The Impact of Intensive Care Unit Admissions Following Early Resuscitation on the Outcome of Patients with Severe Sepsis and Septic Shock

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Background: *Septic shock is a serious condition associated with a high mortality rate. The "Early goal-directed therapy" has been reported as the effective treatment. Whether or not an intensive care unit (ICU) admission can improve the outcomes of septic shock patients, has not been elucidated.*

Objective: *To evaluate the impact of direct ICU admission after initial resuscitation in the emergency room (ER) on the outcomes of patients in septic shock.*

Material and Method: *A prospective cohort study including severe sepsis and septic shock patients who were admitted from the ER during the period from April 2011 to September 2012. The recorded information includes patients' baseline characteristics, hemodynamic parameters, and outcomes. The comparisons were performed between the ICU versus the non-ICU admission groups. The principal outcome was 28-day mortality.*

Results: *Of the 175 enrolled patients, 50 patients were directly admitted to the ICU and 125 patients were admitted to a general medical ward. The ICU patients were younger (58.6±19.7 vs. 66.0±15.1 year-old, p = 0.02), had lower mean arterial blood pressures (57.8±15.3 vs. 66.6±18.4 mmHg, p<0.001) and presented with a higher proportion of metabolic acidosis (60% vs. 33.6%, p = 0.002). In comparison to the non-ICU group, the ICU patients received larger volume resuscitation for the first 24 hours (5,694.4±2,018.5 vs. 5,004.7±1,729.7 ml, p = 0.04); had received norepinephrine (88% vs. 68%, p = 0.007) and/or dobutamine (20% vs. 4.8%, p = 0.003), and were treated for renal replacement therapy (28% vs. 5.6%, p<0.001) in higher proportions. There were trends toward a lower 28 day mortality (18% vs. 25.6%, p = 0.33) among the patients in the ICU group.*

Conclusions: *Apart from the early goal-directed therapy, early ICU admission substantially improves the outcomes of septic shock patients.*

Keywords: *Septic shock, Intensive care unit, ICU*

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Severe sepsis and septic shock, the most serious of consequences in the infection process, are a substantial cause of death worldwide[1-4]. Physicians have spent their efforts on improving the outcome of patients in septic shock. To date, rapid hemodynamic resuscitation with the aim of achieving satisfactory hemodynamic goals within 6 hours of the diagnosis of severe sepsis or septic shock have been proven to be the effective treatment associated with improved outcomes[5]. Early goal-directed therapy in following international guidelines[6-8] for management and the 'surviving sepsis campaign' is the current, available recommendation for medical practice. These guidelines promote the initiation of intravenous fluid resuscitation followed by the administration of an intravenous vasopressor to help raise the patients' blood pressure and restore adequate tissue perfusion in tandem with infectious source controls and organ support as necessary. The severe sepsis/septic shock treatment guidelines at Siriraj Hospital, developed in 2004[9] and revised in 2011, have been provided for medical practitioners throughout Thailand. However, most guidelines recommend only early resuscitation, a maintenance treatment in the first 72 hours have not been clearly established. Consideration regarding the

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continuing infusion of intravenous fluids, the consequences of prolonged use of vasopressors, the complications associated with organ support therapy, the appropriate hemodynamic, respiratory and metabolic monitoring should be continued following early septic shock resuscitation.

The intensive care unit (ICU), a specialized unit, has been developed for providing continuous monitoring to the critically ill patient. The ability of ICUs treatments of patients vary in wide ranges depending on the facility and the purposes of their services. However, the basic monitoring for hemodynamic and respiratory status is available in the most ICUs. The lower proportions of medical personnel to patients help in providing for more effective, individual patient care. In accordance to the advantages of the ICUs' environment, caring for patients with severe sepsis and septic shock should be, in theory, more effective than the care in a general medical unit. The authors' ICU has a bed available for septic shock patients admitted from the emergency department and is designated as a septic shock fast tract bed. However, the information supporting this postulation has been limited. The objective of this study is to evaluate the benefits of the direct admission for the severe sepsis and septic shock patients into the ICU as soon as diagnoses and early resuscitation at the emergency department is done in comparison to a general medical ward admission.

