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Orally derived mesenchymal stem cells in the treatment of vascular diseases: a systematic review and meta-analysis

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Orally derived mesenchymal stem cells (OMSCs) are an emerging source of cells for treating vascular diseases (VDs). In this systematic review and meta-analysis, for the first time, we reviewed the published preclinical studies that examined the potential of OMSCs and their secretome in treating VDs, focusing on their efficacy and therapeutic mechanism. We electronically searched PubMed, Embase, and Web of Science, from the inception of the databases to December 31, 2024, for relevant literature from peer-reviewed journals. The studies focused on treating VDs in animal models using the OMSC-based strategy were included in the review. The articles were classified by disease, injury model, and outcome. A meta-analysis of the OMSC treatment effects on the cerebral ischemia (CI) infarct volume was conducted using random-effects and fixed-effects models. Forty-one studies were included and classified by type: CI, hypoxic-ischemic encephalopathy (HIE), myocardial ischemia (MI), hindlimb ischemia (HI), and others. Each study presented varying degrees of evidence that OMSCs had positive biological and functional effects on the treatment outcomes of VDs, mainly via paracrine effects. Pooled analysis showed that the effect of OMSC treatment compared with control on infarct volume was −2.19 (95% confidence interval: −3.01, −1.37, $p < 0.01$) with the random-effects model and −1.87 (95% confidence interval: −2.44, −1.29, $p < 0.01$) with the fixed-effects model. These results showed that OMSCs can significantly reduce the infarct volume in animal models of CI. Overall, OMSCs show promising potential for treating VDs mainly because of their secretome. However, before moving on to clinical trials, more high-quality preclinical studies with detailed analyses of possible off-target effects are needed.

Keywords Stem cells, Cell transplantation, Experimental animal models, Ischemia, Vascular diseases

Abbreviations

ADSCs	Adipose-derived stem cells
ACVIM	American College of Veterinary Internal Medicine
BDNF	Brain-derived neurotrophic factor
BMMSCs	Bone marrow mesenchymal stromal cells
CI	Cerebral ischemia
CM	Conditioned medium
DPSCs	Dental pulp stem cells
EVs	Extracellular vesicles
OMSCs	Orally derived mesenchymal stem cells
DP-iNCs	Dental pulp-derived induced neural cells
Fb	Fibroblasts
GMSCs	Gingival mesenchymal stem cells
HI	Hindlimb ischemia

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hGMSCs	Human gingival mesenchymal stem cells
HMGB1	High mobility group box 1
hPDLSCs	Human periodontal ligament stem cells
HUVEC	Human umbilical vein endothelial cell
HIE	Hypoxic-ischemic encephalopathy
MSCs	Mesenchymal stem cells
mNSS test	Modified neurological severity score test
MI	Myocardial ischemia
MyD88	Myeloid differentiation primary response 88
NF-κB	Nuclear factor kappa-B
NPCs	Neural progenitor cells
PDLSCs	Periodontal ligament stem cells
P-MCAO	Permanent middle cerebral artery occlusion
pOMSCs	Puppy deciduous teeth stem cells
rDPSCs	Rats dental pulp stem cells
SE	Standard error
SMD	Standard mean difference
SHED	Stem cells from deciduous teeth
SVZ	Subventricular zone
TLR4	Toll-like receptor 4
T-MCAO	Transient middle cerebral artery occlusion
VDs	Vascular diseases

Vascular diseases (VDs) are harmful alterations in the body's vascular system, arising from damage or abnormalities in the blood vessels and failures within the blood vessel network. The major VDs include cerebral ischemia (CI) disease (e.g., stroke, hypoxic-ischemic encephalopathy [HIE]), cardiac ischemia disease (e.g., myocardial ischemia [MI]), and peripheral ischemia disease (e.g., peripheral artery disease). VDs affect people's work and lives and are potentially life-threatening, bringing an inevitable burden on families and society[1,2]. To date, pharmacotherapy (e.g., thrombolytics, neuroprotective agents) and physiatrics (e.g., hypothermia therapy) have been widely used to treat VDs and, when necessary, combined with surgery[3–7]. However, thrombolytic drugs are only effective within 4.5 h of stroke onset[8], and the mortality rate of HIE treated with hypothermia therapy is 25%[9]. A variety of surgical techniques have been developed for the treatment of atherosclerotic diseases, such as atherectomy, plain balloon angioplasty, drug-coated balloons, bare metal, and drug-eluting self-expanding stents[10]. However, these methods are not one-and-done, and over time, the blood vessels will narrow again[11]. Thus, pharmacotherapy and surgery only work within limited time windows and, even then, may lack effectiveness.

Cell-based therapy has recently gained growing attention as it represents a potentially safer and more effective therapeutic approach with an extended treatment window. Given their capacity for self-renewal and multilineage differentiation[12], stem cells offer great potential for the regeneration and repair of damaged tissues. Although embryonic stem cells possess remarkable pluripotency, their clinical application remains limited due to ethical concerns[13]. Mesenchymal stem cells (MSCs), which can be isolated from various adult tissues, including adipose tissue or bone marrow[14,15], exhibit multipotent differentiation[15,16] and significant paracrine effects[17,18]. However, their procurement often requires invasive procedures, which pose additional risks and limit clinical applicability. In contrast, orally derived mesenchymal stem cells (OMSCs), including dental pulp stem cells (DPSCs) and stem cells from human exfoliated deciduous teeth (SHED), can be obtained non-invasively from discarded biological materials such as extracted wisdom teeth or exfoliated deciduous teeth. OMSCs possess comparable or even superior capacities for proliferation, differentiation, and secretion of bioactive factors[19,20], making them an attractive and ethically acceptable source for regenerative therapy.

In recent years, OMSCs, their conditioned media (CM), and OMSC-derived exosomes have been investigated as novel treatment strategies for VDs in several animal studies[21–23]. These studies employed diverse administration routes, including intracranial, intranasal, and systemic delivery, and consistently demonstrated improvements in motor and sensory function. Notably, DPSCs have been shown to promote functional recovery in models of CI[22], while SHED-derived CM provided superior neuroprotective effects compared with those of BMMSCs[21]. OMSCs and their secretome have been shown to exert these therapeutic effects mainly by promoting cell migration[22], enhancing anti-inflammatory effects[24], and inhibiting apoptosis[25].

Although some systematic reviews have examined the effectiveness of stem cells in treating various VDs, research specifically on OMSCs as a unique subtype of MSCs has not been systematically or thoroughly analyzed. Therefore, this systematic review aimed to comprehensively evaluate the therapeutic potential of OMSCs and their derivatives in the treatment of VDs. The review sought to synthesize and analyze evidence from *in vivo* studies to determine the efficacy of various OMSC-based interventions, including cell transplantation, conditioned media, and exosome administration. In doing so, it compared outcomes across different OMSC sources and delivery routes, explored the mechanisms underlying vascular repair, and identified existing limitations in the current body of evidence. Ultimately, the objective was to establish an evidence base that could guide future research and support the clinical translation of OMSC-based therapies for VDs.

Methods

Protocol registration

The protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number CRD42022258794), which is available from: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=258794. This review followed the PRISMA 2020 guidelines.

Search strategy

The literature search scope was from the inception of databases (PubMed, Embase, and Web of Science) to December 31, 2024. Search terms included combinations of "dental mesenchymal stem cells" and "vascular diseases" or their synonyms, as mentioned in Supplementary File 1. Two reviewers screened the literature using the same criteria, and when there were differing opinions, a third reviewer reviewed the literature and helped resolve any discrepancies.

Study selection

We included all studies reporting *in vivo* experiments using OMSCs (including side population cells derived from OMSCs), OMSC-CM, or OMSC-exosomes, regardless of the outcome, in animal models of VDs. Reviews, editorials, conference abstracts, case reports, meta-analyses, studies describing only *in vitro* data, non-English literature, and duplicate studies were excluded. Only animal studies were included in this systematic review.

Data extraction and quality assessment

Two reviewers independently extracted data using the same standards. Any disagreement was discussed with a third reviewer to resolve. Studies were classified based on the disease and injury models studied. The type of animal, source of OMSCs, VD model, administration route, treatment dose, and outcomes were recorded. Key parameters of the experimental design and methodology were extracted[26] to identify whether the (1) species and strains of experimental animals were reported, (2) group and number of experimental animals were specified, (3) experimental animals were randomly assigned, and (4) investigators experimented in a single-anonymized manner. "The ARRIVE Essential 10: Compliance Questionnaire"[27] was used to evaluate the included studies for bias and quality, and scored 18 subitems (Yes: 1; No: 0). The experimental outcomes were summarized qualitatively. The quantifiable indicators were extracted, taking into account the homogeneity of the study and the calculability of the effect size. Only CI studies that reported infarct volume in mm^3 met this criterion; quantitative data were extracted from these studies, and a meta-analysis was conducted.

