Fluid bolus therapy in emergency department patients: indications and physiological changes

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Abstract

Objective: To study the indications for fluid bolus therapy (FBT) and its associated physiological changes in emergency department (ED) patients.

Methods: Prospective observational study of FBT in a tertiary ED. We recorded indications, number, types, and volumes, resuscitation goals, and perceived success rates of FBT. Moreover, we studied key physiological variables before, 10 minutes, 1 hour and 2 hours after FBT.

Results: We studied 500 FBT episodes (750[500-1250]ml). Median age was 59 (36-76) years and 57% were male. Shock was deemed present in 135(27%) patients, septic shock in 80(16%), and cardiogenic shock in 30(6%). Overall, 0.9% saline (84%) was the most common fluid and hypotension the most common indication (70%). "Avoidance of hospital/ICU admission" was the goal perceived to have the greatest success rate (85%). However, while mean arterial pressure (MAP) increased ($p < 0.01$) and heart rate (HR) decreased ($p = 0.04$) at 10 min ($p = 0.01$), both returned to baseline at 1 and 2 hours. In contrast, respiratory rate (RR) increased at 1 ($p < 0.01$) and 2 hours ($p = 0.03$) and temperature decreased at 1 and 2 hours (both $p < 0.001$). In patients with shock, one hour after FBT, there was a median 3 mmHg increase in MAP ($p = 0.01$) but no change in HR ($p = 0.44$), while RR increased ($p < 0.01$) and temperature decreased ($p = 0.01$).

Conclusion: In ED, FBT is used mostly in patients without shock. However, after an immediate hemodynamic effect, FBT is associated with absent or limited physiological changes at 1 or 2 hours. Even in shocked patients, the changes in MAP at 1 or 2 hours after FBT are small.

Keywords: Fluid bolus, emergency department, shock, septic shock, fluid responder. Saline, temperature, respiratory rate, heart rate, blood pressure

Introduction

Fluid bolus therapy (FBT) is one of the cornerstones of resuscitation in acutely unwell patients and has been studied in specific patient subgroups such as septic shock¹⁻⁵, trauma^{6,7} and hypovolemia⁸. In addition, it is used ubiquitously in the emergency department (ED). However, the role of FBT in ED patients remains the subject of ongoing debate⁹ because recent evidence suggests limited sustained physiological efficacy¹⁰⁻¹³ and even an association with harm⁴, possibly mediated by a positive fluid balance¹⁴.

Despite the above concerns and the frequent and early use of FBT in ED, there is limited understanding of its epidemiology, hemodynamic and other physiological effects, even in patients presenting with sepsis. Moreover, there are no data in non-septic ED patients treated with FBT. This is problematic, because appreciation of the epidemiology and physiological changes seen after early FBT may help define current practice, guide ED physicians on their expectations of its likely physiological impact and open the door to interventional studies.

Accordingly, the current study was designed to understand the indications, perceived efficacy, and both early and sustained physiological changes associated with FBT in all treated patients presenting to the ED of a tertiary referral centre in Australia.

In particular, we aimed to test the hypothesis that, in a tertiary level ED of an Australian teaching hospital, FBT would be administered commonly and for heterogeneous indications and be associated with only short-lived and small hemodynamic changes.

Methods

We performed a prospective observational study conducted at a tertiary referral centre ED at Flinders Medical Centre, South Australia. Our study protocol was approved by the institutional ethics Committee (146/14) and trial was registered (ACTRN12615001150538). Patients presenting to the ED were prospectively recruited between May 2014 and March 2015 inclusive.

Flinders Medical Centre ED is a tertiary referral centre in Adelaide, South Australia with approximately 75,000 presentations per year, during the study period there were 56,209 adult presentations and 27,809 admissions. There are 36 adult and 8 pediatric beds in ED with 5 to 10 doctors and 20 to 29 nurses rostered at any one time.

We used a case report form (CRF) for each FBT episode, which was modified from the one recently used in ICU patients¹¹ (Supplementary Figure 1). FBT was defined as ≥ 500 ml of fluid administered in less than an hour. We excluded patients if their age was less than 16 years, were transferred from another hospital, or they already had more

than 1000 ml of fluids administered while being transferred to the hospital. We aimed at including all FBT episodes in the ED.

The CRF was divided in to 2 parts. Part A was for the fluid prescriber and included details of the number, types, and volumes of FBT, resuscitation goals, and their perceived success rates. It also recorded whether the patients had shock (systolic blood pressure ≤ 90 mmHg with evidence/suspicion of organ dysfunction) and the possible types of shock- this was left at the discretion of the treating clinician. Part B requested details regarding physiological effect of these FBT episodes on blood pressure (data presented as mean arterial pressure, MAP mmHg), heart rate (HR, per minute), respiratory rate (RR, per minute) and temperature (Temp, °C). These were recorded before, and 10 minutes, 1 hour and 2 hours after the FBT was completed.

