



ผลของการให้สารน้ำปริมาณมากเทียบกับปริมาณน้อยในห้องฉุกเฉินต่อการเสียชีวิตในผู้ป่วยที่มีภาวะพิษเหตุติดเชื้อ

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Effects of High versus Low Volume of Initial Fluid Resuscitation of Emergency Department Patients with Sepsis and Septic Shock

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บทคัดย่อ

หลักการและวัตถุประสงค์: การให้สารน้ำเป็นการรักษาที่สำคัญในการรักษาผู้ป่วยที่มีภาวะพิษเหตุติดเชื้อ ตามคำแนะนำของแนวทางการรักษาผู้ป่วยพิษเหตุติดเชื้อได้แนะนำให้สารน้ำอย่างน้อย 30 มิลลิลิตรต่อกิโลกรัมในสามชั่วโมงแรกในการรักษาผู้ป่วยกลุ่มดังกล่าว อย่างไรก็ตามคำแนะนำดังกล่าวไม่มีหลักฐานสนับสนุนที่ชัดเจนว่าช่วยลดการเสียชีวิตในผู้ป่วยพิษเหตุติดเชื้อ วัตถุประสงค์ของการศึกษานี้จึงต้องการศึกษาผลของการให้สารน้ำปริมาณดังกล่าวขณะผู้ป่วยเข้ารับการรักษาในห้องฉุกเฉินและการเสียชีวิตในโรงพยาบาล

วิธีการศึกษา: เป็นการศึกษาเชิงพรรณนาโดยการเก็บข้อมูลแบบย้อนหลังในผู้ป่วยที่มีภาวะพิษเหตุติดเชื้อที่มีภาวะเนื้อเยื่อขาดออกซิเจน หรือมีภาวะช็อคที่เข้ารับการรักษาในห้องฉุกเฉิน โดยแบ่งผู้ป่วยเป็นกลุ่มที่ได้รับสารน้ำปริมาณมาก (≥ 30 มิลลิลิตรต่อกิโลกรัม) และกลุ่มที่ได้รับสารน้ำปริมาณน้อย (< 30 มิลลิลิตรต่อกิโลกรัม) ขณะที่รักษาในห้องฉุกเฉิน โดยผลลัพธ์หลักของการศึกษาคือการเสียชีวิตในโรงพยาบาลโดยทำการวิเคราะห์การถดถอยโลจิสติกแบบหลายตัวแปรและกราฟแคพแพล-ไมเยอร์

ผลการศึกษา: มีผู้ป่วยในการศึกษาทั้งสิ้น 355 ราย โดยแบ่งเป็นกลุ่มได้รับสารน้ำปริมาณมาก 159 ราย และได้รับสารน้ำปริมาณน้อย 196 ราย ผู้ป่วย 39 รายในกลุ่มที่ได้รับสารน้ำปริมาณมาก และ 60 รายในกลุ่มที่ได้รับสารน้ำปริมาณน้อยเสียชีวิตในโรงพยาบาลจากการวิเคราะห์โดยการถดถอยโลจิสติกไม่พบความสัมพันธ์ของการได้รับสารน้ำปริมาณมากต่อการลดการเสียชีวิตของผู้ป่วยพิษเหตุติดเชื้อที่มีอาการหรืออาการแสดงของภาวะเนื้อเยื่อขาดออกซิเจน หรือมีภาวะช็อค AOR 0.59 (0.35-1.02) $p = 0.056$

สรุป: ในผู้ป่วยพิษเหตุติดเชื้อที่มีอาการหรืออาการแสดงของภาวะเนื้อเยื่อขาดออกซิเจน หรือมีภาวะช็อค การให้สารน้ำปริมาณมากไม่สัมพันธ์กับการลดการเสียชีวิต

คำสำคัญ: ช็อคพิษเหตุติดเชื้อ, พิษเหตุติดเชื้อที่มีภาวะเนื้อเยื่อขาดออกซิเจน, การให้สารน้ำ, ห้องฉุกเฉิน, การเสียชีวิต

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Abstract

Background and Objective: Fluid administration is the cornerstone treatment in sepsis patients. According to the surviving sepsis campaign guideline suggests an initial fluid 30ml/kg in the first 3 hours for resuscitation; however no clear evidence of the benefits of this suggestion. The objective of this study is to evaluate the effect of fluid resuscitation during admitted in the emergency department (ED) in sepsis with tissue hypoperfusion or septic shock patients and hospital mortality.

