

Early goal-directed therapy in the management of severe sepsis/septic shock in an academic emergency department in Malaysia

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Abstract

Introduction: Early goal-directed therapy (EGDT) is a haemodynamic optimization protocol that is proven to reduce mortality in cases of severe sepsis/septic shock.

Objective: The objective of this study is to determine whether EGDT can be implemented successfully in an academic hospital emergency department with the existing resources and expertise.

Methods: A prospective study was conducted at Emergency Department of Universiti Kebangsaan Malaysia Medical Centre (ED UKMMC) from March until May 2009. Sixteen patients were enrolled in this study. The patients were subjected to EGDT with the aim to achieve all defined haemodynamic endpoints within the first 6 hours of diagnosis. Data was collected regarding achievability of these endpoints.

Results: The mean age of the patients was 58.4 ± 17.4 and the mean APACHE II score on arrival was 24.2 ± 7.6 .

The diagnosis of severe sepsis was made at a mean time of 1.2 ± 1.0 hours from the time of arrival to the emergency department. All patients successfully had a central venous line inserted within 6 hours of diagnosis and the mean time to insertion was 0.7 ± 0.8 hour. The target CVP range was achieved within an average of 2.1 ± 2.2 hours from diagnosis. Out of the 16 patients, 12 (87.5%) achieved the target CVP goal. All patients achieved an MAP of 65 mmHg within the first 6 hours of diagnosis with an average time of 1 hour from time of diagnosis. Eleven (68.8%) patients successfully achieved the target central vein oxygen saturation of 70% and the mean time to achieve this goal was 1.3 ± 0.9 hours. Mean ScvO₂ achieved was 81.6 ± 6.7 . Thus, the success rate for achieving all EGDT goals within the first 6 hours of diagnosis was 62.5% (n=10).

Conclusion: This study demonstrates that EGDT can be implemented in the ED with the current resources and expertise.

Key words: Early goal-directed therapy, sepsis, severe sepsis, septic shock, Emergency Department, critical care

Introduction

Sepsis continues to be a major cause of mortality and

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morbidity throughout the world. The annual incidence of severe sepsis was approximately 3.0 cases per 1,000 of the population. (1) In the United States alone, the incidence of severe sepsis will see an annual increase of 1.5% which may be attributable to an increasing ageing population. (1)

Early goal-directed therapy (EGDT) was proposed by Rivers et al in 2001. This protocol advocates aggressive treatment commencing in the emergency department to achieve certain haemodynamic goals. This achieved a 16% absolute risk reduction for in-hospital mortality. (2)

Numerous studies and meta-analyses support the benefit

of EGDT in severe sepsis deeming it accepted worldwide as the current standard therapy. (3-6) More recent studies concentrate on feasibility of implementation of these guidelines in real emergency department settings and this is where our study stands.

Gao et al published a prospective observational study in 2 teaching hospitals in the United Kingdom on the compliance to the 6-hour and 24-hour sepsis bundles on hospital mortality. The study reported only 52% compliance to the 6-hour sepsis bundle and 30% compliance to the 24-hour sepsis bundle. (7) A single-centre study conducted in an urban academic hospital in the United States demonstrated successful implementation of EGDT at 91%. (4) However, in another survey across 30 academic EDs in the United States showed that only 7% of clinicians reported the use of EGDT. The most commonly cited challenges to implementation of EGDT were lack of specialty monitoring equipment (75%), too many resources required for implementation (43%) and that the protocol required central venous cannulation (36%). (8) Another survey across the United Kingdom revealed that only 4% of hospitals had all the required facilities and were able to implement the sepsis care bundles successfully. (9)

Malaysia is not immune from the global burden of sepsis. In 2008, severe sepsis was the second leading cause of death in the Malaysian Ministry of Health hospitals. (10) To date, there have been no local studies on the implementation or challenges in applying EGDT in emergency departments (ED).

