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Limited echocardiography–guided therapy in subacute shock is associated with change in management and improved outcomes ☆,☆☆

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ABSTRACT

Purpose: The purpose of the study was to compare the effect of limited echocardiography (LE)–guided therapy to standard management on 28-day mortality, intravenous fluid prescription, and inotropic dosing following early resuscitation for shock.
Materials and methods: Two hundred twenty critically ill patients with undifferentiated shock from a quaternary intensive care unit were included in the study. The LE group consisted of 110 consecutive patients prospectively studied over a 12-month period receiving LE-guided management. The standard management group consisted of 110 consecutive patients retrospectively studied with shock immediately prior to the LE intervention.
Results: In the LE group, fluid restriction was recommended in 71 (65%) patients and initiation of dobutamine in 27 (25%). Fluid prescription during the first 24 hours was significantly lower in LE patients (49 [33-74] vs 66 [42-100] mL/kg, $P = .01$), whereas 55% more LE patients received dobutamine (22% vs 12%, $P = .01$). The LE patients had improved 28-day survival (66% vs 56%, $P = .04$), a reduction in stage 3 acute kidney injury (20% vs 39%), and more days alive and free of renal support (28 [9.7-28] vs 25 [5-28], $P = .04$).
Conclusions: Limited echocardiography–guided management following early resuscitation is associated with improved survival, less fluid, and increased inotropic prescription. A prospective randomized control trial is required to verify these results.

1. Introduction

Despite a significant mortality rate, there exists no standard management algorithm for patients following initial resuscitation for shock. The underlying etiology of undifferentiated shock remains predominantly sepsis; and therefore, the Surviving Sepsis efforts (www.survivingsepsis.org) are primarily used to guide initial care [1]. The focus of this study is the period after the treating team has achieved the targets recommended in these guidelines, when intravenous fluid administration has resulted in a central venous pressure (CVP) of 8 to 12 mm Hg and the patient requires ongoing vasopressor support to achieve a mean arterial pressure of at least 65 mm Hg.

Although intravenous fluid is essential to restore perfusion in shock, once the circulation has been adequately expanded, additional fluid results in tissue edema, longer mechanical ventilation (MV), acute kidney injury (AKI), and an increased risk of death [2–4]. Currently, there is no uniform diagnostic approach able to reliably determine which patients will or will not increase organ perfusion in response to additional fluids [5]. In addition to intravenous fluids, inotropes are sometimes added as adjunctive therapy when left ventricular systolic dysfunction is believed to be the cause of inadequate organ perfusion. A 25% incidence of inotrope-induced arrhythmia mandates the use of inotrope only when necessary [1].

Limited echocardiography (LE) is defined in this study as standard parasternal long- and short-axis, apical 4-chamber, and subcostal views with color-flow Doppler and without alternate views. Easily accomplished within 5 to 10 minutes at the bedside, LE provides the treating team with a real-time recommendation for fluid management and the need to add an inotrope [6,7]. Despite the widespread integration of limited echocardiography into clinical practice, there are very limited data on clinical outcomes [8]. We hypothesized that LE-based recommendations for intravenous fluid and inotropes would improve survival compared to standard management in patients with undifferentiated vasopressor-dependent shock. We also hypothesized

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mechanisms through which LE improved outcomes may include reduction in the incidence of AKI and reduced days spent on MV.

2. Materials and methods

2.1. Patients

This study was performed at a quaternary-level hospital (St Paul's Hospital in Vancouver, British Columbia) intensive care unit (ICU) that is the regional cardiovascular center. The study included 220 patients referred to the critical care service with vasopressor-dependent shock despite an intravenous fluid challenge achieving a CVP of at least 8 mm Hg. The intervention arm of the study was conducted over a 12-month period (January 4 to Dec 31, 2012). One hundred ten patients in the intervention arm had an LE performed using a handheld device (V-Scan; GE Healthcare, Pittsburgh, PA), and 110 patients were managed in standard fashion (defined below). All patients were initially mechanically ventilated. Limited echocardiography was performed within 24 hours of admission to the ICU and within 36 hours of admission to the hospital. Study results and recommendations from the LE were communicated verbally and in written format to the treating team during the morning intake rounds. This study was approved by the Providence Health care research ethics board, and consent was waived.

2.2. Protocol

Echocardiography was performed by 1 of 3 intensivists with advanced training (American College of Cardiology Level II) in echocardiography. In no instances were they also the attending physician for the patient. Limited echocardiography included the parasternal long axis to assess aortic and mitral valve function, parasternal short axis at the level of the papillary muscle insertion to assess global left ventricular systolic function, the 4-chamber apical view for left and right ventricular size and function, and the subcostal view to assess the inferior vena cava (IVC) size and respiratory variability and for pericardial fluid. In cases with poor parasternal or apical windows, the equivalent views were obtained from the subcostal approach. In our institution, the outpatient echocardiography laboratory uses "eye-ball" approximation of ventricular function rather than a calculated value via the Simpson method given the excellent correlation in these values. We chose to adopt this well-validated approach [9,10].

