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Original Research Article

Effect of phentolamine adjuvant therapy on hemodynamics and cardiac function in patients with septic myocardial injury

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Abstract

Purpose: *To investigate the effect of phentolamine adjuvant therapy on hemodynamics and cardiac function in patients with sepsis-induced myocardial injury.*
Methods: *A total of 96 patients with sepsis-induced myocardial injury between January 2019 and October 2023 admitted in Hangzhou Fuchun Traditional Chinese Orthopedic Hospital, Hangzhou, Zhejiang, China were randomly and equally assigned to control and study groups. The control group received routine treatment while the study group received phentolamine 5 mg/h for 24 h in addition to routine treatment. Blood lactate levels before and after treatment were compared. Intrathoracic blood volume index (ITBVI), systemic vascular resistance index (SVRI), heart rate (HR), mean arterial pressure (MAP), cardiac troponin I (cTnI) and N-terminal pro-brain natriuretic peptide (NT-proBNP), as well as cardiac index (CI), left ventricular ejection fraction (LVEF), left ventricular end-systolic diameter (LVESD), and left ventricular end-diastolic diameter (LVEDD), were also evaluated before and after treatment. Furthermore, 28-day survival rates and intensive care unit (ICU) stay time were compared.*
Results: *The study group showed significantly lower blood lactate levels at 12, 48, and 72 h after treatment compared to control group ($p < 0.05$). The study group showed significantly higher levels of MAP, ITBVI, SVRI, CI, and LVEF; and significantly lower levels of HR, LVESD, LVEDD, cTnI, and NT-proBNP after 7 days than the control group ($p < 0.05$). No deaths occurred within 7 days after treatment in either group. However, the study group exhibited significantly lower ICU stay time and 28-day mortality than the control group ($p < 0.05$).*
Conclusions: *Phentolamine adjuvant therapy significantly improves hemodynamics, enhances cardiac function, mitigates myocardial injury, and restores blood lactate levels in patients with sepsis-induced myocardial injury. Longer follow-up would be necessary to evaluate long-term effect and potential complications of phentolamine-adjuvant therapy.*

Keywords: *Phentolamine, Sepsis, Myocardial injury, Hemodynamics, Cardiac function*

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INTRODUCTION

Sepsis is a severe, life-threatening condition resulting from a dysregulated host response to infection, leading to tissue damage and dysfunction in multiple organs, including the heart, lungs, kidneys, and liver [1]. In 2017, the global incidence of new sepsis cases reached 48.9 million, with 11 million sepsis-related deaths accounting for 19.7 % of global deaths [1,2]. Myocardial injury is a complication of sepsis, and

statistics show that over 40 % of patients with sepsis worldwide present symptoms of myocardial injury. Without timely and effective treatment, it may progress to heart failure, with a significant risk to life [3].

Phentolamine is a non-selective alpha (α)-adrenergic receptor blocker which dilate blood vessels, improve microcirculation, increase renal blood flow, and have diuretic and detoxifying effects [4]. In addition, it reduces cardiac load, relieves bronchospasm, alleviates vascular resistance, lowers pulmonary artery pressure, and prevents heart failure by effectively improving patient lung ventilation and reducing blood vessel resistance [5].

Sepsis-induced myocardial injury is a significant factor contributing to high mortality rate in septic patients. Myocardial dysfunction associated with sepsis is attributed to several mechanisms, including inflammatory responses, oxidative stress, and microcirculatory dysfunction [1]. Ability of phentolamine to counteract these mechanisms makes it a promising therapeutic agent. Phentolamine improves hemodynamics by dilating blood vessels and reducing systemic vascular resistance, which enhance cardiac output and reduce heart workload. This is particularly important in septic patients, where myocardial depression and hemodynamic instability are common [1]. Furthermore, vasodilatory effect of phentolamine improves microcirculation, thus enhancing tissue perfusion and oxygen delivery, which is fundamental in preventing multi-organ failure in sepsis [3]. Therefore, this study investigated the effect of phentolamine adjuvant therapy on hemodynamics and cardiac function in patients with sepsis-induced myocardial injury.

