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Out-of-Hospital Fluid in Severe Sepsis: Effect on Early Resuscitation in the Emergency Department

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Abstract

Background—Early identification and treatment of patients with severe sepsis improves outcome, yet the role of out-of-hospital intravenous (IV) fluid is unknown.

Objective—To determine if the delivery of out-of-hospital fluid in patients with severe sepsis is associated with reduced time to achievement of goal-oriented resuscitation in the emergency department (ED).

Methods—We performed a secondary data analysis of a retrospective cohort study in a metropolitan, tertiary care, university-based medical center supported by a two-tiered system of out-of-hospital emergency medical services (EMS) providers. We studied the association between delivery of out-of-hospital fluid by advanced life support (ALS) providers and the achievement of resuscitation endpoints (central venous pressure [CVP] ≥ 8 mmHg, mean arterial pressure [MAP] ≥ 65 mmHg, and central venous oxygen saturation [ScvO₂] $\geq 70\%$) within six hours after triage during early goal-directed therapy (EGDT) in the ED.

Results—Twenty five (48%) of 52 patients transported by ALS with severe sepsis received out-of-hospital fluid. Data for age, gender, source of sepsis, and presence of comorbidities were similar between patients who did and did not receive out-of-hospital fluid. Patients receiving out-of-hospital fluid had lower out-of-hospital mean ($\pm$ standard deviation) systolic blood pressure (95 ± 40 mmHg vs. 117 ± 29 mmHg; $p = 0.03$) and higher median (interquartile range) Sequential Organ Failure Assessment (SOFA) scores in the ED (7 [5–8] vs. 4 [4–6]; $p = 0.01$) than patients not receiving out-of-hospital fluid. Despite greater severity of illness, patients receiving out-of-hospital fluid approached but did not attain a statistically significant increase in the likelihood of achieving MAP ≥ 65 mmHg within six hours after ED triage (70% vs. 44%, $p = 0.09$). On average, patients receiving out-of-hospital fluid received twice the fluid volume within one hour after ED

triage (1.1 L [1.0–2.0 L] vs. 0.6 L [0.3–1.0 L]; p 0.01). No difference in achievement of goal CVP (72% vs. 60%; p = 0.6) or goal ScvO₂ (54% vs. 36%; p = 0.25) was observed between groups.

Conclusions—Less than half of patients with severe sepsis transported by ALS received out-of-hospital fluid. Patients receiving out-of-hospital IV access and fluids approached but did not attain a statistically significant increase in the likelihood of achieving goal MAP during EGDT. These preliminary findings require additional investigation to evaluate the optimal role of out-of-hospital resuscitation in treating patients with severe sepsis.

Keywords

sepsis; resuscitation; fluids; intravenous fluids; prehospital

Introduction

Many advances in the care of critically ill patients have come through time-sensitive patient identification and delivery of care in the out-of-hospital setting. Myocardial infarction has been presumptively diagnosed by out-of-hospital providers for over two decades,^{1,2} with improved survival achieved through both prehospital notification and medical treatment in the out-of-hospital phase.^{3–8} Early identification during out-of-hospital care and prompt notification to the emergency department (ED) have been feasible and improved outcomes in patients with acute stroke,^{9–12} traumatic injury,^{13,14} and out-of-hospital cardiac arrest.^{1,18,21}

Patients with severe sepsis have a hospital mortality rate (20%–50%) that greatly exceeds that seen in myocardial infarction, stroke, or traumatic injury.^{4,15,16}

In the past decade, studies of time-sensitive identification and treatment of patients with severe sepsis have shown an absolute reduction in mortality between 5% and 20%,^{17,18} with emphasis on early resuscitation within the first six hours after presentation.¹⁹ The success of early goal-directed therapy (EGDT), when initiated in the ED, has been demonstrated in several observational studies.^{26,29} However, an estimated one-half of patients with severe sepsis arrive to the ED after receiving care, which may include fluid resuscitation, by out-of-hospital providers.^{20,21} Perhaps limited by the difficulty of identifying patients with sepsis in the prehospital phase, the effect of out-of-hospital fluid resuscitation on clinical outcomes in severe sepsis is unknown.

