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Time-to-use of Intravenous Antibiotics in Patients with Sepsis in whom Activation of the Sepsis Fast Track Protocol was Facilitated by the National Early Warning Score

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Abstract

Aim: To examine changes in door-to-antibiotic time in pre- and post-intervention groups.

Materials and Methods: A quasi-experimental study was conducted in the Emergency Department involving adult patients who were diagnosed with sepsis or septic shock in a university-based hospital. The patients were distributed into one of two groups: a pre-intervention or post-intervention group. In the post-intervention group, among patients with a suspected infection and a National Early Warning Score (NEWS) of ≥5, the sepsis fast track protocol was used in the normotensive group and the sepsis with shock fast track protocol was used in the hypotensive group. Our primary outcome was the difference in the door-to-antibiotic time in the pre- and post-intervention groups.

Results: Overall, 117 patients were included in the pre-intervention group and 102 patients in the post-intervention group. The median door-to-antibiotic time in the pre-intervention group was 45 min [interquartile range (IQR): 30-65], and the median door-to-antibiotic time in the post-intervention group was 30 min (IQR: 20-55, p=0.009). However, there was no significant difference in the mortality rate (p=0.194).

Conclusion: Using an activated system with NEWS for screening patients suspected with sepsis helped reduce the door-to-antibiotic time.

Keywords: Antibiotic, emergency department, National Early Warning Score, protocol, sepsis

Introduction

Sepsis is associated with high mortality and morbidity (1). In 2017 the World Health Organization reported more than 30 million cases of sepsis worldwide, and more than six million deaths per year had been attributed to sepsis (2). The mortality rate reached 35.09%, making sepsis the fourth leading cause of death worldwide (3,4). To improve survival in cases of sepsis the Surviving Sepsis Campaign Bundle 2018, guidelines recommend administering empirical intravenous antibiotics within one hour and adequate fluid resuscitation in sepsis cases with hypotension or with serum lactate levels ≥4 millimoles per liter (mmol/L) (1,5-7).

An important factor in prompt management has been the introduction of an accurate and rapid detection tool (8). In a recent study it was found that the quick Sequential Organ Failure Assessment (qSOFA) predicted hospital mortality rates and intensive care unit (ICU) length of stay more accurately than the Systemic Inflammatory Response Syndrome (SIRS) (9). However very recent studies have found the National Early Warning Score (NEWS) to be as effective in the prediction of hospital mortality rate and ICU admission as qSOFA and more accurate in comparison to SIRS (9-12). Somehow, NEWS has been found to have more accuracy in predicting mortality and ICU admission when compared to qSOFA (12-14). However, no previous studies have reported the use of NEWS for early activation of the sepsis code to lessen the time to goal of therapeutic intervention including the administration of empirical antibiotics, fluid resuscitation, or to reduce mortality in the emergency department (ED).

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This study aimed to compare door-to-antibiotic time before and after implementation of NEWS as a sepsis screening tool, where a NEWS ≥5 and suspected infection were used to trigger the activation of the sepsis fast track protocol.

Materials and Methods

Study Design

This study was a retrospective and prospective, quasi-experimental study which was approved by the Research Ethics Committee of Faculty of Medicine of Chiang Mai University (no: 377/2018, date: 03.10.2018). Written informed consent was obtained from patients who were enrolled on the prospective study. This study was registered in the Thai Clinical Trials Registry (www.clinicaltrials.in.th, TCTR20191002001).

Study Setting and Population

Patients who visited the ED from June 1, 2018 to August 31, 2018, prior to the implementation of NEWS as a sepsis trigger tool, were recruited onto the study. The qSOFA criteria had been used for the screening of these patients who were suspected sepsis and action had been taken as for a general patient without the sepsis fast track protocol. These patients were classified as the pre-intervention group. ED patients from October 1, 2018 to December 31, 2018, after the implementation of NEWS as a sepsis screening tool, were included in the post-intervention group. The inclusion criteria were as follows: patients aged 18 years or over with a suspected infection from a medical condition with NEWS ≥5. The exclusion criteria included patients referred from another hospital without available medical records, patients requiring emergency surgery, patients discharged from the ED, patients with a misdiagnosis, patients who had received antibiotics within the last 30 days, or refusal by patient and/or guardian refusal or were not able to consent to participation in the research.

