



Early goal directed therapy versus a protocolized resuscitation care in early management of septic shock

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ABSTRACT

Objective: Multicenter studies showed that early goal directed therapy (EGDT) did not improve outcome in patients with septic shock compared with undefined usual care. The aim of this study was to evaluate the efficacy of a protocolized resuscitation care compared to traditional EGDT in early management of septic shock on short-term mortality.

Design: A randomized controlled trial.

Setting: Emergency Department and Critical Care Units of Alexandria main university hospital.

Patients: 100 adult patients of both genders with septic shock.

Methods: All patients received early fluid resuscitation, empirical broad-spectrum antibiotic therapy and mechanical ventilation if indicated. Then, they were randomly assigned into two groups: Early goal directed therapy (EGDT) group (n = 50) and Protocolized resuscitation care (PRC) group (n = 50).

Results: EGDT group showed 20% reduction in need for vasopressor than PRC group with significant difference (p = 0.001). PRC group showed lower mortality rate than EGDT group but with no significant difference (p = 0.405). There were no differences in ICU stay, mechanical ventilation days and duration of vasopressor (p = 0.091, 0.243, 0.372 respectively).

Conclusion: A Protocolized resuscitation care may be beneficial as compared to EGDT in early management of septic shock with a non-significant trend to decrease mortality.

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1. Introduction

Sepsis is a life-threatening major health problem [1]. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defined sepsis as a life-threatening organ failure due to a dysregulated host response to infection. Septic shock was defined as a subset of sepsis associated with circulatory and cellular/metabolic abnormalities leading to increased mortality. Septic shock could be identified with specific clinical criteria including vasopressor need to keep mean arterial pressure MAP \geq 65 mmHg and serum lactate level >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation [2].

Management of septic shock is a major medical concern [3]. Early goal-directed therapy (EGDT) emerged as a novel approach for reducing sepsis mortality and was incorporated into Surviving Sepsis Campaign guidelines 2012. Early detection of sepsis and rapid initiation of antibiotics was an important concern. EGDT requires insertion of central venous catheter (CVC) to guide resuscitation with IV fluids, vasopressors, and inotropes [4].

According to the current Surviving Sepsis Campaign (SSC) guidelines recommendations, initial fluid bolus can be made using 30 mL/kg IV crystalloids in sepsis

and septic shock patients within the first 3 hours. It is also recommended to guide any additional fluids by frequent reassessment of hemodynamic status using dynamic or static variables to predict fluid responsiveness [5]. Little information is available regarding the use of other protocols for resuscitation rather than EGDT. In addition, multiple studies found that administered initial fluid boluses were not associated with corresponding increase in cardiac output and showed a positive correlation between mortality and positive fluid balance [6–10].

Three randomized trials were done to examine the effect of EGDT on morbidity and mortality: The American Protocolized Care for Early Septic Shock (ProCESS) trial [11], The Australasian Resuscitation in Sepsis Evaluation (ARISE) trial [12] and Protocolized Management In Sepsis (ProMISe) trial [13]. All these trials showed that EGDT was not associated with significant reduction in mortality in patients with septic shock compared to usual care.

Use of Velocity Time Integral of flow through the common carotid artery Doppler (Carotid VTI) and Passive Leg Raising (PLR) were described as markers of volume responsiveness in patients with hemodynamic instability [14]. **Aim of this study** was to assess

the efficacy of a Protocolized Resuscitation Care (PRC) to maintain hemodynamic support using carotid VTI and PLR to guide fluid administration and percentage decline in lactate level after 6 hours of resuscitation to assess tissue oxygenation in early management of septic shock. Primary outcome was 28-day mortality. Secondary outcomes were need for vasopressor, days of mechanical ventilation, and ICU length of stay.

2. Patients and methods

This study was carried out on 100 adult patients of both genders according to sample size calculation. A sample of 100 septic shock patients; 50 per group, was required to estimate average difference in mortality rate between group treated by EGDT and the other treated by PRC = 7%, with precision of 5% using alpha error = 0.05. It could provide a power of 80%. Sample units were randomly selected after fulfilling inclusion criteria. Sample size was calculated using G* power software [15,16].

Patients were admitted to Emergency Department and Critical Care Units in Alexandria main university hospital with septic shock within 6 hours after presentation. Approval of the Medical Ethics Committee of Alexandria Faculty of Medicine was obtained. An informed consent was taken from the patients' next of kin before their enrollment in the study.

