JPPT | Single-Center Retrospective Study

Incidence of Hemodynamic Changes Following Intravenous Acetaminophen Administration in Critically Ill Pediatric Patients

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OBJECTIVE Acetaminophen is a commonly administered analgesic and antipyretic medication that is generally well-tolerated. Recent studies in critically ill adults and subsets of pediatric patients with underlying cardiac disease identify an association between adverse hemodynamic effects with intravenous (IV) acetaminophen. However, the data may not be generalizable to a broader population of critically ill children. The objective of this study was to determine the incidence of hemodynamic changes associated with IV acetaminophen administration in critically ill pediatric medical-surgical patients.

METHODS This was a retrospective observational study of all patients 18 years of age and younger who received at least 1 dose of IV acetaminophen in a pediatric intensive care unit at a quaternary care medical center, between July and December 2018. The primary outcome was the incidence of hypotension, defined as a decrease in mean arterial pressure (MAP) by at least 15% from baseline. Potential risk factors for IV acetaminophen-associated hypotension were assessed.

RESULTS A total of 212 patients received 492 doses of IV acetaminophen. The primary endpoint of hypotension occurred following 24% of doses. An intervention for hypotension, primarily fluid resuscitation, was required for 11.9% of the dose-associated hypotension events. Patients receiving vasoactive infusions had more frequent dose-associated hypotension events than those not receiving infusions; however, no other potential risk factors were identified.

CONCLUSIONS The incidence of hypotension observed in critically ill pediatric patients after IV acetaminophen administration is clinically relevant. Large placebo-controlled trial and further study of the risk factors and mechanism of this hemodynamic change are warranted.

ABBREVIATIONS AHA PALS, American Heart Association's Pediatric Advanced Life Support; AL, arterial line; IV, intravenous; MAP, mean arterial pressure; NIBP, noninvasive blood pressure; PICU, pediatric intensive care unit; pSOFA, pediatric sequential organ failure assessment; UCSF, University of California, San Francisco.

KEYWORDS acetaminophen; adverse reactions; blood pressure; critically ill; drug-related side effects; hemodynamics; pediatrics

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Introduction

Acetaminophen is a commonly used antipyretic and non-opioid analgesic agent in pediatric and adult patients. Other than the well-described dose-dependent hepatotoxicity, acetaminophen is considered safe with minimal side effects. The manufacturer's prescribing information provided for intravenous (IV) acetaminophen states that hypotension may occur in at least 1% of adult and pediatric patients.[1] Results from observational and randomized controlled trials report a wide range of 5% to 56% of hypotension rates after acetaminophen doses.[2–11] The differences in results may be because of the heterogenous definitions of hypotension, the choice of blood pressure measurement method, and the time difference between administration and blood pressure measurement. These studies were also primarily performed in critically ill adult patients. Many also had small sample sizes, thus difficulty in achieving statistical power.[3]

A recent study of critically ill pediatric patients with underlying cardiac disease found that 5% of IV acetaminophen administrations were associated with hypotension, defined as a decrease in mean arterial pressure (MAP) of at least 15% occurring within 180 minutes after the completion of a 15-minute IV infusion. The authors also reported a 20% occurrence rate of dose-associated mild hypotension, defined as

Table 1. Baseline Patient Demographics

Parameter	Value, N = 212 patients (492 doses)*
Patient age, median (IQR), yr	6.2 (1.7–12.9)
Male, n (%)	115 (54.2)
Body weight, median (IQR), kg†	23.4 (12.1–47.2)
Critical care indication, n (%)	
Medical	96 (45.3)
Surgical	116 (54.7)
pSOFA score, median (IQR)‡	3 (1–4.5)
Acetaminophen dose, median (IQR), mg/kg*	15 (12.6–15)
Dose frequency, n (%)*	
Once	19 (3.9)
Scheduled	387 (78.7)
As needed	86 (17.6)
As-needed dose indication, n (%)*	
Pain	34 (39.5)
Fever (≥38.5°C)	12 (13.9)
Pain and fever (≥38.5°C)	40 (46.5)

IV, intravenous; PICU, pediatric intensive care unit; pSOFA, pediatric sequential organ failure assessment

* Acetaminophen dose, frequency, and as-needed dose indication are shown per all doses (N = 492), whereas other parameters are shown per number of patients (N = 212).

† Body weight used for dosing IV acetaminophen.