Material and Method

This is a single medical center's prospective cohort study and includes patients admitted from the emergency department at Siriraj Hospital during the period from the 1st of April, 2011 to the 31st of September, 2012. Patients over 18 years of age and diagnosed with severe sepsis or septic shock as defined in the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference[10] were included. Any patients with the following conditions were excluded: patients' or families' refusal to sign the informed consent, refusal for insertion of a central venous catheter, "Do Not Resuscitate" status with a living will, pregnancy, end-stage malignancies, and existing comorbidities (acute strokes, acute myocardial infarctions, active gastrointestinal bleeding, status epilepticus and/or multiple trauma). Once the diagnosis of severe sepsis or septic shock had been determined, immediate fluid resuscitation was initiated according to Siriraj Hospital's severe sepsis/septic treatment guidelines. Following hemodynamic stabilization, the patients were transferred directly to the medical ICU. Other patients were admitted to the general medical unit if a medical ICU bed was not available.

Data collection

The patient's baseline characteristics, underlying conditions, APACHE II scores, sites of infection, identified pathogens, initial vital signs; baseline hemodynamic parameters and initial laboratory investigations were recorded. The treatment information included amount of fluid resuscitation in the first 72 hours; central venous pressures; vasopressors, types and dosage; antibiotic use and organ support were recorded. The investigators were not directly involved with the patients' treatments. The decisions for type of treatment were dependent on the attending physicians.

The primary outcome of this study was 28-day mortality. The secondary outcomes were as follows: hospital mortality, the achievement of an acceptable macrocirculation target (mean arterial blood pressure >65 mmHg), an acceptable microcirculation target (urine output >0.5 ml/kg/hour, or lactate clearance >10% or $ScvO_2$ >70%) as the goals for the first 6 hours with a proportion of organ support therapy.

Statistical analysis

The patients were separated into two groups: the direct ICU admission group and the general medical unit admission group. The continuous variations were reported as mean $\pm$ standard deviation (SD) and the comparisons between the two groups were performed by an independent sample, t-test. Categorical variations were reported as percentages per group. The Fisher's exact test or the Pearson's Chi-square test was used, as suitable, to identify the differences of categorical variables between the two groups. The p-value of less than 0.05 was considered as statistically significant. The SPSS, version 17, was used for performing the statistical analyses in the present study.

Ethical consideration

The present study has been reviewed and approved by the Siriraj Hospital Ethics Committee, under the Helsinki declaration prior to inclusion of the first patient.

Results

A total of 175 severe sepsis and septic shock patients were included. Of these, 50 patients were directly admitted to the medical ICU and 125 patients

were admitted to general medical units. The information on the patients' baseline characteristics are shown in Table 1. The direct ICU admitted patients were younger and had a lower proportion of patients with a history of a prior stroke than was exhibited by the group admitted to general medical units. The APACHE II scores were not different between the groups; however, the proportion of patients in septic shock was higher among the ICU group when compared to the general ward group. Other patients' demographics including gender, body size, and underlying conditions, had shown no differences between the two groups. The leading infections were noted to be an upper urinary tract infections, followed by pneumonias and intra-abdominal infections. The bacterial pathogens were identified in 75 percent of the patients. Of these, *Escherichia coli* were the leading pathogen, followed by gram negative bacilli and gram positive cocci.

The initial vital signs, hemodynamic status and laboratory investigations are illustrated in the Table 2. The ICU patients had significant lower systemic blood pressures, lower arterial blood pHs, lower PaO_2/FiO_2 and platelet counts than observed in the general ward group. There was a trend toward higher baseline lactate levels among the ICU group but without a significant correlating p-value.

