Magnesium polyethylene glycol: a novel therapeutic agent for traumatic brain injury

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Declaration

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Dedication

This thesis is dedicated to my mother Tophers Sabiiti, who has always believed in me, encouraged and supported me in every way possible.

Publications, presentations and awards

The following articles have been published or accepted for publication or presentation during the period of my Masters candidature, and sections of these articles have been included in the present thesis.

Book Chapter

Diana S. Busingye, Renée J. Turner and Robert Vink (2015) Emerging therapies in traumatic brain injury, in *Critical Care in Traumatic Brain Injury* (DX Cifu, BC Eapen, eds), Future Science Group, London (in press).

Presentation Abstracts

Sabiiti-Busingye D, Turner R, Vink R (2014) Combined magnesium polyethylene glycol as a novel therapy in traumatic brain injury. Aust. Neurosci. Soc. Abstr. P62.

Sabiiti-Busingye D (2014) Magnesium polyethylene glycol: a novel therapy for traumatic brain injury? Proc. Aust. Soc. Med. Res.

Award

Sir Grafton Elliot-Smith award for best student poster presentation, the Australian Neuroscience Society Conference, Adelaide, January 2014.

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ABBREVIATIONS

APP	Amyloid Precursor Protein
ATP	Adenosine Triphosphate
AQP	Aquaporin
BBB	Blood Brain Barrier
Ca^{2+}	Calcium
cAMP	Cyclic adenosine monophosphate
DAB	Diaminobenzidine tetrahydrochloride
CGRP	Calcitonin-gene Related Peptide
CNS	Central Nervous System
CPP	Cerebral Perfusion Pressure
CSF	Cerebrospinal fluid
DAI	Diffuse Axonal Injury
EB	Evans Blue
GCS	Glasgow Coma Scale
H&E	Haematoxylin and Eosin

ICP	Intracranial Pressure
IV	Intravenous
Mg^{2+}	Magnesium
NHS	Normal Horse Serum
NMDA	N-methyl-D-aspartate
NO	Nitric Oxide
PBS	Phosphate Buffered Solution
rpm	Revolutions per minute
SD	Standard Deviation
SEM	Standard Error of Measurement
SP	Substance P
SPC	Streptavidin Peroxidase Conjugate
TBI	Traumatic Brain Injury

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ABSTRACT

A number of experimental studies have shown that decline in intracellular free magnesium is a ubiquitous feature of traumatic brain injury (TBI), and that restoration of magnesium homeostasis improves both cognitive and motor outcome. However, a recent large, randomized clinical trial of magnesium in TBI failed, in part because of poor central penetration of the magnesium salt. Subsequent experimental studies in spinal cord injury have shown that magnesium penetration into the CNS can be facilitated if the magnesium salt is administered in a solution containing polyethylene glycol (PEG), a polymer that facilitates transport across the blood brain barrier and throughout the extracellular space. Accordingly, the current study characterised the therapeutic potential of high and low dose magnesium chloride, either alone or in combination with PEG, on oedema, blood brain barrier permeability, brain histology and functional outcome following moderate diffuse TBI in rats.

Adult male Sprague Dawley rats (350-380 g) exposed to moderate diffuse TBI induced using the impact acceleration injury model, were administered intravenous magnesium polyethylene glycol (Mg PEG) (254 μmoles/kg $MgCl_2$ in 1g/kg PEG), the same concentration (optimal dose) of $MgCl_2$ or PEG alone, or equal volume vehicle at 30 min postinjury. A separate group of surgically prepared animals were neither injured or treated and served as shams. All animals were subsequently assessed for oedema, blood barrier permeability, brain histology and functional outcome for up to 1 week after trauma. Administration of either Mg PEG or optimal dose $MgCl_2$ alone significantly improved all outcome parameters compared to vehicle treated or PEG treated controls with no significant difference between the magnesium treatment groups. Indeed,

magnesium treatment restored all parameters to sham levels. However, intravenous administration of one-tenth the magnesium concentration (25.4 μmoles/kg; low dose) had no beneficial effect on any of the outcome parameters whereas one-tenth the magnesium concentration in PEG (25.4 μmoles/kg $MgCl_2$ in 1g/kg PEG) had the same beneficial effects as optimal dose $MgCl_2$. We conclude that PEG facilitates movement of the magnesium salt across the blood brain barrier following TBI and that the combination of low dose magnesium in PEG significantly attenuates oedema, blood brain barrier permeability and improves motor and cognitive outcome following TBI.