

# Preclinical screening of a potential drug treatment for spinal cord injury using magnetic resonance imaging

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## Introduction

Potential new therapies for treating spinal cord injury (SCI) are currently being developed and tested in animal models. Evaluating the efficacy of a pharmacological treatment depends on accurately quantifying drug-induced improvements in neuropathological state of injured spinal cord (SC). Magnetic resonance imaging (MRI) offers rapid screening of a promising drug for SCI by providing anatomical, structural and functional information about underlying neuronal tissue. Histological analyses from our group have shown that the modulator of cellular redox, S-nitrosoglutathione (also known as GSNO) prevents endothelial dysfunction, facilitates neuroprotection and repair, and promotes locomotor function during recovery following neuronal injury [1]. Our goal is to evaluate the efficacy of GSNO in SCI using MRI and a rat model.

## Materials and Methods

All MRI scans were performed on a 7 T Bruker Biospec USR system (Bruker Inc., Billerica, MA). Sprague Dawley rats (~225 g and ~4 months old) were randomized into two groups: untreated control (n=5) and GSNO-treated (n=5). The SCs of the rats were subjected to a contusion-type injury at the T9 vertebral level [2]. The treatment group received GSNO injection (0.05 mg/kg dose diluted in a 250  $\mu$ l PBS solution) via tail vein at 1 hr postinjury, followed by a daily dose of the same amount, but delivered orally. The rats in the control group received only PBS vehicle of the same quantity. The functional recovery of the injured rat was evaluated daily using locomotor rating scale (or BBB score) [2]. On postinjury day 56, we perfused the animals, excised their vertebral bodies, and scanned the injured SCs using inductively coupled surface coil [3] and performed standard postmortem histological examination.

The injured SCs were scanned in sagittal and axial planes using the parameters:  $T_R/T_E$  = 3000 ms/ 9 and 40 ms, image matrix = 256x256 and averages=4. Field of view and slice thickness were respectively 40 mm X 40 mm and 0.5 mm for the sagittal, and 16 mm X 16 mm and 1 mm for the axial images with no gap. From the acquired data, lesion volumes were quantified using the scanner software and manual segmentation.

## Results and Discussion

BBB scores in Fig 1 indicate that GSNO treated rats had less behavioral deficits and recovered their motor function better when compared to the untreated controls. Sagittal images in Fig. 2 depict lesions formed in all animals. Fig. 3 presents axial images from a control rat and a GSNO-treated rat. The preliminary MRI data obtained so far demonstrate smaller size lesions with morphologically lesser cross-sectional shrinkage in GSNO-treated rats. These favorable outcomes suggest neuro protection and repair roles for GSNO. Decreased inflammation near trauma site and preservation of neurons in Fig. 4 also support these roles. Data analyses and extensive histological preparations are underway to further confirm these roles.

## Conclusion

Preclinical MRI is a feasible method that can be used to sensitively screen the beneficial effects of a drug, such as GSNO, in treating injuries in a rat model of SCI.

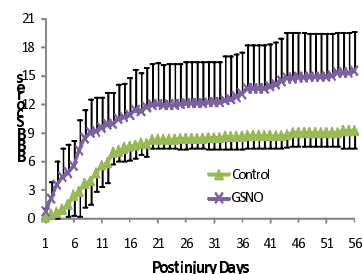


Fig. 1. Locomotor recovery.

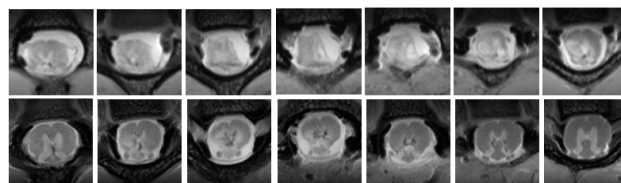


Fig. 3. Axial PD images of injured SCs from a vehicle-treated rat (top row) and a GSNO-treated rat (bottom row).



Fig. 2. Sagittal PD images of injured SCs from vehicle-treated rats (top row) and GSNO-treated rats (bottom row) on day 56.

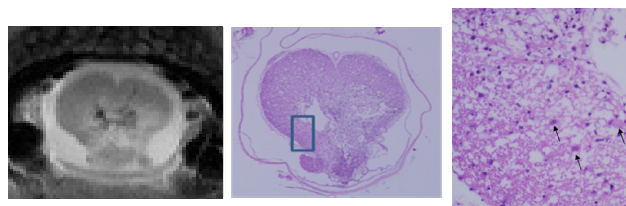


Fig. 4. MRI and H&E stained section of an injured SC from a GSNO-treated rat. Presence of neuronal cell bodies (arrows in the expanded view from the rectangular region) suggests GSNO plays both protective and repair roles.

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**References:** [1] Khan, M., et al. J Cereb Blood Flow Metab, 2005. 25(2): p. 177-92. [2] Bilgen, M. A Neurorehabilitation and Neural Repair 19: 219-226, 2005. [3] Bilgen, M.: Magn. Reson. Med. 52:937-940, 2004.