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Cell Therapy for Ischemic Peripheral Neuropathy

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1. Introduction

Critical limb ischemia due to chronic peripheral arterial occlusive disease, such as arteriosclerosis obliterans and Buerger's disease (thromboangiitis obliterans), damages peripheral nerves and results in an ischemic neuropathy. Clinical and electro-physiologic features of ischemic neuropathy are sensorimotor polyneuropathy with axonal features as previously reported. In particular, symptoms of ischemic neuropathy include painful burning, sensory impairment, and reflex loss. Although ischemic peripheral neuropathy is a major complication of critical limb ischemia resulting in impaired quality of life, effective treatment for ischemic neuropathy is not available at present.

Recently, it has been reported that therapeutic angiogenesis using vascular endothelial growth factor (VEGF) gene transfer for critical limb ischemia improves ischemic neuropathy in animals or humans. Furthermore, Cuevas et al. reported that transplantation of bone marrow stromal cells improved peripheral nerve function in rats.

We reported that therapeutic angiogenesis using autologous transplantation of bone marrow mononuclear cells (BM-MNCs) for peripheral artery disease increased limb perfusion and improved clinical conditions, such as ischemic pain, claudication and ischemic ulcer. BM-MNCs contain various kinds of cell lineages, such as CD34⁺ cells or bone marrow stromal cells, in addition to various growth factors, such as VEGF. Thus, such cells or growth factors can work beneficially for ischemic peripheral neuropathy.

Therefore, in this chapter, we tried to clarify whether cell therapy with autologous transplantation of BM-MNCs improves ischemic neuropathy with critical ischemic limb in humans.

2. Patients and methods

2.1 Study subjects

We prospectively examined 39 patients having chronic bilateral critical limb ischemia, defined as angiographic documentation of severe large artery stenosis or occlusion associated with limb pain at rest and/or non-healing ischemic ulcers. All the patients fulfilled the inclusion criteria and did not have any exclusion criteria for therapeutic angiogenesis using BM-MNCs as described previously. Briefly, they were not candidates for non-surgical or surgical revascularization. We excluded patients with poorly controlled diabetes mellitus (HbA1C>6.5% and proliferative retinopathy) or with evidence of malignant disorder for the

past 5 years. Furthermore, patients in whom neurological scales could not be evaluated due to huge ulcer or limb amputation were excluded. Finally, 14 patients undergoing autologous transplantation of BM-MNCs were enrolled in this study. Age and sex matched 23 healthy volunteers were served as controls to examine neurophysiologic scales (Healthy group). The protocol was approved by the Institutional Ethic Committee of the Kurume University. Written informed consent was obtained from all subjects.

2.2 Collection and transplantation of BM-MNCs

Bone marrow cells were collected from the iliac crest under general anesthesia. We sorted mononuclear cells on CS-3000 blood-cell separator (Baxter, Deerfield, USA) by a density gradient centrifugation method and concentrated them to a final volume of about 30ml immediately after aspiration. We injected the cells with 26-gauge needle into the gastrocnemius muscle of the more ischemic limb (treated limb), and injected saline into the opposite limb (control limb). We injected about 0.5ml of BM-MNCs or saline into each injection site (50 sites, 1-1.5cm deep).

2.3 Clinical features

The severity of rest pain was described and scored by patient from 0 (none) to 10 (maximum) points using visual analogue scale (VAS). Pain free walking distance was separately measured twice as ischemic status before and 4 weeks after transplantation of BM-MNCs. Also, the detailed nature of pain was recorded to exclude symptoms that could be attributable to tissue ischemia rather than neuropathy. To distinguish neuropathic symptoms from ischemic ones, numbness, painful burning, and paresthesia in the toes of foot were defined neuropathic in origin. We excluded symptoms when they exclusively appeared during walk or by use (i.e. foot elevations). Two examiners evaluated the neurological scales. The examiners were blinded to the findings of patients' clinical profile, treatment and to each other's results. The existence of neuropathic symptom was described and scored by the patient from 0 to 1 point (0=without neuropathic symptom, 1=with neuropathic symptom) as neurologic sensory score (NSS). We tested untreated limb to assess the natural course of the disease as control limb. Each patient was evaluated 1 week before and 4 weeks after treatment.

