Title

The epidemiology and effects of fluid bolus administration in the paediatric emergency department.

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Author Contribution

EL had the original study idea. EL and AW wrote the protocol and obtained ethics approval. DJS performed the data extraction. TS wrote the first draft of the resulting paper. All authors contributed to the study concept and design; acquisition, analysis, and interpretation of data;

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Running Title

Fluid resuscitation in the emergency department.

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Abstract

Objective: Fluid bolus therapy (FBT) is recommended as the initial form of acute circulatory support for many disease processes. The epidemiology of its use in the emergency department (ED) is unknown. The aim of this study was to assess indications, use patterns and short term effects of FBT in a paediatric ED.

Methods: Retrospective observational study in the ED of The Royal Children's Hospital, Melbourne, Australia (annual census >90 000) using hospital electronic medical record data for all patients who received an intravenous fluid bolus in the ED over the calendar year 2018. We extracted demographics, indications, volume, content of FBT as well as subsequent vital sign and biochemical changes.

Results: 1539 fluid boluses were administered to 1343/90,000 children (1.5%), 1185 received one, 123 received two, 32 received three, and 3 received four boluses. Fluid bolus

volume of 10ml/kg was used in 45.3%, 20ml/kg in 35.7%, 500ml in 6.4%, and 1000ml in 7.1%. The fluid content was 0.9% saline in 99.9% of cases. The most common indications for FBT were: vomiting / diarrhoea (23%), acute febrile illness (11%), and pneumonia or sepsis (10% each). FBT was associated with a reduction in median heart rate by 6 beats per minute ($p<0.01$), reduction in mean blood pressure by 3mmHg ($p<0.01$), and reduction in venous lactate by 0.2mmol/L ($p<0.01$).

Conclusions: Fluid bolus therapy is a commonly used intervention in the paediatric ED, most often for dehydration. Variability in indications, dose, and effects of FBT warrant further exploration.

List of key words

Fluid Therapy, Resuscitation, Therapeutic Uses, Child, Emergency Service Hospital

Introduction

Fluid bolus therapy (FBT) refers to the rapid intravenous administration of a discrete volume of fluid, with the intention of increasing venous return and cardiac output.¹ It is recommended as the initial form of acute circulatory support for undifferentiated paediatric shock.² In this context, the purpose of FBT is to increase blood flow to hypo-perfused organs. Organ blood flow is determined by trans-capillary pressure (mean blood pressure (MBP) – central venous pressure (CVP)). FBT may increase MBP, and thus organ blood flow, by increasing venous return / cardiac output (CO) ($MBP = CO \times \text{systemic vascular resistance (SVR)}$).³ FBT that does not contribute to increased CO is unlikely to be advantageous and may have the paradoxical effect of increasing CVP and *decreasing* trans-capillary pressure and organ blood flow. This fluid may accumulate in the interstitial space and contribute to end-organ oedema and dysfunction.⁴ Excessive administration of FBT has been associated with deterioration in renal function, acute respiratory distress syndrome, prolonged hospital length of stay and mortality.⁵⁻⁷ FBT may also lead to adverse metabolic complications, such as hyper-chloraemic metabolic acidosis, with the potential to cause harm in unwell patients.⁸ For treating clinicians, this requires balancing the potential beneficial and harmful effects of FBT for individual patients by monitoring physiological and biochemical changes following administration.

While FBT has been described for individual paediatric conditions and is recommended in a number of guidelines such as the Advanced Paediatric Life Support groups, Pediatric

Advanced Life Support, and the Surviving Sepsis Campaign, it is unclear how widespread its use is across all conditions in the ED setting.⁹ Considering the possible morbidity associated with over or under use of FBT it is important to understand how FBT is used in children in ED.¹⁰ We therefore set out to investigate the indications for FBT in the paediatric ED, and assess the use patterns, and short term physiological and biochemical effects.

Methods

Study Design

The study was designed as a retrospective cohort study, and approved by the hospital institutional review board (The Royal Children's Hospital Human Research and Ethics Committee (HREC), approval #38254).

