Intrathecal Autologous Bone Marrow Stem Cell Therapy in Children with Autism Spectrum Disorder

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Autism Spectrum Disorder

- Autism spectrum disorder (ASD), characterized by difficult social communication, restricted interests and repetitive behaviors in early childhood, which cannot be justified by other medical or neurological condition.
- Despite its increasing prevalence, there are still no effective treatments for ASD based on its etiology and pathophysiology

Autism Spectrum Disorder

- In light of the multifaceted nature of ASD, the emerging concept of stem cell based therapeutics for ASD treatment has generated increasing support. For instance, **bone marrow mesenchymal stem cells (BMMSCs)** have been suggested for treatment of ASD by the virtue of their known ability to stabilize the immune system, improve angiogenesis, reinforce cortical plasticity, improve synaptic plasticity

Intrathecal Autologous Bone Marrow Stem Cell Therapy

- There are over ten studies reporting the efficacy and safety of stem cell therapy with different methods including autologous bone marrow mononuclear cells (BMMNCs), fetal stem cells, combined transplantation of human cord blood mononuclear cells (CBMNCs), and umbilical cord-derived mesenchymal stem cells (UCMSCs) in ASD patients
- . However, the majority of them are case report or case series studies that are limited to a few geographical regions, thus not providing sufficient evidence for making firm clinical decisions

Intrathecal Autologous Bone Marrow Stem Cell Therapy in Children with Autism Spectrum Disorder

- The present study was aimed to determine the efficacy and safety of autologous **bone marrow mesenchymal stem cells (BMMSCs)** therapy in comparison with the usual treatment in children with ASD. We used autologous BMMSCs, which are safer in terms of the risk of infections and more available in that they do not require donors, compared with allogenic transplantation.

Intrathecal Autologous Bone Marrow Stem Cell Therapy in Children with Autism Spectrum Disorder

- We chose intrathecal route because of its relative safety (e.g. lower risk of embolism) and better delivery of the cells to treatment target, the brain, which can in turn improve the homing of stem cells. Intrathecal injection has unique features which allow for higher concentrations of stem cells to migrate to the affected site compared with intravenous injection

Study design and settings

- This parallel single-blinded randomized controlled trial was carried out on children having a definite diagnosis of ASD (according to the clinical interview by two child psychiatrists based on DSM-5 criteria), who were referred to the child Psychiatry Clinic of Ibn-e-Sina hospital or the establishments covered by the social welfare organization in Mashhad, Iran, between April and August 2016.

Ethical considerations

- The research plan was described in depth for all patients and their parents. Informed written consent was obtained from all parents.
- Patient confidentially was preserved throughout the study.
- The patients were fully supported by the researchers in the event of any research-related complication and were free to leave the research project at any stage.
- This research project was approved by the Ethics Committee of Mashhad University of Medical Sciences

Inclusion and exclusion criteria

- The inclusion criteria were being aged 5-15 years and having a definite diagnosis of ASD according to DSM-5 criteria based on a structured clinical interview by two child psychiatrists.
- The patients with any of the following were not included in the study: serious complications during the treatment, history of allergic reactions, seizures during the past 6 months, brain trauma, moderate to severe extrapyramidal symptoms, tardive dyskinesia, severe self-injury behaviors, autoimmune diseases, severe hematologic, hepatic, renal, or pulmonary disease, severe focal or systemic infections or hemoglobin < 8 g/dL.
- Moreover, patients receiving any other simultaneous treatments that can affect the stem cell therapy were excluded.

Sample size

- Considering a two-sided α of 0.1 and a study power of 80%, the sample size was calculated to be at least 36 (18 in each group) based on the results of a study by Sharma et al. (Sharma et al., 2012).
- Non-random sampling method was used in this study to select the subjects in both groups. Then the participants were randomly assigned to 2 groups of intervention and control.

Study Design

- Both groups received ASD rehabilitation therapies as usual including educational and rehabilitation services including sensorimotor enhancement, auditory training, occupational therapy, speech therapy, music therapy, and exercise .
- In addition, all patients received risperidone (0.06 mg/kg per day). The intervention group received two injections of autologous BMMSCs during a period of one month. All patients were followed for at least 12 months.

