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Identification of ideal resuscitation pressure with concurrent traumatic brain injury in a rat model of hemorrhagic shock

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ABSTRACT

Background: Traumatic brain injury (TBI) is often associated with uncontrolled hemorrhagic shock (UHS), which contributes significantly to the mortality of severe trauma. Studies have demonstrated that permissive hypotension resuscitation improves the survival for uncontrolled hemorrhage. What the ideal target mean arterial pressure (MAP) is for TBI with UHS remains unclear.

Methods: With the rat model of TBI in combination with UHS, we investigated the effects of a series of target resuscitation pressures (MAP from 50–90 mm Hg) on animal survival, brain perfusion, and organ function before hemorrhage controlled.

Results: Rats in 50-, 60-, and 70-mm Hg target MAP groups had less blood loss and less fluid requirement, a better vital organ including mitochondrial function and better cerebral blood flow, and animal survival (8, 6, and 7 of 10, respectively) than 80- and 90-mm Hg groups. The 70-mm Hg group had a better cerebral blood flow and cerebral mitochondrial function than in 50- and 60-mm Hg groups. In contrast, 80- and 90-mm Hg groups resulted in an excessive hemodilution, a decreased blood flow, an increased brain water content, and more severe cerebral edema.

Conclusions: A 50-mm Hg target MAP is not suitable for the resuscitation of TBI combined with UHS. A 70 mm Hg of MAP is the ideal target resuscitation pressure for this trauma, which can keep sufficient perfusion to the brain and keep good organ function including cerebral mitochondrial function.

1. Introduction

Traumatic brain injury (TBI) is a leading cause of mortality and disability in civilians and military trauma, and it is frequently accompanied by hemorrhagic shock (HS) [1–3]. Concurrent occurrence of HS and TBI can significantly increase the mortality as compared with TBI or HS alone [4,5]. Effective fluid resuscitation can restore and maintain the systemic and

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cerebral circulation, support tissue perfusion and oxygen delivery, and reduce the long-term neurologic damage induced by hypotension and cerebral hypoxia [6].

Traditional treatment protocols for patients with TBI and HS emphasize rapid infusion of large volumes of crystalloids to restore the blood pressure (BP) and cerebral perfusion pressure (CPP) in the prehospital and hospital settings [7]. However, recent experimental and clinical studies showed that early aggressive fluid resuscitation during the period of uncontrolled HS (UHS) can cause severe hemodilution, clot dislocation, and decrease in platelet and coagulant factors, and so on [8]. Permissive hypotension has been advocated as a better resuscitation approach for UHS [9–13]. Meanwhile, recent studies emphasized that crystalloid should be minimized, and blood products such as packed red blood cell (PRBC) and fresh frozen plasma (FFP) are advocated for the damage control resuscitation of severe trauma [14,15]. However, in the presence of TBI, the potential benefits of permissive hypotension and limited fluid resuscitation must be weighed against the fatal consequences of cerebral hypoperfusion. The Brain Trauma Foundation guidelines recommend maintenance of a systolic BP of ≥90 mm Hg to attempt to maintain a CPP >70 mm Hg [7]. Our recent study showed that a target resuscitation pressure of 50–60 mm Hg is the ideal BP for single UHS [10]. Because FFP or PRBC are often difficult to get at a prehospital setting, or at spot site of disaster or accident, we want to know whether this permissive hypotension with hydroxyethyl starch (HES) and small volumes of lactated Ringer solution (LR) can ensure the sufficient cerebral perfusion and to know the ideal target resuscitation mean arterial pressure (MAP) for TBI combined with UHS.

To elucidate this issue, with the rat model of TBI combination with UHS, we investigated the effects of a series of target resuscitation MAPs (50, 60, 70, 80, and 90 mm Hg) on animal survival, the hemodynamic parameters, the cerebral blood flow (CBF), and water content of brain in the present study. The main purpose was to determine the ideal target resuscitation pressure for TBI combined with UHS and provide experimental basis for clinic application.

2. Materials and methods

2.1. Ethical approval of the study protocol

This study was approved by the ethics committee for animal research of the Research Institute of Surgery, Daping Hospital, Third Military Medical University (Chongqing, China). Animal experiments were conducted in accordance with the Laboratory Animal Use and Care Guide published by the US National Institutes of Health (NIH Publication, Eighth Edition, 2011).

2.2. Animal management

Sprague–Dawley (SD) rats (200–250 g), both male and female, obtained from the Animal Center of Daping Hospital, Third Military Medical University, were used for all experiments. On the day of the experiment, rats were first anesthetized with sodium pentobarbital, the total amount was not >50 mg/kg, intraperitoneal. No rats developed apnea. Two catheters were inserted into the right femoral artery and vein for monitoring the MAP, hemorrhage, and fluid infusion, respectively. The left ventricle of the heart was catheterized via the right carotid artery to monitor the left ventricular systolic pressure (LVSP) and maximal change rate of the left intraventricular pressure (±dp/dt max). To prevent clot formation, the rats were injected with heparin (500 U/kg) via a femoral vein catheter. The body temperature was maintained at 37°C with a heating pad.

2.3. Experimental protocol

2.3.1. Experiment phase and management

Experiments included four phases. Phase I was the model stage, in which TBI was first established by a weight-dropping method, as described previously [16]. Briefly, the rat was placed in a prone position, and the head was fixed in a stereotactic frame and underwent a craniectomy over the parietal cortex within the anatomic boundaries outlined by the sagittal, anterior, and posterior cranial sutures. Then, a 20 mg of metal cylinder dropped from 50-cm height onto a 2-mm diameter footplate resting on the dura with a controlled depth of 1.5-mm. The severity of the brain injury is moderate. After TBI, the UHS model was immediately induced by our previous method (transection of splenic parenchyma plus one branch of the splenic artery) [10–12]. When MAP decreased to 40 mm Hg, the UHS model was achieved. Phase II was the resuscitation period during the period of uncontrolled hemorrhage, in which rats were maintained at different target MAPs (50, 60, 70, 80, and 90 mm Hg) for 1 h with HES130 and LR solution at a ratio of 1:2. Phase III was the definitive resuscitation period, in which the splenic artery and vein were fully ligated, and the rats were then given the whole blood and LR solution at a ratio of 1:2 to maintain MAP >90 mm Hg for 2 h. The whole blood was acquired from the normal donor rats. Phase IV was the observation period, which lasted 2 h. The observed parameters are as follows (Fig. 1).

2.3.2. General parameters

One hundred twelve SD rats were randomized to seven groups ($n = 16$ per group) as follows: sham-operated group; no treatment group; and 50-, 60-, 70-, 80-, and 90-mm Hg target MAP groups at phase II. Rats in sham-operated group were

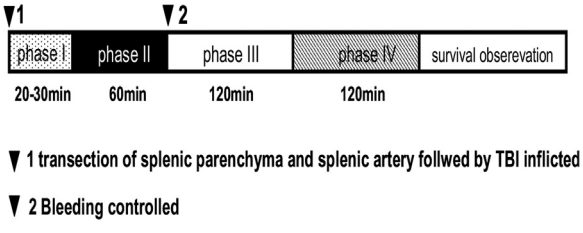

Fig. 1 – The timeline of experiment phases. Phase I: establishment of the model of TBI combined with UHS; phase II: resuscitation with HES and LR solution at a ratio of 1:2 at different target MAP (50, 60, 70, 80, and 90 mm Hg) for 1 h; phase III: definitive resuscitation to MAP at 90–100 mm Hg for 2 h with whole blood and LR solution at a ratio of 1:2; and phase IV: observation period.