Comparison of Two Titration Methods of Vasopressor Infusion to Correct Septic Shock

Kyoung Chul Cha

The Graduate School
Yonsei University
Department of Medicine

Comparison of Two Titration Methods of Vasopressor Infusion to Correct Septic Shock

A Master's Thesis
Submitted to the Department of Medicine
and the Graduate School of Yonsei University
in partial fulfillment of the
requirements for the degree of
Master of Medical Science

Kyoung Chul Cha

January 2005

This certifies that the master's thesis of Kyoung Chul Cha is approved

Thesis Supervisor: Sung Oh Hwang M.D.

Kang Hyun Lee M.D.

Kyu Sang Park M.D., Ph.D.

The Graduate School

Yonsei University

January 2005

Acknowledgement

여러 해 동안 논문을 지도해 주시고 연구자의 자세를 가르쳐 주신 황성오 교수님께 감사드리며, 논문이 나오기까지 교정 및 심사를 하시느라 고생하신 이강현 교수님, 박규상 교수님께도 고마움을 금할 길이 없습니다.

김현 선생님, 이서영 선생님, 김경진 선생님, 김호중 선생님, 그리고 응급의학과 의국원들 모두 제가 일하고 연구하는데 마음의 양식을 주셨던 고마운 분들입니다. 더불어 논문을 마무리하는데 바쁜 시간을 내어 도와준 김윤권 선생님에게도 감사의 뜻을 전합니다.

늘 한결같은 마음으로 저에게 힘을 북돋아준 아내와 부모님께 이 논문을 바칩니다.

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Abstract

Comparison of Two Titration Methods of Vasopressor Infusion to Correct Septic Shock

Kyoung Chul Cha

Department of Medicine

The Graduate School

Yonsei University

Background: Administration of a vasopressor is frequently required in treating septic shock. The conventional method of vasopressor infusion, which includes incremental titration of a vasopressor to raise blood pressure, is sometimes a time-consuming process that might prolong the duration of the shock.

Purpose: This study was to evaluate whether a method of vasopressor infusion that starts from an acceptable maximal dose has advantages over a method of vasopressor infusion that starts from a low dose in patients with septic shock.

Subjects and Methods: Thirty-one patients with septic shock, which was not corrected with fluid resuscitation of 20-30 ㎖/kg, were randomized into two groups. The patients in the low-to-high group (n=18) received a vasopressor in an incremental manner starting from a low dose. The patients in the high-to-low group (n=13) received a vasopressor in a decremental manner starting from an acceptable maximal dose.

The shock durations (time from the beginning of vasopressor infusion to correction of the shock), the length of ICU stay, and the hemodynamic and metabolic parameters, including blood pressure, pulse rate, arterial lactate concentration, anion gap, base excess, and central venous oxygen saturation, before vasopressor infusion, and 2, 4, 6, 12, and 24 hours after vasopressor infusion were compared for the two groups. The length of ICU stay, the length of total hospital stay, the type of discharge, and the survival rate were also compared.

Results: The shock duration was shorter in the high-to-low group than in the low-to-high group (14.7±21 min vs 41.9±41 min, p=0.01). There was no difference between the two groups as to hemodynamic and metabolic parameters. The amount of dopamine infused to reverse the shock tended to be higher in the low-to-high group than the high-to-low group (31.4±37 vs 52.1±92 mg). However, the difference was not significant (p=0.39). The ICU stay was shorter in the high-to-low group than in the low-to-high group (7±7 days vs 10±22 days); however, the difference did not reach statistical significance (p=0.934).

Conclusion: The method of vasopressor infusion starting from acceptable maximal dose shortens the duration of shock compared to the conventional incremental titration method.