Our main objective in this study was to determine whether the delivery of out-of-hospital fluid reduces the time required to achieve goal mean arterial pressure (MAP) ($\geq$ 65 mmHg) in severe sepsis patients receiving EGDT in the ED. We also sought to determine whether out-of-hospital fluid reduces the time to goal central venous pressure (CVP) ($\geq$ 8 cmH₂O) or goal central venous oxygen saturation (ScvO₂) ($\geq$ 70%). We hypothesized that a greater proportion of patients would achieve goal MAP, ScvO₂, and CVP within six hours after ED triage (based on international guidelines) after receiving out-of-hospital fluid compared with patients who did not receive out-of-hospital fluid.

Methods

This study was approved by the institutional review boards of the University of Washington and the University of Pennsylvania, with waiver of informed consent.

Study Design, Setting, and Population

This study is a secondary analysis of a retrospective cohort study designed to monitor the use of EGDT in the ED of the Hospital of the University of Pennsylvania (HUP). HUP is a 700-bed urban, tertiary care hospital with a 56-bed ED that receives approximately 55,000 adult patient visits per year. We screened all ED records (N = 113,725) from January 2005 to December 2006 for patients aged ≥ 18 years, for the following exclusion criteria: 1) discharged from the ED, 2) left against medical advice, 3) transferred to another institution, or 4) primarily evaluated as trauma patients. Among 16,550 eligible patients (Fig. 1), using a previously published method,²² further screening was performed for the following criteria: 1) presence of severe sepsis, 2) transport by city emergency medical services (EMS) to the ED, 3) "protocolized" resuscitation with EGDT, and 4) hospital admission. The EGDT protocol followed the stepwise resuscitation shown in Figure 2,²³ and the eligibility and care of patients receiving this protocol were under the direction of the attending physician. To study the effect of out-of-hospital fluid on the delivery of EGDT in the ED, we excluded patients who did not receive EGDT in the ED and patients transported by basic life support, who were not eligible for out-of-hospital fluid.

Definitions of the Variables

We suspected severe sepsis in patients in whom a serum lactate measurement was performed or patients who had physician documentation of one of the following indicators of severe sepsis in the ED electronic medical record (EMR): sepsis, severe sepsis, septic shock, cryptic septic shock, or administration of EGDT.²⁶ Subjects who met these screening criteria underwent detailed record review for the presence of the following: 1) sepsis, defined as suspected infection and two or more systemic inflammatory response syndrome (SIRS) criteria²⁴; 2) severe sepsis, defined as sepsis associated with hypoperfusion (serum lactate level ≥ 2 mmol/L),²⁵ hypotension, or organ dysfunction^{19,24,25}; and 3) septic shock, defined as hypotension (systolic blood pressure [SBP] <90 mmHg) despite adequate fluid resuscitation (>1500 mL) or the use of vasoactive agents.^{22,24,26,27} Not all severe sepsis cases found using these definitions included the provision of EGDT (Fig. 2).

Our primary exposure of interest was the delivery of out-of-hospital fluid, which we defined as the establishment of intravenous (IV) access and documentation of any IV fluid delivered by out-of-hospital providers. Paramedics in the city of Philadelphia initiate IV access and fluid resuscitation in accordance with the statewide advanced life support (ALS) protocols for Pennsylvania. General practice guidelines call for an immediate 500-mL bolus of normal saline for shock states (including septic shock) and/or hypotension; additional 500-mL boluses are recommended up to a maximum of 2 L or correction of SBP >100 mmHg. No specific protocol for sepsis resuscitation exists. Our primary outcome was the proportion of patients with severe sepsis who reached goal MAP during EGDT. According to the recommendations for the resuscitation endpoints of EGDT provided by multiple

international society guidelines,²⁸ we used a cutoff of six hours elapsed from ED triage to achieve an MAP ≥ 65 mmHg. Our secondary outcomes were the proportions of patients who achieve CVP ≥ 8 mmHg and ScvO₂ $\geq 70\%$ within six hours after ED triage.²⁸ Each time point collected during the study included the date and time in hours and minutes, allowing for precise estimates of the elapsed time between triage and goal. If a subject was placed directly into an ED treatment room prior to triage, we considered the date and time the patient was placed in the room to be the triage time (time zero). If the initial measurement for a resuscitation endpoint was at goal, we considered the time to goal to be the elapsed time between triage and the initial measurement. If the patient never achieved goal endpoints during resuscitation or died prior to six hours, the patient was coded as not reaching goal endpoint. We determined the time to endpoints without regard to patient location, as goal endpoints may have been attained after patient transfer to the intensive care unit.

