



Boletín Médico del Hospital Infantil de México

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RESEARCH PAPER

Fluid balance and acute kidney injury in septic shock[☆]



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Received 26 August 2016; accepted 20 February 2017

KEYWORDS

Fluid balance;
Septic shock;
Acute kidney injury;
Mortality;
Pediatric intensive
care units

Abstract

Background: In patients with septic shock, excessive fluid administration can lead to increased morbidity and mortality. The aim of this study was to evaluate the association between fluid balance, acute kidney injury and mortality in patients with septic shock.

Methods: A study of cases and controls was conducted in a pediatric intensive care unit. The fluid balance in the first 72 h and the presence of acute kidney injury was compared in patients diagnosed with septic shock who died against patients who survived the same condition. Univariate and multivariate analyses were performed.

Results: Forty-five cases and forty-five controls were included in the analysis. Mortality was associated with Pediatric Risk of Mortality (PRISM III) ≥ 26 points (OR 7.5, 95% CI 2.8-18.7; $p=0.000$), Pediatric Logistic Organ Dysfunction (PELOD) ≥ 24 points (OR 11.0, 95% CI 4.1-29.4; $p=0.000$), creatinine ≥ 0.65 mg/dl (OR 5.6, 95% CI 2.2-13.9; $p=0.000$), lactate ≥ 2.5 mmol/l (OR 2.5, 95% CI 1.1-5.9; $p=0.033$), SvO₂ $< 60\%$ (OR 4.6, 95% CI 4.5-4.5; $p=0.001$), positive balance $> 9\%$ in 72 h (OR 4.3, 95% CI 1.6-11.7; $p=0.003$), acute kidney injury (OR 5.7, 95% CI: 2.2-15.1; $p=0.000$). In the multivariate model, the values of PRISM ≥ 26 and PELOD ≥ 24 points were significant.

Conclusions: In patients who died due to septic shock, the multivariate model showed an association with PRISM ≥ 26 and PELOD ≥ 24 and a trend toward association with SvO₂ $< 60\%$ and positive balance of liquids $> 9\%$.

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[☆] Please cite this article as: Martínez-García JJ, León-Sicairos NM, Canizalez-Román A, García-Arellano BA. Balance de líquidos y lesión renal aguda en el choque séptico. Bol Med Hosp Infant Mex. 2017;74:282–288.

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PALABRAS CLAVE

Balance de líquidos;
 Choque séptico;
 Lesión renal aguda;
 Mortalidad;
 Unidad de terapia
 intensiva pediátrica

Balance de líquidos y lesión renal aguda en el choque séptico**Resumen**

Introducción: En el paciente con choque séptico, la administración excesiva de líquidos puede incrementar la morbilidad y mortalidad. El objetivo de este estudio fue evaluar la asociación entre el balance de líquidos, la lesión renal aguda y la mortalidad en pacientes con choque séptico.

Métodos: Se realizó un estudio de casos y controles en una unidad de terapia intensiva pediátrica. Se comparó el balance de líquidos en las primeras 72 h y la presencia de lesión renal aguda en pacientes con diagnóstico de choque séptico que fallecieron contra pacientes que sobrevivieron a la misma patología. Se realizó un análisis univariado y multivariado.

Resultados: Se incluyeron 45 casos y 45 controles en el análisis. La mortalidad se asoció con riesgo pediátrico de mortalidad (PRISM) ≥ 26 puntos (RM 7.5, IC 95% 2.8-18.7; $p=0.000$), disfunción orgánica logística pediátrica (PELOD) ≥ 24 puntos (RM 11.0, IC 95% 4.1-29.4; $p=0.000$), creatinina ≥ 0.65 mg/dl (RM 5.6, IC 95% 2.2-13.9; $p=0.000$), lactato ≥ 2.5 mmol/l (RM 2.5, IC 95% 1.1-5.9; $p=0.033$), SvO₂ $< 60\%$ (RM 4.6, IC 95% 4.5-4.5; $p=0.001$), balance positivo $> 9\%$ en 72 h (RM 4.3, IC 95% 1.6-11.7; $p=0.003$), lesión renal aguda (RM 5.7, IC 95% 2.2-15.1; $p=0.000$). En el modelo multivariado, PRISM ≥ 26 y PELOD ≥ 24 puntos permanecieron significativas.

