

RESEARCH ARTICLE

# Meta-Analysis of the Effect of Mesenchymal Stem Cell Transplantation on Vascular Remodeling after Carotid Balloon Injury in Animal Models

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## Abstract

### Aim

A meta-analysis was conducted to assess the efficacy of mesenchymal stem cell (MSC) transplantation in small animal coronary vessels after balloon injury, to provide data for the design of future pre-clinical experiments and human clinical trials.

### Methods

The search strategy included the PubMed, EMBASE, Chinese Biomedical Literature (CBM), and China National Knowledge Infrastructure (CNKI) databases. The endpoint was the ratio of vascular neointima/media (I/M). Moreover, neointimal area, re-endothelialization, and proliferating cell nuclear antigen (PCNA) expression were analyzed. Pooled analyses were conducted using random effects models. Heterogeneity and publication bias were also explored. All data were analyzed using RevMan 5.2 and Stata 12.0.

### Results

Fifteen studies were reviewed from 238 retrieved animal studies. Compared with controls, MSC transplantation resulted in greater I/M reduction (pooled difference, 0.39; 95% CI, 0.57–0.21;  $P < 0.0001$ ), greater neointimal area reduction (pooled difference, 0.16; 95% CI, 0.22–0.10;  $P < 0.0001$ ), decreased PCNA expression (pooled difference, 17.69; 95% CI, 28.94–6.44;  $P = 0.002$ ), and enhanced re-endothelialization (pooled difference, 3.37; 95%

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CI, 1.78–4.95;  $P < 0.0001$ ). The multivariable meta-regression analysis showed that a higher number of transplanted cells ( $>10^6$ ;  $P = 0.017$ ) and later time point of I/M measurement ( $P = 0.022$ ) were significantly associated with I/M reduction. Subgroup analysis demonstrated a trend for a greater reduction in the ratio of I/M with late MSC transplantation ( $>1$  day), MSCs transplanted through intravenous injection, and atherosclerotic vessels.

## Conclusion

The meta-analysis results demonstrate that MSC transplantation might improve injured vascular remodeling. In addition to greater efficacy with a greater number of transplanted MSCs ( $>10^6$ ), the long-term effect of MSC transplantation appears to be more significant. The findings of this meta-analysis may help to design future, effective MSC trials.

## Introduction

Percutaneous coronary intervention (PCI) is an effective treatment method for coronary heart disease. However, restenosis after PCI seriously affects the long-term prognosis. Post-angioplasty restenosis is caused largely by smooth muscle cell proliferation and neointimal proliferation, as well as elastic recoil [1]. A number of studies have suggested that inward vascular neointimal remodeling is the main cause of restenosis [2]. There is great potential for stem cells to regenerate damaged tissues in cardiovascular diseases [3]; mesenchymal stem cells (MSCs) could differentiate into functional cell types that are able to repair the diseased or injured tissue in which they are localized [4]. Despite an increase in the number of animal experiments studying the effects of MSCs on the repair of vascular injury, there is variation in not only experimental design but also the results. Animal experiments provide relevant information for clinical practice, while pre-clinical studies have to anticipate if the new therapy is feasible and effective. There are still a number of unknowns regarding MSC therapy in clinical practice, including the effect of MSCs on vascular remodeling after carotid balloon injury, effective number of MSCs, appropriate route, and appropriate timing of cell delivery.

The present study includes a meta-analysis and sub-analysis of data from published animal studies investigating the effect of MSC treatment, to assess the effects of MSC transplantation after carotid balloon injury.

## Materials and Methods

### Eligibility criteria

Two reviewers (XXJ and LJP) independently judged the eligibility of the studies. Eligible studies were randomized controlled trials (RCTs) of carotid balloon injury animal models. Additional requirements included MSC transplantation as the only intervention in the experimental group(s) and comparison with a placebo group. The studies were also required to investigate parameters for vascular remodeling (ratio of vascular neointima/media [I/M], neointimal area, re-endothelialization, and positive expression of proliferating cell nuclear antigen [PCNA]) as final outcomes. Reviews, comments, and editorials were excluded.

### Search strategy

We searched the electronic databases PubMed, EMBASE, Chinese Biomedical Literature (CBM), and China National Knowledge Infrastructure (CKNI) (last search was updated on

5 April 2014) using the following key words and search terms: (mesenchymal stem cell OR mesenchymal stromal cell OR bone marrow stromal cells OR bone marrow mesenchymal stem cells OR mesenchymal progenitor cell) AND (endothelium OR vessel OR vascular) AND (carotid balloon injury OR balloon OR angioplasty).

## Data extraction

Two reviewers (XXJ and LJP) independently screened full-text articles. The following information was extracted from the complete manuscripts of each qualified study: basal characteristics, I/M, neointimal area, re-endothelialization, positive expression of PCNA, time point of I/M measurement, and timing of cell therapy after injury. If necessary, data were estimated from figures of the included studies [5]. The I/M data were all expressed as a fraction of 1 (i.e., data presented as percentage values were converted to a fraction).

