Mortality Rate Among Patients with Septic Shock after Implementation of 6-Hour Sepsis Protocol in the Emergency Department of Thammasat University Hospital

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Background: *Septic shock is a major healthcare problem effecting people worldwide with high mortality rate. Administering early and appropriate interventions can help improve the outcome. The 6-hour bundle, launched by the Surviving Sepsis Campaign committee was part of efforts to incorporate evidence-based guideline to clinical practice. There were many reports on outcome improvement of septic shock patients after implementation of the 6-hour bundle at the emergency department.*

Objective: *To compare mortality rate of septic shock patients before and after implementing the 6-hour sepsis protocol at the emergency department of Thammasat University Hospital.*

Material and Methods: *Study was conducted at the emergency department of Thammasat University Hospital. This is an interrupted time, before and after study, comparing between the prospective cohort period after (Oct 2012 to Nov 2013) and the historical control period before (Feb 2011 to July 2012) implementation of 6-hour sepsis protocol. Primary outcome was hospital mortality of septic shock patients. Secondary outcomes included length of hospital stay and predictive factors for mortality of septic shock patients.*

Results: *There were 80 patients included in the pre-intervention group and 75 patients in the post-intervention group. There was significant improvement in management of septic shock patients. Total fluid given in 2 hours in the post-intervention group was significantly higher [2,000 (500-3,000) vs. 1,600 (100-3,600); p = 0.038)] when compared with the pre-intervention group. The entire resuscitation bundles compliance rate was significantly increased in the post-intervention group (37.3% vs. 0%; p<0.001). Regarding each intervention in the 6-hour bundle, included serum lactate measurement, giving fluid bolus ≥500 ml and maintaining MAP ≥65 mmHg, were all significantly increased in rate of compliance (96.0% vs. 2.5%; p<0.001, 100.0% vs. 92.3%; p = 0.029, 100.0% vs. 88.8%; p = 0.003, respectively). Hospital mortality was reduced significantly after implementation of the 6-hour sepsis protocol (18.7% vs. 40.0%; p = 0.005).*

Conclusion: *Septic shock mortality was decreased after implementation of the 6-hour sepsis protocol at the emergency department of Thammasat University Hospital.*

Keywords: *6-hour bundle, Resuscitation bundle, Septic shock, Emergency department, Sepsis protocol*

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Sepsis and septic shock are major health care problems affecting millions of people worldwide, and increasing in incidence[1-5]. Approximately 750,000 new cases of sepsis occur each year in the US, with more than 200,000 deaths per year[6]. In the US, the cost of care for sepsis is estimated at 16.7 billion dollars annually. The mortality rate of sepsis syndrome has remained high, ranging from 20% to 50%[7-10]. The emergency department plays an important part in the chain of survival. Two-thirds of patients with sepsis enter health care system via emergency department[11]. Sepsis is a time critical disease. Administering early and appropriate interventions can help improve the outcome[12]. The paper published in 2001, which evaluated the efficacy of early goal-directed therapy (EGDT), showed 16% absolute reduction in mortality[13]. The important role of emergency care provider in identification of the disease and initiation of resuscitation of septic patient was solidified since then. The surviving sepsis campaign (SCC), the group of collaboration was formed in 2002. The initiative of the group was to reduce the mortality from sepsis by 25% within the next five years[8,14]. The first evidence-based guideline was published in 2004 and the second in

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2008[12,15]. Apart from that, the American college of emergency physician (ACEP) collaborated with SCC to incorporate "treatment bundles" in management of severe sepsis and septic shock[7].

Guidelines are divided into a 6-hour resuscitation bundle and a 24-hour sub-acute care bundle[7,11]. The 6-hour resuscitation bundle composed of three main components, which are early identification, early antibiotics and cultures, and early goal-directed therapy[7]. In recent years, many institutions have recreated the protocol and treatments based on EGDT protocols with good success[16-21]. Moreover, many studies have shown that implementation of a bundle of care at emergency a department may improve the outcome[22-24], and help achieve consistent management of this condition[25]. However, compliance with bundle of care was still low[26,27].

The present study was mainly conducted to assess the impact of the implementation of 6-hour bundle of care for septic shock patients, at the emergency department of Thammasat University Hospital on mortality of patients. Moreover, this study tried to evaluate the accomplishment of incorporating a 6-hour resuscitation bundle of care into real practice.