Table 1. Baseline characteristics of the included patients

Patient's characters	General ward admission (n = 125)	ICU admission (n = 50)	p-value
Age (years)	66.0±15.1	58.6±19.7	0.020
Sex (% male)	48	52	0.740
Body weight (kg)	58.1±19.9	56.1±11.4	0.530
Height (cm)	160.3±10.0	159.7±11.2	0.770
APACHE II score	21.3±7.8	22.0±7.3	0.560
Underlying conditions (%)			
Hypertension	42.4	38	0.620
Diabetes mellitus	33.6	36	0.860
Dyslipidemia	22.4	20	0.840
Malignancy	22.4	12	0.330
Previous stroke	17.6	6	0.060
Chronic kidney disease	11.2	6	0.400
Coronary artery disease	8	16	0.170
Valvular heart disease	5.6	6	1.000
Initial diagnosis (%)			
Severe sepsis	36	10	0.001
Septic shock	64	90	0.001
Source of infection (%)			
Urinary tract infection	27.2	26	1.000
Pneumonia	28.0	20	0.340
Intra-abdominal infection	20.0	16	0.660
Skin & Soft tissue infection	9.6	6	0.560
Positive hemoculture	21.6	26	0.550
Pathogens (%)			
Gram positive cocci	26.6	16	0.170
Staphylococcus aureus	18.0	12	0.100
Coag. Negative Staph.	4.8	2.0	0.180
Streptococcus pneumoniae	2.3	0.6	1.000
Gram negative bacilli	46.0	42	0.740
Escherichia coli	26.7	24	0.820
Klebsiella pneumoniae	8.0	4	0.170
Acinetobacter baumannii	4.8	4	1.000
Pseudomonas aeruginosa	1.6	2	1.000
Unidentified organism	25.0	32	0.450

Table 2. Initial vital signs, hemodynamic status and laboratory investigations

Patient's hemodynamic status	General ward admission (n = 125)	ICU admission (n = 50)	p-value
Temperature (°C)	37.80±1.30	37.70±1.50	0.540
Heart rate (beat/min)	105.60±21.90	111.10±21.00	0.130
Systolic blood pressure (mmHg)	86.90±24.50	73.50±14.50	<0.001
Diastolic blood pressure (mmHg)	51.60±15.00	43.50±8.80	<0.001
Mean arterial pressure (mmHg)	66.60±18.40	57.80±15.30	<0.001
Respiratory rate (time/min)	28.10±6.70	28.80±8.20	0.570
Baseline laboratory values			
Blood sugar (mg/dL)	185.10±127.50	173.30±117.60	0.600
Blood urea nitrogen (mg/dL)	38.90±28.70	39.10±34.20	0.970
Creatinine (mg/dL)	2.20±2.70	2.70±1.80	0.180
Sodium (mEq/L)	135.10±7.90	133.90±5.90	0.290
Potassium (mEq/L)	3.90±0.90	4.10±1.00	0.440
Chloride (mEq/L)	100.70±7.20	93.70±9.00	0.020
Bicarbonate (mEq/L)	18.60±6.10	15.20±6.50	0.006
Arterial blood pH	7.36±0.12	7.24±0.13	<0.001
Metabolic acidosis (%)	33.6	60	0.002
PaO_2 (mmHg)	126.40±68.40	118.40±56.90	0.340
$PaCO_2$ (mmHg)	28.20±9.20	29.00±12.60	0.770
PaO_2/FiO_2	314.20±143.90	220.30±124.70	0.006
Hemoglobin (g/dL)	10.20±2.60	10.20±2.90	1.000
White blood cell (cell/mm^3)	16,080.60±16,191.60	14,044.60±8,300.00	0.280
Platelet (particle/mm^3)	205,496.80±157,219.10	156,163.30±116,995.60	0.050
Serum lactate (mmol/L)	3.90±2.60	5.90±4.70	0.240

Table 3 shows the treatments' the patients received and the outcomes. The direct ICU group received higher volume resuscitation during the first 6 hours and 24 hours after initiation of the septic shock management protocols as well as higher proportions of norepinephrine, dobutamine and adrenaline administration. Central venous catheter (CVC) insertion, renal replacement therapy and the detection of new onset arrhythmias were reported in significantly higher proportions among ICU patients as compared to the non-ICU patients. The achievement of individual target goals including mean arterial pressure, urine output greater than 0.5 ml/kg/hour and lactate clearance were similar among both groups. The rate of achieving the mean arterial pressure target with corresponding levels in urine output or lactate clearances were significantly higher among the ICU group. There was a trend toward lower, 28-day mortality rates and lower hospital lengths of stay among the ICU group, but the numbers were not statistically significant.