## Data analysis

The mean I/M ratios were different between the experimental and control groups. The heterogeneity tests resulted in significant heterogeneity ( $P < 0.1$ ); therefore, a random-effect model was applied [6]. Multivariable meta-regression analysis was performed to find the source of the significant heterogeneity. Continuous variables were estimated as weighted mean differences with 95% confidence intervals (CIs) between the MSC-treated animals and control animals. In the case of multiple experimental groups compared with one control group within one study, the number of animals in the control group was divided equally by the number of experimental groups [5,7]. P-values were reported by statistical hypothesis testing at the two-sided 0.05 level.

From a clinical viewpoint, multivariate meta-analyses were performed for animal model (rabbits or mice), diet (cholesterol or normal), number of MSCs injected ( $\leq 10^6$  or  $> 10^6$ ), the route of cell delivery (intravenous or carotid artery local transplantation), timing of cell therapy after injury ( $< 1$  day or  $\geq 1$  day), and time point of I/M measurement after MSC therapy ( $< 4$  weeks or  $\geq 4$  weeks) to find the factors associated with a reduction in I/M. For further insight, subgroup analyses were performed with the following factors: diet, number of cells injected ( $\leq 10^5$ ,  $10^5$ – $10^6$ ,  $10^6$ – $10^7$ , or  $> 10^7$ ), the route of cell delivery, timing of cell therapy after injury, and time point of I/M measurement after MSC therapy.

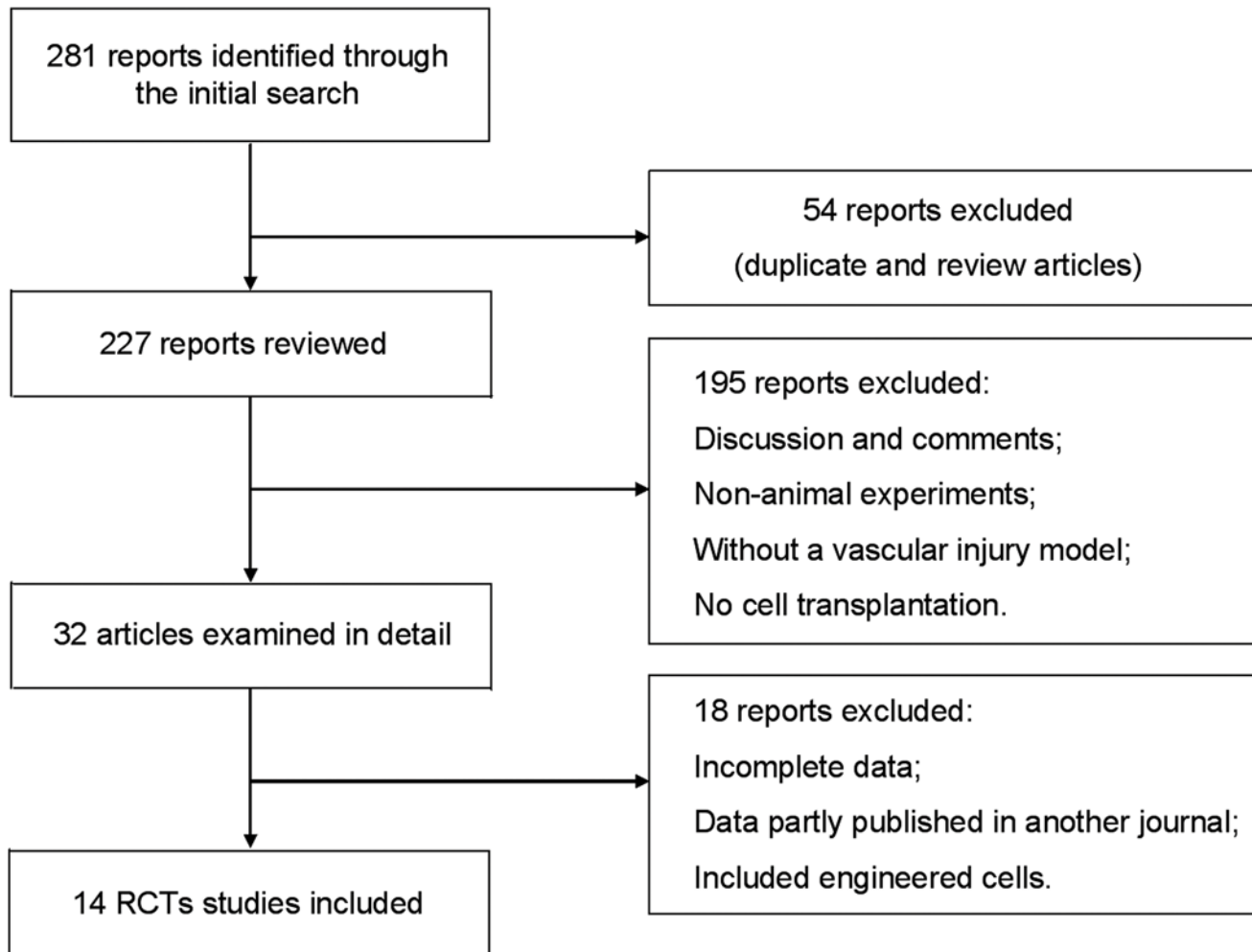
The mean neointimal area, re-endothelialization, and positive expression of PCNA values were also different between the experimental and control groups. The heterogeneity tests resulted in significant heterogeneity ( $P < 0.1$ ); therefore, a random-effect model was applied. The degree of re-endothelialization was assessed using 3 methods: the expression of CD31, vascular endothelial growth factor (VEGF), and ratio of the re-endothelialized area (defined as the area not stained with Evans blue/total injured surface area).