Statistical analysis

For each included study, the means and standard deviations of infarct volumes resulting from CI were extracted for quantitative synthesis. Meta-analysis was conducted using the inverse variance (IV) weighting method under a random-effects model, with between-study variance estimated using the DerSimonian and Laird method. Given the potential differences in measurement scales across studies, standardized mean differences (SMDs) were calculated as the summary effect size, facilitating comparability across diverse outcome metrics. Statistical significance was determined using a two-sided p-value threshold of <0.05. Heterogeneity among studies was assessed using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity[28]. To evaluate the robustness of the results, sensitivity analyses were performed using a fixed-effects model. All meta-analyses were performed using Cochrane Review Manager software (RevMan Web, https://revman.cochrane.org/).

Results

Characteristics of selected studies

A total of 295 studies were obtained after a systematic search in three databases. After the elimination of duplicates, 221 records remained. In the title and abstract screening, 166 articles were excluded because they did not meet the inclusion criteria (unrelated to OMSCs or VDs, reviews/editorials/conference abstracts/notes/meta-analysis, and retraction). After the full-text screening of the remaining 55 records, 14 were excluded because they were either unrelated to or lacked data regarding animal work or the use of OMSCs to treat VDs. Thus, a total of 41 studies published between 2007 and 2024 were included in the systematic review (Fig. 1); In terms of cell type, DPSCs were the most frequently investigated (29 studies used DPSCs from human sources, one of which also studied human periodontal ligament stem cells [hPDLSCs], and three studies used DPSCs from rats), followed by SHED (8 studies), human gingival mesenchymal stem cells (hGMSCs) (1 study) and puppy deciduous teeth stem cells (1 study).

We grouped the 41 studies into 5 categories based on different VDs: (1) CI (20 studies)[21–23,29–45], (2) HIE (5 studies)[24,46–49], (3) MI (4 studies)[25,50–52], (4) Hindlimb ischemia (HI) (7 studies)[38,53–58], and (5) others (6 studies, including subarachnoid hemorrhage [2 studies][59,60], vascular dementia [1 study][61], atherosclerosis [2 studies][62,63], and degenerative valve disease [1 study][64]. One study[38], simultaneously reported on two animal models; therefore, it is included under both CI and HI.

Study quality and bias assessment (Table 1)

The bias and quality of the studies were evaluated based on "The ARRIVE Essential 10: Compliance Questionnaire"[27]. Supplementary file 2 summarizes the evaluation scores of the studies (Table S1) and the criteria used for evaluation (Table S2). In summary, 10 studies did not report the characterization of OMSCs. All studies reported the species of experimental animals, and only 1 study did not report the strain of the experimental animals[54]. One study[38], simultaneously reported on two animal models (CI and HI). Random assignment of experimental animals was reported in 26 out of 41 studies (17 of 20 in CI, 2 of 5 in HIE, 2 of 4 in MI, 1 of 7 in

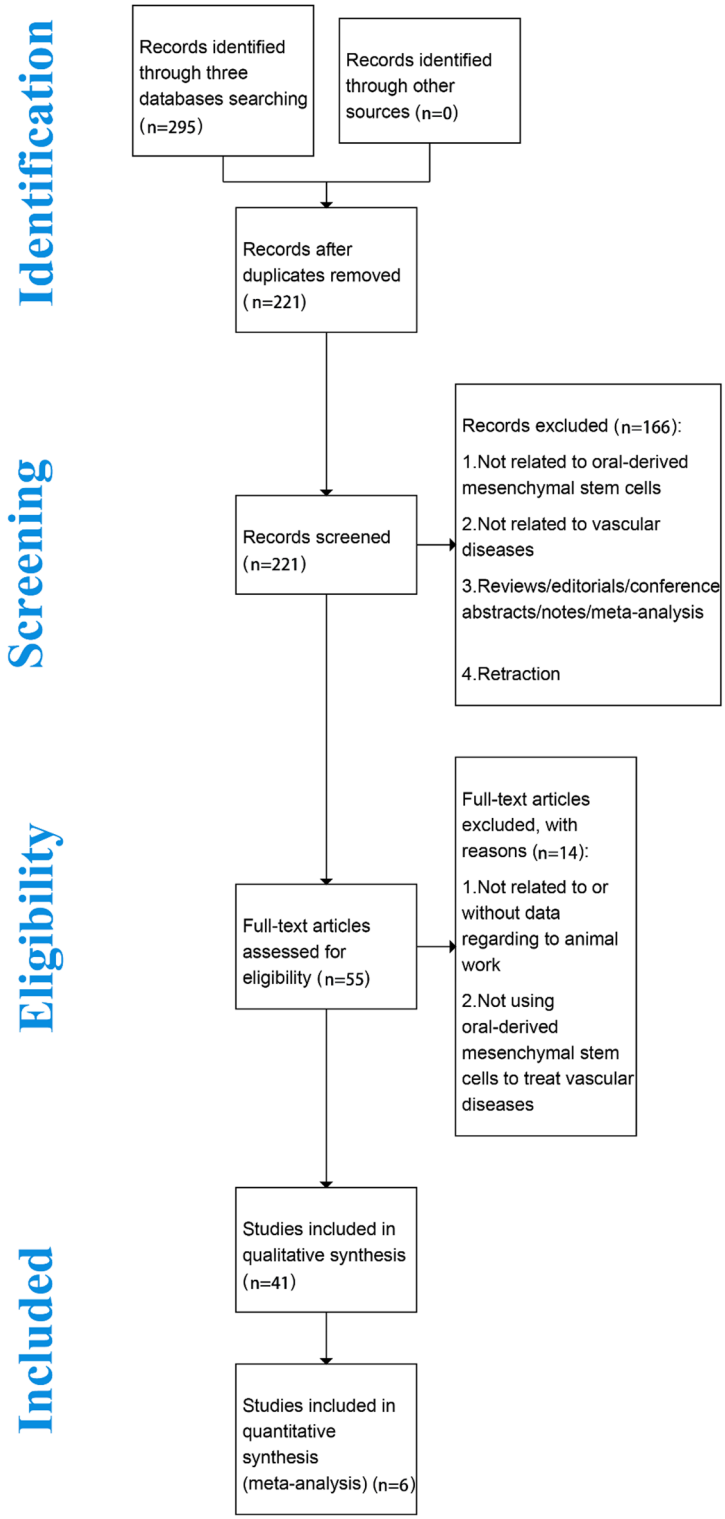

Fig. 1. PRISMA Flowchart.

HI, and 5 of 6 in others). More than half of the studies (21 of 41) reported the blinding of investigators or lab personnel (13 of 20 in CI, 4 of 5 in HIE, 1 of 4 in MI, 2 of 7 in HI, and 2 of 6 in others). Fifteen studies reported both randomization and blindness, accounting for more than one-third of the total. A summary of the study quality and bias assessment is shown in Table 1. For the studies that used OMSC-CM, the details of CM are summarized in Table S3 of Supplementary File 3.

Disease model	OMSCs characterization	Improved outcome, OMSCs vs. control	Improved outcome, OMSCs vs. other cells	Improved outcome, modified OMSCs vs. OMSCs	Animal allocation and flow described		Randomized	Blinded	Published year	Sample size	References
					Strains and species of animals	Number of treated animals (at least one experiment)					
CI	Yes	Yes			Yes	Yes	Yes	Yes	2012	44	22
CI	Yes	Yes	vs. BMMSCs Yes		Yes	Yes	Yes		2017	27	39
CI	Yes	Yes		BDNF+DPSCs vs. Yes	Yes		Yes		2018		43
CI	Yes	Yes			Yes	Yes	Yes	Yes	2018		29
CI	No	Yes			Yes	Yes	Yes		2018	24	30
CI	Yes	Yes	vs. DPSCs Yes		Yes	Yes	Yes		2020	>28	31
CI	Yes	Yes			Yes	Yes	Yes	Yes	2021	at least 56	23
CI	No	Yes			Yes	Yes		Yes	2018	135	32
CI	No	Yes	vs. BMMSCs Yes		Yes	Yes	Yes	Yes	2013	17	21
CI	No	Yes		DP-iNCs vs. Yes	Yes	Yes	Yes	Yes	2022	37	34
CI	No	Yes			Yes	Yes	Yes		2021	18	42
CI	Yes	Yes			Yes	Yes	Yes		2020	36	33
CI	No	Yes			Yes	Yes	Yes	Yes	2014	7	35
CI	Yes	Yes	vs. unfractionated pulp cells Yes		Yes	Yes	Yes	Yes	2011	48	40
CI	Yes	Yes			Yes	Yes	Yes	Yes	2022	122	36
CI	Yes	Yes		miR-34a knockdown hDPSCs vs. Yes	Yes	Yes	Yes	Yes	2023	96	37
CI	Yes	Yes	vs. bone marrow $CD31^{-}$side population cells Yes vs. adipose $CD31^{-}$ side population cells Yes		Yes	Yes		Yes	2012		38
CI	Yes	Yes			Yes	Yes			2009	11	41
CI	Yes	Yes			Yes	Yes	Yes	Yes	2023	72	44
CI	Yes	Yes			Yes	Yes	Yes	Yes	2024		45
HIE	No	Yes			Yes	Yes	Yes		2020	51	49
HIE	Yes	Yes			Yes	Yes		Yes	2012	97	46
HIE	Yes	Yes			Yes			Yes	2017		24
HIE	Yes	Yes			Yes			Yes	2018		47
HIE	Yes	Yes			Yes	Yes	Yes	Yes	2013	36	48
MI	Yes	Yes			Yes	Yes	Yes	Yes	2008	50	50
MI	Yes	Yes	vs. BMMSC-CM Yes vs. ADSC-CM Yes		Yes	Yes			2015		25
MI	Yes	Yes			Yes	Yes			2014	30	51
MI	No	Yes			Yes	Yes	Yes		2024	30	52
HI	Yes	Yes			Yes	Yes			2015	12	53
HI	Yes	Yes			Yes	Yes			2021	60	58
HI	No	Yes	vs. BMMSCs NO vs. BMMSCs-HIF1-α NO	DPSCs- HIF1-α vs. Yes	No strains	Yes	Yes		2021	21	54