2.4 Neurophysiologic scales

Two examiners evaluated the neurological scales. The examiners were blinded to the findings of patients' clinical profile, treatment and to each other's assessment. Conduction studies were performed using techniques described elsewhere (Neuropack MEB-2200, Nihon Kohden Co. Ltd, Japan). Briefly, motor nerve conduction velocities (MNCV) of the tibial nerve were measured. Tibial compound muscle action potentials (CMAP) were also recorded with surface disk electrodes from the abductor hallucis. Sensory nerve conduction velocities (SNCV) or sensory nerve action potentials (SNAP) of the sural nerve were measured. All determinations were made with the patient supine and at the surface temperature between 29-32°C. The same examiner using the identical anatomical landmarks and distances performed repeated studies after treatment. Quantitative vibration threshold time (QVT) was measured using standard techniques by a tuning fork to determine the thresholds of vibration in the legs. We performed these neurophysiologic testing before and 4 weeks after treatment. We also measured MNCV, SNCV, CMAP and SNAP of the healthy group at baseline.

2.5 Assessment of blood flow

We measured ankle brachial pressure index (ABPI) 1 week before and 4 weeks after implantation, the ratio of simultaneously measured systolic pressure of brachial and posterior tibial arteries (ABI-form, Colin, Japan). Digital subtraction angiography (DSA) was performed with the strictly fixed amount of contrast agent, force of contrast injection, and position of the catheter tip at 1 week before and 4 weeks after transplantation. Two radiologists who were blinded to treatment evaluated collateral vessels independently. Angiograms were assessed when contrast flow in the main conducting arteries was most clearly visible. Angiographic evaluation was presented as changes in DSA score: 3+ (rich collateral development), 2+ (moderate), 1+ (slight), 0 (no changes), and 1- (decreased).

2.6 Statistical analysis

Data were expressed as mean \pm SD. Differences between the two groups were analyzed by paired or unpaired Student's *t* test when appropriate. Univariate correlations were analyzed by a Pearson's correlation. Differences with a $p < 0.05$ were considered statistically significant.

3. Results

3.1 Patient's characteristics

Patient's characteristics are shown in Table 1. Nine patients were Buerger's disease and 5 ASO. They all had undergone optimal medical or surgical treatment prior to this study. The average numbers of transplanted mononuclear cells of CD34 positive cells were $4.89 \pm 5.21 \times 10^9$ and $5.46 \pm 4.25 \times 10^7$, respectively (Table 1). During follow up period, no one had major adverse event, such as any cause of death and cardiovascular event.

Patient	Age (y.o.)	sex	Diagnosis	No. of MNCs ($\times 10^9$)	No. of CD34 ⁺ cells ($\times 10^7$)
1	67	M	TAO	2.58	2.63
2	29	M	TAO	2.9	8.48
3	72	F	TAO	1.07	0.92
4	69	M	ASO	1.83	6.82
5	43	M	TAO	4.14	7.18
6	63	M	ASO	1.39	1.17
7	75	M	ASO	1.70	5.03
8	40	M	TAO	5.12	17.05
9	61	M	TAO	13.5	3.3
10	50	M	TAO	16.90	6.5
11	62	M	TAO	11.9	8.3
12	78	M	ASO	1.80	2.9
13	55	F	TAO	2.38	5.1
14	65	F	ASO	1.20	1.1
mean \pm SD	59.2 \pm 14.2			4.89 \pm 5.21	5.46 \pm 4.25

Abbreviations y.o.: years old, M: male, F: female, MNCs: mononuclear cells, TAO: thromboangiitis obliterans, ASO: arteriosclerosis obliterans

Table 1. Patients characteristics and number of implanted cells.

