ARTICLE IN PRESS
YAJEM-57286; No of Pages 5
American Journal of Emergency Medicine xxx (2018) xxx–xxx
Contents lists available at ScienceDirect
American Journal of Emergency Medicine
journal homepage: www.elsevier.com/locate/ajem

Fluid resuscitation in pre-hospital management of septic shock

Romain Jouffroy, M.D. [*,1], Anastasia Saade, M.D., Ph.D. [1], Alexandre Muret, M.D., Pascal Philippe, M.D., Maud Michaloux, M.D., Pierre Carli, M.D., Ph.D., Benoit Vivien, M.D., Ph.D.

Department of Anesthesia & Intensive Care Unit, SAMU, Hôpital Necker Enfants Malades, 149 rue de Sèvres, 75015 Paris, France

1. Introduction

The estimated incidence of sepsis is approximately 300 per 100,000 inhabitants [1,2], making sepsis a major public health problem, with a mortality rate reaching 30% at day 28 (D28) [1,3-5]. The outcome of septic patients relies on the early identification and rapid implementation of appropriate treatments, including hemodynamic optimization and antibiotics administration [3,6]. Hemodynamic failure is frequently encountered in most severe forms of sepsis and often has to be initially managed in a pre-hospital setting. Hypotension and its consequences, i.e. neurological failure and/or weakness, are the most common symptoms for people to call emergency services. In France, out-of-hospital emergencies are managed by the Service d'Aide Médicale d'Urgence (SAMU) [7]. For medical assistance, the SAMU can be reached dialling the number 15. The SAMU hospital-based team is composed of switchboard operators and physicians. Over the phone, the SAMU determine the appropriate level of care to dispatch to the scene, based on patient's symptoms communicated by the patient itself, by a relative or any witness. For life-threatening emergencies, the "Service Mobile d'Urgence et de Réanimation" (SMUR), a mobile intensive care unit (MICU), is dispatched to the scene. The MICU is composed of a driver, a nurse and an emergency physician [7]. MICU is equipped with medical devices and drugs allowing initial management of main organs deficiency (neurological, respiratory and cardiovascular).

The first step in hemodynamic resuscitation relies on early fluid expansion that has to be administered within the first hour [8]. In a lot of situations, fluid resuscitation is initiated in a pre-hospital setting. The benefit of early fluid expansion is described in the management of trauma [9,10] as in septic shock and associated with a hospital mortality decrease [11].

The aim of this study was to describe qualitative and quantitative fluid resuscitation in patients with septic shock managed by MICU in a pre-hospital setting and its adequacy with recommendations [8] to evaluate its impact on mortality at D28.

2. Methods

2.1. Study population

All consecutive patients admitted to the intensive care unit (ICU) of Necker Hospital for septic shock, between January 2012 and January 2014, who received pre-hospital medical care by MICU, were retrospectively analysed. Septic shock was defined according to the surviving sepsis campaign criteria [8].

The primary outcome was mortality at day 28.

Institutional review board (Comité de Protection des Personnes Paris-Ile de France 2 - Number ID-RCB: 2012-A01289-34) approved the study with a waiver of signed informed consent.

2.2. Data collection

Data were extracted from medicals reports (pre-hospital and ICU).

Variables were defined prior to data collection and included: patients' demographic characteristics (age, weight, size, and gender), immunosuppression status, initial pre-hospital vital signs (mean blood pressure, diastolic and systolic blood pressure, heart rate, pulse oximetry, respiratory rate, and temperature), duration of pre-hospital care, and length of stay in the ICU. Immunosuppression was defined by the presence of one or more elements between: diabetes mellitus, chronic renal insufficiency, corticosteroids or another immunosuppressive treatment, infection by human immunodeficiency virus and/or C hepatitis viral.

2.3. Statistical analysis

Qualitative and quantitative characteristics of fluid resuscitation administered in the pre-hospital setting were analysed.

Fluid expansion indexed on body weight (BW) and ideal body weight (IBW) was estimated using Lorentz formula. The "grey zone" concept was applied and 3 categories of patients were defined according to quantitative fluid resuscitation [12,13]. "Low fluid expansion" corresponded to <10 ml/kg IBW, "optimal fluid expansion" to >20 ml/kg IBW and the 'grey zone' was defined as fluid expansion between 10 and 20 ml/kg IBW. The 'optimal fluid expansion' volume was defined according to the Surviving Sepsis Campaign guidelines, describing the association between fluid volume expansion and mortality [8].

