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Clinical trial the MSCs therapy in limb ischemia: Choose the Best Method

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ABSTRACT

There is a substantial amount of data provided in preclinical research and recently made early clinical efforts to evaluate the positive MSC therapy in Limb ischemia disease impacts. The present review is primarily focused on assessing various limb ischemia-related human MSC clinical trials to select the best technique with the highest limb ischemia-related clinical trial MSC efficacy. Five studies met the criteria to be included in this review. MSCs originating from bone marrow Allogenic MSC, bone marrow autogenous MSCs, HUCB MSCs were administered. The injection was intramuscular, Intravenous, and intravenous. The mean follow-up time was between 6 to 60months after MSC therapy. All studies reported improvement from baseline in at least 1 clinical outcome measure, and no study reported major adverse events attributable to MSC therapy. In clinical assessments, the selection of the best method could improve treatment efficacy. Several factors may be involved in the MSC injection efficacy of limb ischemia patients. Both allogeneic and autologous exhibited positive results over placebo. However, it is should be mentioned that autologous MSC investigation has higher cost and toxicity. To reduce the toxicity of derived MSCs while injection, particularly in arterial and intravenous injection, different injection doses can be performed. MI injection at different doses is the best method for diminishing the side effects. To evaluate injection efficacy, different criteria can be adopted, including angiography, ABI index, ulcer healing and amputation, and pain-free walking distance follow-up for up to five years.

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Introduction

Despite the therapeutic novelty of MSC utilization for limb ischemia treatment, there is a substantial amount of data provided in preclinical research and recently-made early clinical efforts to evaluate the positive MSC therapy impacts. In this approach, the patient type is an essential factor1. In general, it is required to obtain consensus on various important aspects. Although peripheral vascular disease is most commonly caused by atherosclerosis, Buerger's disease (which is also referred to as thrombo-angiitis obliterans) represents a less frequently-observed yet important cause (2).

Buerger's disease refers to an inflammatory disorder that distinctly differs from the vascular occlusive disease afflicting young smoker's peripheral arteries (3). A characteristic of this disorder is an inexorable downhill course that occurs even among people that cease smoking after reaching s limb ischemia stage relating to gangrene or ulceration (4).

Cell dosing is also an essential factor (5). Efficacy was seemingly not impacted by the administration site and total cell count. Furthermore, the current regimes (6). It is important that associated clinical endpoints are incorporated

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into future clinical trials beyond the quality of life, walking time, and ankle-brachial index measurements (7). The Society for Vascular Surgery introduced particular objective performance goals (OPGs) for the purpose of defining therapeutic revascularization benchmarks concerning limb ischemia. Research has shown post-administration follow-up to last from three to twelve months (8).

The Society for Vascular Surgery proposed thirty days of assessing safety endpoints, such as amputation, MLAE, and MACE as the standard time for post-procedural events and new devices (9). The present review is primarily focused on assessing various limb ischemia-related human MSC clinical trials to select the best technique with the highest limb ischemia-related clinical trial MSC efficacy.