Universiti Kebangsaan Malaysia Medical Centre (UKMMC) is a tertiary academic centre with 900-bed capacity which includes 17 Intensive Care Unit (ICU) beds, 8 Coronary Care Unit (CCU) beds, 6 High Dependency Ward (HDW) beds and 3 Renal High Dependency beds. EGDT was only recently introduced and was not a part of our standard care protocol. During this study, there was no additional clinical staff or resources utilized. ED UKMMC has 5 priority 1 bays with invasive monitoring capabilities and a point of care arterial blood gas analyzer.

The objective of this study was to determine if EGDT could be implemented successfully in an academic hospital emergency department with the existing resources and expertise.

Materials and methods

Study design and subject population

This prospective observational study was conducted in ED UKMMC with approval from the UKMMC Research Ethics Committee.

A consecutive sampling method was applied and all patients who fulfilled the criteria for severe sepsis/septic shock as defined by the Rivers protocol were included in this study. (2)

Patients must fulfill both component A and B:

- A) Patients presented to the ED with 2 or more of the following criteria:
- 1) Temperature $\geq 38^{\circ}\text{C}$ or $\leq 36^{\circ}\text{C}$
 - 2) White blood cell count ≥ 12000 or $\leq 4000/\text{mm}^3$
 - 3) Heart rate ≥ 90 beats per minute
 - 4) Respiratory rate ≥ 20 breaths per minute or Pa CO₂ < 32 mmHg
- B) Blood lactate concentration ≥ 4 mmol/L or persistent hypotension as evidenced by systolic blood pressure ≤ 90 mmHg despite 20 mL/kg of crystalloids or 8 mL/kg of colloids fluid challenge given over a 30-minute period.

Patients who were below 18 years old, required immediate surgical intervention, had standing “do not resuscitate” orders, transferred out or had any contraindication for central venous cannulation were excluded from this study.

Data collection

Data collection took place from 1st March 2009 to 31st May 2009. All patients who fulfilled the inclusion and exclusion criteria were subjected to EGDT protocol (**Figure 1**) which included:

- 1) Continued fluid challenges of 500-1000 ml of crystalloids or 300-500 ml of colloids over 30 minutes and repeated as appropriate.
- 2) Vasopressor administration of either noradrenaline, starting from 0.1 $\mu\text{g}/\text{kg}/\text{min}$ titrated to effect and/or dopamine, starting from 5 $\mu\text{g}/\text{kg}/\text{min}$ titrated to effect.

- 3) In the instance of the central venous oxygen saturation (ScvO₂) was still below 70% after adequate fluid and vasopressors, packed red cell transfusion will be given if the hematocrit <30%. However, if the hematocrit was ≥30%, an inotrope infusion of dobutamine, starting from 2.5 to a maximum of 20 µg/kg/min will be commenced and titrated until the ScvO₂ ≥70%.

The above protocol was implemented with the following goals:

- 1) Central venous pressure (CVP) of ≥8-12 mmHg (12-15 mmHg in ventilated patients).
- 2) Mean arterial blood pressure (MAP) ≥65 mmHg.
- 3) ScvO₂ ≥70%.

Percutaneous blood culture was taken and appropriate antibiotics were administered.

Data on patient demographics such as age, gender and initial Acute Physiology and Chronic Health Evaluation II (APACHE II) score on admission were collected. Parameters to determine success of EGDT including time taken to establish diagnosis, central venous cannulation and time to reach all haemodynamic endpoints were also documented. Outcome measures were determined by duration of stay in critical care areas, hospital length of stay (LOS) and in-hospital 28-day mortality. Written consent was obtained from the relatives of the patient as the patients were mostly incapacitated during admission due to severe sepsis.

Statistical analysis

Subjects' characteristics were presented by descriptive analysis. Independent t tests were applied as appropriate to compare between the group which achieved EGDT and the group which did not achieve EGDT. P value of less than 0.05 is considered significant.