Predictive performances of pre-hospital fluid volume expansion for mortality was evaluated using adjusted average receiver operating characteristic (ROC) curves obtained by averaging 10,000 bootstrapped samples (sampling with replacement). The aim of this method is to limit the impact of outliers and to allow the provision of more robust presentations [12].

Thereafter, univariate and multivariate analyses were conducted to evaluate the relationship between all covariables and mortality at D28. Variables included in multivariate analysis were chosen considering

* Corresponding author.
E-mail address: romain.jouffroy@aphp.fr (R. Jouffroy).
[1] Contribute equally to the manuscript.

https://doi.org/10.1016/j.ajem.2018.01.078

their potential impact on outcome on one side and on their availability in pre-hospital medicals reports.

Results are expressed as mean with standard deviation for quantitative parameters with normal distribution, or median with interquartile range (25–75) for non-normal distribution and, as absolute value and percentage for qualitative parameters. Results are given as Odds Ratio (OR) with 95% confidence interval (95% CI).

All analyses were performed using R 3.4.2 (http://www.R-project.org; the R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study characteristics

Ninety-five patients initially managed in a pre-hospital setting for septic shock prior to their admission in the ICU were included in this study.

Populations' demographic and clinical characteristics are summarized in Table 1. Fifty-six patients (59%) were male with a mean age of 70 ± 15 years. Septic shock was mainly associated with pulmonary (68%), urinary (16%) or abdominal (8%) infections (Table 2).

The median length of stay in the ICU was of 6 (2−13) days (Table 1). Mortality reached 34% at D28.

3.2. Main measurements

No significant difference was observed in the duration of pre-hospital medical care between alive and deceased patients (101 ± 34 min vs 93 ± 34 min respectively, $p = 0.29$; Table 1). Pre-hospital fluid expansion was performed using crystalloids, e.g. serum saline in 98% of the cases.

Mean pre-hospital fluid expansion was 1158 ± 559 ml in the overall population and reached 1287 ± 553 ml vs 906 ± 487 ml in alive and deceased patients respectively ($p = 0.001$) (Table 1).

Table 1
Demographic, clinical and biological characteristics of patients with septic shock managed by pre-hospital mobile intensive care units.
Quantitative variables are expressed as mean ± standard deviation, apart for "length of stay in the ICU" which has no normal distribution. Qualitative variables are expressed as absolute value and percentage.

	Alive at D28 (n = 63)	Deceased at D28 (n = 32)	Overall population (n = 95)
Age (years)	68 ± 15	73 ± 14	70 ± 15
Weight (kg)	69 ± 14	65 ± 15	67 ± 15
Size (cm)	171 ± 8	168 ± 7	170 ± 8
Male gender	40 (63%)	16 (50%)	56 (59%)
Immunosuppression	35 (56%)	14 (44%)	49 (52%)
Mean blood pressure (mm Hg)	65 ± 21	69 ± 24	72 ± 20
Systolic blood pressure (mm Hg)	90 ± 27	58 ± 19	99 ± 24
Diastolic blood pressure (mm Hg)	55 ± 21	58 ± 19	60 ± 19
Heart rate (beats/min)	120 ± 28	109 ± 27	121 ± 24
Pulse oximetry (%)	89 ± 10	87 ± 12	83 ± 11
Respiratory rate (moves/min)	30 ± 8	33 ± 7	30 ± 9
Duration of pre-hospital care (min)	101 ± 34	93 ± 34	99 ± 34
Length of stay in the ICU (days)	5 (3–14)	6 (2−10)	6 (2–13)
Fluid volume expansion (ml)	1287 ± 553	906 ± 488	1158 ± 559
Fluid volume expansion indexed on BW (ml/kg)	20 ± 10	16 ± 12	18 ± 11
Fluid volume expansion indexed on IBW (ml/kg)	20 ± 9	15 ± 8	18 ± 9
Fluid volume expansion indexed on IBW < 10 ml/kg	11 (42%)	15 (58%)	26 (27.4%)
Fluid volume expansion indexed on 10 < IBW < 20 ml/kg	17 (65%)	9 (35%)	26 (27.4%)
Fluid volume expansion indexed on IBW > 20 ml/kg	35 (81%)	8 (19%)	43 (45.2%)

Table 2
Origin of sepsis of patients with septic shock initially managed in a pre-hospital setting.
Data are expressed as absolute value with percentage.