Publication bias was explored by funnel plot. All analyses were performed with Review Manager Version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) and Stata 12.0.

## Results

### Study characteristics

The search strategy identified 281 articles (Fig. 1). Of the 238 animal studies, 14 were eligible for review (Table 1). Mice (7 studies) and rabbits (7 studies) were used as animal models. The studies investigated the effect of MSC on injured atherosclerotic vessels (6 studies) or injured normal vessels (8 studies). The atherosclerotic vessel models resulted primarily from animals fed a cholesterol diet, while the normal vessel models resulted primarily from animals fed



**Fig 1. Flowchart of studies included in the meta-analysis of animal studies investigating mesenchymal stem cell therapy.** Abbreviations: RCTs = randomized controlled trials.

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a normal diet. MSCs were injected either intravenously ( $n = 4$ ) or near the injured carotid artery ( $n = 10$ ). The MSC doses varied, as summarized by 2 categories: low dose ( $\leq 10^6$ ) in 4 studies and high dose ( $> 10^6$ ) in 9 studies. Timing between vessel injury and cell transplantation was  $< 1$  day (12 studies) or  $\geq 1$  day (2 studies). After cell transplantation, the I/M level was measured at  $< 4$  weeks (4 studies) or  $\geq 4$  weeks (12 studies).

### Meta-analyses

The I/M data are presented as continuous variables, using mean and standard deviation. Pooled analysis showed that the I/M level was 0.39 lower in the experimental group compared with the control group after cell therapy (95% CI, 0.57–0.21;  $Z = 4.25$ ;  $P < 0.0001$ ) with significant heterogeneity ( $P < 0.001$ ; I Square, 98%; Fig. 2).

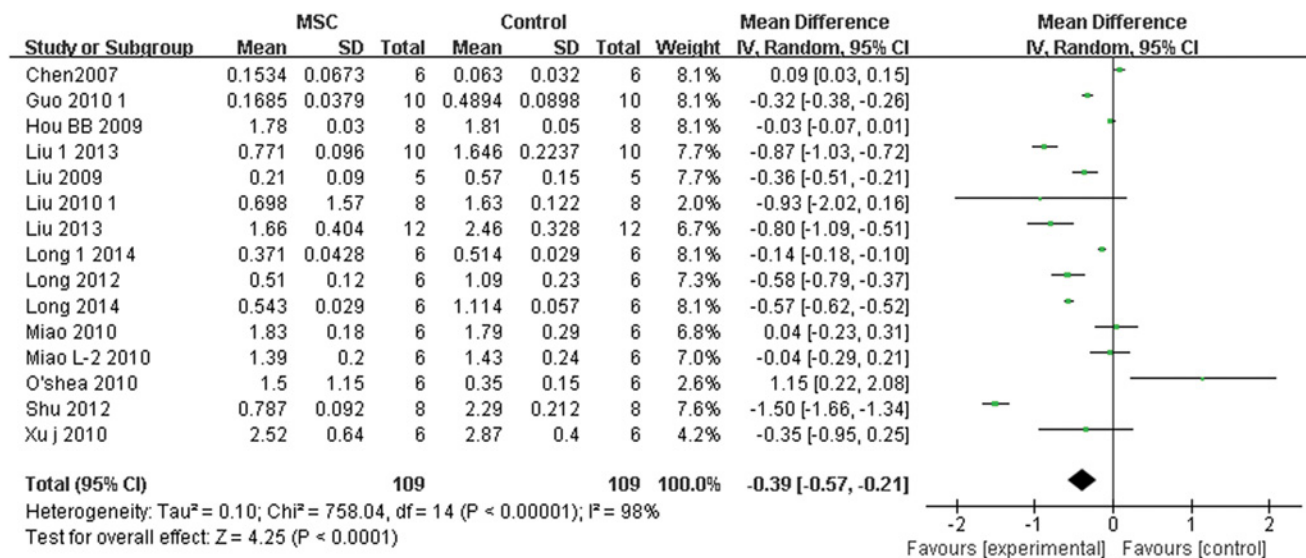
Multivariable meta-regression analysis showed that the number of MSCs transplanted ( $P = 0.017$ ) and time point of I/M measurement after cell therapy ( $P = 0.022$ ) were significantly associated with a reduction in I/M.

