Coadministration of the Human Umbilical Cord Matrix-Derived Mesenchymal Cells and Aspirin Alters Postischemic Brain Injury in Rats

Ali Shams ara, PhD Candidate,* Vahid Sheibani, PhD,† Khadije Esmaeilpour, MSc,† Touba Eslaminejad, PhD Candidate,‡ and Seyed N. Nematollahi-Mahani, PhD*†

Background: Ischemic stroke is an acute brain insult that induces dramatic changes in the neurons. Treatment of brain stroke is one of the main therapeutic targets of neuroprotective therapies. The aim of this study was to evaluate the protective potential of implanted human umbilical cord mesenchymal stem (hUCMs) cells with/without aspirin (ASA) against focal cerebral ischemia. *Methods:* We assessed the migration and distribution of PKH_{26}-labeled cells after transplantation. After day 10 of transient occlusion, we evaluated the effect of ASA and hUCMs on the recovery of learning and memory in rats by Morris water maze. Afterward, animals were sacrificed, and the infarct area in the brain was evaluated using 2, 3, 5-triphenyltetrazolium chloride staining and also by hematoxylin and eosin. *Results:* The recovery of learning and memory in ischemic animals that received ASA and hUCM cells improved significantly compared with the untreated ischemic animals. Coadministration of ASA and hUCM cells did not improve the outcome at a comparable rate with ASA and hUCM cells alone. PKH_{26}-labeled cells were detectable in the ischemic area of the brain tissue sections. 2,3,5-Triphenyltetrazolium chloride staining and histologic examinations showed that treatment with ASA and hUCM cells could significantly alter the ischemic area. *Conclusions:* The results of the present study suggest that ASA and hUCM cells can withstand degenerative changes induced by artificial stroke in the rat. Also the learning and memory disturbance in the ASA and cell-treated animals is less pronounced than ischemic animals. Coadministration of ASA and hUCM cells did not raise the outcome higher than administration of ASA and hUCM cells alone. **Key Words:** Brain ischemia—human umbilical cord matrix-derived mesenchymal cells—aspirin—TTC staining—learning and memory.
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From the *Department of Anatomy, Afzalipour School of Medicine, Kerman; †Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman; and ‡Pharmaceutical Research Center, Neuropharmacology Institute, Kerman University of Medical Sciences, Kerman, Iran.

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Address correspondence to Seyed N. Nematollahi-Mahani, PhD, Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran. E-mail: nnematollahi@kmu.ac.ir.

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Introduction

Brain stroke is a major cause of death worldwide and the leading cause of long-term disability in adults. Most often it happens after microvessels occlusion or anemia in the different regions of brain tissue. Because neuronal death is most often irrevocable, improving the effectiveness of treatments and preventing the brain stroke are of great interest.[1,2] Nonsteroidal anti-inflammatory drugs like aspirin (acetyl-salicylic acid [ASA]) are widely used in prevention of cellular changes that follow brain stroke because they act as an inhibitor of platelet aggregation.[3,4]

ASA is usually used as the treatment of choice in acute ischemic stroke. ASA and other anticoagulating drugs act through preventing the propagation of the blood clots and preventing the complete obstruction of the arteries.[5] These drugs can be administered before or after the onset of stroke. The outcome is most often unsatisfactory, especially when the regeneration of the damaged tissues comes into account. However, we have previously shown that the size of infarcted area is significantly reduced when ASA (30 mg/kg) was given 30 minutes after the onset of stroke.[3]

