International Journal of Stem Cells Vol. 7, No. 2, 2014 http://dx.doi.org/10.15283/ijsc.2014.7.2.63

REVIEW ARTICLE

Efficacy and Safety of Stem Cell Therapies for Patients with Stroke: a Systematic Review and Single Arm Meta-Analysis

Hyunsuk Jeong[1], Hyeon Woo Yim[1,5], Young-seung Cho[2], Yeong-In Kim[3], So-Na Jeong[4], Hyun-bin Kim[5], Il-Hoan Oh[6]

[1]Department of Preventive Medicine, College of Medicine, The Catholic University of Korea, Seoul, [2]Seo-myeon Branch Office of the Community Health Center, Uljin, [3]Department of Neurology, International St. Mary's Hospital, Incheon, [4]Medical Library, Seoul St. Mary's Hospital, Seoul, [5]Clinical Research Coordinating Center, Catholic Medical Center, Seoul, [6]Catholic High-Performance Cell Therapy Center & Department of Medical Lifescience, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background and Objectives: Stem cell-based therapy is a potential new approach in the treatment of stroke. However, the efficacy and safety of these treatments are not yet fully understood. Therefore, we performed a meta-analysis of available single-arm studies using stem cell-based therapy in patients with stroke.

Methods: We searched MEDLINE, EMBASE, and the Cochrane database for studies of stem cell therapy in patients with stroke from its inception through July 2014. The articles included in the search were restricted to the English language, studies with at least 5 patients, and those using cell-based therapies for treating stroke.

Results: Fourteen studies included in the meta-analysis. The pooled mean difference in National Institutes of Health Stroke Scale (NIHSS) scores from baseline to follow-up points was 5.7 points (95%CI: −8.2 to −3.2, I^2=91.5%) decreased. Also the pooled mean difference in modified Bathel index (BI) score was increased by 31.5 points (95%CI: 35.6～14.9, I^2=52.7%) and the pooled incidence rate to achieve on modified Rankin score (mRS)≤2 was 40% (95% CI: 30%～51%, I^2=35.4%) at follow-up points. The pooled incidence rates of death, seizure, and infection were 13% (95%CI, 8～23%), 15% (95%CI, 8～25%), and 15% (95%CI, 8～23%), respectively.

Conclusions: The published data suggest that stem cell-based therapy for patients with stroke can be judged as effective based on single arm clinical studies. However, clinical benefits of stem cell therapy for patients with stroke need further investigation and reevaluation to test the clinical efficacy.

Keywords: Stroke, Stem cells, Systematic review, Meta-Analysis

Introduction

Stroke is a major cause of mortality and disability in adults, and the second leading cause of death worldwide with an annual incidence of 250 to 400 in 100,000 people. This leads to a huge social and economic burden (1). Currently very few therapeutic options are available. The currently available therapies of acute stroke target rapid vessel recanalization and neuroprotection, since without restoration of cerebral blood flow, tissue residing in the penumbral region progresses to cellular death which ultimately expands the core lesion. Recombinant tissue plas-

Accepted for publication November 6, 2014,
Published online November 30, 2014
Correspondence to **Hyeon Woo Yim**
Department of Preventive Medicine, College of Medicine, the Catholic University of Korea, 222 Banpo-dero, Seocho-gu, Seoul 137-701, Korea
Tel: +82-2-2258-7860, Fax: +82-2-2258-3820
E-mail: y1693@catholic.ac.kr

minogen activator (tPA) is the only pharmacological treatment approved for treatment of acute ischemic stroke. The tPA therapy restores the brain function when performed within the time window of 4 to 5 hours after acute ischemic stroke, which limits its use to a small minority (2% to 4%) of patients (2). Moreover, tPA prevents disability in only six patients per 1000 ischemic strokes, and does not reduce the mortality rate (3).

