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Laboratory Investigation

LABORATORY INVESTIGATION

Protection of cerebral microcirculation, mitochondrial function, and electrocortical activity by small-volume resuscitation with terlipressin in a model of haemorrhagic shock

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Abstract

Background: During early treatment of haemorrhagic shock, cerebral perfusion pressure can be restored by small-volume resuscitation with vasopressors. Whether this therapy is improved with additional fluid remains unknown. We assessed the value of terlipressin and lactated Ringer's solution (LR) on the early recovery of the microcirculation, tissue oxygenation, and mitochondrial and electrophysiological function in the rat cerebral cortex.

Methods: Animals treated with LR replacing three times (3LR) the volume bled (n=26), terlipressin (n=27), terlipressin plus 1LR (n=26), 2LR (n=16), or 3LR (n=15) were compared with untreated (n=36) and sham-operated rats (n=17) rats. *In vivo* confocal microscopy was used to assess cortical capillary perfusion, changes in tissue oxygen concentration, and mitochondrial membrane potential and redox state. Electrophysiological function was assessed by cortical somatosensory evoked potentials, spinal cord dorsum potential, and peripheral electromyography.

Results: Compared with sham, haemorrhagic shock reduced the mean (standard deviation) area of perfused vessels [82% (SD 10%) *vs* 38% (12%); P<0.001] and impaired oxygen concentration, mitochondrial redox state [99% (4%) *vs* 59% (15%) of baseline; P<0.001], and somatosensory evoked potentials [97% (13%) *vs* 27% (19%) of baseline]. Administration of terlipressin plus 1LR or 2LR was able to recover these measures, but terlipressin plus 3LR or 3LR alone were not as effective. Spinal cord dorsum potential was preserved in all groups, but no therapy protected electromyographic function.

Conclusions: Resuscitation from haemorrhagic shock using terlipressin with small-volume LR was superior to high-volume LR, with regard to cerebral microcirculation, and mitochondrial and electrophysiological function.

Keywords: brain ischaemia; confocal microscopy; electrophysiology

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Editor's key points

- Haemorrhage is the cause of up to 40% of deaths after trauma.
- Early small volume resuscitation with terlipressin can restore cerebral perfusion after haemorrhagic shock.
- The effect of additional fluid is unclear.
- In an experimental haemorrhage model in rats, resuscitation with low but not high volume fluids plus terlipressin restored cerebral microcirculation and mitochondrial and electrophysiological function.
- Optimum restoration of perfusion after haemorrhage is likely to reduce morbidity and mortality.

Haemorrhage remains a major cause of early death, accounting for 30–40% of trauma mortality, with 33–56% of deaths occurring before arrival at hospital.[1] Life-threatening loss of blood volume causes circulatory collapse.[2] The consequent impairment in oxygen supply to the brain[3] may cause neurological sequelae, most notably altered mentation (including loss of consciousness), seizures, and ischaemic stroke.[2,4,5] The major mechanism is considered to be a cellular energy crisis arising from tissue hypoxia.[3,6,7] In addition to a decrease in the cerebral macrocirculation, studies using animal models of haemorrhagic shock suggest impaired microcirculation[8] and mitochondrial insufficiency.[9] As cell damage potentially starts at the onset of the haemodynamic decompensation,[6,7,10,11] blood supply to the brain must be restored rapidly. However, the optimal method for resuscitation is not established. Standard teaching is to restore adequate volaemia before commencing vasopressor agents. However, despite early fluid resuscitation to restore oxygen delivery to the tissues, cerebral perfusion pressure and oxygenation may fail to recover, especially if there is a persisting loss of vascular tone.[3,12]

Vasopressors can reduce the volume of crystalloid required to recover blood pressure after haemorrhagic shock and can rapidly recover cerebral perfusion pressure during prehospital care.[3,13] Terlipressin, a synthetic analogue of vasopressin, has been proposed for the treatment of haemorrhagic shock,[14,15] and compared with vasopressin, it is longer acting and has higher selectivity for the vasopressin V_1 receptor.[15,16] Although studies in models of haemorrhage have demonstrated that terlipressin can improve cerebral perfusion pressure and tissue oxygenation,[12,17] the efficacy in protecting brain microcirculatory, mitochondrial, and electrophysiological function is unknown. We therefore used confocal imaging to study the circulation and metabolic state of the brain during shock *in vivo*, and in real time. We postulated that small-volume resuscitation with terlipressin would be superior to more aggressive fluid replacement therapy in protecting mitochondrial and electrophysiological function, and perfused vessel density, in a rodent model of haemorrhagic shock.

