Riluzole Attenuates the Decompression Induced Ischemia Reperfusion Injury and Enhances the Beneficial Impact of Decompression in Cervical Spondylotic Myelopathy

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Introduction: Surgical decompression is increasingly recommended as the treatment strategy for CSM and is associated with overall neurological improvement. While beneficial, little is known related to the physiological consequences of decompression in CSM. Here, we hypothesized for the first time that surgical decompression can cause initial harm to the spinal cord due to ischemia reperfusion injury (IRI) and that riluzole, in addition to protecting against chronic spinal cord compression, can prevent this surgical complication to improve overall functional recovery.

Methods: In this study, a very well characterized rat model of CSM that allows for surgical decompression was used. Spinal cord blood flow (SCBF) was evaluated in vivo before and 6 hours after decompression using the Flow Alternative Inversion Recovery MRI technique. The levels of neuronal oxidative damage were also examined before and after the surgical decompression using immunohistochemistry. The potential protective effects of riluzole against the reperfusion induced oxidative damage were evaluated in vivo and in vitro. Then using a a novel experimental paradigm, we examined the synergistic effects of decompression and riluzole. Immunohistochemistry were used to evaluate apoptosis and axonal integrity. Detailed gait analysis was performed using Catwalk. ANOVAs were used for the statistics.

Results: FAIR MRI demonstrated a significant increased SCBF 24 hours after decompression (p=0.013, AVOVA repeated measures) which was associated with an initial neurobehavioral decline as it was indicated by a statistical significant decrease of forelimb stride length (p=0.032, AVOVA repeated measures) and increase in forepaw initial contact (p=0.029, AVOVA repeated measures). Neurobehavioral analysis further revealed that pre and peri-operative administration of riluzole prevented this immediate neurobehavioral decline (p=0.011 for forelimb stride length and p=0.000 for forepaw initial contact, AVOVA repeated measures). It was also found that surgical decompression induced early neuronal oxidative damage – demonstrating hallmarks of IRI. Immunohistochemical tissue analysis and mechanistic in vitro oxidative stress experiments suggested that riluzole, by attenuating oxidative damage and preserving the mitochondrial membrane stability, was able to protect against cell loss caused by IRI. In addition, this work demonstrated that combinatorial strategy consisting of surgical decompression and riluzole markedly improves hand and gait function and attenuates below-level neuropathic pain compared to decompression alone. Finally, combined strategy reduces axonal damage, cellular apoptosis and motoneuronal injury in the cervical area as well as suppressing microglial and activation in the lumbar dorsal horns.

Conclusions: Here we discover the development of a previously unrecognized iatrogenic complication associated with surgical decompression, a procedure that is in wide clinical use and the only current interventional treatment for human CSM. This silent enemy may represent a putative mechanism that can account for post-decompression neurobehavioural decline and neurological complications in surgically treated CSM. Finally this work provides a mechanistic basis to support secondary analysis of the CSM-Protect clinical trial which aims to determine the synergistic effects of riluzole and decompressive surgery in human CSM.