의학석사 학위논문

Effect of Initial Mean Blood Pressure on the Application of CRRT in Septic Shock

패혈성 쇼크에서 초기 평균혈압이 지속적 신대체요법 적용에 미치는 영향

2019 년 2 월

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의학과 내과학 전공

박 희 문

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지도 교수 이 상 민

이 논문을 의학석사 학위논문으로 제출함

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박희문의 의학석사 학위논문을 인준함

2018 년 12 월

위 원 장	주 권 욱	(인)
부위원장	이 상 민	(인)
위 원	류 호 걸	(인)

Abstract

Patients with chronic hypertension had been known to have a lower continuous renal replacement therapy (CRRT) requirement when treated with high-target mean blood pressure (MBP) at 80-85mmHg instead of 65-70mmHg in septic shock. Comparing the MBP for initial 48hours after septic shock between patients with or without CRRT, a basis of the benefit of initial high-target MBP in septic shock will be established.

Patients who underwent CRRT within 5 days after septic shock were defined as "CRRT group", and those who did not undergo CRRT within 5 days after septic shock were defined as "no CRRT group". 85 of 1276 patients who entered intensive care unit at Seoul National University Hospital between Jan 2016 and Dec 2017 were enrolled. Of these, 19 (22.4%) were in CRRT group. There was no difference in age (64.4±1.6 vs 65.4±2.9, p=0.77), male sex (66.7% vs 57.9%, p=0.59), Sequential Organ Failure Assessment (SOFA) score (15.0±0.4 vs 15.6±0.8, p=0.46). Because the average of time till CRRT apply was 30.8±3.6 hours, analysis was done with data during 30hours.

There was a difference in the distribution of MBP range between CRRT group and no CRRT group during the first 30 hours after septic shock. The proportion of MBP 65-75mmHg was significantly higher in CRRT group and CRRT apply risk was also significantly increased (OR 1.081; CI 1.034-1.131). The proportion of MBP 75-85 mmHg was not different between the two groups. The proportion of MBP 85-95 mmHg was significantly higher in the no CRRT group and CRRT apply risk was significantly decreased (OR 0.925; CI 0.875-0.978). ICU mortality (OR 20.00;

CI 5.03-79.54) and hospital mortality (47.7% vs 100.0%, p<0.001) were significantly higher in the CRRT group. There was no difference in the occurrence of arrhythmia event and CVI between two groups. Total ICU mortality was 33.7% and total hospital mortality was 59%.

Therefore, the risk of CRRT apply and ICU or in-hospital mortality could be expected to be reduced when the target of MBP was set to above 85mmHg for initial 30 hours after septic shock.

Keyword : septic shock, mean blood pressure, continuous renal replacement therapy

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1. Introduction

1.1. Background

In 2016, the Septic shock guideline was revised.[1-4] In this guideline, the recommended target mean arterial pressure (MAP) is 65 mmHg with moderate quality of evidence.[5-13] According to a randomized control trial (RCT) study published in 2014, there was no significant difference in mortality on the 28th and 90th day between the MAP 80-85 mmHg target group and the MAP 65-70 mmHg target group. However, patients with chronic hypertension had a lower continuous renal replacement therapy (CRRT) requirement when treated with high-target MAP at 80-85 mmHg.[10] RCT study published in 2016 compared the MAP 60-65 mmHg target group with the MAP 75-80 mmHg target group. There was no difference between the two groups in hospital mortality. However, in patients older than 75 years, mortality and cardiac arrhythmia event were significantly lower in the lower MAP target group.[9] A systemic review of these two studies was recently published in 2018.[14] In this study, there was no difference in the mortality and adverse events. However, in subgroup analysis, among patients who received vasopressor treatment for more than 6 hours before enrollment, the mortality was significantly higher in the high-target group. The author suggested that the mortality was higher due to adding the harmful effect of the higher MAP target to the group with no improvement even though the vasopressor was already used for more than 6 hours. However, in RCT published in 2014, the MAP target was maintained for 5 days or until vasopressor support was terminated, and in RCT published in 2016, the MAP target was maintained during the vasopressor infusion. This mean that the high

MAP target group was exposed to high MAP for a longer period time. Considering the clinical practice, the vasopressor is reduced to target MAP above 65mmHg when the urine output is secured after acute kidney injury (AKI) due to septic shock. In fact, vasopressors such as norepinephrine cause adverse effects such as sinus tachycardia, atrial fibrillation, and limb necrosis.[15-20] Therefore, maintaining high MAP for 5 days or until the vasopressor requirement is abolished is not done in clinical practice.

1.2. Purpose of Research

This study investigated the difference in mean blood pressure (MBP) during initial 48 hours after septic shock between patients with or without CRRT and seeked to estabilish a basis for whether early high MBP targets can lower the risk of CRRT apply in septic shock. Furthermore, this study would suggest changing the MBP target above 65mmHg recommended by the sepsis guideline when the urine output is ensured after maintaining the high MBP target during the initial 48 hours after septic shock.

2. Method

2.1. Study Population

This is a retrospective descriptive study. Patients who underwent intensive care unit (ICU) care at Seoul National University Hospital between January 2016 and December 2017 were included in this study. Patients who underwent CRRT within 5 days after septic shock were defined as "CRRT group", and those who did not undergo CRRT within 5 days after septic shock were defined as "no CRRT group". By checking the entry and discharge ICU records, patients with documented sepsis were screened. The onset of shock was defined as meeting both conditions with a systolic blood pressure (SBP) of less than 90 mmHg and a diastolic blood pressure (DBP) of less than 60 mmHg. In most cases, septic shock occurred in the ward initially, so noninvasive blood pressure (NIBP) data was collected. The MBP data collection was performed from the onset of septic shock to the application of CRRT for the CRRT group, and up to 48 hours after the onset of septic shock for the no CRRT group.

2.2. Definition

2.2.1. Representative MBP

The number of blood pressures measured within one hour for each patient varied. The more unstable the vital sign was, the more the MBP was measured. Thus, in this study, a “representative MBP” of each hour was defined as the mean value of all of MBP data measured during one hour. In Figure 1, the representative MBP at time 1 of patient 2 is 63.3mmHg.

2.2.2. Proportion of MBP

The proportion of representative MBP data within a specific blood pressure range to total measured MBP was defined as a "proportion of MBP." In Figure 1, the proportion of MBP ≥65 mmHg during 7 hours is 80% for patient 1 and 60% for patient 2.

2.2.3. Average MBP

The mean value of total representative MBP data was defined as an "average MBP." In Figure 1, average MBP of patient 1 is 73mmHg.

2.3. Statistical Analyses

Fisher's exact test and Pearson Chi-square were used for the comparison of categorical variables. Mann-Whitney test and Student's t-test were used for the analysis of continuous variables. The correlation between variables was analyzed by logistic regression analysis. Statistical analysis was performed using SPSS 20.0 software and p-value <0.05 was considered statistically significant.