In addition to conventional therapies in brain stroke, stem cells have been introduced as a potential source for the treatment of ischemic brain injury other than anticoagulating agents like ASA. Potential of stem cells to differentiate into many cell lineages under special conditions has attracted the scientist's attention into a valuable source of therapy, particularly in clinical studies in which other therapeutic methods are disappointing. In fact, human umbilical cord matrix-derived mesenchymal stem (hUCMs) cells and mesenchymal stem cell (MSC)–like cells are useful multipotent stem cells that can help the recovery of many injured tissues.[6] hUCMs can differentiate into a variety of cell lineages including myoblasts, hepatocytes, insulin-producing cells, and even neural cells.[7] Lu et al[8] has reported successful differentiation of bone marrow (BMS) cells into neural lineage including astrocytes and neurons. Also, Salehinejad et al[9] reported that hUCMs could successfully differentiate into various neural cells under certain conditions. Cell transplantation could have lead to the repair of damaged brain tissue and functional recovery in preclinical stroke models.[7,10] Although, the proliferation and therapeutic potential of MSCs in the repair of human spinal cord injury have been studied to some extent (Karamouzian et al[11]), none of them has studied the effect of nonsteroidal anti-inflammatory drugs and stem cells coadministration on the brain ischemia repair. Therefore, in the present investigation, we used a rat model of animal stroke to evaluate the potential of hUCMs and ASA in reducing the brain injury volume. To investigate this, we used intraluminal middle cerebral artery occlusion (MCAO) as the method of choice in animal brain ischemia[12] and introduced hUCMs through the tail vein of rats with and without ASA administration. The recovery of learning and memory in the rats was assessed by Morris water maze (MWM), the extent of infarcted area was evaluated by 2,3,5-triphenyltetrazolium chloride (TTC) staining, and histologic changes were determined by hematoxylin and eosin (H&E) staining.

Materials and Methods

Animals and Housing

Male Sprague–Dawley rats with a body weight of 240-280 g from the animal house of the Afzalipour Medical School were allocated into 5 groups (n = 6). Rats were housed under controlled conditions: 23 ± 2°C, 12/12 light/dark, and free access to regular rodents chew and drinking water. Rats were grouped as control (did not receive any intervention), ischemic (underwent transient occlusion of middle cerebral artery [MCA] for 20 minutes), ischemic-ASA (Isch-ASA; received 30 mg/kg ASA through intraperitoneal [i.p.] route 30 minutes after ischemia), ischemic-hUCMs (Isch-hUCM; received hUCMs through tail vein 24 hours after ischemia), and an ischemic-ASA-hUCMs (Isch-ASA-hUCM) group.

Transient MCAO and Reperfusion

Anesthesia was induced by i.p. injection of 400 mg/kg chloral hydrate solution, and the surgery site was shaved carefully. A skin incision was made at the midline of the neck. The neck fascia sheath and muscles were dissected to access the right common carotid artery (CCA); vagus nerve was carefully protected to avoid parasympathetic alteration. The CCA was temporary ligated, and the internal carotid artery was clamped by a microsurgery clamp. The surgery was done according to Tamura et al.[13] A cut through the CCA was made and a 20-mm-long 3-0 monofilament nylon suture (with 1 end sealed by flame and coated with poly-D-lysine) was inserted through CCA to the clamped right internal carotid artery, the clamp was then removed, and the right MCA was occluded by introducing nylon suture into the entrance of MCA. The nylon suture was pulled off after 20 minutes to allow reperfusion, and the animals were returned to their cages after suturing the fascia and skin. During the operation, body temperature was kept at 37°C using a heating lamp. The animals were examined for neurologic signs after 24 hours, and the one with a positive contralateral rotation and forelimb positive test was selected for further examinations.

Isolation of hUCMs

All the materials were purchased from Sigma-Aldrich (St Louis, MO, USA) unless otherwise stated. The method for hUCMs harvesting is described elsewhere.[14] Briefly, umbilical cords (UCs) were obtained from healthy mothers delivering full-term infants by cesarean section after a written consent was obtained. It was transferred to the laboratory in a sterile container, amniotic membrane and cord vessels removed, and the Wharton jelly was cut into 2 mm slices and was seeded onto the culture dishes. Plates were maintained in Dulbecco-modified Eagle medium (DMEM)-F12 supplemented with 10% fetal bovine serum (FBS), penicillin (100 units/mL), streptomycin (60 μg/mL), and amphoteripcin-B (2.5 μg/mL) at 37°C humidified environment with 5% CO_2 in the air. After the cells migrated from the fragment's borders and reached approximately 80% confluence in 2 weeks,

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