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Meta-analysis of preclinical studies of mesenchymal stromal cells for ischemic stroke

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ABSTRACT

Objectives: To evaluate the quality of preclinical evidence for mesenchymal stromal cell (MSC) treatment of ischemic stroke, determine effect size of MSC therapy, and identify clinical measures that correlate with differences in MSC effects.

Methods: A literature search identified studies of MSCs in animal models of cerebral ischemia. For each, a Quality Score was derived, and effect size of MSCs was determined for the most common behavioral and histologic endpoints.

Results: Of 46 studies, 44 reported that MSCs significantly improved outcome. The median Quality Score was 5.5 (of 10). The median effect size was 1.78 for modified Neurological Severity Score, 1.73 for the adhesive removal test, 1.02 for the rotarod test, and 0.93 for infarct volume reduction. Quality Score correlated significantly and positively with effect size for the modified Neurological Severity Score. Effect sizes varied significantly with clinical measures such as administration route (intracerebral > intra-arterial > IV, although effect size for IV was nonetheless very large at 1.55) and species receiving MSCs (primate > rat > mouse). Because many MSC mechanisms are restorative, analyses were repeated examining only the 36 preclinical studies administering MSCs ≥24 hours poststroke; results were overall very similar.

Conclusions: In preclinical studies, MSCs have consistently improved multiple outcome measures, with very large effect sizes. Results were robust across species studied, administration route, species of MSC origin, timing, degree of immunogenicity, and dose, and in the presence of comorbidities. In contrast to meta-analyses of preclinical data for other stroke therapies, higher-quality MSC preclinical studies were associated with larger behavioral gains. These findings support the utility of further studies to translate MSCs in the treatment of ischemic stroke in humans. *Neurology*® 2014;82:1277–1286

GLOSSARY

mNSS = modified Neurological Severity Score; **MSC** = mesenchymal stromal cell; **STAIR** = Stroke Therapy Academic Industry Roundtable.

Stroke remains a major source of disability. Only approximately 5.2% of patients receive tissue plasminogen activator for acute stroke across the United States,[1] with higher rates in some stroke systems.[2] In addition, many patients who do receive acute reperfusion therapies nonetheless have significant long-term disability. Additional forms of therapy are needed to improve outcomes. Abundant evidence suggests that restorative therapies have the potential to reduce poststroke disability.[3] Many such therapies are under study, most with a time window measured in days or weeks rather than hours. This includes many different types of stem cell therapeutic candidates.[4,5]

Mesenchymal stromal cells (MSCs) (also known as marrow stromal cells and marrow stem cells) are a form of multipotent adult stem cells that have received considerable attention, in part because of their relative ease of isolation from tissues such as bone marrow and their immunoprivileged status. The International Society for Cellular Therapy defines MSCs on the basis of adhering to plastic in standard culture conditions, expressing characteristic surface antigens (e.g., CD105 and CD90, but not CD45 or HLA-DR), and having the ability to differentiate in vitro to osteoblasts,

Supplemental data at Neurology.org

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adipocytes, and chondroblasts.[6] Preclinical studies suggest that MSCs do not replace lost neurons after stroke but instead provide benefit through multiple parallel processes that modulate the tissue microenvironment, including paracrine delivery of growth factors, local and distant immunomodulation, reduced apoptosis, reduced perilesional glial scar formation, promotion of axonal outgrowth and synaptic remodeling, astrocytic and oligodendrocyte precursor cell proliferation, neurogenesis, and angiogenesis.[4,7–11] This is a potential advantage over pharmacologic therapies that act via a single treatment mechanism.[7,8,11] In addition, MSCs have an excellent safety record in clinical trials of humans with many different diseases.[12–14]

The purpose of the current study was to review preclinical studies examining MSC therapy after ischemic stroke. The current review, by focusing on one specific cellular therapy for one specific clinical indication, builds on prior meta-analyses that took a broader approach to stem cell therapy.[4,5,15] First, in accordance with recent Stroke Therapy Academic Industry Roundtable (STAIR) recommendations[16] and a recent NIH workshop,[17] the quality of the studies was reviewed. Second, the effect size of MSCs was determined for the most frequently used behavioral and histologic outcomes. Third, the relationship between study quality and effect size was examined, because lower-quality preclinical stroke studies tend to overestimate efficacy.[18–22] Finally, the robustness of MSC efficacy was examined across clinical measures of interest such as dose and timing relative to stroke onset. Given the potential for MSCs as a restorative therapy, analyses were repeated using only preclinical studies that initiated MSC therapy 24 hours or more after stroke onset.