Site of infection	n (%)
Pulmonary	65 (68%)
Urinary	15 (16%)
Digestive	8 (8%)
Cutaneous	2 (2%)
Invasive medical device	2 (2%)
Meningeal	1 (1%)
Dental	1 (2%)
Undefined	2 (2%)

Mean pre-hospital fluid expansion indexed on BW was 18 ± 11 ml/kg in the overall population and 20 ± 10 ml/kg vs 16 ± 12 ml/kg in alive and deceased patients respectively ($p = 0.09$) (Table 1).

Mean pre-hospital fluid expansion indexed on IBW was 18 ± 9 ml/kg in the overall population, 20 ± 9 ml/kg in alive and 15 ± 8 ml/kg in deceased patients ($p = 0.005$) (Table 1).

The area under the average ROC curve [95% CI] (Fig. 1) for pre-hospital fluid expansion and pre-hospital fluid expansion indexed on IBW were respectively of 0.70 [0.58–0.81] and 0.67 [0.55–0.78].

Visual subjective analysis of pre-specified categories (<10, 10–20 and 20 ml/kg fluid expansion indexed on IBW) showed an inversed linear association between fluid expansion indexed on IBW and mortality (Fig. 2).

Absolute values (A) and proportion (B) of patients in the predefined categories of pre-hospital fluid volume expansion indexed on ideal body weight. Black plot represents deceased patients and white plot alive patients.

In univariate analysis, mortality was significantly association with fluid expansion: $p = 0.002$, OR [95% CI] = 0.998 [0.997–0.999], fluid expansion indexed on IBW: $p = 0.007$, OR [95% CI] = 0.93 [0.88–0.97], fluid expansion indexed on IBW < 10 $p = 0.003$, OR [95% CI] = 4.17 [1.89–9.43] and fluid expansion indexed on IBW > 20: $p = 0.006$, OR [95% CI] = 0.27 [0.12–0.57] (Table 3). No significant association was observed between mortality and fluid expansion indexed on IBM between 10 and 20 ml/kg: $p = 0{,}91$, OR [95% CI] = 1.06 [0.47–2.33] (Table 3).

Using logistic regression model, including age, immunosuppression, pre-hospital duration as covariables, association with mortality only remained significant for fluid expansion indexed on IBW: $p = 0.02$, ORa [95% CI] = 0.93 [0.89–0.98], fluid expansion indexed on IBW < 10 $p = 0.005$, OR [95% CI] = 4.03 [1.78–9.41] and fluid expansion indexed on IBW > 20: $p = 0.01$, OR [95% CI] = 0.30 [0.13–0.66] (Table 4).

4. Discussion

Among 95 patients with septic shock initially managed by pre-hospital medical teams and admitted to the ICU, fluid resuscitation was mainly performed using crystalloids. Interestingly, quantitative pre-hospital fluid expansion indexed on ideal body weight was lower than recommended within the first hour. An inversed association between mortality and fluid expansion indexed on ideal body weight was observed. In other words, fluid volume expansion indexed on ideal body weight lower than 10 ml/kg was associated with increased mortality whereas fluid volume expansion indexed on ideal body weight >20 ml/kg was associated with decreased mortality.

Sepsis is characterized by relative and absolute hypovolemia, due to vasodilatation. The body compensate with increased heart rate and blood vessels constriction to maintain blood pressure and organ perfusion. Decompensation results in hypotension with hypoperfusion of peripheral organ leading to organ failure associated with poor prognosis [14].

One major prognosis factor is the early initiation of treatments [15,16]. Bundle of care including early identification of sepsis and early instauration of treatments proved their efficacy in the reduction

Please cite this article as: Jouffroy R, et al, Fluid resuscitation in pre-hospital management of septic shock, American Journal of Emergency Medicine (2018), https://doi.org/10.1016/j.ajem.2018.01.078