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Title

Does fluid bolus therapy increase blood pressure in children with sepsis?

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Author Contribution

All authors contributed to the study concept and design; acquisition, analysis, and interpretation of data; drafting and revising the manuscript; and agree to be accountable for the accuracy and integrity of the work.

Running Title

The effect of fluid therapy in septic children.

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Abstract

Objective: To describe the effect of fluid bolus therapy (FBT) on blood pressure in children with sepsis. Secondary outcomes included the effect of FBT on systemic vascular resistance, shock index, and shock phenotype (warm or cold).

Methods: A prospective observational study in the Emergency Department of The Royal Children's Hospital, Melbourne, Australia. Participants were children meeting international consensus criteria for sepsis who received FBT for tachycardia or hypotension. FBT was defined as 10-20ml/kg of 0.9% Saline. Mean blood pressure (MBP) was recorded at baseline, 5 minutes and 60 minutes after FBT. Total systemic vascular resistance (TSVRi), shock index, and shock phenotype were derived for each time point. Hypotension was defined as MBP < 55 + 1.5 x age (years). Warm shock was defined as TSVRi < 800 dyne s cm^{-5} m^{-2}.

Results: Fifty fluid boluses were recorded in 41 children. Median MBP was 78mmHg (interquartile range (IQR) 63 to 86) at baseline, 72mmHg (IQR 60 to 82) at 5 minutes, and 75mmHg (IQR 66 to 84) at 60 minutes. Hypotension was observed in 16% at baseline, 26% at 5 minutes, and 17% at 60 minutes. Median TSVRi was 1580 dyne s cm^{-5} m^{-2} (IQR 1242 to 2206) at baseline, 1254 dyne s cm^{-5} m^{-2} (IQR 1027 to 1787) at 5 minutes, and 1850 dyne s cm^{-5} m^{-2} (IQR 1265 to 2140) at 60 minutes. Median shock index was 1.60 (IQR 1.34 to 1.90) at baseline, 1.49 (IQR 1.25 to 1.76) at 5 minutes, and 1.37 (IQR 1.22 to 1.61) at 60 minutes. Two percent of cases had warm shock at baseline, 12% at 5 minutes, and 2% at 60 minutes.

Conclusions: MBP initially decreased following FBT for paediatric sepsis, returning towards baseline over the subsequent 60 minutes. The utility of FBT for increasing MBP and its effect on patient centred outcomes in children with sepsis warrants further exploration.

List of key words:

Sepsis; Fluid Therapy; Blood Pressure; Vascular Resistance; Child

Introduction

In adults and children with sepsis and impaired tissue perfusion, fluid bolus therapy (FBT) is the initial recommended treatment.[1, 2] The rationale for FBT administration is to increase tissue perfusion by increasing cardiac output (CO).[3] Tissue perfusion is directly proportional to the pressure gradient across capillary beds (mean blood pressure (MBP) – central venous pressure (CVP)), and inversely proportional to vascular resistance.[4] Current international treatment guidelines for paediatric sepsis suggest administering FBT to restore normal MBP for age,[1] where the underlying modifiable determinants of MBP are CO and systemic vascular resistance (SVR) (MBP = CO x SVR).

In children, limited data are available regarding the effect of FBT on MBP and SVR. Gelbart et. al. systematically reviewed the effect of FBT on multiple outcomes, including changes in physiological variables, in hospitalized children with severe sepsis.[5] Eight studies were identified, none of which assessed the effect of FBT on MBP or SVR. Studies involving mechanically ventilated, hemodynamically stable children undergoing elective neurosurgical and cardiac procedures have shown limited changes in MBP following FBT, with none reporting changes in SVR.[6-8] The effect of FBT on MBP is important, as this is often used as a therapeutic end-point to titrate FBT, and excessive FBT is associated with increased morbidity and mortality in critically unwell children.[9]

Glassford et. al. systematically reviewed the changes in MBP in response to FBT in adults with sepsis.[10] In 33 studies, the median increase in MBP immediately after FBT was 7

mmHg, and after 60 minutes was 3 mmHg compared to baseline. The associated changes in SVR were unknown.