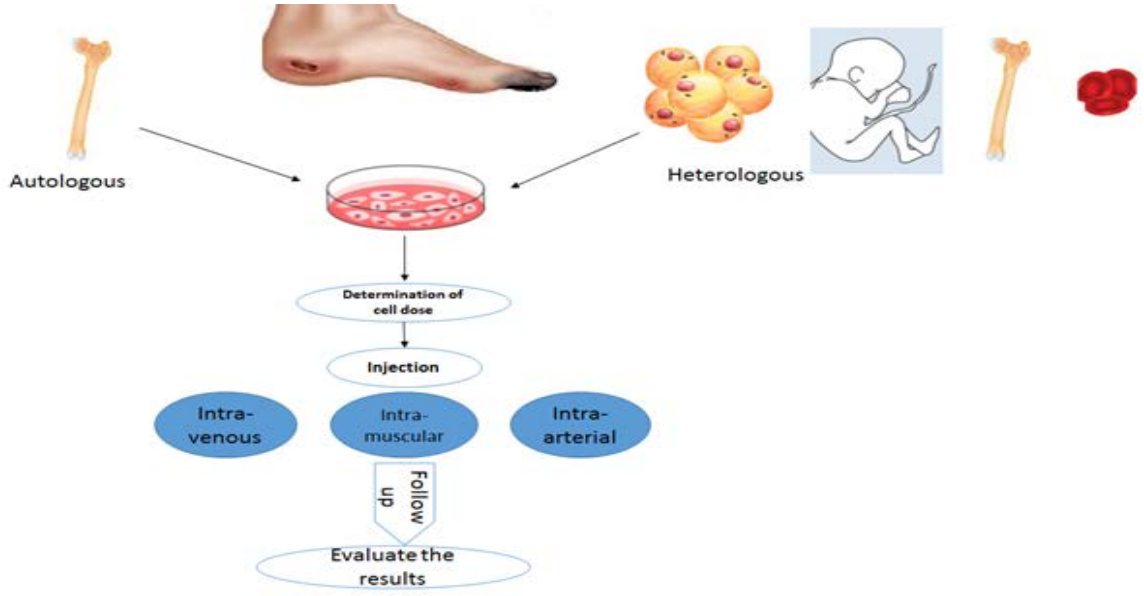

Figure 1: reviews protocol of MSCs in limb ischemia

Stem cell mesenchymal cells can be extracted from a variety of sources, which can generally be autologous or heterologous. The extracted samples can be injected in different concentrations according to individual characteristics. Cells can injection intra-arterial, intravenous or intramuscular. The duration of follow-up can be different in different studies. Choosing the method according to the existing conditions increases the efficiency of therapy.

Literature review

Cause of limb ischemia

Wijnand (2017) and et al, studied sixty-six proven chronic CLI patients, defining the patients as rest pain or non-healing ulcers arising from peripheral artery disease. The patients did not have eligibility for endovascular or surgical revascularization. They evaluated the no-option status based on conventional vascular images (10,11). Gupta (2013) and et al, a TAO-diagnosed man at the age of forty-one with critical chronic ischemia along with ulcerous lesions on the right lower leg. The patient had critical ischemia and ulcers on the left lower Leg, even though they had not smoked for eight years. The patient had undergone left lumbar sympathectomy and epidural spinal cord neurostimulator implantation; however, after femoropopliteal bypass, the patient required a left transtibial amputation four years earlier (12).

Yang (2013) and et al, enrolled eight CLI patients in their phase I trial. The patients were all males and at the age of 31-77. The cases were all found to be not of eligibility for further revascularization for CLI improvement (13).Martin-Rufino (2018) and et al, referred a TAO-diagnosed patient with ulcerous lesions and critical chronic ischemia on the right lower leg at the age of forty-one to the Angiology and Vascular Surgery Department for MSC treatment eligibility assessment in a compassionate utilization scheme. The patient had critical ischemia and ulcers on the right lower leg, even though they had not smoked for eight years. The patient

Underwent left lumbar sympathectomy and epidural spinal cord neurostimulator implantation; however, after femoropopliteal bypass failure, they required a left transtibial amputation four years earlier (14).

Origine of MSC

MSCs enhance vascular and alveolar structures in experimental bronchopulmonary dysplasia (BPD) models. In comparison to male MSCs, more pro-angiogenic and anti-inflammatory factors are secreted by female MSCs. The donor MSC gender impacts MSC therapeutic efficacy concerning attenuating lung injury within an experimental BPD model (15,16). Wijnand (2017) and et al, derived Allogeneic BM-MSCs from health volunteer BM. The cases underwent

a 1:1 randomization for the reception of intramuscular placebo or allogeneic BM-MSC injections (10).Gupta (2013) harvested 85 ml of bone marrow from a healthy female donor at the age of forty-two by standard operating processes (12).Wang (2017) and et al, enrolled thirty-two extremities suffering from tissue loss or rest pain in need of BKA for the reception of intramuscular (IM) injections (17).Yang (2013) and et al, derived post-delivery UCB samples from umbilical veins with the mother's consent (13). Martin-Rufino (2018) and et al, harvested 85 ml of bone marrow from a healthy female donor at the age of forty-two by standard operating processes (13,14).