METHODS

Search strategy. Studies of MSCs in animal models of cerebral ischemia were identified from electronic searches of PubMed and Institute for Scientific Information Web of Science. The following search strategy was used: (mesenchymal OR mesenchymal stem cell OR mesenchymal stromal cell) AND (stroke OR cerebrovascular OR middle cerebral artery OR MCA OR anterior cerebral artery OR ACA). Secondary references were also reviewed. Studies were excluded if the stroke model was hemorrhagic rather than ischemic, published in a language other than English, or the MSC therapy involved additional active components such as gene modification or bioscaffolding.

Data extraction. Data were extracted from all available sources in each paper, including text and graphs. When only graphic presentation was available, values for mean and SD were obtained via quantitative methods on highly magnified images using the line length measuring tool in PowerPoint (Microsoft, Redmond, WA).

A Quality Score estimating methodologic quality was determined for each preclinical study using the scale of Lees et al.,[5] which defined 10 criteria based on STAIR guidelines[16,23]: (1) publication in a peer-reviewed journal, (2) statements describing control of temperature, (3) random assignment of animals to treatment group, (4) allocation concealment, (5) blinded outcome assessment, (6) avoidance of anesthetics with known marked intrinsic neuroprotective properties, (7) use of animals with relevant comorbidities, (8) inclusion of a sample-size calculation, (9) statement of compliance with animal welfare regulations, and (10) inclusion of a statement declaring presence or absence of any conflicts of interest. One point was given for each criterion reported. Potential scores range from 0 to 10, with higher scores indicating greater methodologic rigor.

The effect size of MSC therapy was determined for the 4 endpoints that appeared most frequently across preclinical MSC studies: (1) modified Neurological Severity Score (mNSS), (2) adhesive removal test, (3) rotarod test, and (4) infarct volume. For each, effect size was defined as the improvement in outcome in MSC-treated animals relative to untreated ischemic controls, and calculated using Hedges' g, which is similar to Cohen *d* but more appropriate when examining effect size in smaller samples.[24] Effect size values for the rotarod test were multiplied by −1 because larger values indicate superior outcome, in contrast with the other 3 measures. Two studies scored mNSS in the opposite direction of all other studies; for these, directionality was reversed to maintain consistency. When outcomes were reported at multiple time points, only the final assessments were examined.

Statistical analysis. In bivariate analyses (JMP 9.0; SAS Institute, Cary, NC), 6 clinical variables of interest were examined in relation to Quality Score and each effect size using nonparametric methods (Wilcoxon rank-sum test for categorical variables and Spearman rank-order correlation for continuous variables). The 6 clinical variables of interest were (1) route of administration, (2) species receiving MSCs, (3) species that was MSC source, (4) time of MSC administration relative to stroke onset, (5) degree of MSC immunogenicity (autologous, allogeneic, or xenogenic), and (6) MSC dose. For the 2 effect sizes with the largest number of published data points (mNSS and infarct volume), analyses were repeated using forward stepwise multiple regression ($p = 0.1$ to enter the model; $p = 0.15$ to leave); time and dose were not normally distributed and could not be transformed and so were converted to categorical variables for multiple regression modeling.

Mean effect size, 95% confidence intervals, forest plots, and significance were examined using the inverse-variance method, and with standard mean differences, in Review Manager 5.2.[25] Because substantial heterogeneity was present across endpoints ($I^2 = 47\%–76\%$), random effects models were used.[25]

The potential for publication bias was examined using Funnel plots.[26] These were analyzed in Comprehensive Meta Analysis version 2 (Biostat, Englewood, NJ). Evidence for significant publication bias was assessed using a 2-tailed Egger regression intercept method. Adjusted effect sizes were then estimated by adjusting for any asymmetry using the Duval and Tweedie trim and fill approach.