3. Results

This study screened 1274 patients who entered the ICU at Seoul National University Hospital from 2016 to 2017 and identified 393 patients who were suspected of documented sepsis. Patients without NIBP data, with documented DNR, who expired due to arrest after septic shock, or whose main cause of shock was not septic shock but others such as cardiac arrest, intubation, respiratory acidosis were excluded. This study also excluded the patients who had other AKI causes such as application of extracorporeal membrane oxygenation (ECMO), acute decompensated heart failure (AD-HF), hepatorenal syndrome (HRS), bleeding, contrast induced nephropathy (CIN), and acute glomerulonephritis (AGN). Patients who had already had intermittent dialysis or CRRT before septic shock were also excluded. Patients who did not meet the indications of emergency dialysis (uncontrolled metabolic acidosis, hyperkalemia, pulmonary edema, uremia) among patients who underwent CRRT within 12 hours after septic shock were excluded. It is already known that the prolonged hypotension deteriorates the prognosis of patients with septic shock. Therefore, patients whose proportion of MBP<65mmHg was more than 20% were excluded. The final analysis was performed with 83 patients (18 patients in the CRRT group, 65 in the no CRRT group) (Figure 2).

There was no difference in age, male sex, and body mass index (BMI) between the tw o groups. There was no difference in index of disease severity such as acute physiology and chronic health evaluation (APACHE) II score, sequential organ failure assessment (SOFA) score, and simplified acute physiology score (SAPS) II. Blood lactate level at the time of septic shock was not different between two groups, too. Because there was no difference in baseline glomerular filtration rate (GFR) before septic shock, the effe

ct of baseline kidney function on CRRT application might not be different. Because he morrhage and anemia could cause AKI, so hemoglobin (Hb) at the time of septic shock was compared and there was no difference in Hb between the two groups. There was no difference in volume loading (cc/kg) between the two groups during 3 hours after se ptic shock and also no difference in cumulative vasopressor index (CVI) between the t wo groups (appendix 1). This study conducted the analysis with proportion of MBP, so it was necessary to confirm that there was no difference in the ratio of time of checking BP to total follow up time after septic shock between the two groups. The time point o f the CRRT application in the CRRT group was 29.89 ± 3.90 hours after septic shock. The most common infection focus of septic shock was pneumonia in both groups (66.2 % vs 55.6%)(Table 1). On average, since the CRRT apply was performed within 30 ho urs after the septic shock, the number of subjects in the CRRT group decreased signific antly after 30 hours and the confidence interval became wider (Figure 3). In addition, it can be seen that the graphs of the two groups intersect at 34 hours. So, analysis was d one with data during 30hours after septic shock (Figure 4).

Average MBP during 24, 30 or 48 hours after septic shock was significantly higher in no CRRT group (Table 2). When the proportion of MBP for 30 hours after septic shock was analyzed, there was no difference between the two groups in the proportion of MBP≥65 mmHg, but the proportion of MBP≥70, 75, 80, 85 or 90 mmHg were significantly higher in the no CRRT group (Table 3). ICU mortality and hospital mortality were significantly higher in the CRRT group, but there was no significant difference between the two groups in arrhythmia events. Total ICU mortality was 33.7% and total hospital mortality was 59.0% (Table 4).

In order to identify the risk factors affecting CRRT apply, the logistic regression

was performed with age, BMI, APACHE II score, SOFA score, baseline GFR, Hb at septic shock, lactate level at septic shock, volume loading during first 3hrs after septic shock (cc/kg) and the various proportion of MBP. As a result, the proportion of MBP ≥70, 75, 80, 85, and 90 mmHg were identified as a risk factor of CRRT apply, but the proportion of MBP ≥65 and 95 mmHg were not statistically significant (Table 5). The odds ratio of CRRT apply according to the proportion of MBP ranging from 65-69 mmHg to 92-96 mmHg at 5 mmHg interval in MBP range was confirmed. Significantly reduced CRRT apply risk was shown from 84-88 mmHg to 89-93 mmHg, but significantly increased CRRT apply risk was shown from 65-69 mmHg to 72-76 mmHg (Figure 5, Appendix 2).

The MBP range shown as in Table 6 was divided and the proportion of MBP and odds ratio of CRRT apply of two groups was compared. The proportion of MBP 65-75mmHg was significantly higher in CRRT group and CRRT apply risk was also significantly increased (OR 1.081; CI 1.034-1.131). The proportion of MBP 75-85 mmHg was not different between the two groups. The proportion of MBP 85-95 mmHg was significantly higher in the no CRRT group and CRRT apply risk was significantly decreased (OR 0.925; CI 0.875-0.978) (Table 6). The distribution according to the MBP range of the two groups is shown in Figure 6. The receiver operating characteristic (ROC) curves according to proportion of MBP were shown in Figure 7. The risk of CRRT application was reduced as the proportion of MBP 85-95mmHg increased, and calculated the area under the ROC curve (AUC) was 0.703 ± 0.071, sensitivity was 0.692, and specificity was 0.611 for the cutoff value of 17.265. On the other hand, the risk of CRRT application was increased as the proportion of MBP 65-75mmHg increased, and calculated AUC was 0.768 ± 0.064,

sensitivity was 0.722, and specificity was 0.723 for the cutoff value of 30.515 (Table 7). The results of logistic regression model for CRRT apply with proportion of MBP 85-95mmHg or 65-75mmHg were shown in each Table 8,9. According to these models, a 1% increase in the proportion of MBP 85-95 mmHg reduces the risk of CRRT apply by 0.925 (Table 8), and a 1% increase in the proportion of MBP 65-75 mmHg increases the risk of CRRT apply by 1.081 (Table 9). In the case of in-hospital mortality, only the logistic regression model with a proportion of MBP 65-75 mmHg was significant and the results are shown in Table 10. According to this model, a 1% increase in the proportion of MBP 65-75 mmHg increases the risk of in-hospital mortality by 1.042 (Table 10).

The data of 13 patients of the below 15 percentile and 13 patients of the more than 85 percentile of the proportion of MBP 65-75mmHg was analyzed, and there was no significant difference in baseline characteristics (Table 11). Figure 8 shows the trends of MBP during 30 hours in these groups. The average of MBP during 24, 30, and 48 hours after septic shock was significantly higher in the patient of the below 15 percentiles of the proportion of MBP 65-75mmHg (Table 12). The proportion of MBP 65-75mmHg was significantly higher in the patients of top 15 percentile of the proportion of MBP 65-75mmHg. The proportion of MBP 75-85 mmHg was not different between the two groups. The proportion of MBP 85-95 mmHg was significantly higher in the patients of bottom 15 percentile of the proportion of MBP 65-75mmHg (Table 13). ICU mortality (OR 14.000; CI 1.385-141.485), Hospital mortality (OR 5.333; CI 0.987, 29.393) and the risk of CRRT apply were all significantly higher in the patients of the top 15 percentiles of the proportion of MBP 65-75mmHg. Arrhythmia events were not different between the two groups.