Patients' inclusion criteria were selected according to The Third International Consensus Definitions for Sepsis and Septic Shock (2016) (Sepsis-3) [2]. They included acute change of total SOFA score (Sequential Organ Failure Assessment) ≥ 2 points consequent to infection, quick SOFA (alteration in mental average difference in mortality rate between group treated status, systolic blood pressure ≤ 100 mm Hg, or respiratory rate ≥ 22 /min) and persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 65 mm Hg and having a serum lactate > 2 mmol/L (18 mg/dL) despite adequate volume resuscitation. Exclusion criteria included pregnancy, lower limb amputation, trauma, or active bleeding, need for immediate surgery within 6 hours of diagnosis, cardiogenic and non-cardiogenic pulmonary edema, and difficult transthoracic echocardiographic evaluation.

All data about patients' demographics, principal diagnosis and all clinical, laboratory and radiological parameters were collected at time of enrollment. Initial severity of illness was determined using Acute Physiology and Chronic Health Evaluation II (APACHE II) and SOFA scores [17,18]. Patients were subjected on admission to all possible microbiological culturing prior to antibiotic therapy. They received early fluid resuscitation, early empirical broad-spectrum antibiotic therapy and mechanical ventilation if indicated [5].

All enrolled patients were randomly (even odd randomization) assigned into 2 groups. EGDT group I included 50 patients who were managed according to Surviving Sepsis Campaign international guidelines for management of sepsis and septic shock [2016, 5]. They received EGDT after initial fluid resuscitation with 30 ml/kg crystalloid targeting the 4 goals within 6 hours of resuscitation after CVC insertion. The goals were CVP of 8–12 mm Hg achieved with crystalloid administration in boluses, MAP ≥ 65 mmHg if not achieved with fluid administration (was targeted by initiating and titrating norepinephrine), urine output (UOP) ≥ 0.5 mL/kg/hr, and superior vena cava oxygen saturation (SvcO₂) of 70% with packed red blood cells transfusion if the hematocrit was lower than 30% and dobutamine if the hematocrit was 30% or higher. PRC group II included 50 patients who received a protocolized resuscitation care via adequate peripheral venous access through two steps: assessment of volume responsiveness using carotid VTI and PLR [14,19,20].

Carotid VTI was measured during the passive leg raising maneuver by General Electric healthcare vivid 3 machine, Norway; 2008 using transducer probe 2.5 Mhz. On the two-dimensional image, the optimal image of the long axis view was obtained at the common carotid artery. The sample volume was placed on the center of the lumen, with angulation at no more than 60°, 2 cm proximal to the bulb, and a pulsed wave doppler examination was performed. The velocity time integral in centimeters was determined automatically. VTI was measured before and after tilting the semi-recumbent patient to supine position and raising legs to 45 degrees for 90 seconds. ECHO VTI was measured in association to Carotid VTI with PLR during initial assessment of volume responsiveness. Carotid blood flow was calculated as $\pi \times (\text{carotid diameter})^2/4 \times \text{velocity time integral} \times \text{heart rate}$.

Five steps were performed during resuscitation; Administration of crystalloid boluses (250 ml) if patient was volume responder (carotid VTI increase was greater than 10% with PLR), Continuation of fluid resuscitation till carotid VTI increase was less than 10% with PLR and Echo VTI was measured at this stage for verification, initiation and titration of norepinephrine to maintain hemodynamic support if targets of resuscitation were not achieved after administration of four boluses of fluid, measurement of serum lactate level after 6 hours, and PRBCs transfusion if only the hemoglobin level is less than 7 g/dL. Targets of resuscitation were MAP ≥ 65 mm Hg, UOP > 0.5 ml /kg/hr, and % decline in lactate level is of at least 10% [4,21].

After 6 hours of resuscitation, all enrolled patients in both groups were assessed as regards vital signs, namely mean arterial blood pressure (MAP), heart rate (HR), and respiratory rate (RR), fluids used, need for vasopressor, inotrope need, and need for mechanical ventilation.

Table 1. Baseline patient's criteria in both studied groups at time of enrollment.

	EGDT group (n = 50)	PRC group (n = 50)	Test of sig.	p value*
Sex				
Male	26 (52.0%)	28 (56.0%)	$\chi^2 = 0.161$	0.688
Female	24 (48.0%)	22 (44.0%)		
Age (Years)	58.28 ± 17.45	60.56 ± 15.12	t = 0.698	0.487
Cause of septic shock				
Respiratory	18 (36.0%)	16 (32.0%)	$\chi^2 = 3.407$	0.638
Intra-abdominal	10 (20.0%)	6 (12.0%)		
Urinary tract	8 (16.0%)	10 (20.0%)		
Skin, soft tissue	6 (12.0)	10 (20.0%)		
Catheter related	2 (4.0)	4 (8.0%)		
Unknown	6 (12.0%)	4 (8.0%)		
APACHE II	24.0 ± 5.81	26.24 ± 6.02	t = 1.893	0.061
SOFA score	10.60 ± 2.27	10.16 ± 2.50	t = 0.921	0.359
Serum lactate mmol/L	5.88 (2.90–14.90)	5.80 (2.80–14.20)	MW = 0.152	0.879
CRP mg/L	172 (69.0–425.0)	164 (67.0–416.0)	MW = 1.145	0.252
Serum HCO₃⁻ meq/l	14.2 (3.0–22.80)	15.6 (2.70–26.0)	MW = 1.476	0.140

Qualitative data were described using number and percent, while normally quantitative data were expressed in mean ± SD, abnormally distributed data were expressed in median (Min. – Max.)

t values for Student-t test, MW values for Mann Whitney test. *: Statistically significant at p ≤ 0.05

2.1. Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 24. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov, Shapiro and D'agstino tests were used to verify the normality of distribution of variables, Comparisons between groups for categorical variables were assessed using Chi-square test. Student t-test was used to compare two groups for normally distributed quantitative variables. Mann Whitney test was used to compare between two groups for abnormally distributed quantitative variables. Significance of the obtained results was judged at the 5% level.

3. Results

Figure 1 Patients' flow chart. Current study was carried out on 100 adult septic shock patients of both sexes. They were assigned into two groups using simple randomization (even odd randomization method). EGDT group I included 50 patients who were managed according to SSC guidelines. PRC group II included 50 patients who were managed through two steps: assessment of volume responsiveness using carotid VTI and PLR.

Table 1 There were no statistically significant differences in sex or age in both groups (p=0.688, 0.487 respectively). Regarding the cause of septic shock,

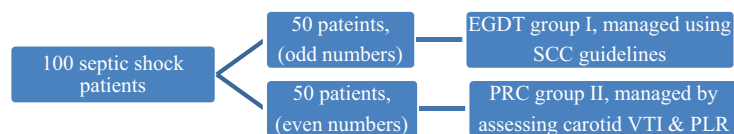


Figure 1. Patients' flow chart.

Table 2. Comparison between both studied groups according to different parameters.

	EGDT group (n = 50)	PRC group (n = 50)	Test of sig.	p value*
MAP				
Admission	52.57 ± 9.32	49.76 ± 8.79	t = 1.549	0.125
After 6 hrs	78.96 ± 10.44	78.28 ± 8.30	t = 0.361	0.719
Heart rate (beats/min)				
Admission	114.92 ± 21.29	105.44 ± 28.30	t = 1.893	0.061
After 6hrs	101.68 ± 16.20	93.64 ± 22.03	t = 2.079*	0.040*
Respiratory rate (cycles/min)				
Admission	34.72 ± 7.84	35.08 ± 6.69	t = 0.247	0.805
After 6 hrs	23.72 ± 6.02	24.28 ± 6.28	t = 0.455	0.650
Fluid therapy (mL)				
Before Randomization	1500 (1000–3250)	1500 (1000–3000)	MW = 1.159	0.247
By the end of 6 hrs	3000 (1250–5000)	1750 (1250–4000)	MW = 4.760	<0.001*
Serum lactate (mmol/L)				
6 hours serum lactate	Not done	3.80 (1.50–13.80)		
Lactate clearance	Not done	23.70 (–55.50–63.0)		

t values for Student-t test, MW values for Mann Whitney test. *: Statistically significant at p ≤ 0.05

MAP: mean arterial blood pressure. Serum lactate was not done in EGDT group after resuscitation according to traditional guidelines which stated that it is a weak recommendation, low quality of evidence [5].

Table 3. Echo & carotid VTI measurements in PRC group.

	Before PLR	With PLR	Variation (%)
Echo VTI Initial			
Min. – Max. (Median)	7.0–32.0 (15.5)	10.0–33.5 (18.3)	1.1–58.3 (21.0)
Endpoint			
Min. – Max. (Median)	8.5–27.6 (20.7)	9.26–29.0 (21.06)	4.5–13.9 (4.6)
Carotid VTI Initial			
Min. – Max. (Median)	3.25–21.3 (7.69)	3.14–21.5 (9.5)	3.5–50.8 (22.08)
Endpoint			
Min. – Max. (Median)	7.3–15.48 (9.5)	7.62–15.0 (9.8)	3.1–9.2 (5.21)

Abnormally distributed data were expressed in Min. – Max. (median). PLR: passive leg raising.

Initial: initial assessment of fluid responsiveness. Endpoint: endpoint of fluid resuscitation.

respiratory infection was the most common cause of septic shock followed by urinary tract infections and intra-abdominal sepsis. There were no statistically significant differences between both groups regarding APACHE II, SOFA score, Serum lactate level, CRP, or Serum HCO₃. ($p=0.061, 0.359, 0.879, 0.252$ and 0.140 respectively).

Table 2 No statistically significant difference was found between both groups regarding vital signs on admission and initial fluids administered before randomization ($p=0.247$). After 6 hours, vital signs were improved in both groups. The target MAP of 65 mmHg or higher had been achieved in both groups with no statistically significant difference in between ($p=0.719$), but the mean heart rate was significantly lower in PRC group ($p=0.040$). Total fluids administered after 6 hours of resuscitation was significantly lower in PRC group ($p<0.001$). Initial serum lactate in group II showed non-significant decline after 6 hours with a median clearance of 23.7. Serum lactate was not

Table 4. Comparison between echo VTI and carotid VTI in PRC group.

	Echo VTI	Carotid VTI	χ^2	p
Initial				
Non-responsive	16(32.0%)	12(24.0%)	0.794	0.373
Responsive	34(68.0%)	38(76.0%)		
Endpoint				
Non-responsive	32(94.1%)	34(100.0%)	2.061	0.493
Responsive	2(5.9%)	0(0.0%)		
Total				
Non-responsive	48(57.1%)	46(54.8%)	0.097	0.756
Responsive	36(42.9%)	38(45.2%)		

Initial: initial assessment of fluid responsiveness. Endpoint: endpoint of fluid resuscitation.

Qualitative data were described using number and percent

Table 5. Correlation between carotid VTI and echo VTI for assessment of fluid responsiveness in PRC group.

	Echo VTI		Sensitivity	Specificity	PPV	NPV
	Non-responsive (n = 48)	Responsive (n = 36)				
Carotid VTI						
Non-responsive (n = 46)	44 (91.7%)	2 (5.6%)	94.44	91.67	89.47	95.65
Responsive (n = 38)	4 (8.3%)	34 (94.4%)				

done in EGDT group after resuscitation according to traditional management guidelines which stated that it is a weak recommendation, low quality of evidence [5].

Table 3 During initial assessment of fluid responsiveness in group II, left ventricular outflow tract velocity time integral (ECHO VTI) showed 21% increase with passive leg raising (PLR) test, while carotid VTI showed 22.08% increase with PLR. At endpoint of fluid resuscitation, ECHO VTI showed 4.6% increase after PLR versus 5.21% increase in carotid VTI measurements.

Tables 4 & 5 In group II patients, fluid resuscitation was guided by carotid VTI with PLR in conjunction with Echo VTI for verification. Among 50 septic shock patients, 34 patients were fluid responsive by carotid & Echo VTI on initial assessment. These patients continued fluid resuscitation guided by Carotid VTI & PLR till variation was $< 10\%$. At this point Echo VTI was assessed for verification; we found that only 2 patients were still fluid responsive. There was no significant difference between Carotid VTI and Echo VTI regarding assessment of fluid responsiveness initially and at end of fluid resuscitation. Carotid VTI in correlation with Echo VTI showed a sensitivity of 94.44% and specificity of 91.67% ($p<0.001$).

Table 6. By the end of 6 hours of resuscitation, need of vasopressor was significantly higher in PRC group ($p=0.001$). There was no statistically significant difference regarding inotropes and mechanical ventilation need in both groups ($p=0.603, 0.685$ respectively). Regarding secondary outcome, duration of vasopressor, mechanical ventilation days and ICU days were more prolonged in EGDT group with no significant difference ($p=0.372, 0.243, 0.091$ respectively). Mortality as a primary outcome was more common among EGDT group with no statistically significant difference between both groups ($p=0.405$).

4. Discussion

This study tried to use a defined protocolized resuscitation care that was based on noninvasive approaches (carotid VTI and PLR) for assessment of volume responsiveness to guide fluid administration and percentage decline in lactate level to assess tissue oxygenation compared to traditional EGDT in management and prognosis of septic shock patients.

Table 6. Outcome in the two studied groups.

	EGDT group (n = 50)	PRC group (n = 50)	Test of sig.	p value
Need for Vasopressor				
Number of patients	40 (80.0%)	50 (100.0%)	$\chi^2 = 11.111$	0.001*
Days	3.0 (0.0–10.0)	2.0 (0.50–9.0)	MW = 0.893	0.372
Need for Inotrope				
Number of patients	10 (20.0%)	8 (16.0%)	$\chi^2 = 0.271$	0.603
Need for MV				
Number of patients	30 (60.0%)	28 (56.0%)	$\chi^2 = 0.164$	0.685
Days	4.0 (0.0–22.0)	3.0 (0.0–14.0)	MW = 1.168	0.243
ICU stay (days)	6.0 (1.0–28.0)	5.0 (1.0–21.0)	MW = 1.689	0.091
Mortality	20 (40.0%)	16 (32.0%)	$\chi^2 = 0.694$	0.405

Qualitative data was described using number and percent, while abnormally distributed data was expressed in median (Min. – Max.). MV = Mechanical Ventilation.

χ^2 values for Chi square test, MW values for Mann Whitney test. *: Statistically significant at $p \leq 0.05$

By 6 hours of resuscitation, vital signs (blood pressure, heart rate and respiratory rate) were improved in both groups. The target MAP of 65 mmHg or higher had been achieved in both groups with no significant difference between them, but the mean heart rate was significantly lower in PRC group. This may be due to lower fluid therapy [8]. Patients in PRC group received significantly less fluid than in EGDT group ($p < 0.001$). ProCESS trial [11] that studied protocol-based EGDT, protocol-based standard therapy or usual care of early-diagnosed septic shock patients in the emergency department showed that the volume of IV fluids administered differed significantly among the groups. ARISE and ProMISe trials [12,13] also showed that patients in the usual care group received less fluid than in EGDT group.

In our study, significant smaller volumes of fluid in PRC group can be explained by use of a highly sensitive and specific dynamic indicators of volume responsiveness during fluid resuscitation (carotid VTI and PLR). It agreed with Marik et al [14] who investigated the use of bioactance and carotid doppler to determine volume responsiveness and blood flow distribution after PLR in patients with hemodynamic instability. The PLR maneuver had a sensitivity of 94% and a specificity of 100% for predicting volume responsiveness and increase in carotid doppler flow had a sensitivity of 94% and specificity of 86%.

By the end of 6 hours of resuscitation, 100% of patients received vasopressors in PRC group that was significantly higher than in EGDT group ($p = 0.001$). Inotrope use was insignificantly higher in EGDT group than in PRC group ($p = 0.603$). ProCESS trial [11] showed that more patients in the 2 protocol-based groups than usual care group received vasopressors. More patients in the protocol based EGDT than in the protocol based standard therapy group or the usual care group received dobutamine.

ProMISe and ARISE trials agreed with ProCESS trial in their results. Use of vasopressors and dobutamine remained higher in EGDT group [12,13]. In contrast to the previous studies, our study showed significant

higher use of vasopressors in PRC group. However, the inotropic use was insignificantly higher in EGDT group. This can be explained by adherence to the study protocol that recommended early use of vasopressors after resuscitation with 4 boluses of fluids (250 ml) and echo-screening for all patients on admission [4].

This study showed prolonged ICU stay, mechanical ventilation days and duration of vasopressor use in EGDT group but without statistical significance. ProCESS trial [11] showed no difference in the length of ICU stay. There was no significant difference in the duration of cardiovascular or respiratory support. In ARISE results [12], there were no significant differences regarding ICU stay, cardiovascular support or respiratory support. The previous results were reinforced by ProMISe trial [13] when it showed that the median length of stay in ICU was significantly greater in the EGDT group than in usual care group.

28-day Mortality was non-significantly less in PRC group than EGDT group. ProCESS trial [11] showed no significant differences in 90-day mortality or 1-year mortality. It concluded that EGDT did not improve outcome. The same results were found in ARISE trial [12] and ProMISe trial [13]. The trios of EGDT trials revealed that EGDT did not improve mortality in patients with early septic shock [11–13].

They disagreed with Rivers et al [22] who showed in-hospital mortality 30.5% in the EGDT group and 46.5% in the standard therapy group. These studies compared undefined usual resuscitation care with original EGDT. In the current study, a protocolized resuscitation care was used. Non-significant Improvement in survival in PRC group can be explained by significant lower fluid therapy. Jones et al, Boyd et al and Maitland et al [6–8] in their studies concluded that excessive fluid therapy has been associated with increased mortality.

This study had some limitations. First, patients received initial fluid resuscitation before randomization, and this may had interfered with results. Second, all enrolled patients were recognized to be in

septic shock. This study did not address the extent to which any of both strategies offer advantages in case of delayed recognition of septic shock.

5. Conclusion

This study showed that, a protocolized resuscitation care (PRC) may be beneficial as compared to EGDT in early management of septic shock. Use of carotid VTI with PLR to guide fluid resuscitation was associated with significant less fluid administered that may improve outcome. There was a non-significant trend to decrease mortality.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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