Data collection occurred at two time points: three months pre-intervention and three months post-intervention, intervention being the implementation of the sepsis fast track protocol. Patients in the pre-intervention group were recruited from June 1, 2018 to August 31, 2018, and included those diagnosed with sepsis or septic shock, according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems, with a NEWS ≥5. From September 1 to September 30, 2018, triage and screening personnel were briefed on the use of NEWS as a screening tool in patients with suspected sepsis (run in phase). If NEWS ≥5, screening personnel were to alert the emergency physician, who would be the one to decide on the activation of the sepsis fast track protocol. The protocol was divided into two sections: a normotensive and a hypotensive group. The normotensive group included patients with a systolic blood pressure (SBP) ≥90 millimeters of mercury (mm Hg) or a mean arterial pressure (MAP) ≥65 mm Hg, and appropriate antibiotics were given during treatment. The hypotensive group included patients with SBP <90 mm Hg or MAP <65 mm Hg. In this group, in addition to appropriate antibiotics, adequate fluid resuscitation would be administered. Data for analysis of the post-intervention group was collected from October 1 to December 1, 2018 by both nurses and physicians. The emergency physicians and the nurses are the same team, no increase population, no have any benefit or punish in pre- and post-intervention group.

Outcome Measures

The primary outcome was the door-to-antibiotic time in patients when NEWS was used as a trigger tool to activate sepsis fast track protocol, in comparison to the door-to-antibiotic time in patients where such a tool was not used. The secondary outcomes examined the door-to-intravenous bolus time (door-to-IV bolus time), door-to-laboratory time (door-to-lab time) taken, lactate clearance, time to admission decision, average hospital length of stay (LOS), and average number of days ICU free, average ventilator free days, and 28-day mortality rate. The door-to-IV bolus time was defined as time between patient arriving at ED to IV bolus being achieved. The door-to-lab time taken was defined as time between patient arriving at ED to blood test taken. The lactate clearance was defined as percentage of blood lactate at arrival minus blood lactate concentration at follow up 2 hours after resuscitation. For lactate clearance, patients in whom there was no follow up of blood lactate, or blood lactate at visit <2 mmol/L or missed data were not included in this outcome. The time to admission decision was defined as time between patient arriving at ED to the nurse receiving the admission order.

Sample Size Calculation

To ensure the number of patients in this study was adequate, the sample size was calculated by independent mean (15). A previous study had reported a mean of door to antibiotics time in the pre-intervention group as 139 minutes [standard deviation (SD)=74] and in the post-intervention group as 81 minutes (SD=39) with an alpha error of 0.05 and a beta error of 0.1, required a sample size of 22 patients in each group (8).

Statistical Analysis

Descriptive statistics were used for categorical data and mean values, standard deviation, medians, and interquartile ranges for continuous data. The Shapiro-Wilk test was used to test a normal distribution. Variables that approximated to a normal distribution were summarized as mean ± SD, and groups were compared using t-tests. Other continuous or ordinary scaled variables were summarized as median, interquartile range, and groups and compared using Mann-Whitney U tests. All statistical

analyses were performed using SPSS® Statistics version 22 (IBM®, Armonk, New York, USA). Statistical significance was designated as $p<0.05$ unless stated otherwise.

Results

There was a total of 539 patients over 18 years of age with sepsis or septic shock, with a NEWS ≥5 and following application of the exclusion criteria, 275 patients were eligible for inclusion in this study. One hundred and seventeen patients were included in the pre-intervention group and 102 in the post-intervention group as shown in Figure 1. Baseline characteristics, including underlying diseases, hospital readmission within three months, vital signs, NEWS, lymphocyte count, and serum lactate did not significantly differ between the pre-and post-intervention groups (Table 1).