Conclusiones: En los pacientes que fallecieron por choque séptico, el modelo multivariado mostró una asociación con PRISM ≥ 26 y PELOD ≥ 24 y una tendencia hacia la asociación con SvO₂ $< 60\%$ y balance de líquidos positivo $> 9\%$.

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1. Introduction

Septic shock approach guided by goals has reduced morbidity and mortality both in adults and children.¹ These guides encompass early recognition of the problem, vascular access, fluid resuscitation, antibiotics therapy and use of vasopressors during the first hour. Early fluid resuscitation is the cornerstone in the management of shock, and it is part of the goal-directed therapy of the "Surviving sepsis" campaign, aimed at restoring the hemodynamic integrity and tissue perfusion.² However, the critical patient has an increased fluid retention secondary to an enlarged capacity of intravascular space and third space, as well as a decreased renal ability to excrete the fluid excess.³⁻⁵ The positive fluid balance has been associated with an increase in morbidity and mortality in patients with acute lung injury and septic shock. Probably this is because excessive fluid administration in patients with sepsis can lead to impairment of respiratory function, increased intraabdominal pressure, clotting disorders and cerebral edema.^{6,7}

Recent observational papers showed an association between fluid overload and increased morbidity and mortality in the pediatric population, especially after cardiac surgery and in children requiring continuous renal replacement therapy.⁸⁻¹² Acute kidney injury contributes directly to the water and sodium clearance and excretion and has been established as a mortality risk factor.^{13,14} In studies were children with septic shock where fluid overload was evaluated, acute kidney injury and the impact on mortality are scarce and the size of the sample is generally small.

This study aimed to compare the positive fluid balance and acute kidney injury (AKI) among a group of pediatric patients who died of septic shock and children with septic shock who survived. The hypothesis assumes that fluid overload and AKI during the first 72 hours was higher in patients who died from septic shock.

2. Methods

The study was conducted in the pediatric intensive care unit (PICU) of the Children's Hospital Dr. Rigoberto Aguilar Pico, in Sinaloa, Mexico, from January 2010 to December 2014. The Institutional Research Committee approved the study.

For the study, physical or electronic records from patients aged ≤ 18 years diagnosed with septic shock and hospitalization in PICU ≥ 72 hours were included. Patient records with hospital admission < 48 hours, deaths or transfer out of the PICU, infants < 30 days and records with incomplete data were excluded. To homogenize the condition in the case and control groups, children with chronic diseases, such as kidney failure, complex congenital heart disease and with surgical correction of congenital heart disease were excluded.

2.1. Operational definition of variables

The fluid balance was estimated by the difference between the total liquids administered and the total of outflows or losses during the first 72 hours of admission to the PICU. The

percentage of patient body weight was expressed according to the following formula:

Income (liters) – Expenses (liters)/admission weight (kg) at PICU x 100

For the fluid balance calculation, admission weight of the patient to PICU¹⁵ was documented.

Septic shock was defined as an acute organ failure (acute renal failure, respiratory failure) in the presence of an infection and the need for vasopressor for more than six hours. Respiratory failure was defined as the need for respiratory support (noninvasive and invasive ventilation).¹⁶

AKI was defined as an increase in serum creatinine \geq 50% of baseline when admitted to PICU and/or urine output $<$ 0.5 ml/kg per hour for six hours, according to the criteria of the Acute Kidney Injury Network (AKIN).¹⁷

Pediatric Risk of Mortality (PRISM) score was defined as the score that estimates the risk of mortality at PICU with the information obtained at admission.¹⁸

The Pediatric Logistic Organ Dysfunction score (PELOD) assigns values to each organ failure according to severity. Subsequently, these values are summarized in a score that corresponds to the sum of the individual scores.¹⁹

Other variables included were age, gender, days of hospitalization in the PICU, ventilation assistance, serum lactate, serum creatinine, the primary site of infection, central venous oxygen saturation (ScvO₂) and AKI.

Patients who died of septic shock were considered as cases and children who survived the septic shock, as controls.

2.2. Sample size

The sample size was estimated according to the comparison of mortality reported by Bhaskar et al.²⁰, wherein the group of patients with septic shock and fluid overload showed a mortality of 37% and in the group with septic shock without fluid overload mortality was 3%, with an alpha of 0.05 and a statistical power (1- β) of 80%. The minimum sample size for each group was 21 cases of patients with septic shock.

