# Haemodynamic changes with paracetamol in critically-ill children.

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**Running title:** Blood pressure falls in children following paracetamol

**Abstract**

**Purpose:** Paracetamol has been associated with a reduction in blood pressure, especially in febrile, critically-ill adults. We hypothesised that blood pressure would fall following administration of paracetamol in critically-ill children and this effect would be greater during fever and among children with a high body surface area to weight ratio.

**Methods:** A 12-month prospective observational study of children (0-16 years) admitted to paediatric intensive care, who underwent pulse contour analysis and received paracetamol concurrently.

**Results:** Mean arterial blood pressure decreased significantly by 4.7% from baseline (95% CI 1.75-8.07%) in 31 children following 148 doses of paracetamol. The nadir was 2-hours post-dose. The effect was pronounced in children with fever at baseline (6.4%, 95% CI 2.8-10%), although this was not statistically significant. There was no simple relationship between this effect and body surface area to weight ratio. The association between a change in blood pressure and changes in heart rate or measured stroke volume was poor; therefore it was likely that a change in the systemic vascular resistance contributes most to this effect.

**Conclusion:** There is a significant but modest reduction in blood pressure post-paracetamol in critically-ill children. This is likely related to a change in systemic vascular resistance.

**Key words:** Paracetamol; Child; Fever; Physiologic monitoring; Critical care

**Introduction:**

Paracetamol is associated with a reduction in blood pressure in critically-ill adults[1-5]. The reported decrease ranges between 7 and 15% from baseline and occurs over the first 2 hours. The haemodynamic mechanism for this blood pressure decrease has been explored using various methods. Some authors have reported a reduction in cardiac output - either due to a reduction in heart rate[6], or due to the diuretic effect of mannitol present in intravenous paracetamol preparations[7]. However, there is also evidence to suggest that the reduction in blood pressure is related to a decrease in the systemic vascular resistance (SVR): (a) peripheral blood flow increases when measured using laser Doppler flowmetry in febrile patients[8]; and (b) a reduction in SVR has been observed following paracetamol administration when measured in a randomised controlled trial of healthy volunteers, but not after an equivalent dose of mannitol alone was given[7].

Although the use of paracetamol has been associated with a modest reduction in mean blood pressure in neonates[9], the haemodynamic effects have not been evaluated in critically-ill children. If the phenomenon is based on a reduction in SVR, this effect may be greater in children, because they have a larger body surface area to weight (BSA-to-weight) ratio than adults.

The hypotensive effect of paracetamol has been most studied during fever[1 2 8]. Fever is an increase in the hypothalamic temperature 'set-point' following pathogen invasion or tissue damage. The hyperthermia of fever is produced by an increase in metabolic rate, and a reduction in surface heat loss, through peripheral vasoconstriction. Paracetamol resets this central 'set-point': this opposes heat-conserving vasoconstriction, explaining a fall in both

SVR and blood pressure. However the haemodynamic impact of paracetamol may be complex given that heart rate also increases with temperature[10].

We hypothesise that (a) critically-ill children will show a significant reduction in blood pressure following paracetamol administration with a reduction in SVR, and (b) this effect will be greatest in children with fever, and those with higher BSA-to-weight ratio.

**Methods:**

We conducted a prospective observational study of children admitted to our paediatric intensive care unit between October 2014 and October 2015, who (a) underwent cardiac output monitoring via pulse contour analysis (Lidco Rapid, LiDCO Ltd, U.K.) and (b) received one or more dose of paracetamol by any route.

The decision to use cardiac output monitoring was made by the treating clinical team. Mean arterial blood pressure (MABP), heart rate (HR) and stroke volume index (SVI) data were recorded every 3-8 seconds by the cardiac output monitor (variable frequency as data automatically compressed for longer recordings). Data points with an inferior signal (as identified by the monitor - for example when the arterial line was being sampled) were excluded. The pulse contour measurements were calibrated using non-invasive (supra-sternal) continuous wave Doppler ultrasound (USCOM Ltd, Australia) at the start of recording, and every 24 hours.