METHODS

General patient information

A total of 96 patients with sepsis-induced myocardial injury admitted to Hangzhou Fuchun Traditional Chinese Orthopedic Hospital, Hangzhou, Zhejiang, China from January 2019 to October 2023 were randomly and equally assigned to control and study groups using a random number table [1]. Control group received routine treatment, while study group received phentolamine in addition to routine treatment. Control group was comprised of 28 males and 20 females, with an age range of 45 - 75 years, mean of 61.48 ± 2.29 years, average body mass index (BMI) of 21.56 ± 2.14 kg/m^2, 22 cases of pulmonary infection, 8 cases of abdominal infection, 7 cases of urinary tract infection, and 1 case of skin infection classified into mild sepsis (15 cases), moderate to severe sepsis (20 cases), and septic shock (13 cases). The study group comprised 27 males and 21 females, with an age range of 45 - 75 years, mean of 61.39 ± 2.31 years, average BMI of 21.61 ± 2.18 kg/m^2, 23 cases of pulmonary infection, 7 cases of abdominal infection, 6 cases of urinary tract infection, and 2 cases of skin infection classified into mild sepsis (14 cases), moderate to severe sepsis (22 cases), and septic shock (6 cases) [6].

Ethical approval

This study was approved by the Hospital's Ethics Committee of Hangzhou Fuchun Traditional Chinese Orthopedic Hospital (approval no. HZ00230512) and conducted in accordance with the guidelines of Declaration of Helsinki [6]. Informed consent was obtained from patients and their families.

Inclusion criteria

Patients who met the diagnostic criteria for sepsis in consensus [7] and guidelines [8], met the diagnostic criteria for myocardial injury in the 2019 White Paper on the assessment and treatment of type 2 myocardial infarction and acute non-ischemic myocardial injury [9], had not used antibiotics, hormones, or the study drugs before enrollment, time interval from onset of septic shock to admission, and then intensive care unit did not exceed 24 h, and patients with complete clinical data.

Exclusion criteria

Patients with a history of surgery within the past 2 years, presence of severe coagulation dysfunction, severe liver, kidney or other vital organs dysfunction, allergy or intolerance to study drugs, and poor compliance.

Treatments

Control group received conventional treatment (anti-infection, maintenance of electrolyte balance, correction of acid-base balance, blood pressure elevation, fluid resuscitation, and low-dose 200 mg/day glucocorticoids (Tianjin Biochem Pharmaceutical Co. Ltd; National Medical Products Administration no. H20065068) [10]. Intravenous infusion of 4 g cefoperazone sulbactam (Zhejiang Conba Pharmaceutical Co. Ltd; National Medical Products Administration no. H20043010) was administered every 12 h, with dosage adjustments based on the specific condition of the patient. Study group received phentolamine hydrochloride (Zhangjiakou

Shengda Pharmaceutical Co. Ltd, Zhangjiakou, China; National Medical Products Administration no. H20020359) dissolved in 20 mL of 0.9 % sodium chloride solution at a concentration of 10 mg/mL and continuously infused through peripheral intravenous access for 24 h in addition to conventional treatment. Treatment duration was 15 days.

Evaluation of parameters/indices

Blood lactate

Peripheral venous blood (3 mL) was collected from the patients before treatment, 12, 48, and 72 h after treatment. The samples were centrifuged at 3000 rpm for 10 min at a radius of 10 cm, and the supernatant was collected and stored at -70 °C. Blood lactate level was measured using an automated biochemical analyzer (Shanghai Elite Biotech Co., Ltd., Shanghai, China).

Hemodynamic indices

Heart rate (HR), mean arterial pressure (MAP), intrathoracic blood volume index (ITBVI), and systemic vascular resistance index (SVRI) were measured in triplicate before and 7 days after treatment using an electrocardiographic monitor (Jiangsu Dawei Medical Equipment Co. Ltd) [4].

Myocardial injury

Peripheral venous blood (3 mL) was aseptically collected, centrifuged and the supernatant was stored at -70 °C. Serum levels of cardiac troponin I (cTnI) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were measured using an automated chemiluminescent immunoassay analyzer (China Thermo Fisher Scientific Co. Ltd, Shanghai, China) on admission day and 7 days after treatment.

Cardiac function

Cardiac function index (CI), left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD) were measured in triplicate before and 7 days after treatment using a color Doppler ultrasound diagnostic instrument (Jiangsu Dawei Medical Equipment Co. Ltd, Xuzhou, China) [2].

Prognosis

A follow-up was conducted at 28 days after treatment to determine the 28-day survival rate and duration of stay in the intensive care unit (ICU).

