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Review Article

Stem Cell Transplantation in Iran: A Systematic Review Article

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Abstract

Background: Stem cell therapy is a new treatment option for different diseases. The aim of this systematic review is assessing the articles that focus on SCT in Iran and evaluate the amount of their success, failure and complication.

Methods: Systematic search was conducted for finding English and Persian papers (controlled trials and cohort studies with follow up) published before March 2015. We searched PubMed, ISI, and SCOPUS as the main international electronic data sources, as well as Iranmedex, Irandoc, and SID as the main domestic databases. Quality assessment of clinical trial and cohort study was performed based on the Consolidated Standards of Reporting Trials (CONSORT) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) check lists respectively.

Results: The 19 published articles in this systematic review included 2 cohort, 13 clinical trial, 3 open label clinical trial and 1 clinical trial pilot study. The stem cell types for transplantation were Mesenchymal (63.15%), mononuclear (31.6%), and fetal liver cell suspension (5.6%). The most SCT was performed at Tehran (68.42%), Shiraz (15.8%), Kerman & Isfahan hospitals (5.26%). The main diseases were decompensated cirrhosis and myocardial infarction (26.31%), MS (15.78%), DM (10.52%), Burger disease, neuroblastoma, sub-acute spinal cord injury and osteoarthritis (5.26%).

Conclusion: The most of cells transplantation are performed successfully in Iran. Cell transplantation may be safely administered to treat patients with disabling disease.

Keywords: Clinical Trial, Cohort, Stem Cell Transplantation, Iran

Introduction

Stem cell transplantation (SCT) is rapidly growing for treatment of disease all over the world. Stem cell therapy is a new treatment option for several diseases (1-5). Stem cells are capable to differentiate into a variety of cell types including neural cells, adipocytes, chondrocyte, osteocytes and odontoblasts (6-8). Stem cells have potential effect to retrieve and repair different tissues and renovate organ functions (9, 10). Some clinical trials proved SCT are useful for treatment of myocardial infarction, and have an effective impact on tissue perfusion and cardiac function (11-13). Dif-

ferent studies supported that hematopoietic stem cells can convert into liver cells (14, 15) and cure liver fibrosis (16). SCT is a promising treatment for cell therapy in autoimmune diseases such as type 1 diabetes (2, 17).

Stem cells differentiate to neural cells and cure (18) some disabling neural disease such as MS and sub-acute spinal cord injury (19, 20). Umbilical cord blood-derived Mesenchymal SCT is a new and useful therapeutic method for Berger and similar ischemic diseases (21, 22). Mesenchymal stem cell (MSC) based therapy holds great promise for the treatment of inflammatory diseases such as rheumatoid arthritis and osteoarthritis (OA) (23, 24). Neuroblastoma is one of the most common solid tumors in children (25) and SCT is better than chemotherapy alone for its treatment (26). Hematopoietic stem cell therapy (HSCT) has become the standard treatment in Iran for many patients with congenital or acquired disorders of the hematologic system and has undergone rapid growth over the past two decades instead of bone marrow transplantation, combination chemotherapy and using drugs. The main indications of HSCT were thalassemia major (36%), leukemia (34%), lymphoma (16%0, and multiple myeloma (7%) in Iran (27). Bone marrow transplantation is available for selected patients with beta-thalassemia or blood cancers such as leukemia (28). In the recent years, SCT has been successfully performed in clinical care in Iran hospitals for many disorders.

We performed this systematic review to describe studies which explained SCT for treatment of disabling disease except hematopoietic disease and assess their success, failures and complication in Iran.

Methods

Data source, Search strategy and eligible studies

Systematic search was conducted for finding English and Persian papers (controlled trials and cohort studies with follow up) that Published from its inception through March 2015. We searched PubMed, Institute of Scientific Information (ISI), and SCOPUS as the main international electronic data sources, as well as Iranmedex, Irandoc, and Scientific Information Database (SID) as the main domestic databases. The reference lists of all the articles and electronic journals were searched for further studies. The medical subject headings (MESH) Entry Terms of PubMed and Emtree of Scopus were used for most comprehensive and efficient searches. For the national search engine, the Persian keywords were equivalent to their English search terms. The key words using MESH for our search as a PICO Abbreviation included: **P**, ("Iran OR Iranian OR Iranians)" [Mesh]), **I**; "stem cell transplantation"[Mesh Terms] OR stem cell transplantation [Text Word]], **C**; comparison group treated with Placebo or conventional therapy, **O**; Disease improvement. Two independent investigators conducted data extraction using inclusion and exclusion criteria. Inclusion criteria for appraising articles were clinical trials and cohort studies with follow up that assessed pure stem cell transplantation in patients with a history of certain disease.