MSC injection

Wijnand (2017) and et al, gave thirty IM injections of placebo (with 20% and 50% sodium chloride 0.9% and 50% human serum albumin) or BM-MSCs (five 106 MSCs in each injection) after intravenous fentanyl-assisted analgesia induction (10). Gupta (2013) and et al, carried out a total of four intravenous MSC infusions on the first, fourth, eleventh, and eighteenth days. Each of the doses had 8.5 × 107 cells (106 cells per kg) (12). They administered intravenous premedication with 1 g of paracetamol, 10 mg of dexchlorpheniramine, and 100 mg of hydrocortisone sodium phosphate and performed the monitoring of post-infusion vital signs for the purpose of avoiding DMSO-induced toxicity (12).

Wang (2018) and et al, performed the clinical and histological analysis of mesenchymal stromal cells in AmPutations(CHAMP) as an open-label, phase I/II, and single-center trial by enrolling a total of 32 patients diagnosed with CLI in need of semi-elective BKA in thirty days for dry gangrene or rest pain. The study was conducted by the Indiana University Institutional Review Board (17).

Yang (2013) and et al, carried out direct intramuscular hUCB-MSC injection into the affected limb by intravenous sedation with propofol (which is monitored anesthesia care, MAC). They diluted 1 ml of 1×107 hUCB-MSCs into the ultimate volume of 20 ml of saline (13).

2-gauge needles were employed to subject each of the twenty injection sites on the limb below the knee to the injection of twenty aliquots of 1 ml (5×105). The selected sites were on the ischemic calf muscle along the peroneal and tibial arteries (13). Martin-Rufino (2018) and et al, carried out a total of four intravenous MSC infusions on the first, fourth,eleventh, and eighteenth days. Each of the doses had .5 × 107 cells (1.06 × 106 cells/kg). They administered intravenous premedication with 1 g of paracetamol, 10 mg of dexchlorpheniramine, and 100 mg of hydrocortisone sodium phosphate and performed the monitoring of post-infusion vital signs for the purpose of avoiding DMSO-induced toxicity (14).

Follow up period

Wijnand (2017) and et al, evaluated the primary outcome (which is the success of therapy in six months) as the composite outcome. For succession, it is necessary that the patient is alive, has no major index limb amputation, has not experienced worsened visual analog pain scale or Rutherford classification, and has enjoyed an analog pain scale or Rutherford classification improvement (10).

Gupta (2013) and et al, carried out a total of four intravenous MSC infusions on the first, fourth, eleventh, and eighteenth days. Each of the doses had .5 × 107 cells (1.06 × 106 cells/kg). They administered intravenous premedication with 1 g of paracetamol, 10 mg of dexchlorpheniramine, and 100 mg of hydrocortisone sodium phosphate and performed the monitoring of post-infusion vital signs for the purpose of avoiding DMSO-induced toxicity (12).

Wang (2018) and et al, applied computer-assisted non-stratified randomization to assign tissue harvest and BKA to patients on the third, seventh, fourteenth, or twenty-first day after the injection(17). They reviewed negative events through clinic visits during a post-procedure six-month period to examine whether allogeneic MSCs and autogenous cBMA would lead to significant infectious, respiratory, or cardiovascular complexities. Furthermore, they collected peripheral blood samples of the patients on the 3rd, 14th, 45th, 90th, 135th, and 180th days to compare with baseline tests for determining alternations in proangiogenic/inflammatory mononuclear phenotypes, miRNA expression, and peripheral cytokine signaling (17).