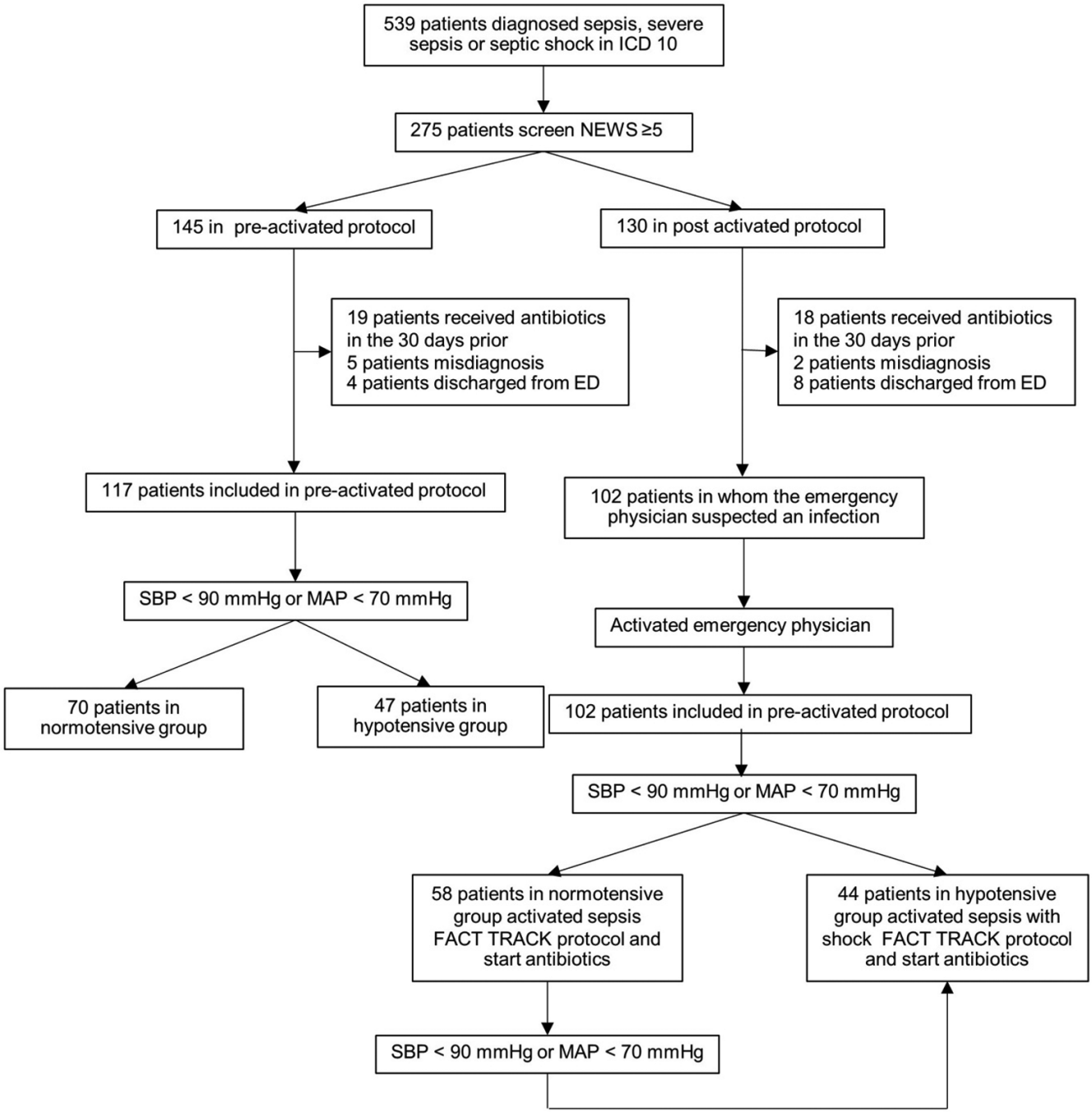

Figure 1. Study flow chart

ED: Emergency department, ICD 10: 10th revision of the International Statistical Classification of Diseases and Related Health Problems, MAP: Mean arterial pressure, mmHg: Millimeters of mercury, NEWS: National Early Warning Score, SBP: Systolic blood pressure