An alternative potential new approach in the treatment of ischemic stroke is cell-based therapy. Preclinical rodent models of ischemic stroke and clinical trials using stem cells or adult and fetal progenitor cells have shown a therapeutic promise. Stem cells are undifferentiated cells that have the capacity to proliferate and differentiate into mature specialized cells (4). However, the effects of these treatments are not yet fully understood and there is a lack of firm evidence on the efficacy and safety of stem cell therapy for those patients due to the absence of sufficiently powered randomized controlled trials. Therefore, we performed a meta-analysis of available single-arm studies using stem cell-based therapy in patients with stroke.

Methods

Search strategy and study selection

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org/). A systematic search and critical review of the literature published from its inception through July 2014 was performed. We searched MEDLINE, EMBASE, and the Cochrane database for studies of stem cell therapy in patients with stroke.

An inclusion criterion was stem cell therapies for stroke patients. We cannot restricted any type of stroke either acute or chronic patients. The excluded studies met the following criteria: (1) Individual case reports (2) irretrievable or unclear data (3) duplicate reports. Article selection process was conducted by two authors independently with standard methods.

Data extraction

Two investigators independently screened all titles and abstracts to identify studies that met the inclusion criteria and extracted relevant data, with divergences resolved by consensus. We included single-arm studies as well as experimental arm of nonrandomized or randomized controlled trials in patients with stroke. The following data were extracted: country of origin, year of publication, numbers of patients who injected stem cells, follow-up period, stem cell type, injected cell dose, route of administration, and disease elapsed time which was classified into either "acute" within 30 days after onset of stroke or "chronic" 30 days or more after onset of stroke. The outcome measures included changes of National Institutes of Health Stroke Scale (NIHSS) and modified Bathel index (BI) scores from the baseline to primary endpoints and the event rate of modified Rankin Score (mRS)$\leq$2 at primary endpoints for evaluating the efficacy and count the frequencies of adverse events for appreciating the safety for stem cell therapy. All data were extracted accordance with the criteria based on the Cochrane Handbook for Systematic Reviews of Interventions (5).

Quality assessment

Quality assessment of single arm studies and experimental study arms was evaluated using the Newcastle Ottawa Scale (NOS) (6). This scale allocates a maximum of 9 stars for quality of selection (up to 4 points), comparability (up to 2 points) and outcome (up to 3 points) of study participants. Overall study quality was defined arbitrarily as poor (score, 0～3), fair (score, 4～6) or good (score, 7～9). Quality assessments were conducted independently by two authors. Disagreements were resolved by discussion between the two authors.

Statistical analyses

We performed random effects model meta-analyses to assess net changes in the same outcome variables. Existence of heterogeneity among effect sizes of individual studies was assessed using the I^2 index and Q statistic. Heterogeneity was analyzed with the I^2 statistic, and heterogeneity was defined as low (25% to 50%), moderate (50% to 75%), or high (>75%) (7). Preplanned subgroup analyses were conducted based on injected cell type, follow-up periods, route of administration, disease elapsed time, and study sample size. Subgroups divided into acute vs. chronic stroke patients, Bone marrow derived mononuclear cells (BM-MNC) vs. other than BM-MNC, injected stem cell through intra-artery vs. other than routes, 6 months vs. 12 month or more follow-ups, and less than 10 vs. 10 or more sample size. We conducted meta-regression analysis to determine factors related to decrease in NIHSS after stem cell therapy. Data analyses were performed using Comprehensive Meta-analysis version 2.2. (Biostat Inc., Englewood, NJ).

Results

Search results

The initial search identified 1482 articles, of which 1392 articles excluded in the first screening. Ninety potentially relevant articles examined in more detail. Of these, 76 were exclude experimental studies, review, editorials, or comment, secondary publication, case reports, or did not reported outcome data. Fourteen of the 90 potentially relevant articles were eligible for meta-analysis (Fig. 1) (8-20).

Characteristics of the included studies

Characteristics of 14 studies are described in Table 1. All studies were published from 2005 to 2013. Study samples size ranged from 5 to 20 patients and follow-up duration from 6 to 60 months. The type of stem cell varied, being either CD34+ cells or bone marrow mononuclear cells, Bone marrow derived mesenchymal stem cell, fetus stem cell, and fetal porcine cell. Stem cells were injected through parenchyma, intrathecal, intra-arterial, or intravenous with the range from 5 to 300 million cell dose. In addition, the overall quality scores of the included single arm studies and experimental study arms were presented in Table 1. Two of 14 studies were assessed the study quality as good, 9 were fair, and 3 were poor.