They applied FISH, FACS, immunohistochemistry, and multiplex arrays to the tissue that was collected during amputation (17). Yang (2013) and et al, studied efficacy improvement endpoints in the limb wound status, angle-bra-

chial index (ABI), and the standardized treadmill test of total and pain-free walking distances at the baseline at each visit in comparison to one week, one month, three months, and six months after limb MSC injection (13). Furthermore, they carried out conventional angiography before and after (six months) hUCBMSC injection for the detection of an increased visible vessel count (13).Martin-Rufino (2018) and et al, conducted a study ten months after treatment completion (14).

Results

Wijnand (2017) and et al, selected the intramuscular route. It was observed that three small RCTs had the potential of MSC intramuscular administration. Furthermore, intra-arterial administration was found to have the risk of iatrogenic artery and adjacent nerve damage, atherosclerotic lesion dislodgment, and vessel wall dissection (10). Allogeneic MSC administration has various benefits over autologous MSC administration, including substantially lower patient burden (since it is not required to subject the patients to BM harvesting) and the prior testability of the cell isolate proangiogenic capacity in allogeneic MSC therapy (10).

The donor MSC isolates were found to have substantial heterogeneity; nearly one-quarter of the isolates did not induce neovascularization enhancement as compared to placebo. For autologous MSC application, the outcomes of the trial and the therapeutic potential are likely to be impacted by such heterogeneity (10). In allogeneic applications, one can select the best donor isolate to diminish treatment response variability. Moreover, the treatment cost significantly differs (10).

A number of clinical works were conducted via allogeneic MSCs for myocardial infarction patients; allogeneic cells were not found to induce detectable alloantibodies or acute rejection. There is a lack of allogeneic BM-MSC studies concerning some no cardiovascular diseases. After allogeneic MSC injection was performed in the vicinity of the fistula tracks of Crohn disease-diagnosed patients (n ¼ 21), they found no local reaction (e.g., inflammation or other rejection signs)(10). Metal analysis of 216 patients who received allogeneic BM-MSCs was performed,reporting solely transient fever and no other infusion-associated toxicity. The systemic lupus erythematosus patients who underwent allogeneic MSC treatment (n ¼ 15) experienced no treatmentassociated negative events in four years (10).

Gupta (2013) and et al, carried out an MBA five months after the first infusion(12). The vasculature exhibited substantial alternations. Ten months after the treatment completion, pain management was improved by Implanting a new spinal cord neurostimulator (12).

The patient needed neither major nor minor amputation in sixteen months after the infusion of MSCs (12). The WIQ distance score of the patient rose from 54 to 64 (of 100), while no changes occurred in the climbing and speed scores (12). Moreover, the EQ-5D scores increased from 0.72 to 0.83 (of 1) and to 90 (of 100) in the descriptive system and VAS, respectively, suggesting a noticeable enhancement in the quality of life (12). Wang (2018) and et al, argued CHAMP to be crucial in the allogeneic MSC biological activity characterization of human tissue. They secondarily aimed to complete the previous open-label phase I trial of Wang (2018) that investigated the IM injection utility of cBMA with MSCs into thirty nonrevascularizable CLI limbs (17). The patients were observed to show a one-year non-amputation survival rate of 86% and a five-year non-amputation survival rate of 74%17. This is comparable to patients with CLI who were subjected to surgical revascularization (17).

Yang (2013) and et al, performed the safety and efficacy assessment of eight patients (three of which had ASO, while the remaining five had TAO) a week after the injection of MSCs (as the baseline) and one,three, and six months after the injection (13). The patients were males and in the age range of 31-77 (13). Five participants were previously subjected to index limb surgical and/or endovascular interventions. The ABI index was not found to have improved after IM injection (from 0.51 at baseline to 0.57 after six months, ($p>0.05$) (13).

The rise in the average pain-free walking distance of treadmill test-subjected patients from 76.3 m at the base month to 189.4 after six months (n=5) was not of statistical significance ($p>0.05$). Four of the patients were incorporated in the investigation with non-healing index limb ulcerations. Three of them Enjoyed full ulceration healing in six months. The six-month follow-up period had no amputation. The six month angiography results indicated enhanced scores as compared to the baseline results for three patients based on the pre-defined run-off vessel, arteriogenesis, and angiogenesis scores (13).