4. Discussion

The target of MBP was recommended above 65mmHg in the sepsis guideline published in 2016.[1-4, 9-13] There are two RCTs and one systemic review as the basis of this recommendation. According to RCT study published in 2014, there was no significant difference in mortality on the 28th and 90th day between the MAP 80-85 mmHg target group and the MAP 65-70 mmHg target group.[10] RCT study published in 2016 compared the MAP 60-65 mmHg target group with the MAP 75-80 mmHg target group and there was no difference in hospital mortality between the two groups.[9] According to a systemic review of these two studies published in 2018, there was no significant difference in the mortality and adverse events regardless of MBP target.[14] However, in RCT published in 2014,[10] the MAP target was maintained for 5 days or until vasopressor support was terminated, and in RCT published in 2016,[9] the MAP target was maintained during the vasopressor infusion. This means that the high MAP target group was exposed to high MAP for a longer period of time in these two studies. On the other hands, the RCT in 2014 reported that patients with chronic hypertension had a lower CRRT requirement when treated with high-target MAP at 80-85 mmHg.[10] Therefore, this study investigated the difference in MBP during initial 48 hours after septic shock between patients with or without CRRT apply and anticipated that by this study a basis for whether early high MBP targets can lower the risk of CRRT apply in septic shock can be estabilished. Furthermore, changing the target of MBP to more than 65mmHg when the urine output is secured after maintaining the high MBP target during the initial 48 hours after septic shock can be suggested.

In most of the case, septic shock occurred in the ward initially, so this study collected NIBP data. Because the blood pressure is checked a lot when the shock is

continued, the MBP at a certain time point cannot be taken as the representative MBP of that time. So, in this study, the representative MBP of each hour was defined as the mean value of all of MBP data measured during one hour. In addition, because septic shock patients have a severe MBP fluctuation, it cannot be interpreted that only comparing the average of the representative MBPs of the CRRT group and the no CRRT group at each time is equivalent to comparing the MBP of the two groups at the whole time. Therefore, the MBP trends of the two groups by analyzing the proportion of MBP was compared. Because the ratio is compared, there can be a big problem that statistical analysis and actual interpretation may be different if there is a significant difference in the total number of MBP measurements between the two groups. This problem was solved in the following way. It is known that prolongation of shock status in septic shock leads to poor prognosis. Thus, to assess the effect of the ratio of MBPs within a given blood pressure range, there should be no difference in the duration of time when the MBP was below 65mmHg between the CRRT group and the no CRRT group. For achieving this purpose, the patients whose proportion of MBP below 65mmHg was above 20% were excluded. After this procedure, there was no significant difference in the proportion of MBP below 65mmHg between CRRT group and no CRRT group. Since the CRRT apply was performed within about 30 hours after the septic shock, the number of subjects in the CRRT group decreased significantly after 30 hours and the confidence interval became wider. In addition, it can be seen that the graphs of the two groups intersect at 34 hours. So, analysis was done with data during 30hours after septic shock. Through the above procedure, data during 30 hours after septic shock from a total 83 patients was

obtained. It was confirmed that there was no significant difference in the ratio of time of checking BP to total follow up duration after septic shock between the two groups (0.978±0.0066 vs 0.964±0.0175, p=0.868). In that way, the difference between statistical analysis and actual interpretation can be reduced.

This study analyzed the differences between the CRRT group and the no CRRT group. There was no difference in baseline characteristics, especially the index of disease severity such as APACHE II, SOFA and SAPS II scores. The CRRT application time point was 29.89 ± 3.90 hours after septic shock in the CRRT group. There was no difference in the proportion of BP check times measured within 30 hours between the two groups. Average MBP during 30 hours after septic shock was significantly higher in the no CRRT group (82.60±0.89 vs 77.56±1.29 p=0.007). ICU mortality (OR 20.00; CI 5.03-79.54) and hospital mortality (47.7% vs 100.0%, p<0.001) were significantly higher in the CRRT group. There was no difference in the occurrence of arrhythmia event and CVI between two groups. Total ICU mortality was 33.7% and total hospital mortality was 59%. In order to identify the risk factors affecting CRRT apply, the logistic regression was performed with age, BMI, APACHE II score, SOFA score, baseline GFR, Hb at septic shock, lactate level at septic shock, volume loading during first 3hrs after septic shock (cc/kg) and the various proportion of MBP. As a result, the proportion of MBP ≥70, 75, 80, 85, and 90 mmHg were identified as a risk factor of CRRT apply. To determine the range of MBP in which CRRT application was different between two groups, the odds ratio of CRRT apply according to the proportion of MBP ranging from 65-69 mmHg to 92-96 mmHg at 5 mmHg interval in MBP range was analyzed. Significantly reduced CRRT apply risk was shown from 84-88 mmHg to 89-93 mmHg, but significantly increased CRRT apply risk was shown from 65-69 mmHg

to 72-76 mmHg. Therefore, when the percentage of MBP in the 65-75 mmHg range was high, the risk of CRRT apply was expected to be high. On the other hands, the higher ratio of MBP within the range of 85-95 mmHg was expected to reduce the risk of CRRT apply. The proportion of MBP 65-75mmHg was expected to be higher in the CRRT group and the proportion MBP 85-95mmHg was expected to be higher in the no CRRT group. Actually, the proportion of MBP 65-75mmHg was significantly higher in CRRT group and CRRT apply risk was also significantly increased (OR 1.081; CI 1.034-1.131). The proportion of MBP 75-85 mmHg was not different between the two groups. The proportion of MBP 85-95 mmHg was significantly higher in the no CRRT group and CRRT apply risk was significantly decreased (OR 0.925; CI 0.875-0.978). ROC curve was analyzed to determine whether the proportion of MBP 65-75 mmHg or 85-95 mmHg can predict the application of CRRT. The risk of CRRT application was reduced as the proportion of MBP 85-95mmHg increased, and calculated the area under the ROC curve (AUC) was 0.703 ± 0.071, sensitivity was 0.692, and specificity was 0.611 for the cutoff value of 17.265. On the other hand, the risk of CRRT application was increased as the proportion of MBP 65-75mmHg increased, and calculated AUC was 0.768 ± 0.064, sensitivity was 0.722, and specificity was 0.723 for the cutoff value of 30.515.

