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Intravenous Vitamin C attenuates hemorrhagic shock-related renal injury through the induction of SIRT1 in rats

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ABSTRACT

To investigate the effect of intravenous Vitamin C (VC) on hemorrhagic shock (HS)-associated rat renal injury and the involved mechanism. Thirty SD rats were randomly assigned to the sham surgery (sham), hemorrhagic shock (HS), HS+100 mg/kg VC (H + VL), HS+500 mg/kg VC (H + VH) and HS+100 mg/kg VC + EX527 (H + VL + E) groups. Tissue and blood samples were collected 6 h after surgery. Kidney pathological changes were scored. Creatinine (CRE), blood urea nitrogen (BUN), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β) levels in serum and Vitamin C levels and superoxide dismutase (SOD) activity and the ability to suppress hydroxyl radical (RAFHR) in plasma were measured. The expression of Sirtuin1 (SIRT1), Acetyl-NF-κB (Ace-NF-κB), heme oxygenase-1 (HO-1), TNF-α, and IL-1β in tissues was analyzed by ELISA or western-blot. In the HS group, the kidney pathological score and CRE, BUN, TNF-α, and IL-1β levels in serum were significantly higher than in the Sham group ($P < 0.05$), while SOD and RAFHR were significantly decreased in the plasma ($P < 0.05$). SOD activity and SIRT1 expression were remarkably lower in the kidney in the HS group than in the Sham group ($P < 0.05$), while MDA, TNF-α, and IL-1β concentrations and Acetyl-NF-κB andHO-1 expression in the kidney showed a noteworthy increase compared to the Sham group ($P < 0.05$). Compared to the HS group, VC treatment led to a remarkable reduction in the kidney pathological score and CRE,BUN,TNF-α, and IL-1β levels ($P < 0.05$), and a significant increase in Vitamin C, SOD, and RAFHR levels in the plasma ($P < 0.05$). Additionally, MDA, TNF-α, IL-1β and Acetyl-NF-κB expression levels were decreased in the kidney ($P < 0.05$), while SOD, SIRT1 and HO-1 levels were notably enhanced. There were no differences between the H + VL and H + VH groups aside from plasma Vitamin C levels. The effect of Vitamin C was decreased after the addition of EX527, which inhibits SIRT1. Intravenous Vitamin C might attenuate HS-related renal injury via the SIRT1 pathway, and it appears that there were no differences in the effects between the high and low doses.

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1. Introduction

Every year, trauma causes 1.5million deaths worldwide and is the primary cause of death among young people, with up to 50% of death being due to hemorrhagic shock (HS) [1,2]. Some diseases such as gastrointestinal hemorrhage, abdominal aortic aneurysm rupture and maternal hemorrhage can also result in HS [3]. Hemorrhagic shock is a form of hypovolemic shock where massive blood loss causes inadequate oxygen delivery, followed by hypoxia in tissues, which can lead to oxidative stress and inflammatory complications. HS may also induce systemic inflammatory response syndrome (SIRS) and even multi-organ dysfunction (MODS) [4,5].

The kidney is a major organ affected in HS. Acute kidney injury (AKI) induced by compensatory hypoperfusion and the following reperfusion has a high mortality rate in the clinic [6,7]. The mechanisms involved are very complex and primarily concerned with inflammatory response, oxidative stress, microcirculation dysfunction, etc. [8].

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The silent mating type information regulation 2 homolog 1 (sirtuin 1,SIRT1) is a histone deacetylase (HDACS)that catalyzes the deacetylation of histones and other non-histone lysine residues [9]. It has been shown to play an important role in aging, inflammation and metabolic regulation [10]. Studies have indicated that SIRT1 has protective effects in AKI caused by ischemia-reperfusion (I/R) injury or sepsis [11–13]. It might also be involved in the deacetylation of key proteins in the pathological process. Researchers have found that SIRT1 exerts anti-inflammatory effects through the deacetylation of NF-κb and the up-regulation of heme oxygenase 1 (HO-1) [14,15].

Vitamin C (VC), also known as ascorbic acid, is a vital water-soluble antioxidant that has been proven to relieve organ injury and inflammatory response in various I/R conditions, such as HS, sepsis and cardiac arrest. Its protective effects might be related to reduced inflammation and oxidation resistance [16,17]. Our previous studies proved that VC promoted protective effects on multi-organ injury and intestinal injury in HS via the mitigation of inflammation and the induction of HO-1 [18,19]; VC also attenuated HS-induced epithelial-dendritic cell transformation in rat intestines [20]. However, the effects of VC on SIRT1 and the relationship between SIRT1 and HO-1 in HS are unknown. Moreover, VC treatment exhibited great outcomes in patients with HS or sepsis in our clinical work, and a relevant clinical study also illustrated that intravenous VC infusion was safe and may positively impact the extent of multiple organ failure in severe sepsis [21]. However, the doses of VC used in anterior studies were different, and the relationship between the VC dose and its effects has not