Statistical analysis

Data was analyzed using Statistic Package for Social Science (SPSS) 22.0 version 22.0 software (IBM, Armonk, NY, USA). Measurement data were presented as mean ± standard deviation (SD) and compared using Students' t-tests. $P < 0.05$ was considered statistically significant.

RESULTS

Blood lactate

Study group showed significantly lower blood lactate levels at 12, 48 and 72 h after treatments compared to control group (Table 1).

Hemodynamic indices

Study group showed significantly higher levels of MAP, ITBVI, and SVRI and lower HR compared to control group ($p < 0.05$; Table 2).

Cardiac function indices

Study group showed significantly higher levels of CI and LVEF after 7 days of treatment compared to control group ($p < 0.05$). Furthermore, study group showed significantly lower LVESD and LVEDD compared to control group ($p < 0.05$; Table 3).

Myocardial injury indices

Study group showed significantly lower levels of cTnI and NT-proBNP compared to control group ($p < 0.05$; Table 4).

Table 1: Levels of blood lactate in patients (mean ± SD; n = 48)

Group	Blood lactic acid (mmol/L)			
	Before treatment	***12 h***	***48 h***	***72 h***
Control	6.61±0.45	5.88±0.39*	2.89±0.57*	1.53±0.22*
Study	6.63±0.48	4.14±0.35*	1.56±0.41*	0.74± 0.11*

*$P < 0.05$ vs before treatment values

Table 2: Hemodynamic indices (mean ± SD; n = 48)

Group	ITBVI (mL/m^2)		SVRI (dyn·s·cm^{-5}·m^2)		HR (time/min)		MAP (mmHg)	
	Before treatment	***7 days after treatment***	***Before treatment***	***7 days after treatment***	***Before treatment***	***7 days after treatment***	***Before treatment***	***7 days after treatment***
Control	755.46±12.35	853.84±13.76	1580.36±101.24	1857.61±100.45	96.75±4.59	92.13±3.92	63.05±4.12	86.08±3.31
Study	755.92±12.31	926.69±14.01*	1596.19±101.37	2193.28±100.48*	96.83±4.62	85.37±3.96*	63.11±4.23	88.92±3.07*
T-value	0.183	25.702	0.766	16.368	0.12	8.405	0.07	4.358
P-value	0.855	<0.05	0.446	<0.05	0.905	<0.05	0.944	<0.05

Note: **P* < 0.05 vs control group

Table 3: Cardiac function indices (mean ± SD, n = 48)

Group	LVEF (%)		LVEDD (mm)		LVESD (mm)		CI (L/(min·m^2)	
	Before treatment	***7 days after treatment***	***Before treatment***	***7 days after treatment***	***Before treatment***	***7 days after treatment***	***Before treatment***	***7 days after treatment***
Control	43.24±4.38	53.87±5.04	61.69±3.12	49.25±3.29	48.06±2.94	38.07±2.61	2.54±0.12	3.07±0.25
Study	43.19±4.32	57.36±5.08*	61.73±3.18	43.74±3.26*	48.09±2.87	33.54±2.56*	2.58±0.13	3.36±0.29*
T-value	0.056	3.379	0.062	8.242	0.051	8.585	1.566	5.247
P-value	0.955	0.001	0.951	<0.05	0.96	<0.05	0.121	<0.05

Note: **P* < 0.05 vs control group

Table 4: Myocardial injury indices (mean ± SD; n = 48)

Group	cTnI (ng/L)		NT-proBNP (ng/L)	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***
Control	4.61±0.85	2.86±0.45	2337.01±505.43	1028.16±255.05
Study	4.63±0.69	1.12±0.47*	2346.98±545.37	622.24±104.98*
T-value	0.127	18.527	0.093	10.196
P-value	0.9	<0.05	0.926	<0.05

Note: **P* < 0.05 vs control group

Prognosis

There was no death within the first 7 days of treatment in both groups. However, study group showed significantly lower ICU admission time and 28-day mortality rate compared to control group ($p < 0.05$; Table 5).