Discussion

The results of the present study can be summarized that direct ICU admission, promptly following initiation of severe sepsis/septic shock resuscitation, promotes more aggressive hemodynamic management and more effective organ support. There was a trend toward improving patients' outcomes among the ICU patients although the survival benefit was not significant. In comparison with the general medical unit patients; the ICU patients had a tendency to be younger, had lower incidences of previous strokes, had shown a lower initial systemic arterial blood pressure, had more cases presenting with severe metabolic acidosis and were diagnosed with septic shock in significantly higher proportions. As expected, the mortality rates in the ICU group are higher than the rates in the general medical group. The reports of lower than 28-day mortality rates and lower instances of hospital mortality among the ICU patients reflect the benefits of monitoring and treatment modalities, including; respiratory, renal and metabolic support during their ICU admission.

Considering hemodynamic monitoring, the rate of central venous catheter insertions for monitoring intravascular volume status was significantly higher

Table 3. Treatment strategy and patient's outcome

Treatment modality & outcome	General ward admission (n = 125)	ICU admission (n = 50)	p-value
Hemodynamic management			
Fluid resuscitation			
Total fluid in the 1st hour	657.10±371.20	663.80±360.30	0.910
Total fluid in 6 hours	2,232.30±1,011.50	2,934.80±1,236.70	0.001
Total fluid in 24 hours	5,004.70±1,729.70	5,694.40±2,018.50	0.040
Total fluid in day 2	1,936.00±1,068.10	1,511.90±1,062.50	0.020
Total fluid in day 3	1,194.60±1,132.50	987.00±1,084.30	0.280
CVP monitoring in 6 hours (%)	13.60	56.00	<0.001
Vasopressors usage			
Norepinephrine (%)	68.00	88.00	0.007
Dose of norepinephrine (mcg/kg/min)	0.17±0.25	0.17±0.13	0.980
Dopamine (%)	11.20	20.00	0.150
Dose of dopamine (mcg/kg/min)	11.80±6.70	11.50±6.20	0.910
Dobutamine (%)	4.80	20.00	0.003
Dose of dobutamine (mcg/kg/min)	4.70±1.20	6.10±5.00	0.420
Adrenaline (%)	1.60	8.00	0.060
Dose of adrenaline (mcg/kg/min)	0.32±0.40	0.91±0.60	0.240
Infectious source control			
Antibiotics initiation in the 1st hour (%)	65.60	52.00	0.120
Surgical drainage (%)	5.90	8.00	1.000
Organ support			
Mechanical ventilation (%)	43.20	56.00	0.140
Renal replacement therapy (%)	5.60	28.00	<0.001
Detection of new onset arrhythmia (%)	12.80	32.00	0.005
Outcome			
Goal achievement at 6th hour			
Mean arterial pressure >65 mmHg (%)	71.20	80.00	0.260
Urine output >0.5ml/kg/hour (%)	68.90	66.00	0.720
Lactate clearance (%)	40.70	33.30	0.770
Macro and microcirculation goals (%)	51.20	68.00	0.050
28 days mortality (%)	25.60	18.00	0.330
Hospital mortality (%)	28.80	22.00	0.450

among the ICU group. With more accurate and continuous monitoring, central venous pressure values assist the physicians with accuracy and confidence in fluid administration. This results in significantly higher volume resuscitation in the first 6 to 24 hours in the diagnosis of septic shock. Concurrent with larger volume resuscitation, vasoactive agents (norepinephrine, adrenaline and dobutamine) are given in higher proportions among the ICU patients. Comprehensive hemodynamic monitoring and management during ICU admissions could play an important role in the achievement of higher values for both mean arterial pressures which reflect the macrocirculation status and better urine output or lactate clearance targets, which are representative of the microcirculation status[11].