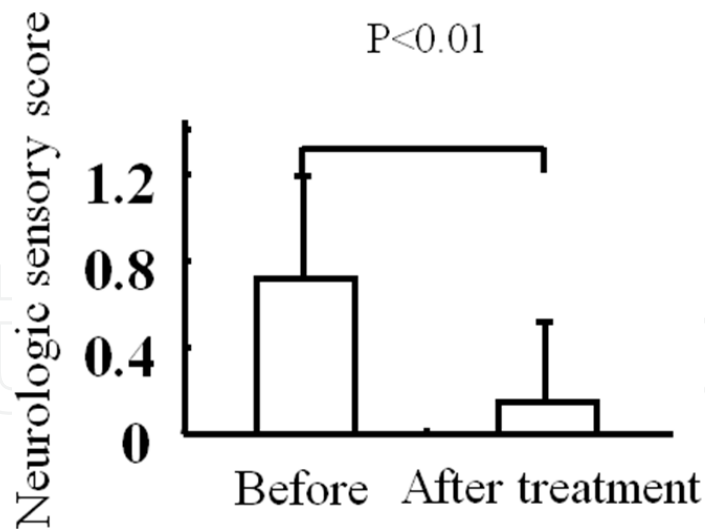
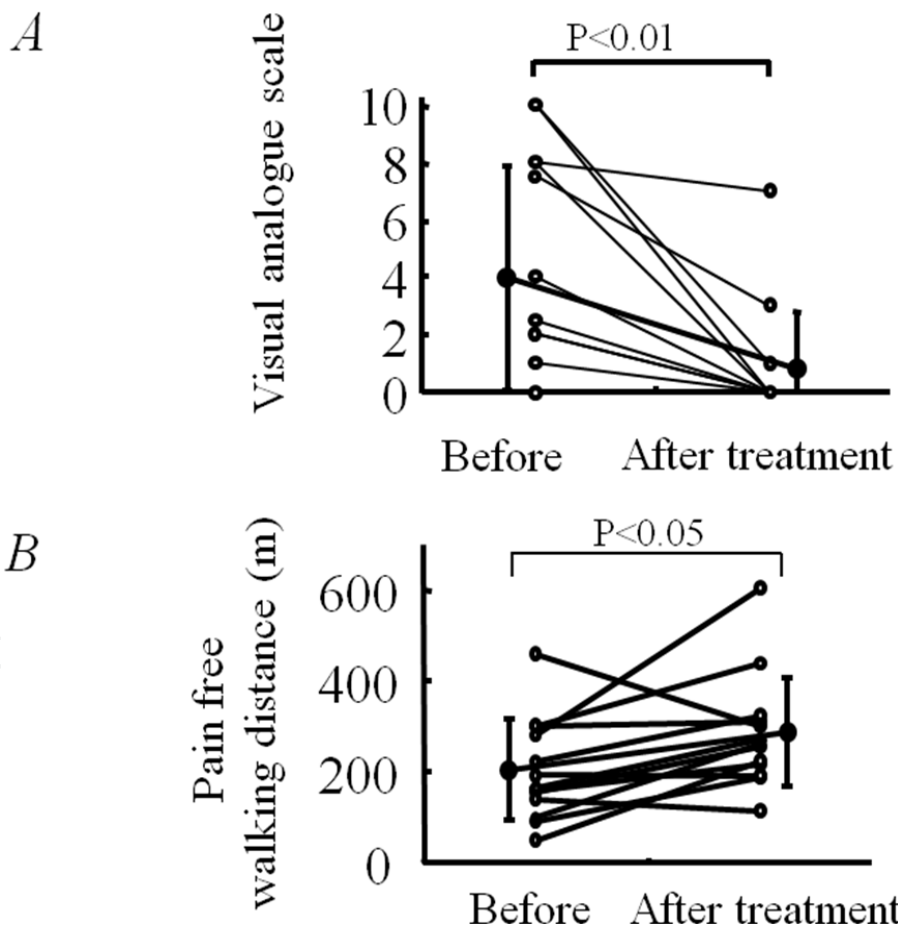


Fig. 1. Neurologic sensory score.



