Randomized Controlled Trial of Ultrasound-guided Fluid Resuscitation of Sepsis-Induced Hypoperfusion and Septic Shock

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Study Protocol

In our protocol we prepared the preplanned, permuted block-of-four randomization list that was blinded to the investigators before patient allocation. Randomization was set at a 1:1 ratio of the ultrasound-guided and usual-care arms. When an eligible patient was identified and informed consent was obtained, demographic data, preexisting condition, bloodwork, diagnostic investigations, microbiologic workups, and blood lactate were collected at ED arrival (hour 0). Prompt empirical antibiotics were given to every patient within one hour after ED arrival. Then, the patient was rapidly assigned in accordance with the randomization and treated with one of the two treatment strategies as follows:

Ultrasound-guided fluid management (UGFM) strategy

In this treatment arm, the treating emer gency physician promptly assessed the IVC diameter to obtain the IVC collapsibility index (IVCCI) (or distensibility index, IVCDI; see below for the description, formulation and measurement method) of each patient while venous access was performed and initial laboratory specimens were collected. A previous study showed that IVCCI > 40% was strongly associated with fluid responsiveness. 24 Accordingly, the patient was given a 10 milliliters (mL)/ kg bolus of 0.9% normal saline solution (NSS) without delay if an IVCCI > 40% was discovered, and serial measurements were immediately performed after each IV bolus was achieved an IVCCI < 40% during our protocol. Then, the rate of IV fluid administration was maintained based on the individual's condition. If the patients in this arm subsequently required endotracheal intubation and MV with sedation within six hours after initiation of therapy , the IVCDI was measured as a replacement for IVCCI. The same amount of NSS was given when IVCDI > 18% 17 until IVCDI < 18% was achieved. The IVC evaluation was serially performed and recorded every two hours until six hours after ED presentation. The same treatment protocol was repeated when the threshold of IVCCI (or IVCDI) percentage for potential fluid responsiveness was identified.

Inferior vena cava diameter measurement and indicators of fluid responsiveness

In our protocol, IVC was identified in longitudinal section in the subcostal area using the curvilinear or phased array transducers (cardiac) of a standard ultrasound machine. The selected area of IVC diameter measurement was set at 2 centimeters distal to the confluence of the hepatic vein by M-mode coupled with two-dimensional mode on frozen screen images using the Sonosite X-porte (Fujifilm Sonosite, Inc., Bothell, WA). All treating physicians including attending staff and residents regularly participated in hands-on training twice a year (as usual basis) by a qualified international instructor in critical care ultrasonography (the third author). The residents who were allowed to perform the study protocol required at least six months

exposure in real clinical experience and had passed formal performance evaluation on ultrasonographic IVC measurement. If the patient was breathing spontaneously, the IVCCI, which reflects the decrease in IVC diameter on spontaneous inspiration, was used. IVCCI is calculated as follows:
[(IVC diametermax - IVC diametermin)/ IVC diametermax]×100%.
If the patient required MV for respiratory support, the IVCDI, which reflects the increase in IVC diameter on mechanical inspiration, was used. IVCDI is calculated as follows:
[(IVC diametermax - IVC diametermin)/ IVC diametermin]×100%.
Sample images of ultrasonographic landmark and respirophasic diameter changes of an IVC during volume expansion are shown in Figures S1A and S1B in the Supplemental material.

Usual-care strategy
Patients were promptly treated with 30 mL/kg loading of NSS in this treatment arm. After the NSS bolus, treatment with either the additional IV fluid or a vasopressor was given at the physicians' discretion during the six-hour study period. The threshold for the need of a vasopressor was set at mean arterial pressure below 65 mm Hg if a patient did not respond to fluid therapy during each treatment protocol, and the time of vasopressor administration was noted. However, ancillary fluid administration was allowed at treating physicians' judgment in both treatment arms. Other adjunctive therapies, such as colloid administration, central venous catheterization, or surgical removal of the infectious source, were not prohibited in our protocol and were used at the discretion of the treating physicians. The study patients were closely monitored while we recorded their clinical parameters every two hours for study purposes. Our resuscitative study protocol stopped at six hours after initiation of the treatment. After this period, patients were treated according to the physicians' judgment.

Outcome Measurements
At six hours after treatment, the cumulative fluid volume was recorded, and blood lactate was obtained for lactate clearance calculation. At 72 hours after ED presentation, the cumulative fluid volume from the initial presentation was again recorded, and the patients were followed for clinical condition evaluation and blood chemistry tests to calculate the SOFA score and assess its change from the hour-zero baseline. The in-hospital requirement and time to start renal replacement therapy or MV were followed and recorded by searching the electronic data summary of a patient. The indication to initiate these life-saving procedures was at the discretion of the treating physicians. To identify the deceased patients for mortality analysis, we retrieved the electronic database of in- and outpatient clinical records or made a telephone call to the patients or their personal contact in every case at 30 days after the day of hospital presentation. The clinical data retrieval was performed and recorded by the trained non-investigators.

Data Analysis
Sample-size determination
According to the results of large trials of septic shock treatment, the 90-day mortality was 30% in the usual-care group.9-11 Based on this information, we calculated that a sample of 254 patients would have a power of 80% to detect a relative reduction of 50% in risk (15 percentage points of absolute risk reduction) in the UGFM group, allowing for a loss to follow-up or withdrawal of 5%. The target number for primary outcome analysis would be 121 patients per

group. One interim analysis was performed after the enrollment of 50% of the patients, with the use of a two-sided symmetric O'Brien–Fleming (or alpha spending method) design.

Statistical analysis

We used Stata version 14.0 (StataCorp LLC, College Station, TX) for all statistical tests and production of graphics. The normally and non-normally distributed data were analyzed using the two independent-samples t test and Mann-Whitney U test, respectively. A $\chi 2$ test with odds ratio (OR) was performed to compare the proportions between the groups. No data were imputed for any missing information. We used the Kaplan-Meier curve and the log-rank test to compare the 30-day mortality between the treatment arms. All tests were two-sided for superiority testing and considered statistically significant at a $p < 0.05$.