In the case of in-hospital mortality, only the logistic regression model with a proportion of MBP 65-75 mmHg was significant. According to this model, a 1% increase in the proportion of MBP 65-75 mmHg increases the risk of in-hospital mortality by 1.042. The data of the top 15 percentile and the bottom 15 percentile of the proportion of MBP 65-75mmHg was analyzed. The average MBP for 30 hours was significantly higher in the patients of bottom 15 percentile. (89.62±1.893

vs 72.85±0.619, p<0.001). The results of proportion of MBP was similar to the previous results between the CRRT group and the no CRRT group. The proportion of MBP 65-75mmHg was significantly higher in the patients of top 15 percentile. The proportion of MBP 75-85 mmHg was not different between the two groups. The proportion of MBP 85-95 mmHg was significantly higher in the patients of bottom 15 percentile. In the case of CRRT apply, 0% was observed in the patients of bottom 15 percentile and 69.2% in the patients of top 15 percentile (p<0.001). ICU mortality (OR 14.000; CI 1.385-141.485), Hospital mortality (OR 5.333; CI 0.987, 29.393) were all significantly higher in the patients of the top 15 percentiles of the proportion of MBP 65-75mmHg. The results of this study indicate that the distribution of MBP was biased toward 65-75 mmHg in CRRT group and toward more than 85 mmHg in no CRRT group. The effect of reducing the risk of CRRT apply and the ICU or in-hospital mortality could be expected when the target of MBP was set to above 85mmHg for 30 hours after septic shock.

This study has several limitations. First, because this study was retrospective study, selection bias and missing data were inevitable. Second, causal relationship cannot be proved because the temporal relationship is unclear. Although there was no difference in APACHE, SOFA, and SAPS scores, patients in the CRRT group were more severe and their MBP could be lower than in no CRRT group. However, there was no significant difference in the proportion of MBP above 65mmHg between the two groups. Thus, the effect of the time of exposure to hypotension did not seem to be significant between the two groups. Further RCT will be needed to establish a basis for whether MBP target to above 85mmHg during initial 30 hours after septic shock can lower the risk of CRRT apply in septic shock.

5. Conclusion

There was a difference in the distribution of MBP range between CRRT group and no CRRT group during the first 30 hours after septic shock. The proportion of MBP 65-75mmHg was significantly higher in CRRT group and CRRT apply risk was also significantly increased (OR 1.081; CI 1.034-1.131). The proportion of MBP 75-85 mmHg was not different between the two groups. The proportion of MBP 85-95 mmHg was significantly higher in the no CRRT group and CRRT apply risk was significantly decreased (OR 0.925; CI 0.875-0.978). Therefore, the risk of CRRT apply and ICU or in-hospital mortality could be expected to be reduced when the target of MBP was set to above 85mmHg for initial 30 hours after septic shock.

6. Tables, Figures, Appendix

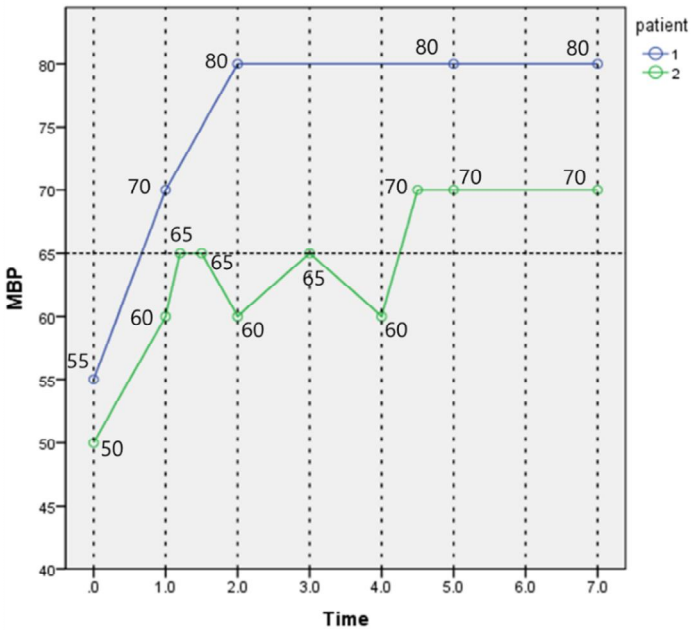

Figure 1 Example for definition

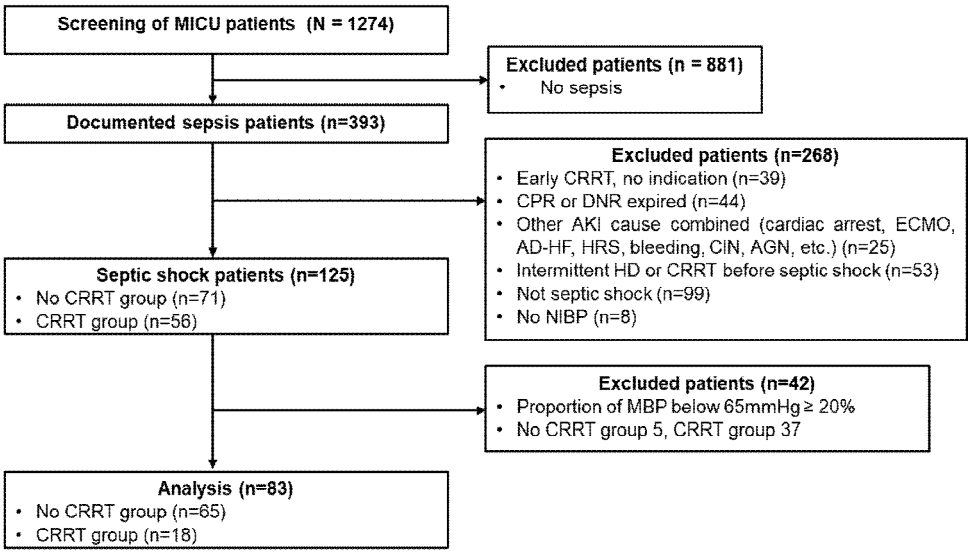

Figure 2 Flow chart

Table 1 Baseline characteristics

Variable	No CRRT group	CRRT group	*p* value
Age (years)	64.43±1.60	64.33±2.88	0.916
Male sex, n (%)	43 (66.2%)	10 (55.6%)	0.408
BMI (kg/m2)	21.46±0.45	22.59±0.75	0.226
APACHE II score	31.11±0.77	33.17±1.73	0.236
SOFA score	15.05±0.43	15.56±0.83	0.583
SAPS II score	79.42±2.26	83.28±4.56	0.435
Baseline eGFR	102.93±6.91	103.27±12.63	0.982
Hb at septic shock	9.91±0.27	10.46±0.72	0.787
Lactate at septic shock	4.03±0.41	5.31±0.86	0.108
Volume loading during first 3hrs (cc/kg)	20.81±1.57	22.28±4.33	0.695
Maximal urine output during 24hrs after septic shock	272.29±23.78	156.25±38.94	†0.026
CVI	4.71±0.22	5.22±0.50	0.280
Ratio of time of checking BP to total follow up duration after septic shock	0.978±0.0066	0.964±0.0175	0.868
Septic shock to CRRT time (hours)		29.89±3.90	
Infection focus			
Pneumonia	43 (66.2%)	10 (55.6%)	
Genitourinary infection	4 (6.2%)	3 (16.7%)	
Gastrointestinal origin	6 (9.2%)	5 (27.8%)	
Hepatobiliary origin	4 (6.2%)	.	
CNS infection	1 (1.5%)	.	
Infective endocarditis	1 (1.5%)	.	
Soft tissue infection	5 (7.7%)	.	
Unknown origin	1 (1.5%)	.	