‡ The pSOFA score was calculated within 24 hours of PICU admission. The score predicts in-hospital mortality rate in a PICU and has a range of 0 to 24, with higher scores indicating worse outcomes.[13,14]

a decrease in MAP by at least 10%. This study only included hemodynamic response measurements to IV acetaminophen doses when no other medications were administered before or after the dose, including vasoactive medications. While this study design minimizes the possibility that other medications are leading or contributing to the hypotension event, it does not accurately reflect the hemodynamic instability that is observed in critically ill children. Therefore, the results are only applicable to a specific pediatric population of patients with congenital heart disease.[6]

With limited data in pediatric patients, it is difficult to determine the generalizability of the hemodynamic effect of IV acetaminophen in critically ill pediatric patients. Therefore, the objective of this study was to determine the incidence of hemodynamic changes associated with IV acetaminophen administration in critically ill children admitted to a pediatric intensive care unit (PICU) at a quaternary care academic medical center.

Materials and Methods

Study Setting and Population. This was a single-center, retrospective observational cohort study of patients 18 years and younger admitted to the PICU at the University of California, San Francisco (UCSF) Benioff Children's Hospital, San Francisco who received at least 1 dose of IV acetaminophen from July 1, 2018 to December 31, 2018. Patients requiring mechanical circulatory support (i.e., extracorporeal membrane oxygenation, ventricular assist device), renal replacement therapies (i.e., continuous renal replacement, intermittent hemodialysis, peritoneal dialysis), or who were pregnant at the time of IV acetaminophen administration were excluded. Doses were excluded if they did not have baseline MAP recorded or had more than 50% of MAP values missing during the observed time frame.

Study Design. Patients who received at least 1 dose of acetaminophen intravenously over 15 minutes during PICU admission were identified and screened for eligibility for analysis from the electronic medical record. All data were collected and stored securely through a web-based Research Electronic Data Capture (REDCap; Vanderbilt University, Nashville, TN) application. Data collected included baseline demographics, such as age, sex, PICU admission indication, and pediatric sequential organ failure assessment (pSOFA) score. Up to 4 IV acetaminophen doses per patient were evaluated, including the time the dose was administered, the dose in milligrams per kilogram, the ordered frequency and indication for as-needed doses. For each dose, the MAP measurement was collected at baseline (within 60 minutes prior to IV acetaminophen administration) and then every hour post-administration for 4 hours. The MAP measurements were obtained from the bedside physiologic monitors (Solar 8000; General Electric, GE Healthcare) via the noninvasive blood pressure (NIBP) device or a transduced arterial catheter system or arterial line (AL). The direct AL blood pressures were preferentially collected over the NIBP measurements when both were present. We also categorized patient

Table 2. Study Outcomes—Incidence of Hypotension

Outcomes	Hypotension (% MAP decrease)	Incidence, (n, %), N = 492 Doses	Incidence, (n, %), N = 212 Patients
Primary	≥15	118 (24)	90 (42.5)
Secondary	≥10	207 (42.1)	138 (65)

MAP, mean arterial pressure

blood pressures by age-normal MAPs as defined in the American Heart Association's Pediatric Advanced Life Support (AHA PALS) reference for vital signs in children.[12]

Body temperatures were collected in the same manner as the MAP data. Any interventions including fluid bolus administration and vasoactive medication infusion titrations were collected for 4 hours following each IV acetaminophen dose. The receipt of other medications that may affect blood pressure, such as vasoactives, antihypertensives, sedatives and analgesics were also collected.

Outcomes. The primary outcome was the incidence of hypotension, defined as a 15% or greater decrease in MAP from baseline within 4 hours of IV acetaminophen administration. Secondary outcomes included the incidence of mild hypotension, defined as a 10% or greater decrease in MAP from baseline; the incidence of age-adjusted hypotension, defined as MAP below the lower bound of normal range per AHA PALS reference for vital signs; change in MAP in millimeter mercury (mm Hg) from baseline; proportion (%) of doses associated with hypotension at each hour for a total of 4 hours post-administration; proportion (%) of hypotensive episodes requiring fluid bolus or vasopressor medication interventions; and potential risk factors for IV acetaminophen-induced hypotension, such as age, baseline MAP, severity of illness measured by the pSOFA score, use of vasoactive medications, and concomitant use of sedatives or opioids.

