Remote Ischemic Conditioning in Traumatic Brain Injury

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Abstract: Traumatic Brain Injury (TBI) is a major cause of disability, with no effective treatments for repetitive mild TBI (RmTBI). Remote Ischemic Conditioning (RIC) shows promise in stroke and may aid RmTBI recovery by reducing neuroinflammation. Using a mouse model, we found RIC significantly improved motor function post-RmTBI ($p < 0.05$), though anxiety and cognition remained unaffected. Ongoing studies will explore RIC's effects on neuroinflammation and sex-based differences, highlighting its potential for clinical translation in RmTBI treatment.

Conceptual Framework

Traumatic Brain Injury (TBI) is a leading cause of death and disability globally, with tremendous health and socioeconomic consequences (1, 2). Repetitive mild TBI (RmTBI; like concussion) can significantly alter brain structure and function and manifest a breadth of neurological symptoms and neurodegeneration; however, there are no effective treatments (2). Remote Ischemic Conditioning (RIC) is an endogenous, multifunctional protective intervention that shows promise as a safe treatment in ischemic stroke (3, 4). RIC involves brief, cyclical periods of restricted blood flow that leads to release of neuroprotective factors which can reduce neuroinflammation and blood-brain barrier impairments - key drivers of RmTBI pathology. RIC has not been studied RmTBI, rendering this current study novel (3). This study aims to explore if RIC can improve functional recovery following RmTBI. Thirty twoP56 male C57BI/6 mice were divided into four groups: sham/sham, RIC/sham, sham/RmTBI, and RIC/RmTBI. RIC treatment consisted of four cycles of5 mins of ischemia and 5 mins of reperfusion with pressure cuffs placed around the animals' hindlimbs, repeated daily for 14 consecutive days. Sham groups did not receive cuff inflation/deflation. Closed-headed RmTBI was then delivered using the lateral impact model where acutely anesthetized animals received 1 mTBI at 24-hour intervals for 5 consecutive days at 5 m/s projectile velocity. Sham animals were anesthetized but not impacted by the projectile. 1-3 days following RmTBI, a neurobehavioral test battery was performed to evaluate anxiety, motor function and cognition. Animals were then perfused for immunohistochemical analysis of inflammatory markers. Among behavioral tests, we found that RmTBI significantly increased foot slips on the beam walk assay compared sham animals ($p < 0.05$). Notably, RIC significantly reduced this motor dysfunction ($p < 0.05$). Other behavioral tests assessing anxiety (open field test) and cognition (novel object recognition) did not show any significant differences between the groups. Neuroinflammatory analyses are ongoing. Our initial findings support the efficacy of RIC for reducing neurological dysfunction caused by RmTBI. Future efforts will focus on sex-based differences in RIC effects on RmTBI pathology. RIC's effects on neuroinflammation will also be investigated by exploring gliosis and cytokine release. There is an unmet need for effective and safe interventions to modify the course of RmTBI. Given RIC's accessibility and efficacy in motor improvement, translation into clinical practice holds considerable promise, marking a paradigmatic shift in traditional approaches in RmTBI management.

References

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