Continued

Disease model	OMSCs characterization	Improved outcome, OMSCs vs. control	Improved outcome, OMSCs vs. other cells	Improved outcome, modified OMSCs vs. OMSCs	Animal allocation and flow described		Randomized	Blinded	Published year	Sample size	References
					Strains and species of animals	Number of treated animals (at least one experiment)					
HI	Yes	Yes	vs. bone marrow $CD31^{-}$side population cells Yes vs. adipose $CD31^{-}$ side population cells Yes		Yes	Yes		Yes	2012		[38]
HI	Yes	Yes			Yes				2008		[55]
HI	Yes	Yes		HUVECs + hDPSCs vs. Yes	Yes	Yes			2022	40	[57]
HI	Yes	Yes	vs. DPSCs Yes		Yes	Yes		Yes	2022	18	[56]
Subarachnoid Hemorrhage	Yes	Yes			Yes	Yes			2019		[59]
Subarachnoid Hemorrhage	Yes	Yes			Yes	Yes	Yes	Yes	2024	120	[60]
Vascular Dementia	Yes	Yes			Yes	Yes	Yes		2021	150	[61]
Atherosclerosis	Yes	Yes	vs. Fb Yes		Yes	Yes	Yes		2018	21	[62]
Atherosclerosis	No	Yes		DPSCs + HGF vs. Yes	Yes	Yes	Yes		2024	36	[63]
Degenerative valve disease	Yes	Yes			Yes	Yes	Yes	Yes	2016	20	[64]

Table 1. Summary of the results and quality assessment of the studies. ADSCs: adipose-derived stem cells; BDNF: brain-derived neurotrophic factor; BMMSCs: bone marrow-derived mesenchymal stem cells; CM: conditioned medium; CI: cerebral ischemia; DP-iNCs: dental pulp-derived induced neural cells; DPSCs: dental pulp stem cells; OMSCs: orally derived mesenchymal stem cells; Fb: fibroblasts; hDPSCs: human dental pulp stem cells; HI: hindlimb ischemia; HIE: hypoxic-ischemic encephalopathy; HUVEC: Human umbilical vein endothelial cell; MI: myocardial ischemia.

CI studies (Table 2)

The studies of CI models can be divided into transient middle cerebral artery occlusion (T-MCAO) (15 studies), permanent middle cerebral artery occlusion (P-MCAO) (4 studies) and chronic CI (1 study). The T-MCAO models were established using the intraluminal thread to block the right or left middle cerebral artery and reperfusion after 2 h (8 of 15 studies), 1.5 h (5 of 15 studies), 1 h (1 of 15 studies), or 0.5 h (1 of 15 studies) of occlusion. In addition to the intraluminal thread, coagulation and cutting of the MCA and photothrombosis were also used in the P-MCAO model. A study on chronic CI used ligation of bilateral carotid arteries. All but two studies of T-MCAO and one study of P-MCAO used mice as the research model, while the others used rats. DPSCs were investigated in 17 studies; 13 used human DPSCs, while 4 used rat and porcine DPSCs. The other three studies utilized SHED and SHED-CM as the treatment group. Most studies used intracranial administration. Tail-vein injection, femoral vein cannula, intra-arterial, and intranasal administration were also reported. The cell injection amount ranged from $2*10^4$ to $6*10^6$ cells. The CM volume and exosome dosage were 100 µl SHED-CM, 10 µg total protein, and 100 µg exosome, respectively. The studies utilized various CI models, with transient middle cerebral artery occlusion (T-MCAO) being the most common, predominantly in mice. Treatment involved OMSCs, their CM, or exosomes, administered via multiple routes.

Nineteen of the 20 studies reported improvements in functional tests of motion or sensation. Fourteen studies demonstrated that transplantation of OMSCs (including exosomes and CM with OMSCs) significantly reduced infarct volume compared with the control group. Different studies also reported that OMSC-based transplantation reduced corpus callosum atrophy[22], ameliorated cerebral edema[23,36,37,45], and improved body weight[43,44] in subject animals. Whether injected through the tail vein or intracranially, the transplanted OMSCs migrated to the ischemic area[21,22,30,31,39,40,45], survived[21,39,40], and were not found in systemic organs[39]. In another study[42], in which hDPSCs were injected through the femoral vein, the cells were found to remain in the brain for 4 weeks. Seven studies described the effects of OMSC-based transplantation on neural regeneration, including differentiation into neurons and astrocytes[22,39,41], reduction of neuron damage[29,32,33], and expression of more neural markers[21,30], and neurotrophic factors[21,40]. Four reports revealed that hDPSCs reduced microglial activation[29,32] and astrogliosis[39,42]. In addition, OMSC treatment inhibited inflammation[23,29,32] and apoptosis[33,36,37,45]. Only two studies[32,39], in which hDPSCs were injected into the tail vein, reported the promotion of angiogenesis. Notably, Yew et al.[42] reported that neither angiogenesis nor synaptogenesis in peri-infarct tissue

Animals	Injury	OMSCs	Administration	Dose	Outcomes	Improved functional outcomes (compared to control group)	References
Rats	T-MCAO (intraluminal thread) for 2 h, followed by reperfusion	hDPSCs	Intracranial injection	$6*10^6$ cells	1. Improved functional outcomes (3/5); 2. Long-term cell viability; 3. Cells migrated to lesion boundary area; 4. Cells differentiated into neurons and astrocytes; 5. Reduced corpus callosum atrophy	Neurological scores test (neurological dysfunction evaluation); Step test (forelimb somatosensory and motor asymmetries); Adhesive tape removal test (correct paw and mouth sensitivity and correct dexterity)	22
Rats	T-MCAO (intraluminal thread) for 2 h, followed by reperfusion	hDPSCs	Tail vein injection	$4*10^6$ cells	1.Iimproved functional outcomes (1/1); 2. Reduced infarct volume; 3. Cells not found in systemic organs; 4. Cells migrated to lesion boundary area; 5. Cells differentiated into neurons and astrocytes; 6. Promoted angiogenesis; 7. Inhibited astrogliosis	Modified neurological severity score (mNSS) test (neurological function evaluation)	39
Rats	T-MCAO (intraluminal thread) for 2 h, followed by reperfusion	rDPSCs	Tail vein injection	$3*10^6$ cells	1. Cells expressed neural-specific markers; 2. Improved weight; 3. Improved functional outcomes (2/2)	Adhesive removal test; mNSS test	43
Rats	T-MCAO (intraluminal thread) for 1.5 h, followed by reperfusion	hDPSCs	Tail vein injection	$1*10^6$ cells	1. Reduced infarct volume; 2. Improved functional outcomes (4/4); 3. Reduced microglial activation; 4. Reduced pro-inflammatory cytokines; 5. Reduced neuronal damage	Abnormal posture score test (grade); Hemiparesis score test (grade); Forelimb grip strength test (the maximal value is recorded as the forelimb grip strength); Rotarod performance test (examine the locomotory coordination ability)	29
Rats	T-MCAO (intraluminal thread) for 2 h, followed by reperfusion	rDPSCs	Tail vein injection	$1*10^6$ cells	1. Reduced infarct volume; 2. Migrated to ischemic areas; 3. Expressed more neural-specific markers		30
Rats	T-MCAO (intraluminal thread) for 2 h, followed by reperfusion	hPDLSCs/ hDPSCs	Tail vein injection	$3*10^6$ cells	1. Reduced infarct volume; 2. Improved functional outcomes (1/1); 3. Cells migrated earlier toward the ischemic areas	mNSS test	31
Mice	T-MCAO (intraluminal thread) for 2 h, followed by reperfusion	hDPSCs-exosome	Tail vein injection	10 μg total protein	1. Alleviated brain edema; 2. Reduced infarct volume; 3. Improved functional outcomes (1/1); 4. Inhibited the I/R-mediated TLR4 and NF-κB activation; 5. Attenuated the neuroinflammation of post-I/R and post-OGD/R; 6. Inhibited the HMGB1 cytoplasmic translocation	mNSS test	23
Rats	T-MCAO (intraluminal thread) for 1.5 h, followed by reperfusion	hDPSCs	Tail vein injection	$1*10^6$ cells	1. Reduced infarct volume; 2. Improved functional outcomes (4/4); 3. Reduced microglial activation; 4. Reduced pro-inflammatory cytokine; 5. Alleviated neuronal damage; 6. Reduced blood-brain barrier leakage; 7. Increased tight junction protein levels 8. Increased angiogenesis in the cortical ischemic border zone	Abnormal posture score test; Hemiparesis score test; Forelimb grip strength test; Rotarod performance test	32
Rats	P-MCAO (intraluminal thread)	SHED-CM	Intranasal administration	100 μl CM	1. Improved functional outcomes (1/1); 2. Reduced infarct volume; 3. Promoted neuron and endothelial cell markers	Modified motor disability test	21
Mice	P-MCAO (coagulating and cutting)	hDPSCs	Intracranial injection	$1*10^5$ cells	1. Improved functional outcomes (2/2)	Paw-dragging ratio (forelimb sensorimotor recovery); Forelimb usage ratio (forelimb sensorimotor recovery)	34