Results

During the study period, there was a total of 18,621 patients seen in the ED. Out of this, 424 patients were priority 1. Only 16 patients were enrolled into the study. The demographics and baseline characteristics of these patients are listed in **Table 1**. The mean APACHE II score on arrival for these

patients was 24.2.

Table 2 shows EGDT haemodynamic endpoints achievement. The objective variables included time to diagnosis, time to central venous line (CVL) insertion, time taken to achieve CVP, MAP and ScvO₂ goals.

Table 3 shows the outcomes of the patients enrolled. The variables are admission to critical care area, critical care area LOS, hospital LOS and in-hospital 28-day mortality.

Discussion

The primary goal of this study was to determine compliance of implementing EGDT in the management of severe sepsis/septic shock in our ED and specifically to demonstrate that the end points could be reliably achieved within 6 hours of diagnosis. Performing the EGDT protocol requires early diagnosis, invasive monitoring and early treatment with the appropriate use of fluids, vasopressors, inotropes and blood transfusion within the first 6 hours of diagnosis. With this in mind, the data on time to achieve diagnosis, invasive monitoring and haemodynamic endpoints were collected.

In this study, we found that ED doctors took an average of 1.2 hours to diagnose severe sepsis/septic shock. Unfortunately, there was no comparable data for time taken to make the diagnosis of severe sepsis/septic shock in the literature. Delay in obtaining confirmatory laboratory results and administering fluid challenge may explain the length of time taken to reach a diagnosis at our centre.

All patients had a CVL successfully inserted within 6 hours of diagnosis. The haemodynamic endpoints; CVP, MAP and ScvO₂ targets were reached in 12 (87.5%), 16 (100%) and 11 (68.8%) patients respectively. The overall compliance to EGDT goals was 62.5% (10 out of 16 patients) which was comparable to a 52% compliance rate in a study done in the UK (7) though lower than the 90% compliance rate achieved by a study conducted in the US. (4) This reflects how EGDT was implemented at our centre while concurrently running normal services without additional resources.

Table 4 compares the time to central line insertion and achievement of EGDT endpoints between our center (UKMMC) and Cooper University Hospital, an academic medical center in New Jersey, United States, where Trezciak

et al had conducted a retrospective study. (4) The comparison was made to show that our efficiency in executing EGDT goals here was comparable to a center in a developed country with different settings. Nonetheless, contrary to the study done at Cooper University, the personnel involved in delivery of care in our centre were aware that the time intervals were recorded. It is plausible that the Hawthorne effect has occurred, resulting in the ED personnel complying with the 6 hour time target.

In terms of outcomes, we found that although EGDT was achieved in 10 out of 16 patients enrolled, the mortality rate was unfortunately higher in that group. The median APACHE II score in those who achieved EGDT but died (n=7) was 30 which correlates to a 75% death rate. Although these patients achieved EGDT, their severity of illness

on presentation as reflected by the APACHE score would have contributed to the high mortality rate in this group. Furthermore, 4 out of the 7 who died were not admitted to the ICU due to inavailability of ICU beds.

The small sample size obtained was due to time limitation in recruiting prospective subjects. A longer duration of study would have provided a larger sample size and reduced sample bias.

Conclusion

This study demonstrates that EGDT can be implemented in the ED with our current resources and expertise.

Table 1. Basic characteristics of EGDT subjects

Characteristics	EGDT (n=16)
Age (years)	
Mean±SD	58.4±17.4
Range	21-86
Gender (n)	
Male	12 (75%)
Female	4 (25%)
APACHE II score on arrival	
Mean±SD	24.2±7.6
Temperature (°C)	
Mean±SD	38.1±1.9
Heart rate (beats/minute)	
Mean±SD	122.8±23.6
Respiratory rate (breaths/minute)	
Mean±SD	34.4±13.5
PaCO ₂ (mmHg)	
Mean±SD	25.6±10.2
White cell count (/mm ³)	
Mean±SD	20.8±12.3
Systolic BP (mmHg)	
Mean±SD	103.9±42.4
Lactate (mmol/L)	
Mean±SD	6.3±4.9