Study Setting and Population

The study setting was the Emergency Department (ED) of The Royal Children's Hospital, Melbourne, Australia; a tertiary children's hospital with an annual ED census of >90 000 children. All patients who received an IV fluid bolus during the calendar year 2018 were included in the study.

Patients were identified via a search of the electronic medical record system (Epic, Verona, WI, USA) for orders to administer a fluid bolus in the ED via the intra-venous or intra-osseous route. No patients were excluded. There was no comparison group.

We extracted demographic data, indications, frequency of use, volume, content of FBT as well as vital signs and metabolic markers. Ten percent of source data records were manually checked for accuracy of extracted data (130 records).

Definitions

Indications were defined as ICD 10 codes used at patient discharge from ED or hospital as assigned by the treating clinicians.

Fluid bolus was defined as the rapid administration of a pre-defined fluid volume and content. Rapid administration was defined by method of delivery (via pressure bag or push-pull method, *not* via infusion pump).¹¹ Blood, blood products, dextrose-only fluids, and fluids administered as a vehicle for medication administration were excluded.

Vital signs extracted included systolic blood pressure (SBP), mean blood pressure (MBP), heart rate, respiratory rate and SpO₂. We used vital signs recorded immediately prior to and first available within 30 minutes after fluid bolus administration. Vital signs were categorised as normal/abnormal using age-based thresholds.¹² Tachycardia as defined by Goldstein et. al.;¹³ hypotension (SBP) as defined by Gebara;¹⁴ hypotension as defined by Pediatric Logistic Organ Dysfunction Scors (PELOD-2).¹⁵

The biochemical values extracted included venous lactate, pH and serum creatinine.

Biochemical values were recorded immediately prior to and first available within 2 hours of fluid bolus administration.

Statistical Analysis

Descriptive statistics were used to report the study outcome measures. Non-parametric data were reported as median and interquartile range (IQR). The difference in median physiological and biochemical values before and after FBT were compared using Wilcoxon's signed ranks test. Categorical variables were compared using the Fishers Exact test. The physiological and metabolic changes were calculated using the median values and percentage change. Statistical analysis was performed using Stata 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Results

Fluid bolus characteristics: Between January 1st 2018 and December 31st 2018, a total of 1539 fluid boluses were administered to 1343 children of the 90,000 patients presenting to ED (1.6%); 1185 received 1 bolus, 123 received 2 boluses, 32 received 3 boluses, and 3 received 4 boluses). The fluid content was 0.9% saline in 1538/1539 (99.9%) and Ringers lactate in 1/1539 (0.1%). The fluid bolus volume was 10ml/kg in 697/1539 (45.3%), 20ml/kg in 550/1539 (35.7%), 500ml in 98/1539 (6.4%), and 1000ml in 109/1539 (7.1%). Eighty-five patients (5.5%) were administered a volume of FBT other than those listed. Seven hundred and seventy patients of one-thousand forty-three (57.3%) received a total volume of FBT of

10 ml/kg, 525/1343 (39.1%) received 11-20 ml/kg, 30/1342 (2.2%) received 21-30 ml/kg, 14/1343 (1.0%) received 31-40 ml/kg, 2/1343 (0.1%) received 41-50 ml/kg, 2/1343 (0.1%) received 51-60 ml/kg, and 0/1343 received >60ml/kg (figure 1).

Patient characteristics: The median age of children receiving FBT was 5.6 years (IQR 1.7 to 12.8 years) and 787/1343 (58.6%) were male. The most common indications for fluid bolus administration were: vomiting / diarrhoea (22.8%), acute febrile illness (11.3%), and acute lower respiratory tract infection or sepsis (9.9%). The distribution of FBT and admission diagnosis are shown in Table 1.

Following FBT administration, 66/1343 (5%) patients were discharged home, 296/1343 (22%) were admitted to a short-stay unit, 967/1343 (72%) were admitted to a hospital ward, 12/1343 (1%) were admitted to an intensive care unit, and 1/1343 (0.07%) died within the ED.