Haemodynamic data from the hour before paracetamol was given, the hour paracetamol was given and four hours post-paracetamol administration, were compared. As a summary measure, we used the mean of 200 consecutive values of MABP, HR and SVI centred around the hour mark i.e. if data were recorded every 3 seconds, mean values between 5 minutes before (3 seconds x 100 readings) and 5 minutes after the hour were used. In addition, we collected data on the following confounders from the electronic health record: vasoactive drug doses; fluid administered as a bolus of >=5ml/kg; sedation changes, furosemide, mean airway pressure changes (all expressed as increase, decrease or no change) and physiotherapy (expressed as a binary variable).

The data were analysed using multi-level linear regression modelling, with (a) either MABP, HR or SVI as outcome variables; (b) time, expressed as hours from the paracetamol dose (i.e. -1, 0, 1, 2, 3, 4), along with the above confounders as fixed effect variables, and (c) each dose administration and patient as random effect variables. This enabled us to evaluate changes in MABP, HR and SVI in relation to the time from the paracetamol dose, evaluating the effect per dose, per patient. This controlled for the assumption that each patient may not have the same haemodynamic effect with paracetamol as another, and the effect may vary between doses in the same patient. Each patient therefore was their own control, with a comparison made before and after paracetamol.

Change in MABP is either due to HR, SV or SVR (pressure = flow x resistance). Although SVR is calculated by the Lidco Rapid pulse contour analyser, a static central venous pressure is assumed. We do not routinely measure or target central venous pressure in our intensive care unit, especially as femoral venous liens are used preferentially to internal jugular or subclavian venous lines. Therefore we used linear regression to examine the effect of HR and SVI on MABP: from the coefficient of determination (adjusted $R^2$, the proportion of change in MABP explained by the changes in HR and SVI) we inferred the relative effect of SVR on MABP (i.e. $1-R^2$).

To test our two *a priori* hypotheses we added temperature to our model, and analysed children separately according to whether they had a fever (defined as a temperature >38$^{o}$C) at baseline. We similarly analysed children separately according to BSA-to-weight ratio quartiles~~, and those with and without fever at baseline (axillary/oesophageal temperature>=38$^{o}$C at time-points -1 or 0) using a time-point interaction term for both in~~

~~the multi-level regression models~~. Analyses were carried out using Microsoft Excel (Microsoft Corp, WA, USA) and r (ww.cran.r-project.org).

Data were collected as a part of a locally registered service evaluation. Informed consent was not required as only non-identifiable, routinely collected clinical data were used.

**Results:**

Thirty-one children received 148 paracetamol doses during cardiac output monitoring. Median age was 37 months (IQR 18-109 months). One hundred and twenty seven (85%) doses were intravenous (Table 1). Doses ranged from 10-15mg/kg. MABP decreased post-paracetamol, with the nadir at two hours (2 hours post intravenous dose; 3 hours post enteral dose). The mean reduction in blood pressure was small – from 68 to 65 mm Hg; the median reduction was from 67 mm Hg to 64 mm Hg. However the top quartile decrease ranged from 9 mm Hg to 32 mm Hg, a percentage change between 12.5 to 34.8% from baseline. The effect was mostly consistent following intravenous paracetamol, with a more variable change in blood pressure following enteral paracetamol (although the number of enteral doses was relatively small). Systolic blood pressure followed a similar pattern, although diastolic blood pressure was largely unchanged during the time period. (Figure 1)

Following multi-level regression analysis, MABP decreased significantly two hours post-paracetamol by a mean of 4.7% (95% CI 1.8-8.1%; $p<0.05$) i.e. 3.3 mmHg decrease from a mean baseline of 68 mmHg. This decrease was largely secondary to a reduction in systolic blood pressure, which decreases by a mean of 6.9% (95% CI 3.6-10.9%; $p<0.05$) i.e. 7 mmHg decrease from a mean baseline systolic of 101 mmHg. Diastolic blood pressure did not change significantly. HR and SVI both decreased, reaching statistical significance on multi-variable analysis (Table 2).