Panel A: Visual analogue scale significantly decreased one month after autologous transplantation of BM-MNCs.

Panel B: Pain free walking time significantly increased one month after autologous transplantation of BM-MNCs.

Open circles indicate individual value. Closed circle indicate average value.

Fig. 2. Improvement of ischemic symptoms.

3.2 Subjective symptoms

Before treatment, 10 of 14 patients (71.4%) had neuropathic symptoms with average NSS of 0.71 ± 0.47 (Figure 1). Four weeks after treatment, only 2 patients had neuropathic symptoms, and averaged NSS was decreased to 0.14 ± 0.36 ($p < 0.01$ vs. before treatment, Figure 1). VAS significantly improved (3.93 ± 3.92 to 0.79 ± 1.79 , $p < 0.01$, Figure 2A) after treatment. Pain free walking distance significantly increased (201 ± 110 to 317 ± 197 , $P < 0.05$, Figure 2B) after treatment

3.3 Nerve functions

MNCV and CMAP could be measured in the treated limb of all patients, and in the control limb of 12 patients. SNCV and SNAP could be measured 11 of 14 patients in the treated limb, and 10 of 14 patients in the control limb. Figure 3 shows the representative waveform of MNCV and CMAP before and one month after treatment. Before treatment, both MNCV and CMAP were significantly smaller in the treated limb than those in the healthy group (Table 2). Treatment significantly increased both MNCV and CMAP only in the treated limb (Table 2) but not in the control limb. MNCV was recovered to the level of healthy group but CMAP was still depressed after transplantation of BM-MNCs (Table 2). SNCV and SNAP of the patients did not differ to those of the healthy group. SNCV and SNAP were not improved by treatment (Table 2). QVT was significantly improved only in the treated limb, but not in the control limb after treatment (Table 2).

