International Journal of Cardiology 201 (2015) 668–683

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Intra-carotid arterial administration of autologous peripheral blood-derived endothelial progenitor cells improves acute ischemic stroke neurological outcomes in rats☆

Yung-Lung Chen [a,1], Tzu-Hsien Tsai [a,1], Christopher Glenn Wallace [b], Yi-Ling Chen [a], Tien-Hung Huang [a], Pei-Hsun Sung [a], Chun-Man Yuen [c], Cheuk-Kwan Sun [d], Kun-Chen Lin [e], Han-Tan Chai [a], Jiunn-Jye Sheu [f], Fan-Yen Lee [f,2], Hon-Kan Yip [a,g,h,i,*,2]

[a] Division of Cardiology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
[b] Department of Plastic Surgery, University Hospital of South Manchester, Manchester, UK
[c] Division of Neurosurgery, Department of Surgery, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
[d] Department of Emergency Medicine, Department of Medical Research, E-DA Hospital, I-Shou University, Kaohsiung, Taiwan
[e] Department of Anesthesiology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
[f] Division of thoracic and Cardiovascular Surgery, Department of Surgery, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
[g] Institute for Translational Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
[h] Center for Shockwave Medicine and Tissue Engineering, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
[i] Department of Medical Research, China Medical University Hospital, China Medical University, Taichung, Taiwan

ARTICLE INFO

Article history:
Received 28 October 2014
Received in revised form 5 January 2015
Accepted 7 March 2015
Available online 11 March 2015

Keywords:
Acute ischemic stroke
Endothelial progenitor cells
Infarct volume
Angiogenesis factors
Oxidative stress

ABSTRACT

Objective: We tested the hypothesis that transfusion of autologous peripheral blood-derived endothelial progenitor cells (PBDEPC) via the internal carotid artery could reduce brain-infarct zone (BIZ) and neurological deficit in rats following acute ischemic stroke (IS) induced by 50-min left middle cerebral artery occlusion.
Design: Adult male Sprague–Dawley rats (n = 60) were equally divided into group 1 [sham control (SC)], group 2 [SC-PBDEPC (5.7×10^6/kg)], group 3 (IS), group 4 [IS-low-dose PBDEPC (1.7×10^6/kg)], group 5 [IS-high-dose PBDEPC (5.7×10^6/kg)]. Groups 2 to 5 received G-CSF (35 μg/kg subcutaneously) for 4 days before drawing blood for PBDEPC culture.
Measurements and main results: By day 90, BIZ determined by histopathology (area) and brain MRI (volume) were highest in group 3, lowest in groups 1 and 2, higher in group 4 than in group 5 (all $p < 0.0001$), and not significantly different between groups 1 and 2. Sensorimotor functional results exhibited an opposite pattern of BIZ among groups 3 to 5 ($p < 0.005$). Angiogenesis biomarkers (SDF-1α, CXCR4, VEGF, angiopoietin-1) significantly increased progressively from groups 1 and 2 to group 5 (all $p < 0.0001$). Oxidative-stress (NOX-1, NOX-2, oxidized protein), apoptotic (cleaved caspase 3 and PARP, mitochondrial Bax), inflammatory (MMP-9, TNF-α, AQP-4, GFAP, iNOS), and brain-damaged (cytosolic cytochrome-C) biomarkers showed an identical pattern, whereas anti-inflammatory (Bcl-2), mitochondrial preservation (mitochondrial cytochrome-C, PGC-1α), and endothelial function (CD31+, vWF+, eNOS) biomarkers, and vessel density showed an opposite pattern of BIZ among these five groups (all $p < 0.001$).
Conclusion: Higher-dose was superior to lower-dose EPC treatment for reducing BIZ and improving neurological functional outcome.

© 2015 Elsevier Ireland Ltd. All rights reserved.

☆ Author's contributions: YL Chen and TH Tsai participated in the design of the study, data acquisition, and analysis as well as drafting the manuscript. HT Chai, JJ Sheu, PH Sung, CM Yuen, Wallace C and KC Lin were responsible for the laboratory assay and troubleshooting. YL Chen, TH Huang, CK Sun and HK Yip participated in data acquisition, analysis, and interpretation. FY Lee and HK Yip conceived of the study, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

* Corresponding author at: Division of Cardiology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, 123, Dapi Road, Niaosung Dist., Kaohsiung City 83301, Taiwan.
E-mail address: han.gung@msa.hinet.net (H.-K. Yip).

[1] Equal contribution.
[2] Indicates equal contribution in this study compared with the corresponding author.

http://dx.doi.org/10.1016/j.ijcard.2015.03.137
0167-5273/© 2015 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Acute ischemic stroke (IS) remains a leading cause of mortality and disability worldwide [1–4], and yet, despite better understanding of prevalence, etiology, and IS mechanisms, advancements in imaging leading to earlier and more accurate diagnosis, and improved antithrombotic agents, a universally accepted effective and safe management strategy for patients with acute IS remains undefined [5–8]. Thrombolysis with tPA is an emerging treatment with promising results in specific patient groups; however, the contraindications restrict its scope in clinical practice [9–13]. Furthermore, tPA appears to have a relatively high incidence of intracranial bleeding complications [9–13]. Therefore, an alternative treatment needs to be developed for patients with acute IS, particularly for those who are not candidates for thrombolysis.