Key Words: Hemodynamic, Sepsis, Septic shock, Vasopressor therapy

I. Introduction

Severe sepsis is one of the most significant challenges in critical care. Each year, more than 750,000 people in the U.S. will develop severe sepsis, and more than 215,000 will die from septic shock.1) Septic shock has a high mortality rate, up to 45 precent.2) Vasodilation induced by release of various vasoactive cytokines into the bloodstream is a major contributing factor in septic shock, and the main causes of death include cardiovascular compromises, such as heart failure, circulatory failure, and multiple organ failure.3) Maintenance of tissue oxygenation and perfusion is the mainstay in preventing death from septic shock. An early therapeutic goal of septic shock is to shorten the shock duration and to restore the tissue perfusion by using fluid resuscitation and vasopressor therapy.4,5)

With conventional vasopressor infusion, a vasopressor is started at a low dose and titrated to an appropriate dosage to maintain adequate blood pressure. Another, more potent vasopressor is infused if the blood pressure cannot be maintained at the maximal pharmacological dose of a vasopressor. Consequently, substantial time is required to determine the infusion rate of the vasopressor for adequate vasopressor response. Even a small time delay might be a serious deleterious prognostic factor during septic shock. On the other hand, if a vasopressor is infused from an acceptable maximal dose, it might shorten the time necessary to maintain adequate perfusion pressure and, consequently, reduce the duration of septic shock. Although a relatively high dose of vasopressor might precipitate adverse side effects, such as cardiac arrythmias or myocardial ischemia, a method of vasopressor infusion starting from an acceptable maximal dose has never been tried to correct septic shock.

This study was to evaluate whether a method of vasopressor infusion that starts from an acceptable maximal dose has advantages over a method of

vasopressor infusion that starts from a low dose in patients with septic shock. the primary end point was the duration of septic shock, and the secondary end point was the survival rate.

II. Subjects and methods

1. Subjects

Thirty-one patients with septic shock who presented at the Emergency Department of Wonju Christian Hospital were enrolled. The study period was the year from May 2003 through March 2004. The criteria for inclusion were fulfillment of at least two of the criteria for systemic inflammatory response syndrome, a systolic blood pressure no higher than 90 mmHg after a crystalloid fluid resuscitation of 20 to 30 ml per kilogram of body weight, and a blood lactate concentration of 2 mmol per liter or more. The criteria for exclusion from the study were an age of less than 18 years, septic shock associated with trauma, concomitant cardiogenic shock after acute coronary syndrome, and uncured cancer as an associate illness.

2. Methods

1) Randomization of the patients and vasopressor infusion methods

The patients were randomly assigned either to the high-to-low group or to the low-to-high group. The patients in the high-to-low group received dopamine starting from 50 ㎍/kg/min, which was tapered off by 5 ㎍/kg/min every 5 min till the systolic blood pressure was maintained around 100 mmHg. If shock was not corrected by dopamine up to 50 ㎍/kg/min, norepinephrine was additionally applied. Patients received norepinephrine starting from 50 ㎍/min, which was tapered off by 5 ㎍/min every 5 min till the systolic blood pressure was maintained around 100 mmHg at which time the dopamine was

rapidly tapered off. The patients in the low-to-high group received dopamine starting from 20 μg/kg/min which was increased by 5 μg/kg/min every 5 min till the systolic blood pressure was maintained around 100 mmHg. If shock was not corrected by dopamine up to 50 μg/kg/min, norepinephrine was additionally applied. Patients received norepinephrine starting from 20 μg/min which was increased by 5 μg/min every 5 min till the systolic blood pressure was maintained around 100 mmHg, at which time the dopamine was rapidly tapered off (table 1).

Table 1. Comparison of the two methods of vasopressor infusion

	Low-to-high	High-to-low
Dopamine	Start the dopamine from 20μg/kg/min and increment it by 5 μg/kg/min. every 5 min till SBP is maintained around 100 mmHg.	Start the dopamine from 50 μg/kg/min and decrement it by 5μg/kg/min every 5 min till SBP is maintained around 100 mmHg.
Norepinephrine[a]	Start the norepinephrine from 20 μg/min. and increment it by 5 μg/min. every 5 min till SBP is maintained around 100 mmHg.	Start the norepinephrine from 50 μg/min. and decrement it by 5 μg/min every 5 min till SBP is maintained around 100 mmHg.