Continued

Animals	Injury	OMSCs	Administration	Dose	Outcomes	Improved functional outcomes (compared to control group)	References
Rats	P-MCAO (photothrombosis)	hDPSCs	Femoral vein cannula injection	$4*10^5$ cells	1. Improved functional outcomes (2/4); 2. Cells remained in the brain; 3. Reduced reactive astrogliosis; 4. Accelerated recovery without modifying initial infarct formation	Forelimb placing test (measure of recovery of forelimb motor response); First attempt success in the skilled reaching (measure of recovery of forelimb motor response)	42
Rats	Permanent occlusion of both carotid arteries	SHED	Intracranial injection and Tail vein injection	$2*10^4$ cells; $2*10^5$ cells;$2*10^6$ cells	1. Improved functional outcomes (1/1); 2. Reduced neuronal damage; 3. Inhibited apoptosis	Morris water maze (MWM) test (a well-validated method for evaluating learning and memory)	33
Rats	P-MCAO (intraluminal thread)	SHED	Intracranial injection	$1*10^6$ cells	1. Improved functional outcomes (1/1); 2. Reduced infarct volume; 3. SHED survived and migrated from the original injection site to the peri-infarct area; 4. SHED expressed neurotrophic factors; 5. SHED enhanced the migration of NPCs from the SVZ to the peri-infarct; 6. No evidence of differentiation of SHED into neurons or endothelial cells	Modified motor disability scale	35
Rats	T-MCAO (intraluminal thread) for 2 h, followed by reperfusion	CD31-/CD146-side population cells from porcine dental pulp	Intracranial injection	$1*10^6$ cells	1. Cells survived and migrated to the peri-infarct area; 2. Cells expressed neurotrophic factors; 3. improved functional outcomes; 4. Reduced infarct volume; 5. Cells enhanced the migration of NPCs from the SVZ to the peri-infarct area; 6. no evidence of differentiation of the cells into neurons or endothelial cells	Modified motor disability scale	40
Rats	T-MCAO (intraluminal thread) for 1.5 h, followed by reperfusion	hDPSCs	Intracranial injection	$1*10^5$ cells	1. Improved functional outcomes (1/1); 2. Alleviated brain edema; 3. Reduced infarct volume; 4. Inhibited cell death/apoptosis; 5. Promoted neuronal survival; 6. Ameliorated neuronal apoptosis;	mNSS test	36
Mice	T-MCAO (intraluminal thread) for 1 h, followed by reperfusion	hDPSCs	Intracranial injection	$6*10^5$ cells	1. Alleviated histopathological damage; 2. Reduced apoptosis; 3. Improved functional outcomes (2/2); 4. Alleviated brain edema; 5. Reduced infarct volume	mNSS test; rotarod test	37
Rats	T-MCAO (intraluminal thread) for 2 h, followed by reperfusion	CD31- side population cells from porcine dental pulp	Intracranial injection	$1*10^6$ cells	1. Reduced infarct volume; 2. Improved functional outcomes (1/1);	Motor disability score	38
Rats	T-MCAO (intraluminal thread) for 1.5 h, followed by reperfusion	hDPSCs	Intracranial injection	$1–2*10^5$ cells	1. Showed normal brain morphology; 2. Improved functional outcomes (1/1); 3. Cells survived and differentiated into mature neurons	Swing test	41
Continued							

Animals	Injury	OMSCs	Administration	Dose	Outcomes	Improved functional outcomes (compared to control group)	References
Rats	T-MCAO (intraluminal thread) for 0.5 h, followed by reperfusion	hDPSCs and hDPSCs-CM	Intra-arterial transplantation and intranasal transplantation	2*10^6 cells or 1 ml CM	1. Improved functional outcomes (1/1); 2. Reduced infarct size; 3. Increased body weight; 4. Regulated expression of neurotrophic and angiogenic factors;	Neurological function	44
Rats	T-MCAO (intraluminal thread) for 1.5 h, followed by reperfusion	hDPSC-derived extracellular vesicles (EVs)	Tail vein injection	100 μg of hDPSCs EVs	1. Alleviated the brain edema; 2. Improved functional outcomes (2/3); 3. Reduced infarct volume; 4. DPSC-EVs were going into the brain; 5. Showed neuroprotective effects on neurons; 6. Reduced I/RI-induced neuronal apoptosis;	Neurological scoring; spatial learning and memory;	45

Table 2. Summary of CI studies. CM: conditioned medium; CI: cerebral ischemia; extracellular vesicles: EVs; OMSCs: orally derived mesenchymal stem cells; hDPSCs: human dental pulp stem cells; HMGB1: high mobility group box 1; hPDLSCs: human periodontal ligament stem cells; mNSS test: modified neurological severity score test; NF-κB: nuclear factor kappa-B; P-MCAO: permanent middle cerebral artery occlusion; rDPSCs: rats dental pulp stem cells; SHED: stem cells from deciduous teeth; SVZ: subventricular zone; TLR4: toll-like receptor 4; T-MCAO: transient middle cerebral artery occlusion.

was the primary cause of faster recovery in the hDPSC-treated group. Sugiyama, et al.[35] found no evidence of differentiation of transplanted cells into neurons and endothelial cells; however, OMSCs enhanced the migration of neural progenitor cells (NPCs) from the subventricular zone (SVZ) to the peri-infarct region[21,40]. miR-877-3p was considered to be transferable through DPSC-extracellular vesicles (EVs), demonstrating neuroprotective effects and the potential to promote the survival and recovery of neurons after ischemia[45]. Finally, it was reported that hDPSC-exosomes inhibited I/R-mediated toll-like receptor 4 (TLR4) and nuclear factor kappa-B (NF-κB) activation, as well as high mobility group box 1 (HMGB1) cytoplasmic translocation[23], and that hDPSCs reduced blood-brain barrier leakage and increased tight junction protein levels[32].

Meta-analysis of infarct volume in CI

Based on the quantifiable indicators we extracted, only the CI studies reported infarct volume in mm^3 provided adequate homogeneity and calculability of the effect size; therefore, only these studies were included in a meta-analysis. Two papers reported infarction volume as a percentage (unit: %), while another article reported infarction area as a percentage (unit: %). These were not included in the meta-analysis. Missing data were excluded, including reports that contained only the infarction ratio or lacked sample size information. Six studies were pooled[21,29,32,35,39,40]. Data on infarct volume in CI studies were pooled, and the studies were divided into two subgroups based on the study endpoint: short-term (within 10 days) and long-term (10 + days) follow-up. The p-value of the test for subgroup difference was 0.0006 ($p < 0.05$) (Fig. 2). If the subgroup effect was ignored, the overall heterogeneity was 40% (< 50%). As heterogeneity was reduced to 0% within each subgroup, this indicated that the duration of follow-up significantly influenced the treatment effect; both subgroups showed a significantly greater treatment effect than the control group (p-values < 0.00001). When using the fixed-effects model to investigate sensitivity (Fig. 3), the pooled standardized mean differences for the short- and long-term follow-up periods were − 1.56 (95% confidence interval: − 2.16, − 0.96) and − 5.23 (95% confidence interval: − 7.23, − 3.23), respectively, which were identical to that yielded by the random-effects model (since $I^2 = 0\%$). The overall (combination of the two groups) pooled standardized mean difference estimated by the fixed-effects model was − 1.87 (95% confidence interval: − 2.44, − 1.29), which was slightly lower than the difference of − 2.19 (95% confidence interval: − 3.01, − 1.37) estimated by the random-effects model. The funnel plot (Fig. 4) was slightly asymmetric, thus suggesting a low level of publication bias.