Material and Method

The present study was conducted at the emergency department of tertiary care, teaching hospital, of Thammasat University in Pathumthani Province. The average number of emergency department visits was 35,000 to 40,000 visits per year. This was an interrupted time, before and after study, comparing the prospective cohort period after (Oct 2012 to Nov 2013) and the historical control period before (Feb 2011-July 2012) implementation of intervention. During Sep 2011 to Jan 2012 period, Thammasat University Hospital was affected by a major flood event. Therefore, that specific time period was not included in the present study. The 6-hour sepsis protocol was developed based on SSC guideline and was approved by the working group, composed of infectious specialists, pulmonary specialists and emergency physician. The final protocol was implemented as a pilot process during a 2-month period, from Aug 2012 to Sep 2012. A lecture was developed for all staff working at the emergency department in order to improve the knowledge and understanding in 6-hour resuscitation bundle for treating septic patients before the implementation of the protocol. Sample size estimation for each group was 41.

The eligible subject was the emergency department, age over 18 years old, diagnosed with septic shock. The investigators assessed the medical record of the eligible subject and inclusion was made if the eligible subject met the criteria of septic shock according to the ACCP/SCCM consensus conference definition[28]. The exclusion criteria included, conditions against of central line placement, designation in do-not-resuscitate (DNR) form, death or dropping out before 6-hour resuscitation period was completed, previously resuscitated from other health care facilities, and referred out to other hospitals after acute treatment. The present study was approved by institutional review board (IRB) of Faculty of Medicine of Thammasat University.

The data collected were demographics, co-morbid diseases, laboratory data, general inflammatory and tissue-perfusion variables for diagnosis of sepsis[28], site of infections, treatment according to 6-hour resuscitation bundle, length of hospital stay and outcome status. The main outcome of the study was hospital mortality. The secondary outcomes were 7-day, 28-day mortality, duration of hospital admission and independent predictive factors of hospital mortality in septic shock patients.

"Time zero" was defined as the time meeting criteria for the specific intervention. Time zero for obtaining serum lactate, blood cultures and antibiotic therapy was stated at the moment when patients initially met diagnostic criteria for sepsis. Time zero to initiate other measures according to 6-hour resuscitation bundle was considered when hypotension occurred. The time zero for diagnosis of sepsis and the first presentation of hypotension was determined by searching through all clinical documentations, including the assessment by physician and nursing staffs at emergency department in the medical records, bedside flow sheeting, all tests requested and physician's order within 6 hour-period.

Definitions

The American college of chest physicians/ society of critical care medicine (ACCP/SCCM) definitions were used for clinical conditions. Systemic inflammatory response syndrome (SIRS) was defined as a syndrome with more than one of the following criteria, body temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg, and white blood cell count >12,000 cells/mm^3 or <4,000 cells/mm^3 or >10% band forms. Sepsis was defined as systemic response to infection, manifested by two or more of the SIRS. Septic shock

was defined as sepsis-induced hypotension (a systolic blood pressure of <90 mmHg or a reduction >40 mmHg from baseline in the absence of other causes of hypotension) plus hypo-perfusion abnormalities despite adequate fluid resuscitation (20-40 ml/kg fluid challenge)[7,28].

Sepsis resuscitation bundle (6-hour bundle) was defined according to the one developed by SSC steering committee in partnership with the institute for healthcare improvement (IHI)[7,29]. The 6-hour resuscitation bundle should be initiated once sepsis or septic shock was established, and completion of the bundle was certified once endpoint was accomplished. The 6-hour bundle was composed of collecting serum lactate, obtaining blood cultures prior to antibiotic therapy, administering the patients with broad spectrum antibiotic within 3 hours of presentation at emergency department, treating hypotension with initial minimum 20 ml/kg or 500-1,000 ml of crystalloid or colloid equivalent, applying vasopressor for hypotension when non-responsive to initial fluid resuscitation to maintain mean arterial pressure $\geq$65 mmHg, achieving central venous pressure (CVP) of $\geq$8 mmHg and central venous oxygen saturation ($ScvO_2$) of $\geq$70% in the event of septic shock[30,31].

General variable abnormalities were defined according to the updated sepsis definition from 2008 SSC International guidelines for management of sepsis and septic shock, which included fever (>38.3°C), hypothermia (temperature <36.0°C), tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >20 breaths/min) and altered mental status[7,15]. Hyperlactatemia, which is tissue-perfusion variable, was defined as lactate level >2 mmol/L[7].