Methods: This is a retrospective cohort study of adult patients with sepsis induced tissue hypoperfusion or septic shock who visited the emergency department. The enrolled patients were divided into high volume fluid resuscitation group ($\geq 30\text{ml/Kg}$) and low volume fluid resuscitation group ($< 30\text{ml/Kg}$) according to total fluid resuscitation during admitted in the ED. The primary outcome was in hospital mortality. Multivariable logistic regression and Kalan-Meier graph were used to analyze the outcome of the study.

Results: A total of 355 patients were enrolled into the study, 159 patients were in high volume fluid resuscitation group and 196 patients were in low volume fluid resuscitation group. Thirty-nine patients in high volume fluid resuscitation group and sixty patients in low volume fluid resuscitation group were dead. Multivariable logistic regression showed no association of high volume fluid resuscitation and survival benefit in sepsis with tissue hypoperfusion or septic shock patients AOR 0.59 (0.35-1.02) $p= 0.056$.

Conclusions: In sepsis with tissue hypoperfusion or septic shock patients, high volume of fluid resuscitation was not associated with decreased hospital mortality.

Keywords: septic shock, sepsis with tissue hypoperfusion, fluid resuscitation, emergency department, mortality

Introduction

Sepsis is a dysregulation of the immune response to infection associated with high morbidity and mortality incidence. According to surviving sepsis campaign guideline: fluid resuscitation, blood culture collection, blood lactate monitoring, antibiotic and vasopressor administration may reduce mortality.¹

The 2018 surviving sepsis campaign guideline recommended initial 30 mL/Kg administration of intravenous fluid within the first 3 hours to the sepsis induced hypotension or septic shock patients.² This recommendation based on evidence of the average of pre randomization fluid from ProCESS, ARISE and ProMISe trials.³⁻⁵ However, some previous studies show that the benefits of 30 mL/Kg of fluid resuscitation are controversial.⁶⁻⁸

Even though some previous studies revealed that the early and rapid within 2-3 hours of fluid administration may reduce the mortality of sepsis patients^{9,10}, there are limited evidence in the emergency department setting. Therefore, we were interested in evaluating fluid resuscitation in early phase of sepsis patients during admitted in the emergency department on mortality outcome.

The aim of this study was to evaluate the high volume (≥ 30 mL/Kg) of fluid resuscitation and low volume (< 30 mL/Kg) of fluid resuscitation in the emergency department on mortality of sepsis patients.

Materials and Methods

Study Design and Setting

This was a retrospective cohort study that assessed the patients presented at the Emergency Department (ED), Khon Kaen hospital, from 1st January 2021-31st December 2022. The study protocol was approved by the Institutional Review Board of Khon Kaen hospital under a waiver of informed consent. Participants and Eligibility Criteria

The patients diagnosed sepsis and admitted to the ED, Khon Kaen hospital were assessed for eligibility. The inclusion criteria as followings; age ≥ 18 years old, diagnosed sepsis with signs/symptoms or laboratory data of tissue hypoperfusion or septic shock, received fluid resuscitation at the ED

The exclusion criteria as followings; incomplete data, patients who were transferred to other hospitals.