Stem cell therapies have been developed for many diseases refractory to traditional management strategies [14–18]. Of these, ischemia-related organ dysfunction has attracted the most intensive research, with successful translation to human and animal subjects and promising results [14–18]. Undoubtedly, different types of stem cells have different phenotype function. Abundant studies have shown that mesenchymal stem cells (MSCs), especially those of adipose-derived MSC have capacity of anti-inflammation and immunomodulation [14,19,

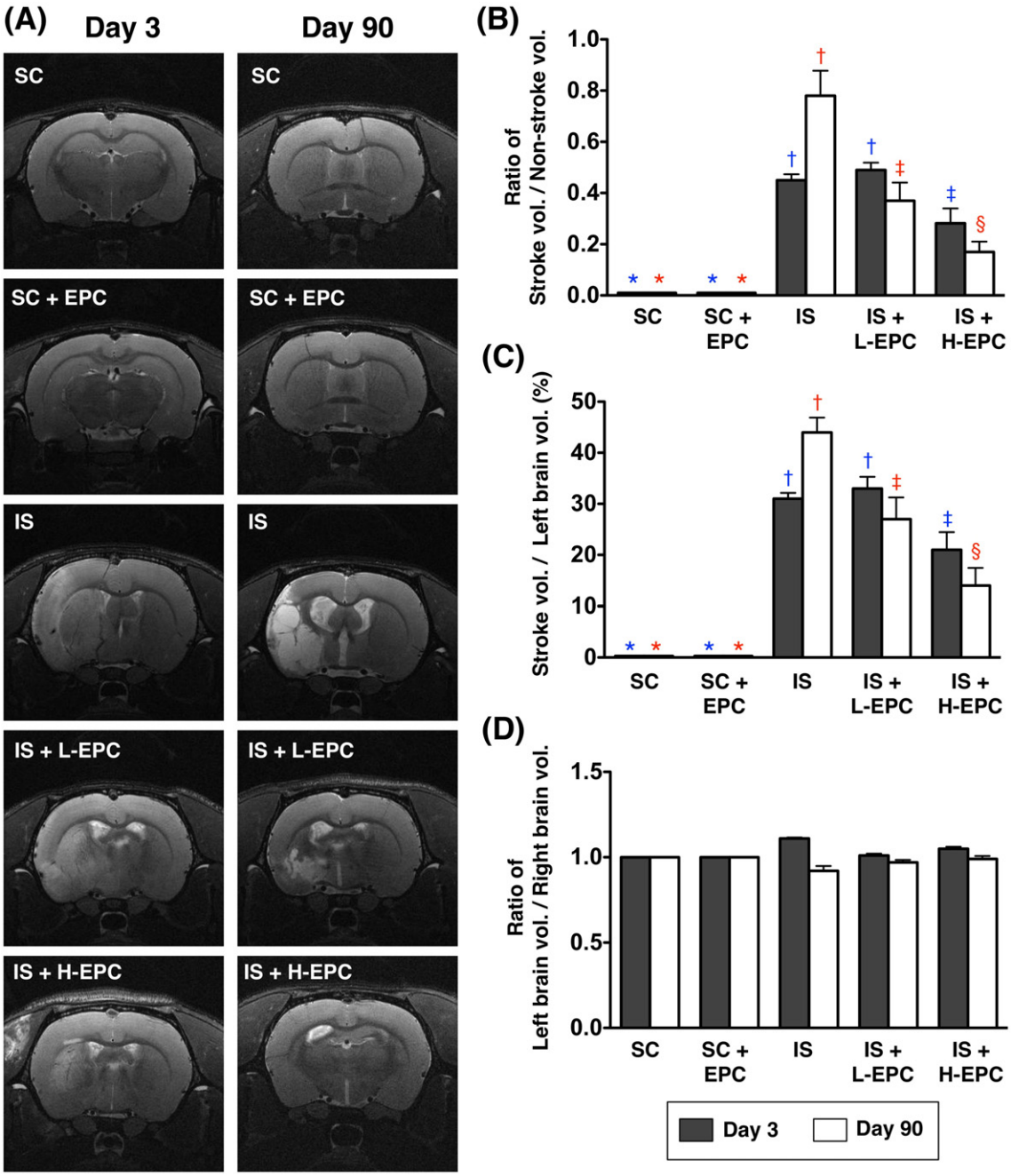

Fig. 1. Brain magnetic resonance imaging (MRI) finings in animals prior to and by day 90 after acute ischemic stroke (IS) (n = 6). A) Illustrating brain MRI findings of brain infarction zone (white color). B) Ratio of stroke volume to non-stroke volume of right hemisphere, at day 3: * vs. other groups with different symbols (*, †, ‡), $p < 0.0001$; at day 90: * vs. other groups with different symbols (*, †, ‡, §), $p < 0.0001$. Vol = volume. C) Stroke volume dived by left brain volume (i.e., left hemisphere) × 100%, at day 3: * vs. other groups with different symbols (*, †, ‡), $p < 0.0001$; at day 90: * vs. other groups with different symbols (*, †, ‡, §), $p < 0.0001$. D) Ratio of left brain volume to right brain volume, for days 3 and 90, all p value > 0.5. All statistical analyses were performed by one-way ANOVA, followed by Bonferroni multiple comparison post hoc test. Symbols (*, †, ‡, §) indicate significance (at 0.05 level). SC = sham control; EPC = endothelial progenitor cell; IS = ischemic stroke; L = low-dose; H = high-dose.

Download English Version:

https://daneshyari.com/en/article/5966390

Download Persian Version:

https://daneshyari.com/article/5966390

Daneshyari.com