Table 5: ICU admission time and 28-day mortality rate (mean ± SD; n = 48)

Group	ICU Admission time (days)	28-Day mortality rate (%)
Control	13.01±4.06	17(35.42%)
Study	9.81±3.52	10(20.83%)
P-value	< 0.05	< 0.05

DISCUSSION

Sepsis has become a major cause of death in critically ill patients with gram-negative bacteria as main pathogens, followed by fungi and viruses [10]. Sepsis-induced myocardial injury damages the myocardium during the development, and the mortality rate of patients with sepsis increases significantly after developing myocardial injury. Currently, specific mechanism of sepsis-induced myocardial injury is not fully understood but studies have found that sepsis-induced myocardial injury is closely related to metabolism, hemodynamics, and other aspects of cellular injury [11,12]. For patients with sepsis, intensive anti-infection therapy is the key to treatment. Although cefoperazone/sulbactam has a strong antibacterial effect, the efficacy is limited when used alone and may not effectively inhibits the high mortality rate [13].

Phentolamine dilates blood vessels, reduces peripheral vascular resistance, reduces cardiac load, increases cardiac output, and enhances myocardial contractile function [13-15]. Results of this study showed that study group showed significantly lower levels of blood lactate at 12, 48, and 72 h after treatment compared to control group. This suggests that phentolamine adjuvant therapy improves blood lactate levels and hypoxia in patients with sepsis-induced myocardial injury. This may be because such patients experience microcirculation disorders, leading to poor capillary perfusion and elevated blood lactate levels, which further triggers a hypoxic state [16].

Phentolamine effectively relieves peripheral vascular spasm, improves visceral blood perfusion and microcirculation, helps dilate micro-vessels, improves supply of blood and oxygen to the body, reduces anaerobic respiration of cells, and decreases blood lactate levels. Results of this study showed that study group exhibited significantly higher MAP, ITBVI, SVRI, CI, and LVEF; and lower HR, LVESD, LVEDD, cTnI, and NT-proBNP levels compared to control group. This suggests that phentolamine-adjuvant therapy improves hemodynamics, enhances cardiac function, and reverses myocardial injury in patients with sepsis-induced myocardial injury [17]. This is likely because, with routine treatment, patients have already received basic treatments such as anti-infectives and maintenance of normal metabolism.

Hemodynamic indices such as SVRI is usually used to measure the size of peripheral resistance, ITBVI is used to assess cardiac preload, MAP accurately reflects status of the heart and blood vessels, and HR is used to detect heart abnormalities such as myocardial ischemia and arrhythmia. Furthermore, cardiac function indices such as CI, LVESD, LVEDD, and LVEF are used to evaluate the pumping function of the left ventricle; cTnI and NT-proBNP are indices of myocardial injury, with cTnI being a myocardium-specific structural protein involved in myocardial contraction. When the concentration of calcium ions in the cytoplasm of myocardial cells reaches a certain level, cTnI dissociates from myosin, causing myocardial contraction [17-19]. When cTnI levels abnormally increase, it indicates impaired myocardial contractile function. Also, NT-proBNP is a fragment of the precursor of brain natriuretic peptide secreted by ventricular cells, and brain natriuretic peptide promotes sodium excretion, diuresis, and vasodilation. When NT-proBNP levels abnormally increase, it indicates the possibility of heart failure or cardiovascular disease [20-22].

Phentolamine alleviates inflammatory damage caused by infection and accelerates the clearance of oxygen free radicals, thus preventing excessive free radicals from causing damage to the myocardium. Also, it enhances myocardial contractility to improve microcirculation perfusion, increases cardiac output, and promotes cardiac function recovery. Results of this study showed that there were no deaths in both groups within the first 7 days of treatment. The ICU admission time and 28-day mortality rate of study group was significantly lower compared to control group. This suggests a good prognosis for phentolamine-adjuvant therapy.

Limitations of this study

This study involved a relatively small sample size

of 96 patients, which may limit generalizability of the findings. Larger-scale studies are needed to confirm these results. Also, this study was conducted at a single hospital, which may introduce bias related to local practices and patient population characteristics. Multi-center studies would help to validate the findings across different settings. Furthermore, the follow-up period was limited to 28 days.

CONCLUSION

Phentolamine-adjuvant therapy improves hemodynamics, enhances cardiac function, reverses myocardial injury, restores blood lactate levels, and promotes recovery in patients with sepsis-induced myocardial injury. Longer follow-up would be necessary to evaluate long-term effects and potential complications of phentolamine-adjuvant therapy.

