

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Artesunate protects against the organ injury and dysfunction induced by severe hemorrhage and resuscitation

This is a pre print version of the following article:

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1522573> since 2015-08-07T14:25:48Z

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

P106

**ARTESUNATE PROTECTS AGAINST THE ORGAN INJURY
AND DYSFUNCTION INDUCED BY SEVERE HEMORRHAGE
AND RESUSCITATION**

R. Sordi¹, K. Nandra¹, F. Chiazza², N.S. Patel¹, M. Collino², K. Brohi¹, and C. Thiernemann*¹.

¹Queen Mary University of London, London, United Kingdom,

²University of Turin, Turin, Italy

Introduction: Hemorrhagic shock (HS) is a common cause of death in severely injured patients and is associated with impairment of organ perfusion, systemic inflammatory response and multiple organ failure. There is no specific therapy that reduces organ dysfunction in HS. Artesunate is recommended by the WHO as the drug of choice for the treatment of falciparum malaria. Artesunate is superior to quinidine in improving survival in patients with complicated malaria, and also exhibits anti-inflammatory effects. The aim of the present study was to evaluate the effects of artesunate on organ injury and dysfunction associated with HS in the rat.

Methods: Male Wistar rats were subjected to HS under sodium thiopentone anesthesia (120 mg/kg; i.p.). The mean arterial pressure (MAP) was reduced to 30 T 2 mmHg for 90 min, followed by resuscitation with the shed blood over 5 min. Rats were treated with artesunate (2.4 or 4.8 mg/kg; i.v.) or vehicle upon resuscitation. Four hours later, organ injury and dysfunction and the signaling events involved in the observed protective effects of artesunate were investigated.

Results: When compared to sham-operated rats, HS resulted in a significant decrease in creatinine clearance (from 1.36 T 0.08 to 0.09 T 0.03 mL/min) as well as rises in serum creatinine (from 32.5 T 1.6 to 108.2 T 5.5 Hmol/L), aspartate aminotransferase (from 132.8 T 22.9 to 1076 T 109 U/L), alanine aminotransferase (from 47.9 T 4.1 to 325.9 T 34.2 U/L) and lactate (from 0.7 T 0.3 to 2.9 T 0.3 mmol/L), indicating the development of renal dysfunction, liver and muscular injury and organ ischemia (pG0.05 for all parameters). HS also caused a significant increase in lung myeloperoxidase activity (lung inflammation). Western blotting of kidney and liver tissue from HS rats revealed decreases in the phosphorylation of eNOS and glycogen synthase kinase-3" (GSK-3"), and increases in phosphorylation of I.B and nuclear translocation of NF-.B p65 subunit. Treatment of HS-rats with artesunate protected animals against the organ injury and dysfunction induced by HS. Artesunate increased the activation of Akt and eNOS, inhibited the activation of GSK-3" and NF-.B activation, and attenuated the increase in serum TNF-! associated with HS.

Conclusions: Administration of artesunate on resuscitation attenuated the organ injury and dysfunction associated with HS by a mechanism that may involve activation of the AkteNOS survival pathway, and/or inhibition of GSK-3" and NF- .B (reducing inflammation). Artesunate, a well-known, safe and low cost antimalarial drug, may represent a novel approach to reduce the organ injury and dysfunction associated with HS. A single-centre placebo-controlled randomized phase II clinical trial aimed at evaluating the effects of artesunate in patients with severe hemorrhage following trauma is planned at Barts Health NHS Trust.