Collection of Variables and Data Quality

We collected data from three sources for all subjects: 1) the out-of-hospital record, 2) the ED EMR, and 3) inpatient medical records. Out-of-hospital records are completed by city paramedics and emergency medical technicians (EMTs) using a handheld touch pad, with drop-down menus to prompt data entry. These records are considered part of the permanent hospital record for each patient and are available for review 24 hours after hospital arrival, as mandated by the Commonwealth of Pennsylvania. We abstracted pertinent demographic, comorbidity, laboratory, physiologic, and treatment data from data sources using four trained investigators with a predrafted form (DFG, MEM, RAB, and JH). Severity of organ dysfunction was quantified using the Sequential Organ Failure Assessment (SOFA) score, a previously validated scoring system used to quantify the degree of organ dysfunction for critically ill patients in the ED or intensive care unit.^{29,30} Completeness and accuracy of data abstraction were verified by one of the other investigators, with adjudication, if necessary, performed by one investigator (DFG). Vital status (alive or dead) was determined at hospital discharge.

Statistical Analysis

We expressed descriptive data as median with interquartile range (IQR) or mean with standard deviation (SD) for continuous variables and frequencies or percentiles for discrete variables. We compared variables using the Wilcoxon rank sum test, Student's t-test, Fisher's exact test, or chi-square test, as appropriate. We calculated relative risk to determine the crude association between the delivery of out-of-hospital fluid and achievement of goal MAP, CVP, or ScvO₂ within six hours after ED triage. We evaluated cumulative incidence curves with the log-rank test to illustrate the relationship between delivery of out-of-hospital fluid and the time to goal MAP as a continuous variable. We did not adjust for potential confounding variables in this cohort because of the high likelihood of biased coefficients in models fit using small sample sizes.³¹ All tests for statistical significance were two-tailed ($p < 0.05$), and analyses were conducted using STATA version 10.0 (StataCorp LP, College Station, TX).

Results

A total of 216 patients admitted with severe sepsis were transported by city EMS. Of these, 52 patients were transported by ALS and received EGDT (Fig. 1). Twenty-five patients (48%) received fluid resuscitation in the out-of-hospital phase of care. Among 27 patients not receiving IV fluid, 10 patients (37%) had unsuccessful IV access placement. As shown in Figure 3, delivery of out-of-hospital fluid was administered to only 42% of patients with an initial ED serum lactate level ≥ 4 mmol/L, and 64% of patients who were hypotensive en route to the ED.

We observed no associations between the receipt of out-of-hospital fluid and age, gender, presence of comorbidities, or source of sepsis (Table 1). Patients receiving out-of-hospital fluid had lower outof-hospital SBP, lower initial SBP on ED arrival, and higher ED SOFA scores than patients not receiving out-of-hospital fluid. Patients receiving out-of-hospital fluid had higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, higher likelihood of shock, and greater hospital mortality, although these comparisons did not reach statistical significance (Table 1).

Overall, 29 of 52 patients (56%) achieved goal MAP, 33 of 52 patients (63%) achieved goal CVP, and 21 of 52 patients (40%) achieved goal ScvO₂ within six hours after ED triage. Table 2 presents the primary and secondary results stratified by out-of-hospital fluid status. Patients receiving out-of-hospital fluid approached but did not attain a statistically significant increase in the likelihood of achieving MAP ≥ 65 mmHg (70% vs. 44%, $p = 0.09$) within six hours after ED triage. The cumulative incidence trend for the time to achievement of the goal MAP (Fig. 4) demonstrates separation between groups within two hours after ED triage (log rank $p = 0.07$). Rates of achievement of ScvO₂ $\geq 70\%$ and CVP ≥ 8 mmHg at six hours were not significantly different between groups. On average, patients who received out-of-hospital fluid resuscitation received twice as much fluid in the first hour after ED arrival than those patients not receiving out-of-hospital fluid resuscitation (1.1 L vs. 0.6 L; $p = 0.01$) (Table 3). During EGDT in the ED, no differences were present in the total volume of fluid delivered at six hour after ED triage, or in the use of mechanical ventilation, vasopressors, or blood transfusion (Table 3).