**Table 1. Characteristics of the animal studies included in the meta-analysis.**

First author (year)	n	Type of animal	Diet	Number of MSCs	Route of delivery	Time of MSC therapy after injury	Time point of I/M measurement
Chen (2007)[8]	6	Mice	Normal	2×10 <sup>6</sup>	Carotid artery	<1 day	28 days
Guo (2010)[9]	10	Rabbits	Cholesterol	2×10 <sup>7</sup>	Intravenous	<1 day	28 days
Hou (2009)[10]	8	Mice	Cholesterol	1×10 <sup>6</sup>	Carotid artery	<1 day	60 days
Liu (2009)[11]	5	Rabbits	Normal	1×10 <sup>5</sup>	Carotid artery	<1 day	28 days
Liu 1 (2013)[12]	10	Rabbits	Cholesterol	2×10 <sup>7</sup>	Carotid artery	<1 day	28 days
Liu 2 (2013)[13]	12	Mice	Normal	5×10 <sup>7</sup>	Intravenous	<1 day	28 days
Liu (2010)[14]	8	Rabbits	Cholesterol	2×10 <sup>7</sup>	Carotid artery	<1 day	28 days
Long (2012)[15]	6	Rabbits	Cholesterol	1.5×10 <sup>7</sup>	Intravenous	≥1 day	28 days
Long (2014)[16]	6	Rabbits	Normal	1×10 <sup>8</sup>	Intravenous	≥1 day	14 days or 28 days
Miao (2010)[17]	6	Mice	Normal	5×10 <sup>2</sup>	Carotid artery	<1 day	14 days or 28 days
O'Shea (2010) [18]	6	Rabbits	Normal	1×10 <sup>5</sup>	Carotid artery	<1 day	14 days
Shu (2012)[19]	8	Mice	Normal	5×10 <sup>6</sup>	Carotid artery	<1 day	28 days
Xu (2010)[20]	6	Mice	Normal	2×10 <sup>6</sup>	Intravenous	<1 day	28 days
Liao (2012)[21]	8	Mice	Cholesterol	Not reported	Carotid artery	<1 day	42 days

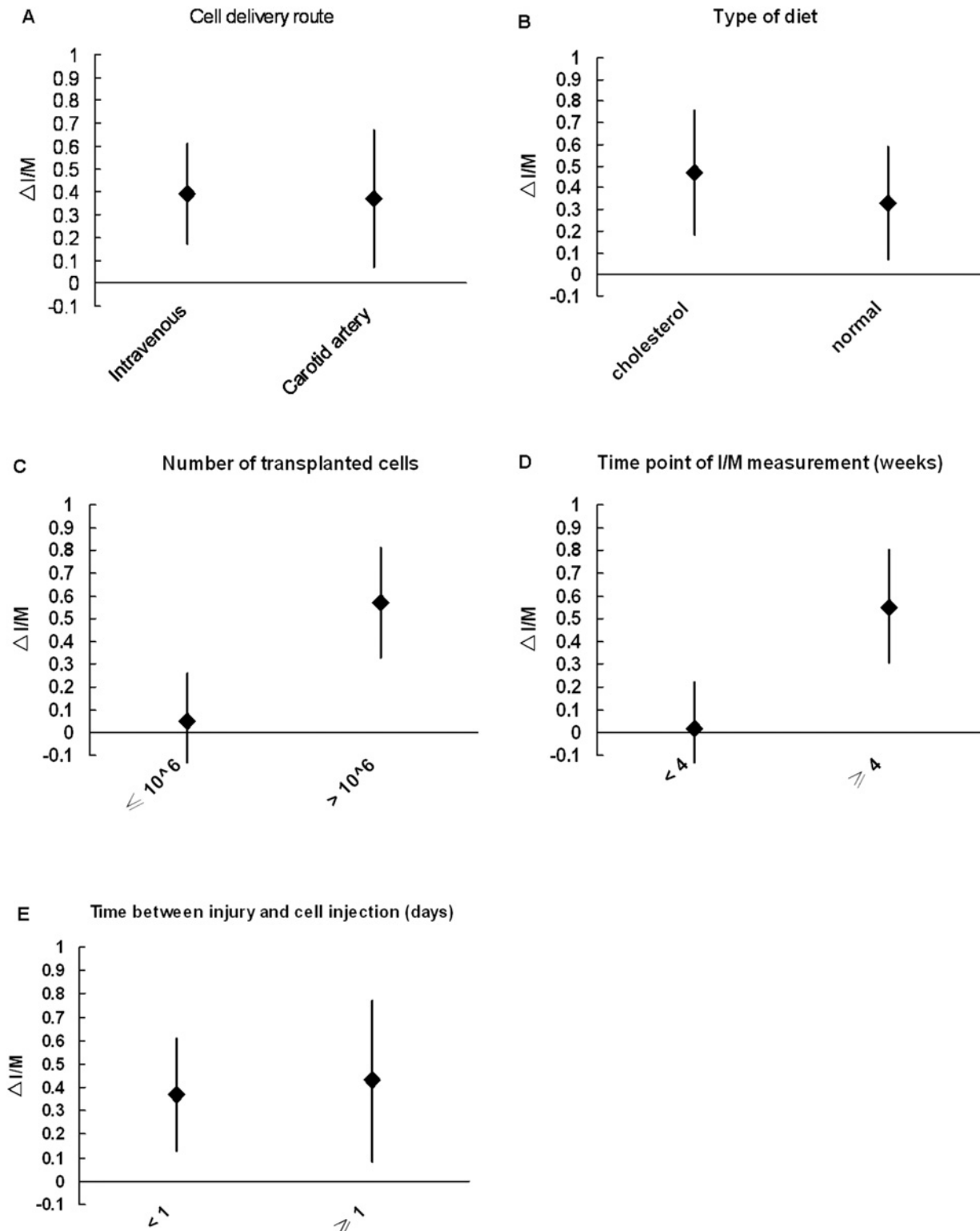
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Fig. 3 shows the results of the subgroup analyses. In studies with low MSC doses ( $\leq 10^6$ ), the I/M (95% CI, -0.15–0.26) was 0.05 lower in the MSC group versus the control group. In studies with high MSC doses ( $> 10^6$ ), the I/M was significantly lower (mean difference, 0.57; 95% CI, 0.33–0.81;  $P < 0.001$ ). The sub-analyses also demonstrated that the I/M measured at 14 days ( $< 28$  days) was 0.02 (95% CI, -0.18–0.22) lower in the MSC group compared with the control group, while the I/M measured at  $\geq 28$  days was significantly lower, by 0.55 (95% CI, 0.31–0.80;  $P < 0.001$ ). The studies that used an intravenous injection route showed a 0.39 lower I/M in the MSC group compared with the control group (95% CI, 0.17–0.61;  $P < 0.001$ ), while the arterial injection route resulted in a 0.37 (95% CI, 0.07–0.67;  $P < 0.001$ ) lower I/M. After carotid balloon