These CRF were stapled with the fluid chart and were collected from multiple places in the ED. Extensive training and teaching sessions was done for the nurses and doctors at multiple time points during the conduct of the study to help with compliance. Demographic details of these patients were collected retrospectively from an existing ED information system¹⁵.

Sample size calculation

We did not have any previous data to help us with sample size calculation. Hence, we performed a planned interim analysis after collecting data from 100 FBT episodes. Based on similar study in ICU¹¹ and a recent survey at the Australian and New Zealand Intensive Care Society¹⁶, we defined fluid responders as those with an increase in MAP of ≥ 5 mmHg at 1 hour after administration of FBT. As 14% of patients were classified as responders at the interim analysis, we assumed a true prevalence of 0.14, with a

sensitivity of 0.8, specificity of 0.9, and power of 95% and desired precision of 0.05 and estimated that we would need to study 498 FBT episodes to detect such an increase.

Statistical analysis

Statistical analyses were performed using PASW 22.0 software (SPSS Inc, Chicago, IL). Data were tested for normality and normalised by log transformation where necessary. Data are reported as means (SD), or median (IQR), or as percentage as appropriate for the distribution. Data were compared with an independent sample t test or Mann-Whitney U test or chi square test as appropriate. Differences between variables over time were analysed by paired t test (to compare with baseline) or a repeated-measures ANOVA (for multiple time points). Patients presenting with shock were examined separately. A conventional alpha level of < 0.05 was used for all significance testing.

Results

Patient demographics

We studied 500 FBT episodes in 452 patients. The median age was 59 years; 57% of patients were males and 65% of the patients had estimated weights between 60-90 Kg (Table 1).

Shock was deemed present in approximately a quarter of patients at the time of fluid administration. One in five patients was discharged home and, among those admitted to hospital, the median length of stay was 2 days and hospital mortality 4% (Table 1).

Overall, 0.9 % saline was the most commonly FBT fluid (84%) and the median (IQR) amount of FBT fluid given was 750 (500-1250) ml. The majority of patients received only one fluid bolus (Table 1).

Indications and perceived success rate

Multiple indications could apply to a single episode; however, 'Low blood pressure' was the most common indication for FBT (70%), followed by 'avoidance of ICU/ hospital admission' (35%). The perceived success rate ranged from 52% to 85%. The indication of 'avoidance of admission to hospital/ ICU' was perceived by ED clinicians to be the most successful (85%) indication (Table 2).

Physiological changes

Ten minutes after the administration of FBT, there was a median increase of 4 mmHg in MAP (80 (60-98) to 84 (66-96); $p=0.001$) and a median decrease in HR (82 (72-100) to 78 (70-98); $p=0.04$) of 4 beats/min, with no change in body temperature ($p=0.12$) and RR ($p=0.62$). However, MAP and HR changes were not sustained at 1 and 2 hours after the administration of FBT. In contrast, body temperature ($^{\circ}\text{C}$) decreased (37.3 (36.5-37.7) to 36.7 (36.1-37.5); $p<0.01$ at 1 hour, 37.3 (36.5-37.7) to 36.5 (36.0-37.5); $p<0.01$ at 2 hour) and RR (per minute) increased (19 (16-23) to 23 (18-25); $p<0.01$ at 1 hour, 19 (16-22) to 22 (18-24); $p=0.03$ at 2 hour) (Table 3).

In patients with shock and septic shock, 1 hour after FBT, there was a small but significant increase in MAP (mmHg) (65 (56-74) to 68 (58-78); $p=0.01$, 64 (56-74) to 66 (58-78); $p=0.04$ respectively), with a decrease in body temperature ($^{\circ}\text{C}$) (37.1 (36.2-37.9) to 36.7 (36.1-37.6); $p=0.01$, 37.4 (36.4-37.9) to 36.6 (36.1-37.5) $p<0.01$

respectively), increase in RR (per minute) (19 (16-22) to 22 (18-24); $p<0.01$, 19 (16-24) to 22 (19-25); $p=0.01$, respectively) and no change in HR (Table 4).

After administration of FBT, on repeated measures analysis of variance, there was no overall change in MAP ($p=0.44$) and HR ($p=0.37$); but there was a significant decrease in temperature ($p=0.01$) and increase in RR ($p=0.04$) when examined across all time points. When all patients with shock were examined separately there was no change in MAP ($p=0.23$), HR ($p=0.47$) and temperature ($p=0.09$) but there was an increase in RR ($p=0.03$) after administration of FBT (Supplementary Figure 2).