Methods

Experiments adhered to the Home Office (UK) 1986 Scientific Procedures Act and European Directive 2010/63/EU and results are reported according to relevant aspects of the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines, with University College London animal Ethics Committee approval.

Rats (male, in-house, Sprague Dawley, ~150 g) were housed in groups of five in pathogen free cages with a 12 h light/dark cycle at 22°C with standard rat pellets available *ad libitum*. Rats were anaesthetised without recovery throughout the experiments using isoflurane delivered via a vaporizer (induction 5% in an induction cage, maintenance 1.5–2% via nose cone; Iso-Flo, Abbott Labs, Maidenhead, UK) while spontaneously breathing room air. Adequacy of anaesthesia was assessed by ensuring the absence of withdrawal reflex after paw and ear pinch, and by monitoring the values of heart rate, mean arterial pressure (MAP), and respiratory rate to noxious stimulation. Rectal temperature (36–37°C; underblanket, Harvard Apparatus, Cambridge, UK), direct MAP (left femoral artery connected to a pressure transducer; World Precision Instruments, Hitchin, UK), respiratory rate, and end-tidal carbon dioxide ($ETCO_2$; via orotracheal intubation, Microcap, Oridion, Needham, MA, USA) were continuously monitored. The femoral vein was cannulated for fluid and drug administration. A craniotomy ~8 mm in diameter (centred at bregma −2 mm, lateral 2.5 mm) was performed over the left somatosensory cortex and the animals either imaged using *in vivo* confocal microscopy, or assessed electrophysiologically, for the rest of the experiment.

In vivo confocal microscopy

The skull was fixed to a custom-made titanium bar using dental cement (Contemporary Ortho-Jet Powder, Lang Dental Manufacturing Co., Wheeling, IL, USA) mixed with cyanoacrylate glue. The dura was removed, and platinum(II)-5,10,15,20-tetrakis(2,3,4,5,6-pentafluorophenyl)porphyrin (PtPFPP)-based phosphorescent oxygen-sensitive microbeads (Luxcel Biosciences, Cork, Ireland) applied to the cortex. The craniotomy was then sealed with a glass coverslip and petroleum jelly. Time-lapse fluorescence images were acquired with a laser-scanning confocal microscope (512 by 512 pixels, optical slice 37.1 μm; LSM 5 Pascal, Zeiss, Jena, Germany) to assess mitochondrial redox state by imaging endogenous flavoprotein fluorescence (excitation: 488 nm; emission: 505–570 nm), and changes in local oxygen concentration (ex: 543 nm; em: 650 nm). At termination, i.v. fluorescein isothiocyanate-dextran 70 kDA (FITC-dextran; 0.5 mg i.v.; ex: 488 nm; em: 505–570 nm; Sigma-Aldrich, Poole, UK) and topical tetramethylrhodamine methyl ester (TMRM; 1 μM; ex: 543 nm; em: 585 nm; T-668, Molecular Probes, Invitrogen, Paisley, UK) were imaged to establish perfused vessel density and mitochondrial membrane potential, respectively. Images were processed using Fiji/Image J 1.48v (NIH, Bethesda, MD, USA).

Electrophysiology

The right tibial nerve was stimulated (DS2, Digitimer, Welwyn Garden City, UK) percutaneously at the ankle (10 Hz, twice supramaximal), with recording electrodes at the vertebral level T10/T11, and on the cortical dura (−2 mm from bregma, 2.5 mm from midline), with reference electrodes on nearby inactive tissue. Another recording electrode was placed over the ipsilateral metatarsal musculature, with a reference electrode in the third digit. The ground electrode was inserted under the lumbar skin. Recordings of the somatosensory evoked potentials, cord dorsum potentials, and electromyographic signals were amplified (Neurolog System, Digitimer), observed on an oscilloscope (Sigma 60, Nicolet, Madison, WI, USA), and stored as averaged (n=20) compound action potentials. They were monitored as measures of cortical, spinal, and muscular function, respectively.

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