Shock index (heart rate / systolic blood pressure) has been proposed as an early marker of disease severity in children with sepsis, and shock index changes in response to therapy as a predictor of clinical outcome.[11-13] However, variable age-based cut-off values between studies and conflicting evidence for identification and prognostication of septic children have limited its clinical utility.

The primary aims of this study was to measure changes in MBP in the first hour following FBT in children with sepsis. Secondary aims included monitoring changes in total systemic vascular resistance index (TSVRi), shock index, and shock phenotype (warm or cold shock) over the study period.

Methods

The study was designed as a prospective observational cohort study. The study setting was the Emergency Department (ED) of The Royal Children's Hospital, Melbourne, Australia; a tertiary-level dedicated paediatric hospital with an annual ED census of >90 000 children. The study was part of a project examining multiple physiological changes following FBT in children with sepsis.[14] Written informed consent from parents and / or study participants was obtained prior to enrolment.

Inclusion criteria were: clinically suspected sepsis according to international consensus criteria (fever or hypothermia AND tachycardia (mean HR >2 standard deviations above normal for age) OR bradycardia (for infants <1year old mean HR <10th percentile for age) OR tachypnoea (respiratory rate >2 standard deviations above normal for age)[15] and treating clinician intention to treat with FBT for tachycardia or hypotension. Hypotension was defined as MBP < 55 + 1.5 x age (years).[16] FBT was defined as a 10-20ml/kg bolus of intravenous crystalloid solution administered at room temperature over 10 minutes according to standard practice. Exclusion criteria were: uncorrected structural cardiac disease, non-curative goals of therapy, and where the child's family were non-English speaking.

Study procedures included the recording of systolic, diastolic, and mean blood pressure via oscillometric non-invasive cuff, heart rate, capillary refill time, and trans-thoracic echocardiogram performed immediately prior to, 5 minutes after, and 60 minutes after FBT. Recorded echocardiogram images were de-identified, randomized, and interpreted by a Paediatric Cardiologist blinded to the patient identity and status pre / post FBT. CI and heart rate changes following FBT have been previously reported,[17] and permission for their use in deriving TSVRi and shock index was obtained from Wolters Klewer Health, Inc (license no: 432221292107). The principal investigator performed all sonographic recordings, and has the qualification of Post-Graduate Certificate in Clinical Ultrasound (The University of Melbourne, Australia).

Statistical methods: Non-parametric data were reported as median and interquartile range (IQR). Derivation of total systemic vascular resistance index (TSVRi) was performed using the following formula: TSVRi = MBP x 79.92/CI.[18] Shock index was calculated as: heart rate / systolic blood pressure.[11] CVP was not used in the calculation of TSVRi as no study participants had central venous access at the time of enrolment. TSVRi >1600 dyne s cm^{-5} m^{-2} was used to define cold shock, and TSVRi <800 dyne s cm^{-5} m^{-2} to define warm shock.[19] The clinical correlates of shock phenotype (pulse pressure, diastolic blood pressure, and capillary refill time) for participants in cold and warm shock were compared at each study time point. Post hoc sensitivity analysis was performed excluding participants who received a repeat fluid bolus over the study period. Statistical analysis was performed using Stata 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

The study was approved by the hospital institutional review board (The Royal Children's Hospital Human Research and Ethics Committee, approval #33169A) and registered with the Australian and New Zealand Clinical Trials Registry (ACTRN 12614000824662).

Results

Between August 2013 and February 2017, 50 fluid boluses were recorded in 41 participants. **From a prior quality improvement study, we estimated that approximately 770 children were treated with fluid boluses for sepsis over this time period.[20] The primary barrier to patient enrolment was availability of the principal investigator on-site and not in the role of treating clinician at the time of patient presentation. These circumstances**

resulted in a prolonged enrolment period relative to sample size. Enrolment, allocation, follow-up, and analysis data are presented in figure 1. FBT content was 0.9% NaCl in all cases, and FBT volume was 20ml/kg in 44 cases and 10ml/kg in 6 cases. Demographic and clinical data were recorded for all participants.

