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Case Report

Towards Future Indications of Therapeutic Utilization of Stem Cells: a Case Report of Application after Hypoxic Encephalopathy

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Abstract

To date, stem cell therapy is a novel treatment method especially in irreversible end organ damage. We present a case of a 21-yr-old man, who admitted in Sina Hospital, Tehran University of Medical Sciences, Iran with open left femur fracture following car accident. Developing fat emboli syndrome led to cardiac arrest. Despite of efforts to optimize supportive care and neuroprotective strategies, the level and content of conscious did not improve. We performed stem cell therapy and he was discharged home with mild neurologic deficit on hospital day 116. This is the first case of stem cell therapy applied to a postarrest victim with severe evidently irreversible neurological injuries. This therapy could be considered to improve neurological recovery in patients following cardiac arrest.

Keywords: Cardiopulmonary cerebral resuscitation, Cardiac arrest, Hypothermia, Stem cell therapy

Introduction

Recent medical interventions represent increase in the number of cardiac arrest survivors (1). Functional outcomes of survivors are variable. In fact, severe neurological sequelae are common (2). Despite advances in CPCR and accomplishment of neuroprotective strategies, only 3% to 7% of survivors obtain their preceding level of function (3).

Stem cell therapy is a novel treatment method especially in irreversible end organ damage. In this intervention, cells entered in to damaged tissue are able to differentiate, renew themselves and reproduce damaged areas. Based on results of the studies cell replacement therapies (Such as embryonic stem cells, neural stem cells, bone marrow-derived stem cells) have the possibility of offering a novel potential treatment of various medical problems like cancer, type1 diabetes mellitus, stroke, cardiac failure, muscle damage, celiac disease, neurological disorders and many others (4-13).

We describe here a new possible treatment alternative for improving neurological deficit after cardiac arrest.

Case report

A 21-year-old man without any medical history presented to Sina Hospital, Tehran University of Medical Sciences, Iran after open left femur frac-

ture following car accident. At arrival in the emergency department, the patient was hemodynamically stable. All the necessary evaluations were performed. Non-contrast computerized tomography of the brain, abdomen and pelvic were normal, no problem in chest X-ray and plasma/urine drug screen was negative. Approximately 12 h later the presentation of fat emboli syndrome gradually developed over 24 h, leading to acute respiratory distress syndrome, hypoxia and cardiac arrest. Cardiopulmonary resuscitation initiated at once. He was resuscitated for over 25 min before the return of spontaneous circulation. After initial assessment and stabilization process of airway, ventilation and circulation, he was admitted to the intensive care unit.

His hemodynamic state was stabilized. Consequently, he did not require any vasopressor or inotropic supports. Twelve-lead electrocardiogram showed sinus tachycardia with non-specific ST changes. First neurological examination revealed coma (Glasgow Coma Scale score, 5) with decorticate posturing, and bilateral pupils were dilated to 8 mm in diameter. Six hours later, this was decreased to 3 mm in diameter. A bedside echocardiogram showed no effusion, no ventricular dysfunction, and no global hypokinesis. Transabdominal ultrasound, results was normal. Chest radiograph demonstrated a right lower lobe infiltrate. Non-contrast computerized tomography of the brain indicated brain atrophy and hydrocephalus ex-vacu with fourth, third and lateral ventricles (Fig. 1). Urine and plasma drug screen was negative. Usage of illicit drug was excluded. All the means of neuroprotective support measures were delivered, other than induced mild hypothermia. Mean arterial pressure maintained above 90 mmHg. The patient was remained on mechanical ventilation to achieve normocapnia (Arterial Blood Gas: pH: 7.45, Pco_2: 34 mmHg, Po_2: 110 mmHg, and oxygen saturation, 98%). We prevented fever, and the patient's temperature was 36.5 °C on admission day. Tight glycemic control have been performed, blood sugar glucose measurement at 72 h postarrest was less than 120 mg/dL. Insulin infusion was not necessary.

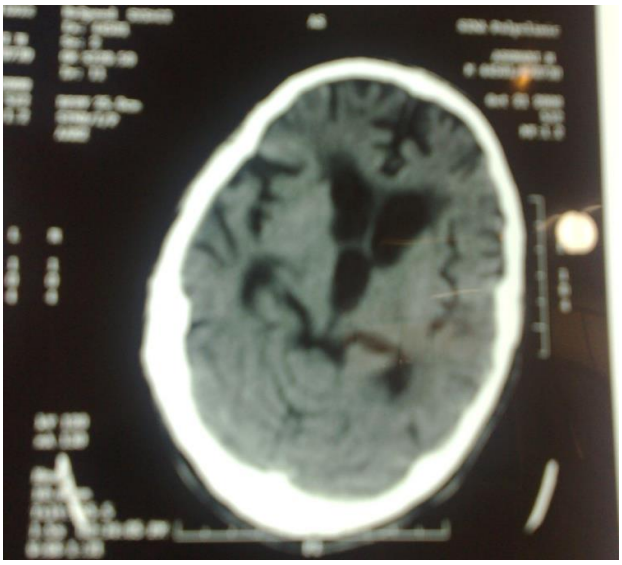

Fig. 1: Computed Tomography (CT) image showed brain atrophy and ex vacu hydrocephalus with of fourth, third and lateral ventricles