**Fig 2. Forest plot showing the impact of mesenchymal stem cell (MSC) therapy on neointima/media, compared with controls.** Abbreviations: SD = standard deviation, IV = independent variable, 95% CI = 95% confidence interval.

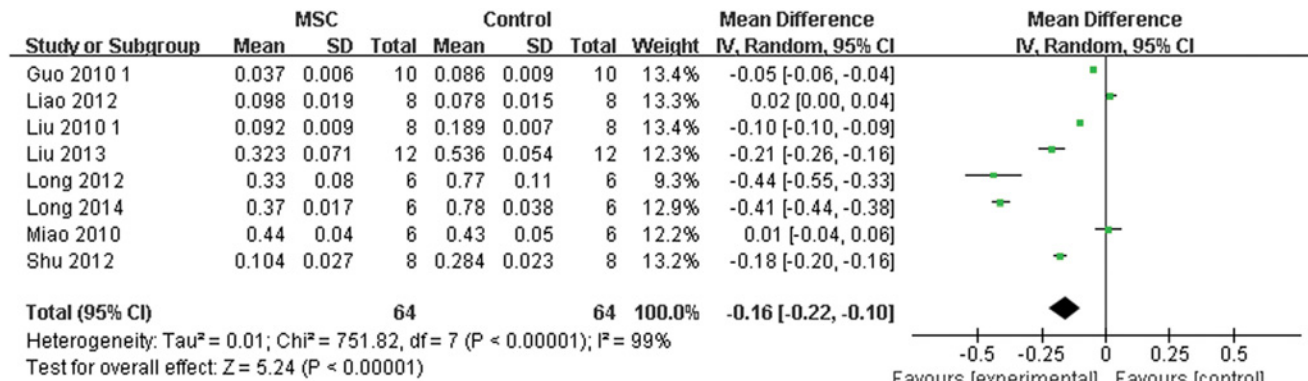
doi:10.1371/journal.pone.0120082.g002



**Fig 3. Sensitivity analysis showed a trend towards greater reduction in neointima/media (I/M) with mesenchymal stem cell (MSC) engraftment, compared with controls, with (A) intravenous cell transplantation route ( $P = 0.139$ ); (B) cholesterol diet ( $P = 0.629$ ); (C) high cell numbers ( $> 10^6$ ;  $P = 0.017$ ); (D) I/M measurement later after MSC engraftment ( $\geq 4$  weeks;  $P = 0.022$ ); and (E) later cell engraftment ( $\geq 1$  day;  $P = 0.437$ ).**

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**Fig 4. Forest plot showing the impact of mesenchymal stem cell (MSC) therapy on neointimal area, compared with controls.** Abbreviations: SD = standard deviation, IV = independent variable, 95% CI = 95% confidence interval.