MAP responders and non-responders

Overall, sixteen percent of patients experienced an increase in MAP of at least 5 mm Hg at 1 hour after FBT administration. These patients were classified as MAP responders ($n=71$) and the rest as MAP non-responders ($n=382$). Responders were younger ($p=0.01$), had a lower baseline MAP and a higher HR (both $p<0.01$). Moreover, 56% of patients presenting with shock and 67% of patients with septic shock were MAP non-responders (Table 5A). Finally, more patients with septic shock were classified as MAP non-responders ($p<0.01$) and more patients with hypovolemic shock were classified as MAP responders ($p<0.01$) (Table 5B).

Discussion

Key findings

We performed, what is to our knowledge, the first prospective observational study of FBT in adult ED patients to define its epidemiology and associated physiological changes. We found that FBT was most commonly administered for hypotension and in patients without shock, with shock being present in only about one in four patients and other indications such as “avoidance of admission”, “clinical hypovolemia” and “others” being relatively common. Finally, with the exception of hypovolemic shock, sustained physiological changes in blood pressure and heart rate were minimal. In contrast, there was an overall sustained and significant increase in respiratory rate and decrease in body temperature.

Relationship to previous studies

The median MAP before FBT was 80 mmHg. This finding is similar to that reported in patients presenting with infection in the ED, where the mean MAP before FBT was 78 mmHg¹², indicating a disconnection between perceived hypotension and its documentation although the volume given in the current study was less than previously reported^{3, 12}.

Other indications such as “avoidance of admission”, which had a high perceived success rate are clinically nebulous, never reported before, and perhaps very specific to the study ED or EDs in general. Some of the indications mentioned as “others” were specified as “headaches”, “nausea”, “deconditioning”, and represent real world triggers of FBT that have also never been investigated before.

Indications such as clinical hypovolemia are difficult to quantify in the ED from a research point of view as only vital signs are typically documented. However, such clinically diagnosed hypovolemia was associated with a high rate of responsiveness and

perceived success rate. Overall the perceived success rate was higher in the study ED than in a similar study of ICU patients presenting with sepsis where additional hemodynamic objective measurements beyond vital signs were more easily available¹¹.

Though there is some evidence in favour of early use of fluid resuscitation in patients with sepsis^{17,18}, recent large trials have shown no benefit for early goal directed therapy^{2,3,5}. Despite these large clinical studies in the ED, there is very little evidence addressing the question of whether FBT achieves the expected physiological responses^{12,19}. We found that, in general, FBT failed to deliver what surveyed clinicians report they expect to achieve¹⁶. In particular, in our study, even in patients presenting with shock or septic shock the magnitude of the increase in MAP at 1 hour was small. These findings are similar to those seen in ICU patients^{11,20}. Moreover, such limited changes occurred despite it being likely that other simultaneous interventions (antibiotics and anti-pyretics) were applied that might be expected to help recovery, decrease febrile vasodilatation, increase blood pressure, and bias observations in favour of improved MAP after FBT.

We found a possible association of FBT with an increase in RR. Such increase in RR may reflect a compensation for the hyperchloremic acidosis associated with 0.9% saline²¹ (84% of FBT) or a degree of pulmonary edema or both. We recently reported a similar finding in healthy volunteers in whom we simultaneously demonstrated interstitial pulmonary edema following FBT²². FBT (often administered at room temperature) was associated with a decrease in body temperature, an observation similarly reported in ICU patients¹¹. Whether the small increase in MAP seen in our patients after FBT represents the effect of volume expansion or the vasoconstrictive effect of mild hypothermia remains unclear.

Low MAP is a common indication^{11,23} but despite the high perceived success rate of FBT in restoring an adequate MAP and the findings at 10 minutes, the sustained changes in MAP at 1 and 2 hour were minimal with only one in six patients being classified as MAP responders in our study. Moreover, although such responders had a lower baseline MAP and higher heart rate, approximately half of patients with shock and septic shock were non-responders. This is in line with recent data where a sustained rise in blood pressure was not seen in 40% of patients¹². Finally, patients with hypovolemic shock (92% responders) represented the only group where there is a clear physiological rationale for early use of FBT. Consistent with such thinking, their response rate was high.