He received routine seizure prophylaxis. Laboratory data results were nondiagnostic (Table 1). Despite of ICU team efforts to optimize supportive care and neuroprotective strategies, the level and content of consciousness did not improve, Glasgow Coma Scale score was 5 with decorticate posturing after 47 days. Nonconvulsive status epilepticus ruled out by electroencephalogram monitoring. After discussion of the risks and benefits of cell therapy, the family agreed and permitted the initiation of this therapy as the possible last therapeutic option. Before cell therapy a complete laboratory tests ordered (Table 1). Embryonic stem cells were administered by intravenous injection. Flow cytometry for counting endometrial stem cells that are isolated from endometrium and immunochemistry staining for detection of stem cells marker such as STRO-1, CD 146, CD 90, CD 133, CD 117, and Oct-4 has been performed. Finally, immunocytochemical analysis for differentiated cells with antibodies was conducted. Supportive care proceeded post stem cell therapy (PSCT). Gradually following the second week of PSCT, the patient's consciousness level enhanced. He began to open his eyes and withdraw from painful stimuli. Progressively he could localize to pain and spontaneous eye opening.

Table 1: Laboratory data of 21-yr-old man, admitted in Sina Hospital, Tehran University of Medical Sciences, Iran

	A	B	C	D
White –cell count 1000/mm^3	8.9	12.5	10.1	9.6
Hemoglobin g/dl	9.7	8.9	11.8	13.3
Platlet 1000/mm^3	310	208	190	15
Erytrocyte sedimentation rate mm/h	55	-	9	10
Glucose mg/dL	99	100	121	98
Blood urea nitrogen mg/dL	28	15	22	10
Creatinine mg/dL	0.7	0.5	0.7	0.5
Triglyceride mg/dL	246			115
Cholestrol mg/dL	109			107
High-density lipoprotein mg/dL	10			29
Low-density lipoprotein mg/dL	61			49
Albumin g/dl	3	3.1	2.9	3.4
Sodium mEq/L	140	135	140	140
Potassium mEq/L	4.1	4	3.9	4.3
Calcium mg/dL	8.1	8	7.9	8.2
Magnesium mg/dL	1.6	2.1	2.2	1.9
CD[1]3 % of Lymphocyte		50	57	
CD4 % of Lymphocyte		28	37	28
CD8 % of Lymphocyte		19	20	24
CD16 % of Lymphocyte		8	8	14
CD19 % of Lymphocyte		6	12	1`0
CD20 % of Lymphocyte		7	8	9
IgM [2] g/L		45	84	308
IgG [3] g/L		541	795	995
IgA[4] g/L		75	105	146
IgE [5] IU/ml		24.5	42	6
Circulating immune complexes mg/ml		0.2	0.1	2

A= at admission; B =before stem cell therapy; and C =1 month later; D =3 month later
[1]CD = cluster of differentiation, [2]IgM=Immunoglobulin M, [3]IgG= Immunoglobulin G, [4]IgA=Immunoglobulin A, [5]IgE= Immunoglobulin E

On fourth week PSCT he was able to look intentionally and obey only simple command such as eye closing and hand grasping. Tracheostomy and nasogasrtic tube were removed on week six. On second month, he was examined by our neurologists. No definite sensorimotor neurological deficits were confirmed. He could smile, cry, and obey some of the complex requests but verbal communication was difficult for him. Eventually he was discharged and returned home on tenth week PSCT. No stem cell related adverse event and complication was observed during the research.

We have followed him several times since 2008 and observed that his mental state and his most recent memory function have been gradually improved. He could walk independently. His orientation to time and place, memory, judgment, attention, perception, vocabulary, calculating ability is completely normal but he has only degrees of slurred speech and he repeats each sentence more than 2 times. Non-contrast computerized tomography of the brain performed in 2010 and it revealed no progression in brain atrophy and hydrocephalus ex-vacu with fourth, third and lateral ventricles (Fig. 2).

Discussion

The leading cause of death in North America is cardiac arrest, with more than 350, 000 deaths annually (14).

