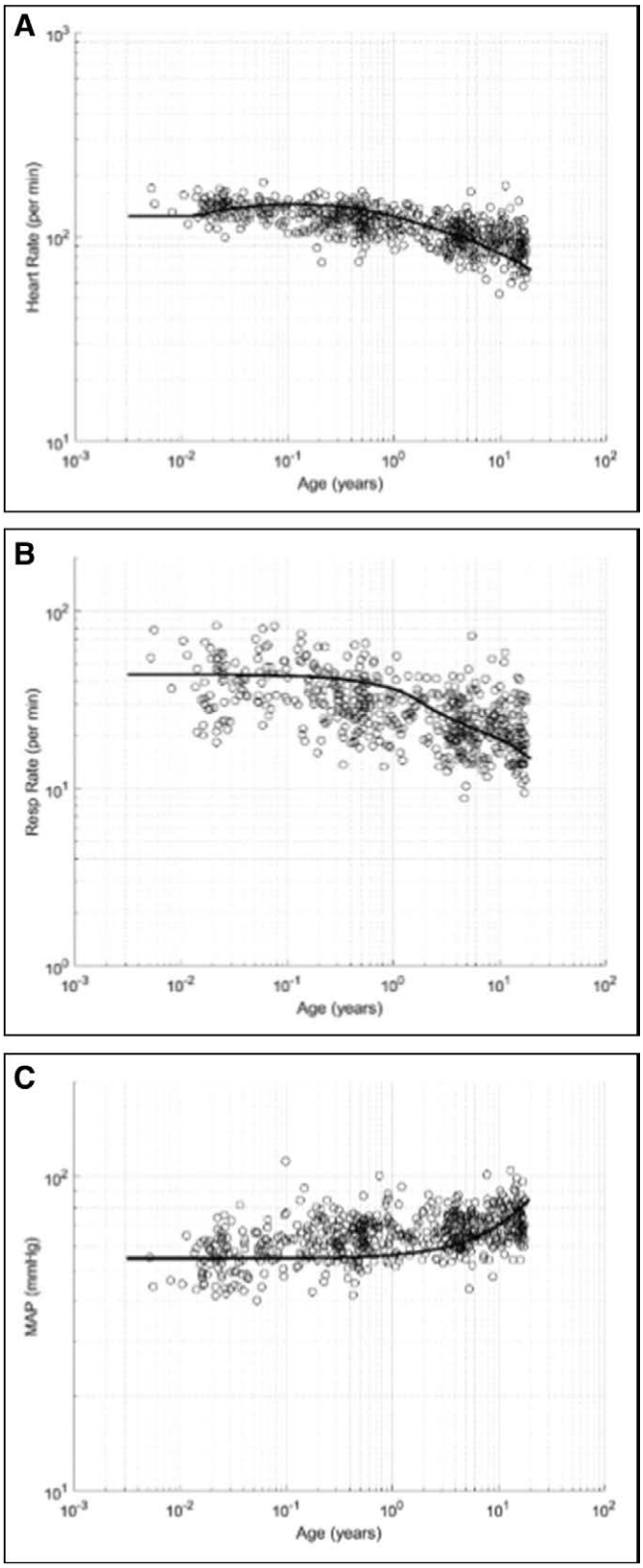

Figure 2. The distributions of heart rate (**A**), respiratory rate (**B**), and mean arterial pressure (MAP) (**C**) versus age. These are the respective averages of the raw signals measured during the baseline (control). The median value of a healthy population as a function of age (*solid line*).