*Mechanistic explanation of blood pressure changes:* To understand the relative contributions of HR, SV and SVR on the effect of blood pressure, we used a linear regression model, with change in MABP from baseline at two hours as the outcome, and the change in HR and SV over the same period as predictors. A change in SVI significantly predicted a

change in MABP. The adjusted $R^2$ value from this model, which evaluates the proportion of the change in MABP explained by the changes in HR and SVI, was only 5%. By inference therefore, most (i.e. approximately 95%) of the change is blood pressure is related to a change in vascular resistance. When the derived SVRI from the cardiac output monitor (with static central venous pressure) was used in the model, (i.e. change in MABP at 2 hours as the outcome and change in HR, SV and SVR as predictors) the $R^2$ value was 0.84.

*Effect of fever on reduction in blood pressure:* ~~We analysed the pre-specified subgroup of children with fever. Fifty-four children had a fever (≥38°C) at baseline.~~ To analyse the effect of fever we included temperature separately into the multi-level regression model, and analysed the subgroup of doses where children were febrile at baseline (temperature >38°C). Fifty four doses (36%) of paracetamol were given when the children had a fever. Temperature did not have an independent effect on mean blood pressure. With temperature included in the model, the reduction in mean blood pressure at two hours was 5.6% ( 95% CI 1.7-21.6%) – while the mean difference is similar, the confidence intervals are wider given the number of missing data points as temperature is not always measured continuously or hourly. Following multi-variable analysis of the sub-group with fever, the reduction in blood pressure was 4.4% of baseline at two hours (95% CI 1.5-12.3%), which remained statistically significant ($p<0.05$).

*Effect of body surface area to weight ratio on reduction in blood pressure:* When analysed for each quartile of BSA-to-weight ratio, MABP dropped with the lower three BSA-to-weight ratio quartiles post-paracetamol, but not the top quartile, where paradoxically there was no significant change in blood pressure [MABP decrease quartile 1: 5.3% (95% CI 0.9, 10.4%); quartile 2: 4.5% (95% CI 0.3, 10.0%); quartile 3: 6.2% (95% CI 2.1, 11.3%); quartile 4: 1.0%

(95% CI -3.4, 7.1%)]. When tested using BSA-to-weight ratio as an interaction term (as above), there was no significant difference in the effect of paracetamol on MABP between the quartiles ($p>0.05$).

**Discussion:**

Critically-ill children show a significant reduction in their mean blood pressure, with the greatest fall observed 2 hours post-paracetamol administration. This fall is poorly explained by stroke volume and heart rate changes alone, implying a likely role of a change in SVR as the main effector of the fall in blood pressure. This effect is seen in children with and without fever, although paradoxically not in children with the highest BSA-to-weight ratio in our cohort.

While the change in blood pressure is statistically significant, we do acknowledge the overall effect is small: a 4.7% reduction from a mean baseline of 68 mmHg amounts to a drop in blood pressure of just over 3 mmHg. The change in systolic blood pressure is expectedly greater, with a near 7% reduction i.e. a reduction from a mean baseline of 101 mmHg to 94 mmHg. One can question the clinical significance of this. However we noted that for 33/148 doses of paracetamol, a fluid bolus was given within the following 4 hours. Similarly in 7/148 doses, the dose of norepinephrine was increased. This is likely to be a reaction to a change in haemodynamics: either the reduction in blood pressure or the bedside cardiac output data on display (we have not tested the effect of having a persistent display of haemodynamic parameters by the bedside on the number of interventions or outcome).