[a] If shock was not corrected by dopamine up to 50 μg/kg/min., norepinephrine was applied and dopamine was tapered off.

2) Measurements and hemodynamic monitoring

We measured the multiple organ dysfunction score (MODS)[6], the simplified acute physiology score (SAPS) II[7], and the shock index (systolic blood pressure/heart rate) of all patients for severity and as a prognostic factor. For central venous pressure monitoring and blood sampling, a central venous catheterization (central venous catheter, 14 G, Arrow® International, USA) was performed through the right internal jugular vein or the right subclavian vein by using the Seldinger method[8] and for continuous blood pressure monitoring (Solar® 8000 Modular patient monitor, GE Medical System, USA), an arterial cannulation were performed through the radial artery or the femoral artery.

The shock duration was defined as the length of time from the beginning of vasopressor infusion to the correction of the shock. The total amount of dopamine and norepinephrine infused during resuscitation were measured.

Also, the blood pressure, heart rate, white-blood-cell count, arterial blood pH, arterial lactate concentration, base excess, anion gap, and central venous

oxygen saturation before vasopressor infusion, and 2, 4, 6, 12, and 24 hours after vasopressor infusion were measured. The length of ICU stay, the total hospital stay, and in-hospital mortality was investigated.

3. Statistical analysis

The differences in the hemodynamic parameters, the shock duration, the amount of vasopressor infusion, the length of ICU stay, the length of total hospital stay, MODS, SAPS II, and the shock index between the two groups were tested by using the Student's t-test. The type of discharge was tested by using the χ^2-test. A conditional logistic regression was done to investigate factors influencing survival. Statistical significance was determined at the 95% confidence level.

III. Results

1. Demographic data for the patients

Thirty one patients with septic shock were enrolled during the study period. Thirteen patients were assigned to the high-to-low group, and eighteen patients to the low-to-high group. The mean age and the sex ratio for the two groups were not statistically different. The major cause of septic shock was pneumonia, followed by urinary tract infection and empyema in the order. The MODS, SAPS II, and shock index, which reflect disease severity, were similar between the two groups (table 2).

Table 2. Demographic data for the patients

	High-to-low group (N=13)	Low-to-high group (N=18)	*p*
Age (years old)	64±18	67±7	0.574
Sex			0.44
Male	9	10	
Female	4	8	
Diagnosis (%)			
Pneumonia	7(55)	10(55)	
Urinary tract infection	3(23)	4(22)	
Empyema		2(11)	
Lung abscess	1(14)		
Scrub typhus	1(14)		
Tuberculosis peritonitis		1(6)	
Submandibular abscess	1(14)		
SBP [a]		1(6)	
MODS [b]	6±2	7±3	0.360
SAPS II [c]	44±18	47±15	0.576
Shock index	1.6±0.4	1.5±0.4	0.559

[a] SBP: spontaneous bacterial peritonitis, [b] MODS: multiple organ dysfunction score, [c] SAPS II: a new simplified acute physiology score

2. Shock duration and amount of vasopressor infused during shock resuscitation

The shock duration was shorter in the high-to-low group than the low-to-high group (16.3±21 vs 40.3±36 minutes, p=0.028)(Figure 1).

The amount of dopamine infused to reverse the shock tended to be higher in the low-to-high group than in the high-to-low group (31.4±37 vs 52.1±92 mg). However, the difference did not reach statistical significance (p=0.39). The total amount of dopamine infused during the first 24 hours was 841±557 mg in the high-to-low group, and 653±426 mg in the low-to-high group, but that difference was not statistically different (p=0.32). Two cases from each group received norepinephrine because shock was not corrected with a maximal dose of dopamine. The amount of norepinephrine infused to reverse the shock was 0.2±0.5 mg in the high-to-low group and 0.4±1.5 mg in the low-to-high group (p=0.636). The total amount of norepinephrine infused during first 24 hours was 8.2±13 mg in the high-to-low group, and 17.4±31 mg in the low-to-high group, but that difference was not statistically different (p=0.277).

