Effects and safety of different anisodamine doses on EVLW at early stage of septic shock patients

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Objective: To investigate the effects and safety of different anisodamine doses on EVLW at early stage of septic shock patients. Method: A total of 63 patients with septic shock were enrolled in ICU, and they were randomly divided into control group (C group, 20 cases), normal anisodamine doses group (N group, 25 cases, anisodamine 20–40 mg/d), high anisodamine doses group (H group, 18 cases, anisodamine 80 mg/d). To observe the dynamic changes of temperature (T), heart rate (HR), oxygenation index (OI), cardiac index (CI), intrathoracic blood volume index (ITBVI), and extravascular lung water index (EVLWI). Results: 12 h after treatment, compared with C and N group, CI and ITBVI significantly increased in H group, EVLWI significantly decreased in H group. Meanwhile, T and HR significantly increased in H group, oxygenation index significantly decreased in H group. Some patients are unable to tolerate anisodamine treatment which leads to cessation of experiment. Compared with C group, EVLWI, CI, ITBVI, oxygenation index significantly improved in N group (P<0.05), mortality rates significantly decreased (P<0.05). Conclusions: Normal anisodamine doses would significantly decreased EVLWI and significantly improved outcomes, high anisodamine dose is not recommended on EVLWI in patients with septic shock.

1. Introduction

Septic shock is major causes of mortality in intensive care unit (ICU) patients, mortality ranging from 25% to 65%. Despite Surviving Sepsis Campaign has made a great effort to decrease mortality for sepsis and septic shock which management significantly advances, treatment of septic shock is still a major global challenge for clinicians that has no better interventions to decrease mortality[1-6]. Anisodamine is an active component that was first isolated from a traditional medicinal herb in 1960s. Some animal and clinical studies have confirmed the potential role of anisodamine to improve outcomes in septic shock. In different kinds of shock models, anisodamine significantly alleviated the progress of shock and increased the survival rate of the animals than that of other commonly used vasoactive drugs, such as norepinephrine, phenoxymethylamine, dopamine, and aramine. The therapeutic effects include the inhibition of thromboxane synthesis, granulocyte and platelet aggregation and anti-vascular paralysis[7,8]. Although this drug is widely used in clinical practice in China, there is little clinical evidence from well-designed clinical trial that demonstrates its effectiveness in patients with septic shock. The aim of the study is to investigate the effects and safety of different anisodamine doses on extravascular lung water (EVLW) at early stage of septic shock patients.

2. Materials and Methods

2.1. General information

A total of 63 patients with septic shock were enrolled in ICU of our hospital which included 36 male cases and 27 female cases, their mean age was (46.8±22.5) years. The causes included 23 cases with intraperitoneal infection, 27 cases with pulmonary infection, 5 cases with acute pancreatitis and 8 cases with acute trauma.
Inclusion criteria met septic shock diagnostic criteria in Surviving Sepsis Campaign International Guidelines for Management of Sepsis and Septic Shock 2012. Exclusion criteria were pregnancy, contraindication of femoral arterial conduct, age of <18 years, done not obtained consent of familiarity or patients for procedure and end of MODS.

2.2. Methods

The patients accepted early septic shock bundle treatment and randomly divided into control group (C group, 20 cases, no anisodamine), normal anisodamine doses group (N group, 25 cases, anisodamine 20–40 mg/d), high anisodamine doses group (H group, 18 casesanisodamine 80 mg/d). To observe the dynamic changes of temperature (T), heart rate (HR), oxygenation index (OI), cardiac index (CI), intrathoracic blood volume index (ITBVI), and extravascular lung water index (EVLWI).

2.3. Monitoring goals

To observe the APACHE II (acute physiology and chronic Health evaluation scoring system APACHE II) score, inflammation parameters, lactic Acid, oxygenation index, the volume of fluid resuscitation. Pulse indicator continuous cardiac output (PICCO) technique was utilized for measuring Cardiac index, EVLWI, ITBVI, SVRI before placed arterial conduct 0 h and after which 3, 6, 9, 12, 24, 48, 72, 96 and 120 h.