Exclusion criteria were articles that did not use pure stem cell transplantation (combination of stem cells with other cells) in clinical trials and cohort studies with follow up, cohort studies without follow up.

Quality assessment of clinical trial and cohort studies was performed based on the Consolidated Standards of Reporting Trials (CONSORT) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) check lists.

Data extraction

Quality evaluation of articles

Two independent researchers conducted data extraction using pre-specified inclusion and exclusion criteria. The JAMA users guide quality assessment scales for clinical trials was used to assess quality of included articles (complementary note). This user guide includes three main questions about internal validity, external validity and results of studies. We used internal validity items for appraising articles. Internal validity had six key questions about: 1) Randomization, 2) allocation of treatment, 3) blinding of patient and physician, 4) similarity of control and intervention groups, 5)

follow-up period, and 6) the type of analysis. The item got "1" score if the item score was "yes". Then we aggregated the score of all six items. We considered a study eligible to be included if it fulfilled 3 of maximum 6 score. Discrepancies were resolved by discussion between reviewers and reaching to consensus.

Quality assessment based on JAMA used guide was conducted on all 17 clinical trials included for systematic review (Fig. 1).

STROBE 2007 Statement (complementary note) Checklist used for assessing the items that should be included in reports of cohort studies. It consisted 22 items that we considered essential for good reporting in this systematic review. These items relate to the article's title and abstract, the introduction, methods, results, discussion sections and other information. We considered a study eligible to be included if it fulfilled 2/3 of total scores of consort and strobe checklists (that have mentioned in supplementary note).

The following characteristics were extracted:

SCT type, first author and hospital name, date of study and its publication, sample size (male/female), type of disease, primary & secondary outcomes, hypothesis of study, lab tests, complications, inclusion and exclusion criteria of each article. Discrepancies were resolved by discussion between reviewers and reaching to final consensus.

Results

Characteristics of included studies

The initial search identified 636 citations, of which 231were duplicate, and 405 were examined in more detail which 366 were excluded according title and abstract. Thirty nine full text articles assessed by user guide. Ten articles excluded because had not required data, 10 articles failed in critical appraisal. Finally19 studies were found related to study domain (Table 1). Final articles included 2 cohort studies, 13 clinical trials, 3 open label clinical trial study and 1 clinical trial pilot study. The most frequent stem cell types for transplantation were Bone Marrow-derived Mesenchymal stem cell (BM-MSC) (63.15%), Bone Marrow-derived mononuclear stem cells (BM-MNC) (31.6%) and fetal liver derived cell suspension (5.6%). BM-MNC was used in cohort studies with follow up. The mean age of patients was 40.34 years old in intervention group and 36.47 years old in control group. All transplantations were performed at unicentral places. SCT was performed at Tehran hospitals (68.42%), Shiraz hospital (15.8%), Kerman (20) & Isfahan (12) hospitals. The main disease were end stage liver disease (decompensated cirrhosis) and myocardial infarction (each one 26.31%), multiple sclerosis (MS) (15.78%), diabetes mellitus (DM) (10.52%), Burger disease, neuroblastoma, sub-acute spinal cord injury and OA (5.26%) (Table 1-2). The main transplant solution was normal saline. The most important hypothesis before transplantation of mesenchymal and mononuclear stem cells were focusing on potential power of them as multipotent progenitor cells to treat disease. In all studies common lab tests were flow cytometry analysis and CBC-diff. First purpose of studies was evaluation of the efficacy and safety procedure of SCT in treatment of disease and the second purpose was reserve process, promote survival and cute the disease. In SCT in patient with myocardial infarction, cell therapies had no serious adverse events such as arrhythmias, neoplasia, myocardial infarction, cerebrovascular events. MSC transplantation had no complication in treatment of decompensated liver cirrhosis, MS, DM, knee OA, Burger disease, and spinal injury. The least transplant complications were gastrointestinal problems, mucositis, fever, Infection and seizure in neuroblastoma.