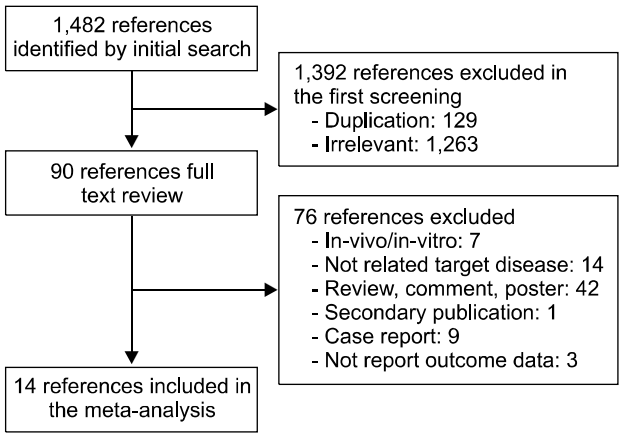

Fig. 1. Flow diagram of studies included in this review.

Main findings

Ten out of 14 included studies have evaluated the efficacy of stem cell therapy using changing score in NIHSS (8-11, 13-16, 18, 20). The pooled mean difference in NIHSS from baseline to follow-up points was 5.7 points (95%CI: −8.2 to −3.2, I^2=91.5%) decreased. Six studies have reported BI score to assess the efficacy of the treatment (10, 14, 18-21). The pooled mean difference in BI score was increased by 31.5 points (95%CI: 35.6～14.9, I^2=52.7%). Seven studies have counted the number of patients who have achieved 2 or less in mRS (8-11, 14, 16, 17, 20). The pooled incidence rate to achieve on mRS≤2 was 40% (95% CI: 30%～51%, I^2=35.4%) at follow-up points (Fig. 2).

Ten out of 14 studies have reported incidence of adverse events such as death, seizure, and infection after injection of stem cell (8-17). The pooled incidence of occurring infection, seizure, and death after cell transplant were 15%

Table 1. Characteristics of included studies

Study	Country	No. of Patient	Follow-up (month)	Cell type	Route of delivery	Cell dose* (×100,000)	NOS§ score
Wang (2013)	China	8	12	BMC: CD34	Intrathecal	18	5
Bhasin (2013)	India	6	6	MSC†: BM derived	Intravenous	55	6
Prasad (2012)	India	11	6	BM-MNC‡	Intravenous	80	4
Bhasin (2012)	India	12	6	BM-MNC	Intravenous	56	3
Moniche (2012)	Spain	10	6	BM-MNC	Intra-aterial	159	6
Friedrich (2012)	Brazil	20	6	BM-MNC	Intra-aterial	221	3
Honmou (2011)	Japan	12	12	MSC: BM derived	Intravenous	110	3
Savitz (2011)	USA	10	6	BM-MNC	Intravenous	10	5
Battistella (2011)	Brazil	6	6	BM-MNC	Intra-aterial	300	4
Lee (2010)	Korea	16	60	MSC: BM derived	Intravenous	5	7
Suárez-Monteagudo (2009)	Cuba	5	12	BM-MNC	Parenchymal	34	4
Monteagudo (2009)	Cuba	5	12	BM-MNC	Parenchymal	35	4
Rabinovich (2005)	Russia	10	6	Fetus stem cell	Parenchymal	200	5
Savitz (2005)	USA	5	48	Fetal Porcine Cell	Parenchymal	20	7
Bang (2005)	Korea	5	12	MSC: BM derived	Intravenous	100	2

*Cell dose: Mean or median dose; †MSC: Mesenchymal stem cell; ‡BM-MNC: Bone marrow derived mononuclear cells; §NOS score: Quality assessment score using New-Castle Ottawa Scale.