Across these studies, OMSC-based interventions consistently improved neurological function, reduced infarct volume and other structural brain injuries, and demonstrated cell migration to ischemic regions, neural protection and regeneration, modulation of glial responses, inflammation, and apoptosis, and, in a few studies, angiogenesis. Mechanistically, suggested pathways included enhanced NPC migration, transfer of neuroprotective miRNAs via extracellular vesicles, inhibition of TLR4/NF-κB signaling, and preservation of blood–brain barrier integrity. Meta-analysis of infarct volume data from six CI studies demonstrated a robust and significant reduction in infarct size with OMSC-based treatment in both short- and long-term follow-up, with low heterogeneity within subgroups and only slight evidence of publication bias, supporting a genuine and durable therapeutic effect.

HIE Studies (Table 3)

The HIE disease model was used in 5 studies (4 used rats and 1 used mice). The surgical method was ligation or cauterization of the unilateral carotid artery and hypoxia treatment for 20 min, 1 h, and 2 h. All cells were from human sources (SHED, SHED-CM, and hDPSCs). The routes of administration included external jugular vein injection, subdural injection, intracardiac injection, and ventricular injection. The numbers of transplanted cells were 1*10^5, 2*10^5, and 1*10^6 cells, and the volume of the CM was 2 μl. All articles reported functional outcomes that improved following treatment. Three studies[46,47,49] analyzed brain tissue damage after OMSC-based therapy,

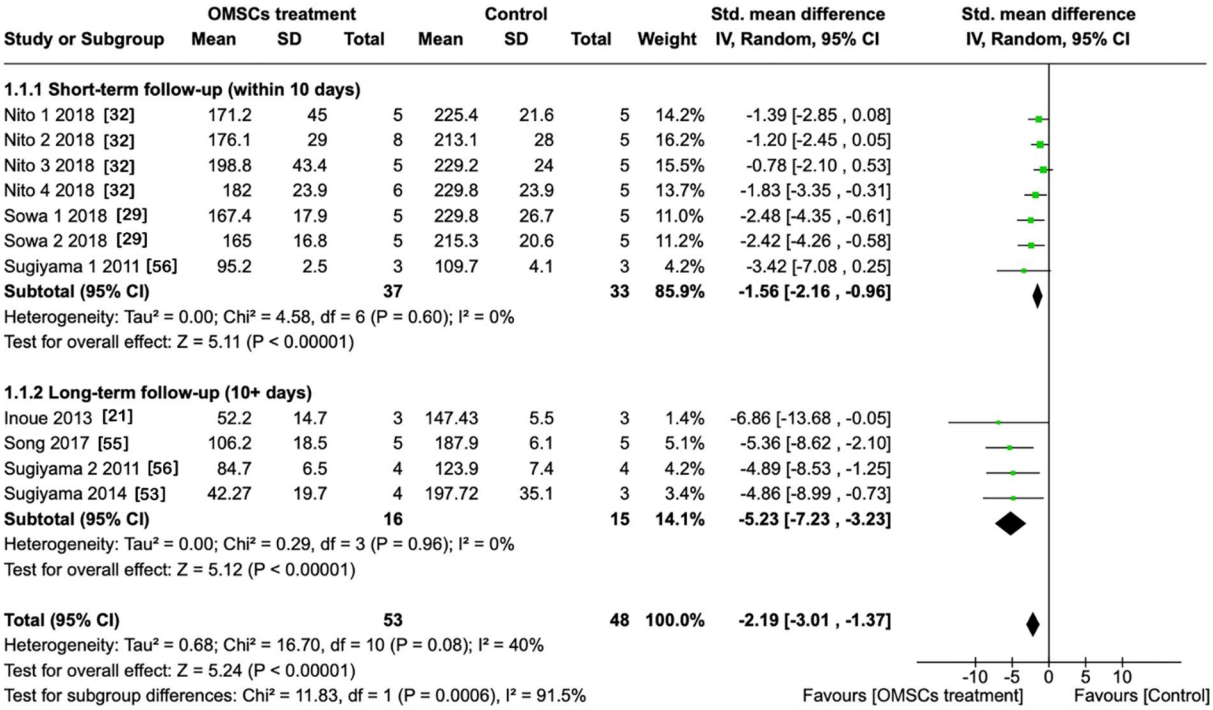

Fig. 2. Meta-analysis for the effect of OMSCs on infarct volume in CI models (random-effects model). If multiple sets of data were in the same study, these are represented by ordinal numbers (e.g., Nito 1 2018, Nito 2 2018). CI: cerebral ischemia; OMSCs: orally derived mesenchymal stem cells.

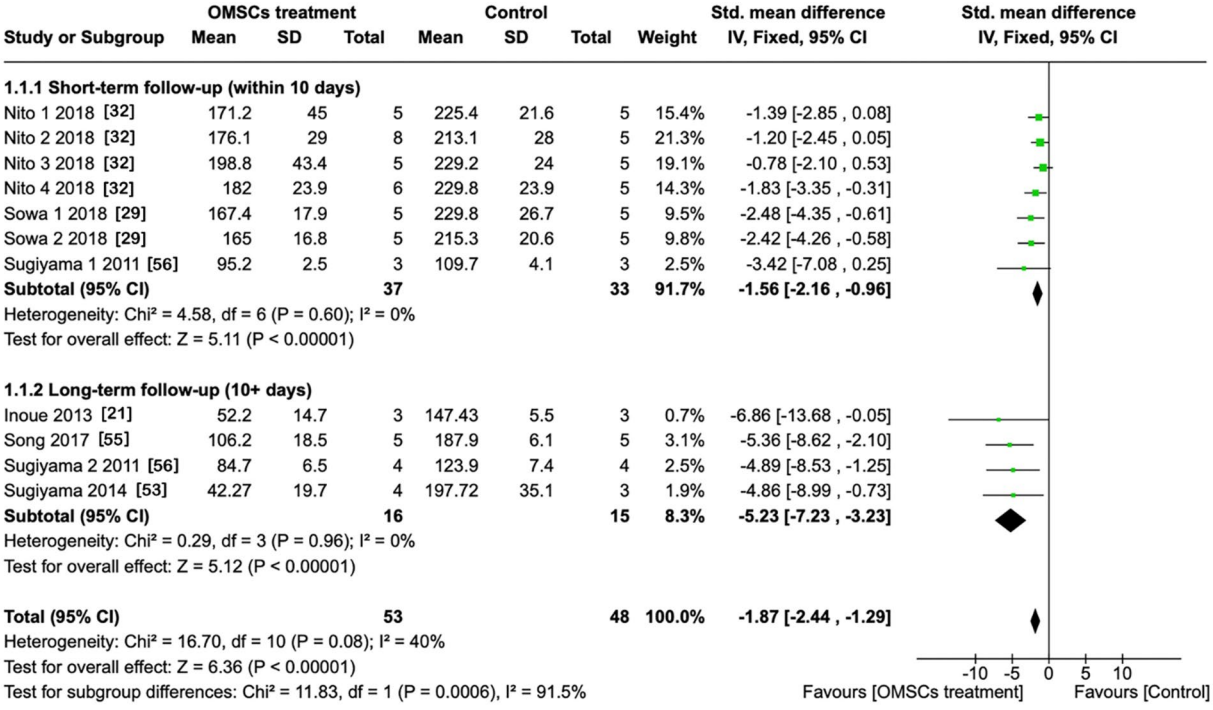

Fig. 3. Meta-analysis for the effect of OMSCs on infarct volume in CI models (fixed-effects model). If multiple sets of data were in the same study, these are represented by ordinal numbers (e.g., Nito 1 2018, Nito 2 2018). CI: cerebral ischemia; OMSCs: orally derived mesenchymal stem cells.