2.3. Statistical analysis

For the analysis of demographic and clinical variables, descriptive statistics were used. According to the non-normal data distribution, medians and interquartile ranges (IQR) or proportions were used. For comparisons between groups, the continuous variables were compared by Mann-Whitney U test for non-normal distribution variables. The unvaried analysis was performed between the dependent and independent variables. For this analysis, the categorical variables were transformed into indicator variables and the continuous variables into dichotomous variables when analyzing the best cut on the ROC (Receiver Operating Characteristic) curve. Variables with p -value \leq 0.1 were introduced to multivariate analysis. A value of $p <$ 0.05 was considered statistically significant for all comparisons. The statistical analysis was performed with the SPSS package version 22.0.

3. Results

During the study period, 925 patients were admitted to the PICU, of which 16.9% (157/925) were diagnosed with septic shock. Sixty-seven patients did not meet the inclusion criteria, and 90 patients were included in the final analysis: 45 cases (non-survivors) and 45 controls (survivors). The median age was 12 months [IQR (25-75) 4-65 months]. Male gender presented a frequency of 60% (54/90). The median for fluid balance at 72 hours was 141 ml [IQR (25-75) -99-427 ml]. A percentage of 36.6% (33/90) presented acute kidney failure (Table 1). All patients received vasopressors and assistance with mechanical ventilation.

Univariate analysis showed that a PRISM \geq 26 points (OR 7.5; 95% CI 2.8-18.7), a PELOD \geq 24 points (OR 11.0; 95% CI 4.1-29.4), creatinine \geq 0.65 mg/dl (OR 5.6; 95% CI 2.2-13.9), lactate \geq 2.5 mmol/l (OR 2.5; 95% CI 1.1-5.9), ScvO₂ $<$ 60% (OR 4.6; 95% CI 4.5-4.5), positive balance $>$ 9% of weight in 72 hours (OR 4.3; 95% CI 1.6-11.7) and acute kidney injury (OR 5.7; 95% CI 2.2-15.1) were associated with mortality (Table 2).

Multivariate analysis showed that a PRISM \geq 26 points (OR 4.24; 95% CI 1.27-14.07) and a PELOD \geq 24 points (OR 3.74, 95% CI 1.16-12.09) remained significantly associated with mortality. Variables like ScvO₂ (OR 3.49; 95% CI 0.99-12.29) and positive balance $>$ 9% of weight in 72 hours (OR 3.91; 95% CI 0.98-15.47) showed a tendency to be associated with mortality, while AKI was not statistically significant (Table 3).

4. Discussion

Septic shock is characterized by increased capillary permeability. Given the need to maintain an acceptable intravascular volume to preserve cardiac output, large quantities of fluids are administered, which contribute to fluid overload and affect multiple organs. In patients with acute lung injury, fluid overload increases the risk of morbidity and mortality.²⁰⁻²³ There is a limited number of pediatrics studies that evaluate fluid overload, acute kidney injury, and septic shock mortality. Bhaskar et al.²⁰ conducted a case-control study nested in a cohort to evaluate the association between fluid overload and mortality in children going into shock. Mortality was higher in the group with fluid overload (26% in the group with overload compared to 6% in the group without fluid overload, $p = 0.03$). In this sample, 114 patients with shock from different etiologies were included. In contrast, the present study included only children with septic shock with very similar baseline characteristics; fluid balance and overload were significantly higher, and values were statistically significant in univariate analysis in patients who did not survive.²⁰ These findings differ with data reported by Sinitsky et al.²², who studied a retrospective cohort with 636 patients with different diagnoses. (The most prevalent were from a respiratory origin, with 59%). The purpose of this study was to explore the association of fluid overload during the first 48 hours of invasive ventilation with the ventilation period and the mortality.

Fluid overload was significantly associated with patients who did not survive and had the following characteristics:

Table 1 General characteristics of the patients.