Table 1. Baseline characteristics			
	Pre-intervention (n=117)	**Post-intervention (n=102)**	**p value**
Group - n (%)			
Normotensive group	47 (42.0)	44 (43.14)	0.657
Hypotensive group	70 (59.8)	58 (56.9)	0.657
Male - n (%)	66 (56.4)	48 (47.1)	0.213
Age - years	64.4±18.7	65.5±18.2	0.643
Medical condition - n (%)			
Diabetes mellitus	19 (16.2)	22 (21.6)	0.404
Hypertension	42 (35.9)	45 (44.1)	0.271
Dyslipidemia	23 (19.7)	26 (25.5)	0.384
Cancer	33 (25.2)	30 (29.4)	0.962
Chronic kidney disease	17 (14.5)	18 (17.6)	0.658
Cerebrovascular disease	17 (14.5)	24 (23.5)	0.126
Readmission within 3 months-n (%)	39 (33.3)	32 (31.4)	0.869
Temperature - degrees Celsius	37.9±1.5	38.0±1.3	0.579
Heart rate - beats per min	107.1±24.2	111.5±25.9	0.197
Respiratory rate - times per min	29±16.9	25±8.9	0.102
SBP - mmHg (IQR)	105.5 (83.0-130.5)	91.5 (77.5-131.0)	0.248
MAP - mmHg (IQR)	72.5 (61.0-90.5)	67.5 (58.0-100.5)	0.072
Oxygen saturation - % (IQR)	90.0 (84.0-96.0)	93.5 (89.0-97.0)	0.693
NEWS - score (IQR)	9.0 (7.0-10.5)	8.5 (7.0-11.0)	0.679
White blood cell count - $x10^3$ cell/cu.mm (IQR)	12.0 (5.6-21.2)	11.6 (6.3-16.0)	0.843
Serum lactate - mmol/L (IQR)	3.05 (1.8-4.6)	2.5 (1.9-3.8)	0.297

Data presented as mean ± SD or median (interquartile range), depending on distribution.
cell/cu.mm: Cell per cubic millimeter, IQR: Interquartile range, lab: Laboratory, MAP: Mean arterial pressure, min: Minute, mmHg: Millimeters of mercury, NEWS: National Early Warning Score, mmol/L: millimole per liter, SBP: Systolic blood pressure, SD: Standard deviation, n: Number

After implementing the sepsis fast track protocol, the median door-to-antibiotic time was 34 minutes (20 to 55); this was statistically significantly lower from the pre-intervention median time of 45 minutes (30 to 65; p=0.009). Median door-to-lab time taken in the post-intervention group was lower than the pre-intervention group [18 (8-40) vs 11 (5-20); p=0.003]. However, there were no difference in door-to-IV bolus time, time to an admission decision, average hospital LOS, average ICU free days, average ventilator free days, and 28-day mortality rate (Table 2).