RESULTS

All studies. ***Study characteristics.*** A total of 46 studies and 62 MSC treatment arms were identified (table 1, and table e-1 on the *Neurology*® Web site at Neurology.org). MSCs improved outcomes (behavioral

Table 1 Characteristics of reviewed studies

Clinical measure	All studies	Studies administering MSCs ≥24 h poststroke
No. of publications	46	36
No. of MSC treatment arms	62	46
Source of MSCs		
Rat	35	27
Human	22	16
Mouse	5	3
Species receiving MSCs		
Rat	56	40
Mouse	4	4
Primate	2	2
Range of MSC doses, MSCs/kg	3.6×10^4 to 4.3×10^7	2.6×10^5 to 4.3×10^7
Route of MSC administration		
IV	43	31
IC	14	11
IA	5	4
Time of MSC administration		
0–8 h poststroke	16	—
24 h poststroke	25	25
>24 h to 1 wk poststroke	16	16
>1 wk to 30 d poststroke	4	4
MSC immunogenicity		
Autologous	1	—
Allogeneic	37	30
Xenogenic	24	16

Abbreviations: IA = intra-arterial; IC = intracerebral; MSC = mesenchymal stromal cell. Note that the primate data are derived from *Macaca fascicularis*, a subhuman primate with a gyrencephalic brain.

Table 2 Proportion of studies meeting each Quality Score criterion

Quality Score criterion	Studies meeting criterion, %
Published in peer-reviewed journal	100
Control of temperature	80
Avoided neuroprotective anesthetics	80
Statement confirming compliance with animal welfare requirements	80
Random treatment assignment	70
Blinded outcomes	65
Allocation concealment	26
Conflict of interest statement	22
Animals with comorbidities	15
Sample size calculation	2.2

or histologic) in 44 of the 46 studies and in 54 of the 62 treatment arms.

Quality Score. The median Quality Score across the 46 studies was 5.5 (interquartile range 4–7, range 2–8; table 2). The Quality Score was not related ($p > 0.1$) to any of the 6 clinical variables of interest (route, species receiving, species of MSC source, time, immunogenicity, and dose).

Effect size. The effect size for MSC administration was consistently very large (table 3 and figure 1, A–D), ranging from 0.93 to 1.78 and exceeding 1 for all 3 behavioral measures. The Quality Score correlated with effect size for mNSS ($r = 0.39$, $p < 0.04$), indicating that the higher the study quality, the greater the improvement in behavioral recovery associated with MSC treatment.

Clinical correlates of effect size. Bivariate analysis revealed that effect size was related to some of the clinical variables of interest (table 4). Clinical variables correlating with behavior (mNSS) differed from those correlating with infarct volume reduction.

Multiple regression using stepwise forward modeling reached findings that were overall concordant with bivariate analyses. For mNSS effect size, dose survived as the only significant predictor (larger behavioral gains from MSCs were associated with lower doses). For infarct volume reduction effect size, time of MSC administration (larger effect when MSCs were given early, i.e., 0–8 hours poststroke) and degree of MSC immunogenicity (larger effect when MSCs were autologous or xenogeneic) survived as significant predictors.

Presence of comorbidities did not reduce MSC effects: for the 6 studies (8 treatment arms) that used animals with comorbidities (hypertension, increased age, 2 weeks of hyperglycemia ["diabetes mellitus"]), MSC effect sizes did not differ from values found in the 40 studies (54 treatment arms) that did not include animals with comorbidities. Also, although 18 of the studies (22 of the treatment arms) involved one investigator (Dr. Michael Chopp), this cluster of high productivity did not drive the current results, because effect sizes were actually smaller in Dr. Chopp's studies as compared with other laboratories (mean mNSS effect size 1.66 vs 3.11, $p = 0.022$; mean infarct volume reduction effect size 0.41 vs 2.15, $p = 0.0004$). The other behavioral effect sizes and the Quality Score from Dr. Chopp's laboratory did not significantly differ from other laboratories.