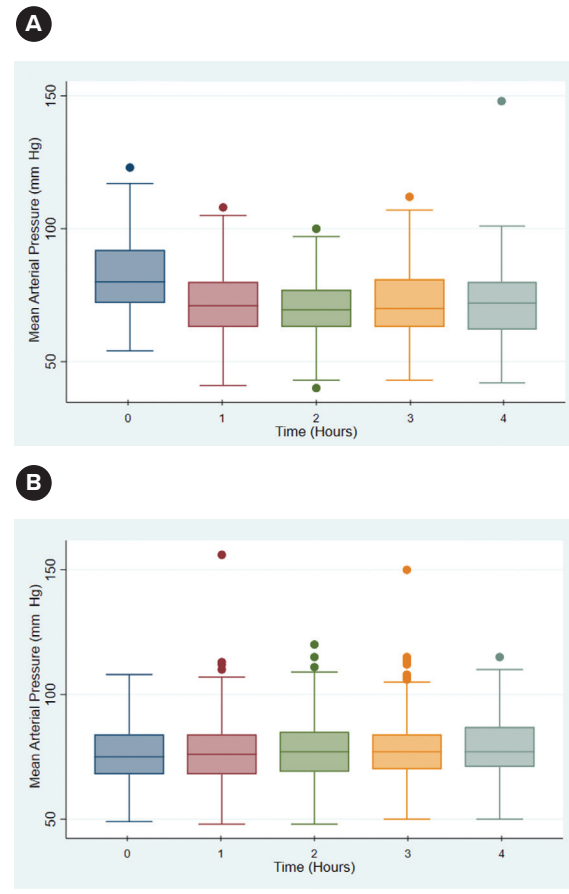
Statistical Analysis. Baseline demographics were analyzed using descriptive statistics. Unpaired continuous variables were analyzed using *t* test or Wilcoxon rank sum test for parametric and nonparametric data. Categorical variables were analyzed using the χ^2 test or the Fisher exact test, where appropriate. The primary outcome of incidence of hypotension was analyzed using descriptive statistics. Statistical data analyses were performed using Stata/IC version 16 software (StataCorp LLC, College Station, TX).

Results

A total of 250 patients received at least 1 dose of IV acetaminophen from July to December 2018. After exclusion, 212 patients who received a total of 492 doses were included in the final analysis (see Supplemental Figure). The median age was 6.2 years old (IQR, 1.7–12.9). Medical and surgical admission indications were evenly represented in our patient population. The median pSOFA score was 3 (IQR, 1–4.5), which indicates a predicted in-hospital mortality rate of less than 3%.[13,14] The median IV acetaminophen dose was 15 mg/kg (IQR, 12.6–15); most administered doses were scheduled doses rather than as-needed doses (78.7%). Other baseline demographics and characteristics are outlined in Table 1.

The primary endpoint of hypotension occurred following 24% (118/492) of IV acetaminophen dose administrations affecting 42.5% (90/212) patients. The secondary endpoint of mild hypotension occurred after 42.1% (207/492) of doses affecting 65% (138/212) of patients (Table 2). 11.9% of the hypotensive events required an intervention, which was primarily fluid resuscitation with crystalloid solutions. Furthermore, the patients with hypotension events had a higher baseline MAP compared with those without hypotension (Figure). Patients who had hypotension events received vasoactive drug infusions more frequently than patients without hypotension events (7.8% vs 1.6%; p = 0.04);

Figure. Median mean arterial blood pressure (MAP) measurements (mm Hg) by hour following a 15-minute intravenous infusion of acetaminophen in 2 patient groups.
(A) Hypotension group (n = 90)*. Boxes represent the upper, median, and lower percentile of MAP values. The adjacent lines represent the minimum and maximum MAP values. The dots represent the outliers of MAP values at a given hourly time frame.
(B) No hypotension group (n = 122)†.



* –15% MAP change.
† No change in MAP by 15%.

Table 3. Potential Patient Risk Factors for IV Acetaminophen-associated Hypotension

Intervention	No Hypotension (n = 122)	Hypotension, −15% MAP change (n = 90)	p value
Patient age, median (IQR), yr	6.3 (2.1–13.1)	5.5 (1.2–12.5)	0.29
Critical care indication, median (IQR), n (%)			
Medical	60 (40.2)	36 (40)	0.18
Surgical	62 (50.8)	54 (60)	
Acetaminophen dose, median (IQR), mg/kg	15 (12.3–15)	15 (14.3–15)	0.18
pSOFA score, median (IQR)	3 (1–4)	3 (1–5)	0.43
Baseline MAP*, median (IQR), mm Hg	75 (70–87)	77.5 (69–90)	0.29
Baseline body temperature (°C), median (IQR)*	37.1 (36.7–38.1)	36.9 (36.6–37.3)	0.096
Fever incidence (≥38°C), n (%)	17 (13.9)	5 (5.5)	0.067
Vasoactive drugs, † n (%)	2 (1.6)	7 (7.8)	0.04
Antihypertensive drugs, † n (%)	0 (0)	2 (2.2)	0.098
Sedatives, n (%)†	21 (17.2)	21 (23.3)	0.27
Analgesics, n (%)†	19 (15.6)	18 (20)	0.40