BMI body mass index, APACHE acute physiology and chronic health evaluation score, SOFA sequential organ failure assessment score, SAPS simplified acute physiology score, CVI cumulative vasopressor index, † *p*-value<0.05

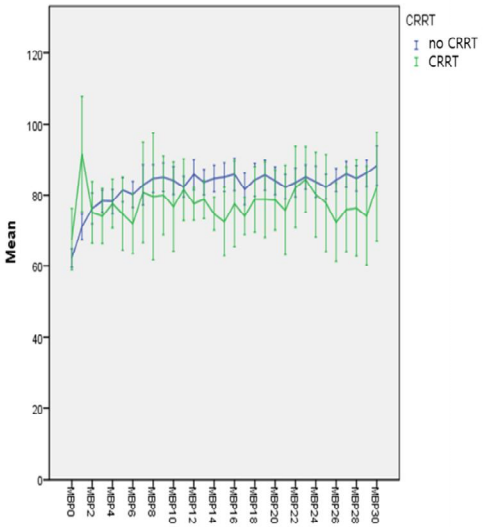

Figure 3 Mean blood pressure during 30hrs

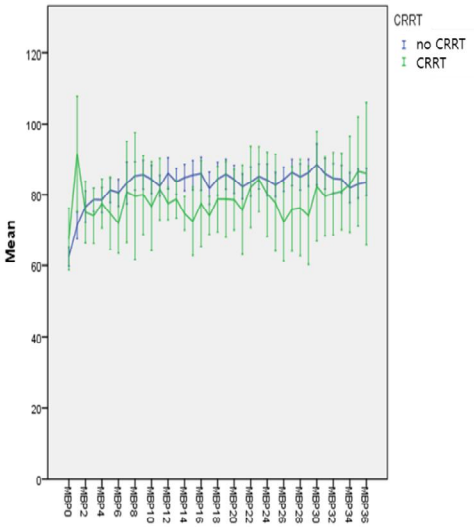

Figure 4 Mean blood pressure during 36hrs

Table 2 Average MBP after septic shock

Variable	No CRRT group	CRRT group	*p* value
Average MBP during 24hrs	82.00±0.89	77.61±1.28	†0.018
Average MBP during 30hrs	82.60±0.89	77.56±1.29	†0.007
Average MBP during 48hrs	83.72±0.89	77.89±1.39	†0.002

† p-value<0.05

Table 3 Proportion of MBP during 30hours after septic shock

Variable	No CRRT group	CRRT group	*p* value
Proportion of MBP below 65mmHg	8.67±0.77	9.09±1.30	0.598
Proportion of MBP above 65mmHg	91.33±0.77	90.91±1.30	0.598
Proportion of MBP above 70mmHg	82.87±1.50	74.44±2.79	† 0.005
Proportion of MBP above 75mmHg	67.30±2.40	49.52±4.58	† 0.001
Proportion of MBP above 80mmHg	55.19±2.60	38.75±5.18	† 0.005
Proportion of MBP above 85mmHg	41.33±2.59	24.92±4.42	† 0.003
Proportion of MBP above 90mmHg	28.39±2.42	16.30±3.81	† 0.018
Proportion of MBP above 95mmHg	17.78±2.11	9.58±3.07	† 0.017

† p-value<0.05

Table 4 Mortality and arrhythmia events

Variable	No CRRT group	CRRT group	Odds ratio [95% CI]	*p* value
ICU mortality (%)	20.0%	83.3%	20.00 [5.03,79.54]	† <0.001
Hospital mortality (%)	47.7%	100.0%		† <0.001
Arrhythmia events	18.5%	33.3%	2.208 [0.690,7.067]	0.203
Total ICU mortality (%)	33.7%			
Total hospital mortality (%)	59.0%			

† p-value<0.05

Table 5 Logistic regression model for CRRT apply

Variable	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	*p* value	Odds ratio [95% CI]	*p* value
Proportion of MBP above 65mmHg	0.985 [0.888-1.092]	0.769		
Proportion of MBP above 70mmHg			0.947 [0.905,0.991]	† 0.018
Proportion of MBP above 75mmHg			0.954 [0.925,0.984]	† 0.003
Proportion of MBP above 80mmHg			0.963 [0.937,0.991]	† 0.009
Proportion of MBP above 85mmHg			0.958 [0.927,0.990]	† 0.010
Proportion of MBP above 90mmHg			0.963[0.927,1.000]	‡ 0.051
Proportion of MBP above 95mmHg	0.966 [0.917,1.017]	0.183		

† p-value<0.05, ‡ p-value : marginal significant

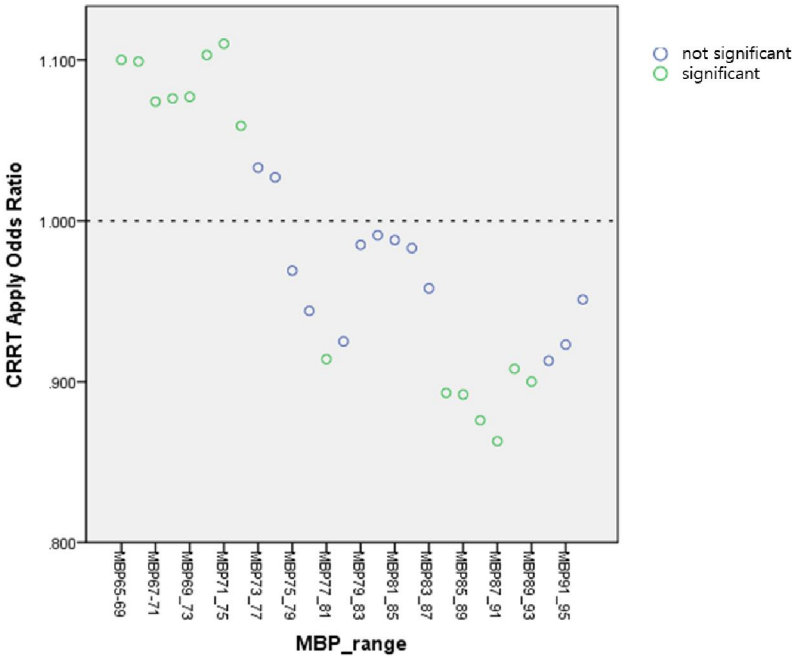

Figure 5 Odds ratio of CRRT apply according to the proportion of MBP

Table 6 Logistic regression model for CRRT apply and distribution of each group according to proportion of MBP

