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BRIEF COMMUNICATION

Early versus delayed vasopressor administration in patients with septic shock

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Abstract

Aim: This study aimed to investigate the association of early vasopressor initiation with improved septic shock outcomes.

Methods: This multicenter observational study was conducted in 17 intensive care units in Japan and included adult patients with sepsis admitted to the intensive care unit from July 2019 to August 2020 and treated with vasopressor therapy. Patients were divided into the early vasopressor group (≤1 h from sepsis recognition) and the delayed vasopressor group (>1 h). The impact of early vasopressor administration on risk-adjusted in-hospital mortality was estimated using logistic regression analyses adjusted by an inverse probability of treatment weighting analysis with propensity scoring.

Results: Among the 97 patients, 67 received vasopressor therapy within 1 h from sepsis recognition and 30 received vasopressor after 1 h. In-hospital mortality was 32.8% in the early vasopressor group and 26.7% in the delayed vasopressor group ($p = 0.543$). The adjusted odds ratio for in-hospital mortality was 0.76 (95% confidence interval 0.17–3.29) when comparing patients in the early vasopressor with those in the delayed vasopressor group. The fit curve from the mixed-effects model showed a relatively lower trend toward an infusion volume over time in the early vasopressor group than in the delayed vasopressor group.

Conclusion: Our study did not reach a definitive conclusion for early vasopressor administration. However, early vasopressor administration may help avoid volume overload in the long course of sepsis care.

KEYWORDS
sepsis, vasopressor

INTRODUCTION

The guidelines pertaining to the timing of vasopressor initiation for patients with sepsis and fluid-resistant hypotension are ambiguous,[1] although earlier initiation of key therapies, including appropriate antibiotics and fluid resuscitation, can definitely reduce mortality risk. This study aimed to investigate the association of early vasopressor initiation with improved septic shock outcomes.

METHODS

This multicenter observational study was conducted in 17 intensive care units (ICUs) at tertiary hospitals in Japan and

TABLE 1 Demographics, characteristics, and outcomes comparing patients with sepsis in the early and delayed vasopressor groups.

Demographics, characteristics, and outcomes	Early vasopressor, *n* (%) 67 (69.1)	Delayed vasopressor, *n* (%) 30 (30.9)	*p* value
Age, years	72 (62–81)	72 (63–80)	0.70
Sex			
Male	42 (62.7)	21 (70.0)	0.49
BMI (kg/m^2)	21.6 (18.4–25.3)	21.9 (16.9–23.6)	0.71
Admission source			
From emergency department	65 (97)	30 (100)	0.34
Clinical frailty scale	4 (3–5)	4 (3–5)	0.66
Charlson comorbidity index	1 (0–3)	1 (1–6)	0.07
Suspected site of infection			
Lung	23 (34.3)	16 (53.3)	0.20
Abdomen	18 (26.9)	3 (10.0)	
Urinary tract	14 (20.9)	4 (13.3)	
Soft tissue	3 (4.5)	1 (3.3)	
Endocarditis	1 (1.5)	0 (0)	
Intravenous catheter	1 (1.5)	0 (0)	
Implant device	0 (0)	1 (3.3)	
Other	2 (3.0)	0 (0)	
Unknown	5 (7.5)	5 (16.7)	
Positive blood cultures	44 (65.7)	16 (53.3)	0.25
SOFA score	10 (8–12)	9 (6–10)	<0.01
NPPV use	1 (1.5)	1 (3.3)	<0.01
Mechanical ventilation use	36 (53.7)	5 (16.7)	
Adherence to the hour-1 bundle			
Measure lactate level	66 (98.5)	30 (100)	0.50
Obtain blood cultures	61 (91.0)	20 (66.7)	<0.01
Broad-spectrum antibiotics	42 (62.7)	4 (13.3)	<0.01
Administration of crystalloid[a]	66 (98.5)	28 (93.3)	0.174
Apply vasopressors	67 (100)	0 (0)	—
Time to vasopressors initiation (h)			
≤1	67 (100)	NA	NA
1–2	NA	15 (50.0)	
>2–3		5 (16.7)	
>3–4		3 (10.0)	
>4–5		3 (10.0)	
>5–6		1 (3.3)	
>6			3 (10.0)
Total amount of fluid in 6 h (ml)	3000 (2200–4250)	2645 (1740–3900)	0.12
Ventilator-free days	15 (0–24)	19 (0–28)	0.21
ICU-free days	6 (0–20)	13 (0–21)	0.28
Length of hospital stay (days)	21 (8–50)	30 (16–49)	0.31
Crude 28-day mortality	17 (25.4)	7 (23.3)	0.83
Crude in-hospital mortality	22 (32.8)	8 (26.7)	0.54
Place after discharge			
Transfer	24 (53.3)	14 (63.6)	0.42
Home	21 (46.7)	8 (36.4)	
Adjusted odds ratio for in-hospital mortality (95% confidence interval)	0.76 (0.17–3.29)		0.72