Participant demographic and outcome data are presented in Table 1. Four participants were receiving heated, humidified, high flow nasal cannula oxygen therapy throughout the study period; none experienced escalation of respiratory support during study investigations. No participants were receiving inotropic support at the time of study observations, 5 (12%) subsequently received inotropic support. Bacterial or viral pathogens were identified in 56% of participants. There was no significant change in median participant body temperature over the study period (37.8^{o}C at baseline, 37.7^{o}C 5 minutes after fluid bolus administration, and 37.5^{o}C 60 minutes after fluid bolus administration).

Changes in median MBP, TSVRi, and shock index over the study period are shown in Table 2. The proportion of participants with hypotension and warm shock at each time point are included. Paired MBP data at baseline, 5 minutes after FBT, and 60 minutes after FBT are presented in Figure 2.

The clinical correlates of cold and warm shock defined by TSVRi are listed in Table 3.

Nine participants received a repeat fluid bolus over the study period. On sensitivity analysis, changes in MBP and TSVRi over the study period were not significantly different after exclusion of these participants from analysis (supplementary Table 1).

Discussion

In children meeting international consensus criteria for sepsis who were administered FBT, we observed an initial reduction in median MBP which subsequently returned to near-baseline within 60 minutes of administration. The initial reduction in median MBP was associated with an increase in the proportion of study participants meeting international age-based consensus criteria for hypotension, and resulted in part from a reduction in systemic vascular resistance. Widened pulse pressure and decreased diastolic blood pressure were observed in participants with warm shock.

Multiple experimental sepsis models have demonstrated the conversion from cold to warm shock following FBT,[21-23] an effect which can be attenuated by inhibiting nitric oxide synthase[24] and may be mediated by a baroreceptor-mediated reduction in circulating catecholamines or flow-related vasodilation. In a hyperdynamic ovine sepsis model comparing liberal (40ml/kg) versus restrictive (no FBT) fluid resuscitation strategies, Byrne et. al. found that SVR was lower and vasopressor requirement higher in the liberal fluid resuscitation group.[25] Higher levels of atrial natriuretic peptide (ANP) and endothelial degradation products in the liberal fluid resuscitation group support the hypothesis that fluid

resuscitation may induce ANP-mediated shedding of the endothelial glycocalyx,[26] which may impair its role in regulating vascular tone.[27, 28]

A significant reduction in SVR has been observed following FBT in several clinical studies, with preservation of MBP through an increase in CO.[29-31] Bihari et. al. found an increase in median MBP of 4mmHg ($p<0.01$) in the first 10 minutes following FBT in septic and non-septic adults in the ED,[32] while Lipscey et. al. found no significant change in MBP following FBT at any time point in adults with infection-associated hypotension.[33] These contrasting findings may have resulted from differences in study populations; only 16% had sepsis in the study by Bihari et. al., while all had infection-associated hypotension in the study by Lipscey et. al.. These results suggest that FBT in septic patients with warm shock may not result in an increase in MBP.

Over the first hour following FBT, we observed an overall trend towards improvement in shock index. Whether this is associated with improved patient-centred outcomes is unclear, and caution interpreting this finding in light of the results of the FEAST study is warranted, where improved early markers of perfusion following FBT were associated with higher mortality.[34]

Limitations

The study was small, single centre, and observational. The changes in study observations cannot be assumed to imply causality. It is possible that other therapeutic interventions or

disease progression influenced study findings. At the time of participant enrolment, patients had a presumptive clinical diagnosis of sepsis, yet some had an alternate final (discharge) diagnosis. The response to fluid bolus therapy in non-septic patients may have been different to that in patients with sepsis. The failure to include CVP in the calculation of TSVRi may have introduced a source of error, though TSVRi and SVRi are highly correlated.[35] Study observations only occurred for the first hour after fluid bolus administration, and we cannot say what the clinical implications were after this time.

Conclusions

We observed a reduction in MBP following FBT for paediatric sepsis, with return towards baseline over the subsequent 60 minutes. The implications of these findings for vital organ perfusion and patient outcome warrant further investigation.