Variable	No CRRT group	CRRT group	Odds ratio [95% CI]	p value
Proportion of MBP 60-70mmHg	16.52±1.65	28.10±3.08	1.063 [1.018,1.110]	† 0.005
Proportion of MBP 60-75mmHg	29.68±2.32	47.84±4.51	1.064 [1.025,1.104]	† 0.001
Proportion of MBP 65-70mmHg	10.89±1.16	21.66±3.04	1.096 [1.033,1.163]	† 0.002
Proportion of MBP 65-75mmHg	**24.04±1.86**	**41.40±4.41**	**1.081 [1.034,1.131]**	**† 0.001**
Proportion of MBP 65-80mmHg	39.31±2.12	54.42±4.97	1.047 [1.013,1.083]	† 0.006
Proportion of MBP 70-75mmHg	15.57±1.25	24.93±2.73	1.096 [1.032,1.163]	† 0.003
Proportion of MBP 70-80mmHg	30.84±1.68	37.95±3.60	1.037 [0.996,1.079]	0.075
Proportion of MBP 70-85mmHg	44.24±1.80	51.39±3.19	1.030 [0.984,1.078]	0.209
Proportion of MBP 70-90mmHg	57.14±1.81	59.22±2.64	0.995 [0.951,1.041]	0.820
Proportion of MBP 75-80mmHg	18.46±1.16	16.42±2.15	0.960 [0.901,1.022]	0.202
Proportion of MBP 75-85mmHg	**31.85±1.49**	**29.85±2.69**	**0.960 [0.910,1.012]**	**0.128**
Proportion of MBP 75-90mmHg	44.76±1.75	37.68±2.45	0.930 [0.880,0.981]	† 0.008
Proportion of MBP 80-85mmHg	16.56±1.14	15.69±2.55	0.967 [0.905,1.034]	0.330
Proportion of MBP 80-90mmHg	29.46±1.48	23.52±3.10	0.930 [0.879,0.984]	† 0.011
Proportion of MBP 80-95mmHg	38.99±1.85	29.93±3.97	0.941 [0.901,0.983]	† 0.007
Proportion of MBP 85-90mmHg	15.60±1.00	9.70±1.81	0.889 [0.819,0.964]	† 0.005
Proportion of MBP 85-95mmHg	**25.13±1.54**	**16.10±2.71**	**0.925 [0.875,0.978]**	**† 0.006**
Proportion of MBP 90-95mmHg	12.19±1.02	7.47±1.71	0.913 [0.837,0.996]	† 0.040

† p-value<0.05

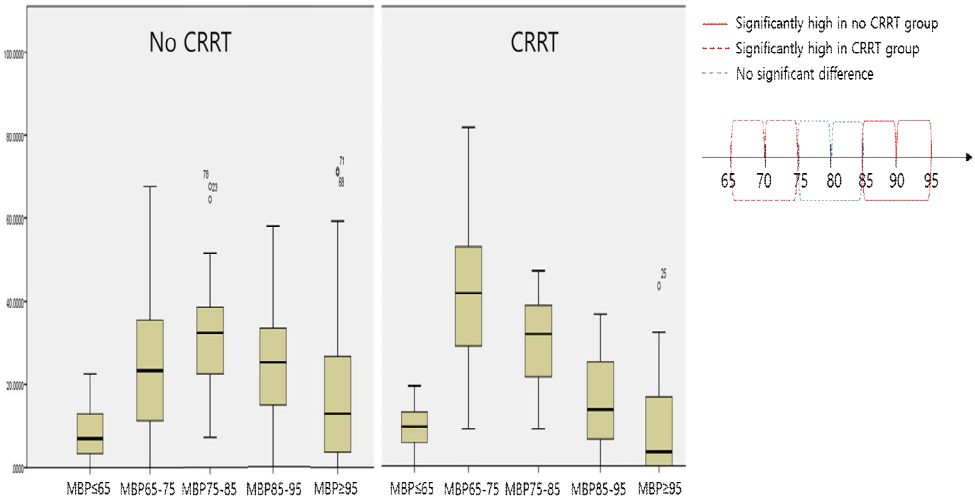

Figure 6 Distribution of each group according to proportion of MBP

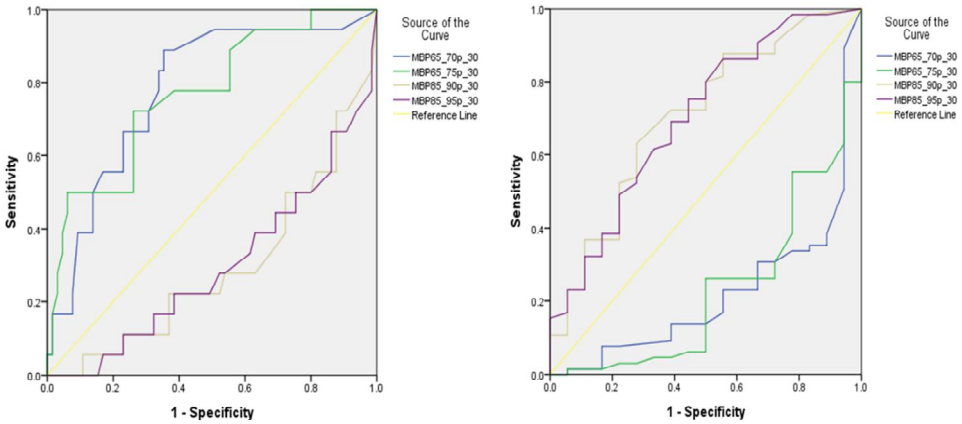

Figure 7 Receiver operating characteristic (ROC) curve according to proportion of MBP

Table 7 Area under the ROC curve (AUC), cutoff value, sensitivity, specificity according to proportion of MBP

Variable	AUC	Cutoff value	Sensitivity	Specificity
Proportion of MBP 65-70mmHg	0.779±0.061	13.115	0.722	0.692
Proportion of MBP 65-75mmHg	**0.768±0.064**	**30.515**	**0.722**	**0.723**
Proportion of MBP 85-90mmHg	0.706±0.071	12.330	0.389	0.277
Proportion of MBP 85-95mmHg	**0.703±0.071**	**17.265**	**0.692**	**0.611**

Table 8 Logistic regression model for CRRT apply with proportion of MBP 85-95mmHg