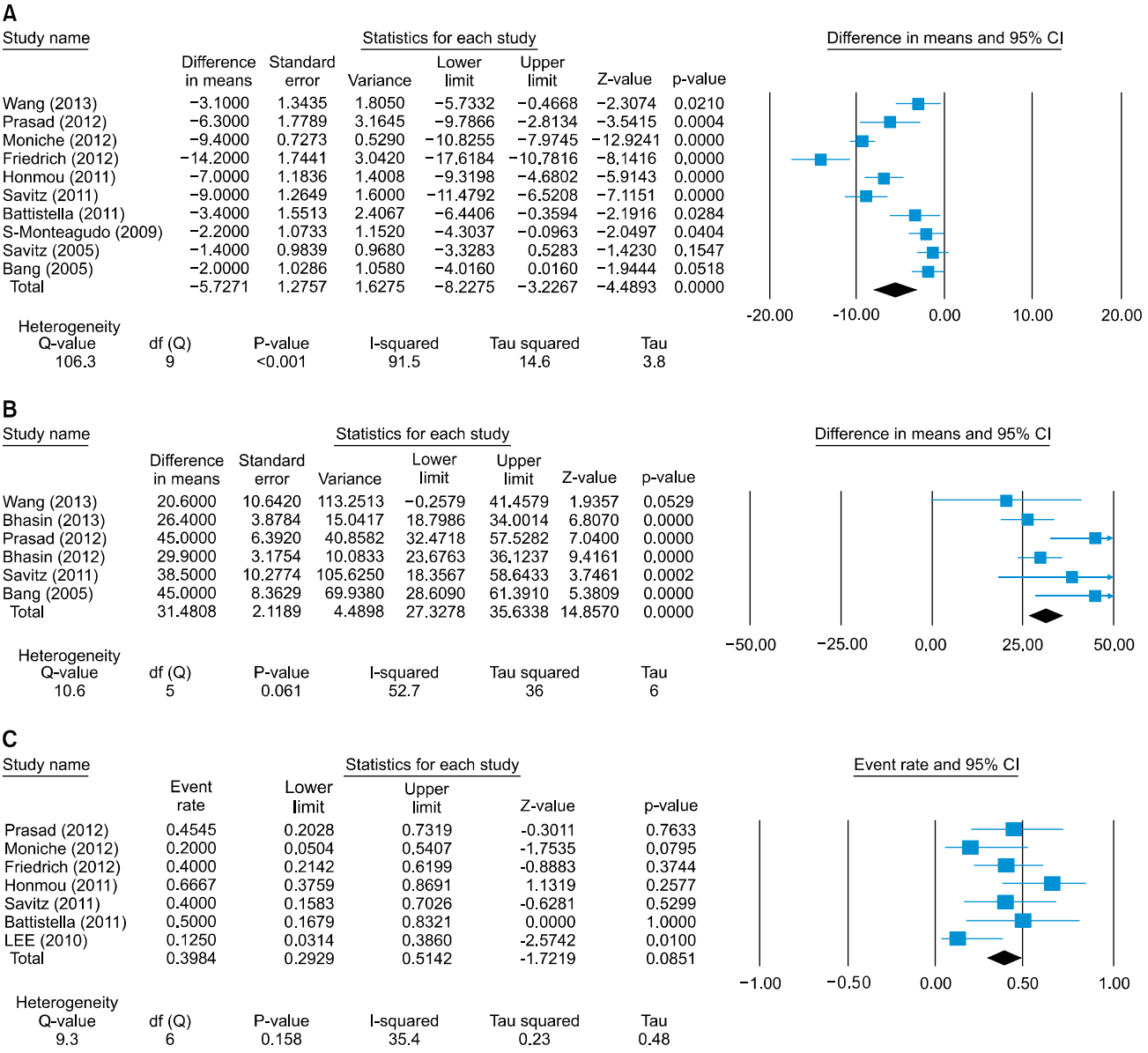

Fig. 2. Forest plots of mean differences from baseline to follow-up points in (A) National Institutes of Health Stroke Scale (NHISS) (B) Bathel index (BI) and (C) the event rate of modified Rankin Score (mRS)≤2 at follow-up points.