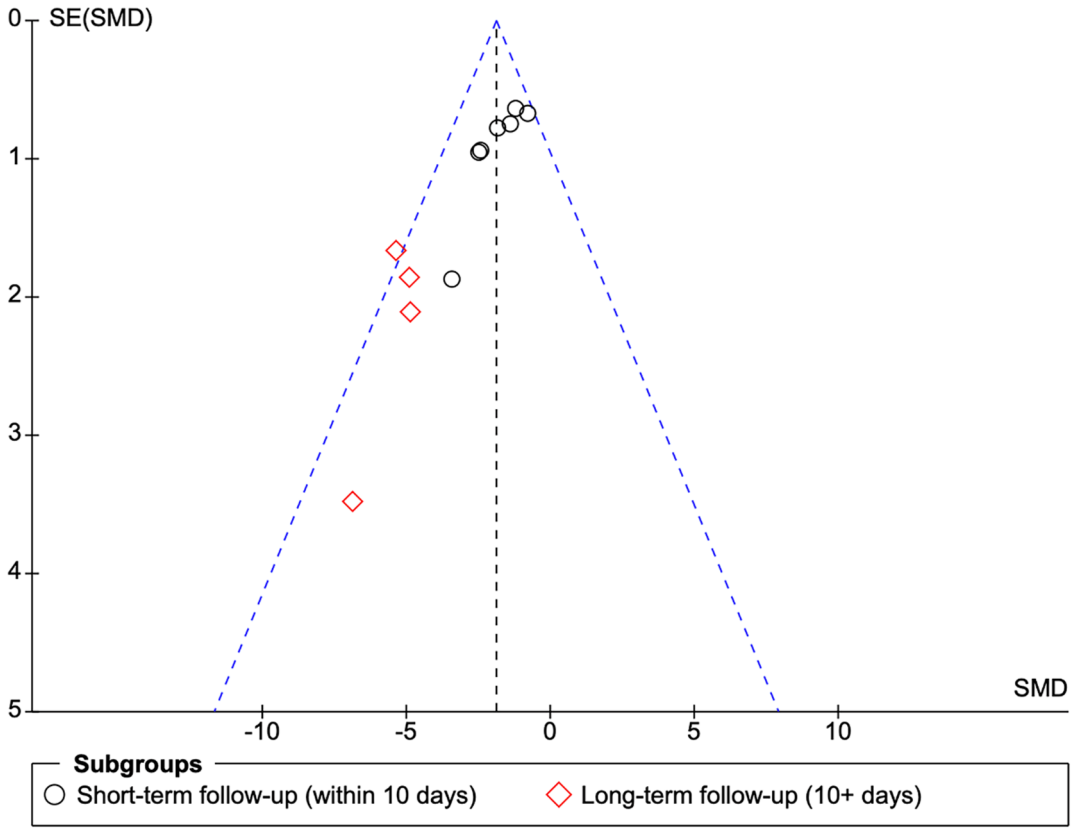

Fig. 4. Funnel plot for publication bias. SE: standard error; SMD: standard mean difference.

Animals	Injury	OMSCs	Administration	Dose	Outcomes	Improved functional outcomes (compared to the control group)	References
Rats	Left carotid artery double ligated, 1 h hypoxia	SHED	Right external jugular vein injection	$1*10^5$ cells	1. Reduced apoptosis; 2. Suppressed oxidative stress; 3. Decreased M1 microglia; 4. Increased M2 microglia; 5. Improved functional outcomes (2/4); 6. Reduced proinflammatory cytokines; 7. Non-improved cerebral volume	Rotarod treadmill (measured time of the animal remained on the rod); Gait analysis (evaluated the natural walking)	49
Mice	Right common carotid artery cauterized, 20 min hypoxia	SHED and SHED-CM	Below the dura injection	$2*10^5$ cells or 2 µl CM	1. Displayed better survival over time; 2. Improved functional outcomes (1/1); 3. Reduced cerebral tissue loss; 4. Reduced apoptosis; 5. Improved pathological score; 6. Reduced proinflammatory cytokines	Foot-fault test (assessing locomotor function in rodent models of central nervous system disorders)	46
Rats	Right common carotid artery electrocauterized, 2 h hypoxia	hDPSCs	Below the dura injection	$1*10^6$ cells	1. Improved functional outcomes (3/3); 2. Increased expression of anti-apoptotic proteins; 3. Enhanced neurogenic potential; 4. Promoted angiogenesis; 5. Facilitated cortical blood flow; 6. Enhanced neurite regeneration; 7. Enhanced anti-inflammatory effect	Body swing test (measured body asymmetry); Locomotor activity test (calculated vertical activity, vertical movement time, and number of vertical movements); Grip strength test	24
Rats	Right common carotid artery electrocauterized, 2 h hypoxia	hDPSCs	Intracardiac injection	$1*10^6$ cells	1. Improved functional outcomes (2/3); 2. Differentiated into astrocytes; 3. Non-reduced cerebral damage (reduced brain weight)	Novel-Object Recognition test (assess learning and memory ability); Morris Water Maze test (investigate the spatial memory)	47
Rats	Left carotid artery double ligated, 2 h hypoxia	hDPSCs	Left lateral ventricle injection	$1*10^5$ cells	1. Improved functional outcomes (3/3); 2. Differentiated along neuronal and/or glial lineages	T-maze test (measuring exploratory behavior); Radial water maze test ((investigate the spatial memory)); Postural reflex test	48

Table 3. Summary of HIE studies. CM: conditioned medium; OMSCs: orally derived mesenchymal stem cells; hDPSCs: human dental pulp stem cells; HIE: hypoxic-ischemic encephalopathy; SHED: stem cells from deciduous teeth.

and only one showed that SHED and SHED-CM transplantation reduced brain tissue loss compared with the control group[46]. Three studies[24,46,49] using hDPSCs showed that transplanted cells promoted the differentiation of neural lineages; one of these studies also reported that hDPSCs promoted angiogenesis and renal cortical blood flow[24]. Inhibition of apoptosis and inflammation was reported in all three studies. SHED and SHED-CM also improved survival rates and pathological scores[46]. Kitase et al. (2020) reported that SHED suppressed oxidative stress, decreased M1 microglia, and increased M2 microglia.

MI Studies (Table 4)

The four articles on MI used rats (permanent ligation of the left descending coronary artery/ anterior descending coronary artery), mice (ligation of the left anterior descending artery for 30 min), and rabbits (permanent ligation of the left anterior descending artery). When $1.5*10^6$ hDPSCs were transplanted into rat myocardium, rat origin vessels increased, but did not differentiate into cardiac and smooth muscle cells[50]. Similarly, in a rabbit model, SHED injection increased neovascularization and myocardial cells, but their source was not explained[51]. Moreover, both studies reported a recovery of functional outcomes. SHED-CM (500 µl) inhibited apoptosis and inflammation in mice after injection through the jugular vein system[25]. hDPSC-EV treatment decreased the number of pro-inflammatory macrophages in the infarct area, thereby promoting the resolution of inflammation[52]. Reductions in infarct areas were reported in all studies.

HI Studies (Table 5)

Seven studies on HI were identified. Except for one study that reported that hDPSCs promoted the increase of CCL5 and VEGF expression[54], the name of the ligated artery was not clearly specified. The remaining six studies all reported that animal models were established by femoral artery ligation. Approximately 70% of the studies (5 of 7) used blood flow imaging techniques and demonstrated that OMSC therapy enhanced blood reperfusion[53,55,57,58]. It was also reported that OMSCs improved functional outcomes (functional scoring and ischemia scoring)[54,57,58] and reduced inflammation, fibrosis, and necrosis[56,57]. All seven studies utilized intramuscular injection and showed an increase in vascular structure.

Other VD Studies (Table 6)

Two studies utilized rDPSCs-CM[59] and hDPSCs-exosomes[60] for treating a rat model of subarachnoid hemorrhage, respectively. The decrease in Iba-1 positive cells demonstrated that rDPSCs-CM alleviated neuroinflammation[59]. Improvements in microcirculation and cognitive and motor impairments were also reported[59]. Exosomes obtained from hDPSCs could also alleviate neuroinflammation and inhibit microglial pyroptosis[60].

One study described the treatment of rats with ligation of the bilateral common carotid artery using DPSCs from humans[61]. Following injection into the tail vein, cells (2 × 10^7 cells) migrated into the brain and improved neural marker expression (DCX, NeuN, and NF200) and functional outcomes (eight-arm maze test).

hGMSCs alleviated atherosclerosis in mice fed with high-fat food, which induced atherosclerosis via intravenous injection[62]. This study also observed that cell therapy reduced the expression of inflammatory monocytes (Ly-6C^{hi}) and modulated cytokine expression (IFN-γ, IL-4, and IL-17 A). Similarly, hDPSCs decreased the ratio of neutrophils and monocytes and reduced inflammation[63].

In the only included RCT[64], dogs with chronic heart valve disease were used as research subjects, and strict enrollment criteria were established. Standard treatment of heart failure combined with intravenous puppy deciduous teeth stem cells (pOMSCs) was used as the experimental group, and standard treatment of heart failure

Animals	Injury	OMSCs	Administration	Dose	Outcomes	Improved functional outcomes (compared to control group)	References
Rats	Permanent ligation of the left descending coronary artery	hDPSCs	Intramyocardial transplantation	$1.5*10^6$ cells	1. Improved functional outcomes (1/1); 2. Cells not differentiated into cardiac or smooth muscle cells; 3. Increased vascular density; 4. Reduced infarcted area	Echocardiographic test (measured cardiac function)	50
Mice	Left anterior descending artery (LAD) was ligated for 30 min, then loosened for reperfusion	SHED-CM	Infused systemically via the jugular vein	500 µl CM	1. Reduced infarct area; 2. Suppressed apoptosis; 3. Suppressed inflammatory responses		25
Rabbits	Permanent left circumflex coronary artery was ligated	SHED	Intravenously through rabbit marginal ear vein	$1*10^6$ cells	1. Reduced infarct area; 2. Increased myocardial cells and neovascularization; 3. Improved functional outcomes (1/3)	Heart rate test (measured cardiac function)	51
Rats	Permanent ligation of the left anterior descending (LAD) coronary artery	hDPSCs-extracellular vesicles (EVs)	Intramyocardial injection	$2.5*10^9$ particles/mL	1. Reduced infarct size; 2. Decreased the expression of M1 markers in the infarct area; 3. Reduced the infiltrating M1 macrophages in the infarcted area		52

Table 4. Summary of MI studies. CM: conditioned medium; extracellular vesicles: EVs; OMSCs: orally derived mesenchymal stem cells; hDPSCs: human dental pulp stem cells; MI: myocardial ischemia; SHED: stem cells from deciduous teeth.