	Univariable analysis		Multivariable analysis	
Variable	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age	1.003 [0.957,1.051]	0.901		
BMI	1.093 [0.885,1.350]	0.409		
APACHE II	1.074 [0.950,1.214]	0.253		
SOFA	0.974 [0.772,1.229]	0.823		
Baseline GFR	1.003 [0.992,1.015]	0.571		
Hb at septic shock	1.149 [0.858,1.537]	0.351		
Lactate at septic shock	1.132 [0.951,1.347]	0.163		
Volume loading during first 3hrs (cc/kg)	0.979 [0.932,1.028]	0.394		
CVI	1.106 [0.821,1.489]	0.507		
Proportion of MBP 80-95mmHg	0.905 [0.842,0.973]	† 0.007	0.925 [0.875,0.978]	† 0.006

† p-value<0.05

Table 9 Logistic regression model for CRRT apply with proportion of MBP 65-75mmHg

Variable	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age	1.008 [0.957,1.061]	0.771		
BMI	1.112 [0.890,1.390]	0.352		
APACHE II	1.091 [0.956,1.245]	0.196	1.100 [0.983,1.232]	0.098
SOFA	1.010 [0.794,1.285]	0.933		
Baseline GFR	1.005 [0.993,1.017]	0.454		
Hb at septic shock	1.150 [0.822,1.609]	0.415		
Lactate at septic shock	1.190 [0.988,1.434]	0.067	1.151 [0.978,1.356]	0.090
Volume loading during first 3hrs (cc/kg)	0.961 [0.907,1.018]	0.175		
CVI	0.948 [0.686,1.310]	0.747		
Proportion of MBP 80-95mmHg	1.097 [1.040,1.157]	†0.001	1.081 [1.034,1.131]	†0.001

† p-value<0.05

Table 10 Logistic regression model for in-hospital mortality with proportion of MBP 65-75mmHg

Variable	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age	1.009 [0.960,1.059]	0.729		
BMI	0.879 [0.727,1.064]	0.186		
APACHE II	1.099 [0.998,1.211]	0.056	1.091 [0.997,1.194]	0.059
SOFA	1.167 [0.967,1.409]	0.108	1.148 [0.971,1.358]	0.107
Baseline GFR	1.002 [0.991,1.012]	0.736		
Hb at septic shock	0.838 [0.636,1.103]	0.208		
Lactate at septic shock	1.126 [0.937,1.354]	0.207		
Volume loading during first 3hrs (cc/kg)	1.032 [0.984,1.083]	0.193		
CVI	0.703 [0.498,0.994]	0.046	0.772 [0.579,1.030]	0.079
Proportion of MBP 65-75mmHg	1.046 [1.008,1.086]	†0.019	1.042 [1.006,1.079]	†0.021

† p-value<0.05

Table 11 Baseline characteristics of the top 15 percentile and the bottom 15 percentile of the proportion of MBP 65-75mmHg

Variable	Below 15th percentile (n=13)	More than 85th percentile (n=13)	*p* value
Age (years)	60.92±3.99	59.85±4.22	0.626
Male sex, n (%)	7 (53.8%)	9 (69.2%)	0.420
BMI (kg/m2)	21.33±0.92	22.20±1.13	0.561
APACHE II score	32.15±1.69	31.69±1.84	0.855
SOFA score	15.62±1.03	15.62±0.64	0.393
SAPS II score	81.54±4.25	78.15±3.37	0.539
Baseline eGFR	99.69±21.84	89.23±12.28	0.680
Hb at septic shock	10.59±0.55	10.77±0.91	0.870
Lactate at septic shock	4.35±0.91	3.92±0.68	0.959
Volume loading during first 3hrs (cc/kg)	22.42±4.12	27.00±5.74	0.521
Maximal urine output during 24hrs after septic shock	220.00±38.78	184.46±63.03	0.166
CVI	4.00±0.20	4.92±0.50	0.140
Ratio of time of checking BP to total follow up duration after septic shock	0.958±0.027	0.986±0.014	0.168

BMI body mass index, APACHE acute physiology and chronic health evaluation score, SOFA sequential organ failure assessment score, SAPS simplified acute physiology score, CVI cumulative vasopressor index

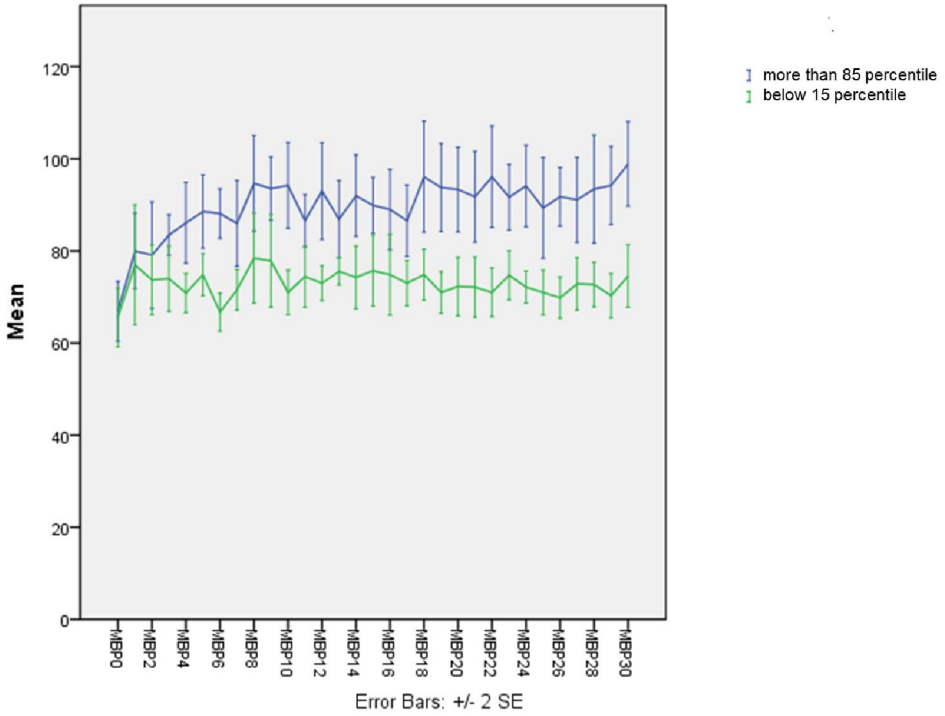

Figure 8 MBP during 30hrs of the below 15 percentile and more than 85 percentile of proportion of MBP 65-75mmHg

Table 12 Average MBP after septic shock of the top 15 percentile and the bottom 15 percentile of the proportion of MBP 65-75mmHg