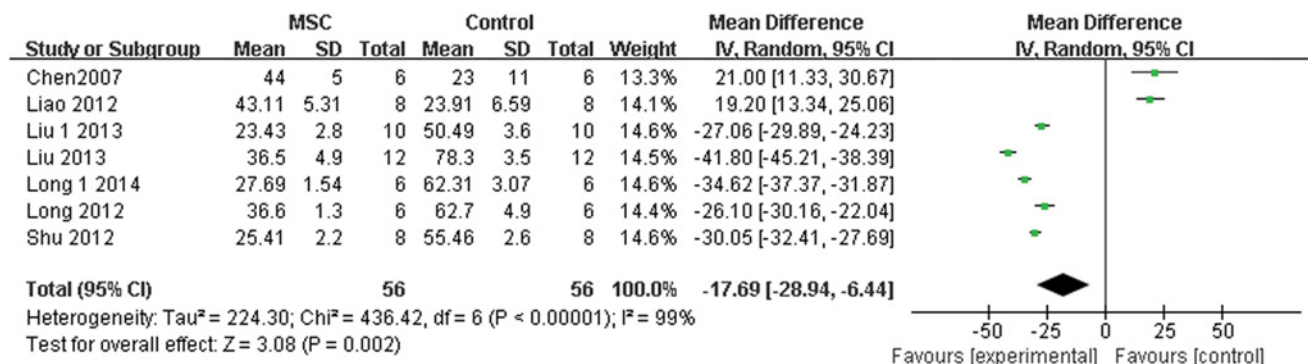
doi:10.1371/journal.pone.0120082.g004

injury, atherosclerotic vessels had significantly lower I/M than normal vessels in the MSC group compared with the control group (mean difference 0.47 and 0.33, respectively; 95% CI, 0.18–0.76 and 0.07–0.59, respectively; P < 0.001). Early stage (<1 day) MSC therapy resulted in significantly lower I/M (mean difference, 0.37; 95% CI, 0.13–0.61; P < 0.001) in the MSC group versus the control group. However, late stage (≥1 day) MSC transplantation resulted in significantly lower I/M than early stage (mean difference, 0.43; 95% CI, 0.08–0.77; P < 0.001).

Studies using rabbits resulted in significantly lower I/M in the MSC group versus the control group (mean difference, 0.42; 95% CI, 0.22–0.62; P < 0.001), and studies with mice showed a smaller difference in I/M (mean difference, 0.37; 95% CI, 0.04–0.70; P < 0.001).

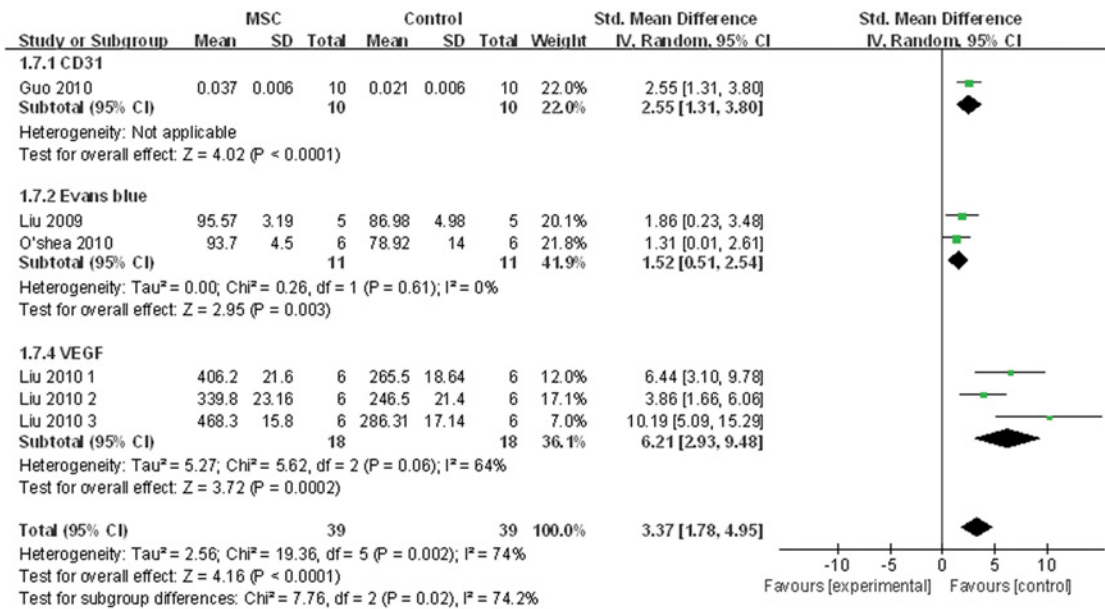
The mean neointimal area and positive expression of PCNA are presented as continuous variables, using mean and standard deviation. Pooled analysis showed that the neointimal area was 0.16 lower in the MSC group compared with the control group (95% CI, 0.22–0.10; Z = 5.24; P < 0.0001; Fig. 4). The positive expression of PCNA was 17.69 lower in the MSC group compared with the control group (95% CI, 28.94–6.44; Z = 3.08; P = 0.002; Fig. 5).