Martin-Rufino (2018) and et al, detected no negative allograft rejection signs or effects after four infusions of allogeneic MSCs. They proposed an observable regression of trophic right foot changes in the patient after three months.

The patient was found to have a nearly full remission of ulcers and restituted skin integrity six months after the infusions. It was reported in five months of follow-up that the patient experienced reduced rest pain and disappeared paresthesia. Also, they measured ABI to be 0.47 and observed a palpable pedal pulse. However, a controversial correlation was found between ABI and functional performance. The WIQ distance of the patient rose from 54 to 64 (of 100), while no changes occurred in the climbing and speed scores.

In addition, the EQ-5D scores enhanced from 0.72 to 0.83 in the descriptive system and VAS, suggesting a noticeable enhancement in the quality of life. They carried out an MRA five months after the first infusion, and no substantial vasculature change was observed. Ten months after the treatment completion, pain management was improved by implanting a new spinal cord neurostimulator. The patient needed neither major nor minor amputation in sixteen months after the infusion of MSCs (14(. Table 1 shows review of 5 study on MSCs injection in limb ischemia.

Table 1: Review of 5 study on MSCs injection in limb ischemia.

Study	Couse of limb ischemia	Source of MSCs	Dose	injection	Follow-up	Result	Ref
Wijnand (2017)	CIL	Allogenic/BM-MSCs	106	intravenous	6 months	Diminish treatment response variability,Decreasing costs, no local reaction	(10)
Gupta (2013)	TAO	Allogenic/BM-MSCs	8.5×107	intravenous	18 days	Pain management, nor neither major nor minor amputation	(4)
Yang (2013)	CLI	Allogenic UCB-MSCs	5×105	intravenous	6 months	ABI index was not found, rise in average pain-free walking	(13)
Wang (2018)	CLI	Allogenic/BM-MSCs	250×106	Intramuscular	180 days	Injection of MSCs cannot induce revascularization , non-amputation survival rate 85%	(17)
Martin-Rafino (2018)	TAO	BM-MSCs	5×107	intravenous	10 months	No negative allograft rejection	(14)

Conclusion

Mesenchymal stem cell (MSC) therapy is entering a challenging phase after the completion of many preclinical and clinical trials. Among the major hurdles encountered in MSC therapy are inconsistent stem cell potency, poor cell engraftment and survival, and age/disease-related host tissue impairment. The recognition that MSCs primarily mediate therapeutic benefits through paracrine mechanisms independent of cell differentiation provides a promising framework for enhancing stem cell potency and therapeutic benefits. Once numerous preclinical and clinical trials have been completed, a challenging stage of MSC therapy occurs. The major MSC therapy hurdles include age/disease-associated host tissue impairment, low engraftment and survival rates, and stem cell potency inconsistency.

MSCs are recognized to be a mediator of therapeutic advantages through cell differentiation-independent paracrine mechanisms. This represents a promising framework to improve therapeutic advantages and stem cell potency. In clinical assessments, the selection of the best method could improve treatment efficacy. Several factors may be involved in the MSC injection efficacy of limb ischemia patients. First, a larger number of randomized patients should be employed in the selection of case groups. MSCs could be derived from different human sources; however, it is important whether MSCs are allogeneic or autologous. Both allogeneic and autologous exhibited positive results over placebo. However, it is should be mentioned that autologous MSC investigation has higher cost and toxicity. To reduce the toxicity of derived MSCs while injection, particularly in arterial and intravenous injection, different injection doses can be performed.

MI injection at different doses is the best method for diminishing the side effects. To investigate the final results, no examination shorter than six months is typically employed. For allogeneic injections, it is possible to continue follow-up for up to five years. To evaluate injection efficacy, different criteria can be adopted, including angiography, ABI index, ulcer healing and amputation, and pain-free walking distance. Research has shown that amputation reduces by 74-86% in limb ischemia patients by using allogeneic MSCs.

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Conflict of interest

There is no any kind of conflict of interest in this article.

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