Patient outcomes and disposition

There was one death in a patient with an acute lower respiratory tract infection who received 1 fluid bolus. The child had significant co-morbidities including cerebral palsy with a Gross Motor Function Classification System level V and end stage pulmonary hypertension.

Three patients received 4 fluid boluses with the following diagnoses and dispositions: urinary tract infection with persistent tachycardia and hypotension who was admitted to a paediatric

ward, septic shock with a lower respiratory tract focus who was commenced on noradrenaline and admitted to the paediatric intensive care unit (PICU), and septic shock with a renal focus and acute renal failure who was admitted to a paediatric ward.

A total of 13 patients were admitted to PICU following FBT with the following diagnoses: 5/13 (38%) sepsis, 3/13 (23%) hypotension, 2/13 (15%) status epilepticus, 1/13 (8%) multi-trauma, 1/13 (8%) anaphylaxis, 1/13 (8%) asthma. Nine of thirteen PICU admissions (69%) received 1 bolus, 3/13 (23%) received 2 boluses, and 1 (8%) received 3 boluses.

A total of 40 patients were discharged home from ED following FBT, 35/40 (88%) received 1 fluid bolus and 5/40 (12%) received 2 boluses.

Physiological and biochemical effects: FBT was associated with a reduction in median heart rate by 6 beats per minute ($p<0.01$) and a reduction in mean blood pressure by 3mmHg ($p<0.001$). Median respiratory rate decreased by 1 breath per minute ($p<0.01$) and there was no change in oxygen saturations following FBT. FBT was associated with a reduction in venous lactate by 0.2 mmol/l ($p<0.01$), a reduction in pH by 0.02 ($p<0.01$) and a fall in serum creatinine by 2 μ mol/l ($p<0.01$) (Table 2). The physiological and biochemical effects of FBT by fluid volume (10 ml/kg vs. 20 ml/kg) are presented in Supplementary Table 1. There was no significant difference in the patient characteristics for those receiving 10 ml/kg vs. 20 ml/kg or in the physiological or biochemical effects.

Using age-based thresholds for defining cardiovascular organ dysfunction, the proportion of patients with tachycardia, hypotension, and elevated serum lactate are shown in Table 3.

Tachycardia and lactate changed significantly before and post FBT, SBP and MBP did not.

The proportion of patients with tachycardia, hypotension, and elevated serum lactate pre and post FBT by fluid volume (10 ml/kg vs. 20 ml/kg) are presented in Supplementary Table 2.

There was no significant difference in effect between FBT volumes.

Discussion

FBT is recommended as the initial form of acute circulatory support for many disease processes. This retrospective observational study at a large urban paediatric ED is the first to describe the use patterns of FBT in children across disease processes and provides an overview of FBT use in the ED setting. We found that FBT was a commonly administered intervention, with 1.7% of all patients presenting to the ED over a 1-year period receiving fluid boluses. While a single fluid bolus was administered in the majority of cases (1185/1539; 77%) patients received up to 4 boluses with a maximum of 60 ml/kg administered.

The fluid bolus content was 0.9% saline in almost all cases. This is the fluid recommended in treatment guidelines for undifferentiated shock, and is in keeping with clinicians self-reported preferential use of 0.9% saline as an initial resuscitation fluid.^{16, 17} There is concern, however, that the use of large volumes of 0.9% saline as a resuscitation fluid may lead to hyperchloraemic metabolic acidosis.¹⁸ The implications for patient-centred outcomes remain

uncertain, with the majority of literature focussed on adult ICU patients receiving maintenance rather than resuscitation fluids.¹⁹ Within this group, however, some evidence suggests that balanced fluids may reduce mortality in the setting of sepsis, when compared to 0.9% saline.²⁰

The most common volume of fluid administered was 10 ml/kg, though treatment guidelines suggest using bolus volumes of 20 ml/kg for undifferentiated shock.¹⁶ The reason for this observation is unclear, particularly in light of clinicians self-reported preferential use of 20ml/kg as an initial fluid bolus volume.¹⁷ The preferential use of a fluid bolus volume of 10 ml/kg may have resulted from the use of FBT as a treatment for dehydration rather than shock, or due to clinician concern for precipitating volume overload. Only a small proportion of patients were given large volume resuscitation, and the majority of these had dehydration and not shock. The ideal volume of FBT to administer in shock is unknown, though treatment guidelines recommend up to 60 ml/kg before considering other forms of acute circulatory support.¹⁶