IV, intravenous; MAP, mean arterial pressure; pSOFA, pediatric sequential organ failure assessment

* Baseline MAP and baseline temperature taken prior to initial IV acetaminophen dose.
† Drugs administered concomitantly within 4 hours of IV acetaminophen dose administration.

however, no other differences were identified (Table 3).

When using AHA PALS age adjusted values to define hypotension, 29.2% of patients (62/212) had hypotension events after IV acetaminophen administration. Patients between the ages of 10 and 18 experienced the highest incidence of hypotension and younger patients tended to develop less hypotension (Table 4).

Discussion

Among critically ill pediatric patients who received at least 1 dose of IV acetaminophen, this study demonstrated a higher incidence of hypotension than previously described in the literature. We found that 24% of IV acetaminophen doses were associated with an episode of hypotension, affecting 42.5% of patients. Of the doses associated with hypotension, approximately 11% of doses required an intervention. In comparison to the pediatric patients with underlying cardiac disease studied by Achuff et al,[6] our study included a broader patient population of general medical and surgical critically ill pediatric patients and were older in age. While Achuff et al[6] evaluated hemodynamic response in patients who received no other medications for the hour before and after the 15-minute IV acetaminophen dose administration, our study examined all doses of IV acetaminophen, regardless of concomitant medications that may also have hemodynamic effects. Concomitant vasoactive medication use was more common in patients with hypotension; yet it was difficult to determine whether IV acetaminophen alone required need for vasoactive medications or if there were other factors. While there are other characteristics of patients that may not have been accounted for, this present study may be more representative of a real-world critical care setting.

The dose events associated with hypotension in this study had a higher baseline MAP. In prior observational and randomized controlled studies, patients with lower blood pressures at baseline were at higher risk for developing hypotension.[5,9] Patients in the older age group also tended to have more hypotension, which calls for further investigation. However, the exact mechanism and risk factors for developing hypotension from IV acetaminophen remains unknown.

One limitation of this study is its retrospective design, where the data available were highly dependent on documentation in the electronic medical record. Pain scores were initially collected for as-needed doses of IV acetaminophen for pain. However, inconsistent documentation of pain scores made it difficult to identify whether the presence of pain and/or the relief of pain with IV acetaminophen were associated with hemodynamic changes in this sample. In addition, 2 sources of MAP measurement data (invasive via AL vs. NIBP) were used because not all PICU patients had an AL in place for invasive hemodynamic monitoring. Arterial line readings are considered the gold standard for measuring accurate blood pressure in critically ill patients. The variability of accuracy between the 2 different methods can over- or underestimate blood pressures. Despite this limitation, data from only 1 measurement method was used for

Table 4. Blood Pressure Measurements Relative to Age Normal MAPs

Age (mo)	Normal MAP Ranges by Age Categories (mm Hg)*	Patients (n, %)	Patients With Baseline MAPs Below Lower Bound of Normal Range (n, %)	Patients With MAPs Below Lower Bound of Normal Range After IV Acetaminophen Doses (n, %)
<1	45–60	0 (0)	0 (0)	0 (0)
1–<12	50–62	35 (16.5)	0 (0)	2 (5.7)
12–<36	49–62	39 (18.4)	0 (0)	1 (2.6)
36–<72	58–69	29 (13.7)	2 (6.9)	3 (10.3)
72–<120	66–72	34 (16.0)	9 (26.4)	13 (38.2)
120–<144	71–79	15 (7.1)	4 (26.7)	9 (60.0)
144–216	73–84	60 (28.3)	19 (31.7)	34 (56.7)
Total		212	34 (16.0)	62 (29.2)

IV, intravenous; MAP, mean arterial pressure

* Per American Health Association's Pediatric Advanced Life Support.