Animals	Injury	OMSCs	Administration	Dose	Outcomes	Improved functional outcomes (compared to the control group)	References
Mice	Removed and ligated left femoral artery bilaterally	hDPSCs-CM	Intramuscular injection	0.3 ml CM	1. Improved perfusion; 2. Increased CD31-positive microvessels		53
Rats	Ligated femoral artery	hDPSCs	Intramuscular injection	$5*10^6$ cells	1. Improved functional outcomes (1/1); 2. Improved perfusion; 3. Promoted muscle fiber regeneration and angiogenesis (CD31 + lumens)	Functional scoring (semiquantitative assessments of limb function)	58
Mice	Ligated the right arterial vessel	hDPSCs	Intramuscular injection	$5*10^5$ cells	1. Improved CCL5 and VEGF expression; 2. Improved functional outcomes (1/3); 3. Promoted capillary density	Ischemia scoring (assessment of foot lesions)	54
Mice	Ligated left femoral artery	$CD31^-$ side population cells from porcine dental pulp	Intramuscular injection	$1*10^6$ cells	1. Improved perfusion; 2. Enhanced capillary density;		38
Mice	Ligated left femoral artery	$CD31^-$; $CD146^-$side population cells from dental pulp	Intramuscular injection	$1*10^6$ cells	1. Improved perfusion; 2. Enhanced capillary density		55
Mice	Ligated and removed femoral artery	hDPSCs	Intramuscular injection	$1*10^6$ cells	1. Improved functional outcomes (1/1); 2. Improved perfusion; 3. Reduced inflammation; 4. Decreased fibrosis; 5. Enhanced capillary density	Ischemia score	57
Mice	Ligated and removed left fermoral artery	SHED (and hDPSCs)	Intramuscular injection	$1*10^6$ cells	1. Reduced foot necrosis; 2. Reduced fibrosis; 3. Enhanced vascular density; 4. Cells migrated to the vessels		56

Table 5. Summary of HI studies. CM: conditioned medium; OMSCs: orally derived mesenchymal stem cells; hDPSCs: human dental pulp stem cells; HI: hindlimb ischemia; SHED: stem cells from deciduous teeth.

Animals	Injury	OMSCs	Administration	Dose	Outcomes	Improved functional outcomes (compared to control group)	References
Rats	Injecting fresh autologous blood into the cisterna magna, with the animal in a head-down position	rDPSCs-CM	Intrathecal injection	20 µl CM	1. Alleviated neuroinflammation; 2. Improved microcirculation; 3. Improved functional outcomes (1/1)	Rotarod test	51
Rats	Inserting monofilament nylon suture into the stretched external carotid artery and advancing it to the bifurcation of the anterior and middle cerebral arteries.	hDPSCs-exosomes	Gradual caudal vein administration	100 µg exosomes	1. Mitigated neurological deficits and brain water content following EBI Post-SAH; 2. Inhibited microglial activation and pro-inflammatory cytokine expression 24 h post-SAH; 3. Inhibited microglial cell pyroptosis		60
Rats	Bilateral common carotid arteries were ligated with a surgical suture	hDPSCs	Tail veins injection	$2*10^7$ cells	1. Migrated into the brain; 2. Increased neural marker expression; 3. Improved functional outcomes (1/1)	Eight-arm maze test	61
Mice	Feeding a high-fat diet	hGMSCs	Intravenous injection	$2*10^6$ cells	1. Reduced the frequency of inflammatory monocytes/macrophages; 2. Decreased the plaque size and lipid deposition		62
Mice	Feeding a high-fat diet	hDPSCs	Intravenous injection	$1*10^6$ cells	1. Alleviated atherosclerotic lesions; 2. Reduced the percentages of monocytes and neutrophils and regulates macrophage polarization; 3. Reduced inflammation in local aortic tissues		63
Dogs	Dogs with heart murmurs of moderate and high intensity and atrioventricular valve regurgitation at stage C of heart failure according to ACVIM classification system were recruited to this study	Puppy deciduous teeth stem cells (pOMSCs)	Intravenous injection	$1*10^6$	1. Improved functional outcomes (3/3)	(1) Left ventricular ejection fraction; (2) ACVIM functional class; (3) Quality of life scores	64

Table 6. Summary of Other VD studies. ACVIM: American College of Veterinary Internal Medicine; CM: conditioned medium; OMSCs: orally derived mesenchymal stem cells; exos: exosome; hDPSCs: human dental pulp stem cells; hGMSCs: human gingival mesenchymal stem cells; rDPSCs: rats dental pulp stem cells; VDs: vascular diseases.

alone was used as the control group. The results showed that the experimental group of dogs had improved heart function (including left ventricular ejection fraction) and American College of Veterinary Internal Medicine (ACVIM) functional class and quality of life scores.

Discussion

This systematic review of preclinical studies on the use of OMSCs for the treatment of VDs summarizes treatment evidence from several animal models of different VDs. The studies demonstrate that OMSC-based therapies are effective in animals with induced CI, HIE, MI, HI, subarachnoid hemorrhage, vascular dementia, and atherosclerosis in achieving favorable treatment outcomes. In these studies, OMSCs of different species (humans and rats) and tissues (DPSCs, SHED, PDLSCs, and GMSCs) were used in different forms (cells, CM, and exosomes) for treatment. These studies provide evidence for establishing disease models as standard modeling methods, as they are a prerequisite for evaluating whether OMSCs can effectively treat VDs. However, some articles did not report details on randomization and blinding, and in some cases lacked details on the number of samples.

While several systematic reviews have explored the potential of various stem cell types for treating VDs, our work is the first to focus exclusively on OMSCs. For instance, a previous systematic review by Nagpal et al.[65] broadly examined the role of MSCs in stroke, including BMMSCs and adipose-derived stem cells (ADSCs), concluding that MSCs improve functional outcomes primarily through paracrine actions. However, that review did not differentiate between MSC sources, potentially overlooking the unique advantages of OMSCs, such as their neural crest origin and superior proliferative capacity. Similarly, Wang et al.[66] conducted a meta-analysis on MSC therapy for myocardial infarction, reporting a significant reduction in infarct size. While informative, their analysis pooled data from BMMSCs, ADSCs, and umbilical cord-derived MSCs, introducing significant heterogeneity and failing to identify which cell type might be optimal. In contrast, our focused analysis of OMSCs, despite a smaller number of included studies for meta-analysis, provides a more homogeneous and specific evaluation of this cell source, revealing a clear signal of efficacy in CI models and highlighting its potential for other VDs for which quantitative synthesis was not yet possible.

Improvement in functional outcomes in experimental animals is a direct manifestation of physiological rehabilitation, as noted in the articles included in our study (Tables 2, 4, 5 and 6). Functional experiments were performed in 75.6% of the studies (31 of 41). The positive changes in local and systemic functions demonstrated the effectiveness of OMSC-based treatment. Although improvements in functional outcomes have been demonstrated in prior studies of stem cell therapy for VDs, the survival and differentiation of transplanted cells have been rarely reported[67–70]. Functional recovery by DPSCs after CI is most likely accomplished through DPSC-mediated paracrine effects rather than neural differentiation[22]. A similar proposed mechanism has also been reported for SHED[46,49], which was observed to secrete paracrine factors that support and protect the brain microenvironment after HIE[49]; however, the cell differentiation status after transplantation was not reported. It is worth noting that differentiation and the paracrine effect are not mutually exclusive. In vascular dementia, implanted DPSCs can differentiate into the neural lineage and accelerate axon growth through the paracrine effect[61].