The most common indication for FBT was dehydration from acute gastrointestinal illness. At the time of FBT, the majority of patients were not tachycardic or hypotensive, and did not have raised serum lactate. Nor was there a difference between observed patient characteristics in those receiving 10 ml/kg vs. those receiving 20 ml/kg. This highlights the frequency of use of FBT for rapid IV rehydration rather than for the treatment of shock, and raises the question of which factors contribute to clinical decision making when deciding to use one volume of

FBT over another. FBT used to treat dehydration due to volume loss may have a different benefit:risk profile compared to its use to treat organ hypoperfusion due to shock, particularly if shock results from systemic inflammation. In one of the conditions known to cause dehydration without systemic inflammation, diabetic keto-acidosis, Kuppermann et. al. found that large volume fluid resuscitation was not associated with an increased risk of developing cerebral oedema (injury).²¹ This stands in contrast to the finding that FBT in children with a febrile illness and poor perfusion *was* associated with cerebral and pulmonary oedema.²² Further study is needed to define the patient groups that may benefit or that may be harmed by FBT.

We found that FBT administration was associated with a reduction in HR, and a reduction in the number patients with tachycardia by 8.6% (an expected effect). FBT was also associated with a minor reduction in MBP, and an increase in the number of participants with hypotension by 1.8% (an un-expected effect). Within the limitations of this observational study, where more unwell children may have received higher FBT volume, we did not find a dose effect on the degree of circulatory organ dysfunction when comparing 10 ml/kg vs 20 ml/kg as fluid bolus volume. FBT has been described as resulting in the conversion from cold to warm shock.²³ This may result from baroreceptor-mediated reduction in sympathetic tone, from flow-related vasodilation, or from ANP-mediated shedding of the endothelial glycocalyx, which may impair its role in regulating vascular tone.²⁴⁻²⁶ We also observed a minor reduction in serum lactate and a reduction in the number of patients with lactate >4mmol/L by 2.9% (an expected effect). Normalisation of serum lactate to <2mmol/L has

been associated with reduced mortality in paediatric sepsis,²⁷ perhaps suggesting it has a role as a therapeutic target in those with an elevated serum lactate at baseline.²⁸

Limitations

Maintenance fluids, fluids administered with medication, and fluid balance was not measured as part of this study. In addition, we did not capture data on the administration of blood or blood products, which may have an important role in the understanding FBT use in trauma. Our case identification also focussed on ED administration; we did not analyse if patients received further boluses on paediatric wards or in PICU. While based on a large and comprehensive electronic dataset we did not include important historical and clinical information, which may be important in clinical decision making. Data for some vital signs and biochemical markers were missing, this was a limitation due to the observational nature of this study.

Conclusion

FBT is widely used in children in the paediatric ED. Based on the limited evidence behind current fluid recommendations, clarification of the indications, volume, and content of FBT is a current research priority.

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Figure 1. Total volume of fluid bolus therapy administered per patient presentation in the Emergency Department.

Table 1. Admission diagnosis and distribution of fluid boluses.

Number of fluid boluses (total)	1539				
Number of patients	1343				
Age, years; median (IQR)	5.6 (1.7 to 12.8)				
Male, n (%)	787 (51.1)				
Admission diagnosis	Total (n=1539)	1 fluid bolus (n=1185)	2 fluid boluses (n=123)	3 fluid boluses (n=32)	4 fluid boluses (n=3)
Anaphylaxis	16	13	2	1	
Cardiac	8	7	1		
Dehydration	26	26			
Endocrine					
Diabetic keto-acidosis	10	10			
Other	13	12	1		
Gastrointestinal (including abdominal pain)	43	34	7	2	

