

Autologous bone marrow derived mononuclear cells for the treatment of drug resistant epilepsy

Abstract

Epilepsy is a neurological disorder characterized by two or more unprovoked seizures with abnormal brain activity, Cognitive and behavioral changes usually accompanies epilepsy, like hallucinations delusions and apathy. Of all cases of epilepsy 30% are resistant to conventional treatment. Drug resistant epilepsy is defined as recurrent seizures refractory to a regimen of two or more antiepileptic drugs. Stem cell therapy is a possible alternative with minimal side effects; it is currently used for treatment of variety of diseases including neurological disorders like multiple sclerosis and stroke. In this clinical study, 20 Iraqi patients included, aged 2-39 year. 8 females and 12 male with multidrug resistant epilepsy, at least after 3 months of diagnosis and treatment. The 20 patients were kept on drugs, more than 2 drugs 80%, 2 drugs 20%, all the patients underwent autologous bone marrow mononuclear cells infusion intravenously. Mononuclear cell counts ranges from $2-4 \times 10^8$ per product with 97 % viability. Two sessions done in 8 weeks' time. Out of 20 patients 13 patients showed improvement (65%) in seizure activity in form of 50-100% reduction in 6 months after stem cell therapy, in addition there was improvement in appetite and sleep rhythm. Autologous bone marrow derived mononuclear cells systemic infusion is a safe clinical procedure with promising results in drug resistant epilepsy.

Keywords: antiepileptic drugs, stem cell therapy, marrow mononuclear cells

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Introduction

Epilepsy is a neurological disorder characterized by two or more unprovoked seizures with abnormal brain activity (Excessive electrical discharge affecting neurons leading to recurrent seizures); Cognitive and behavioral changes usually accompanies epilepsy, like hallucinations delusions and apathy.^{1,2} Epilepsy affects more than 60 million patients all over the world, with main preference to low socioeconomic groups.³

Common epilepsy treatment is mainly symptomatic aiming at seizure suppression, Antiepileptic drugs reduce the overall brain firing through activating the GABA (gamma aminobutyric acid) ergic channels, in addition the long use of antiepileptic drugs can lead to undesirable effect. Of all cases of epilepsy 30% are resistant to conventional treatment. Drug resistant epilepsy is defined as recurrent seizures refractory to a regimen of two or more antiepileptic drugs.⁴⁻⁷ Most classic treatment strategies concentrate on neurological aspect neglecting the neuropsychiatric part of the problem. Surgical intervention is effective method to treat epilepsy but applicable in only 50 % of cases with the possible side effects like brain damage. Surgical procedures include the partial removal of seizure generating brain tissue.⁸ So there is a need for more efficient and less toxic treatment.

Stem cell therapy is a possible alternative with minimal side effects, currently used for treatment of variety of diseases including neurological disorders like multiple sclerosis and stroke.⁹ Stem cells can treat both biologic and psychiatric outcome of epilepsy. The goal is to enhance stem cell differentiation and growth toward the GABA ergic lineage and rewire The GABA deficient neural circuitry seen in epilepsy. Preclinical results in stem cell therapy showed promise in treating epilepsy as they reduce the frequency of spontaneous seizure activity, the stem cell sources are:

- 1-hippocampal precursors
- 2-neural stem cell

- 3-GABAergic precursor cells
- 4-systemic bone marrow derived mononuclear cells
- 5-mesenchymal stem cells

The use of bone marrow derived mononuclear cells and mesenchymal stem cells proposed the method to truly address the root cause of pathophysiology includes the secretion of growth factors like (VEDG, GDNF, HGF) which enhance neurogenesis.¹⁰ Autologous administration of stem cells has the following advantages over the allogeneic ones:

- Safety related to tumorigenesis and cell mutation.
- 2-No need to administer immune suppressive drugs as the cells are autologous.

Patients and methods

Patients characteristics and selection

Patient's selection was based on the World Medical Association Declaration of Helsinki: in accordance with the Iraqi guidelines for stem cell therapy. Intervention was performed after gaining written informed consent from all the patients/relatives in case of affection of higher mental functions).¹¹ A single armed clinical study, 20, aged 2-39 year. 8 females and 12 male with resistant multidrug treated epilepsy, at least after 3 months of diagnosis and treatment.

Product preparation and infusion:

Bone marrow aspiration was done under local anesthesia or general anesthesia, depending on the individual case. Around 2% of total blood volume of bone marrow was aspirated from the posterior iliac crest after proper sterilization using bone marrow aspiration needle (size according to the patient) and collected in heparinized syringes. Mononuclear cells (MNCs) were obtained by filtration. The isolated MNCs were checked for viability manually and confirmed on automated cell count machine. The separated MNCs ($2-4 \times 10^8$

8) per product were administered immediately after filtration. The mononuclear cells products were infused into antecubital vein (average 40 cc). The total mononuclear cell count ranges from 2×10^8 to 4×10^8 for the whole product.