Implications of study findings

Our observations imply that in ED patients, FBT may be used more heterogeneously than currently reported in clinical studies or recommended and that, with the exception of patients with hypovolemia²⁴, there may be little sustained change in blood pressure after its administration. Moreover our findings imply that, even in septic shock patients, a sustained response to FBT is not the norm. Finally, they suggest that the more predictable and sustained changes seen after FBT are an increase in respiratory rate and a decrease in body temperature. The former may be undesirable and the latter is of unknown clinical meaning.

Strengths and limitations

This study has multiple strengths. To our knowledge, it is first and largest observational study with details of indications and hemodynamic and other physiological changes after FBT in adult ED patients at multiple time points. As such, it provides novel data about the largely unexplored area of FBT in a wide cohort of ED patients outside the conventional ICU cohorts of sepsis and shock and gives a more real life description of

its use in ED. Moreover, it provides data about the discrepancy between the perceived success of FBT and its associated actual hemodynamic changes.

However, this study has several limitations. First, it is single centre in nature and despite our best efforts to capture the majority of the FBT with repeated in-service training sessions; we are unable to comment on the number of cases where FBT occurred without the use of the study CRF. However, we believe that, with 500 observational sets, our findings are very likely representative of FBT in ED. Similarly some of the hemodynamic data at 2 hours were not recorded if the patient was transferred to the ward/ICU where they may have had additional fluids or vasopressors administered. However, a similar study in septic ED patients¹² confirms our findings. We decided to limit our study to FBT ($\geq 500\text{ml}$) administered in less than one hour for pragmatic reasons, hence we did not record detailed data on exactly how fast such fluid was given. However, given the follow-up at 1 and 2 hours, it seems unlikely that such information would materially alter our conclusions. Overall, 0.9% saline was the most common fluid and other fluid types are underrepresented. However, 0.9% saline is still probably the most common fluid used worldwide for FBT. Finally, dynamic or invasive measures such as central venous pressure, cardiac output and other methods of assessing fluid responsiveness were not applied. However, early use of central catheters is not common in ED in the Australasian setting and FBT has either minimal or no sustained effect on cardiac output in critically ill patients²⁵ or healthy volunteers²². Finally, this is not a randomized controlled study and we do not know what would have happened to these patients if they had not received FBT.

Conclusions

In patients presenting to the ED, FBT is mostly administered in the absence of shock and appears associated with minimal hemodynamic changes at 1 hour. Even in shocked patients, the hemodynamic changes are of limited magnitude and FBT is more

commonly associated with increased respiratory rate and lower temperature. If major increases in blood pressure and decreases in heart rate are the key physiological goals of FBT in ED patients, our findings suggest the need to investigate alternative approaches to achieve them.

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Figure Legends

Supplementary Figure 1: Example of the data collection sheet used in the study

Supplementary Figure 2: Change in mean arterial pressure (MAP), heart rate, body temperature and respiratory rate at 10 minutes, 1 hour and 2 hour after the administration of all fluid bolus (solid line) (n=303) and fluid bolus in shock patients (n=66) (dotted line). Analysed with repeated measures ANOVA. Data presented as Median (IQR).

Table 1: Demographic features and details of 500 episodes of FBT administered in 452 patients examined in the study.

Age (years)	59 (36-76)
Male n (%)	259 (57%)
Weight (Kg) n (%)	
< 40	4 (1%)
40- 59	32 (7%)
60-89	294 (65%)
90-119	95 (21%)
≥ 120	27 (6%)
ED Priority n (%)	
1	62 (14%)
2	201 (44%)
3	143 (32%)
4	46 (10%)
Outcome n (%)	
Discharged Home	84 (19%)
Admitted to Ward	297 (66%)
Admitted to ICU	54 (12%)
Transferred to another Hospital	13 (3%)
Operation theatre	4 (1%)
Hospital Length of stay (days)	2 (0-8)
TIMM probability of death ¹⁵	0.011 (0.002-0.038)
Hospital Mortality	19 (4%)
Number of fluid boluses n (%)	
1	424 (94%)
2	12 (3%)
>2	16 (4%)
Amount of administered fluid (ml)	750 (500-1250)
Shock ^s n (%)	135 (27%)
Septic	80
Cardiogenic	30
Hypovolemic	28
Obstructive	6

Unknown	5
Type of fluid bolus n (%)	
0.9% Saline	421 (84%)
Hartmann	29 (6%)
Gelofusine	20 (4%)
4% Albumin	18 (4%)
Red blood cell	12 (2%)

* Data presented as Median (IQR); \$ Shock present when fluid bolus was administered, 14 patients had more than 1 cause of shock

Indication	Rationale (%)	Success rate perceived by treating clinician (%)
Low blood pressure	70	57
Increased heart rate	30	52
Clinical hypovolemia	31	74
Avoid admission to ICU/Hospital	35	85