Definitions

According to Sepsis-3 definitions; sepsis was defined as the infection induced dysregulation of immune responsiveness causing organ dysfunction, which was indicated by an increased Sequential Organ Failure Assessment (SOFA) score of 2 points or more.¹¹ Signs/symptoms or laboratory data of tissue hypoperfusion represented by one of the following criteria: altered mental status (Glasgow Coma Score < 15), hypotension, skin mottling, low urine output (< 0.5 mL/Kg/hr), delay capillary refill > 3 seconds, serum lactate > 4 mmol/L.^{12,13}

Septic shock was a sepsis condition with adequate fluid resuscitation but needed vasopressor to maintain mean arterial pressure (MAP) ≥ 65 mmHg and elevation of serum lactate (> 2 mmol/L).¹¹

Data collection

The data were derived from the electronic database of Khon Kaen hospital. Patients diagnosed sepsis during admission at the ED, Khon Kaen hospital from 1st January 2020-31st December 2022 were screened and enrolled according to the eligibility. Baseline characteristics data; sex, age, body mass index (BMI), comorbidities were collected. Diagnosis, treatment details, main source of infection, amount of initial fluid resuscitation, type of fluid, time to antibiotic, laboratory data, location of admission, length of hospital stay, hospital mortality and 7-day mortality were collected. The initial fluid resuscitation was calculated by the total amount of fluid resuscitation during admitted in the ED, divided actual weight of patients on the day at ED arrival and divided into high volume fluid resuscitation group (received initial fluid resuscitation ≥ 30 mL/Kg) and low volume fluid resuscitation group (received initial fluid resuscitation < 30 mL/Kg).

Sample size calculation

According to the sample size estimation for cohort study formula¹⁴

$$N_{\text{exposure}} = \left[\frac{z_{1-\alpha/2} \sqrt{pq(1+1/r)} + z_{1-\beta} \sqrt{p_1q_1 - p_2q_2/r}}{p_1 - p_2} \right]^2$$

$p_1 = P(\text{outcome/exposure})$, $q_1 = 1 - p_1$

$p_2 = P(\text{outcome/unexposure})$, $q_2 = 1 - p_2$

$p = p_1 + p_2r$, $q = 1 - p$ $r = N_{\text{exposure}} / N_{\text{unexposure}}$

α = The level of significance, 0.05

β = 0.2 (80% power)

From Wang et al. study⁸, hospital mortality of high volume fluid resuscitation was 48% and 32% in low to medium volume fluid resuscitation, the sample size estimation of this study was 159 per group and we calculated missing data 10% therefore, the sample size of this study was 350.

Outcomes

Primary outcome was in hospital-mortality. Secondary outcomes included length of hospital stay > 7 day, 7-day, and 28-day mortality.

Statistical Analysis

All baseline variables were examined using descriptive statistic. Continuous variables were presented using either mean and standard deviation or median and range as appropriate. The t-test or Mann-Whitney U test was used to analyze between groups differences. Categorical variables were presented using frequent count and percentage and Chi-square test was used to determine the baseline differences.

The primary and secondary outcomes were analysed and presented as odds ratio (OR) and 95% confidence interval. The important demographic variables that influence the outcomes, ($p < 0.2$) were included in multivariable analysis by using multiple logistic regression and presented as adjusted odds ratio (AOR) and 95% confidence interval. A Kaplan-Meier graph was performed for the cumulative probability of survival in patients who received high versus low volume of fluid resuscitation. The log-rank test was used among two groups. Statistical significance determined as $p < 0.05$. All data analysis were performed using STATA version 16.

