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Does Stem Cell Therapy Hold Promise In The Management Of Traumatic Brain Injuries? A Literature Review of Animal Studies

Ayaz M Khawaja MD; Maira Mirza; Gabriel Rodriguez MD; Hassan Aziz MD

Introduction

There are no neuroprotective and neuroregenerative treatments available for Traumatic Brain Injury (TBI). Clinical trials investigating potential treatments such as therapeutic hypothermia and progesterone have failed. Pre-clinical studies indicate there may be a role of stem-cells in promoting neuroprotection/neuroregeneration in-vivo in animal models of TBI. We aim to provide a pre-clinical literature review into stem-cells as a potential therapeutic option in TBI-animal models.

Methods

Using the terms “traumatic brain injury”, “stem-cell”, “preclinical”, and “animal studies”, a literature search was conducted on Pubmed and Google Scholar. Studies were included if there was an in-vivo animal model of TBI with either intravenous or intra-cortical stem-cell transplantation, along-with a control group, and investigated either motor or behavioral outcomes, or a combination.

Results

Twenty-seven studies (n=1184 animals) satisfied the criteria (Table-1). 774/1184 (65.4%) animals were investigated for outcomes. 17 studies harvested stem-cells from human-source, whereas 10 harvested stem-cells from animal-source. Bone-marrow stromal-cells (BMSC) were used in 17 studies, neural stem-cells (NSC) in 7, and miscellaneous in 3. 450/774 (58.1%) animals received any stem-cell transplantation, whereas 324 were controls. Of animals receiving stem-cell transplantation (450), 339 (75.3%) showed significantly better outcomes relative to control animals in each individual study, with exception of one study. Amongst transplanted animals, functional outcomes did not differ significantly when grouped by stem-cell type (p=0.553), transplantation route (p=0.054), and source (p=0.784) (Figure 1). Animals were followed-up until 1 week (n=5 studies), 2 weeks (n=10), 4 weeks (n=5), or >4-weeks (n=7).

Conclusions

This pre-clinical data demonstrates that stem-cell transplantation may have treatment potential in TBI as shown by improvement in functional outcome in as many as three-quarters of all animals that were treated with stem-cells. This data provides a foundation for the design of clinical translational studies.

Learning Objectives

By conclusion of this session, participants should be able to:

1. Recognize that there are currently no neuroprotective and neuroregenerative treatments available for traumatic brain injury
2. Discuss, in small groups, the available evidence on the impact of stem cell therapy on outcomes in pre-clinical animal models of TBI
3. Understand that Stem cell therapy may be the next investigative frontier for patients with TBI and that this literature review provides a foundation for clinical translational studies

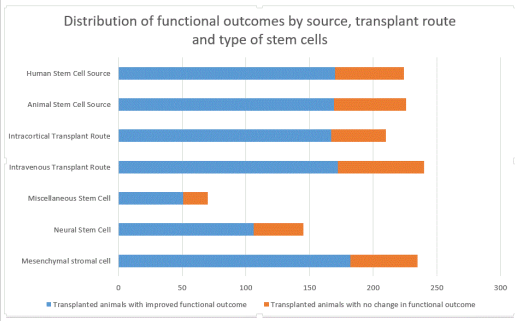
Table 1

Table 1: Table showing results of animal literature investigating the impact of stem cell transplantation on pre-specified functional outcomes. The results columns indicates the number of animals that met the outcome of interest amongst those that received any stem-cell transplantation

Study	Animals (n)	SC type/ route/ source	Outcome/follow-up (weeks)	*Results** (n)	Controls (n)
Mahmood (2001)	16	BMSC/IV/rat	NSS; RTR; 2	4/4	8
Mahmood (2001)	12	BMSC/IV/rat	RTR; NSS; 2	4/4	8
Mahmood (2001)	66	BMSC/IC/rat	RTR; 4	8/8	24
Philips (2001)	59	NSC/IC/rat	MWM; CSN; RPT; 1	26/26	8
Riess (2002)	65	NSC/IC/human	RPT; RTR; MWM; 12	26/52	13
Lu (2002)	24	UCB/IV/human	RTR; NSS; 4	8/8	16
Mahmood (2002)	20	BMSC/IC/rat	RTR; 1	4/8	8
Lu (2002)	36	NSC/IC/rat	RTR; NSS; 2	18/27	9
Mahmood (2003)	27	BMSC/IV/human	NSS; RTR; 4	9/18	9
Mahmood (2004)	34	BMSC/IC/rat	NSS; 2	13/13	16
Shear (2004)	35	NSC/IC/rat	RTR; MWM; 52	7/7	12
Mahmood (2005)	60	BMSC/IV/human	NSS; 2	30/30	30
Mahmood (2006)	40	BMSC/IV/rat	NSS; 12	20/30	10
Gao (2006)	24	NSC/IC/human	MWM; 1	6/6	10
Lu (2006)	60	BMSC/IV/rat	ASR; FGS; 2	12/16	16
Riess (2007)	38	ESC/IC/murine	RTR; CNS; 6	10/10	11
Mahmood (2007)	32	BMSC/IV/rat	NSS; MWM; 5	8/24	8
Bhang (2007)	28	BMSC/IC/human	RTR; 2	14/14	7
Qu (2008)	12	BMSC/IV/rat	MWM; FFT; 5	6/6	6
Harting (2009)	21	BMSC/IV/rat	NSS; MWM; 2	0/10	11
Harting (2009)	18	NSC/IC/rat	RTR; NSS; MWM; 2	2/6	6
Kim (2010)	128	BMSC/IV/human	RTR; NSS; 2	16/16	16
Ma (2012)	48	NSC/IC/rat	LTM; GWT; 8	21/21	21
Zhang (2013)	125	BMSC/IV/rat	NSS; 4	6/6	6
Guan (2013)	42	BMSC/IC/human	NSS; MWM; 4	12/12	12
Chang (2013)	32	BMSC/IV/human	IPMT; PAP; 1	16/16	8
Tajiri (2014)	82	ADSC/IV/human	EBST; FA; PG; RAWM; 1	33/52	15
	1184			339/450	324

n = Number; SC = Stem cells, MSC = Mesenchymal stem cells; BMSC = Bone Marrow Stromal Cells; UCB = Umbilical cord blood; NSC = Neural stem cells; ESC = Embryonic stem cells; ADSC = Adipose derived stem cells; IC = intracerberal; IV = intravenous; NSS = Neurological severity score; MWS = Morris Water Maze; RTR = Rotarod test; RPT = Rotating pole test; CSN = Composite Neuroscore; FFT = Foot Fault Test; IPMT = Inclined Plane Motor Test; PAP = Passive Avoidance Performance; ASR = Acoustic Startle Response; FGS = Forelimb Grip Strength; EBST = Elevated body swing test; FA = Forelimb Akinesia; PG = Paw Grasp; RAWM = Radial arm water maze; LTM = Latency to move; GWT = Gridwalk test

Figure 1



Distribution of functional outcomes by source, transplant route and type of stem cells

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