Fig. 6 shows the degree of re-endothelialization with each of the 3 assessment methods. Pooled analysis showed that MSC engraftment could enhance vascular re-endothelialization after carotid balloon injury (pooled difference, 3.37; 95% CI, 1.78–4.95; Z = 4.16; P < 0.0001).



**Fig 5. Forest plot showing the impact of mesenchymal stem cell (MSC) therapy on the positive expression of proliferating cell nuclear antigen (PCNA), compared with controls.** Abbreviations: SD = standard deviation, IV = independent variable, 95% CI = 95% confidence interval.

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**Fig 6. Forest plot showing the impact of mesenchymal stem cell (MSC) therapy on re-endothelialization, compared with controls.** CD31, Evans blue, and vascular endothelial growth factor (VEGF) were used as the indices reflecting the degree of re-endothelialization. Abbreviations: SD = standard deviation, IV = independent variable, 95% CI = 95% confidence interval, CD31 = the expression ratio of CD31, VEGF = vascular endothelial growth factor, Evans blue = the ratio of re-endothelialized area (defined as the area not stained with Evans blue/total injured surface area).

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### Sensitivity analysis

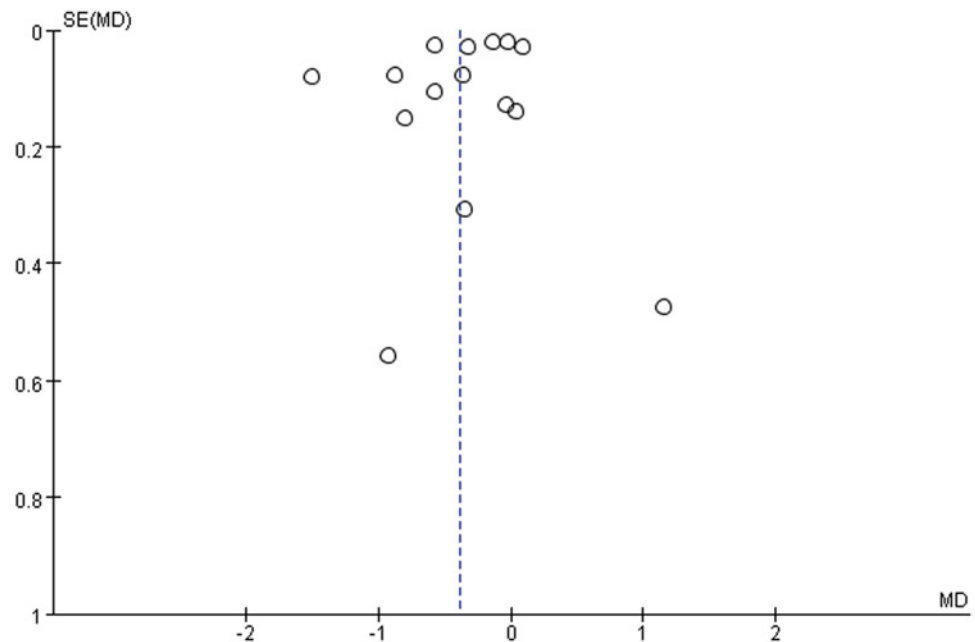
The number of cells transplanted (P = 0.017) and time point of I/M measurement after MSC therapy (P = 0.022) were significant factors for I/M reduction. A trend was observed (Fig. 3) for greater improvement with MSC engraftment with a higher number of cells transplanted (>10<sup>6</sup>) and later engraftment (≥1 day). Local MSC engraftment, around the carotid artery, showed less effect than intravenous engraftment. Animals fed with cholesterol had greater reductions in I/M than animals fed a normal diet. During the follow-up, the late effect of MSC transplantation appeared to be more significant. No trend in I/M differences was observed based on animal type (P = 0.914). The funnel plot for I/M suggests a lack of publication bias, as values were evenly distributed around the overall estimate (Fig. 7).

### Discussion

The present meta-analysis revealed that MSC engraftment reduces vascular remodeling after coronary vessel balloon injury, evidenced by lower/smaller I/M, neointimal area, and positive expression of PCNA in addition to enhanced re-endothelialization after MSC transplantation. In addition, the meta-analysis revealed that the number of transplanted MSCs and time point of I/M measurement were significant factors for vascular remodeling. Furthermore, the subgroup analysis indicated that late therapy (>1 day), the atherosclerotic vascular model, and intravenously injected MSCs were beneficial for I/M reduction. These results were not affected by the type of animal studied.

MSCs are multipotent cells derived from bone marrow that have the ability to differentiate into cells of mesenchymal and nonmesenchymal origin [22], such as osteocytes [23], chondrocytic, adipocytes [24,25] and myocytes [26]. Moreover, MSCs appear to function through paracrine mechanisms that exert immunosuppressive, anti-inflammatory, anti-apoptotic and other organ-protective and repair-stimulating actions [22,27,28]. As a candidate therapy, MSCs have





**Fig 7. Funnel plot for neointima/media.** Blue-dotted line shows the overall estimated mean difference. No obvious evidence for publication bias was found. Abbreviations: MD = mean difference, SE = standard error.