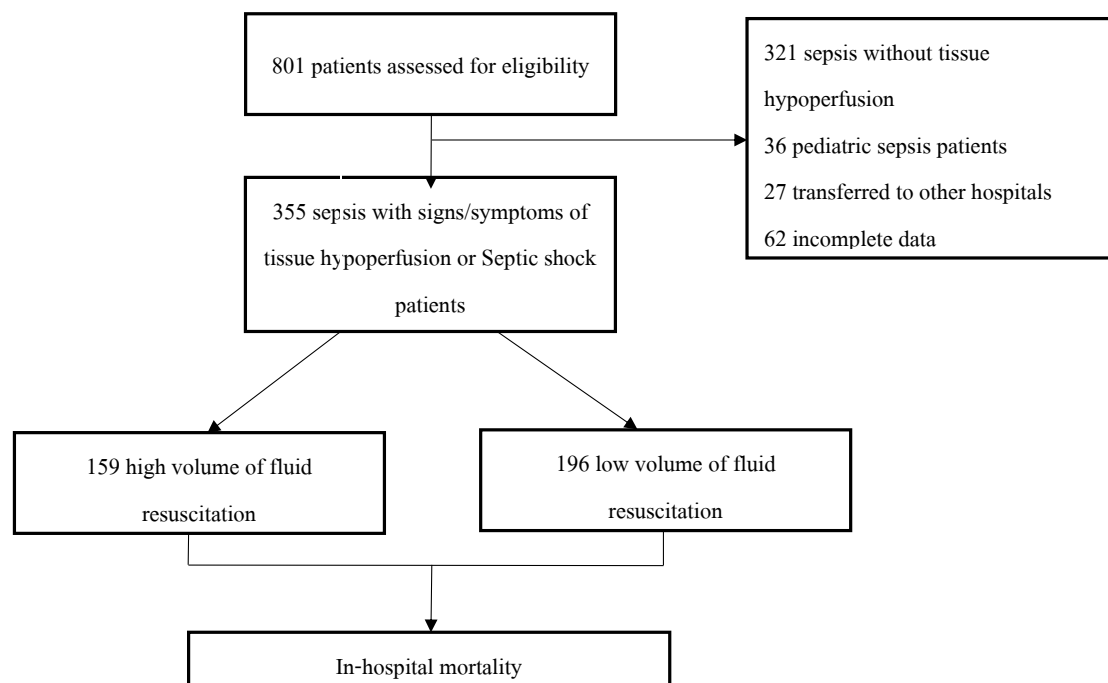


Figure 1 Study flow

Results

A total of 801 patients were assessed for the eligibility. Of these, 355 patients who met the criteria for sepsis with tissue hypoperfusion or septic shock and were enrolled in the study (Figure 1). One hundred fifty-nine patients were in the high volume fluid resuscitation group and 196 were in low volume fluid resuscitation group. The most common source of infection was pneumonia. Almost fifty percent of the patients developed septic shock; the high volume resuscitation group had higher number of septic shock patients (60.37%) than the low volume resuscitation group (35.20%). The amount of initial fluid resuscitation was significantly higher in the high volume resuscitation group ($p<0.001$); the median volume of fluid resuscitation was 38.46 (33-48) mL/Kg and 16.70 (8-22) mL/Kg in high volume resuscitation group and low volume resuscitation group, respectively. The initial blood lactate level was 6.50 ± 0.31 and 5.28 ± 0.40 mmol/L in the high volume resuscitation and low volume resuscitation group, respectively. The most common type of fluid resuscitation was mixed type (normal saline and balanced crystalloid administration).

The mortality of patients in this study were 99 of 355 patients, 39 patients from high volume resuscitation group and 60 patients from low volume resuscitation group (Table 1).

From the univariate analysis, factors that may affect mortality ($p<0.2$) were sex, pneumonia, urinary tract infection, underlying coronary artery disease, underlying diabetes mellitus, septic shock, on mechanical ventilation at ED. All of these were included in the multivariable logistic regression analysis (Table 2). After the adjustment from the important variables, the amount of initial fluid resuscitation was not independently associated with in hospital mortality, AOR 0.59 (0.35-1.02), $p=0.056$. The secondary outcomes including length of hospital stay >7 day, 7-day mortality and 28-day mortality, the high volume fluid resuscitation were not associated with outcome improvements when compared to low volume fluid resuscitation, AOR 0.87 (0.54-1.41), 0.86 (0.48-1.54) and 0.60 (0.36-1.01), respectively (Table 3). The Kaplan-Meier graph of the hospital mortality showed the mortality in high volume resuscitation group was not significant difference from the low volume resuscitation group (Figure 2).