Discussion

The present systematic review aimed to assess data from clinical trials and cohort studies with follow-up to find success, failures and complications of cell transplantation in Iran. The results presented here confirmed that BM-MSCs may be safely administered to treat patients with disabling disease.

Table 1: Main characteristics of eligible studies of SCT in Iran

N	Reference number	Y.P	Disease name	Disease duration	Follow-up (month)	Sample size (M/F)	Purpose of study
1	15	2013	Cirrhosis	Nm	12	27/0	To evaluate the efficacy of autologous MSCT in cirrhosis
2	31	2012	Cirrhosis	Nm	20.5	18/14	To evaluate the efficacy of autologous MSCT in cirrhosis
3	29	2011	Cirrhosis	Nm	24	3/3	To study the safety, feasibility and clinical outcome of SCT
4	16	2009	Cirrhosis	Nm	6	4/4	To study satisfactory tolerability of MSCT for the treatment of ESLD
5	41	2007	Cirrhosis	Nm	12	2/2	Assess changes in MELD score, liver volume, and quality of life of the cirrhotic patients
6	42	2012	MI	75 days	60	18/0	Investigate the efficacy and LV functional improvement after intramyocardial injection of CD133+ in patients with AMI who were candidates for CABG
7	11	2007	MI	Less than 3 months prior to admission for surgery	14	21/6	To evaluate SCT impact on tissue perfusion and contractile performance
8	12	2012	MI	History of anterior MI	6	24/8	To study SCT impact on repairing the cardiac tissue after acute MI
9	13	2011	MI	2 weeks	6	16/4	To study SCT impact on repairing the cardiac tissue after acute MI infarction
10	43	2007	MI	Acute ST-elevation MI	4	8/4	Enhanced recovery of contractile function
11	19	2012	MS	8.2 years	12	6/19	Myelin repair in MS
12	36	2007	MS	Progressive disease	13- 26	3/7	Improvement in MS patients and halted disease progression in others
13	44	2005	MS	31 years	7	2/3	MS immunomodulation by SCT
14	17	2012	Diabetes	5-11 years	12	22/34	Treatment of various types of diseases including diabetes mellitus
15	2	2011	Diabetes	up to 20 weeks	12	…	To examine the effect of MSCT on treatment of type 1 diabetic patients
16	20	2012	Spinal injury	Nm	12-33	24/7	To evaluate the effects of SCT from different sources on patients with spinal cord injury
17	24	2011	Knee OA	10 years	12	2/2	Reverse the OA process with MSCT
18	26	2012	Neuroblastoma	11 years	12	7/2	Finding more effective and Less toxic therapy for neuroblastoma (compare chemotherapy)
19	22	2010	Burger	Nm	24	6/0	Management of obstructive vascular diseases involving the extremities

*MI: Myocardial infarction, MS: Multiple sclerosis, OA: osteoarthritis, Nm: not mentioned*Ig: intervention group, Cg: control group, MSCT: Mesenchymal SCT, MELD: Model for End-Stage Liver Disease, LV: Left ventricular, CABG: coronary artery bypass graft