Table 2:
Indications and perceived success

rate of FBT

Ongoing losses	30	75
Others[#]	30	63

Multiple indications may apply to a single patient

The three most common reasons for “others” were headache, nausea and deconditioning/ not coping at home

Table 3: Effect of measured variables before, 10 minutes, 1 hour and 2 hours after fluid boluses

Fluid Bolus (n=351)	Before FBT	10 minutes after FBT	P value
MAP (mm Hg)	80 (60-98)	84 (66-96)	<0.01
Heart rate (per minute)	82 (72-100)	78 (70-98)	0.04
Temperature (°C)	37.2 (36.4-37.8)	37.0 (36.1-37.6)	0.12
Respiratory rate	18 (16-22)	18 (16-24)	0.62
Fluid Bolus (n=453)	Before FBT	1 hour after FBT	P value
MAP (mm Hg)	80 (61-96)	81 (63-94)	0.23
Heart rate (per minute)	83 (72-96)	84 (74-100)	0.24
Temperature (°C)	37.3 (36.5-37.7)	36.7 (36.1-37.5)	<0.01
Respiratory rate	19 (16-23)	23 (18-25)	<0.01
Fluid Bolus (n=341)	Before FB	2 hour after FB	P value
MAP (mm Hg)	81 (63-95)	80 (62-94)	0.27
Heart rate (per minute)	82 (73-97)	84 (75-101)	0.11
Temperature (°C)	37.3 (36.5-37.7)	36.5 (36.0-37.5)	<0.01
Respiratory rate	19 (16-22)	22 (18-24)	0.03

Data presented as Median and IQR

Table 4: Changes in measured variables before and 1 hour after FBT in patients with shock and septic shock

Patients with shock at time of administering fluid bolus (n=128)			
	Before FBT	1 hour after FBT	P value
MAP (mm Hg)	65 (56-74)	68 (58-78)	0.01
Heart rate (per minute)	96 (86-114)	98 (86-112)	0.44
Temperature (°C)	37.1 (36.2-37.9)	36.7 (36.1-37.6)	0.01
Respiratory rate	19 (16-22)	22 (18-24)	<0.01
Patients with septic shock at time of administering fluid bolus (n=70)			
	Before FB	1 hour after FB	P value
MAP (mm Hg)	64 (56-74)	66 (58-78)	0.04
Heart rate (per minute)	97 (87-112)	96 (85-114)	0.34
Temperature (°C)	37.4 (36.4-37.9)	36.6 (36.1-37.5)	<0.01
Respiratory rate	19 (16-24)	22 (19-25)	0.01

Data presented as Median and IQR

Table 5: Demographic and hemodynamic profile of A) patients B) patients with shock at the time of FBT administration - classified as MAP responders and MAP non-responders after FBT.

5 A			
	Responders (n=71)	Non-responders (n=382)	P value
Age	52 (32-70)	59 (40-79)	0.01
Sex (Male)	40 (56%)	217 (57%)	1.00
Baseline Mean arterial pressure (mm Hg)	60 (51 – 71)	82 (60 – 96)	<0.01
Baseline heart rate (per minute)	98 (89-115)	81 (71-94)	<0.01
Baseline respiratory rate(per minute)	19 (17-22)	19 (16-21)	0.88
Baseline temperature (°C)	37.2 (36.3-37.9)	37.3 (36.4-37.8)	0.31
Shock present (n=128)	56 (44%)	72 (56%)	0.06
Septic shock present (n=70)	23 (33%)	47 (67%)	<0.01
5 B			
	Responders (n=56)	Non responders (n=72)	P value
Age	54 (35-70)	55 (38-75)	0.24
Sex	31 (55%)	40 (56%)	1.00
Baseline Mean arterial pressure (mm Hg)	60 (50 – 70)	61 (52 – 73)	0.55
Baseline heart rate (per minute)	98 (86-116)	97 (81-109)	0.33
Baseline respiratory rate(per minute)	19 (17-23)	19 (17-22)	0.77
Baseline temperature	37.2 (36.3-37.8)	37.1 (36.2-37.9)	0.41
Type of shock^s			
Septic shock (n=70)	23 (33%)	47 (67%)	<0.01
Cardiogenic shock (n=27)	12 (44%)	15 (56%)	0.58
Hypovolemic shock (n=26)	24 (92%)	2 (8%)	<0.01

Responders were defined as increase in mean arterial pressure by ≥ 5 mm Hg one hour after the fluid bolus.

\$ Type of shock when fluid bolus was administered, 14 patients had more than 1 cause of shock

Data presented as percentage or Median and IQR

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