Note: Reported counts (proportions) for categorical variables and median (interquartile range) for continuous variables.

Missing data: BMI = 1; total amount of fluid in 6 h = 4.

Abbreviations: BMI, body mass index; CI, confidence interval; ICU, intensive care unit; NA, not available; NPPV, noninvasive positive pressure ventilation; SOFA, Sequential (Sepsis–Related) Organ Failure Assessment.

[a]A patient classified a bundle adherence completion if a patient did not meet the indication of aggressive crystalloid administration.

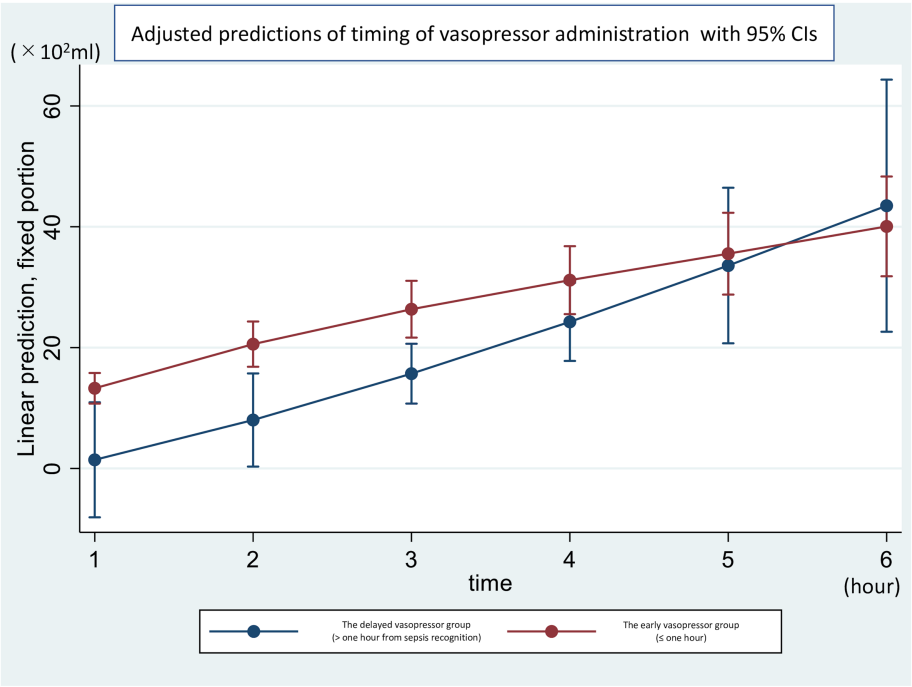

FIGURE 1 The fit curve of infusion volume in the early vasopressor group and the delayed vasopressor group within 6 h from sepsis recognition. CI, confidence interval.