(95% CI: 8∼23%), 14% (95% CI: 8∼25%), and 13% (95% CI: 8∼23%) respectively (Table 2).

The likelihood of publication bias has been tested by using funnel plot and Egger test for NIHSS. Funnel plot was symmetric shape and the Egger test was not significant (p=0.120), suggesting less susceptibility to publication bias.

Subgroup and meta-regression analyses on the changes in NIHSS

We conducted subgroup analysis to explore the source of heterogeneity in NIHSS with respect to patients' characteristics, injected cell type and dose, route of administration, follow-up period, and sample size of study. Stem cell therapy more effective to acute patients (mean difference=−8.0; 95%CI: −10.7 to −5.7), Bone marrow derived mononuclear cells (mean difference=−7.0 (95%CI: −9.3 to −4.6), higher cell dose (mean difference=−7.1 (95%CI: −10.1 to −4.1), intra-artery injection (mean difference=−8.9; 95%CI: −10.7 to −5.4), short term follow-up studies (mean difference=−8.5; 95%CI: −10.6 to −6.4), and studies of 10 or more sample size (mean difference=−9.0; 95%CI −10.1 to −8.1). However, the results showed that the substantial heterogeneity still remained

Table 2. Pooled incidence of adverse events

Study	Death	Seizure	Infection
Friedrich (2012)	2/20	0/20	2/20
Moniche (2012)	0/10	2/10	3/10
Battistella (2011)	0/6	2/6	NA
Honmou (2011)	0/12	0/12	0/12
Savitz (2011)	1/10	0/10	NA
LEE (2010)	5/16	3/16	3/16
Suárez-Monteagudo (2009)	0/5	0/5	0/5
Rabinovich (2005)	0/10	0/10	NA
Savitz (2005)	0/5	1/5	0/5
Bang (2005)	0/5	NA	0/5
Pooled incidence (95% CI)	13% (8～23%)	15% (8～25%)	15% (8～23%)

Table 3. Subgroup analysis to explore the source of heterogeneity on changes in NIHSS

Subgroup	Mean difference (95% CI)	I^2
Patients' characteristics		
Acute stoke	−8.0 (−10.7 to −5.4)	92
Chronic stroke	−3.2 (−5.5 to −0.8)	69
Follow−up period		
6 months	−8.5 (−10.6 to −6.4)	83
12 months or more	−2.9 (−4.7 to −1.1)	69
Cell type		
BMC	−7.0 (−9.3 to −4.6)	94
Non BMC	−3.4 (−7.9 to 1.0)	56
Route of delivery		
Intra-artery	−8.9 (−12.3 to −5.5)	90
Other routes	−4.0 (−6.0 to −2.0)	84
Cell dose		
10^8	−7.1 (−10.1 to −4.1)	92
10^7	−3.9 (−6.6 to −1.2)	84
Study sample size		
Less than 10	−2.0 (−4.0 to −1.9)	0
More than 10	−9.0 (−10.1 to −8.1)	72

(Table 3).

We conducted meta-regression analysis to determine factors related to decrease in NIHSS after stem cell therapy. The results showed that NIHSS score decrease was related to patients' characteristics, study duration, injected cell type and cell dose, and study sample size in univariate meta-regression. Stem cell therapy was more effective for acute stroke patients than chronic ones. Also the results from short term follow-up (6 months) studies showed more effective than those of long term follow-up (12 or more months) ones, BM-MNC injection was more effective than other stem cell types, intra-artery injection showed more effective than any other administration routes, higher cell dose was more effective than lower ones, and sample size was also related with the efficacy of stem cell therapy (Table 4).