Characteristics	All patients (n = 90)	Non-survivors (n = 45)	Survivors (n = 45)	p value
Age (months)*	12 (4-65)	14 (4-142)	12 (2-136)	0.114
Weight (kg)*	9.7 (4.9-20.1)	9.9 (5.0-28.0)	9.6 (4.4-23.0)	0.311
Gender n (%)				
Male	54 (60)	28 (62)	26 (58)	0.667
Female	36 (40)	17 (38)	19 (42)	
Time of stay in the PICU (days)*	17 (7-28)	17 (5-28)	16 (9-28)	0.412
PRISM*	26 (21-33)	32 (25-39)	23 (19-26)	0.000
PRISM \geq 26 [n (%)]	52 (57.7)	36 (80.0)	16 (35.6)	0.000
PELOD*	26 (21-34)	34 (26-43)	21 (16-26)	0.000
PELOD \geq 24 [n (%)]	48 (53.3)	36 (80.0)	12 (26.7)	0.000
Creatinine (mg/dl)*	0.57 (0.40-0.95)	0.83 (0.50-1.1)	0.46 (0.40-0.63)	0.000
Creatinine \geq 0.65 mg/dl [n (%)]	40 (44.4)	29 (64.4)	11 (24.4)	0.000
Lactate (mmol/l)*	2.8 (2.0-4.2)	3.1 (2.5-4.9)	2.0 (2.3-3.1)	0.050
Lactate \geq 2.5 mmol/l [n (%)]	52 (57.7)	31 (70.0)	21 (46.7)	0.033
ScvO ₂ (%)*	65 (54-77)	53 (35-70)	74 (63-85)	0.000
ScvO ₂ < 60% [n (%)]	38 (0.42)	27 (60.0)	11 (24.4)	0.001
Positive fluid balance > 9% weight 72 hours [n (%)]	27 (30.0)	20 (44.4)	7 (15.6)	0.003
AKI [n (%)]	33 (36.7)	25 (55.6)	8 (17.8)	0.000
Infectious site [n (%)]				0.061
Respiratory	41 (45.5)	22 (49)	19 (42)	
Abdominal	24 (26.7)	13 (29)	11 (24)	
Urinary tract	9 (10.0)	5 (11)	4 (9)	
CNS	8 (8.9)	5 (11)	3 (7)	
Others	8 (8.9)	0	8 (18)	

* median (IQR 25-75).

PICU, Pediatric Intensive Care Unit; PRISM, Pediatric Risk of Mortality; PELOD, Pediatric Logistic Organ Dysfunction; ScvO₂, Central venous oxygen saturation; AKI, acute kidney injury; CNS, central nervous system.**Table 2** Univariate analysis of clinical and laboratory characteristics among non-survivors and survivors septic shock pediatric patients.

Characteristics	Non-survivors (n = 45)	Survivors (n = 45)	OR (95% CI)	p value
Age (months)*	14 (1-207)	12 (1-185)	—	0.114
Male [n (%)]	28 (52)	26 (48)	0.83 (0.35-1.9)	0.667
Time of stay in the UTIP (days)*	15 (3-18)	12 (3-18)	—	0.264
PRISM \geq 26 [n (%)]	36 (80.0)	16 (35.6)	7.25 (2.8-18.7)	0.000
PELOD \geq 24 [n (%)]	36 (80.0)	12 (26.7)	11.0 (4.1-29.4)	0.000
Creatinine \geq 0.65 mg/dl [n (%)]	29 (64.4)	11 (24.4)	5.6 (2.2-13.9)	0.000
Lactate \geq 2.5 mmol/l [n (%)]	31 (70.0)	21 (46.7)	2.5 (1.1-5.9)	0.033
ScvO ₂ < 60% [n (%)]	27 (60.0)	11 (24.4)	4.6 (1.9-4.5)	0.001
Positive fluid balance > 9% weight 72 hours [n (%)]	20 (44.4)	7 (15.6)	4.34 (1.6-11.7)	0.003
AKI [n (%)]	25 (55.6)	8 (17.8)	5.70 (2.2-15.1)	0.000

* median (IQR 25-75).

OR, Odds Ratio; 95% CI, 95% confidence interval; PICU, Pediatric Intensive Care Unit; PRISM, Pediatric Risk of Mortality; PELOD, Pediatric Logistic Organ Dysfunction; ScvO₂, central venous oxygen saturation; AKI, acute kidney injury.

PRISM with a high score, younger age, patients requiring vasopressors, patients with continuous renal replacement therapy, high oxygenation index at 48 hours, and days of invasive ventilation. No significant association between the

percentage of fluid overload and mortality was found. In this study, organic failure was not evaluated, and no patients with septic shock were included. Abulebda et al.¹⁵ conducted a multicenter retrospective study in 17 intensive care

Table 3 Multivariate analysis.