Statistical analysis

Descriptive statistics were used for analyzing the characteristics of the patients. Chi-square or Fisher's exact test were used for comparing between two groups of categorical data. Student's t-test or Mann-Whitney U test were used for comparing between two groups of continuous data. A multivariate analysis of predictive factors of mortality was performed by logistic regression method. A p-value of 0.05 or less was considered statistically significant. Statistical analysis was performed with SPSS 17.0.

Results

Comparison between pre- and post-intervention groups

In the post-intervention group, a total of 75 patients who met the diagnostic criteria of septic shock were included and prospectively evaluated. In the pre-intervention, historical controlled group, a total of 80 patients with septic shock were included and retrospectively evaluated. Baseline characteristics are shown in Table 1. There were no significant differences in overall baseline characteristics between the two groups except more percentage of tachypnea patients (76.3% vs. 60%; p = 0.030), and lower level of bicarbonate (19.5$\pm$5.8 vs. 21.4$\pm$4.8; p = 0.27) in the pre-intervention group. The top three most common sources of infection in both groups were urinary tract, respiratory and intra-abdominal infections. Most of the patients from the pre- and the post- intervention groups were similarly admitted to general ward of medical unit.

Management of septic shock and compliance with 6-hour resuscitation bundle

Regarding management of septic shock at the emergency department, there were no significant differences between the groups in terms of time-to-antibiotics therapy, vasopressors used and the total fluid given within 6-hour period. Total volume of Initial fluid bolus administered within 2-hour period was significantly higher in the post-intervention group [2,000 (500-3,000) vs. 1,600 (100-3,600); $p = 0.038$) when compared with the pre-intervention group. There was significantly more proportion of patients, whom $ScvO_2$ was measured and whom inotropic agent was administered in order to achieve the goal of $ScvO_2$ reached 70% or more, in the post-intervention group (66.7% vs. 6.3%; $p<0.001$ and 16.0% vs. 3.8%; $p = 0.013$, respectively) when compared with the pre-intervention group.

Compliance rate with the entire 6-hour bundle was significantly higher in the post-intervention group (37.3% vs. 0%; $p<0.001$). Regarding evaluation of compliance with each intervention in the 6-hour bundle, measurement of serum lactate, initial administration of fluid bolus $\geq$500 ml, treating hypotension (maintaining MAP $\geq$65 mmHg), were all significantly higher in application rates for the post-intervention group (96.0% vs. 2.5%; $p<0.001$, 100.0% vs. 92.3%; $p = 0.029$, 100.0% vs. 88.8%; $p = 0.003$, respectively) in comparison with the pre-intervention group. Management of septic shock patients in both groups are demonstrated in Table 2

Outcome

Outcome of the patients are demonstrated in Table 3. There were no significant differences regarding

Table 1. Baseline characteristics of patients with septic shock presented at emergency department of Thammasat University Hospital

	80 pre-intervention group No. (%)	75 post-intervention group No. (%)	*p*-value
Age, years; mean (SD)	65.5 (14.6)	63.9 (18.0)	0.562
Male	38 (47.5)	34 (45.3)	0.787
Present of underlying conditions	74 (92.5)	69 (92.0)	0.907
General variables abnormalities			
Hypo-/hyperthermia	39.0 (48.8)	32 (42.7)	0.447
Tachycardia	61 (76.3)	49 (65.3)	0.135
Tachypnea	61 (76.3)	45 (60.0)	0.030
Altered mental status	31 (38.8)	21 (28.0)	0.157
Laboratory data			
Sodium (mEq/L); mean (SD)	132.2 (11.45)	132.6 (5.6)	0.811
Potassium (mEq/L); mean (SD)	4.0 (0.9)	3.9 (0.9)	0.656
Bicarbonate (mEq/L); mean (SD)	19.5 (5.8)	21.4 (4.8)	0.027
Creatinine (mg/dL); median (min-max)	1.7 (0.4-9.7)	1.5 (0.5-9.8)	0.487^{++}
Hematocrit (%); mean (SD)	33.7 (12.2)	37.9 (1.3)	0.114
White blood count (total/mm^3) x10^3; median (min-max)	13.1 (0.2-65.0)	11.9 (0.3-42.0)	0.678^{++}
Hyperlactatemia*, (n^1 = 2, n^2 = 72)	2 (100)	58 (80.6)	>0.999^{+}
Source of infection			
Urinary	25 (31.3)	29 (38.7)	
Respiratory	25 (31.3)	16 (21.3)	
Intra-abdominal	16 (20.0)	24 (32.0)	
Primary bacteremia	2 (2.5)	1 (1.3)	
Febrile neutropenia	2 (2.5)	1 (1.3)	0.199
Skin and soft tissue	1 (1.3)	1 (1.3)	
Multiple sources	5 (6.3)	0	
Other infection	0	1 (1.3)	
Unknown	4 (5.0)	2 (2.7)	
Evident of infection			
Culture proven infection	75 (93.8)	74 (98.7)	0.211^{+}
With septicemia	27 (36.0)	27 (36.5)	
			0.951
Without septicemia	48 (64.0)	47 (63.5)	
Location of admission			
ICU	9 (11.2)	6 (8.0)	
			0.494
Ward	71 (88.8)	69 (92.0)	
Unit			
Medical	73 (91.2)	68 (90.7)	
			0.899
Surgical	7 (8.8)	7 (9.3)	