Table 4. Meta-regression analysis to assess the relationship between the changes NIHSS and study characteristics

Study characteristics	Mean difference (95% CI)	p
Acute stroke (vs. chronic stroke)	−3.6 (−5.2 to −1.9)	0.006
6 month follow-up (vs. 12 mo or more)	−3.4 (−5.1 to −1.7)	0.001
BMC* (vs. other stem cells)	−5.0 (−7.5 to −2.5)	0.001
IA† (vs. other routes)	−4.5 (−6.5 to −2.4)	0.007
10^8 cell dose (vs. 10^7 cell dose)	−4.7 (−6.9 to −2.4)	0.099
10 or more sample size	−4.7 (−6.9 to −2.4)	0.005

*BMC: Bone Marrow derived stem Cells; †IA: intra-arterial.

Discussion

Approximately16 million first-ever strokes occur each year, leading to nearly 6 million deaths (22). Nevertheless, very few therapeutic options are available. Stem cell therapy is being investigated for treating stroke with promising results. Several preclinical studies have indicated that there was a structural and/or functional recovery after intracerebral, intra-arterial, and intravenous therapy with different cell types (23, 24). A recent meta-analysis of 117 preclinical stroke studies indicated that for structural structural and functional outcomes were improved (25). Although preclinical studies for stroke are encouraging, there are still many questions regarding the possible mechanisms of action of the cells and the optimal treatment protocol and the effects of these treatments are not yet fully understood.

In the present single arm meta-analysis, we demonstrated that stem cell therapy was associated with significant improvements in behavioral and functional capacity in patients with stroke. We calculated pooled mean differences between baseline and follow-up points with the universal neuro-physiological assessment tools for stroke. There was significant improvement in motor and behavioral function and functional capacity after stem cell therapy.

However, there are several limitations that should be mentioned. Due to the paucity of randomized controlled trials, this systematic review primarily evaluated cohort studies. With the use of single-arm studies, the observation bias could not be detected in published article, which is a source of heterogeneity. Despite these important limitations, the 5.7 points reduction in NIHSS

score represents improvement of stroke symptoms. The change in the scores in the NIHSS was a powerful factor in predicting an excellent outcome after stroke with an increasing of 1 point in a patient's NIHSS score decreases the likelihood of an excellent outcome by 17% (26). Many stroke trials define favorable outcome as mRS grade ≤ 2 (27, 28). A previous study showed that the mRS cut off score 2 differed greatly between patients with total anterior circulation infarcts and those with lacunar or partial anterior circulation infarcts (29). The present study showed that 40% (95%CI, 39～51%) of patients achieved mRS≤2. It reflected that stem cell therapy is effective for stroke patents. The Changes BI scores between baseline and follow-up point was 31.5 points (95% CI, 27.3～35.6). A study on predicting discharge status at commencement of stroke rehabilitation, BI score difference was about 34 point between initial and discharge, even though the absolute difference in BI score not always represent recovery of the symptoms (30). Further research might be conducted to confirm the significant score change using this scale to assess the treatment efficacy in stroke patients.

When it comes to incidence adverse events, it should be categorized and evaluated with standardized methods based on common toxicity criteria. Though the limitations still remained, 10 of 14 studies reported Incidence rates of death, seizure, or infection during follow-up (8-17). Among the 4 studies reported that there was no adverse event occurred (11, 12, 14, 15). Seven patients among the 3 studies were died after transplantation due to myocardial infarction, pulmonary embolism, recurrence stroke, and pneumonia (9, 10, 17). Six patients of 4 studies reported seizure during follow-up (8, 13, 16, 17). Most of them considered as a serious adverse event though most of them were successfully treated with antiepileptic drug. Eight patients among the 3 studies reported incidence of infection (8, 9, 17). Seven out of 8 patients were infected urinary tract and one was respiratory infection. The pooled incidence rates of death, seizure, and infection were 13% (95%CI, 8～23%), 15% (95%CI, 8～25%), and 15% (95%CI, 8～23%), respectively.

Meta-regression analyses, exploring the source of heterogeneity, indicated that the treatment effects might be associated with patients' characteristics (acute or stroke patients), follow-up period, injected cell type and cell dose, and study sample size. We did not conduct multiple meta-regression analysis because there was not sufficient number of studies was included in the analysis.

