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Resuscitative effect of centhaquin after hemorrhagic shock in rats

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ABSTRACT

Background: Centhaquin is a cardiovascular active agent that significantly reduced blood lactate levels and enhanced resuscitative effect of hypertonic saline. The present study was carried out to determine the resuscitative effect of centhaquin and compare that with large-volume lactated Ringer (LR) solution in hemorrhaged rats.

Materials and methods: Male, adult Sprague–Dawley rats were anesthetized with urethane, and a pressure catheter SPR-320 was placed in the left femoral artery; another pressure–volume catheter SPR-869 was placed into the left ventricle through carotid artery. Hemorrhage was induced by withdrawing blood from the right femoral artery, and the mean arterial pressure (MAP) was maintained at 35 mm Hg for 30 minutes after which resuscitation was performed using LR solution (LR-100) (100% shed blood volume), centhaquin (0.017, 0.05, and 0.15 mg/kg) dissolved in LR (100% shed blood volume), or LR-300 (300% shed blood volume). Arterial blood gases and cardiovascular parameters were determined before the induction of hemorrhage and at various times after hemorrhage.

Results: It was found that survival time after resuscitation with LR-100 was 78 ± 10 min. Centhaquin in doses of 0.017 and 0.05 mg/kg significantly improved survival time to 291 ± 57 and 387 ± 39 min, respectively. Blood lactate levels (millimoles per liter) increased from 7.22 ± 0.67 at hemorrhage to 10.20 ± 0.61 at 60 min after resuscitation with LR-100. On the other hand, blood lactate levels significantly decreased to 3.55 ± 0.07 and 4.08 ± 0.28 at 60 min after resuscitation with 0.017 and 0.05 mg/kg doses of centhaquin, respectively. Centhaquin in these doses produced a 55% and 59% increase in MAP, respectively, compared with a 29% decrease by LR-100. A decrease in systemic vascular resistance of 57% and 41% was observed with 0.017 and 0.05 mg/kg doses of centhaquin, respectively, compared with a 6% decrease by LR-100. LR-100 decreased cardiac output (CO) by 28%, whereas 0.017 and 0.05 mg/kg doses of centhaquin increased it by 260% and 180%, respectively. LR-300 commonly used for resuscitation was found to increase MAP and CO. Compared with LR-300, centhaquin (0.05 mg/kg) significantly improved survival time, increased CO, and was effective in resuscitation of hemorrhaged rats.

Conclusions: Centhaquin was found to be more effective than LR-300 as an effective resuscitative agent for the treatment of hemorrhagic shock in rat.

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1. Introduction

Shock because of severe hemorrhage accounts for a large proportion of posttraumatic deaths, particularly during early stages of injury [1]. Most of the deaths because of hemorrhage occur in the first 6 h after trauma [2], and many of these deaths can be prevented [3]. Shock is accompanied by circulatory failure, which is mainly responsible for mortality and morbidity. The current recommended fluid therapy of using large volumes of lactated Ringer (LR) solution is effective in restoring hemodynamic parameters but presents logistic and physiological limitations [4]. Resuscitation with large volume of crystalloids has been associated with secondary abdominal compartment syndrome, pulmonary edema, cardiac dysfunction, and paralytic ileus [5]. Hence, there is a need for a small-volume resuscitative solution. Our aim was to develop a resuscitative agent that can improve the survival time and can be used for resuscitation in hypovolemic shock.

Centhaquin (Fig. 1) is a cardiovascular active agent. It was found to produce positive inotropic effect and increase ventricular contractions of isolated perfused rabbit heart [6]. Centhaquin did not affect spontaneous contractions of the guinea pig right auricle but significantly potentiated positive inotropic effect of norepinephrine [7]. Direct or indirect positive inotropic effect of centhaquin may lead to an increase in cardiac output (CO). Centhaquin produced a decrease in mean arterial pressure (MAP) and heart rate (HR) in anesthetized rats and conscious freely moving cat and rat [8] because of its central sympatholytic activity [8–10]. When administered locally into the dog femoral artery, centhaquin (10 and 20 μg) increased blood flow, which was similar to that observed with acetylcholine and papaverine. However, the vasodilator effect of centhaquin could not be blocked by atropine or dibenamine [7]. Direct vasodilator or central sympatholytic effect of centhaquin is likely to decrease systemic vascular resistance (SVR), which combined with an increase in CO may improve regional blood circulation after hemorrhagic shock.