* Hyperlactatemia was defined as lactate level >2 mmol/L, $^{+}$ Fisher exact test, $^{++}$ Mann-Whitney U test

length of hospital stay between the groups. However, 7-day, 28-day and hospital mortality rates were significantly reduced in the post-intervention group (12.0% vs. 27.5%; $p = 0.017$, 14.7% vs. 30.0%; $p = 0.034$, 18.7% vs. 40.0%; $p = 0.005$, respectively) compared with the pre-intervention group.

Factors associated with in-hospital mortality of septic shock

Univariate analysis was applied for identifying the factors associated with in-hospital mortality of septic shock as shown in Table 4. Tachypnea and hyperlactatemia are the two characteristics found to be

Table 2. Treatment and performance of bundle compliance

Type of measure	80 pre-intervention No. (%)	75 Post-intervention No. (%)	*p*-value
Time-to-antibiotic, minutes; median (min-max)	90 (10-660)	70 (5-220)	0.561[++]
Initial fluid bolus in 2 hour, ml; median (min-max)	1,600 (100-3,600)	2,000 (500-3,000)	0.038[+]
Total fluid bolus in 6 hour, ml; mean (SD)	2,097 (922)	2,369 (715)	0.093
Vasopressors			
No	4 (5.0)	7 (9.3)	0.358[+]
Yes	76 (95.0)	68 (90.7)	
Norepinephrine	65 (85.6)	65 (95.6)	
Dopamine	9 (11.8)	2 (2.9)	0.364[+]
Both	2 (2.6)	1 (1.5)	
Inotropic agent			
Dobutamine	3 (3.8)	12 (16.0)	0.013[+]
Measure CVP within 6 hours	75 (93.8)	75 (100.0)	0.059[+]
Measure $ScvO_2$ within 6 hours	5 (6.3)	50 (66.7)	<0.001[+]
6-hour resuscitation bundle			
Serum lactate measured	2 (2.5)	72 (96.0)	<0.001[+]
Blood culture prior to antibiotics	75 (93.8)	74 (98.7)	0.211[+]
Broad spectrum antibiotics within 3 hours	68 (89.5)	72 (96.0)	0.209[+]
Initial fluid resuscitation ≥500 ml	72 (92.3)	74 (100.0)	0.029[+]
Maintain MAP ≥65 mmHg	71 (88.8)	75 (100.0)	0.003[+]
CVP ≥8 mmHg	68 (90.7)	74 (98.7)	0.063[+]
$ScvO_2$ ≥70%	2 (40.0)	3 (64.0)	0.359[+]
Entire 6-hour bundle compliance	0	28 (37.3)	<0.001[+]

[+] Fisher exact test, [++] Mann-Whitney U test

Table 3. Outcome of septic shock patients presented at the emergency department

Outcome	80 pre-intervention group	75 post-intervention group	*p*-value
Hospital stay, days; median (min-max)	7.5 (1.0-361.0)	9.0 (0-49.0)	0.184[++]
Mortality, n (%)			
7-day	22 (27.5)	9 (12.0)	0.017[+]
28-day	24 (30.0)	11 (14.7)	0.034[+]
Hospital	32 (40.0)	14 (18.7)	0.005[+]

[+] Fisher exact test, [++] Mann-Whitney U test

associated with hospital mortality. In terms of management at emergency department, time-to-antibiotics, initial fluid bolus given in 2-hour and 6-hour period were predictors of decreasing mortality. Regarding 6-hour bundle, serum lactate measured, administration of broad-spectrum antibiotics within 3 hours of presentation of sepsis or septic shock, initial fluid bolus ≥500 ml and maintaining MAP ≥65 mmHg were predictive factors of septic shock mortality.