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many advantages [22,29], including easily isolated and amplified from the bone marrow [30] and immunologically tolerated as an allogeneic transplant [29,31].

A number of studies have indicated that MSCs are candidates for cell therapy in coronary heart disease, including myocardial infarction (MI) [32] and ischemic heart disease [33]. With regards to MI, MSCs might improve angiogenesis after MI, reduce MI size, and improve heart function, as demonstrated through animal studies [34] and clinical use [35–37]. As a result, studies have also investigated the effect of MSCs on restenosis after PCI; however, the results have been inconclusive, and MSC use has not been applied clinically.

The mechanisms of vascular restenosis after PCI have remained unclear, while it is known that restenosis after angioplasty is caused largely by smooth muscle cell proliferation and neointimal proliferation, as well as elastic recoil [1]. Inward remodeling might also contribute to restenosis [2]. Some studies have shown that MSCs can improve vascular remodeling and prevent neointimal formation [9–17,19,20], while other studies found that MSCs increase neointimal formation and aggravate vascular remodeling [8,18,21].

The present meta-analysis, which analyzed the I/M, neointimal area, positive expression of PCNA, and degree of re-endothelialization as parameters indicating vascular remodeling after carotid balloon injury, showed that MSC transplantation could improve vascular remodeling and prevent neointimal formation. Furthermore, the I/M results suggested that vascular remodeling is significantly influenced by the number of MSCs transplanted, with a higher number of cells ( $>10^6$ ) resulting in a greater reduction in I/M. This result supports those of other meta-analyses regarding the effect of MSC transplantation on other clinical diseases [5,7]. Collectively, these findings indicate that future studies of MSC therapy for restenosis should focus on transplantation of a higher number of MSCs ( $>10^6$ ).

I/M reduction was also influenced by the time point of measurement; a greater reduction in I/M was measured at later times ( $\geq 4$  weeks) after MSC injection. It may be likely that the reduction in intimal remodeling with MSC therapy is only evident over time. However, the

results of MSC therapy for ischemic heart disease in pre-clinical studies do not agree with the present findings [5]. The follow-up duration in these studies may not have been long enough; the majority of the studies followed the patients up for no more than 4 weeks, while only one study measured I/M at 5 weeks [10]. Therefore, the long-term effect of MSC therapy on intimal remodeling was previously unknown. Future pre-clinical studies should study the effectiveness of MSC treatment over a longer period.

The subgroup analysis indicated that a greater benefit in intimal remodeling is realized with MSC injections administered  $\geq 1$  day after vascular injury. In the acute setting ( $< 24$  h), cellular retention and survival are likely influenced by the local hostile microenvironment. Furthermore, MSC therapy tended to be more effective with injured atherosclerotic vessels than with injured normal vessels. Meanwhile, the effectiveness of MSC transplantation was similar between intravenous and carotid artery delivery routes as well as between animal types. Further research is required to determine if there is a best administration route, while the efficacy of MSC may be the same regardless of species (animal or human).

Meta-analyses of animal studies are not common, yet they are recommended in many settings and can often guide research, even clinical endeavors. Performing meta-analyses of animal studies may be a useful way to evaluate the effects of therapies for designing future animal experiment and pre-clinical trials. Our meta-analysis is the first systematic review and meta-analysis of animal models to evaluate the effects of MSC therapy in injured vessels, demonstrating that MSC therapy can lead to improvements in vascular remodeling. Moreover, we analyzed the factors influencing vascular remodeling after balloon injury, which could form the basis for future large animal experiments and even human clinical trials. To date, trials for MSC therapy have been performed primarily in small animals. In our opinion, more animal experiments of different species, especially nonhuman primate trials, should be performed in order to assess the efficacy and safety of MSC therapy before human clinical trials.

## Limitations

A limitation of the present study was the presence of obvious heterogeneity. Furthermore, the analysis was based on study outcomes; we did not have access to individual data. However, the risk of erroneous estimates was minimized through the use of random-effect analysis. The observed outcomes were influenced by many factors, such as the diversity in animal type, vascular conditions, cell delivery method, number of cells, time of injection after balloon injury, and follow-up after cell therapy. We performed multivariate analysis, as an exploratory tool, that showed the number of cells and follow-up duration after cell therapy could influence the meta-analysis results. Despite these limitations, our results are highly relevant for future clinical trials.

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## Author Contributions

Conceived and designed the experiments: XXJ LJP FL. Performed the experiments: XXJ HZ KJL JCD. Analyzed the data: XXJ SGL ZZ YQ JZ LHW. Contributed reagents/materials/analysis tools: LJP SGL JMH YTW YXW WJ. Wrote the paper: XXJ LJP. Critical revision of the manuscript: LJP WJZ FL.

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