Regarding the timing of injection, preclinical studies have shown that cell therapy increased functional recovery after acute, subacute, and chronic stroke (24). Infusion timing and duration of follow-up period seemed to explain the heterogeneity found in the studies; however, a considerable degree of heterogeneity was still observed among the included trials. This might be due to differences in patients' characteristics, such as different causes and severity at baseline and various treatment protocols, or otherwise unknown biases in those studies.

Conclusion

The published data suggest that stem cell-based therapy for patients with stroke can be judged as effective based on single arm clinical studies. However, clinical benefits of stem cell therapy for patients with stroke need further investigation and reevaluation to test the clinical efficacy.

Acknowledgments

This research was supported by a grant (10172MFDS993) from Ministry of Food & Drug Safety in 2014.

Potential conflict of interest

The authors have no conflicting financial interest.

References

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson L, Truelsen T, O'Donnell M, Venketasubramanian N, Barker-Collo S, Lawes CM, Wang W, Shinohara Y, Witt E, Ezzati M, Naghavi M, Murray C; Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet 2014;383:245-254
2. Molina CA. Reperfusion therapies for acute ischemic stroke: current pharmacological and mechanical approaches. Stroke 2011;42(1 Suppl):S16-S19
3. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC Jr, Kwiatkowski T, Levine SR, Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, Albers G, Bluhmki E, Wilhelm M, Hamilton S; ATLANTIS Trials Investigators; ECASS Trials Investigators; NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;363:768-774
4. Mora-Lee S, Sirerol-Piquer MS, Gutiérrez-Pérez M, Gomez-Pinedo U, Roobrouck VD, López T, Casado-Nieto M, Abizanda G, Rabena MT, Verfaille C, Prósper F, García-Verdugo JM. Therapeutic effects of hMAPC and hMSC transplantation after stroke in mice. PLoS One 2012;7:e43683
5. Higgins JPT, Altman DG, Sterne JAC. Assessing risk of bias