Factors that achieved statistical significance from multivariate logistic regression analysis were hyperlactatemia, total fluid given in 6 hours and administration of broad-spectrum antibiotics within 3 hours as demonstrated in Table 5.

Discussion

To our knowledge, the present study is one of the few experimental studies reporting on the effect of implementation of 6-hour bundle of care on mortality of septic shock in Thailand[32,33]. However, this is the first, before and after intervention study conducted at the emergency department setting. Among patients who

Table 4. Univariate analysis of predictive factors for hospital mortality of septic shock patients

Factors	Odds ratio	95% CI	*p*-value
Age, years	1.01	0.99-1.03	0.270
Present of underlying conditions	1.29	0.33-4.99	0.713
General variable abnormalities			
Hypo-/hyperthermia	0.52	0.25-1.06	0.076
Tachycardia	2.02	0.88-4.65	0.095
Tachypnea	3.49	1.43-8.52	0.006
Altered mental status	2.11	1.03-4.31	0.040
Laboratory data			
Sodium	0.96	0.93-1.00	0.105
Potassium	1.08	0.75-1.56	0.658
Bicarbonate	0.96	0.90-1.02	0.256
Creatinine	1.00	0.84-1.19	0.989
Hematocrit	0.99	0.96-1.03	0.787
White blood count	1.00	1.00-1.00	0.818
Hyperlactatemia	3.16	1.62-6.17	0.001
Management			
Time-to-antibiotics	1.00	1.00-1.01	0.046
Initial fluid bolus in 2 hours	0.99	0.99-1.00	0.011
Total fluid in 6 hours	0.99	0.99-1.00	<0.001
Measure CVP within 6 hours	0.26	0.04-1.66	0.157
Measure $ScvO_2$ within 6 hours	0.46	0.21-1.01	0.053
6-hour resuscitation bundle achievement			
Serum lactate measured	0.26	0.12-0.57	0.001
Blood culture prior to antibiotics	0.83	0.14-4.74	0.842
Broad-spectrum antibiotics within 3 hours	0.13	0.03-0.53	0.004
Initial fluid bolus ≥500 ml	0.07	0.01-0.64	0.018
Maintain MAP ≥65 mmHg	0.10	0.02-0.52	0.006
CVP ≥8 mmHg	1.47	0.67-3.21	0.328
$ScvO_2$ ≥70%	1.36	0.99-1.88	0.057
Compliance with all 6-hour resuscitation bundle	0.33	0.11-1.03	0.057

Table 5. Multivariate analysis of predictive factors for hospital mortality of septic shock patients

Factors	Odds ratio	95% CI	*p*-value
Hyperlactatemia	2.73	1.38-5.40	0.004
Total fluid in 6 hours	0.99	0.99-1.00	0.003
6-hour resuscitation bundle achievement			
Broad-spectrum antibiotics within 3 hours	0.18	0.03-0.90	0.037

came to the emergency department of Thammasat University Hospital with septic shock, both groups shared similar overall baseline characteristics, with the exception of bicarbonate level and number of tachypnea patients. Mean age of patients from both groups of the present study was higher than other Asian studies[34-36]. However, average age was not different from previous studies conducted in Thailand[32,33]. The top three common sites of infections, including urinary tract, respiratory and intra-abdominal were the same as others[30,37,38]. The rate of positive blood cultures was similar to the report of Siriraj Hospital[39]. In the present study, Intensive care unit (ICU) admission rate was lower than another study conducted in the United States[40]. This could be explained from the limitation of the critical care facility and ICU crowding in our hospital setting.

Comparison with other studies should be

carefully assessed since study designs were varied. Some studies were conducted in ICU setting[27,34,35,41], while others were conducted in ED setting[20,25,42]. Some included septic shock patients[17,20,30,32,33,43], while others included severe sepsis and septic shock patients in their studies[21-23,34,38,44,45]. Emergency department and ICU settings differed in terms of causative organisms-community or hospital acquired. Severe sepsis and septic shock may also affect the outcome due to the differences in severity of the disease.