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Competing Interests

None declared

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Table 1. Demographic and outcome data for included patients.

Demographic data	Included participants (n=41)
Age- years; median (IQR)	1.5 (0.5-3.88)
Male n(%)	26 (63)
Co-morbidities n(%)	14 (34)
Malignancy	7 (17)
Cerebral palsy	4 (10)
Solid organ transplant	1 (2)
Chronic lung disease	1 (2)
Type 1 diabetes	1 (2)
No co-morbidity n(%)	27 (66)
Blood culture taken	41 (100)
Antibiotics administered	41 (100)
Pathogen Identified	23 (56)
Virus	10 (24)
Respiratory Syncytial Virus	3 (7)
Enterovirus	2 (5)
Parainfluenza	2 (5)
Influenza	1 (2)
Human metapneumovirus	1 (2)
Parechovirus	1 (2)
Bacteria	13 (32)
Staphylococcus aureus	4 (10)
Streptococcus pneumoniae	3 (7)
Streptococcus mitis	3 (7)
Group a Streptococcus	1 (2)
Escherischia coli	1 (2)
Pneumocystis	1 (2)
Mycoplasma	1 (2)
Coagulase negative Staphylococcus	1 (2)

Organ support therapy[2]	
Non-invasive ventilation	8 (20)
Invasive ventilation	9 (22)
Inotrope	5 (12)
Renal replacement	0 (0)
Extracorporeal membrane oxygenation	0 (0)
Intensive care unit admission	15 (37)
Length of stay- hours, median (IQR)	97 (52-167)
Hospital admission	41 (100)
Length of stay- hours, median (IQR)	93 (48-210)
28-day mortality	1 (2)
Discharge diagnosis	
Pneumonia / acute lower respiratory tract infection	10 (24)
Sepsis	9 22)
Meningitis	6 (15)
Viral illness	4 (10)
Bronchiolitis	3 (7)
Febrile neutropenia	2 (5)
Staphylococcal scalded skin syndrome	1 (2)
Epiglottitis	1 (2)
Colitis	1 (2)
Food protein induced enterocolitis syndrome	1 (2)
Acute demyelinating encephalomyelitis	1 (2)
Diabetic keto-acidosis	1 (2)
Dehydration	1 (2)

IQR=interquartile range, [2]ventilatory support is reported as the maximal level required during hospital admission.

Table 2. Hemodynamic variables prior to, 5 minutes after, and 60 minutes after fluid bolus therapy.

Hemodynamic variable	Prior to fluid bolus therapy (n=50)	5 minutes after fluid bolus therapy (n=50)	60 minutes after fluid bolus therapy (n=41)
MAP (mmHg); median (IQR)	78 (63 to 86)	71 (60 to 82)	75 (66 to 84)
Hypotension; n (%)	8 (16)	13 (26)	7 (17)
TSVRi [36]; median (IQR)	1580 (1242 to 2206)	1254 (1027 to 2140)	1850 (1265 to 2140)
Warm shock; n (%)	1 (2)	6 (12)	1 (2)
Shock index; median (IQR)	1.60 (1.34 to 1.90)	1.49 (1.25 to 1.76)	1.37 (1.22 to 1.66)

MBP=mean blood pressure; IQR=interquartile range; TSVRi=total systemic vascular resistance index (NB TSVRi was calculated in 49 cases prior to fluid bolus therapy, in 49 cases 5 minutes after fluid bolus therapy, and in 38 cases 60 minutes after fluid bolus therapy), warm shock was defined as TSVRi <800 dyne s cm^{-5} m^{-2}. Shock index=heart rate / systolic blood pressure.

Table 3. Shock phenotype† prior to, 5 minutes after, and 60 minutes after fluid bolus therapy.