Haematological	18	16	2		
Infection					
Abscess / soft tissue infection	15	12	3		
Febrile illness	174	156	14	4	
Fever and risk of neutropaenia	47	40	5	2	
Meningo-encephalitis	12	10	2		
Respiratory tract infection					
Upper	27	23	4		
Lower	153	132	16	4	1
Sepsis	149	124	17	8	
Urinary tract infection	28	26	2		
Vomiting / diarrhoea	351	329	18	4	
Headache / migraine	35	31	2	2	
Neurological					
Altered conscious state	6	5		1	
Collapse / faint	7	7			
Seizure	29	26	3		
Other	3		3		
Respiratory	3	3			
Surgical	104	92	9	3	
Toxidrome	25	21	4		
Trauma					
Burn	5	4	1		
Head injury	4	4			
Single injury	9	7	1		1
Multiple injuries	18	16	1		1
Other	12	6	5	1	
Disposition following fluid bolus					
Discharge home, n (%)	66 (5.0)				
Admission short stay unit, n (%)	296 (22.0)				
Admission hospital ward, n (%)	967 (72.0)				
Admission intensive care unit, n (%)	12 (1.0)				
Died within Emergency Department, n (%)	1 (0.1)				
Fluid bolus content					
0.9% saline, n (%)	1538 (99.9)				
Ringer's lactate, n (%)	1 (0.1)				
Fluid bolus volume					
Total volume, ml (IQR)	293 (140 to 500)				
Bolus volume 10ml/kg, n (%)	697 (45.3)				
Bolus volume 20ml/kg, n (%)	550 (35.7)				
Bolus volume 500ml, n (%)	98 (6.4)				
Bolus volume 1000ml, n (%)	109 (7.1)				
Other	85 (5.5)				

Duration of administration, min; mean (SD)	23.4 (10.4)
Number of fluid boluses administered	
1	1185 (77.0)
2	123 (8.0)
3	32 (2.1)
4	3 (0.2)

Table 2. Physiological and biochemical changes following fluid bolus therapy.

Variable (# observations)	Prior to fluid bolus administration; median (IQR)	After fluid bolus administration; median (IQR)	Change; n (%)	P value

HR (1476), bpm	128 (11 to 156)	122 (98 to 148)	-6 (-5)	<0.01
SBP (1400), mmHg	105 (96 to 115)	103 (93 to 113)	-2 (-2)	<0.01
DBP (1273), mmHg	66 (56 to 76)	63 (54 to 71)	-2 (-3)	<0.01
MBP (1274), mmHg	79 (70 to 88)	76 (68 to 84)	-3 (-4)	<0.01
RR (1451), brpm	27 (22 to 40)	26 (22 to 38)	-1 (-4%)	<0.01
SpO2 (1447), %	99 (97 to 100)	99 (98 to 100)	No change	0.37
Lactate (756), mmol/L	1.9 (1.4 to 2.7)	1.7 (1.3 to 2.5)	-0.2 (-10)	<0.01
pH (753)	7.38 (7.33 to 7.41)	7.36 (7.31 to 7.41)	-0.02 (<1)	<0.01
Creatinine (966), umol/L	37 (28 to 53)	35 (26 to 51)	-2 (-5)	<0.01

HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, MBP = mean blood pressure, RR = respiratory rate, SpO2 = peripheral oxygen saturations.

Table 3. Proportion of patients with cardiovascular organ dysfunction prior to and following fluid bolus therapy.

Variable	Prior to fluid bolus administration	After fluid bolus administration	Change (%)	P value
Tachycardia, n (%)	580 (37.7)	448 (29.1)	-8.6	<0.01
Hypotension (SBP), n (%)	67 (4.4)	72 (4.7)	0.3	0.36
Hypotension (MBP), n (%)	118 (7.7)	146 (9.5)	1.8	0.04
Lactate >4mmol/L , n (%)	80 (5.2)	35 (2.3)	-2.9	<0.01

Tachycardia as defined by Goldstein;¹³ hypotension (SBP) as defined by Gebara;¹⁴ hypotension (MBP) as defined by PELOD-2.¹⁵

EMM_13437_EMA fluid bolus study figure 1.tiff

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