With regard to management of septic shock, there was improvement in time-to-administration of broad-spectrum antibiotics after implementation of 6-hour bundle. Compared with other studies, duration of time-to-antibiotics, were shorter in the post-implementation group or the 6-hour bundle compliant group[21,23]. The early administration of antimicrobial therapy was recommended within the time of ED care or once septic shock was suspected[46]. The post-intervention group significantly received more volume of initial fluid bolus in the first 2-hour periods and volume of fluid resuscitation in 6 hours. These findings were similar to the other studies that found more volume of fluid resuscitation in the post-intervention group or the 6-hour-bundle compliant group when compared with the control group or the non-compliant group[23,34,43]. Initial fluid resuscitation is an important process during the first hour of severe sepsis and septic shock. However, once patients received adequate fluid challenge, further fluid administration should be practiced with caution. More volume might not improve cardiac output and any further global hypoperfusion. It should be kept in mind that the risk of developing interstitial edema and further compromising micro-vascular dysfunction could occur[10]. As a result, the 6-hour protocol, used at the emergency department of Thammasat University Hospital, had combined fluid challenge technique to initial treatment with volume resuscitation and recommended administration of vasopressors, once patients received 500 to 1,000 ml of fluid, which was slight modification of 1,000 ml volume recommended in SCC guideline[15] in order to avoid fluid overload especially in the elderly. There was a significant increasing rate of $ScvO_2$ measurement and administration of inotrope after the implementation of 6-hour bundle. This could be explained from the attempt to achieve $ScvO_2 \geq 70\%$ according to the 6-hour bundle goal[31]. There was also a significant increasing rate of $ScvO_2$ measurement in the after intervention group in another study[43]. Compliance rate with $ScvO_2$ measurement in the post-intervention group was the same in comparison with other prospective studies (66.7% vs. 63%)[24]. However, there were many debates upon using $ScvO_2$ as one of the target of resuscitation. Although low $ScvO_2$ could reflect imbalance of tissue oxygenation and demand, septic shock patients usually have a normal or increased $ScvO_2$ due to reduced oxygen extraction[47]. Normal $ScvO_2$ cannot exclude tissue hypoxia. Therefore, it could not perfectly reflect inadequacy of tissue oxygenation nor provide guidance for optimal resuscitation. According to SCC, achieving $ScvO_2$ is a Grade 2C recommendation[15]. Combining other endpoints, such as urine output, other hemodynamic monitoring and lactate normalization[48,49], to evaluation, would be more helpful in guidance of optimal therapeutic approaches. In the present study, 16% of patients required inotropes at the emergency department was quite similar to the previous study, which showed that 13.7% of the EGDT group required inotropic therapy[13]. This was relevant to an estimate of 10% of septic shock patients having myocardial dysfunction as one of the main clinical features[50].

The rate of entire 6-hour bundle compliance was significantly higher in the post-intervention group. With regard to each element of the resuscitation bundle, the rate of serum lactate measured was increasing significantly. This finding was similar to another quasi-experimental study conducted in Spain[30]. There was significant improvement in accomplishing the goals to treat hypotension (maintain MAP $\geq$65 mmHg) and to give adequate initial volume of resuscitation. Apart from that, the rate of achievement in other interventions was also trending upward in the post-intervention group. These findings shared the similarity with other studies, which compared the rate of 6-hour intervention compliance before and after implementation of sepsis protocol[30,33,34]. Implementing protocol or bundle of care, helped improve early recognition and rapid initiation of important measures regarding the management of septic shock.

According to the main outcome of the study, there was significant reduction of hospital mortality of septic shock patient in the post-intervention group. Mortality rate was decreased by 21.3%, which was closed to the goal of SCC[7]. After implementing the protocol, length of hospital stay did not significantly change in duration. The reports from other experimental studies showed decreasing mortality and decreasing length of hospital stay of septic shock patients after implementation of the protocol for management of septic shock patients[30,32,33]. Other studies shared similar

outcome[23,34], although including severe sepsis patients to the studies. Several studies made comparison between the compliant group and the non-compliant group regarding mortality rate and length of hospital stay. The compliant group had lower mortality rate than the other reports[41,20,24]. In addition, there was a small study, reporting reduced mortality rate in compliant septic patents in the ICU setting[21]. Careful consideration should be made since all studies implemented 6-hour bundle and 24-hour bundle for the treatment, which could affect the whole process more than just implementing only the 6-hour bundle. In the present study, the author focused on the initial period of resuscitation of septic shock. Therefore, the author started by implementing the 6-hour bundle at the emergency department. Further study about combining 6-hour bundle and 24-hour bundle should be conducted. This may involve intensivist and staff at intensive care units, which requires further protocol development and education process.