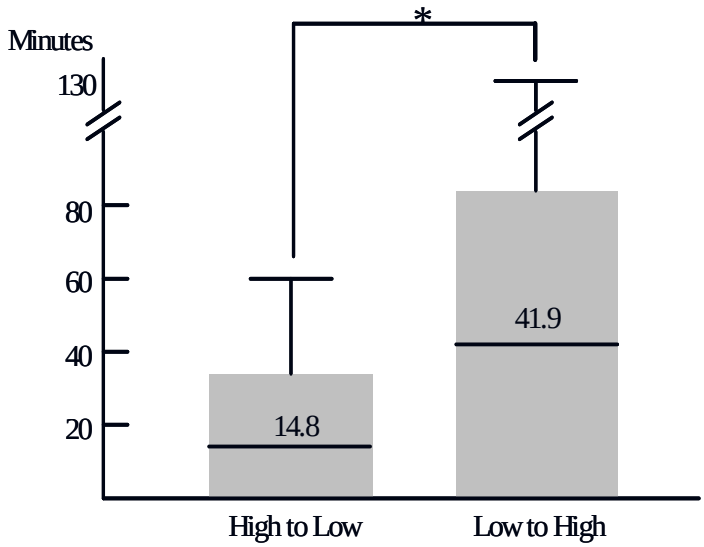

Fig. 1. Shock duration. Time from vasopressor infusion to correction of shock was shorter in the high-to-low group than in the low-to-high group (*p=0.011).

3. Comparison of hemodynamic and oxygenation profiles

There was no significant difference in the hemodynamic parameters between the two groups. The oxygenation profiles and the acid-base balance, including pH, arterial lactate, anionic gap, and systemic venous saturation, were not different between the two groups (Table 3).

Table 3. Comparison of hemodynamic and metabolic parameters between two groups

Time (hours)	Group	SBP [a] (mmHg)	DBP [b] (mmHg)	MAP [c] (mmHg)	Heart rate (Beats/min.)	pH	Lactate (mmol/L)	BE [d] (mmol/L)	AG [e] (mmol/L)	SvO_2 [f] (%)
Initial	HTL [g]	79±31	50±46	60±8	122±29	7.39±0.1	7.4±5	−7.3±5	23.4±6	60±22
	LTH [h]	73±7	46±8	55±7	105±27	7.27±0.2	6.4±4	−9.0±6	20.4±6	65±22
2	HTL	111±22	60±13	77±15	129±22	7.30±0.1	6.8±4	−9.7±8	21.9±7	61±22
	LTH	104±28	59±8	75±9	120±26	7.28±0.1	5.0±3	−7.6±9	18.0±7	68±22
4	HTL	113±20	59±13	77±14	129±22	7.32±0.1	6.3±5	−7.4±5	23.1±9	72±12
	LTH	112±21	59±11	76±12	110±18	7.32±0.1	5.4±4	−6.2±7	17.9±5	62±19
6	HTL	119±25	63±16	82±16	126±22	7.34±0.1	6.5±5	−6.1±4	20.7±4	67±10
	LTH	109±17	63±13	78±12	119±24	7.30±0.1	5.3±3	−7.1±8	18.5±5	72±15
12	HTL	119±20	67±8	84±12	112±25	7.34±0.1	5.0±3	−5.6±4	18.0±5	68±24
	LTH	104±15	60±7	74±8	111±25	7.31±0.1	4.1±1	−6.2±8	17.5±4	71±13
24	HTL	116±30	65±14	82±18	115±24	7.37±0.1	3.1±2	−5.4±5	19.7±7	78±18
	LTH	108±18	61±11	78±15	108±32	7.30±0.1	4.7±2	−5.7±8	18.3±7	80±15

