



Efficacy of mesenchymal stem cell therapy for the management of Chronic stroke patients in Pakistan; Randomized Control Trial

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Abstract

Objective

The main objective of this study is to assess the efficacy of mesenchymal stem cell therapy for the management of chronic stroke

Methods

In this randomized control trial patients were placed in two groups who received intravenous injections of autologous mesenchymal stem cells at the same time placebos were also given to the patients. The



clinical and neurological parameters of the patients were measured before and after the completion of the treatment.

Results

The results of the study revealed that mesenchymal stem cells were infused among the patients with a mean of 4.49×10^7 . The patients didn't experience any adverse effects pre and post-treatment. Glasgow outcome scale showed some significant clinical improvement in receiving mesenchymal stem cell therapy as compared to placebo.

Conclusion

Mesenchymal stem cell therapy is safe to use as it helps to improve the condition of stroke along with neurological conditions.

Keywords: Cell therapy, chronic, mesenchymal stem cells, stroke

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Introduction

According to World Health Organization (WHO), stroke is defined as "a rapidly developing clinical sign of focal or global disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death with no apparent cause other than vascular origin" [1]. Globally, it is one of the most common neurological disorders leading to death [2]. Every year approximately 15 million new cases are increased [3]. Over the years, the prevalence of stroke has widely increased especially in those countries which are low-income [4]. Pakistan is considered one of the most richly populated countries in the world, and studies conducted in Karachi revealed that the prevalence of stroke is 4.8% and 19.1% [5,6]. As the population ages, strokes are likely to become a bigger health and social burden for society. Stroke causes long-term reliance, mortality, and impairment in adults, and its treatment is also quite expensive for patients [7,8]. Time is the most important factor affecting the appropriate execution of the interventions held for acute stroke and defining the patient's final prognosis in the treatment of strokes, which is a dynamic process. Due to the patient's delayed admission to the hospital, the window of time during which the treatment is effective is passed by a large number of patients [9,10]. The main cause of refusal of treatment from the patients is the lack of awareness of signs and risk factors associated with patients [9], or a hope that the symptoms would fade or

improve on their own, which has been identified in several studies as one of the main causes behind the extension of this period between the onset of the symptoms and the arrival at the hospital [11]. The general public also knows less about stroke than it does about other diseases like cancer, AIDS, or acute coronary syndrome, even though stroke is a disease with a high prevalence and severity [12]. There is currently no treatment available to help patients regain their neurological function. The sub-ventricular zone displayed active neurogenesis, producing new neurons with the same properties as their deceased counterparts, according to recent research on intra-cerebral bleeding in animal models [13]. However, after a stroke, very few mature dead neurons were successfully replaced although several newly produced neurons die within the first few weeks [14]. Various studies conducted on animal models have shown that mesenchymal stem cells, neural stem cells, embryonic stem cells, umbilical cord blood cells, and other cell types have all been successfully used for the restoration of nerves [15]. Hence, for this purpose consistent and accessible cell supply is essential. Bone marrow-derived mesenchymal stem cells, have been demonstrated to produce trophic factors which help in neuro-regeneration and neuro-restoration after stroke [16].

A study conducted by Band et al., revealed that autologous mesenchymal stem cell infusions were safe and effective for stroke patients [17].

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This study is conducted to assess the efficacy of mesenchymal stem cell therapy in stroke patients.

Material and Methods

This study was conducted in the public hospital of Karachi where 10 patients were randomized into the control and treatment group. All the participants were informed regarding the aim and objective of the study. Informed consent was taken from all the patients. Hence, the ethical committee of the hospital has approved the study. The study included those patients who were already stroke patients for one year with severe disability and those patients were excluded who had severe co-morbidity along with those who were unwilling to participate. With the onset of intracerebral hemorrhage Computed tomography (CT) scan was conducted among stroke patients immediately on the day before the first injection of either MSC or placebo. Magnetic resonance imaging (MRI, 1.5 Tesla) of the brain was performed. Follow-up of patients was completed in the 40th week upon study completion. After the first and second infusion of autologous mesenchymal stem cell, the safety of the patient and efficacy of the treatment was assessed till the 40th week. Hence immediate or delayed adverse responses were observed such as allergic responses, and local and systematic complications. Extended Glasgow Outcome Scale results were also utilized to monitor the progression of patients' disabilities over time [18].

Statistical analysis

In the study, SPSS version 21 was performed for Statistical analysis. Non-parametric Wilcoxon's rank sum test was used to compare variables collected from the treatment and control groups on the presumption that the data were normally distributed. The scores of the Extended Glasgow Outcome Scale of the patients at the time of evaluations were analyzed using a paired t-test with one-sided testing. Hence Fisher's exact test was used to analyze the incidence of clinical neurological improvement between the treatment and control groups of patients. If $P < 0.05$, differences between groups were considered significant. Differences between groups were considered significant if $P \leq 0.05$.