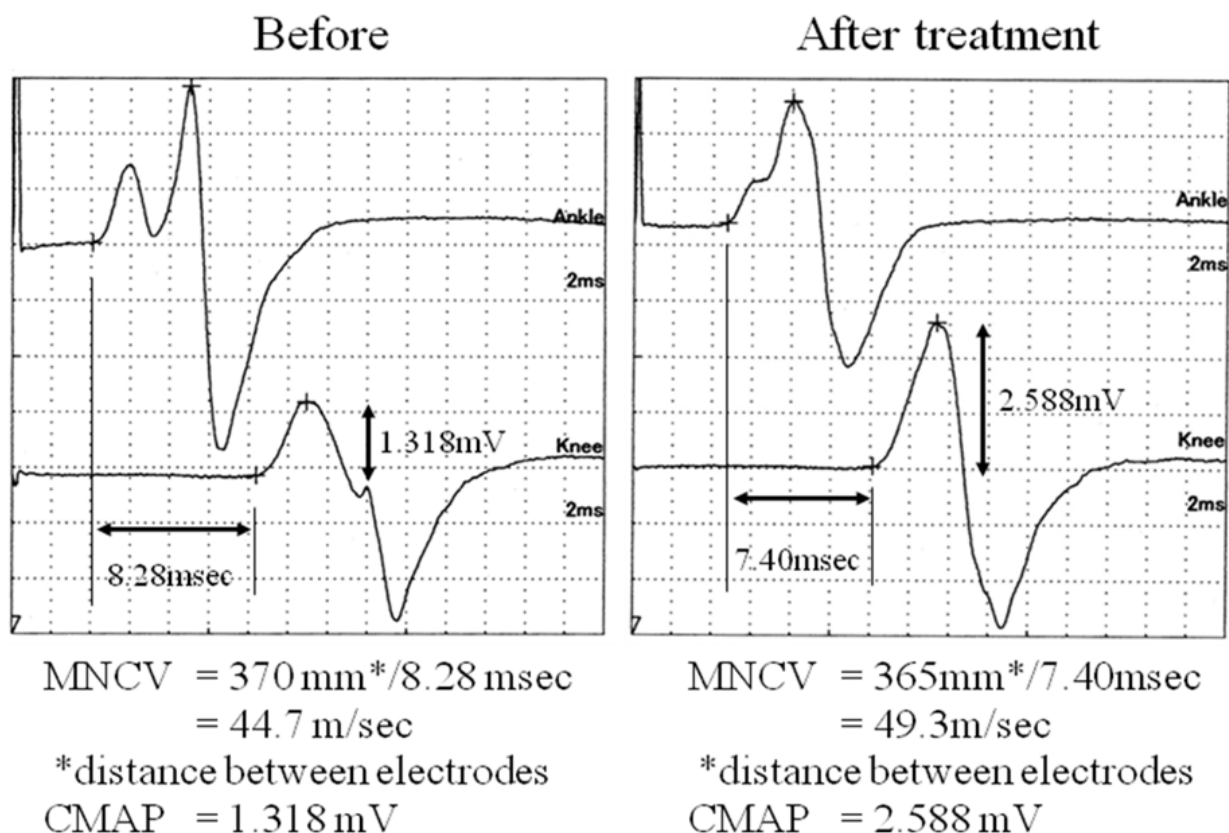


Fig. 3. Representative waveforms of MNCV and CMAP. MNCV and CMAP increased one month after autologous transplantation of BM-MNCs.

Nerve function	Healthy group N=23	Patients N=14			
		before	after	before	after
		Control limb		Treated limb	
MNCV (m/sec)	50.4±6.94	47.3±3.0	44.8±3.0	41.1±6.5**	43.9±6.2
CMAP (mV)	5.3±2.8	4.9±4.3	5.2±5.2	2.3±2.7*	3.6±3.5¶*
SNCV (m/sec)	50.0±10.7	49.5±3.7	48.3±4.5	46.8±4.3	46.5±4.9
SNAP (µV)	10.2±8.9	8.4±2.1	8.6±3.1	7.6±3.8	8.7±4.4
QVT (sec)	NM	10.5±3.2	11.1±4.0	9.2±2.7	11.5±3.5

Values are expressed as mean±SD. Differences between the two groups were analyzed by paired or unpaired Student's t test. Univariate correlations were analyzed by a Pearson's correlation.

Abbreviations VAS: visual analogue scale, MNCV: motor nerve conduction velocity, CMAP: compound muscle action potential, SNCV: sensory nerve conduction velocity, SNAP: sensory nerve action potential, QVT: quantitative vibration threshold time. N/A: not available, NM: not measured, SD: standard deviation

*: p<0.05 vs. healthy group, **: p<0.01 vs. healthy group, ¶: p<0.05 vs. before treatment, :p<0.01 vs. before treatment.

Table 2. Effects of nerve functions. (Based on data originally presented by Arima, K. et al.).

3.4 Assessment of blood flow

Before treatment, ABPI was significantly decreased in the treated and control limbs. After treatment, ABPI was significantly increased only in the treated limb (0.59±0.24 to 0.70±0.20, P=0.035), but not in the control limb (0.89±0.20 to 0.89±0.20, N.S.). DSA score in the treated limb was significantly increased after treatment (0.0±0.0 to 0.86±0.77, p<0.05, Figure 4).

4. Discussion

The major findings of this study are the following two. First, autologous transplantation of BM-MNCs significantly improved subjective ischemic and neuropathic symptoms in patients with critical limb ischemia. Second, autologous transplantation of BM-MNCs improved not only peripheral blood perfusion but also peripheral nerve function.