Forest plots and effect size. Effect sizes were substantial and significant for each of the 4 measures examined (figure 1, A–D, and table 3). In figure 1, A and B, selected examples of subgroups are shown to further illustrate the impact of some of the clinical variables of interest. Thus, while the mNSS effect size was found to vary according to route of administration (table 4), results remained significant for all 3 routes (figure 1A). For infarct volume reduction (figure 1B),

Table 3 Effect size for MSC administration in preclinical studies of ischemic stroke

	All studies			Studies administering MSCs ≥24 h poststroke		
Measure	Effect size, mean	95% CI	No.	Effect size, mean	95% CI	No.
mNSS	1.78	1.43–2.12	28	1.76	1.41–2.10	26
Adhesive removal test	1.73	1.26–2.19	22	1.80	1.32–2.28	21
Rotarod test	1.02	0.49–1.55	14	1.07	0.45–1.69	12
Infarct volume reduction	0.93	0.62–1.24	43	0.57	0.35–0.80	34

Abbreviations: CI = confidence interval; mNSS = modified Neurological Severity Score; MSC = mesenchymal stromal cell. For each effect size, reported as Hedges' g, the 95% CI does not cross zero and the *p* value for overall effect was ≤0.001, indicating that results favor MSCs.

MSC effects were highest in the early hours poststroke and remained significant out to 1 week poststroke but not thereafter.

Evaluation for publication bias. Funnel plots (figure e-1) examined effect size in relation to standard error and in each case suggested significant ($p \leq 0.0001$) publication bias to the left of the estimate, i.e., studies with a smaller effect size than current mean values were underreported. However, after adjusting for these asymmetries, mean effect sizes nonetheless remained very large (1.41 for mNSS, 1.23 for adhesive removal, 1.14 for rotarod, and 0.62 for infarct volume reduction).

Studies administering MSCs ≥24 hours poststroke. ***Study characteristics.*** MSCs may have particular utility as a restorative therapy given their mechanisms of action, and so analyses were repeated examining only the 36 preclinical studies that administered MSC ≥24 hours poststroke, among which there were 46 MSC treatment arms (table 1).

Quality Score. Among these studies, median Quality Score remained 5 (interquartile range 4.25–7). The Quality Score varied in relation to time poststroke ($r = -0.37$, $p < 0.02$), being higher in studies with shorter times from stroke onset to MSC administration.

Effect size. In this subgroup of studies, effect sizes remained large for all 4 measures (table 3, figure e-2). Quality Score was again related to effect size for mNSS ($r = 0.42$, $p < 0.04$; figure 2A).

Clinical correlates of effect size. Bivariate analysis found that the relationships between clinical variables and MSC effect size that were observed across all studies generally remained significant when examining only those studies administering MSCs ≥24 hours poststroke (figure 2, B–D).

Multiple regression using stepwise forward modeling found that for mNSS effect size, route (intracerebral > intra-arterial + IV) and degree of immunogenicity (xenogeneic > allogeneic) remained as significant predictors, while for infarct volume reduction effect size, species receiving MSCs (primate > rat + mouse) survived as a significant predictor.

Forest plots of effect size. Overall, results were little changed when restricting analysis to studies administering MSCs ≥24 hours poststroke, with effect size remaining >1.0 for all 3 behavioral measures (table 3, figure e-2).