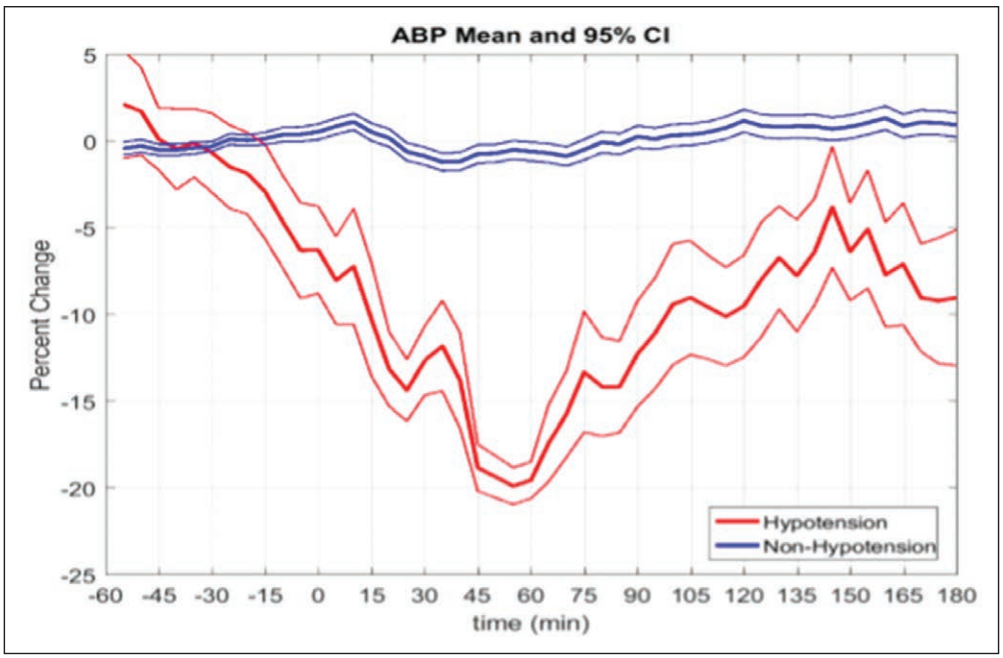

Figure 3. Mean percent change of mean arterial pressure (ABP) from baseline as a function of time (with 95% CI). *Red* depicts drop in MAP which is sustained to greater than 15% for up to 30 min. *Blue line* depicts those doses without MAP drop.

of concomitant medications, there was a low number of "first doses" available for analysis, and no difference in response was found. Most reported analyses are patients' subsequent exposure.

One in 20 IV acetaminophen administrations (5%) was associated with hypotension, and one in five (20%) was associated with relative hypotension. **Figure 3** offers a visualization of the mean percent change of MAP from baseline as a function of time (with 95% CI). The red line depicts drop in MAP which appears to be sustained greater than or equal to 15% from baseline for up to 30 minutes before recovery back to baseline. For the time period –60 to –30 minutes, there is a large variance in the response that covers 0% change in MAP. This wide variance and small relative change in MAP prior to the administration of the IV acetaminophen preclude us from saying that the change is significant an hour before the administration. The CI only starts to significantly change at –30 minutes, which is within the range where there exists documentation envelope of the taken time for the medication administration. The distribution of the MAP percent changes is displayed in **Figure 4*A*** along with the distribution of MAP change per interquartile range of the baseline data in **Figure 4*B***. These plots facilitate the visualization of how the 15% drop threshold relates to the statistical occurrence of such reactions with respect to the intrinsic variance of the baseline data. The change is at least one time the IQR of the baseline data, meaning that it is outside the 75th percentile.

The possible association between several physiologic factors and acetaminophen-induced hypotension is summarized in **Table 2**. This contains results from *t* tests for the difference in means. Univariate analysis revealed hypotension was associated with age, baseline MAP, and skin temperature (p = 0.05, 0.03, and 0.04). Concerning gender, the results reflect Fischer's exact test for the respective contingency tables. This categorical variable does not show significant association with hypotension reaction. The correlation coefficients among age, MAP, and skin temperature were computed, and these variables do not exhibit high correlation (coefficients < 0.2). Thus, all three variables were used for logistic regression analysis. Those results are shown in **Table 3**. After logistic regression analysis, "younger" patients and those with slightly (+1.5%) elevated baseline from reference range MAP experience more hypotension (–15% drop) after IV acetaminophen administration.

With respect to possible intervention required after hypotension, any medications that were administered 60 minutes after IV acetaminophen were evaluated. Of those patients who had hypotension after IV acetaminophen, 16% received medications that reflect the need to increase MAP including initiation of a vasoactive medication including epinephrine or vasopressin via continuous infusion and/or the addition normal saline bolus (≥ 10 cc/kg), albumin bolus (≥ 10 cc/kg).

