Xenon treatment improves short-term and long term outcomes in a rodent model of traumatic brain injury

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Background. Traumatic brain injury (TBI) is a leading cause of morbidity and mortality throughout the world. Despite improvements in medical care, current clinical TBI treatment is mainly supportive and no specific neuroprotective drugs are available. TBI arises from external forces applied to the head, resulting in immediate and irreversible damage, or 'primary injury'. In addition, early, and long-lasting, secondary injury cascades are triggered. Many of the debilitating functional impairments observed in patients result from the potentially preventable 'secondary injury'. Over-activation of N-methyl-D-aspartate (NMDA) receptors is thought to play a key role in secondary injury development. Xenon is a noble gas and general anaesthetic that is a competitive inhibitor of the NMDA receptor at the glycine binding site [1-3]. Xenon has been shown to be neuroprotective in models of brain ischemia. Much less is known about xenon effect in the context of traumatic brain injury.

Objectives. Our work focused on evaluating xenon's neuroprotective efficacy in the reproducible controlled cortical impact (CCI) animal model of blunt traumatic brain injury, that includes elements found after moderate to severe TBI in humans, such as contusional lesion, brain oedema, elevated intracranial pressure and neurological impairment.

Methods. Adult C57BL/6 male mice (n=196) were fixed in a stereotactic frame under anaesthesia and underwent a right parietal cortical impact, delivered by a custom-made electro-pneumatic impactor with a 3-mm diameter flat tip perpendicular to the brain surface. Impact velocity of 8 m/s, impact duration of 150 ms and brain penetration depth of 1.0 mm were used. Throughout the procedure core body temperature was monitored and feedback-controlled. Animals were randomly assigned to control (75% nitrogen:25% oxygen) and xenon treated (30%, 50% or 75% xenon:25% oxygen, balanced with nitrogen) groups. Short term and long term outcomes, both functional and histological, were measured by researchers blinded to treatment. Statistical significance was assessed with one-way and two-way ANOVA with Bonferroni's post hoc test.

Results. Our study showed 75% xenon significantly ($p<0.05$) reduced contusion volume 24 hours after injury and significantly ($p<0.05$) improved neurologic outcome up to 4 days after injury & clinically relevant locomotor parameters 1 month after injury. Xenon treatment significantly ($p<0.05$) reduced contusion volume when given up to 3 hours after injury and significantly ($p<0.05$) improved neurologic outcome when given up to 1 hour after injury. Significant ($p<0.05$) reductions in contusion volume and improvement in neurologic outcome 24 hours after injury were also achieved with 30% and 50% xenon concentrations.

Conclusions. Our results show in an animal model of TBI that xenon improves functional outcomes and reduces contusion volume. We demonstrate both a reduction in the development of secondary injury and improvement in long term translationally relevant motor outcomes. Our findings, including the demonstration of long term neuroprotection and a clinically relevant therapeutic time window, support the idea that xenon may be of benefit as a neuroprotective treatment in TBI patients.

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