Univariate analysis of predictive factors for hospital mortality of septic shock patients showed many significant factors, which could be grouped into characteristics of patients and interventions applied to the patients. One of the important predictive characters was hyperlactatemia. The predictive value of lactate level in septic shock had long been showed in other studies[51,52]. The interventions, which were significant predictive factors for mortality, were time-to-antibiotics, total fluid given in 2 hours and 6 hours and $ScvO_2$ measured within 6 hours. Regarding the 6-hour-bundle, serum lactate measured, antibiotic therapy within 3 hours, initial fluid bolus $\geq$500 ml, maintaining MAP $\geq$65 mm Hg, $ScvO_2$ $\geq$70% and compliance to entire 6-hour bundle were all predictive factors for hospital mortality. However, from multivariate analysis hyperlactatemia, total fluid given in 6 hours and administration of antibiotics within 3 hours were found to be independent predictors of mortality. The result was different from other studies, which were varied in study design as stated earlier[34,35]. Therefore, it was too complicated to make the comparison.

From the result of the present study, implementation of 6-hour bundle protocol for treating septic shock at the emergency department helped decrease mortality, and improved adherence to important measures for treating this group of patients. Simple measures such as early administration of antibiotics with proceeding blood cultures taken, serum lactate measured, adequate initial volume placements and maintaining MAP $\geq$65 mmHg should be maintained. Continuous education system should also be developed in the future to maintain good clinical practice. Hence, for some other complicated measures, which are still being debated such as CVP $\geq$8 mmHg or $ScvO_2$ $\geq$70%, need to weigh the downside against the value of these measures. More advanced and non-invasive hemodynamic monitoring techniques, if showing significant value for resuscitating septic shock from other updated studies in the future may also replace the inferiority of CVC insertion. Cost-effectiveness evaluation should be carefully studied before implementing this advanced technology to our hospital settings. So far, CVC insertion and monitoring of CVP are still practical and able to be maintained in our hospital settings. Implementing the 6-hour bundle helped improve detection and early activation of appropriate treatment of septic shock patients at the emergency department of Thammasat University Hospital.

There were some limitations of the present study. First, data obtained from the historical controlled group were limited. In the emergency department setting of Thammasat University Hospital, all parameters needed for evaluation according to common severity scoring systems, which are generally used in the ICU, for example APACHE, SOFA or MEDS scores were impractical. Comparison of severity between two groups of septic patients in the present study could not be perfectly done due to this limitation. Second, duration of prospective period of the after intervention group should be extended in order to include more samples to the study. This could help improve the significance of the result. Moreover, by doing so could assist in monitoring the sustainability of the practice and behavior of emergency department staff after implementing the protocol for longer period of time. Further studies about measures that could help improve adherence to the protocol, is also suggested. Third, the present study focused mainly on the impact of bundle of treatment initially given in 6-hour period, which could not totally reflect the entire continuing process of acute management of septic shock. Including 24-hour bundle or other important measures for treating critically ill septic patients within the 24-hour period should be conducted in the future study, in order to demonstrate appropriately the effect of the whole 24-hour period of treatment, which is also crucial.

Conclusion

The effect of implementing 6-hour sepsis protocol at the emergency department of Thammasat

University Hospital was decreasing hospital mortality of septic shock patients with statistical significance. The 7-day and 28-day mortality were also reduced with statistical significance in the post-intervention group. Length of hospital stay of septic shock patients diagnosed at the emergency department was not significantly different before and after implementation of the protocol.

What is already known in this topic?

Implementation of sepsis protocol at the emergency department setting reduces mortality rate of septic shock patients. Although this has already been proved in other countries, this is the first experimental study conducted at emergency department setting of Thailand. This helps prove the benefit of applying 6-hour sepsis protocol to the emergency department of tertiary care hospitals in Thailand.

Potential conflicts of interest

None.

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อัตราการเสียชีวิตของผู้ป่วย septic shock ภายหลังการนำแนวทางการดูแลรักษาผู้ป่วย sepsis ใน 6 ชั่วโมงแรกมาใช้ที่ห้องฉุกเฉิน โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ

ยาใจ อภิบุณโยภาส

ภูมิหลัง: *ภาวะช็อคเหตุพิษติดเชื้อ (septic shock) เป็นภาวะที่มีอัตราการเสียชีวิตสูงจึงเป็นปัญหาสำคัญทางสาธารณสุขในระดับนานาชาติ การให้การรักษาอย่างเหมาะสมและรวดเร็วมีส่วนช่วยในการปรับปรุงผลการรักษาของผู้ป่วย แนวทางการรักษาภาวะติดเชื้อภายใน 6 ชั่วโมงแรกจัดทำโดย the surviving sepsis campaign committee ได้รับการพัฒนามาจากแนวทางการรักษาซึ่งอ้างอิงจากหลักฐานเชิงประจักษ์โดยนำมาประยุกต์ใช้กับการดูแลรักษาผู้ป่วยกลุ่มนี้ มีรายงานผลการศึกษามากมายถึงผลการรักษาที่ดีขึ้นของผู้ป่วยภาวะช็อคเหตุพิษติดเชื้อภายหลังการนำแนวทางการรักษาดังกล่าวมาใช้กับการดูแลรักษาผู้ป่วยที่ห้องฉุกเฉิน*