DISCUSSION

A significant prevalence of hypotensive response to IV administration of acetaminophen in this population of critically ill children with underlying cardiac disease was demonstrated and can be clinically relevant requiring intervention. The literature with respect to the acute side effects of IV acetaminophen in the critically ill population is limited, especially in the pediatric population. In 2016, Cantais et al (20) reported in a small numbered, but multicenter study that 54% of adult ICU patients experienced greater than or equal to 15% change in MAP and 35% of those patients required intervention. Recently, Schell-Chaple et al (21) reported in a placebo-controlled study of 40 adult patients that IV acetaminophen offers only modest fever reduction in critically ill patients, but also reported clinically important reductions in blood pressure. Kelly et al (22) reported a prevalence of hypotension of one in eight doses in adults compared with enteral dosing. Interpreting this into clinical practice, hypotensive events are common following parenteral administration of IV acetaminophen in the adult population and may be underrecognized or more likely underreported as agreed by Duncan et al (10)

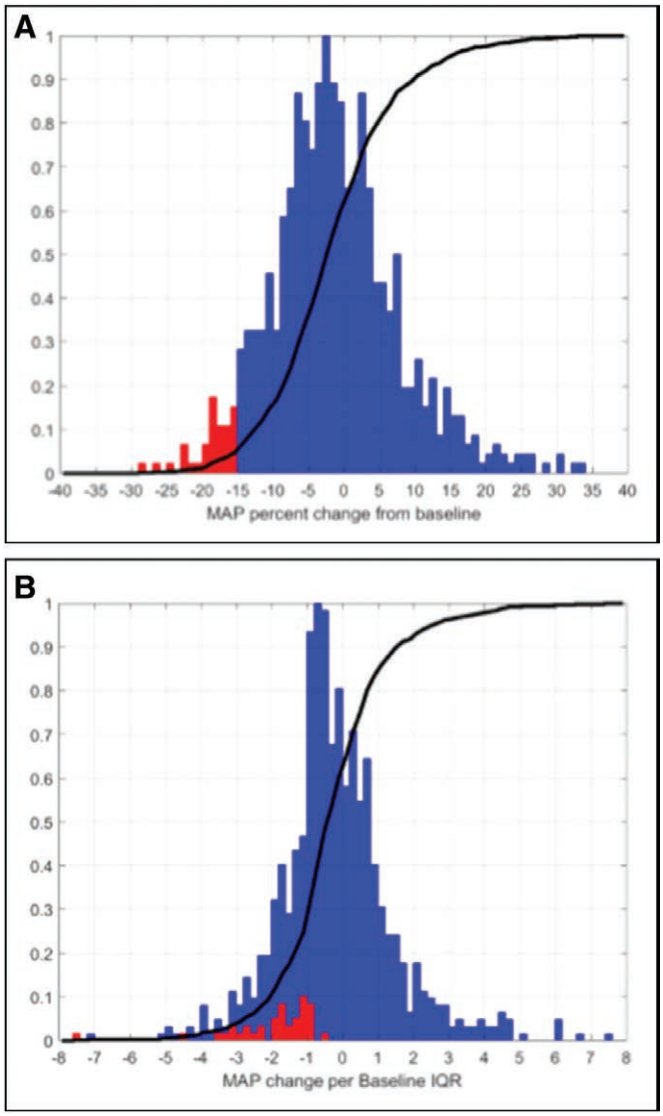

Figure 4. A, The distribution of the mean arterial pressure (MAP) percent changes at 60 min for the acetaminophen doses. Fifteen percent decrease in MAP (*red*) as related to population. **B**, The distribution of MAP change per interquartile range (IQR) of the baseline data 15% decrease in MAP (*red*) as related to population.

who also reported hemodynamic instability with IV acetaminophen dosing in an adult ICU population. The manufacturer lists small pediatric studies reported for patients with fever receiving IV acetaminophen, and hemodynamic effects including hypotension were listed as moderate adverse events (23). A recent case report describes profound hypotension and cardiac arrest in a child without anaphylaxis following IV acetaminophen and could not be attributed to any other clinical factors (24).