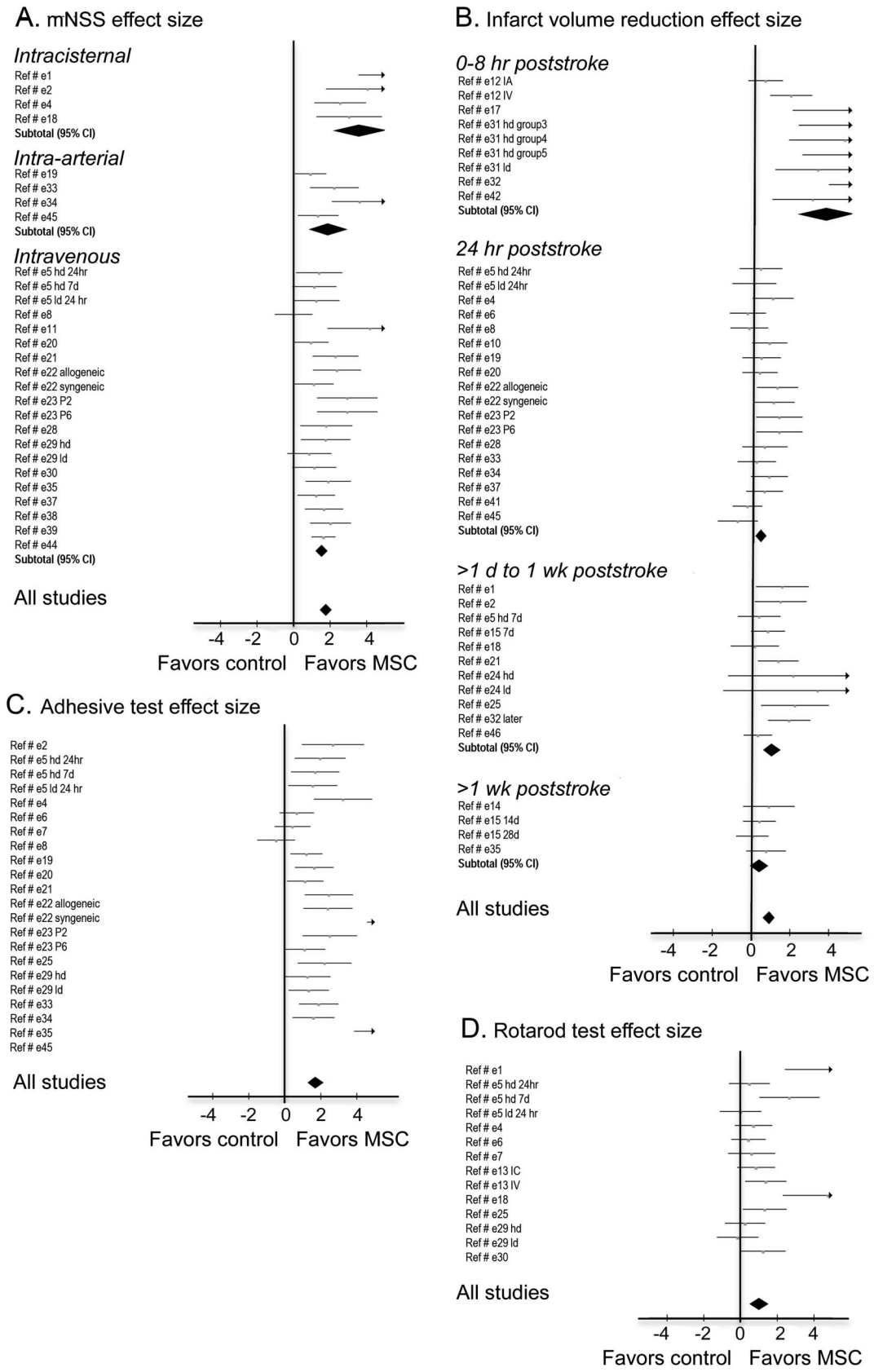
Evaluation for publication bias. Funnel plots (figure e-3) again suggested significant ($p \leq 0.0002$) publication bias in each case, to the left of the estimate. Despite this, effect size estimates adjusted for funnel plot asymmetry again remained very large for the 3 behavioral measures (1.43 for mNSS, 1.29 for adhesive removal, and 1.07 for rotarod), and was 0.42 for infarct volume reduction.

DISCUSSION

The current meta-analysis examined preclinical studies of MSCs in the treatment of ischemic stroke and found that this cellular therapy improves outcome, with very large effect sizes. Effects were robust across species, delivery route, time of administration in relation to stroke, MSC immunogenicity, and MSC dose. These results support further translational studies of MSCs in the treatment of ischemic stroke in humans.

The quality of preclinical MSC studies was reviewed given the important bearing this has on translational potential.[16,17] The median Quality Score value in the current study was 5.5, slightly higher than the value of 4 found across all preclinical stem cell stroke studies by Lees et al.[5] using the same Quality Score. It is important that higher study quality was associated with larger behavioral gains related to MSC administration (figure 2A). This is in contrast to the preclinical data for many other stroke therapies, where higher study quality has repeatedly been associated with smaller efficacy.[18] The tendency for lower-quality studies to overestimate intervention effects also exists in human trials[27] and meta-analyses of human stroke therapies.[19–22] That the reverse was true, with MSC higher-quality studies showing larger behavioral gains, increases confidence in their therapeutic translational potential.