4.1 Neuropathy in patients with critical limb ischemia

Several studies have reported neuropathy at the frequency of 5-31% in patients with chronic and critical limb ischemia. The mechanisms of neuropathy in patients with limb ischemia are multifocal because they have frequently have associated disease like diabetes mellitus. Weinberg et al reported that the degree of ischemia, as estimated with ABPI, correlated with clinical neuropathy. Thus it is suggested that limb ischemia is the major factor of peripheral neuropathy in patients with critical limb ischemia.

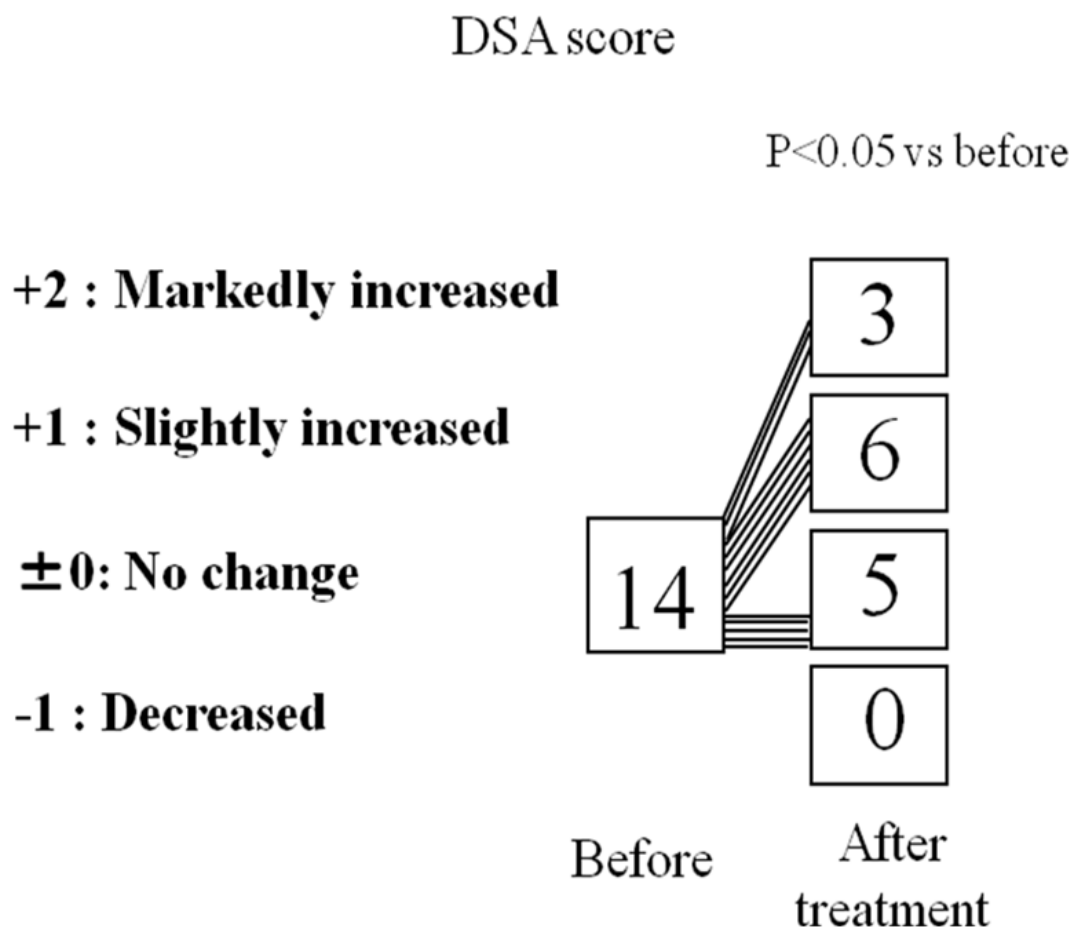


Fig. 4. Time course of DSA score after autologous transplantation of BM-MNCs in the treated limb. In the treated limb, DSA score significantly improved one month after autologous transplantation of BM-MNCs ($P<0.05$). DSA indicates digital subtraction angiography.