Discussion

In this cohort of patients hospitalized with severe sepsis, patients receiving out-of-hospital fluid resuscitation approached but did not attain a statistically significant increase in the likelihood of achieving goal MAP within six hours after ED triage during EGDT, despite higher measures of severity of illness. Although not statistically significant, our preliminary data suggest that, on average, patients receiving out-of-hospital fluid have approximately 50% increased chance of achieving an MAP ≥ 65 mmHg within six hours after ED triage, relative to patients not receiving out-of-hospital fluid. We also observed that up to one-third of patients with out-of-hospital hypotension did not receive out-of-hospital fluid resuscitation, and that a significantly larger volume of fluid was delivered in the first hour of EGDT in the ED among patients who received out-of-hospital resuscitation.

The overall proportions of patients achieving hemo-dynamic goals after ED triage (MAP 65 mmHg, ScvO₂ 70%, and CVP 8 cmH₂O) in the current study are similar to those of previously reported cohorts using EGDT protocols adopted from Rivers et al.^{17,19,32–34} Comparisons are limited, though, as we stratified our analysis by the use of out-of-hospital fluid, used alternate definitions of time zero when calculating time-based outcomes, and reported a lower proportion of patients with septic shock than similar studies.¹⁷ Comparing our patients who did not receive out-of-hospital fluid with those in a large multicenter, educational intervention trial of EGDT where ED triage was time zero,¹⁷ we observed a similar proportion of patients who achieved hemodynamic endpoints during ED resuscitation. Taken together, the patients and hospital resuscitation procedure herein are comparable with those in prior reports of early care of severe sepsis.

Potential mechanisms for the shorter time to achievement of goal MAP in patients receiving out-of-hospital fluid include differences in the process of care during EGDT and physiologic changes resulting from out-of-hospital resuscitation. First, patients arriving with IV access and concomitant fluid delivery may receive a greater level of attention, even when managed by the same protocol (Fig. 2), as IV access has already been established in the field. In support of this hypothesis, we observed a greater volume of fluid in the first hour after ED triage among those with out-of-hospital fluid resuscitation, but no difference, on average, in total volume of fluid delivered in the ED at six hours after triage. Alternatively, the use of vasopressors may have occurred earlier in patients receiving out-of-hospital fluid, contributing to a shorter time until achievement of goal MAP. Severity of illness, as measured by SOFA score and initial SBP measurements,^{29,35} was worse among those receiving out-of-hospital fluid, and may also account for some differences in the EGDT process. Second, fluid resuscitation in the outof-hospital phase may increase left heart filling pressures or stroke volume, increasing MAP and cardiac output.^{36,37} Given that the fluid volumes delivered in the ED at six hours after triage were equivalent, on average, between groups (Table 3), the use out-of-hospital fluid may have better optimized patients' volume status prior to ED arrival. We note, however, that no difference in initial CVP on ED arrival or time to achievement of CVP 8 mmHg during EGDT was present between groups. Technical issues related to CVP measurement may also have influenced these values.³⁸

Given the improved mortality observed among severe sepsis patients who achieve hemodynamic goals during EGDT in larger studies,^{32,39} our preliminary results may have important implications for severe sepsis patients who are transported by EMS. Despite being indicated in nearly all patients, out-of-hospital IV fluids were administered in surprisingly few patients, suggesting that improved prehospital identification of sepsis or more rigorous fluid protocols may enable earlier resuscitation in additional patients. Importantly, out-of-hospital IV access and delivery of fluid are feasible with minimal time cost in the out-of-hospital phase,^{39,40} yet more than one-third of patients not receiving fluid in our cohort had unsuccessful IV catheter placement. Our preliminary findings and the reported feasibility of this health service intervention in other cohorts argue for larger studies of protocolized out-of-hospital IV access and fluid resuscitation in appropriately identified noninjured patients while studying relevant clinical outcomes (e.g., development of acute respiratory failure or death).