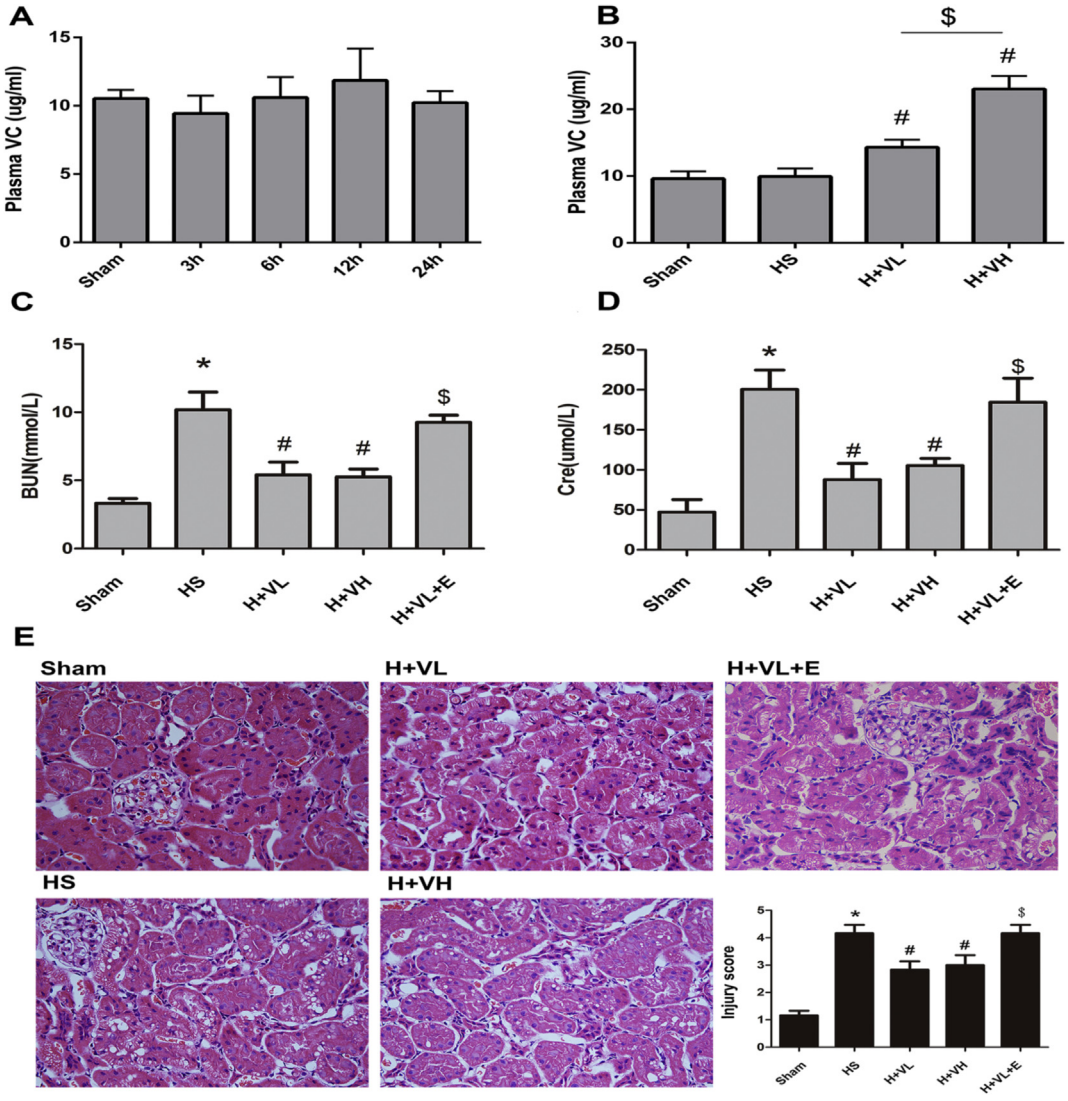

Fig. 1. Vitamin C (VC) relieved hemorrhagic shock (HS)-related histological renal injury and elevated the VC concentration in HS rat plasma.
A. Plasma VC levels at 3 h,6 h, 12 h, and 24 h after hemorrhagic shock. B. The plasma VC concentration in rats from different groups 6 h after the operation. C. BUN serum levels at 6 h after surgery. D. CRE serum levels at 6 h after surgery. E. The kidney injury score in each group. The renal samples obtained at 6 h after surgery were stained with hematoxylin and eosin. Magnification: 400X. Scale bar: 20 μm. Sham - the rats treated with normal saline (NS) and the sham surgery. HS - the rats treated with NS and the HS surgery. H + VL - the rats treated with low-dose VC(100 mg/kg) and the HS operation. H + VH - the rats treated with high-dose VC(500 mg/kg) and the HS operation. H + VL + E - the rats treated with low-dose VC (100 mg/kg), EX527 and the HS surgery. Data are the mean ± SEM. n = 6/group. *$p < 0.05$ compared to the Sham group. #$p < 0.05$ compared to the HS group. $$p < 0.05$ compared to the H + VL group.

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