Although the baseline serum blood urea nitrogen and creatinine had not shown differences between the groups, the ICU patients had shown lower arterial blood gas pHs and were in severe metabolic acidosis in higher proportions than the general medical group. Persistent, severe metabolic acidosis suppresses myocardial function and blunts the effects of vasoactive agents resulting in intractable hypotension[12]. In an attempt to reverse this situation, renal replacement therapy is indicated. The availability of continuous renal replacement therapy, which is less deleterious regarding the hemodynamic effects, allow the physician to reverse metabolic acidosis, correct electrolyte imbalances and improve renal function of the hemodynamically

unstable patient who is not suitable for standard intermittent hemodialysis[13].

Arrhythmias are one of the significant complications noted in septic shock patients. Several studies have included the critically unstable patients admitted in ICUs, the majority of them are severe sepsis or septic shock, have reported incidences of arrhythmias ranging from 9% to 40%[14,15]. These new onset arrhythmias may be responsible for sudden cardiovascular collapse which is considered a major cause of death among septic shock patients treated under early goal directed therapy[5]. Early detection at the onset of an arrhythmia allows the physician to provide effective treatment and prevent serious hemodynamic effects of the arrhythmias. Continuous ECG monitoring during the ICU admission is another advantage of how early ICU admission could improve the outcomes related to septic shock.

However, ICU admissions may be associated with more invasive interventions. Several, procedure related complications will have a negative effect for the patients' prognosis. Common complications of central venous catheter insertion include; bleeding, pneumothorax, air emboli and cardiac arrhythmias that should be recognized immediately and treated expeditiously[16]. Hospital acquired infections, primarily resulting from antibiotic resistance pathogens, is another serious complication associated with ICU admissions. Frequent and numerous catheter insertions are important risk factors for the development of hospital acquired infections. Along with ICU policies for the reduction of hospital acquired infections, diligence to precautions that include; frequent hand washing, closed endotracheal tube suctioning, elevation of the head at >30-45 degrees, daily oral care with the use of chlorhexidine[17] and expeditious catheter removal, when possible, may decrease secondary infections and improve patients' outcomes.

The limitation of the present study is that it is a cohort study. Unlike randomized control trials, the selection of patients into particular groups is subjective to the attending physicians. From the results of the present study, the directly ICU admitted patients are younger and had relatively lower blood pressures and had been associated with more instances of severe metabolic acidosis. The differences in the patients' baseline characteristics could possibly mask the benefits of ICU treatment on patient outcomes. The relatively small population of the ICU admitted patients is another important limitation of the present study. Further investigations which include larger populations are needed to evaluate the benefits of ICU care for the management of severe sepsis and/or septic shock.

Potential conflicts of interest

None.

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ผลการรักษาผู้ป่วยภาวะช็อกจากการติดเชื้อในหออภิบาลผู้ป่วยวิกฤตเปรียบเทียบกับการรักษาในหอผู้ป่วยอายุรกรรมทั่วไป

สุรัตน์ ทองอยู่, ทนุวงศ์ เวียรศิลป์, ไชยรัตน์ เพิ่มพิกุล

ภูมิหลัง: ภาวะช็อกจากการติดเชื้อถือเป็นความเจ็บป่วยเฉียบพลันที่รุนแรง สัมพันธ์กับอัตราการเสียชีวิตที่สูง การรักษาเพื่อเพิ่มความดันโลหิตและการไหลเวียนของเลือดไปสู่อวัยวะส่วนปลายอย่างเพียงพอใน 6 ชั่วโมงแรก สามารถลดอัตราการเสียชีวิตของผู้ป่วยได้ หลังจากนั้นการรับผู้ป่วยเข้ารับการรักษาในหออภิบาลผู้ป่วยวิกฤต อาจลดการเสียชีวิตของผู้ป่วยกลุ่มนี้ลงได้