Limitations And Future Research

We recognize a number of limitations to our analysis. First, the estimates of the likelihood of achieving goal MAP, CVP, and ScvO₂ during EGDT after out-of-hospital fluid resuscitation derive from a single municipal EMS agency and receiving hospital. Out-of-hospital interventions, transport times, and patient characteristics from our two-tiered, urban EMS system may not be generalizable to other EMS systems.^{41,42} However, the EGDT protocol (Fig. 2) from which our outcomes were derived has been successfully implemented in many EDs, although bundle compliance is known to vary between institutions.⁴³ Second, we were unable to adjust for severity of illness and other confounding variables because of small sample size. However, we would expect patients with greater severity of illness to have prolonged times to achievement of goal hemodynamic endpoints, a conservative bias that adds strength to our findings. Similarly, no difference in mortality was observed between patients who did and did not receive out-of-hospital fluid, an outcome we were underpowered to address in this study.

Third, we hypothesized that larger out-of-hospital fluid volume may affect time to goal MAP in a “dose–response” fashion, yet we were unable to study this because fluid volume was not routinely recorded on EMS run sheets. Without access to out-of-hospital fluid volume, we were unable to determine the incremental benefit of larger volumes of out-of-hospital fluid compared with IV access alone. Future studies that characterize the type and volume of out-of-hospital fluid will be essential to understanding the causal relationship between out-of-hospital fluid resuscitation and clinical outcomes. Finally, the definition of time zero as ED triage in time-based outcomes, in accordance with the international society guidelines, may not be appropriate in all patients as some will meet the criteria for EGDT at differing time points during their ED stays.³²

Conclusions

The out-of-hospital phase is the first opportunity to deliver IV fluid to critically ill patients, and less than half of patients admitted with severe sepsis received out-of-hospital fluid resuscitation. In patients with severe sepsis who were transported by EMS, we observed, on average, a greater volume of fluid delivered in the first hour after ED triage, and a clinically relevant, nonsignificant increase in the likelihood of achieving goal MAP within six hours after ED triage among patients receiving out-of-hospital fluid. We cautiously interpret these hypothesis-generating results as an indicator of the need for larger prospective studies to evaluate the effect of out-of-hospital fluid in appropriately identified patients on both their ED process of care and clinical outcomes.

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Figure 1.

Diagram of cohort construction. ALS = advanced life support; BLS = basic life support; ED = emergency department; EGDT = early goal-directed therapy; EMS = emergency medical services.

Department of Emergency Medicine Severe Sepsis Pathway

Figure 2.

Early goal-directed therapy protocol used in the emergency department during the time period of study (2005–2006). ABG = arterial blood gas; ACTH = adrenocorticotrophic hormone; APACHE = Acute Physiology and Chronic Health Evaluation; CVC = central venous catheter; CVP = central venous pressure (mmHg); HgB = hemoglobin (g/dL); HR = heart rate (bpm); IJV = internal jugular vein; IV intravenous; MAP = mean arterial pressure (mmHg); Norepi = norepinephrine; NS = normal saline; PRBCs = packed red blood cells; RR = respiratory rate (breaths/min); SBP = systolic blood pressure (mmHg); SCV = subclavian vein; ScvO₂ = central venous oxygen saturation; SIRS = systemic inflammatory

response syndrome; Stim = stimulation; T = temperature (°F); WBC = white blood cell count ($\times 10^9/L$). Lactate level is measured in mmol/L.

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Figure 3.

Proportion of patients with severe sepsis receiving out-of-hospital fluid, with upper bound of 95% confidence interval. SBP = systolic blood pressure; ED = emergency department; SOFA = Sequential Organ Failure Assessment (score).

Figure 4. Cumulative incidence curve for achievement of mean arterial pressure (MAP) $\geq$ 65 mmHg after emergency department (ED) triage during early goal-directed therapy. Log rank test comparing patients with and without out-of-hospital fluid, $p = 0.07$.