Hypotensive patients and Normotensive patients were separated in a subgroup analysis, baseline characteristics of patients (Tables 3 and 4), including treatment received, did not significantly differ, apart from one exception, in the normotensive group there was a lower prevalence of cerebrovascular disease in the pre-group than in the post-group (12.9 vs 39.8; p=0.013). In the post-intervention normotensive group, door-to-antibiotic time was found to be statistically significantly reduced, median pre-intervention 44.5 (30.0 to 64.3) minutes and post-intervention 25.0 (20.5 to 51.5) minutes; p=0.003, but there was no significant difference in the hypotensive group. Likewise, in the post-intervention group, door-to-lab time taken was also found to be reduced, again with statistical significance, median pre-intervention 16.5 (6.8 to 27.3) minutes, post-intervention 11.5 (5.5 to 20.0) minutes; p=0.005. There were no other significant differences found. With regards to the hypotensive group, time to admission decision increased, with statistical significance, median pre-intervention being 213.0 (173.0 to 300.0) minutes, and post-intervention 273.0 (196.3 to 327.5) minutes; p=0.025.

Discussion

This study found activation of code sepsis using NEWS to detect sepsis patients earlier significantly reduced time to antibiotic administration. Several studies have been conducted to compare different sepsis screening tools. Usman et al. (16) and Thodphetch et al. (17) found that NEWS as a sepsis screening tool had higher sensitivity in comparison to qSOFA, SIRS, and Search Out Severity Score. Screening tools with a higher sensitivity are believed to result in more rapid detection of sepsis and thus more prompt management. Seymour et al. (6) found that the administration of antibiotics prior to 0.95 hours can reduce the mortality rate

Table 2. Primary and secondary outcomes			
	Pre-intervention (n=117)	**Post-intervention (n=102)**	**p value**
Door-to-antibiotic time - min (IQR)	45.0 (30.0-65.0)	30.0 (20.0-55.0)	0.009
Door-to-IV bolus time - min (IQR)	12.0 (6.0-32.0)	8.5 (5.0-20.0)	0.150
Door-to-lab time taken - min (IQR)	18.0 (8.0-40.0)	11.0 (5.0-20.0)	0.003
Lactate clearance - %	23.1±28.7	17.0±37.3	0.339
Time to admission decision - min (IQR)	225.0 (175.0-297.0)	223.0 (180.5-297.0)	0.919
Average hospital LOS - day (IQR)	8.0 (4.0-17.0)	7.0 (5.0-13.0)	0.603
Average ICU free days - day (IQR)	6.0 (3.0-12.0)	7.0 (3.0-10.0)	0.885
Average ventilator free days - day (IQR)	6.0 (2.5-10.0)	7.0 (3.0-10.0)	0.773
28-day mortality rate-n (%)	35 (29.9)	31 (30.4)	0.194

Data presented as mean ± SD or median (interquartile range), depending on distribution.
ICU: Intensive care unit, IQR: Interquartile range, IV: Intravenous, lab: Laboratory, LOS: Length of stay, min: Minute, SD: Standard deviation, n: Number