Table 1 Baseline characteristics of the patients

Baseline characteristics	High volume resuscitation group (N=159)	Low volume resuscitation group (N=196)	p-value
Age, mean $\pm$ SD, year	63.64 $\pm$ 15.14	60.95 $\pm$ 16.76	0.120
Age > 60 years, No. (%)	100 (62.89)	112 (57.14)	0.139
Male gender, No. (%)	94 (59.11)	128 (65.31)	0.411
Comorbidities, No. (%)			
Hypertension	62 (38.99)	70 (35.71)	0.673
Diabetes Mellitus	56 (35.22)	61 (31.12)	0.302
Chronic kidney disease	26 (16.35)	18 (9.18)	0.031
Chronic obstructive pulmonary disease	11 (6.91)	21 (10.71)	0.250
Liver cirrhosis	8 (5.03)	9 (4.59)	0.794
Others	3 (1.88)	3 (1.53)	0.765
Body mass index, mean $\pm$ SD, Kg/m ²	20.25 $\pm$ 0.28	21.43 $\pm$ 0.30	0.003

Table 1 Baseline characteristics of the patients (Cont.)

Baseline characteristics	High volume resuscitation group (N=159)	Low volume resuscitation group (N=196)	p-value
Source of infection, No. (%)			
Pneumonia	84 (52.83)	113 (57.65)	0.191
Intra-abdominal infection	23 (14.46)	18 (9.18)	0.097
Urinary tract infection	16 (10.06)	20 (10.20)	0.955
Soft tissue infection	5 (3.14)	5 (2.55)	0.698
Bacteraemia	6 (3.77)	5 (2.55)	0.474
Others	26 (16.35)	35 (17.85)	0.675
Septic shock, No. (%)	96 (60.37)	69 (35.20)	0.010
On mechanical ventilation at ED, No. (%)	115 (72.32)	133 (67.86)	0.262
Initial vital signs at ED			
Systolic blood pressure, median (IQR), mmHg	88.50 (77-116)	112 (90-137)	0.001
Diastolic blood pressure, mean (IQR), mmHg	53 (48-65)	67 (52-82)	0.004
Mean arterial pressure, median (IQR), mmHg	63.83 (58-82)	81.83 (64-100)	0.001
Heart rate, mean±SD, beat per minute	107.10±2.04	109.21±1.72	0.427
Type of fluid, No. (%)			0.009
Normal saline	35 (22.01)	71 (36.22)	
Balanced crystalloids	12 (7.54)	15 (7.69)	
Mixed type	112 (70.44)	110 (56.12)	
Initial fluid resuscitation, median (IQR), ml	2,137(1,815-2,500)	901.93(500-1,100)	0.001
Initial fluid resuscitation, median (IQR), mL/Kg	38.46 (33-48)	16.70 (8-22)	0.001
Time to antibiotics, mean±SD, minutes	38±5.45	41±2.13	0.365
Initial blood lactate, mean±SD, mmol/L	6.50±0.31	5.28±0.40	0.060
ICU admission, No. (%)	33 (20.75)	35 (17.86)	0.362
Total fluid accumulation*, median (IQR) ml	4,157 (2,145-8,115)	2,815 (1900-3,250)	0.002
Length of hospital stay, mean±SD, day	6.80±0.75	6.65±0.46	0.862
In-hospital mortality, No. (%)	39 (24.52)	60 (30.61)	0.172

*Fluid accumulation was calculated from overall fluid intake minus fluid output from patient's admission until discharge

Table 2 Factors associated with hospital mortality of sepsis patients

Variables	Crude Odds Ratio	95%CI	p-value
Sex	0.93	0.65-1.33	0.130
Pneumonia	1.42	0.88-2.29	0.145
Urinary tract infection	0.67	0.25-1.42	0.198
Underlying coronary artery disease	0.67	0.40-1.11	0.119
Underlying diabetes mellitus	0.74	0.44-1.24	0.197
Septic shock	1.23	0.88-2.84	0.200
Lactate $\geq$ 4 mmol/L	1.61	1.00-2.58	0.004
On mechanical ventilation at ED	2.26	1.27-4.01	0.003

Table 3 Association of initial fluid resuscitation and outcomes in sepsis patients