Table 1

Descriptive Data of Advanced Life Support Patients Receiving Early Goal-Directed Therapy

Variable	Out-of-Hospital Fluid	No Out-of-Hospital Fluid	p-Value
<i>N</i> (%)	25 (48%)	27 (52%)	—
Age, yr	66 ± 15	63 ± 16	0.47
Gender—male	15 (60%)	13 (48%)	0.39
Comorbidity	17 (68%)	17 (63%)	0.7
Sepsis source			
Respiratory	7 (28%)	11 (41%)	0.39
Urologic	9 (38%)	7 (25%)	0.55
Bacteremia	4 (17%)	4 (15%)	0.9
Other	5 (20%)	11 (41%)	0.14
Initial EMS vital signs			
Systolic blood pressure, mmHg	95 ± 40	117 ± 29	0.03
Heart rate, beats/min	104 ± 32	105 ± 31	0.87
Respiratory rate, breaths/min	19 ± 6	20 ± 6	0.57
Glasgow Coma Scale score	14 (8–15)	15 (11–15)	0.3
Oxygen saturation, %	87 ± 27	97 ± 3	0.1
Initial ED vital signs			
Systolic blood pressure, mmHg	99 ± 26	119 ± 27	0.01
Heart rate, beats/min	107 ± 29	113 ± 31	0.44
Respiratory rate, breaths/min	23 ± 7	26 ± 8	0.16
Oxygen saturation, %	97 (94–99)	97 (95–99)	0.51
Central venous pressure, cmH ₂ O	9 (6–15)	9 (4–13)	0.56
ScvO ₂ , %	74 ± 13	70 ± 14	0.34
Initial lactate level, mmol/L	5 (3–7)	5 (4–7)	0.81
SOFA score	7 (5–8)	4 (4–6)	0.01
APACHE II score	22 ± 7	19 ± 6	0.11
Shock present	15 (60%)	12 (44%)	0.26
Intensive care unit admission	19 (76%)	24 (89%)	0.9
Hospital mortality	10 (40%)	4 (15%)	0.19

Data are presented as *n* (%), median (interquartile range), or mean ± standard deviation, as appropriate.

ALS = advanced life support; APACHE = Acute Physiology and Chronic Health Evaluation; ED = emergency department; EMS = emergency medical services; ScvO₂ = central venous oxygen saturation; SOFA = Sequential Organ Failure Assessment.

Table 2

Association between the Delivery of Out-of-Hospital Fluid and Achievement of Goal Endpoints of Resuscitation within Six Hours of Emergency Department Triage*

Variable	Out-of-Hospital Fluid	No Out-of-Hospital Fluid	Unadjusted Relative Risk (95% CI)
MAP 65 mmHg	17/24 (70%)	12/26 (44%)	1.53(0.9, 2.65)
CVP 8 cmH ₂ O	18/25 (72%)	15/25 (60%)	1.2(0.8, 1.8)
ScvO ₂ 70%	13/24 (54%)	9/25 (36%)	1.5(0.8, 2.9)

Data are presented as *n/N* (%).

CI = confidence interval; CVP = central venous pressure; MAP = mean arterial pressure; ScvO₂ = central venous oxygen saturation.

* Data not available: MAP, 2 subjects, CVP, 2 subjects, ScvO₂, 3 subjects.

Table 3

Characteristics of Early Goal-Directed Therapy in the Emergency Department*

Variable	Out-of-Hospital Fluid	No Out-of-Hospital Fluid	p-Value
Resuscitation procedure after ED triage			
Intravenous fluid delivered in first hour, L	1.1 (1.0–2.0)	0.6 (0.3–1.0)	0.01
Intravenous fluid delivered in first six hours, L	3.0 (2.5–4.5)	3.0(2.0–4.3)	0.3
Use of vasopressors	8 (32%)	8 (30%)	0.9
Blood transfusion	1 (4%)	1 (4%)	0.9
Mechanical ventilation	8 (32%)	10 (37%)	0.8
Elapsed time to clinical endpoints after ED triage, min			
CVP 8 cmH ₂ O	216 (181–287)	292 (131–365)	0.7
MAP 65 mmHg	241 (195–281)	349 (192–427)	0.1
ScvO ₂ 70%	242 (188–393)	366 (191–673)	0.3

CVP = central venous pressure; ED = emergency department; MAP = mean arterial pressure; ScvO₂ = central venous oxygen saturation.* Data are presented as median (interquartile range) or *n* (%), as appropriate.