[a] SBP: systolic blood pressure; [b] DBP: diastolic blood pressure; [c] MAP: mean arterial pressure, [d] BE: base excess; [e] AG : anion gap; [f] SvO_2: central venous oxygen saturation; [g] HTL: High-to-low; [h] H: Low-to-high

4. Adverse cardiovascular events

Seven patients of the high-to-low group and eight patients of the low-to-high group had sinus tachycardia before vasopressor infusion. Sinus tachycardia developed after vasopressor infusion in one of six patients that had no sinus tachycardia in the high-to-low group and in two of the ten patients in the low-to-high group that had no sinus tachycardia (p=0.345).

There was no difference in the incidence of adverse cardiovascular events between the two groups. Transient ventricular bigeminy was found in one patient of the high-to-low group. Supraventricular tachycardias developed in two patients of the low-to-high group. Atrial fibrillation developed in one patient of each group. There was no significant electrocardiographic change suggesting myocardial ischemia. No episode of severe hypertension was found during vasopressor infusion.

5. Length of ICU and hospital stay, and prognosis

The lengths of ICU stay and hospital stay were not different between the two groups (ICU stay, 8±7 days in the high-to-low group vs 9±19 days in the low-to-high group, p=0.834; hospital stay, 15±15 days in the high-to-low group vs 14±19 days in the low-to-high group, p=0.958). Seven patients (69%) of the high-to-low group and six patients (33%) of the low-to-high group were discharged alive. The high-to-low group tended to have a higher survival rate, but the difference did not reach statistical significance (p=0.053).

IV. Discussion

Our study suggests that in patients with septic shock uncorrectable with fluid infusion vasopressor infusion starting from an acceptable maximal dose (high-to-low vasopressor infusion) might shorten the shock duration compared to conventional incremental infusion. Early reversal of shock is critical to prevent multiple organ system failure from hypoxic tissue injury. A small delay in shock reversal might translate into severe injuries to various vital organs, resulting in multiple organ-system failure and death. Also, a high-to-low vasopressor infusion might reduce the mortality from septic shock by shortening the shock duration without increasing adverse effects.

In a clinical setting, physicians frequently meet difficult situations in which a low dose of a vasopressor cannot reverse septic shock and a higher dose of a vasopressor is required to maintain perfusion pressure. It is recommended that the initial dose of dopamine to correct the shock be 10 μg/kg/min and that of norepinephrine be 0.5-1.0 μg/min.[9] However, there has been no clinical report regarding an effective starting dose for dopamine and norepinephrine in septic shock. It can be supposed that the conventional incremental method has been used to minimize the side effects associated with high dose vasopressors. However, there have been no reports on the kinds or degrees of side effects related to the initial dose or the total amount of the vasopressor. As expected, in this study, a higher starting dose of the vasopressor was able to raise the blood pressure within a shorter period of infusion without any increase in side effects.

Freidman et al.[10] reported that arterial lactate concentration and the gastric mucosal pCO_2 could be used as prognostic factors in severe sepsis. Bernadin et al.[11] reported that the mean arterial pressure and the arterial lactate concentration were prognostic factors for short-term survival during the first

24 hours in septic shock. The severity of lactic acidosis in critically ill patients correlated with the overall oxygen debt and survival. So, lactate determinations may be useful as an ongoing monitor of perfusion as resuscitation proceeds.[12] Prolongation of shock duration results in an increased lactate concentration. Hence, rapid restoration of adequate perfusion pressure will ameliorate tissue hypoxia and resolve lactic acidosis. The high-to-low vasopressor infusion method might be superior to the low-to-high method in terms of reducing the duration of septic shock. Recently, several studies reported that norepinephrine was a better vasopressor than dopamine in septic shock treatment.[13-15] Most physician, however, choose dopamine as the first vasopressor in septic shock. When the conventional infusion method is applied, there will be an inevitable time delay in switching from dopamine to norepinephrine because dopamine will be titrated incrementally before the maximal dose of dopamine proves not to be effective in that patient. When the high-to-low dose method is applied, norepinephrine will be immediately introduced after dopamine if the initial acceptable dose of dopamine is not effective.