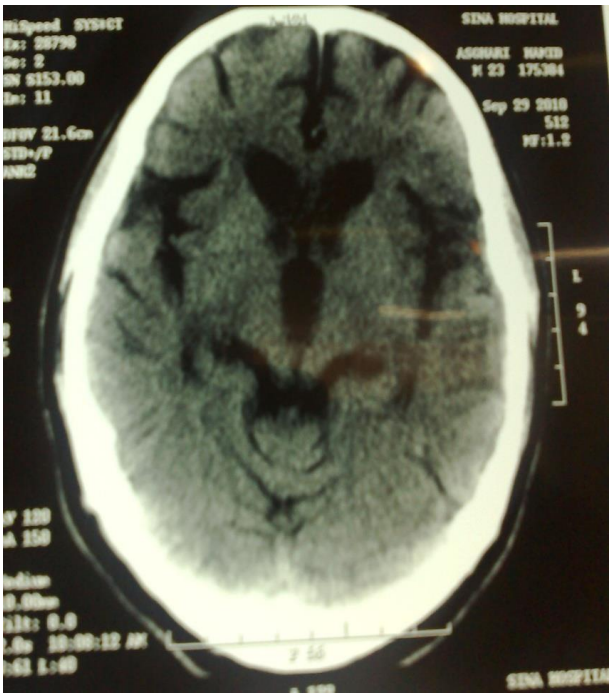

Fig. 2: Non-contrast computerized tomography of the brain showed any progression in brain atrophy and hydrocephalus ex-vacu with fourth, third and lateral ventricles after two years

Prognosis of survivors are variable, but poor neurological outcome is common (2), with only 3% to 7% achieve their preceding level of function (3). The economic effect of cardiac arrest was the subject of a cost-effectiveness study (15). In-patient rehabilitation lasts a mean of 41.5 days so the economic burden of survivors of anoxic brain injury is noticeable (16).

This patient suffered from severe neurological damage following cardiac arrest. In spite of optimized cardiopulmonary function and systemic perfusion, continued care in an appropriately equipped intensive care unit and using appropriate neuroprotective strategies other than induced hypothermia, no improvement was detected in his neurologic status. Although all the sedative medications were subsequently discontinued, the patient did not awake and decorticate posture were noticeable, during forty-six days of ICU stay.

Previous literature has demonstrated the effect of barbiturate thiopental used in a controlled clinical trial. Although thiopental decreased metabolism, edema formation, intracranial pressure (ICP), seizure activity, it failed to show a therapeutic benefit (17).

Otherwise, glucocorticoid treatment to the study agent (thiopental or placebo) did not show additional benefit (18). Another study found no advantage in the treatment with the calcium channel blocker lidoflazine (19). Hyperglycemia was associated with poor recovery after cardiac arrest (20). Another controlled clinical trial found no outcome difference with intravenous magnesium, despite its antiarrhythmic effects and ability to block excitatory neurotransmitters (21).

Therapeutic hypothermia is presently available for cerebral protection (14). The 2005 Emergency Cardiac Care Guidelines approved hypothermia as an IIa recommendation in ventricular fibrillation and ventricular tachycardia cardiac arrest (22). Therapeutic cooling remains underutilized in spite of level IIa recommendation from the American Heart Association and two randomized control trials (22-26). Unfortunately, induced hypothermia was not available in our setting.

We had fully reviewed and searched the relevant literatures to determine whether another therapeutic option has been described after cardiac arrest (search words: cardiac arrest, neurologic improvement outcomes). Our search revealed no studies or case reports for improving neurologic outcome after cardiac arrest. Therefore, we decided to offer him the benefits of stem cell therapy as a last shot. We hypothesized that endometrial stormal cells are more suitable candidate for cell therapy for cell regeneration, based on the following properties high levels of growth factors and capability of angiogenesis, ability to inhibit inflammatory responses suitable for our case, lack of karyotypic abnormalities and tumorogenecity.

Eventually successes in animal models have led to case experimentations, human studies, and transplant trials in the human population. Clinical trials for Parkinson's disease, Huntington's chorea, Spinal cord injury, and Stroke were conducted previously (27, 28).

Stem cell technology has been tried as a novel technique to study human motor neurons (Especially for ALS) that indicates satisfying results (29,

30). There were reports of improvement in a clinical trial with autologous transplantation of NSCs for patients with open brain trauma (31).

Our case report has illustrated that stem cell therapy shall improve the content and level of consciousness after cardiac arrest. This outcome suggests that stem cells may have the potential to differentiate into appropriate neurons and consequently regenerate injured neurons' function. Although stem cell therapy is still a long way off, there are rationales to be optimistic about its positive effects for treating neurological injuries, and regenerate lost function of the brain. Moreover, we should emphasize that optimal care of patients with cardiac arrest depends on coordinated integration of prehospital, emergency department, cardiology, intensive care medicine, and rehabilitation care.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgments

The authors declare that there is no conflict of interests.

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