MAP data collection for an individual patient. We were also unable to assess if interventions administered after hypotension episodes were prompted by the decrease in MAP or were ordered for another patient-specific indication. Lastly, we recognize the ambiguity in defining hypotension in the pediatric population and that currently, there is no consensus-driven guideline for specific hemodynamic monitoring in children. More recently, Nahum et al[15] similarly looked at children with septic shock and evaluated hypotension using varying definitions: decrease of blood pressure (mean arterial, systolic or diastolic measurements) relative to baseline and below age normal values. They found that depending on the definition used, the number of hypotension events differed. Therefore, to standardize our definition, we used those for hypotension from previous studies and relied on age-specific MAPs per the AHA PALS guideline.[6,12] Overall, the findings from this study prompt the consideration of monitoring blood pressure after administration of IV acetaminophen as a standard practice, especially in critically ill patients with indications for maintaining target perfusion with specified blood pressure target. The incidence of hypotension from this study and the current literature warrants adding IV acetaminophen administration to the differential diagnosis for hypotension in PICU patients.

Conclusion

The incidence of hemodynamic changes observed in critically ill pediatric patients after IV acetaminophen administration is clinically relevant and is more common than reported in the current prescribing information. This result merits consideration in close blood pressure monitoring and should be included as part of the differential diagnosis workup in critically ill children with hemodynamic instability. Larger placebo-controlled trials and further research is warranted to identify the physiologic mechanism of acetaminophen-associated hypotension as well as potential risk factors to help guide anticipatory monitoring and management of hypotension in this at-risk patient population.

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References

1. Ofirmev [package insert]. Hazelwood, MO: Mallinckrodt Pharmaceuticals, Inc; June 2020.
2. Schell-Chaple HM, Liu KD, Matthay MA, et al. Effects of IV acetaminophen on core body temperature and hemodynamic responses in febrile critically ill adults: a randomized controlled trial. *Crit Care Med*. 2017;45(7):1199–1207.
3. Maxwell EN, Johnson B, Cammilleri J, et al. Intravenous acetaminophen-induced hypotension: a review of the current literature. *Ann Pharmacother*. 2019;3(10):1033–1041.
4. Yaman A, Demir B, Belen FB, et al. Paracetamol infusion-related severe hypotension and cardiac arrest in a child. *Turk J Pediatr*. 2016;58(5):550–553.
5. Allegaert K, Naulaers G. Haemodynamics of intravenous paracetamol in neonates. *Eur J Clin Pharmacol*. 2010;66(9):855–858.
6. Achuff B, Moffett BS, Acosta S, et al. Hypotensive response to IV acetaminophen in pediatric cardiac patients. *Pediatr Crit Care Med*. 2019;20(6):527–533.
7. Krajcova A, Matousek V, Duska F. Mechanism of paracetamol-induced hypotension in critically ill patients: a prospective observational cross-over study. *Aust Crit Care*. 2013;26(3):136–141.
8. Cantais A, Schnell D, Vincent F, et al. Acetaminophen-induced changes in systemic blood pressure in critically ill patients: results of a multicenter cohort study. *Crit Care Med*. 2016;44(12):2192–2198.
9. Kelly SJ, Moran JL, Williams PJ, et al. Haemodynamic effects of parenteral vs enteral paracetamol in critically ill patients: a randomised controlled trial. *Anaesthesia*. 2016;71(10):1153–1162.
10. Ray S, Brick T, Raman S, et al. Haemodynamic changes with paracetamol in critically-ill children. *J Crit Care*. 2017;40(Aug):108–112.
11. Nahum E, Friedman M, Kaplan E, et al. The hemodynamic effect of intravenous paracetamol in children: a retrospective chart review. *Paediatr Drugs*. 2019;21(3):177–183.
12. Samson RA, Schexnayder SM, Hazinski MF, et al, eds. *Pediatric Advanced Life Support: Provider Manual*. Dallas, TX: American Heart Association; 2016.
13. Matics TJ, Sanchez-Pinto LN. Adaptation and validation of a pediatric sequential organ failure assessment score and evaluation of the sepsis-3 definitions in critically ill children. *JAMA Pediatr*. 2017;171(10):e172352.
14. Lalitha AV, Satish JK, Reddy M, et al. Sequential organ failure assessment score as a predictor of outcome in sepsis in pediatric intensive care unit. *J Pediatr Intensive Care*. 2021;10(2):110–117.
15. Nahum E, Weissbach A, Kaplan E, et al. Hemodynamic effects of intravenous paracetamol in critically ill children with septic shock on inotropic support. *J Intensive Care*. 2020;8(14): https://doi.org/10.1186/s40560-020-0430-0