Results

We performed a randomized, controlled trial in a small sample size of approximately 10 patients (five females and five males), with a mean age of 42 years (range: 41-59 years), who had experienced intracerebral hemorrhage for a year, to assess the safety and effectiveness of autologous mesenchymal stem cell therapy. CT scan of 10 patients revealed that the basal ganglia region was the area where a cerebral hemorrhage of 52 mL (12–75 mL) was located initially. The lesion areas were compared between the treatment and control groups. Patients in the treatment group had statistically lower body weights than those in the control group.

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Table1- Characteristics of patients administered intravenous autologous mesenchymal stem therapy

Patients ID	Gender/Age	Site of hemorrhage	Ct Scan Readings	Hemorrhage Volume (mL)	Viability	MSC (x10)	MSC/kg (x10)
P#1	M/48	Right Basal ganglia	4.3x5.5x5.6	74	94.8	3.0	5.43
P#2	F/50	Left Basal ganglia	4.0x2.0x3.0	11	91.2	3.1	5.12
P#3	M/56	Right Frontal lobe	6.5x4.9x.2.0	63	90.2	3.2	5.41



P#4	F/54	Left Frontal lobe	5.5x4.3x4.9	21	95.6	1.43	2.13
P#5	M/52	Right Temporal lobe	2.3x4.0x3.2	73	88.9	4.4	13.1
P#6	F/50	Left Frontal lobe	6.1x4.1x3.2	71	98	5.4	6.19
P#7	F/49	Right temporal lobe	7.1x2.3x5.1	70	90.1	5.6	11.3
P#8	F/48	Left Frontal lobe	4.1x6.1x4.9	67	98	6.5	12.6
P#9	M/47	Left Frontal lobe	7.4x2.5x4.7	55	92	8.1	9
P#10	M/42	Right Temporal lobe	6.7x2.3x4.1	52	91	7.1	10.8

Table 2-Extended Glasgow Outcome Scale scores (n = 5) treatment group

Duration of study	Extended Glasgow outcome scale						
	P#1	P#2	P#4	P#6	P#8	P#10	p-value
1 st week	4	5	3	3	4	3	
12 th week	4	6	4	3	4	3	1
16 th week	4	4	4	3	4	4	1
24 th week	3	3	3	3	4	4	0.18
36 th week	3	3	4	3	4	5	0.08
48 th week	3	3		-	-	5	0.04

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Discussion

This study was conducted to assess the efficacy of mesenchymal stem cell therapy by administering intravenously for improving the neurological outcomes of stroke patients. Despite modern advancements in neurosurgery, intracerebral hemorrhage victims frequently experience severe, long-lasting, and disabling symptoms such as impairments in terms of motor and cognitive functioning. Although, poor neurological recovery continues. It is essential to create treatment approaches that will encourage neurological healing. The therapeutic efficacies of different cell types have been researched recently due to the increased interest in stem cell-based therapy [19]. Certain categories of cell types have been

considered to be challenging for widespread application. Human neural stem cells could be used but they can only be obtained through aborted fetuses [20].

Bone marrow-derived cells showed excellent potential for initial effectiveness and safety [21].

The results of the study revealed that intravenous administration of mesenchymal stem cells in stroke patients did not experience any adverse consequences along with no morphological or phenotypic changes occurred. Patients did not suffer any infusion-related toxicity or problems during or after the mesenchymal stem cell infusion which is similar to a study conducted by Rodríguez-Frutos et al., according to his preliminary findings,



intravenous injection of mesenchymal stem cells does not cause any noticeable side effects. Another study conducted by Honmou, O et al., revealed that no adverse events were observed among stroke patients during the administration of autologous mesenchymal stem cells [22]. Various findings of clinical trials of MSC therapy reveal that neuro-restoration, increased neuronal plasticity, and a decrease in lesion volume are observed. Lesions at the sub-ventricular zone have been observed in a large number of stroke patients [23]. The geographical lesions outside the sub-ventricular zone, where endogenous neurogenesis continues into adulthood and enhance endogenous neuro-regeneration, may be associated with the likely positive benefits of mesenchymal stem cell therapy [23]. In the study to exclude the confounding factors from the observation of mesenchymal stem cell-mediated neurological recovery, was supplied with mesenchymal stem cell therapy to patients who had a significant neurological disability and stable baseline scores with the follow-up of one year with the onset of intracerebral hemorrhage.

Conclusion

In the study, it has been suggested that intravenous infusion of autologous bone marrow-derived mesenchymal stem cell therapy is effective and safe to regain the neurological functions of stroke patients.

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