With the novel approach to analyze an enormous amount of continuous hemodynamic data including millions of beat to beat systolic blood pressures surrounding recorded medication administration in a pediatric CVICU, we can correlate hemodynamic changes with medication records. Important to note, in the ICU setting where multiple medications are given simultaneously, it is difficult to isolate associated hemodynamic changes away from confounders including other medication administrations temporally related to each other. By evaluating hemodynamic changes after IV acetaminophen in complete isolation of all other medications, we have collected a robust dataset. This prevalence study eliminated any potential confounders from a pharmaceutical interaction. As such, the dataset may be representing a "lower" acuity cohort (i.e., receiving no other medications including vasoactives within the 120-min window surrounding IV acetaminophen administration), and it may be inferred that higher acuity patients may show an exaggerated effect. Future analysis will include patients undergoing titration/escalation of vasoactive temporally related to IV acetaminophen administration.

The exact mechanism whereby IV acetaminophen induces hypotension is uncertain and has yet to be clarified (25). Some speculate that the excipients of IV acetaminophen including cysteine may play a role. Studies in hypertensive humans and animal models of hypertension have shown that N-acetylcysteine, a stable cysteine analogue, lowers blood pressure by means of lowering systemic vascular resistance (SVR) (26). Decreases in cardiac index and drops in SVR have also been reported in critically ill adults following the administration of both acetaminophen and acetaminophen-related compounds as shown by Krajčová et al (27) in a cross-over study with six adult patients measuring data with in situ pulse wave contour cardiac output monitors. The possibility that cardiac output is directly reduced with IV acetaminophen administration would be clinically important especially in fresh postoperative pediatric cardiac patients including cardiopulmonary bypass. The hypotensive effect of IV acetaminophen has been speculated to be due to the separate effect of the stabilizing compound, mannitol, that is found in many current formulations of IV acetaminophen. This notion is supported by knowledge that mannitol can, even in small quantities, cause episodes of transient hypotension. As acetaminophen has negligible solubility in aqueous solutions, the commercially available IV formulations contain mannitol (up to 3.91 g/100 mL acetaminophen) as a stabilizing ingredient (16). However, attempting to separate the effects of mannitol diluent, a triple cross-over study from 2016 using healthy volunteers reported that IV acetaminophen caused a transient decrease in blood pressure immediately after infusion, and these effects were not seen with mannitol or normal saline as comparisons (28). The study, as would be expected, did not included pediatric patients who may have a more dramatic response to even small amounts of diluent. The aim of our study was to identify an association between IV acetaminophen and hemodynamic effects to pediatric CVICU patients and report prevalence and thus cannot establish causality.

In our analysis, younger patients were at higher risk for IV acetaminophen-induced hypotension. Critical illness may change pharmacokinetics, especially in younger patients (29, 30). Pharmacokinetics studies have admittedly enrolled very few neonates and young children and thus those populations may be at particular risk (17). Allegaert et al (8) described that size (as measured by weight) was an important covariate for determining acetaminophen clearance in neonates and that age

TABLE 2. Univariate Analysis

Variables	95% CI	*p*
Log age	(−0.94 to −0.02)	0.047
Male gender	(0.30–1.13)	0.120
Weight—reference weight	(−1.62 to 1.34)	0.545
Dose/weight	(−0.77 to 0.84)	0.450
MAP—reference MAP	(6.99–13.4)	0.027
HR—reference HR	(−6.65 to 6.67)	0.260
RR—reference RR	(−6.98 to −0.76)	0.378
Temperature 1 (central)	(−0.68 to 0.41)	0.306
Temperature 2 (skin)	(−2.34 to 0.01)	0.043

HR = heart rate, MAP = mean arterial pressure, RR = respiratory rate.

has a greater contribution after neonatal life, so that both age and size contributed to 91% of clearance variance throughout childhood in that study (31). There is the additional consideration that IV acetaminophen may cause harm in the low body weight elderly adults a correlate to our younger and failure to thrive patients, especially in the CVICU, who may lack sufficient skeletal muscle (glutathione stores) to metabolize the higher levels of acetaminophen attained from the IV formulation (13).