The time-course of blood pressure changes in our cohort are more prolonged than previously described. Most studies report changes over the first 2 hours only and therefore cannot be directly compared. However in our cohort the nadir of the blood pressure reduction was at 2 hours (and 3 hours if enteral paracetamol was used). Blood pressure does return to baseline by 4 hours post dose. This may be an effect unique to critically-ill

children and needs further exploration. We did not explore any dose related interactions, nor did we correlate the effect to serum levels of paracetamol.

The observed blood pressure effect of paracetamol is likely due to a reduction in vascular resistance, as has been reported in previous adult studies[7, 8]. This is consistent with the hypothesis that paracetamol may release the vasoconstriction induced by fever. However although the blood pressure reduction was greater in children with fever, statistically we were unable demonstrate this difference to be significant. Regardless, the effect may still be the same if paracetamol was used for analgesia: the analgesic effect of paracetamol may be releasing stress induced vasoconstriction. Paracetamol reduces both HR and SV, as well as SVR. The reduction in cardiac index associated with paracetamol has been described previously[6]. The mechanism behind this is unknown: Chiam et al hypothesised that this reduction may be due to SV changes secondary to mannitol used as a stabilizer in most intravenous paracetamol formulations. However in a randomised controlled trial of healthy volunteers, Chiam et al did not observe this effect: cardiac index increased in their experiment with both paracetamol and a dose equivalent mannitol infusion[7]. However the time course of blood pressure change we describe in our patients is different. The haemodynamic effects may also vary between healthy volunteers and in critical illness – paracetamol may have a mild negative inotropic effect, which can only be observed in haemodynamically compromised patients. It is also likely that the variables are not mutually independent e.g. HR reduction may improve cardiac output and blood pressure in the context of diastolic dysfunction. Therefore the effect of each variable may be unique to each individual's haemodynamic state at any given time.

Our data do not support the hypothesis that children a higher BSA-to-weight ratio will have a greater drop in blood pressure due to peripheral vasodilation. This may be due to a lack of power with sub-group analysis. However our hypothesis was based on peripheral vasodilation being the dominant mechanism. Given our findings that blood pressure changes are seen even in those without fever, central vasodilation, potentially from the analgesic effect of paracetamol, may explain the fall in MABP. This needs further exploration.

Our study has some limitations. Although the number of paracetamol doses studied is large, the number of patients is small. Nevertheless the sample size is comparable to similar studies in adults. We do not have control subjects in whom paracetamol was not used. We have not accounted for the dose or serum levels of paracetamol: most doses were intended as 15mg/kg, although weights were often estimated in unplanned admissions. We used the Lidco Rapid pulse contour analyser. Pulse contour analysis offers the advantage of producing a continuous measure, with bedside display and data capture. However pulse contour analysis is not well validated for use in children. In our analysis, trends were more important than the absolute values – each patient was their own control. The measurements were calibrated using suprasternal Doppler measurements. Although suprasternal Doppler measurements of haemodynamic variables has its own drawbacks (inter and intra-user variability), this is increasingly more widely accepted as a monitoring technique[11]. There are also concerns regarding calibration drift with pulse contour analysis: this has been reported as occurring over 2-4 hours[12]. Although not systematically tested, when suprasternal Doppler measurements were taken every 4 hours, the agreement with pulse contour measurements remained relatively stable in our population, even up to 24

hours. We would recommend a prospective study with using an alternative cardiac output measurement technique to verify our findings. Despite this, the blood pressure changes were directly observed from the arterial catheter, and therefore are not subject to the limitations of the cardiac output monitor.

Our observation that blood pressure decreases following paracetamol administration in critically-ill children is consistent with findings in adults. Although the effect size on blood pressure is modest, given the proportion of interventions following each dose of paracetamol, this needs careful consideration in critically children. The recent HEAT trial did not show any harm or benefit of paracetamol when compared to placebo[13]. In children with shock, a change in systemic haemodynamics, or the compensatory treatment, may alter the balance between physiological cost and benefit of paracetamol treatment.