Table 2: Eligible articles of effectiveness of SCT in Iran

N	Reference number	Disease name	Intervention	Control (placebo)	First outcome	Second outcome
1	15	Cirrhosis	Mesenchymal stem cell (MSC) in Normal saline	Normal saline	No procedural complications both groups	SCT contribute to liver regeneration after injury
2	31	Cirrhosis	Autologous stem cell transplantation	BM MNC ,CD 133positive bone marrow cells/CD 34positive bone marrow cells	Improves liver function	Low incidence rate of HCC
3	29	Cirrhosis	Autologous transplantation of Bone Marrow-derived Mononuclear and CD133+ Cells	MNC Group	The safe and feasible treatment, No adverse event and hospital admission, no significant changes in liver enzymes	A bridge to liver Transplantation, Liver function improvement.
4	16	Cirrhosis	Autologous MSC	No control group	Liver function Improvement, Cr decrease, Alb increase	Clinical liver function indices improvement in, satisfactory tolerability
5	41	Cirrhosis	Bone Marrow MSC Transplantation	No control group	Feasible and safe treatment	Improvements in liver function tests and MELD scores of some patients
6	42	MI	Local Autologous Transplantation of CD133+ Enriched Bone Marrow Cells	Autologous Transplantation of CD133+ Enriched Bone Marrow Cells	A safe and feasible procedure	Not show any major benefits in our patients
7	11	MI	Local Autologous Transplantation of CD133+ Enriched Bone Marrow Cells	Autologous Transplantation of CD133+ Enriched Bone Marrow Cells	Global LVEF did not differ between intervention and control patients	LV end-systolic volume and end-diastolic volume were slightly smaller at 6 months follow up in both groups
8	12	MI	Autologous MSC infusion	NM	Regeneration of infracted myocardium, enhance neovascularization of ischemic myocardium	Mild increases in LVEF
9	13	MI	GCSF/SC/Bd	Normal saline infusion	A positive effect of G-CSF on neovascularization in the paranecrotic area	Favorable effect on global cardiac function but without affecting the EF under clinical conditions
10	43	MI	Bone marrow mononuclear cells	No control Group	Increase LVEF in echocardiography from a mean of 31.78±7.56% at baseline to 38.89±6.97% at 4 months	Enhances left ventricular contractile recovery
11	19	MS	Single intrathecal injection of ex-vivo expanded MSCs	No control Group	Some improvement in EDSS in some patients	Improve/stabilize the course of progressive MS with no serious adverse effects
12	36	MS	MSC	No control Group	Small improvement in EDSS score in one patient	Feasibility treatment, Some degree of improvement in their sensory, pyramidal, cerebellar function
13	44	MS	BM MSCs Intrathecally	Improvement in sensory & cerebellar function	No change in first MRI findings	It is a safe procedure, some degree of improvement and some no disease progression
14	17	Diabetes	Fetal Liver-Derived Cell Suspension Allotransplantation	5ml of normal saline(iv)	Significant decrease in HbA1c levels in type 1 and 2 diabetes groups without any rise in the fasting c-peptide	No insulin free in the first year, no significant effects on glycemic control
15	2	Diabetes	MSC	No control group	Reduction insulin dose, C-Peptid increased, No significant change in the mean of FBS	A novel treatment for type1 diabetes
16	20	Spinal injury	autologous BMC transplantation into CSF via LP	Conventional treatment without BMC transplantation	Marked recovery (a two-grade improvement from baseline, from ASIA A to ASIA C) in intervention group	45.5%in the study group and 15 % in control group showed marked recovery in neurological function
17	24	Knee OA	MSC	No controls were selected for comparison	The physical parameters improved slightly, in comparison to subjective parameters	Subjective parameters improved highly with MSC transplantation, while physical parameters improved much less, no improvement on X-rays
18	26	Neuroblastoma	Autologous transplantation/ allogeneic transplantation of full matched sibling + chemotherapy	Chemotherapy	Low relapse, high complete remission	Transplantation is better than chemotherapy alone, SCT is significantly better than BM
19	19	Burger	Mononuclear cells CD34+ and CD133+ cells	No control Group	Significant improvement of limb temperature in the affected area, Rest pain, pain-free walking distances, O2 saturation	Dramatic improvement in ischemic signs and symptoms due to distal circulation improvement

*MI: Myocardial infarction, MS: Multiple sclerosis, OA: osteoarthritis, BM MNC: Bone marrow derived-mononuclear cell, MNC: Mono nuclear cell, BM: Bone marrow, SC: subcutaneous, Nm: not mentioned, BM: Bone marrow, EDSS: expanded disability status scale, HCC: Hepatocellular carcinoma, LV: left ventricle, LVEF: left ventricular ejection fraction

The number of clinical trials has dramatically increased and assessing their success and complication are very important (14). Most of SCT performed in Tehran hospitals and another performed in Shiraz, Isfahan and Kerman. The main cells for transplantation were mesenchymal, mononuclear and human fetal liver-derived stem cell respectively. The main disease for cell transplantation was decompensated cirrhosis (29) and myocardial infarction (13), MS (19) and DM (17). The least articles were about cell transplantation in OA (24), Berger disease (22), neuroblastoma (26) and sub-acute Spinal cord injury (20). The results presented here confirmed that autologous BM-MSCs are safe to treat patients and had no serious complications in Iranian patients (2, 30, 31). Moreover, the relative risks of mortality and morbidity, measured by incidence of disease complication such as hospital re-admission, were not significantly increased in patients who received BM-MSC treatment compared with placebo (15, 17). The pattern in favors of benefits across all clinical outcomes manifested excellent feature, particularly because each outcome received contribution from different studies. However, we could not use met analysis most probably because of the qualitative outcome of all Studies and the low number of some disease trials such as knee OA, Burger, neuroblastoma and spinal cord injury (20, 22, 24, 26). Common interpretation is also available because of the similar comparisons being made in the review. Although this was small sample in some articles, there was a trend towards an improvement in patient symptom and disease outcome in patients who had received BM-MSC compared with controls (24, 31). Thus, future trials would need to incorporate more robust outcome measures that are patient centered and RCT should be done instead of cohort studies and clinical trials with small number. This review article is based on a comprehensive search strategy.