Table 3. Baseline characteristics in subgroup analysis by normotensive group and hypotensive group						
	Pre-intervention normotensive (n=70)	**Post-intervention normotensive (n=58)**	**p value**	**Pre-intervention hypotensive (n=47)**	**Post-intervention hypotensive (n=44)**	**p value**
Male sex - n (%)	42 (60.0)	31 (53.5)	0.571	23 (48.9)	17 (38.6)	0.437
Age - year	63.0±17.7	67.3±17.8	0.181	71.0 (54.0-89.0)	66.0 (59.8-78.8)	0.950
Medical condition - n (%)						
Diabetes mellitus	11 (15.7)	13 (22.4)	0.709	8 (17.0)	9 (20.5)	0.880
Hypertension	22 (31.4)	28 (48.8)	0.078	20 (42.6)	17 (38.6)	0.868
Dyslipidemia	14 (20.0)	16 (27.6)	0.424	9 (19.2)	10 (22.7)	0.872
Cancer	19 (27.1)	13 (22.4)	0.682	14 (29.8)	17 (38.6)	0.504
CKD	13 (18.6)	14 (24.1)	0.582	4 (8.5)	4 (9.1)	1.000
Cerebrovascular disease	9 (12.9)	19 (32.8)	0.013	8 (17.0)	5 (11.4)	0.638
Readmission within 3 months - n (%)	24 (34.3)	19 (32.8)	1.000	15 (31.9)	13 (29.6)	0.986
Temperature - degree Celsius (IQR)	38.60 (37.8-39.7)	38.50 (37.8-39.1)	0.992	37.3±1.37	337.5±1.38	0.508
Heart rate - beats per min	108.7±19.7	113.6±27.3	0.235	104.8±29.9	109.5±25.2	0.417
Respiratory rate - times per min (IQR)	29.0 (24.0-37.0)	28 (22.5-35.0)	0.218	28.0 (22.0-40.0)	24.0 (20.5-32.0)	0.583
SBP - mmHg	129.1±28.9	138.9±28.5	0.184	81.0 (70.0-91.0)	81.0 (72.3-95.5)	0.381
MAP - mmHg	88.0 (78.5-97.8)	93.0 (112.0-141.8)	0.004	61.0 (56.0-69.0)	59.5 (56.3-76.0)	0.862
Oxygen saturation - % (IQR)	91.0 (87.3-94.0)	92.0 (89.3-95.0)	0.530	88.0 (78.0 -97.0)	95.0 (86.8-98.0)	0.199
NEWS - score (IQR)	8.0 (7.0-9.0)	8.0 (7.0-10.0)	0.325	9.5±3.3	9.0±2.8	0.416
White blood cell count x10^3 cell/cu.mm (IQR)	13.4 (4.5-20.8)	10.3 (5.2-17.0)	0.553	8.9 (5.8-21.9)	12.2 (7.7-16.7)	0.715
Serum lactate - mmol/L (%)	3.8 (3.0-4.9)	3.9 (2.8-5.5)	0.820	4.7 (3.7-6.3)	3.6 (2.8-6.3)	0.091

Data presented as mean ± SD or median (interquartile range), depending on distribution.
cell/cu.mm: Cell per cubic millimeter, IQR: Interquartile range, MAP: Mean arterial pressure, min: Minute, mmHg: Millimeter of mercury, NEWS: National Early Warning Score, mmol/L: Millimole per liter, SBP: Systolic blood pressure, SD: Standard deviation, n: Number, CKD: Chronic kidney disease

in sepsis (6). The findings from these studies led to the surviving sepsis campaign in 2018 the outcomes of which recommended the administration of adequate empirical intravenous antibiotics within the first hour of treatment. In addition, it was found that the activation of the sepsis care system in the ED causes faster intervention than conventional treatment (18-20). Furthermore, activation of the system was found to reduce door-to-lab time significantly. Such findings were in agreement with a study by Hayden et al. (8) which concluded that faster lab results resulted in a faster diagnosis, using the SOFA score, according to the Third International Consensus Definitions for Sepsis and Septic Shock (SEPSIS-3) definition. However, in our study there were no differences with regard to time to fluid resuscitation. This resulted from patients with a lower MAP score in our study being triaged

Table 4. Primary and secondary outcomes in subgroup analysis by normotensive group and hypotensive group						
	Normotensive group			Hypotensive group		
	Pre-intervention (n=71)	Post-intervention (n=58)	p value	Pre-intervention (n=47)	Post-intervention (n=44)	p value
Door-to-antibiotic time - min (IQR)	44.5 (30.0-64.3)	25.0 (20.5-51.5)	0.003	41.0 (23.0-58.0)	37.5 (19.0-83.5)	0.617
Door-to-IV bolus time - min (IQR)	-	-	-	12.0 (6.0-32.0)	10.00 (5.0-24.8)	0.143
Door-to-lab time taken - min (IQR)	16.5 (6.8-27.3)	11.50 (5.5-20.0)	0.005	9.0 (3.0-15.0)	9.0 (5.0-18.3)	0.299
Lactate clearance - % (IQR)	35.2 (9.2-45.3)	35.0 (7.5-47.2)	0.890	22.0 (13.3-38.2)	13.3 (-1.3-31.4)	0.335
Time to admission decision - min	260.4±104.9	229.8±108.1	0.109	213.0 (173.0-300.0)	273.0 (196.3-327.5)	0.025
Average hospital LOS - day (IQR)	8.0 (6.0-21.5)	14.5 (8.3-17.8)	0.863	9.0 (4.0-32.0)	7.0 (5.0-12.0)	0.633
ICU free days - day (IQR)	7.0 (4.0-13.0)	7.0 (4.0-10.5)	0.435	4.0 (0.0-9.0)	6.0 (2.0-9.0)	0.296
Ventilator free days - day (IQR)	7.0 (4.0-12.3)	7.0 (3.0-10.5)	0.642	4.0 (0.0-9.0)	6.0 (2.0-9.0)	0.279
28-day mortality rate - n (%)	11 (15.7)	15 (25.9)	0.230	24 (51.0)	16 (36.4)	0.230