At the mechanistic level, the effects of OMSCs include migration, differentiation, and alleviation of apoptosis and inflammation. DPSCs injected via the tail vein can cross the blood-brain barrier and survive and differentiate at the boundary of the ischemic region, ultimately reducing cerebral edema and infarct volume[30]. In HIE, DPSCs can migrate to the injury site and closely associate with the surrounding astrocytes without reducing tissue loss[47]. The injected OMSCs can differentiate into neural and endothelial cells, and SHED-CM is also believed to enhance the differentiation and migration of endogenous NPCs[21]. OMSC-related transplantation also protects against insult by reducing inflammation and apoptosis[23,25,29,30,32,33,45,48,50,59,62,63]. Li et al. reported for the first time that DPSC-exosomes can attenuate cerebral ischemic inflammation and provide protection by inhibiting the HMGB1/TLR4/Myeloid differentiation primary response 88 (MyD88)/NF-κB pathway[23].

Notably, some studies have attempted to modify OMSCs. DPSCs combined with brain-derived neurotrophic factor (BDNF) may promote neuropathologic rehabilitation[43]. HGF not only can enhance the neuroprotective effect of DPSCs[43], but also assist DPSCs in ameliorating atherosclerosis[63]. Compared with hDPSCs, anti34a-hDPSCs were more effective in inhibiting apoptosis, reducing cerebral edema and infarct volume, and improving motor function[37]. Other studies have reported the promotion of neuron and neurite regeneration by IGF1R+DPSCs[24], as well as an increase in VEGF secretion due to HIF1-α overexpression, thereby enhancing recovery from HI[54]. Moreover, we found that there were five reports comparing the therapeutic effects of OMSCs with other MSCs. With the exception of one study from Moradi et al.[54], the remaining four studies showed that OMSCs had a superior therapeutic effect to that of BMMSCs or ADSCs[21,25,38,39]. Additionally, when comparing OMSCs internally, it appears that SHED and PDLSCs are more effective than DPSCs.[31,56]. These findings suggest that there is still significant potential for research on OMSC-based treatment strategies in VDs. This comparative advantage of OMSCs over other MSC types is a critical finding that distinguishes our review. A meta-analysis on stem cell treatment for peripheral artery disease[71] found that MSC therapy was effective; they did not find a significant difference between cell sources, likely due to the heterogeneity of the included studies and the lack of direct head-to-head comparisons. Our review, by specifically extracting data from studies that performed such direct comparisons, provides stronger evidence for the potential superiority of OMSCs, particularly in neuroprotection and angiogenesis. This highlights the importance of not just pooling all "MSCs" together but investigating the nuanced differences between tissue sources.

OMSCs show promising therapeutic potential as a novel treatment for VDs. However, the key to treatment success in animal studies may depend on the type of animal model used, the administered dose, and the timing of intervention. For example, while stroke has different levels of severity and the best window for rescue, the majority of animal experiments have been limited to the investigation of a specific disease stage. In contrast,

clinical treatment in humans is much more complex. In addition, unlike rapidly life-threatening diseases such as cancer, many patients with VDs can survive for a long time despite varying degrees of organ damage. Further advances in the clinical application of stem cell therapy may also be hindered by patient hesitancy to enroll in clinical trials and government restrictions due to ethical and safety issues. Unlike traditional small-molecule drugs, exogenous cells can survive, proliferate, and differentiate in the body for a longer period. For stem cell transplantation, there is a risk of tumor formation, which is a long-term, low-probability but fatal risk. This makes it difficult to completely eliminate potential hazards in preclinical animal experiments. Although current clinical studies on the use of stem cells to treat VDs have not yet involved OMSCs, early clinical trials of intravenous autologous BMMSCs transplantation in stroke patients have shown safe and effective results[72]. This makes the future clinical prospects of OMSCs worthy of anticipation. In addition, it is worth emphasizing that the majority of studies included in this systematic review employed whole-cell-based therapeutics, while a few studies utilized OMSC-based CM and EVs (including exosomes). These two treatment approaches, whole stem cell versus secretome therapies (e.g., CM and EVs), could differ in terms of risks, regulatory considerations, and pretreatment requirements. However, the emerging evidence also suggests that whole mesenchymal cell therapies also exert their effects mainly through their secretome rather than through differentiation[73].

One limitation of this systematic review was that only 6 studies met the criteria for inclusion in the meta-analysis. Although having a larger number of studies can improve the statistical power and robustness of a meta-analysis, high-quality analyses can still be conducted with fewer studies if they are comprehensive and methodologically sound. The key considerations are the quality, relevance, and availability of studies suitable for pooling rather than just the number of studies. Emphasizing rigorous study selection and data synthesis is more important than reaching a specific numerical threshold. Scientific evidence suggests that, in practice, at least 5 studies are necessary to achieve greater statistical power than individual studies within a random-effects meta-analysis[71].

Approximately half of the included articles did not have a clear blinding method. The core purpose of blinding is to ensure that the expectancy effects are evenly distributed between the treatment group and the control group. When blinding fails, this balance is disrupted, thereby creating "activated expectancy bias". Apart from the introduction of blinding, there are also aspects such as the determination of sample size and the method of randomization, which may all reduce the quality of the studies, ultimately introducing heterogeneity, increasing bias, and even misleading the interpretation of the results. This risk of bias across the included studies may have led to an overestimation of OMSC efficacy. While 75.6% of studies reported functional outcomes, only 15 studies (36%; 15/41) reported combined randomization and blinding. The lack of clear blinding methods is particularly concerning for functional outcome scores, as it can introduce expectation bias where the investigators' preconceptions may potentially result in higher scores of improvement. Consequently, the significant effect sizes observed in our meta-analysis must be interpreted with caution, as incomplete methodological rigor across the included studies may have inflated the therapeutic benefits.

Another limitation was potential publication bias; many unpublished preclinical studies may have used OMSCs to treat VDs but have yielded non-significant results. A limitation of the included studies was that they did not explore the possible adverse events of OMSC transplantation in depth; these remain to be determined by further studies before proceeding to clinical trials. Clinical treatment strategies involving OMSCs are still in their infancy, and evaluating their safety and effectiveness in humans is a priority.

Methodological heterogeneity remains a significant barrier to the clinical translation of MSC-based therapies. Across the included studies, we observed substantial variability in cell sources (e.g., hDPSCs, SHED, PDLSCs, GMSCs, etc.), dosages (ranging from $2*10^4$ to $2*10^7$ cells), and delivery routes (including intracranial, intranasal, intramuscular, arterial, and venous injections). Furthermore, the timing of intervention and the follow-up duration varied significantly, and the meta-analysis results confirmed that follow-up time significantly influenced the treatment effect size ($p = 0.0006$). Such diversity in experimental design limits cross-study comparability and underscores the need for standardized preclinical protocols to confirm effectiveness before advancement to human trials.

To the best of our knowledge, this is the first systematic review to focus on the therapeutic effects of OMSCs and their secretome in *in vivo* VD models. OMSCs hold considerable translational potential in the treatment of VDs due to their accessibility, ethical acceptability, and robust regenerative properties, positioning them as a promising alternative to MSCs obtained from bone marrow or adipose tissue. OMSCs exhibit potent angiogenic, anti-inflammatory, and anti-apoptotic effects, primarily mediated through their secretome, a complex mixture of cytokines, growth factors, extracellular vesicles, and exosomes. This paracrine signalling can promote tissue repair, enhance neovascularization, and modulate immune responses, all of which are essential for restoring vascular integrity following ischemic or inflammatory injury. The OMSC secretome, in particular, has emerged as a feasible cell-free therapeutic option that overcomes many limitations associated with direct stem cell transplantation, such as immune rejection, limited cell survival, and tumorigenic risks. Such findings suggest that OMSC-derived factors could be developed into standardized biologic formulations suitable for clinical use, offering reproducible and safe treatment modalities for patients with cerebrovascular, peripheral, or ischemic vascular conditions.

Looking ahead, future studies should focus on several critical areas to bridge the gap between preclinical evidence and clinical application. First, standardized protocols for OMSC isolation, culture, and characterization are needed to ensure reproducibility and comparability across studies. Second, the molecular composition and mechanisms of action of the OMSC secretome require in-depth profiling using advanced omics approaches to identify key therapeutic effectors. Third, optimized methods for exosome purification, storage, and delivery must be developed to ensure stability and bioactivity for clinical use. Additionally, rigorous dose–response studies, long-term safety evaluations, and large-animal models are essential to establish efficacy and minimize translational risks. Finally, well-designed early-phase clinical trials should be initiated to validate preclinical

outcomes and define the therapeutic window, delivery route, and target patient populations most likely to benefit from OMSC-based interventions. By addressing these research priorities, OMSCs and their secretome have the potential to evolve from promising experimental therapies into clinically viable interventions for the treatment and prevention of vascular diseases.

Data availability

This article and its supplementary information files include all data generated or analyzed during this study.

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Author contributions
Q.C. contributed to conceptualization, methodology, formal analysis, and writing (original draft preparation). Q.C. and D.S.T. completed the collection and collation of the data. O.L.T.L. and C.M. contributed to guidance, validations and review of the manuscript. W.L.D. undertook the conceiving the idea, guidance, reviewing, editing, and finalizing the manuscript. All authors read and approved the final manuscript.

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Declarations

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