**Declaration of interests:** MJP is chief investigator on an NIHR HTA trial investigating the clinical efficacy of a permissive approach to fever in critically ill children.

**Funding:** We have no conflicts of interest to declare. This work was undertaken at Great Ormond Street Hospital/UCL Institute of Child Health, which received a proportion of funding from the Department of Health's NIHR Biomedical Research Centre's funding scheme.

**Authors' contributions:**

SRay, NK, MJP contributed to the design and conception of the study; SRay, TB and SRaman contributed to data acquisition; SR and PJB analysed the data; SR and MJP drafted the article; all authors revised and approved the final version.

**Acknowledgements:**

We would like to thank Dr Sina Mahjoob for his initial data collection; the nurses of the Paediatric Intensive Care Unit at Great Ormond Street Hospital for their health record management and the children and families of Great Ormond Street Hospital.

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| Patient number | Weight (kg) | Body Surface Area ($m^2$) | Fever (baseline temperature >=38°C) | Age (months) | Diagnosis | Intra-venous doses of paracetamol | Total paracetamol doses |
|---|---|---|---|---|---|---|---|
| 1 | 13.3 | 0.58 | Yes | 38 | RSV bronchiolitis | 6 | 11 |
| 2 | 10.5 | 0.48 | No | 26 | Pneumonia | 1 | 1 |
| 3 | 11.4 | 0.48 | No | 26 | CMV pneumonitis | 4 | 4 |
| 4 | 18 | 0.74 | Yes | 64 | Septic shock, acute appendicitis | 7 | 7 |
| 5 | 4 | 0.24 | No | 1 | Bronchiolitis | 0 | 2 |
| 6 | 15 | 0.64 | Yes | 49 | Streptococcal pneumonia | 9 | 9 |
| 7 | 28.5 | 1.05 | Yes | 123 | Staphylococcal pneumonia | 4 | 4 |
| 8 | 8 | 0.36 | No | 6 | Bronchiolitis | 0 | 3 |
| 9 | 8.8 | 0.41 | Yes | 15 | Pneumonia | 2 | 2 |
| 10 | 65 | 1.71 | No | 156 | Status asthmaticus | 3 | 3 |
| 11 | 9 | 0.33 | Yes | 35 | Septic shock | 10 | 10 |
| 12 | 28 | 0.97 | Yes | 89 | Post cardiac arrest, primary cardiac arrhythmia | 0 | 1 |
| 13 | 8.5 | 0.31 | No | 8 | Pneumonia | 5 | 5 |
| 14 | 10 | 0.47 | No | 14 | Empyema | 1 | 5 |
| 15 | 29.3 | 0.88 | No | 41 | Influenza pneumonitis | 0 | 1 |
| 16 | 3.6 | 0.22 | No | 1 | Group B Streptococcal sepsis | 0 | 3 |
| 17 | 12 | 0.54 | Yes | 30 | Toxic shock syndrome | 3 | 3 |
| 18 | 65 | 1.69 | Yes | 167 | ARDS | 11 | 11 |
| 19 | 14 | 0.57 | Yes | 37 | Aspiration pneumonia | 2 | 2 |
| 20 | 11.2 | 0.48 | No | 31 | Influenza pneumonitis, aplastic anaemia | 11 | 11 |
| 21 | 60 | 1.6 | No | 141 | Renal cell carcinoma | 6 | 6 |
| 22 | 11.11 | 0.52 | No | 22 | Propionic acidaemia | 3 | 3 |
| 23 | 8.1 | 0.35 | Yes | 18 | Metapneumovirus bronchiolitis | 0 | 2 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 24 | 56 | 1.71 | No | 180 | Subdural empyema | 2 | 2 |
| 25 | 72 | 1.86 | Yes | 181 | Crohn's disease | 3 | 3 |
| 26 | 45 | 1.27 | Yes | 147 | Post cardiac arrest | 1 | 1 |
| 27 | 22 | 0.83 | Yes | 95 | Staphylococcal pneumonia | 2 | 2 |
| 28 | 10 | 0.49 | No | 23 | Neutropenic sepsis | 9 | 9 |
| 29 | 17 | 0.76 | Yes | 75 | Haemophagocytic lymphohistiocytosis | 10 | 10 |
| 30 | 5.3 | 0.26 | Yes | 2 | Sepsis, congenital hyperinsulinism | 1 | 1 |
| 31 | 58 | 1.57 | No | 114 | Septic shock | 11 | 11 |