In the univariate analysis, temperature measured at the skin was significantly higher in those who had hypotensive events after IV acetaminophen administration perhaps speculating vasodilation or decreased SVR. Vasodilation in healthy volunteers with increased skin blood flow, and this physiologic mechanism may be consistent with our findings from skin temperature probes (28). If increased SVR is associated, then one would assume that critically ill patients may be at greater risk of IV acetaminophen-induced hypotension as they may be less likely to be able to autoregulate vascular tone (29).

The baseline MAP elevation initially shows a higher risk of blood pressure drop below the 15% threshold. At first interpretation, this may seemingly not reveal a clinically relevant finding. However, the initial mean elevation of MAP was +1.5%, and the defined threshold in this study was –15% such that a neonate with MAP of 45 mm Hg (+1.5% reference range) initially would still drop to 38 mm Hg or more after IV acetaminophen administration signally, a potentially dangerous event in a fragile infant after cardiac surgery. Other explanations for drop in MAP many include the treatment of pain or fever; however, a concomitant drop in HR and RR would also have been recorded which was not associated. In the presence of unmanaged pain, most patients would manifest tachycardia and the resolution of that tachycardia once pain is managed. In this dataset, significant heart rate "change" was not associated with IV acetaminophen administration. There may be patient experience where HR and BP changes are isolated in response to pain/inadequate analgesia which may not be represented. This study did not demonstrate any relation between hemodynamic changes and antipyretic action of acetaminophen in that the central temperature change was not significantly different between those who had hypotension and those who did not. Since these measures were not significantly associated with a hypotensive reaction, it is unlikely that this mechanism is the primary cause of the observed drop in MAP.

In this broad range study including pediatric cardiac surgical patients, the rate of hypotensive episodes is much greater than the rate (1:1,000–1:10,000) quoted by the manufacturer (16, 23). This highlights the difference in physiology between healthy subjects used for pharmacokinetics studies before licensing and the critically unwell. It raises the question whether IV acetaminophen-induced hypotension is related to ICU patient morbidity and the outcome of critically ill patients only previously studied in adults (30, 32).

To improve patient safety in our ICUs, preventive measures should be targeted primarily on the most severely ill patients, and thus, increased awareness around medication events may prevent unplanned, untoward iatrogenesis. The emerging high throughput technology and continuous data collection described in this study may uncover subacute clinical changes heralding more clinical importance than previously recognized. These effects are clinically as important given how frequently the drug is administered IV to hospitalized pediatric patients.

With evidence of higher prevalence of physiologic effects of IV acetaminophen, its use for analgesia in the postoperative setting especially in younger age groups should be limited and the decision to change to enteral formulation as soon as possible justified.

This retrospective study has limitations including a lack of subgroup analysis including procedure or diagnosis. Future research efforts will analyze and define more at-risk populations within the pediatric cardiac ICU and would be necessary to determine causality. Although this study has its limitations,

TABLE 3. Logistic Regression

Variables	Coefficient (Per SD)	*p*	Patients With MAP Drop, Median (IQR)	Patients Without MAP drop, Median (IQR)
Log age	−0.32	0.05	−1.27 (−2.59 to 0.73)	−0.15 (−1.72 to 1.64)
MAP—reference MAP	+0.39	0.01	9.37 (4.66–14.36)	4.87 (−1.89 to 11.86)
Temperature 2 (skin)	−0.09	0.09	34 (30–37)	34 (31–36)

IQR = interquartile range, MAP = mean arterial pressure.

its findings are still important for understanding the potential prevalence of this the effect.

CONCLUSIONS

There is a significant hemodynamic response to IV administration of acetaminophen in a population of critically ill children with underlying cardiac disease and justifies controlled studies in the pediatric perioperative and critical care setting. The results have important implications for daily clinical practice and the management of pain and fever in the critically ill infant and child. The added impact on individual patient hemodynamics and physiologic instability will require further study.

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