One of the most important finding in this systematic review is being a great interest in Iran to take benefits of bone marrow stem cells to treat cirrhosis. We found that using SCT provides a potentially supportive modality to organ transplantation in the management of end stage liver diseases. It is safe and feasible in Iran. This finding is similar to Khan et al. article finding that approved marked clinical improvement in all clinical and biochemical parameters after SCT in cirrhotic patient (32).

Also in patients with acute myocardial infarction, reperfusion of the artery occlusion significantly improves acute and late clinical outcome. The study result demonstrated SCT effect in healing of the infarction area. This result is similar to the clinical research that is performed in Germany. These results manifested that selective intracoronary transplantation of human autologous adult stem cells is possible under clinical conditions and it can lead to repair myocardial scar after infarction (33).

The therapeutic effects of fetal liver-derived cell suspension was not positive on glycemic control in one study (17), but the main reason that mentioned in this article, is heterogeneity of patients. Longer follow-up is necessary to obtain certain result. MSC had positive effect for control of type 1 diabetes in another article. Larijani et al. result was similar to voltarelli et al. finding (2). Voltarelli et al. investigation performed in Brazil and concluded that SCT will increase beta cell function in patients (34). Our results suggest that MSCs is a novel treatment for type 1diabetes.

MS is an inflammatory autoimmune disease involving the central nervous System and leads to the myelin sheath degeneration, oligodendrocytes and the axons. We found in our review that SCT could improve MS symptoms and prevent from disease progression (19). MSC transplantation was a clinically safe procedure and induced immediate immunomodulatory effects (35, 36). This finding is consistent with karussis et al. research (35). He demonstrated the Safety and immunological effects of MSC in patients with multiple sclerosis and amyotrophic lateral sclerosis.

OA is a cartilage damaging process and No treatment is available to improve and reverse this process. In this systematic review results were encouraging about SCT in OA but not excellent finding detected. The authors mentioned that technique Improvement may improve the results. (24). Wakitani et al. concluded that SCT could repair articular cartilage defects in humans (37).

Therapeutic angiogenesis with SCT is a treatment strategy for no-option patients with critical limb ischemia. In this review, We found that Autologous mononuclear cells (CD34+/CD133+ collected from peripheral blood following G-CSF mobilization) was effective and safe in Burger treatment(22). Kajiguchi et al. found SCT can improve claudication in patients too. He found circulating CD34+ and CD133+ cells persistently improved claudication in patients with Burger's disease (38).

We found that SCT via LP is a feasible and safe technique in Iran, and there is a potential tendency to treat spinal cord injury in patients (20). Mc Donald et al. manifested transplant-derived cells survived and differentiated into astrocytes, oligodendrocytes and neurons, and cured the lesion area in rats. Hans found SCT remyelinate and restore locomotion after spinal cord injury (39).

SCT is better than chemotherapy alone in neuroblastoma patients and is effective to treat high risk children, with encouraging long-term survival (26). Similarly, Su lio et al. concluded that embryonic stem cells can differentiate into oligodendrocytes and myelination in culture and are effective after spinal cord injury (40).

The main limitation of our systematic review was the lack of enough RCT (random clinical trials). The most articles were clinical trials without randomization, low sample size and selection control groups. The best suggestion is designing appropriate RCT with large sample size to gain robust evidence about SCT success, failures and complications in treatment of disease in Iran.

Conclusion

SCT is a safe and feasible procedure for treatment of cirrhosis, myocardial infarction, MS, DM, Burger, Knee OA, spinal injury and neuroblastoma in Iran and can improve quality of life for patients. SCT is done in Iran as well as other countries with high success and the least complications.

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.

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