Preparation and injection of bone marrow mesenchymal stem cells

- The intervention group underwent general anesthesia Then, bone marrow aspiration was performed
- BMMNCs were isolated from bone marrow aspirate and were prepared in the technical process for intrathecal injection.

Preparation and injection of bone marrow mesenchymal stem cells

- In the next step, the patients in intervention group were hospitalized again for injection of the MSCs. Then, about 0.5-1×10^8 autologous MSCs derived from the patients' bone marrow per 2.0 ml were injected intrathecally under anesthesia.
- In the absence of any complication, the patients were discharged after 72 hours. One month later, a second injection was performed according to the same procedure with $0.3\text{-}0.5\times10^8$ cells per 2.0 ml being injected intrathecally this time.

Side effects of stem cell therapy

- After each injection, the patients were visited on alternate days to assess for possible complications during the first week following their discharge from the hospital. During the one-year follow-up period, they were checked via phone contact on a monthly basis for any possible complications such as pain in the

Data collection

- Baseline demographic data including age and sex were gathered.
- Patients were assessed using childhood autism rating scale (CARS), Gilliam autism rating scale-second edition (GARS-II), and clinical global impression (CGI) at the baseline, as well as 6 and 12 months after intervention.
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Results

- Overall, 36 children with ASD were included in two groups of intervention (N=18) and control (N=18). However, four patients in the intervention group abandoned the study before any intervention.

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Results

- Overall, 32 patients in two groups of intervention (n=14) and control (n=18) completed the study, of which 27 (84.4%) were male.
- Mean age was 9.50±2.14 years.
- The two groups also had no significant difference in terms of sex distribution (P=0.075).

Results

- **At the baseline**, the groups showed no significant differences in terms of the main outcomes, namely CARS total score, GARS-II autism index, CGI global improvement, and CGI severity of illness scores.

Results

- The improvements in CARS total score, GARS-II autism index, and CGI global improvement showed no significant differences between the groups over 12 months.

Results

- There was no significant difference in **CARS total score** between the two groups neither at the 6th month nor at the 12th
- However, the mean score of **‘relationship to people’ subscale** was significantly lower in the intervention group after **12 months** (P=0.001), indicating a more remarkable improvement in this group after a one-year follow-up.

- ,**CGI severity of illness**, in spite of showing no significant at baseline and 6 months after intervention, was **significantly different** between the two groups **12 months** after the intervention (P=0.049).
- The mean difference from baseline in CGI severity of illness score was significantly higher in the intervention group at 12th month (P=0.004), which indicates that the intervention group showed higher clinical improvement in their symptoms at 12th month .

Comparison of Clinical Global Impressions (CGI) outcomes, before the intervention, as well as 6 and 12 months after the intervention

**Repeated measures ANOVA test was used to calculate time*group interaction

Variables	Time-point	Intervention (n=14)		Control (n=18)		Between-group comparison	
		Mean	SD	Mean	SD		
Severity of illness	Baseline	4.43	0.65	4.44	0.86	0.954*	F=6.719 P=0.002**
	6 months Change	3.71 -0.71	0.61 0.46	4.06 -0.38	0.87 0.50	0.223* 0.071*	
	12 months Change	3.07 -1.35	0.73 0.49	3.78 -0.66	1.11 0.68	0.049* 0.004*	
Global improvement	Baseline	3.36	0.50	3.56	0.51	0.279*	F=1.411 P=0.252**
	6 months Change	3.29 -0.07	0.47 0.61	3.72 0.16	0.83 0.70	0.088* 0.326*	
	12 months Change	2.86 -0.50	0.77 0.65	3.56 0.00	1.29 1.08	0.084* 0.139*	

Side effects

- In general, injection-related side effects, also short-term and long-term complications in the12 months of follow up were not observed in any of the patients.

Conclusion

- The augmentation of stem cells to common ASD treatment in our sample population had promising results in some autism-related indicators compared with the conventional treatment, but generally it was not mainly superior to the routine rehabilitation treatments

Conclusion

- According to our results, although the use of autologous BMMSCs is mainly safe, their efficacy, given the costly and complex preparation and injection processes is unfavorable.
- However, further studies on the safety and efficacy of different stem cell therapy methods in ASD are still necessary.

For more information please go to the published article:

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