Outcomes	High volume resuscitation group (N=159)	Low volume resuscitation group (N=196)	Adjusted Odds ratio (AOR)	95%CI	p-value
Primary outcome					
In-hospital mortality	39	60	0.59	0.35-1.02	0.056
Secondary outcomes					
Length of hospital stay >7day	46	64	0.87	0.54-1.41	0.269
7-day mortality	29	37	0.86	0.48-1.54	0.058
28-day mortality	37	59	0.60	0.36-1.01	0.053

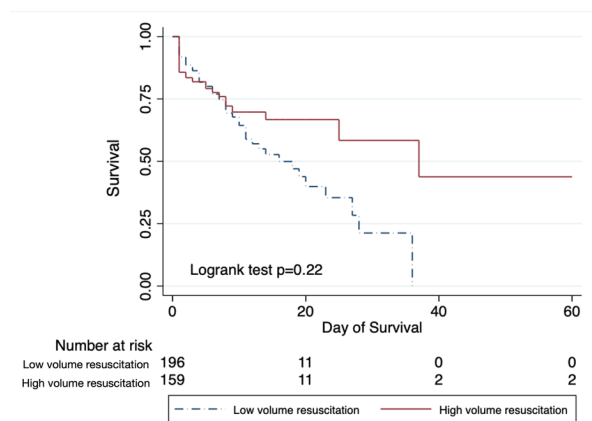


Figure 2 The Kaplan Meier curve of hospital mortality stratified by initial fluid resuscitation groups

Discussion

Our study demonstrated that high volume fluid resuscitation (≥ 30 mL/Kg) in the ED was not associated with decrease in-hospital mortality. Moreover, high volume resuscitation was not

associated with 7-day, 28-day mortality and length of hospital stay.

Intravenous fluid administration is one of the important treatments in sepsis patients, especially the patients with hypotension or septic shock, fluid bolus is the cornerstone management to restore adequate oxygenation and tissue perfusion.¹⁵ From the pathophysiology of septic shock, which is a distributive shock, vasoplegia causes relative hypovolemia. Therefore, intravenous fluid administration may benefit to shock reversal. The 2021 surviving sepsis campaign guideline suggests the initial 30 mL/Kg fluid administration in sepsis induced hypotension or septic shock patients to restore tissue perfusion. However, from a current knowledge, the tissue hypoxia in septic shock is not only described by the vasoplegic process but also by the damage of glycocalyx of the endothelium.¹⁶ Therefore, the benefit of the suggestion of a large amount of volume

resuscitation is controversial and may lead to adverse outcomes such as invasive mechanical ventilation requirement, acute respiratory distress syndrome development and increased mortality.^{8,17-19}

This study showed similar findings to Yohannes S et al. that reported high or low initial fluid resuscitation of sepsis with hypoperfusion or septic shock patients were not associated with mortality.¹⁷

Furthermore, Permpikul C et al. study showed the benefits of early vasopressors administration that increase the rate of shock controlled and decrease the chance of complications such as cardiogenic pulmonary edema and arrhythmia.²⁰ Therefore, fluid management in septic shock patients is not one size fit for all because patients have differences in severity of shock, source of infection, previous comorbidities, etc. which require different amounts of fluid resuscitation. Additionally, increased evidence supports the individualized fluid strategy for management in septic shock.^{21,22}

The strength of our study is the assessment of fluid resuscitation in the very early period of sepsis which quite limits current data assessment of the amount of fluid received in the ED and the outcomes of the patients.

There are few limitations in this study. First, it is a retrospective study therefore lack of some data that affect the outcomes. Second, even though our study did not find the benefit of high volume of initial fluid resuscitation when compared to low volume resuscitation, we had limitation about the total time of initial fluid resuscitation in the ED. Therefore, the data of accurate time of initial fluid resuscitation should be collected and analyzed in the future study.

Conclusion

Our study demonstrates that the ED patients with sepsis induced hypoperfusion or septic shock who were resuscitated with high volume fluid (≥ 30 mL/Kg) was not associated with decreased mortality when compared to with low volume fluid (< 30 mL/Kg).

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