**Table 1: Characteristics of children with cardiac output monitoring given doses of paracetamol**. Weight was either measured or estimated. Body surface area was calculated using weight and height data (as calculated by the Lidco Rapid pulse contour analyser).

| Time-points (hours after paracetamol dose) | Mean arterial blood pressure, mm Hg (95% CI) | % change from baseline (95% CI) | Heart rate, beats per minute (95% CI) | % change from baseline (95% CI) | Stroke volume index, ml/m$^2$ (95% CI) | % change from baseline (95% CI) |
|---|---|---|---|---|---|---|
| -1 | 68.3 (63.5, 73.2) | | 130.1 (121.8, 138.4) | | 32.6 (27.4, 37.7) | |
| 0 | 67.5 (61.2, 73.8) | -1.2 (-3.6, 0.9) | 131.4 (121.0, 141.8) | 1.0 (-0.7, 2.5) | 32.7 (26.6, 38.8) | 0.4 (-2.8, 2.7) |
| 1 | 66.1 (59.8, 72.4) | -3.3 (-5.9, -1.1) | 129.6 (119.2, 140.1) | -0.4 (-2.1, 1.2) | 32.1 (26.0, 38.1) | -1.6 (-5.2, 1.0) |
| 2 | 65.1 (58.8, 71.4) | -4.8 (-7.5, -2.5) | 126.8 (116.4, 137.3) | -2.5 (-4.4, -0.8) | 31.4 (25.3, 37.4) | -3.7 (-7.6, -0.8) |
| 3 | 65.8 (59.5, 72.1) | -3.7 (-6.3, -1.4) | 126.2 (115.7, 136.6) | -3.0 (-5.0, -1.3) | 31.6 (25.5, 37.7) | -3.0 (-6.9, -0.2) |
| 4 | 66.7 (60.4, 73.1) | -2.3 (-4.9, -0.1) | 127.5 (117.0, 138.0) | -2.0 (-3.9, -0.3) | 32.7 (26.6, 38.7) | 0.3 (-3.0, 2.7) |

**Table 2: Changes in mean arterial blood pressure, heart rate and stroke volume index with paracetamol.** Paracetamol is given at time-point 0. Mean values with 95% confidence intervals of mean arterial blood pressure, heart rate and stroke volume index are shown, after correcting for vaso-active drug doses, fluid boluses, furosemide, sedation, mean airway pressure changes and physiotherapy in a multi-level linear regression model. Percentage changes from baseline (time-point -1) with 95% confidence intervals are provided in the adjacent columns. Statistically significant values are shown in red. Blood pressure decreases post-paracetamol, with a nadir at time-point 2, without fully recovering back to baseline. Heart rate also decreases, with a nadir at 3 hours. Stroke volume index decreases with a nadir at 2 hours, but recovers back to baseline within 4 hours.

**Figure 1: Bean plot showing distribution of mean, systolic and diastolic arterial blood pressure following 148 paracetamol doses in 31 patients.** Paracetamol is given at time 0. There is a fall in mean and systolic arterial blood pressure, reaching a nadir 2 hours post-dose (4.7% and 6.9% of baseline respectively). This reduction in blood pressure is significant on multivariate analysis using a multi-level regression model (95% confidence interval 1.8-8.1% for mean and 3.6-10.9% for systolic blood pressure). The diastolic blood pressure however is relatively unchanged.