Rivers et al.[16] reported that early goal directed therapy could reduce the in-hospital mortality and improve the hemodynamic parameters, including mean central venous oxygen saturation, arterial lactate concentration, base excess, and pH, during the interval from 7 to 72 hours. The high-to-low vasopressor infusion method will facilitate achievement of the early goal in treating septic shock, which might lead to early correction of tissue hypoxia and contribute to reducing mortality.

A high dose of dopamine or norepinephrine is sometimes associated with adverse effects, including cardiac arrhythmia, gangrene in the extremities, tachycardia, visceral vessel contraction, and cardiac ischemia, due to increased tissue oxygen demand.[17,18] In this study, a few non-life-threatening

arrhythmias developed during vasopressor infusion. However, the high-to-low vasopressor infusion method did not increase the risk of adverse cardiovascular effect. There were no cases of cardiac ischemia, gangrene in the extremities, or hypertension requiring treatment.

In this study, no significant differences were observed in the hemodynamic parameters, the arterial lactate concentration, the acid-base balance, and the central venous oxygen saturation between the two groups. These findings contain several implications. Even though the arterial pressure returned to normal more rapidly in the high-to-low group, a normalization of perfusion pressure did not always mean complete relief of tissue hypoxia. Intense vasoconstriction of the peripheral arteries might lead to continuous production of lactate. In addition, high-to-low vasopressor infusion does not induce any hemodynamic deterioration that might be caused by a transient high plasma concentration of catecholamines during high dose infusion.

The survival rate tended to be higher in the high-to-low group than in the low-to-high group, even though statistical significance was not proven. This finding suggests that the infusion method of a vasopressor might affect the prognosis for patients with septic shock. Further study with a large population of septic shock patients is required to validate the survival benefit of the high-to-low infusion method over the low-to-high method.

This study has several limitations. First, we could not measure the details of hemodynamic status, such as vascular resistances, pulmonary capillary wedge pressures, or ventricular stroke works. We had little time to perform pulmonary artery catheterization to get more precise hemodynamic parameters. Furthermore, patients with septic shock are not always required to undergo pulmonary artery catheterization. To avoid hypovolemia, we infused 20~30㎖/kg of crystalloid fluid as an initial resuscitation measure and maintained a central venous pressure of higher than 15 cmH_2O with additional infusions of the

crystalloid fluid. Second, we defined the shock duration as the length of time from the beginning of vasopressor infusion to restoration of blood pressure. Recovery of normal blood pressure from hypotension does not always mean actual correction of shock because tissue hypoxia may persist. The easiest way to assess the immediate effect of a vasopressor during emergency care is to observe the arterial blood pressure. Also, in clinical settings, it is very difficult to repeat measurements of the oxygenation indices to determine the response to the vasopressor. The third limitation is the relatively small number of patients. A large, multicenter, randomized controlled trial is needed to validate the efficacy of the high-to-low vasopressor infusion method.

V. Conclusion

A method of vasopressor infusion starting from an acceptable maximal dose shortens the duration of shock compared to a conventional incremental titration method.