วัตถุประสงค์: เพื่อเปรียบเทียบผลการรักษาผู้ป่วยภาวะช็อกจากการติดเชื้อในหออภิบาลผู้ป่วยวิกฤต กับการรักษาในหอผู้ป่วยอายุรกรรมทั่วไป

วัสดุและวิธีการ: เป็นการศึกษาโดยการเก็บข้อมูลไปข้างหน้า รวบรวมผู้ป่วยภาวะช็อกจากการติดเชื้อ ที่เข้ารับการรักษาในห้องฉุกเฉิน ระหว่างวันที่ 1 เมษายน พ.ศ. 2554 ถึง วันที่ 30 กันยายน พ.ศ. 2555 ผู้ป่วยจะได้รับการรักษาตามคำแนะนำการรักษาผู้ป่วยภาวะช็อกจากการติดเชื้อของโรงพยาบาลศิริราช หลังจากนั้นผู้ป่วยจะได้รับการส่งตัวเข้ารับการรักษาในหออภิบาลผู้ป่วยวิกฤตทันที ในกรณีที่ไม่สามารถส่งผู้ป่วยเข้ารับการรักษาในหออภิบาลผู้ป่วยวิกฤตได้ ผู้ป่วยจะถูกส่งเข้ารับการรักษาที่หอผู้ป่วยอายุรกรรมทั่วไป ผู้นิพนธ์บันทึกข้อมูลพื้นฐาน ของผู้ป่วยรวมทั้งการรักษาที่ได้รับและผลการรักษา ผลลัพธ์หลักของการศึกษานี้คืออัตราการเสียชีวิตที่ 28 วัน

ผลการศึกษา: มีผู้ป่วย 175 ราย เข้าร่วมในการศึกษานี้ โดยผู้ป่วย 50 ราย ได้รับการรักษาในหอผู้ป่วยวิกฤต ผู้ป่วยอีก 125 ราย ได้รับการรักษาในหอผู้ป่วยอายุรกรรมทั่วไป ผู้ป่วยกลุ่มที่รับการรักษาในหอผู้ป่วยวิกฤตมีอายุน้อยกว่า (อายุเฉลี่ย 58.6±19.7 เทียบกับ 66.0±15.1 ปี, p = 0.02) มีความดันโลหิตเฉลี่ยต่ำกว่า (57.8±15.3 เทียบกับ 66.6±18.4, p<0.001) และมีภาวะเลือดเป็นกรดในอัตราส่วนที่สูงกว่า (ร้อยละ 33.6 เทียบกับ 60, p = 0.002) สำหรับการรักษาที่ผู้ป่วยได้รับพบว่า กลุ่มที่รับการรักษาในหอผู้ป่วยวิกฤตได้รับสารน้ำใน 24 ชั่วโมงแรกมากกว่า (5,694.4±2,018.5 เทียบกับ 5,004.7±1,729.7, p = 0.04) ได้รับยา norepinephrine ในอัตราที่สูงกว่า (ร้อยละ 88 เทียบกับ 68, p = 0.007) ได้รับยา dobutamine ในอัตราที่สูงกว่า (ร้อยละ 20 เทียบกับ 4.8, p = 0.003) และได้รับการรักษาทดแทนไต ในอัตราที่สูงกว่า (ร้อยละ 28 เทียบกับ 5.6, p<0.001) ผลการรักษาพบว่าอัตราการเสียชีวิตที่ 28 วันของกลุ่ม ที่รับการรักษาในหอผู้ป่วยวิกฤตมีแนวโน้มต่ำกว่า (ร้อยละ 18 เทียบกับ 25.6, p = 0.33) แต่ยังไม่มีนัยสำคัญทางสถิติ

สรุป: หลังได้รับการรักษาเบื้องต้นตามคำแนะนำการรักษาผู้ป่วยภาวะช็อกจากการติดเชื้อแล้ว การส่งผู้ป่วยเข้ารับการรักษาต่อเนื่องในหอผู้ป่วยวิกฤตส่งเสริมให้ผู้ป่วยได้รับการรักษาที่เหมาะสม และอาจลดอัตราการเสียชีวิตของผู้ป่วยได้