วัตถุประสงค์: *วัตถุประสงค์หลักเพื่อศึกษาเปรียบเทียบอัตราการเสียชีวิตของผู้ป่วยก่อนและหลังการใช้แนวทางการรักษามาใช้ วัตถุประสงค์รองคือเปรียบเทียบระยะเวลาการนอนโรงพยาบาลก่อนและหลังการนำแนวทางการรักษามาใช้และศึกษาปัจจัยที่ใช้ทำนายการเสียชีวิตของผู้ป่วยภาวะช็อคเหตุพิษติดเชื้อ*

วัสดุและวิธีการ: *สถานที่ศึกษาวิจัยที่แผนกฉุกเฉินของโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติเป็นการศึกษาด้วยวิธี interrupted time แบบก่อนและหลังเปรียบเทียบระหว่างช่วงหลัง (เดือนตุลาคม พ.ศ. 2555 ถึง เดือนพฤศจิกายน พ.ศ. 2556) กับช่วงก่อน (เดือนกุมภาพันธ์ พ.ศ. 2554 ถึง เดือนกรกฎาคม พ.ศ. 2555) การนำแนวทางการรักษาภาวะติดเชื้อใน 6 ชั่วโมงแรกมาใช้ที่ห้องฉุกเฉิน*

ผลการศึกษา: *ผู้ป่วยที่อยู่ในกลุ่มก่อนการนำแนวทางการรักษามาใช้มีจำนวน 80 ราย ผู้ป่วยในกลุ่มหลังมีจำนวน 75 ราย พบว่าการรักษาผู้ป่วยภาวะช็อคเหตุพิษติดเชื้อมีการปรับปรุงขึ้นหลังจากการนำแนวทางการรักษามาใช้สารน้ำที่ให้ทางหลอดเลือดดำในระยะเวลา 2 ชั่วโมงแรก มีปริมาณเพิ่มขึ้นอย่างมีนัยสำคัญ [2,000 (500-3,000) vs. 1,600 (100-3,600); p = 0.038)] ในแง่ของการปฏิบัติตามแนวทางการรักษาภาวะติดเชื้อภายใน 6 ชั่วโมงแรกพบว่า อัตราการปฏิบัติตามแนวทางแบบครบทั้งหมดเพิ่มขึ้นอย่างมีนัยสำคัญในกลุ่มหลังนำแนวทางการรักษามาใช้ (37.3% vs. 0%; p<0.001) เมื่อพิจารณา แยกตามการรักษาแต่ละชนิดที่ประกอบในแนวทางการรักษาทั้งหมดพบว่ามีอัตราการปฏิบัติตามที่เพิ่มขึ้นหลายชนิดได้แก่ การส่งตรวจระดับค่าแลคเตทในเลือด การให้สารน้ำทางหลอดเลือดดำอย่างรวดเร็วปริมาณตั้งแต่ 500 มิลลิลิตรขึ้นไปในช่วงแรกและการรักษาระดับ mean arterial pressure ให้มีค่ามากกว่าหรือเท่ากับ 65 มิลลิเมตรปรอท (96.0% vs. 2.5%; p<0.001, 100.0% vs. 92.3%; p = 0.029, 100.0% vs. 88.8%; p = 0.003 ตามลำดับ) นอกจากนี้ยังพบว่าอัตราการเสียชีวิตของผู้ป่วยภาวะช็อคเหตุพิษติดเชื้อ ในกลุ่มหลังการนำแนวทางการรักษามาใช้ลดลงอย่างมีนัยสำคัญ เมื่อเทียบกับกลุ่มก่อนนำแนวทางการรักษามาใช้ (18.7% vs. 40.0%; p = 0.005)*

สรุป: *อัตราการเสียชีวิตของผู้ป่วยภาวะช็อคเหตุพิษติดเชื้อลดลงอย่างมีนัยสำคัญภายหลังการนำแนวทางการรักษาภาวะติดเชื้อภายใน 6 ชั่วโมงแรกมาใช้ที่ห้อง ฉุกเฉินโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ*