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Autologous Bone Marrow Cell Therapy for Autism: An Open Label Uncontrolled Clinical Trial

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Abstract

Aim: The aim of this study is to assess the safety and effectiveness of autologous bone marrow mononuclear stem cell (BMMNC) transplantation in patients with autism.

Materials and Methods: An uncontrolled clinical trial was carried out on 24 children with autism aged 3 to 16 years. The intervention consisted of two intrathecal administrations of stem cells.

Results: Improvements in behaviors, emotional and intellectual functions were seen in 19 patients (79.2%) while 2 cases (8.3%) showed no changes and 3 other cases (12.5%) presented with more severe symptoms. The overall severity of autism lessened after transplantation. The total CARS score was significantly improved. Of the 15 CARS domains, two domains (Body Use and Intellectual Response) showed statistically significant improvement 3 months after transplantation. After 6 months, significant improvement was also observed in 3 additional domains.

Conclusion: Autologous BMMNC transplantation appears to be a safe and effective therapy for patients with autism.

Trial Registration: ClinicalTrials.gov Identifier: NCT02627131 Registered on December 08, 2015.

Keywords: Autism; Stem cells

Introduction

Autism Spectrum Disorders (ASD) are a group of heterogeneous neuro developmental disorders characterized by dysfunctions in social interaction, communication and presence of repetitive and stereotypic verbal and non-verbal behaviors [1]. The prevalence of autism worldwide was estimated to be per 1000 children in 2012 [2]. The prevalence in the United States was roughly 1% in 2006, having increased by 57% since 2002 [3]. Current estimate of the lifetime costs of caring for a child with autism ranges from $3.5-5 million USD. To accommodate the complex needs of families with members affected by autism, the United States incurs estimated costs that total nearly $90 billion USD annually [2]. Different approaches have been used to manage this condition including behavioral interventions and medications. Medications help to relieve the signs and symptoms associated with autism: Selective Serotonin Reuptake Inhibitors (SSRI) to manage anxiety or depression, antipsychotics to decrease behavioral abnormalities, anticonvulsants to control seizures and methylphenidate to treat attention deficit hyperactive disorder. However, these pharmacological interventions fail to address the core symptoms of autism including limited interests in activities or play, social interactions and relationships, verbal and nonverbal communication [4]. The path physiology and mechanisms of autism have not been thoroughly clarified. Among many theories, neural hypo perfusion and immune deregulations have been reported to be the two major physiological alterations and correlated with the severity of autism symptoms [5]. Hematopoietic Stem Cells (HSCs) have been proved to promote blood perfusion to the ischemic brain area through angiogenesis in animal models [6,7]. Preclinical models on rats and hippocampus have shown that human umbilical cord blood mononuclear cells (HUCB MNCs) can significantly improve the microenvironment of the aged hippocampus and rejuvenate the aged neural stem/progenitor cells, therefore suppress inflammation [8,9]. Mesenchymal stem cells (MSCs) demonstrated immune regulatory properties by suppressing T cells, B cells, NK cells as well as dendritic cells [10,11]. Whole Bone Marrow Mononuclear Cells (BMMNCs) which consist of both HSCs and MSCs could potentially produce a better and synergic effect as compared to each cell line alone [12-14].

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Table 1: Patients' characteristics.

Sex		
	Male	23 (95.8%)
	Female	1 (4.2%)
Age (years)		
	Median	6
	Min	3
	Max	16
	Mean	7.1
	Standard Deviation	3.2
Weight (kg)		
	Median	25
	Min	16.5
	Max	54
	Mean	28.3
	Standard Deviation	10.8
CARS Score		
	Median	45.8
	Min	32.5
	Max	53
	Mean	44.8
	Standard Deviation	5.5
Mononuclear cells transplanted per one kg of body weight ($^{*}10^{6}$)		
	Median	17.7
	Min	5
	Max	49.7
	Mean	19.3
	Standard Deviation	10
CD34+ cells transplanted per one kg of body weight ($^{*}10^{6}$)		
	Median	2.1
	Min	0.3
	Max	6.1
	Mean	2.1
	Standard Deviation	1.3

It has been proven that, presence of maternal antibodies to fetal nerve tissue [15], atypical levels of proinflammatory cytokines in the cerebral spinal fluid [16], overexpression of immune-related gene networks [17] may contribute to pathogenesis of immune pathology in the brains of patients with ASD. In addition, excessive microglial activation leading to aberrant nerve connectivity [18,19] can cause immune regulation or modulation of brain connectivity among ASD patients. There were evidences of a chronic up-regulation of inflammatory cytokines in the ASD brain [20,21]. Buehler et al. [22] have reported the correlations between pro-inflammatory cytokine levels and autistic symptoms [22].

Some ground-breaking studies have shown promising results suggesting that stem cell therapy could be an additional treatment for autism [23-25], however further research is needed to demonstrate the safety and effectiveness of this approach. The aim of our study was to evaluate the safety and effectiveness of BMMNCs in the management of autism at Vinmec International Hospital.

Table 2: Adverse events.

Adverse events	N (%)
Vomiting	3 (12.5%)
Transient increased hyperactivity	20 (83.3%)
Prolonged increase in hyperactivity	4 (16.7%)
Conjunctivitis	2 (8.3%)
Fever	0 (0%)
Bleeding	0 (0%)
Hematoma	0 (0%)
Seizures	0 (0%)
Neurological deficits	0 (0%)
Others	0 (0%)

Materials and Methods

Study Design

It is an open label uncontrolled clinical trial of 24 patients with autism. The study started in April 2014 and was completed in December 2015.

Patient Selection Criteria

Patients of both sexes, aged between 3 and 16 years with a confirmed diagnosis of autism according to the diagnostic criteria for autism spectrum disorder in Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [1], and a CARS score ≥ 37 were recruited at Vinmec International Hospital for this study. The exclusion criteria were epilepsy, hydrocephalus with ventricular drain, coagulation disorders and allergy to anesthetic agents, severe health conditions such as cancer, failure of heart, lung, liver or kidney, active infections.

Intervention

The intervention included 2 intrathecal administrations of autologous BMMNCs at baseline and 3 months afterward conducted by certified anesthesiologists.

Isolation of BMMNCs

Bone marrow aspiration from the bilateral posterior iliac crest was performed under general anesthesia in the operating theatre. The volume collected depends on the patients' body weight as followed: 8 ml/kg for patients under 10 kg; [80 ml + (body weight in kg - 10) x 7 ml] for patients above 10 kg but no more than 200 ml in total. BMMNCs were separated from the aspirate using the density gradient centrifugation (Ficoll method) [26]. The BMMNCs were counted and checked for viability. Hematopoietic stem cells (CD34+) were also counted.

CD34+ HPC (hematopoietic progenitor cells) was counted by Flow cytometer using Stem Kit Reagent- Beckman Coulter. BMNCs were stained with 7AAD, CD45-FITC and CD34-PE and then run in Navios flow cytometer and analyzed by Navios software. The results are viability, the percentage of and also the absolute number of CD35+, CD45, HPC.

Transplantation of BMMNCs

The MNCs were divided into two doses: one was given immediately after processing and the remaining dose was stored to administer 3 months after the first dose. The remaining dose was mixed with cryoprotectants (10% DMSO Dextran in the ratio of

Table 3: Childhood Autism Rating Scale (CARS).

Outcome measure	Baseline	3 months		6 months	
	Mean ± SD	Mean ± SD	P-values*	Mean ± SD	P-value*
Relating to People score	3.1 ± 0.4	3.2 ± 0.4	0.33	3.1 ± 0.4	1
Imitation score	2.9 ± 0.4	2.8 ± 0.3	0.33	2.8 ± 0.4	0.26
Emotional Response score	2.9 ± 0.5	3.1 ± 0.5	0.009	2.9 ± 0.4	0.81
Body Use score	2.9 ± 0.6	2.4 ± 0.7	0.03	2.5 ± 0.6	0.01
Object Use score	3.0 ± 0.4	2.9 ± 0.6	0.3	2.8 ± 0.5	0.06
Adaptation to Change score	2.8 ± 0.4	2.9 ± 0.3	0.08	2.7 ± 0.5	0.82
Visual Response score	3.0 ± 0.5	3.0 ± 0.6	1	2.7 ± 0.6	0.02
Listening Response score	2.8 ± 0.5	2.8 ± 0.6	0.8	2.7 ± 0.6	0.07
Taste, Smell, Touch score	2.8 ± 0.4	2.8 ± 0.5	0.5	2.6 ± 0.4	0.03
Fear or Nervous score	2.4 ± 0.4	2.3 ± 0.5	0.33	2.2 ± 0.4	0.04
Verbal Communication score	3.3 ± 0.5	3.2 ± 0.4	0.26	3.1 ± 0.5	0.08
Nonverbal Communication score	3.2 ± 0.5	3.2 ± 0.6	0.75	3.1 ± 0.5	0.16
Activity Level score	2.9 ± 0.5	2.9 ± 0.4	1	2.9 ± 0.4	1
Level & Consistency of Intellectual Response score	3.1 ± 0.5	2.8 ± 0.5	0.006	2.8 ± 0.5	0.006
General Impression score	3.2 ± 0.4	3.1 ± 0.4	0.19	3.0 ± 0.3	0.08
Total CARS score	44.8 ± 5.5	42.9 ± 5.7	0.01	42.2 ± 6.2	0.0004

*Paired t-test as compared to baseline

1:1), and then the product was transferred to decreased temperature system. Until the product reached – 90° C, it was stored in Liquid *Nitrogen Vapor Phase* Storage *Systems* for the second transplantation [27]. The route of administration was in trathecal between the 4th and 5th lumbar vertebrae. The procedures were conducted in the recovery room and the transplantation lasted for 30 minutes.

Clinical Assessment

Clinical examinations were performed by a certified and experienced psychologist and a pediatric neurologist at baseline, 3 months and 6 months afterwards with a special focus on the Childhood Autism Rating Scale (CARS).

In terms of the post interventional monitoring, all patients were monitored by pediatric neurologists and psychologists, whereas follow-up examinations/observations after the transplantation were conducted by a pediatric neurologist after 3 months and 6 months. If any information was missing, an independent psychologist was contact the patient and their caregivers via phone.

Laboratory and Imaging Diagnostics

Magnetic resonance imaging and electroencephalography of the brain, hematologic and biochemistry profile including HIV, HBV, and HCV tests were performed in all patients.

Statistical Analysis

Each individual is a unit of analysis. Paired t-test was used to compare the total CARS score and its 15 domains at 3 months and 6 months with those at baseline. A p-value less than 0.05 were considered statistically significant. All statistical analyses were performed using STATA (*Version* 11.2, Stata Corp, and College Station, Texas).

Ethics Statement

The study protocol was reviewed and approved by the Institutional Review Board of Vinmec International Hospital on March 17, 2014. The committee evaluated the ethical aspects of the study in accordance with World Medical Association Declaration of Helsinki [19]. The study was explained in detail to the parents of the participants. Written informed consent was obtained well before patient enrolment in every case.

Results

Patients' characteristics

A cohort of 24 patients with autism was included in this study. There were 23 males (95.8%) and 1 female (4.2%). The age median was 6 years old (range: 3-16 years old). The weight median was 25 kg (range: 16.5-54.0). The median for CARS score at baseline was 45.8 (range: 32.5-53.0). Patients' characteristics were summarized in (Table 1).

Adverse events

No severe complications were recorded during the procedure. After transplantation, vomiting was observed in 3 (12.5%) of the cases, which was well-managed with medications. There were no other infections except for 2 cases of conjunctivitis, which were considered as coincidences. Transient hyperactivity was found in 20 patients, which was self-relieved within 2 weeks. There were 4 cases with increased hyperactivity that lasted for more than 6 months and required continuing medications. Adverse events during and after stem cell transplantation were described in (Table 2).

CARS scores before and after stem cell transplantation

The overall severity of autism improved after transplantation. The total CARS score was significantly lower 3 months and 6 months after transplantation as compared to baseline (p=0.01 and 0.0004, respectively). Of the 15 CARS domains, two domains (Body Use and Intellectual Response) showed statistically significant improvement 3 months after transplantation. After 6 months, significant improvement was also observed in 3 additional domains (Visual Response Score; Taste, Smell, Touch Score and Fear or Nervous Score).

There were 7 other domains with lower CARS scores (i.e. less severe) after transplantation but they were not statistically significant

Table 4: Changes in CARS score among patients with improvement.

Changes in CARS score	Frequency	Percent (%)	Cumulative (%)
0.5	1	5.26	100
1	1	5.26	94.74
2	1	5.26	89.47
2.5	3	15.79	84.21
3	5	26.32	68.42
3.5	2	10.53	42.11
4	2	10.53	31.58
4.5	1	5.26	21.05
7.5	1	5.26	15.79
8.5	1	5.26	10.53
10	1	5.26	5.26
Total	19	100	

(Imitation; Object Use; Adaptation to Change; Listening Response; Verbal Communication; Nonverbal Communication and General Impression).

No CARS score change was observed in the rest of 3 domains (Relating to People; Emotional Response and Activity Level).

Comparison of CARS scores before and after stem cell transplantation was presented in (Table 3).

Magnitude of CARS score changes in patients with improvement

Improvement was seen in 19 patients (79.2%) while 2 cases (8.3%) showed no changes and 3 other cases (12.5%) presented with more severe symptoms (higher CARS score after transplantation). Subgroup analysis was carried out among 19 patients with improvement in CARS total score. The mean reduction in CARS score was 3.8 (range: 0.5-10.0). The most common reduction in CARS score was 3 (mode). The cumulative proportion of patients with a reduction in CARS score of 3 or above was 68.4%. Details on changes in CARS score were described in (Table 4).

Five cases without improvement after transplantation of stem cells included 4 males and 1 female. The age median was 6 years old (range: 4 –8 years old). The weight median was 26 kg (range: 18 - 30). The median for CARS score at baseline was 42.0 (range: 36 - 52.0). These characteristics were described in (Table 5).

Discussion

In our study of the 24 patients with autism, intrathecal transplantation of autologous BMMNCs was apparently safe with no severe adverse events recorded during and after the procedure. The vomiting rate was lower in comparison with the trial of Sharma et al. [26] (12.5% versus 17.9%). Transient hyperactivity rate was higher compared to Sharma's report (16.7% versus 3.1%) [24] the overall severity of autism was ameliorated after stem cell transplantation. The total CARS score was significantly lower 6 months after transplantation (42.2 ± 6.2) as compared to baseline (44.8 ± 5.5). The mean of CARS scores before transplantation of the group with improvement (19 patients) was higher than the group without improvement (45.1 versus 43.9). However, this difference was not statistically significant (t= - 0.41, p= 0.68). Among the 15 CARS domains, significant improvement was observed in Body Use; Intellectual Response; Visual Response Score; Taste, Smell, Touch Score and Fear or Nervous Score. In the study of Yong-Tao et al. [23], improvement was also observed in Body Use, Visual Response and Taste, Smell, Touch Score. However, Yong-Tao et al. [23] did not find favorable changes in Intellectual Response and Fear or Nervous Score. On the contrary, improvement in Relating to people and General Impression was seen in the study of Yong – Tao et al. [23] but not observed in our study [28]. The magnitude of change in total CARS score was smaller than what observed in the trial by Yong – Tao et al. [23] using allogenic cord blood mononuclear cells: 46.43 ± 8.65 at baseline and 37.14± 10.15 at 6 months [28]. It was hard to compare the changes in autism severity in our study and the trial of Sharma et al. [26] because they used Indian Scale for Assessment of Autism (ISAA), a derivative of CARS in their study and their follow-up duration was longer (i.e. an average of 12.7 months). However, favorable findings toward a less severe condition were observed in their study. ISAA median scores before and after cell therapy was 115.5 and 97, respectively [24]. We preferred autologous BMMNCs in this study because there were no risks of rejection, anaphylaxis or side effects of immunosuppressive drugs that go along with allogenic transplantations. Stem cells were administered intrathecally so it was minimally invasive while assuring efficient delivery to the brain. Intracranial transplantation seems more targeted at the sites of lesions but it was not chosen by our research team due to their invasive nature. Intravenous injection was not our route of choice, either. In animal models, it was observed that most of the IV transplanted cells were caught at the lung, spleen, kidney and intestine [29]. The strategy to transplant autologous BMMNCs intrathecally was also applied in other studies [23,24].

The study has some limitations. It was an open label uncontrolled clinical trial. In addition, the follow-up time of 6 months was relatively short. Therefore, there might be more long term improvement to be monitored and evaluated. Future studies should further explore the optimal doses of stem cells and frequency of transplantation.

Conclusion

Our study demonstrated evidences to support the safety and effectiveness of BMMNCS transplantation in the management of autism. A larger randomized controlled trial with long-term follow-up are needed to have more accurate conclusion.

List of Abbreviations

ASD: Autism spectrum disorders

Table 5: Characteristics among patients without improvement.

No	Sex	Age (Years)	Weight (Kg)	CARS Score (at baseline)	Mononuclear cells transplanted per one kg of body weight ($^{*}10^{6}$)	CD34+ cells transplanted per one kg of body weight ($^{*}10^{6}$)
1	Male	4	18	52	23.72	3.06
2	Male	8	25	36	14.19	2.73
3	Male	8	26	48	26.23	2.55
4	Male	6	30	42	23.83	2.01
5	Female	8	27.5	41.5	10.47	2.21

BMMNCs: Bone Marrow Mononuclear cells

CARS: Childhood Autism Rating Scale

GMFCS: Gross Motor Function Classification System

GMFM: Gross Motor Function Measure

ISAA: Indian Scale for Assessment of Autism

MSCs: Mesenchymal stem cells

SSRI: Selective Serotonin Reuptake Inhibitors

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