DECLARATIONS

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Ethical approval

This study was approved by the Hospital's Ethics Committee of Hangzhou Fuchun Traditional Chinese Orthopedic Hospital (approval no. HZ00230512).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

REFERENCES

1. *Song Q, Liu Y, Tian Y. Theacrine alleviates inflammation and lung injury in septic mice by mediating SIRT3. Trop J Pharm Res 2023; 22(11): 2259-2264 doi: 10.4314/tjpr.v22i11.3*
2. *Rello J, Valenzuela-Sanchez F, Ruiz-Rodriguez M, Moyano S. Sepsis: A review of advances in management. Adv Ther 2017; 34(11): 2393-2411.*
3. *Purcarea A, Sovaila S. Sepsis, a 2020 review for the internist. Rom J Intern Med 2020; 58(3): 129-137.*
4. *Napolitano LM. Sepsis 2018: Definitions and guideline changes. Surg Infect 2018; 19(2): 117-125.*
5. *Hunt A. Sepsis: an overview of the signs, symptoms, diagnosis, treatment and pathophysiology. Emerg Nurse 2019; 27(5): 32-41.*
6. *World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310: 2191-2194.*
7. *Evans T. Diagnosis and management of sepsis. Clin Med 2018; 18(2): 146-149.*
8. *Prescott HC, Ostermann M. What is new and different in the 2021 surviving sepsis campaign guidelines. Med Klin-Intensiv Med 2023; 118(2): 75-79.*
9. *Guirgis F, Black LP, DeVos EL. Updates and controversies in the early management of sepsis and septic shock. Emerg Med Pract 2018; 20(10): 1-28.*
10. *Zhou Z, Yin Q. Aromadendrin protects mouse liver from sepsis-induced injury by inhibiting NF-κB signaling pathway. Trop J Pharm Res 2022; 21(6): 1237-1242 doi: 10.4314/tjpr.v21i6.15*
11. *Fleischmann-Struzek C, Rudd K. Challenges of assessing the burden of sepsis. Med Klin-Intensiv Med 2023; 118(2): 68-74.*
12. *Carter BL, Underwood J. Sepsis and the brain: a review for acute and general physicians. Clin Med 2022; 22(5): 392-395.*
13. *Van Der Poll T, Van De Veerdonk FL, Scicluna BP, Netea MG. The immunopathology of sepsis and potential therapeutic targets. Nat Rev Immunol 2017; 17(7): 407-420.*
14. *Liu D, Huang SY, Sun JH, Zhang HC, Cai QL, Gao C, Li L, Cao J, Xu F, Zhou Y, et al. Sepsis-induced immunosuppression: mechanisms, diagnosis and current treatment options. Military Med Res 2022; 9(1): 56.*
15. *Vincent JL. Current sepsis therapeutics. Ebiomedicine 2022; 86: 104318.*

16. Haak BW, Wiersinga WJ. The role of the gut microbiota in sepsis. Lancet Gastroenterol 2017; 2(2): 135-143.
17. Wu Q, Xiao Z, Pu Y, Zhou J, Wang D, Huang Z, Hou D. TnI and IL-18 levels are associated with prognosis of sepsis. Postgrad Med J 2019; 95(1123): 240-244.
18. Abumayyaleh M, Nunez-Gil IJ, El-Battrawy I, Estrada V, Becerra-Munoz VM, Uribarri A, Fernandez-Rozas I, Feltes G, Arroyo-Espliguero R, Trabattoni D, et al. Sepsis of patients infected by SARS-CoV-2: Real-world experience from the international HOPE-COVID-19-registry and validation of hope sepsis score. Front Med-Lausanne 2021; 8: 728102.
19. Su Y, Yin X, Huang X, Guo Q, Ma M, Guo L. Astragaloside IV ameliorates sepsis-induced myocardial dysfunction by regulating NOX4/JNK/BAX pathway. Life Sci 2022; 310: 121123.
20. Prescott HC, Angus DC. Enhancing recovery from sepsis: A Review. JAMA-J Am Med Assoc 2018; 319(1): 62-75.
21. Yu J, Zheng R, Yang P, Wang D. Construction of a predictive model and prognosis of left ventricular systolic dysfunction in patients with sepsis based on the diagnosis using left ventricular global longitudinal strain. J Intensive Care 2022; 10(1): 29.
22. Wang L, Dai W, Zhu R, Long T, Zhang Z, Song Z, Mu S, Wang S, Wang H, Lei J, et al. Testosterone and soluble ST2 as mortality predictive biomarkers in male patients with sepsis-induced cardiomyopathy. Front Med-Lausanne 2023; 10: 1278879.