Table 2. EGDT haemodynamic end points achievement

Time to diagnosis (hours)	
Mean±SD	1.2±1.0
Time to CVL insertion (hours)	
Mean±SD	0.7±0.8
CVL insertion achieved within 6 hours of diagnosis (%)	100
Time to CVP goal achieved (hours)	
Mean±SD	2.1±2.2
CVP goal achieved within 6 hours of diagnosis (%)	87.5 (n=12)
Time to achieve MAP goal (hours)	
Mean±SD	1.0±1.3
MAP goal achieved within 6 hours of diagnosis (%)	100
Time to achieve ScvO2 goal (hours)	
Mean±SD	1.3±0.9
ScvO2 goal achieved within 6 hours of diagnosis (%)	68.8 (n=11)
ScvO2 (%)	
Mean±SD	81.6±6.7
All goals achieved within 6 hours of diagnosis (%)	62.5 (n=10)
Emergency department length of stay (hours)	
Mean±SD	5.6±1.4

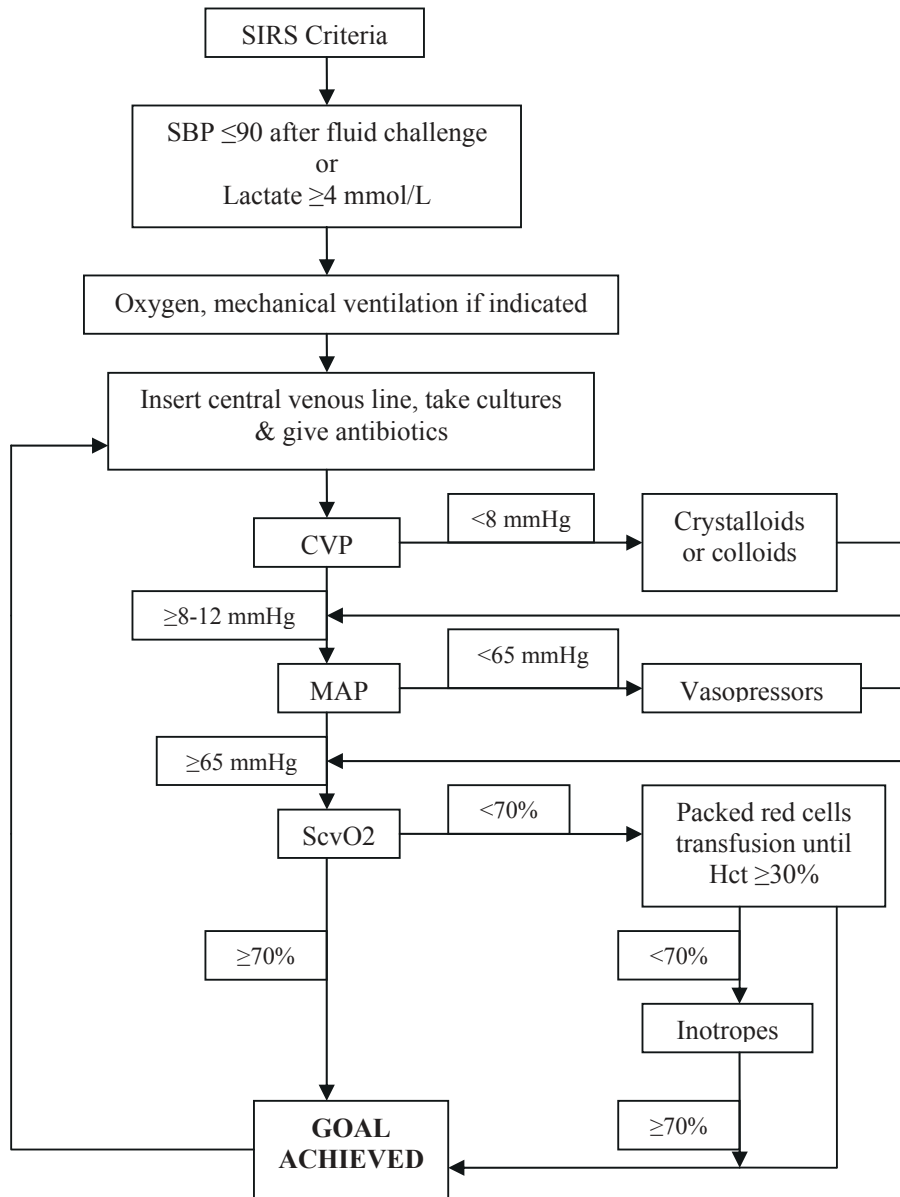
Table 3. Outcomes: EGDT achieved vs EGDT not achieved

	EGDT achieved (n=10)	EGDT not achieved (n=6)	p value
Admitted to critical care area (%)	70 (n=7)	50 (n=3)	
Hospital length of stay (days)			
Mean	4.5	12.8	0.06
In-hospital 28-day mortality (%)	70.0 (n=7)	33.3 (n=2)	0.17

Table 4. Comparison of EGDT goals achievement times between UKMMC and Cooper University Hospital

Variables	UKMMC (n=16)	Cooper University Hospital (n=22)
Central line insertion (hours)		
Mean±SD	0.7±0.8	2.1±1.7
Median	0.5	1.5
Range	0-3.4	1-8
CVP goal achieved (hours)		
Mean±SD	2.1±2.2	6.3±3.8
Median	1.5	6.0
Range	0-5.6	1-14
MAP goal achieved (hours)		
Mean±SD	1.0±1.3	5.6±3.2
Median	0.5	4.0
Range	0-4.3	2-13
ScvO2 goal achieved (hours)		
Mean±SD	1.3±0.9	6.4±4.0
Median	1.0	5.0
Range	0.4-3.3	2-16

Figure 1. Early goal-directed therapy protocol



Legend: Adapted from Rivers et al (2)

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303-10.
2. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.
3. Otero RM, Nguyen HB, Huang DT, Gaijeski DF, Goyal M, Gunnerson KJ, et al. Early goal-directed therapy in severe sepsis and septic shock revisited: concepts, controversies, and contemporary findings. *Chest* 2006;130:1579-95.
4. Trzeciak S, Dellinger RP, Abate NL, Cowan RM, Stauss M, Kilgannon JH, et al. Translating research to clinical practice: a 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department. *Chest* 2006;129:225-32.
5. Jones AE, Brown MD, Trzeciak S, Shapiro NI, Garrett JS, Heffner AC, et al. The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: a meta-analysis. *Crit Care Med* 2008;36:2734-9.
6. Garcia AJ, Doshi P, Otero RM, Cannon CM, Rivers EP. Early sepsis management: a meta-analysis of published studies. *Ann Emerg Med* 2008;52:S59.
7. Gao F, Melody T, Daniels DF, Giles S, Fox S. The impact of compliance with 6-hour and 24-hour sepsis bundles on hospital mortality in patients with severe sepsis: a prospective observational study. *Crit Care* 2005;9:R764-70.
8. Jones AE, Focht A, Horton JM, Kline JA. Prospective external validation of the clinical effectiveness of an emergency department-based early goal-directed therapy protocol for severe sepsis and septic shock. *Chest* 2007;132:425-32.
9. McNeill G, Dixon M, Jenkins P. Can acute medicine units in the UK comply with the Surviving Sepsis Campaign's six-hour care bundle? *Clin Med* 2008;8:163-5.
10. Health Facts 2008. Health Informatics Centre. Planning and Development Division. Ministry of Health Malaysia [Online]. 2009 May 1 [cited 2010 Jul 15]; Available from: URL: http://www.moh.gov.my/images/gallery/stats/health_fact/Health_Fact_2008_LANDSKAP.pdf