Outcomes measured for safety included immediate reactions after cell infusion and evidence of tumor formation at 6 months to one year. Patients were followed monthly after the procedure for 1 year to determine clinical progress regarding seizure activity.

Follow up:

Patients were monitored regularly for any immediate adverse effects for 3 days after the cell therapy. The patients were advised for regular follow-up at 1 month. Were monitored for any long-term adverse effects. The patients were followed up for minimum of 6 months.

Results

20 Iraqi patients diagnosed with resistant epilepsy (2-39 years) were included in this study. 12 male patients and 8 female with age range of 2-39 years, The 20 patients were kept on drugs, more than 2 drugs 80% 2 drugs 20%, all the patients underwent autologous bone marrow mononuclear cells infusion intravenously. Mononuclear cell counts ranges from $2-4 \times 10^8$ per product with 97 % viability.

Two sessions done in 8 weeks' time:

Two patients had mild fever 24 hours within infusion which responded to simple antipyretics. None of the patients had serious adverse events.

Out of 20 patients 13 patients showed improvement (65%) in seizure activity in form of 50-100% reduction in 6 months after stem cell therapy, in addition there was improvement in appetite and sleep rhythm.

The response rate was 65% 2 female patients showed total disappearance of epileptic seizures within 4 weeks of the procedure then recurred with final 80% reduction of seizures in one case after 6 months from the 2 procedures (Table1). The other patients showed reduction in the epileptic activity varying from 50-70% after doing a couple of intravenous autologous bone marrow derived mononuclear cells infusion.

Time from performing the procedure till getting improvement ranges from 2-16 weeks after autologous bone marrow mononuclear cell infusions.

Discussion

Autologous bone marrow derived mononuclear cells is a possible safe alternative to treat cases of drug resistant epilepsy and all drug side effects in addition to remaining seizure activity but with minimal cellular infusion side effects, so our main concern was patients safety.¹² Stem cells can treat both biologic and psychiatric outcome of epilepsy¹³ The proposed mechanism of action for those infused cells is enhancing stem cell differentiation and growth toward the GABAergic lineage and rewiring The GABA deficient neural circuitry seen in epilepsy. That can be exerted through humoral and cellular ways.¹⁴

Preclinical results in stem cell therapy showed promise in treating epilepsy as they reduce the frequency of spontaneous seizure activity, and there are many studies showing safety of the autologous bone

marrow derived mononuclear cells and even autologous bone marrow derived mesenchymal stem cells in cases of brain stroke.^{15,16}

In regard to safety since our procedure is autologous intravenous with minimal manipulations, in addition it is simple noninvasive and use of these cells does not hold the risk of any graft versus host diseases or tumors.

Failure of response in the 7 patients might be related to the severity of the brain lesion or the dose of stem cells given in the treatment session, frequent successive procedure will maintain the positive anti-seizure effects (Table 1). The possible mechanism of action includes the secretion of many growth factors in addition to immunomodulation and suppression of inflammatory response in addition other important factors is the sum of the product given in the general circulation leading to possible pulmonary trapping.¹⁷⁻²⁰

Table 1 Clinical characteristics and response to treatment

Response	Response rate	anticonvulsants	Sex	Age	patient number
No		>2 drugs	M	6 y	1
Yes	70%	>2 drugs	F	21 y	2
Yes	50%	>2 drugs	F	2y	3
No		2 drugs	F	5 y	4
Yes	70%	2 drugs	M	4 y	5
Yes	50%	>2 drugs	M	11 y	6
Yes	50%	>2 drugs	F	15 y	7
Yes	50%	>2 drugs	F	9 y	8
Yes	70%	>2 drugs	F	39 y	9
Yes	80%	2 drugs	F	30 y	10
No		>2 drugs	M	7 y	11
No		2 drugs	M	2 y	12
Yes	50%	>2 drugs	M	30 y	13
Yes	80%	>2 drugs	M	14 y	14
No		>2 drugs	M	22 y	15
Yes	60%	>2 drugs	F	8 y	16
No		>2 drugs	M	11 y	17
Yes	80%	>2 drugs	M	25 y	18
Yes	50%	>2 drugs	M	18 y	19
No		>2 drugs	M	30 y	20

Definitely and logically using higher number of stem cells given in other methodology like intrathecal or intra-arterial can give better results.

Acknowledgments

None.

Conflicts of interest

Author declares that there is none of the conflicts.

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