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Abstract in Korean

패혈성 쇼크 환자에서 혈압상승제 투여 방법에 따른 혈역학적 효과 비교

연세대학교 대학원

의학과

차경철

배경 및 목적 : 중증의 쇼크 환자에서 쇼크로부터의 빠른 소생은 쇼크에 의한 합병증의 발생을 감소시킬 수 있을 것이다. 패혈성 쇼크를 치료하는 과정에서 혈압상승제의 투여 방법은 쇼크의 기간과 혈압상승제에 대한 인체의 반응에 영향을 줄 수 있다. 이 연구의 목적은 패혈성 쇼크 환자에게 혈압상승제를 투여하는 방법으로써 혈압상승제를 저용량으로부터 증량하는 방법(저-고용량법)과 혈압상승제를 최대 투여허용량으로부터 줄여나가는 방법(고-저용량법)의 혈역학적 효과를 비교하는 것이다.

대상 및 방법 : 패혈성 쇼크(수축기 혈압 90 mmHg이하, 동맥혈 lactate> 2 mmol/L, SIRS 점수>2)로 응급센터에 내원한 비외상 성인(18세 이상) 환자로서 초기 쇼크 치료를 위하여 20-30 ml/kg의 정질액(crystalloid solution)을 투여한 후에도 쇼크가 교정되지 않는 31예를 무작위로 저-고용량법 또는 고-저용량법으로 치료하였다. 심근경색 등 심근 수축력 감소에 의한 쇼크, 출혈, 탈수에 의한 쇼크, 말기 암 등의 비가역성 질환이 있는 경우는 대상에서 제외하였다. 혈압상승제는 도파민(dopamine)을 먼저 투여한 후, 10분 이상 50 μg/kg/min.의 도파민 투여로도 수축기 혈압을 100 mmHg이상 유지할 수 없는 경우에 노르에피네프린

(norepinephrine)을 투여하였다. 저-고용량법 군에서 도파민은 20 μg/kg/min로 투여를 시작하여 수축기 혈압이 100 mmHg이상에 도달할 때까지 5분 간격으로 5 μg/kg/min씩 증가시켜 가면서 투여하였고, 노르에피네프린은 5 μg/min로 투여를 시작하여 수축기 혈압이 100 mmHg이상에 도달할 때까지 5분 간격으로 5 μg/min씩 증가시켜 가면서 투여하였다. 고-저용량법 군에서 도파민은 50 μg/kg/min로 투여를 시작하여 수축기 혈압이 100 mmHg이상에 도달하면 5 μg/kg/min씩 줄여나가면서 투여하였고, 노르에피네프린은 50 μg/min로 투여를 시작하여 수축기 혈압이 100 mmHg이상에 도달하면 5 μg/min씩 줄여나가면서 투여하였다. 두 군간 쇼크 시간(분), 중심정맥혈 산소포화도(%), 동맥혈의 pH, blood lactate, base deficit, anionic gap, MODS score, SAPS II, 투여된 혈압상승제의 양, 합병증, 병실 입원 기간, 중환자실 입원 기간, 사망률을 비교하였다.

결과 : 연구대상에 포함된 31예(평균 연령: 65±13세, 남자 19예) 중 저-고용량법 군이 18예, 고-저용량법 군이 13예였다. 두 군간에 성별, 연령 및 수액 투여량, MODS score, SAPS II score, shock index, 합병증의 차이는 없었다. 쇼크 시간은 고-저용량법 군이 14.7±21분으로 저-고용량법 군의 41.9±41분보다 짧았다(p=0.01). 쇼크 교정을 위해 투여된 도파민의 용량은 고-저용량법 군이 31.4±37 mg으로서 저-고용량법 군의 52±92 mg보다 적었으나 유의한 차이는 없었다(p=0.395). 중환자실 입원 기간은 고-저용량법 군과 저-고용량법 군이 각각 7±7 일, 10±22일로 고-저용량법 군에서 짧았지만, 유의한 차이는 없었다(p=0.834).

결론 : 패혈성 쇼크 환자에서 혈압상승제를 최대 투여허용량으로부터 줄여나가는 방법이 저용량으로부터 증량하는 방법보다 쇼크 기간을 단축시킨다.

Key words: Hemodynamic, Sepsis, Septic shock, Vasopressor therapy