included all adult patients diagnosed with sepsis by Sepsis-3 admitted to the ICU and treated with vasopressor therapy from July 2019 to August 2020. Patients were divided into the early vasopressor group (≤1 h from sepsis recognition) and the delayed vasopressor group (>1 h) because applying vasopressor within 1 h is part of the surviving sepsis campaign hour-1 sepsis bundle.[1] The primary outcome was in-hospital mortality, whereas the secondary outcome was fluid volume within 6 h from sepsis recognition. The impact of early vasopressor administration on risk-adjusted in-hospital mortality was estimated using logistic regression analyses adjusted by an inverse probability of treatment weighting (IPTW) analysis with propensity scoring. Patients' age, sex, admission source (emergency department, ward, or ICU), Charlson comorbidity index, mechanical ventilation use, Sequential Organ Failure Assessment (SOFA) score in each organ, hour-1 bundle adherence except vasopressors administration, and the amount of fluid at 6 h after sepsis recognition were adjusted. The relationship between the fluid volume within 6 h and the timing of vasopressor administration were also examined.

RESULTS

Among the 97 patients, 67 (69.1%) received vasopressor therapy within 1 h from sepsis recognition and 30 (30.9%) received vasopressor after 1 h (Table 1). The median SOFA scores in the early vasopressor and the delayed vasopressor groups were 10 (interquartile range [Q1–Q3]: 8–12) and 9 (Q1–Q3: 6–10), respectively (p <0.01). Use of mechanical ventilator was greater in the early vasopressor group (36/67, 53.7%) compared with the delayed vasopressor group (5/30, 16.7%; p <0.01). Patients in the early vasopressor group adhered to the hour-1 bundles (obtaining blood cultures and using broad-spectrum antibiotics) when compared with those in the delayed vasopressor group.

The median fluid volume from sepsis recognition to 6 h was 3000 (Q1–Q3: 2200–4250) ml in the early vasopressor and 2645 (Q1–Q3: 1740–3900) ml in the delayed vasopressor group (p = 0.12). In-hospital mortality was 32.8% (22/67) in the early vasopressor group and 26.7% (8/30) in the delayed vasopressor group (p = 0.543). The adjusted odds ratio for in-hospital mortality was 0.76 (95% confidence interval 0.17–3.29) when comparing patients in the early vasopressor group with those in the delayed vasopressor group. The fit curve from the mixed-effects model, which was adjusted with IPTW, showed a relatively lower trend toward an infusion volume over time in the early vasopressor group than in the delayed vasopressor group. (Figure 1).

DISCUSSION

The timing of vasopressor initiation for patients with sepsis remains controversial. Some prospective and retrospective studies support early vasopressor initiation,[2,3] whereas others do not.[4] Early vasopressor initiation has been shown to control shock, and not increase adverse events, such as renal replacement therapy requirements. It also avoids volume overload, similar to our findings. However, these results may not indicate early vasopressor administration, regardless of the preload

dependency.[5] In addition, during the clinical course of sepsis, the decision to initiate vasopressor therapy should be taken while ensuring a balance between fluid amount and patient response. Our study as well as previous studies would have had limitations such as small sample size and reverse causation.

Our study did not reach a definitive conclusion for early vasopressor administration. However, early vasopressor administration may help avoid volume overload in the long course of sepsis care.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study is available with the corresponding author on reasonable request.

ETHICS STATEMENT

Approval of the Research Protocol with Approval No. and Committee Name: The study protocol was reviewed and approved by the ethics committee of all participating institutions in the Japanese Association for Acute Medicine (JAAM) study group. The study was also approved by the Ethical Review Board of Osaka University Hospital (Institutional), the representative for the JAAM MAESTRO study, in accordance with the Declaration of Helsinki and following STROBE guidelines, and granted a waiver of informed consent (Protocol title: A multicenter, prospective observational study of new criteria for sepsis [Sepsis-3]; IRB number 18323; approval date February 8, 2019).

Informed Consent: Not applicable.

Registry and the Registration No. of the Study/Trial: Not applicable.

Animal Studies: Not applicable.

Conflict of Interest: None declared.

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