In a previous study, we found that centhaquin enhanced resuscitative effect of hypertonic saline [11]. It significantly decreased blood lactate levels and increased MAP, stroke volume, and CO compared with hypertonic saline. It is thought that cardiovascular actions of hypertonic saline and centhaquin are mediated through the ventrolateral medulla in the brain [10,12], and centhaquin may be augmenting the effect of hypertonic saline. To determine the effect of centhaquin by itself, in the present study, we used LR solution, which does not have any centrally mediated cardiovascular effects. Large volume of LR is the most commonly used fluid therapy [13]; therefore, we compared the resuscitative effect of centhaquin with LR administered three times the volume of blood loss.

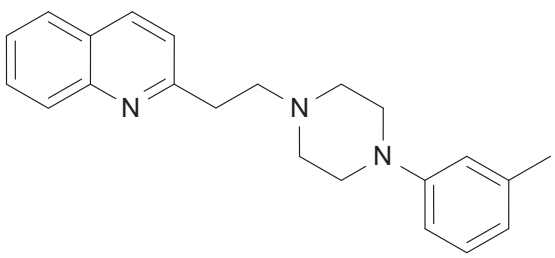

Fig. 1 – Structure of centhaquin (2-[2-(4-(3-methyphenyl)-1-piperazinyl) ethyl]-quinoline).

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (340–380 g) (Harlan, Indianapolis, IN) were housed for at least 4 d before being used in a room with controlled temperature (23 ± 1°C), humidity (50 ± 10%), and light (6:00 AM to 6:00 PM). Food and water were made available continuously. Animal care and use for experimental procedures were approved by the Institutional Animal Care and Use Committee. All anesthetic and surgical procedures were in compliance with the guidelines established by the Animal Care Committee.

2.2. Drugs and chemicals

Centhaquin was synthesized by Dr Shridhar Andurkar, Department of Pharmaceutical Sciences, Midwestern University, Downers Grove, IL, USA, using a procedure described earlier [9]. Urethane (ethyl carbamate) (Sigma-Aldrich, St Louis, MO), Lactated Ringer's Injection, USP (Hospira, Inc, Lake forest, IL), and Heparin Sodium Injection, USP (APP Pharmaceuticals, LLC, Schaumburg, IL) were used.

2.3. Determination of cardiovascular response

The animals were anesthetized with urethane dissolved in isotonic saline. Urethane was administered in a dose of 1.5 g/kg body weight via intraperitoneal injection. Urethane was selected as an anesthetic agent because it produces long lasting (8–10 h) anesthesia with minimal cardiovascular and respiratory system depression. It produces a level of surgical anesthesia characterized by the preservation of cardiovascular reflexes [14]. Briefly, anaesthetized rats were immobilized on a surgical board equipped with controlled heating pad. Blood P_{O_2}, P_{CO_2}, and pH were maintained using tracheotomy cannula connected to a rodent ventilator (Model 683; Harvard Apparatus Inc, Holliston, MA). The animals were ventilated with 2.5 ml of room air at the rate of 60 strokes/min. Right carotid artery was exposed to measure the left ventricular performance. Surgical suture (Deknatel, Research Triangle Park, NC) was secured around the proximal end of the carotid artery, and an ultraminiature pressure–volume (P-V) catheter SPR-869 (Millar Instruments, Houston, TX) was inserted through a tiny incision made near the proximal end of the artery. The P-V terminal of the catheter was connected to MPVS-300 P-V unit (AD Instruments, Mountain View, CA) through PEC-4D and CEC-4B cables and advanced into the left ventricle to obtain the P-V signals. The P-V loops were continuously recorded (1000/s) using MPVS-300 P-V unit and PowerLab 16/30 data acquisition system (AD Instruments). CO was determined using LabChart-7.00 and PVAN analysis program (Millar Instruments). MAP and HR were measured by