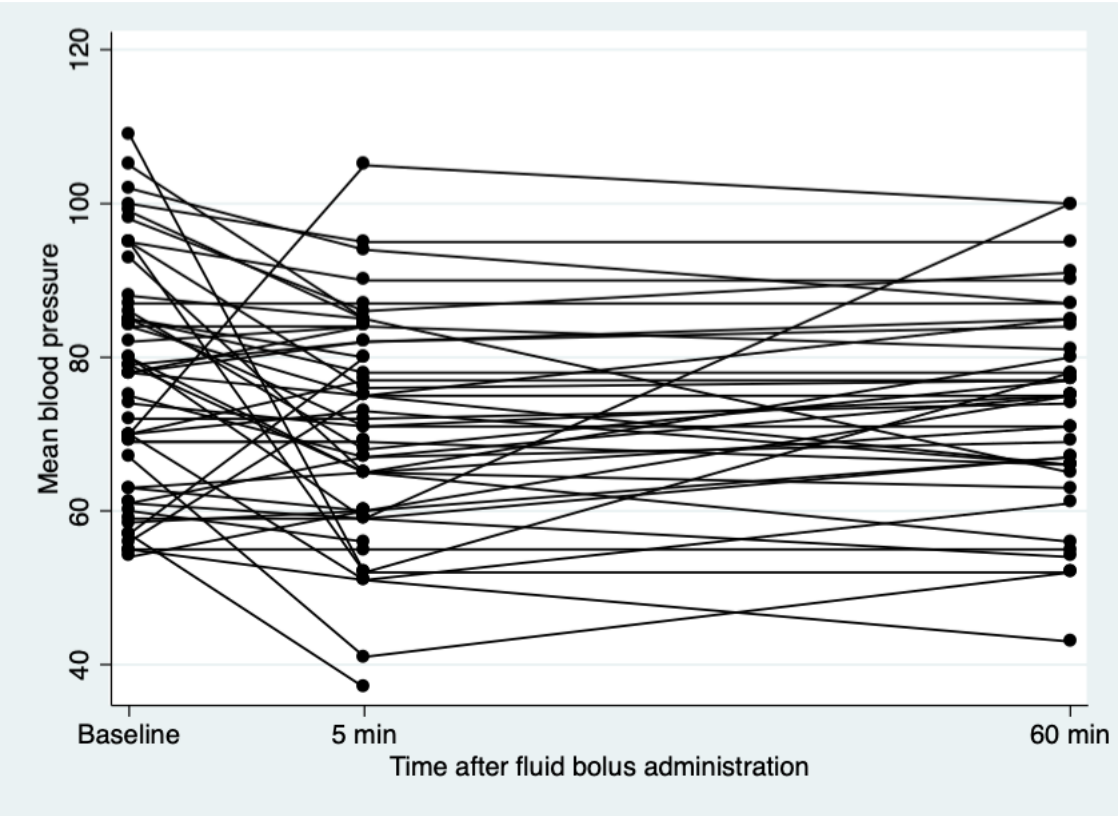
Blood pressure variable	Prior to fluid bolus therapy (n=49)		5 minutes after fluid bolus therapy (n=49)		60 minutes after fluid bolus therapy (n=38)	
	Cold Shock (n=24)	Warm Shock (n=1)	Cold Shock (n=14)	Warm Shock (n=6)	Cold Shock (n=24)	Warm Shock (n=1)
Pulse Pressure, mmHg; median (IQR)	37.5 (29 to 49)	66	38.5 (30.5 to 53.5)	45 (30.5 to 59)	43.5 (33.5 to 48)	45
Diastolic Blood Pressure, mmHg; median (IQR)	65 (55 to 76)	37	57 (51 to 66.5)	40.5 (37 to 42.5)	61.5 (53 to 66)	47
Capillary refill time, sec; median (IQR)	3 (2 to 3)	3	3 (2 to 3)	3 (2 to 3)	3 (2 to 3)	4

†cold shock = total systemic vascular resistance >1600 dyne s cm^{-5} m^{-2}, warm shock = total systemic vascular resistance <800 dyne s cm^{-5} m^{-2}.
IQR = interquartile range.

Figure Legends

Figure 1. Study flow diagram.

Figure 2. Paired mean blood pressure (mmHg) values at baseline, 5 minutes after fluid bolus administration, and 60 minutes after fluid bolus administration.



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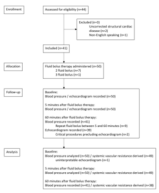

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