Data presented as mean ± SD or median (interquartile range), depending on distribution.
ICU: Intensive care unit, IQR: Interquartile range, IV: Intravenous, lab: Laboratory, LOS: Length of stay, min: Minute, SD: Standard deviation, n: Number

as a resuscitation case, and thus most patients would receive rapid fluid administration regardless of sepsis fast track use. This study shows no statistical difference in the 28-day mortality rate, possibly due to insufficient numbers of patients, or possibly that the door-to-antibiotic time in the pre-intervention group was less than other studies (18). Future studies with larger number of patients are needed to verify this.

In our subgroup analysis, we found that the activation of sepsis fast track reduced door-to-antibiotic time and door-to-lab time. However, for the hypotensive group, there were no significant differences in door-to-antibiotic time, door-to-lab time, and time to fluid administration between the pre- and post-intervention groups. An explanation for this is probably because patients in the hypotensive group were triaged as resuscitation cases, thus would receive prompt intervention regardless of protocol activation. However, this study does highlight how the protocol helps personnel to have an increased focus on sepsis as regards normotensive patients. Time to admission decision was increased in the study, a finding which was in line with those published by both Hayden et al. (8) and Permpikul et al. (21). Both studies found that rapid diagnosis and management in the "golden hour", including administering norepinephrine in septic shock patients reduced the duration of shock, pulmonary edema, and new-onset arrhythmia, another field of septic shock which needs further investigation.

Study Limitations

As this study was a quasi-experimental study, some information obtained retrospectively may be missing. As for the post-intervention group, using NEWS as a screening tool screens by the severity of the case; thus, this may not be inclusive of instances where the infection was not initially suspected. In addition, the numbers of patients with sepsis according to the SEPSIS-3 definition were not analyzed in this study as a diagnostic study; nonetheless, the ED uses the SEPSIS-3 definition to guide diagnosis (1). Additionally, if at any time the physician does not suspect sepsis after activation of the protocol, the physician will indicate in the records that sepsis was not suspected and re-designate the case as an infectious or non-infectious case instead.

Conclusion

Using NEWS as a trigger tool to activate the sepsis fast track protocol helps to reduce the door-to-antibiotic time in patients suspected of sepsis in the ED.

Ethics

Ethics Committee Approval: This study was a retrospective and prospective, quasi-experimental study which was approved by the Research Ethics Committee of Faculty of Medicine of Chiang Mai University (no: 377/2018, date: 03.10.2018).

Informed Consent: Written informed consent was obtained from patients who were enrolled on the prospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: P.T., B.W., T.C., T.T., Concept: P.T., B.W., T.C., T.T., Design: P.T., B.W., T.C., T.T., Data Collection or Processing: P.T., B.W., T.C., T.T., Analysis or Interpretation: P.T., B.W., T.C., T.T., Literature Search: P.T., B.W., T.C., T.T., Writing: P.T., B.W., T.C., T.T.

Conflict of Interest: The authors declare they have no competing interest.

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