Figure 1 MSC effect size across all studies



Forest plot shows mean effect size and 95% CI for (A) mNSS, (B) infarct volume reduction, (C) adhesive removal test, and (D) rotarod test. Values for effect size were very large and highly significant and were robust across numerous variables such as (A) route of MSC administration and (B) time of MSC administration after stroke. CI = confidence interval; hd = higher-dose group; IA = intra-arterial; IC = intracerebral; ld = lower-dose group; mNSS = modified Neurological Severity Score; MSC = mesenchymal stromal cell; P2 = 2 passages in culture; P6 = 6 passages in culture.

Table 4 Bivariate relationships between clinical measures and MSC effect size

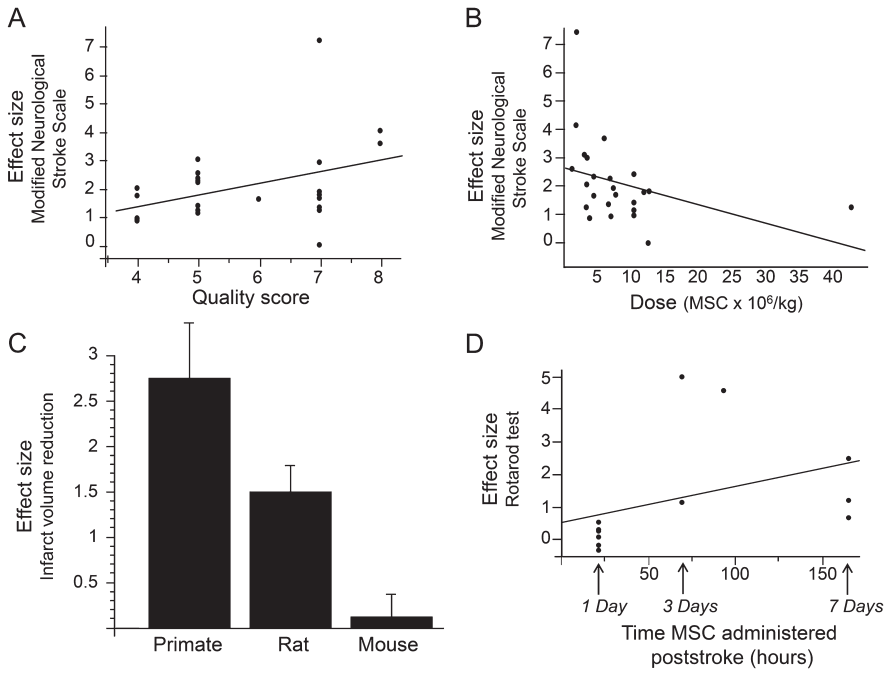
Effect size for mNSS		Effect size for infarct volume reduction	
Correlates with	***p***	**Correlates with**	***p***
Route of administration (IC > IA > IV)	0.025	Degree of MSC immunogenicity (autologous > xenogeneic > allogeneic)	0.01
MSC dose ($r = -0.63$)	0.0003	Time MSCs administered poststroke ($r = -0.32$)	0.038
		Species studied (primate > rat > mouse)	0.048
		MSC source (human > rat > mouse)	0.036

Abbreviations: IA = intra-arterial; IC = intracerebral; mNSS = modified Neurological Severity Score; MSC = mesenchymal stromal cell.
In addition, effect size for rotarod test correlated with time MSCs were administered poststroke ($r = 0.61$, $p = 0.02$). Effect size for adhesive removal test did not correlate with any of the 6 clinical variables of interest. The results include all available studies; when analyses were repeated using only those studies administering MSCs ≥24 hours poststroke, results were very similar.

A significant favorable effect of MSCs was reported in 44 of the 46 studies and in 54 of the 62 treatment arms. Mean MSC effect sizes were overall very large, for example, for mNSS averaging 1.78 across all studies and 1.76 across studies administering MSCs ≥24 hours poststroke. In general, an effect size of 0.2 equates to a small effect, 0.5 to a medium effect, and ≥0.8 to a large effect.[27,28] In this context, MSC effects in the preclinical ischemic stroke literature can be classified as very large. Overall, effect sizes for structural (infarct volume reduction) and behavioral (mNSS, adhesive removal test, and rotarod test) MSC effects were of comparable magnitude, similar to the findings by Janowski et al.[4] Effect sizes remained substantial after adjusting for potential publication bias.