in included studies. In: Higgins JPT, Green S, edtor. Cochrane Handbook for Systematic Reviews of Interventions. Version5.1.0 (updated March 2011). Cochrane Collaboration; 2011
6. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs
7. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods 2006;11:193-206
8. Moniche F, Gonzalez A, Gonzalez-Marcos JR, Carmona M, Piñero P, Espigado I, Garcia-Solis D, Cayuela A, Montaner J, Boada C, Rosell A, Jimenez MD, Mayol A, Gil-Peralta A. Intra-arterial bone marrow mononuclear cells in ischemic stroke: a pilot clinical trial. Stroke 2012;43:2242-2244
9. Friedrich MA, Martins MP, Araújo MD, Klamt C, Vedolin L, Garicochea B, Raupp EF, Sartori El Ammar J, Machado DC, Costa JC, Nogueira RG, Rosado-de-Castro PH, Mendez-Otero R, Freitas GR. Intra-arterial infusion of autologous bone marrow mononuclear cells in patients with moderate to severe middle cerebral artery acute ischemic stroke. Cell Transplant 2012;21 Suppl 1:S13-S21
10. Savitz SI, Misra V, Kasam M, Juneja H, Cox CS Jr, Alderman S, Aisiku I, Kar S, Gee A, Grotta JC. Intravenous autologous bone marrow mononuclear cells for ischemic stroke. Ann Neurol 2011;70:59-69
11. Honmou O, Houkin K, Matsunaga T, Niitsu Y, Ishiai S, Onodera R, Waxman SG, Kocsis JD. Intravenous administration of auto serum-expanded autologous mesenchymal stem cells in stroke. Brain 2011;134:1790-1807
12. Rabinovich SS, Seledtsov VI, Banul NV, Poveshchenko OV, Senyukov VV, Astrakov SV, Samarin DM, Taraban VY. Cell therapy of brain stroke. Bull Exp Biol Med 2005;139: 126-128
13. Savitz SI, Dinsmore J, Wu J, Henderson GV, Stieg P, Caplan LR. Neurotransplantation of fetal porcine cells in patients with basal ganglia infarcts: a preliminary safety and feasibility study. Cerebrovasc Dis 2005;20:101-107
14. Bang OY, Lee JS, Lee PH, Lee G. Autologous mesenchymal stem cell transplantation in stroke patients. Ann Neurol 2005;57:874-882
15. Suárez-Monteagudo C, Hernández-Ramírez P, Alvarez-González L, García-Maeso I, de la Cuétara-Bernal K, Castillo-Díaz L, Bringas-Vega ML, Martínez-Aching G, Morales-Chacón LM, Báez-Martín MM, Sánchez-Catasús C, Carballo-Barreda M, Rodríguez-Rojas R, Gómez-Fernández L, Alberti-Amador E, Macías-Abraham C, Balea ED, Rosales LC, Del Valle Pérez L, Ferrer BB, González RM, Bergado JA. Autologous bone marrow stem cell neurotransplantation in stroke patients. An open study. Restor Neurol Neurosci 2009;27:151-161
16. Battistella V, de Freitas GR, da Fonseca LM, Mercante D, Gutfilen B, Goldenberg RC, Dias JV, Kasai-Brunswick TH, Wajnberg E, Rosado-de-Castro PH, Alves-Leon SV, Mendez-Otero R, Andre C. Safety of autologous bone marrow mononuclear cell transplantation in patients with non-acute ischemic stroke. Regen Med 2011;6:45-52
17. Lee JS, Hong JM, Moon GJ, Lee PH, Ahn YH, Bang OY; STARTING collaborators. A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. Stem Cells 2010;28:1099-1106
18. Wang L, Ji H, Li M, Zhou J, Bai W, Zhong Z, Li N, Zhu D, Zhang Z, Liu Y, Wu M. Intrathecal Administration of Autologous CD34 Positive Cells in Patients with Past Cerebral Infarction: A Safety Study. ISRN Neurol 2013;2013:128591
19. Bhasin A, Srivastava MV, Mohanty S, Bhatia R, Kumaran SS, Bose S. Stem cell therapy: a clinical trial of stroke. Clin Neurol Neurosurg 2013;115:1003-1008
20. Prasad K, Mohanty S, Bhatia R, Srivastava MV, Garg A, Srivastava A, Goyal V, Tripathi M, Kumar A, Bal C, Vij A, Mishra NK. Autologous intravenous bone marrow mononuclear cell therapy for patients with subacute ischaemic stroke: a pilot study. Indian J Med Res 2012;136:221-228
21. Bhasin A, Srivastava M, Bhatia R, Mohanty S, Kumaran S, Bose S. Autologous intravenous mononuclear stem cell therapy in chronic ischemic stroke. J Stem Cells Regen Med 2012;8:181-189
22. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. Lancet Neurol 2007;6:182-187
23. Mendez-Otero R, de Freitas GR, André C, de Mendonça ML, Friedrich M, Oliveira-Filho J. Potential roles of bone marrow stem cells in stroke therapy. Regen Med 2007;2: 417-423
24. Bliss TM, Andres RH, Steinberg GK. Optimizing the success of cell transplantation therapy for stroke. Neurobiol Dis 2010;37:275-283
25. Lees JS, Sena ES, Egan KJ, Antonic A, Koblar SA, Howells DW, Macleod MR. Stem cell-based therapy for experimental stroke: a systematic review and meta-analysis. Int J Stroke 2012;7:582-588
26. Adams HP Jr, Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, Woolson RF, Hansen MD. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology 1999;53:126-131
27. Grotta J. Lubeluzole treatment of acute ischemic stroke. The US and Canadian Lubeluzole Ischemic Stroke Study Group. Stroke 1997;28:2338-2346
28. Franke CL, Palm R, Dalby M, Schoonderwaldt HC, Hantson L, Eriksson B, Lang-Jenssen L, Smakman J. Flunarizine in stroke treatment (FIST): a double-blind, placebo-controlled trial in Scandinavia and the Netherlands. Acta Neurol Scand 1996;93:56-60
29. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 1991;337:1521-1526
30. Shah S, Vanclay F, Cooper B. Predicting discharge status at commencement of stroke rehabilitation. Stroke 1989;20: 766-769