Variable	Below 15th percentile	More than 85th percentile	*p* value
Average MBP during 24hrs	89.15±1.667	72.85±0.659	†<0.001
Average MBP during 30hrs	89.62±1.893	72.85±0.619	†<0.001
Average MBP during 48hrs	89.85±1.990	73.23±0.611	†<0.001

† p-value<0.05

Table 13 Proportion of MBP during 30hours after septic shock of the top 15 percentile and the bottom 15 percentile of the proportion of MBP 65-75mmHg

Variable	Below 15th percentile	More than 85th percentile	*p* value
Proportion of MBP below 65mmHg	4.82±0.80	11.71±1.96	†0.010
Proportion of MBP 65-75mmHg	5.20±0.60	56.54±2.71	†<0.001
Proportion of MBP 75-85mmHg	32.55±4.62	28.22±2.99	†0.438
Proportion of MBP 85-95mmHg	34.01±3.95	7.86±1.58	†<0.001

† p-value<0.05

Table 14 Mortality and arrhythmia events of the top 15 percentile and the bottom 15 percentile of the proportion of MBP 65-75mmHg

Variable	Below 15th percentile	More than 85th percentile	Odds ratio (95% CI)	*p* value
ICU mortality (%)	7.7%	53.8%	14.000 [1.385,141.485]	†0.030
Hospital mortality (%)	38.5%	76.9%	5.333 [0.987,29.393]	†0.047
CRRT (%)	0%	69.2%		†<0.001
Arrhythmia events	50%	50%	1.000 [0.161,6.200]	1.000

† p-value<0.05

Appendix

Appendix 1 Cumulative vasopressor index (CVI)

Vasopressor	Dose range 1 point	Dose range 2 points	Dose range 3 points	Dose range 4points
Dopamine (mcg/kg/min)	0<dose≤5	5<dose≤10	10<dose≤15	>15
Epinephrine (mcg/kg/min)	-	0<dose≤0.05	0.05<dose≤0.1	>0.1
Norepinephrine (mcg/kg/min)	-	0<dose≤0.05	0.05<dose≤0.1	>0.1
Phenylephrine (mcg/kg/min)	-	0<dose≤0.4	0.4<dose≤0.8	>0.8
Vasopressin (units/min)	-	-	-	Any dose

Appendix 2 Odds ratio of CRRT apply according to the proportion of MBP ranging from 65-69 mmHg to 92-96 mmHg at 5 mmHg interval in MBP range

MBP range (mmHg)	Odds ratio	*p*-value	MBP range (mmHg)	Odds ratio	*p*-value
65-69	1.1	0.006	79-83	0.985	0.704
66-70	1.099	0.003	80-84	0.991	0.798
67-71	1.074	0.006	81-85	0.988	0.723
68-72	1.076	0.006	82-86	0.983	0.664
69-73	1.077	0.009	83-87	0.958	0.336
70-74	1.103	0.002	84-88	0.893	0.019
71-75	1.11	0.006	85-89	0.892	0.011
72-76	1.059	0.037	86-90	0.876	0.005
73-77	1.033	0.302	87-91	0.863	0.002
74-78	1.027	0.411	88-92	0.908	0.032
75-79	0.969	0.358	89-93	0.9	0.021
76-80	0.944	0.139	90-94	0.913	0.059
77-81	0.914	0.037	91-95	0.923	0.092
78-82	0.925	0.07	92-96	0.951	0.298

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8. 국문초록

만성 고혈압이 있는 환자들에서 패혈성 쇼크가 발생하였을 때 80-85mmHg를 목표 평균혈압으로 잡았을 때가 기존 가이드라인의 65-70mmHg를 목표 평균혈압으로 잡았을 때보다 지속적 신대체요법의 필요를 줄일 수 있다는 보고가 있다. 이에 금번 연구에서 패혈성 쇼크시에 지속적 신대체요법을 필요로 했던 군과 그렇지 않았던 군의 초기 48시간 동안의 평균혈압을 비교함으로써 패혈성 쇼크에서 초기 높은 평균혈압의 목표 설정이 지속적 신대체요법의 위험도를 감소시킬 수 있는지에 대한 근거를 확인하고자 연구를 진행하였다.

패혈성 쇼크 이후 5일 이내에 지속적 신대체요법을 시행한 환자를 "CRRT group", 시행하지 않은 환자를 "no CRRT group"으로 정의하였다. 서울대학교병원에 2016년 1월부터 2017년 12월까지 중환자실에 입실한 1276명을 대상으로 스크리닝을 진행하였고 85명의 환자가 금번 연구의 대상자가 되었다. 이 중 19명(22.4%)가 CRRT group에 속했다. 나이 (64.4±1.6 vs 65.4±2.9, p=0.77), 남성의 비율 (66.7% vs 57.9%, p=0.59), Sequential Organ Failure Assessment (SOFA) score (15.0±0.4 vs 15.6±0.8, p=0.46) 등에는 차이가 없었다. CRRT group에서 지속적 신대체요법은 패혈성 쇼크 후 평균 30.8±3.6 시간 후에 진행되었고 이 때문에 30시간 이후에는 CRRT group의 연구대상자수가 급격히 줄어들어 이에 패혈성 쇼크 후 초기 30시간동안의 데이터로 분석을 진행하였다.

패혈성 쇼크 후 초기 30시간 동안의 평균혈압의 분포는 CRRT group과 no CRRT group에서 유의미한 차이가 있었다. 전체 측정된 평균혈압 중 평균혈압이 65-75mmHg 범위에 있는 비율은 CRRT group에서 유의미하게 높았으며 이 범위의 비율이 높을수록 지속적 신대체요법의 위험도가 유의미하게 증가하였다 (OR 1.081; CI 1.034-1.131). 평균혈압이 75-85mmHg 범위에 있는 비율은 두 군 사이에 차이가 없었다. 평균혈압이 85-95mmHg 범위에 있는 비율은 no CRRT group에서 유의미하게 높았으며 이 범위의 비율이 높을수록 지속적 신대체요법의 위험도는 감소하였다 (OR 0.925; CI 0.875-0.978). 중환자실 사망률 (OR 20.00; CI 5.03-79.54)과 병원내 사망률 (47.7% vs 100.0%, $p<0.001$) 은 CRRT group이 유의미하게 높았다. 두 군 사이에 부정맥의 발생이나 승압제 요구량의 차이는 유의미하지 않았다. 총 중환자실 사망률은 33.7% 였고 총 병원내 사망률은 59%였다.

따라서 패혈성 쇼크시 초기 30시간 동안 목표 평균혈압을 85mmHg 이상으로 설정할 경우 지속적 신대체요법의 위험도 및 중환자실 사망률, 병원내 사망률의 감소 효과를 기대해볼 수 있을 것으로 생각된다.

주요어 : 패혈성 쇼크, 평균혈압, 지속적 신대체요법

학 번 : 2017-27157