2.4. Statistical analysis

Data were analyzed using SPSS version 19.0. Variables were presented as mean ± standard deviation. Comparisons were made using student \( t \) test, and chi square tests. \( P < 0.05 \) was considered as statistically significant.

3. Results

12 h after treatment, compared with C and N group, CI and ITBVI significantly increased in H group, EVLWI significantly decreased in H group. Meanwhile, T and HR significantly increased in H group, oxygenation index significantly decreased in H group. Some patients were unable to tolerate anisodamine treatment which leads to cessation of experiment. Compared with C group, EVLWI, CI, ITBVI, oxygenation index significantly improved in N group (\( P < 0.05 \)), mortality rates in C group was 29.6% and which in N group was 22.3% that significantly decreased (\( P < 0.05 \)). See Table 1.

4. Discussion

EVLW is the amount of water that is contained in the lungs outside the pulmonary vasculature. It corresponds to the sum of interstitial, intracellular, alveolar and lymphatic fluid, not including pleural effusions. Intracellular and lymphatic fluid might be ignored because...
of that has no significantly changes usually. EVLW majorly includes interstitial and alveolar fluid which correlated with pulmonary edema. EVLW accumulates abnormally in a substantial fraction of severe sepsis patients without recognized respiratory complications. These subtle abnormalities of pulmonary function may represent subclinical lung injury. EVLW has prognostic implications for patients with severe sepsis and ARDS, and correlates with the severity of lung injury. EVLW or EVLWI is an independent predictor of mortality in patients with septic shock. Repeated measurements of EVLW or EVLWI over time, rather than a too-early measurement, seem to be more appropriate for predicting outcome.

Anisodamine is a muscarinic antagonist with pharmacological effects similar to atropine. It was first isolated from a traditional medicinal herb *Scopolia tangerica* Maxim in 1960s, been known as 654-2 also. Some animal studies have confirmed the role of anisodamine in improving microcirculation in septic shock, and other potential therapeutic effects include the inhibition of thromboxane synthesis, granulocyte and platelet aggregation and anti-vascular paralysis

In this study, 12 h after high anisodamine doses treatment, compared with C and N group, CI and ITBVI significantly increased in H group, EVLWI significantly decreased in H group, which indicated that anisodamine would significantly improve hemodynamics. Meanwhile, T and HR significantly increased in H group, oxygenation index significantly decreased in H group. Some patients were unable to tolerate anisodamine treatment because of its side effect which leads to cessation of experiment. Anisodamine is a muscarinic antagonist, thus high anisodamine doses might induced muscarinic antagonism such as increasing HR, T and urinary retention, even atropinization. Although high anisodamine doses would better decreased EVLW and improved hemodynamics, meanwhile, because of its increasing side effect leads to cessation of experiment. Compared with C group, PaO2/FiO2, CI, ITBVI, and EVLWI significantly improved in N group (*P* < 0.05) mortality rates in C group was 29.6% and which in N group was 22.3% that significantly decreased (*P* < 0.05). Normal anisodamine doses avoiding its side effect, decreasing leakage of EVLW, improving mortality rates of 28 d.

Increased EVLW in Septic shock occurs based on uncontrollable inflammatory response induced by inflammatory mediators in early and advanced stages, which leads to microvascular damage and, subsequently, to increase pulmonary vascular and epithelial permeability, the greater the outward fluid filtration from microvessels. Possible mechanisms for the anti-shock action of anisodamine were increased fluidity of cell membrane and deformability of erythrocyte, improved microcirculation perfusion, inhibited cathepsin and lysosomes, which through activated the cholinergic anti-inflammatory pathway that involvement of the α7 nicotinic acetylcholine receptors (nAChR)

Anisodamine decrease EVLWI in septic shock patients and improve hemodynamics that maybe concerned with the mechanism.

Collectively, anisodamine would significantly decreased EVLWI in septic shock patients and improved hemodynamics, decreased mortality rates and improved outcomes, high anisodamine doses would significantly decrease EVLWI in septic shock patients and improved hemodynamics also, but which not recommended on EVLWI in patients with septic shock because of its side effect.

References