Therapies given in the early hours after stroke generally aim to reduce the injury, while therapies started days to weeks after stroke generally aim to promote repair. MSCs may have potential for both therapeutic time windows. Regarding acute stroke therapies, MSCs reduced infarct volume (table 3). This reduction was highest when MSCs were initiated at the earliest times (table 4 and figure 1B), i.e., at 0 to 8 hours after stroke onset, a finding that is consistent with acute stroke

Figure 2 Clinical correlates of effect size among studies introducing MSCs in the restorative therapy time window



For the studies that introduced MSCs ≥24 hours poststroke: (A) higher Quality Score was associated with greater behavioral effects of MSCs ($r = 0.42$, $p < 0.04$). (B) Lower MSC doses were associated with greater behavioral effects ($r = -0.58$, $p < 0.002$). (C) The effect size of MSCs on infarct volume reduction varied in relation to the species being studied and was highest in subhuman primates (mean ± SEM, $p < 0.03$). (D) The effect size of MSC therapy for the rotarod test varied in relation to time of MSC administration relative to stroke; effect sizes were higher in studies with later time of MSC introduction ($r = 0.77$, $p < 0.004$). Values for effect size are Hedges' g. MSC = mesenchymal stromal cell.

neuroprotective therapies in general. It is noteworthy that MSCs significantly reduced infarct volume even when initiated at 1 day or 1 week after stroke onset, a time when ischemic injury is generally completed.[29] Infarct volume reduction might therefore reflect many different processes including tissue salvage, but also cellular proliferation[30] and reduction in delayed neuronal death.[31,32] Regarding restorative stroke therapies, MSCs introduced ≥24 hours poststroke had a very large and favorable effect on behavioral outcomes (table 3). Restorative therapies, as with acute stroke therapies, have discrete time windows for maximum therapeutic effectiveness.[30,33,34] For example, Ren et al.[33] found that behavioral outcome was improved when osteogenic protein-1 was initiated 1 or 3, but not 7, days poststroke. Consistent with this, MSCs may also have optimal therapeutic time windows for neural repair, because some behavioral gains from MSCs were increased when therapy was initiated later than 24 hours poststroke (figure 2D). Behavioral gains associated with administration of MSCs days to weeks poststroke might reflect many different restorative or immunologic processes.[4,7,8,11] Together, these results emphasize that translational MSC studies need to carefully consider optimal time windows for various therapeutic targets. This issue is of particular importance to consideration of autologous MSC therapies. Current culture methods generally require 2 to 3 weeks to produce appreciable numbers of MSCs from a patient's own tissues, and the potential advantages of autologous cell therapy may be justified if human studies defining the treatment time window suggest that such a delay does not compromise therapeutic efficacy.

The current review builds on prior meta-analyses of stem cell therapy, each of which had its own approach.[4,5,15] Janowski et al.,[4] reviewing studies up to 2006, reported numerous useful findings, but combined results across many types of stem cells and neurologic disorders. Lees et al.[5] provided key insights and focused on ischemic stroke, but also combined results across many different cell therapies, as well as cell engineering. Dharmasaroja[15] reviewed reports up to 2007, did restrict analysis to MSC treatment of ischemic stroke, but did not consider study quality or treatment effect size. The current review is focused on one specific cellular therapy for one specific clinical indication. This approach is intended to directly inform therapeutic translation, because regulatory approval is generally given for a specific therapy and a specific clinical indication.

Effects of MSCs after stroke varied in relation to several clinical measures, and the nature of these findings is promising for human applications. For example, findings in relation to species studied (primates with best MSC responses) and species of MSC source (human MSCs with greatest effects) encourage further translational studies (figure 2C and table 4). Findings in relation to route were also encouraging. Administration of MSCs using more invasive methods provided significantly greater benefit (table 4). However, effects of MSCs given IV, while reduced vs invasive routes, nonetheless remained very large (figure 1A and table 4). Availability of noninvasive treatment options would likely increase treatment impact. Regarding the time window for therapeutic efficacy, MSC effects remained very large when treatment was initiated 1 day, 1 week, or 1 month poststroke. Many patients do not access medical care in time to benefit from current acute stroke reperfusion therapies,[35,36] and so current results provide hope that, should MSCs prove effective in humans, the time window will be wide enough for many patients to access treatment.