Left and right ventricular systolic function was graded as normal, moderate (left ventricular ejection fraction [LVEF] 30%-45%), or severe systolic dysfunction (LVEF <30%). The pericardium was assessed for evidence of effusion or possible tamponade, whereas the IVC diameter's fluctuation with respiration was graded as either less than or greater than 15%. Treatment recommendations were 1 of 4 depending upon the LE: (1) less than 15% fluctuation of the IVC diameter (dIVC) with respiration and normal left ventricular function = discontinue fluid administration and continue vasopressors alone; (2) greater than 15% dIVC and normal left ventricular function = 20 to 40 mL/kg intravenous fluid administration; (3) greater than 15% dIVC and moderate to severe left ventricular dysfunction = 10 to 20 mL/kg intravenous fluid and dobutamine 5 μg/(kg min); (4) moderate to severe left ventricular systolic dysfunction and a dIVC less than 15% = dobutamine 5μg/(kg min) and fluid restriction. Right ventricular dysfunction was deemed present if there was bowing of the intraventricular septum throughout the cardiac cycle and a right ventricle at least as large as the left ventricle in the apical 4-chamber view. Valvular pathology was noted and graded as per American Society of Echocardiography guidelines only using color Doppler and observation of valve motion. If compatible with severe valvular stenosis or regurgitation, a formal echocardiogram was requisitioned and performed for a compete assessment.

One hundred ten consecutive patients admitted prior to January 4, 2012, with non–LE-guided, standard management of shock were enrolled into this study following informed consent to review records from the critical care research database. St Paul's Hospital standard shock guidelines adhere closely to the 2012 Surviving Sepsis guidelines [11]. They suggest 20 to 40 mL/kg initial intravenous fluid and further fluids as appropriate. A central line is placed in the jugular or subclavian positions, and intravenous fluid is administered until a CVP of 8 to 12 mm Hg is achieved. Further fluid boluses are at the discretion of the treating team. Noradrenaline is the suggested initial vasopressor if the mean arterial pressure remains below 65 mm Hg. Once patients are transferred to the ICU, dobutamine may be added for a central venous oxygen saturation less than 70% and evidence of ongoing hypoperfusion (urine output < 0.5mL/[kg h] or an arterial lactate > 2 mmol/L). This control population was chosen to avoid bias from the intervention (in a nonrandomized or blinded trial) and to acquire the most representative population in which to assess the intervention.

2.3. Statistical analysis

The primary outcome was 28-day mortality. Secondary outcomes included fluid prescription during the first 4 days and measurement of organ dysfunction, calculated as days alive and free of renal replacement therapy (RRT) or MV [12]. Patients with end-stage renal failure were excluded from the days alive and free of RRT. All patients were classified according to the current Kidney Disease: Improving Global Outcomes guidelines for AKI based on serum creatinine (SCr) (www.kdigo.org). An *AKI (stage 1)* was defined by SCr rise of at least 26.5 μmol/L within 48 hours or SCr increase of at least 1.5-fold from the baseline reference value. *Stage 2 AKI* was defined as a 2.0- to 2.9-fold increase from baseline reference SCr. *Stage 3 AKI* was defined as an at least 3-fold increase from baseline reference SCr, or an increase of 354 μmol/L, or commenced on RRT irrespective of stage of AKI. The reference SCr is defined as the lowest creatinine value recorded within 3 months of the event, or from repeat SCr within 24 hours, or estimated from the nadir SCr value if a patient recovers from AK. Patients with chronic kidney disease at admission were excluded.

Our primary analysis used Kaplan-Meier estimation of survival function; univariate analyses was performed using χ^2 for categorical data and either Kruskal-Wallis tests or *t* tests for continuous data. All tests were 2-sided. Differences in baseline characteristics were considered significant if $P < .05$ and were subsequently used in a Cox proportional hazards model to determine the risk of mortality associated with LE. Although nonsignificant, we forced the Acute Physiology and Chronic Health Evaluation (APACHE) II score as a covariate in the statistical model. Subgroups according to etiology of shock were analyzed using stratified Cox regression and the Breslow method of ties. All analyses were performed using R (version 2.8.1, www.R-project.org) and SPSS version 16.0 (SPSS Inc., Chicago, IL) statistical software packages.

3. Results

A total of 220 patients were included in this study: 110 in the LE cohort and 110 in the standard management group. All patients were followed up to 28 days for mortality, with outcome data available for all patients included in the study. Table 1 describes the baseline LE patients compared to standard management. As markers of chronic health, APACHE II, age, and the presence of chronic organ failures influence outcome independently of intervention. The LE and standard management groups did not differ with respect to these variables. The discharge diagnosis pertaining to the cause of shock was predominantly vasodilatory (78% LE and 75% standard management) followed by cardiac (12% LE and 15% standard management).