Variable	OR	95% CI	<i>p</i> value
PRISM \geq 26	4.24	1.27-14.07	0.018
PELOD \geq 24	3.74	1.16-12.09	0.027
Creatinine \geq 0.65 mg/dl	5.47	0.57-52.31	0.140
Lactate \geq 2.5 mmol/l	1.12	0.32-3.85	0.857
ScvO ₂ < 60%	3.49	0.99-12.29	0.051
Positive fluid balance > 9% weight 72 hours	3.91	0.98-15.47	0.052
AKI	2.27	0.21-24.67	0.499

OR, odds ratio; 95% CI, 95% confidence interval; PICU, Pediatric Intensive Care Unit; PRISM, Pediatric Risk of Mortality; PELOD, Pediatric Logistic Organ Dysfunction; ScvO₂, central venous oxygen saturation; AKI, acute kidney injury.

units to assess the association between fluid balance and mortality risk stratified into three categories (low, intermediate, and high) with a validated scale called PERSEVERE (PEdiatRiC SEpsis biomarkEr Risk modEL)—in a very heterogeneous group of 317 patients with septic shock. The authors evaluated fluid balance during the first 24 hours, accumulated fluid balance in 7 days and mortality within 28 days in all three categories. Fluid overload was most often associated with mortality in only the low-risk group, with a marginal result to consider it a risk (OR 1.035; 95% CI 1.004-1.066, $p=0.024$). Patients who did not survive were younger, with a more severe disease, renal failure, and with fluid overload and balance at 24 hours. The results of this study are similar those obtained in this research, except age, which was not homogeneous in both study groups.

Sepsis and septic shock are the leading causes of AKI and this association dramatically increases mortality, especially in patients with fluid overload. Fluid overload and oliguria in patients with septic shock were important factors in the increased mortality at 28 days.²⁴⁻²⁹ Li et al.²⁴ conducted a study in a prospective cohort for eight months in a PICU to assess the impact of fluid overload during the first 24 hours of admission on the development of AKI and mortality. Among a sample of 370 patients, they reported a mortality of 15.6% to the patients with fluid overload versus 2.6% in the group of patients without fluid overload; 18.8% on patients with AKI versus 4.2% with no AKI ($p < 0.001$). In this study, a significant sample included patients with a wide diagnostic heterogeneity. The septic patient sample was reduced: 28 patients without overload and ten patients with fluid overload. These results matched with this study at 72 hours, where a statistically significant association between fluid overload and AKI was found in the univariate analysis but not in the multivariate analysis.

Liquids are the cornerstone in the treatment of patients in a critical condition. Although the benefits of acute and early fluid resuscitation in patients with septic shock and AKI have been accepted, doubts about the benefits of aggressive fluid resuscitation in these patients exist with the available information. Uncertainty lies mainly in liquid volume, its

characteristics, and time of administration. An association between fluid overload and increased risk of AKI and mortality has been observed. In a study in 30 intensive care units with a sample of 2526 patients, Wang et al. reported an incidence of AKI during the first 72 hours in 1172 patients (46.3%); fluid overload increased 4.5 times the risk and severity of AKI.²⁹

The fact that fluid overload is associated with AKI does not prove a cause-effect relationship. In patients with severe sepsis, AKI and fluid overload share the same effects at the endothelial level due to an inflammatory response, an ischemic process or an ischemia-reperfusion injury; as a result, a capillary leak and multiple organ failures may present. Therefore, the patients in a more severe state have a more severe endothelial damage and develop a faster fluid overload and an AKI after the liquid administration.

The limitations of the present study are those of a retrospective study that does not guarantee the accuracy of the data from the clinical record, besides not ensuring homogeneity, representativeness and simultaneity of cases and controls. Although all patients received vasopressors and mechanical ventilation assistance, homogeneity is not guaranteed. The main limitation is that the volume and fluid balance before the admission to the PICU were not considered.

The statistical inference to other PICU is limited; the sample was not probabilistic for convenience, and although the sample size was calculated by the difference in proportions, data was obtained from a PICU with a different mortality rate. Based on the preceding, it is considered that the outcome could change onwards the statistical association between fluid balance > 9% and mortality in patients with septic shock by increasing the sample size.

In conclusion, the multivariate model found a significant association between the risk of mortality and organ dysfunction, assessed by the PRISM III and PELOD, respectively, in patients who died from septic shock. Also, there is a tendency of association between ScvO₂ < 60% and the positive fluid balance > 9% at 72 hours with mortality in patients with septic shock. However, no statistically significant difference was found due to the sample size.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Funding

There was no external funding. The authors funded expenses arising from this research.

Conflict of interests

The authors declare no conflicts of interest of any nature.

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