Translating these results into clinical trials of MSCs in human patients raises a number of questions. First, how will cells be stored until the patient with stroke is ready to be treated? In order to maintain biological stability of the therapeutic product, cells that have completed expansion in culture must be administered rapidly or frozen until needed. Optimal translation of MSCs to humans may therefore require additional studies focused on issues such as effects of storage, transportation, and thawing.[37–39] Second, which MSC administration route(s) should be pursued as a priority? The intracerebral route showed larger effects than IV, but a neurosurgical procedure may not be trivial for some patients with recent stroke, and the IV route did provide very large behavioral benefits (figure 1A). The optimal choice for MSC administration route might depend on individual factors and priorities. Third, is the dose-response curve for MSCs linear or U-shaped? Some behavioral benefits were reduced at the highest MSC doses (figure 2B and table 4), possibly reflecting prior observations that larger MSC doses can potentially affect organ perfusion.[40–42] Fourth, how can concomitant experience be controlled, or at least measured? Brain repair after stroke occurs on the basis of experience-dependent plasticity[43,44]—efficacy of flu vaccine may vary little with posttreatment behavior but successful brain repair needs behavioral reinforcement—and it remains to be understood how MSC effects will interact with differences in environment and rehabilitation care, or with the human psychosocial experience of stroke. Fifth, can allogeneic cells be administered without concomitant immunosuppressive drugs early after stroke? The current preclinical data, and at least some nonstroke human data, suggest that allogeneic MSCs are safe and efficacious, but studies of MSCs after stroke in humans thus far have focused on autologous cells,[45–48] and so trials

examining the safety of allogeneic MSCs in humans are needed. Sixth, other concerns frequently raised in the study of human brain repair also require attention: which patient subgroups will be most responsive,[49] how do MSC effects interact with common drugs,[50] and does genetic variation affect treatment efficacy?[51] Finally, what are the most important mechanisms of action of MSCs after stroke in humans? Cellular therapies such as MSCs act through numerous restorative and immunomodulatory processes in parallel.[4,7,8,11] Insight into the mechanism of action can optimize therapeutic application, e.g., for identifying patient subgroups most likely to derive benefit. However, preclinical models incompletely recapitulate human disorders,[52,53] particularly in the immune system, important to MSCs. For example, Seok et al.[54] performed a systematic comparison of genomic responses between murine models and human inflammatory diseases and found a poor ("close to random") correlation. Some questions related to translating MSCs as a therapy for humans may therefore be most directly addressed by careful studies in human subjects, rather than additional studies in rodents, an approach supported by the excellent safety record that MSCs have to date in clinical trials of humans with noncerebrovascular conditions.[12–14,55,56]

In the current meta-analysis of MSCs in the treatment of ischemic stroke, preclinical studies showed very large and favorable effects on behavioral outcomes. A number of factors support translation to humans, including robustness of preclinical findings across variables such as species studied, species that was the source of the MSCs, time of MSC administration after stroke, and route of administration. Initial experience in small studies of MSCs in humans with stroke has been promising,[45–48,57] MSCs have an overall excellent safety record in clinical trials of human subjects across numerous diagnoses,[12–14,55,56] and MSCs have demonstrated efficacy in nonstroke conditions such as graft versus host disease, where MSCs have been the basis for the first stem cell therapy approved in North America. Overall, the current review suggests utility in further translational studies of MSCs in human patients with ischemic stroke.

AUTHOR CONTRIBUTIONS

Kate Xie and Quynh Vu: contributed to drafting the manuscript, study design, data analysis, and statistical analysis. Mark Eckert and Weian Zhao: contributed to drafting the manuscript, study design, and data analysis. Steven C. Cramer: contributed to drafting the manuscript, study design, data analysis, and statistical analysis.

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