In this study, our patients had not only ischemic symptoms (rest pain and claudication) but also neuropathic symptoms. Because ABPI was significantly decreased and because we excluded patients with diabetes mellitus, we think the nature of neuropathic symptoms is related to limb ischemia. Furthermore, nerve function in the patients was severely impaired compared with the healthy group. Thus, the etiology of peripheral neuropathy in our patients was probably ischemic in its origin. Although our patients had bilateral limb ischemia, the nerve function at baseline was impaired only in the treated limb. The reason is not clear at present but the difference in the severity of limb ischemia may explain it.

Apart from MNCV or CMAP, SNCV and SNAP of ischemic limb before treatment were similar to those of healthy subject. The reason of such different effect of limb ischemia on motor and sensory nerves is unknown, but may be due to the size of nerve fibers. The size of motor nerve (5-15 micrometer) is larger than sensory nerve (0.5-13 micrometer). Previous pathologic studies reported that decrease in the population of large myelinated fibers was observed in ischemic peripheral neuropathy. The damage of nerve fiber may be smaller for the sensory nerve than the large motor nerve in the presence of ischemia, which may account for the preserved SNCV and SNAP.

4.2 Autologous transplantation of BM-MNCs improved neuropathy

Recently, we reported that autologous transplantation of BM-MNCs increased limb perfusion and improved symptoms and ulcers in human ischemic limb. In this study, we confirmed our previous findings that autologous transplantation of BM-MNCs significantly improved ABPI and DSA score in treated limbs. This treatment significantly improved not only ischemic pain (VAS, pain free walking time) but also neuropathic symptoms. Furthermore, transplantation of BM-MNCs significantly improved objective peripheral nerve functions (MNCV, CMAP and QVT) in the treated limb, but saline injection did not affect the nerve functions. These results indicated that the effects of the treatment were not related to natural course or non-specific effects. Thus, it is concluded that autologous transplantation of BM-MNCs improved not only peripheral blood perfusion but also ischemic peripheral neuropathy.

4.3 Mechanisms of improvement of peripheral neuropathy

The several mechanisms may contribute to the improvement of peripheral nerve function. First, the improvement may be caused by better blood perfusion after autologous transplantation of BM-MNCs. On this issue several conflicting results were reported.

There were several therapeutic strategies for improving blood perfusion, such as surgical revascularization or therapeutic angiogenesis induced by VEGF gene transfer. Hunter et al. examined electrophysiological changes of nerves after surgical revascularization. They reported no improvement of multiple electrophysiological outcome measures after surgical revascularization, suggesting that ischemic neuropathy may be an irreversible condition. On the other hand, Simovic et al. reported that VEGF gene transfer improved the neuropathic symptoms, CMAP and QVT, but not nerve conduction velocity. They speculated that the differences of efficiency between surgical revascularization and VEGF gene transfer were related to the size of restored vessels after treatments. In fact, surgical revascularization mainly restores blood flow of large vessels, and neovascularization from angiogenic cytokines, such as VEGF, principally involves small vessels including the vasa-nervorum (<180 micrometer), the nutrient arteries of peripheral nerves. Furthermore, it is reported that VEGF gene transfer improves peripheral nerve perfusion and function through regeneration of vasa-nervorum in rats with streptozotocin-induced diabetes. In this study, electrophysiological study showed improvement of nerve functions in addition to neuropathic symptoms. It is reported that variety of cytokines, such as VEGF, are contained in transplanted bone-marrow fluid or secreted by transplanted BM-MNCs. Thus, such various angiogenic cytokines might have improved nerve perfusion and function in this study.

Second, nerve regeneration might have occurred after transplantation of BM-MNCs. It is reported that VEGF also has regenerative and protective function for peripheral nerve. Furthermore, Cuevas et al. reported that implantation of bone-marrow stromal cells improved peripheral nerve function via nerve regeneration in animals. They reported that implanted cells participated in nerve regeneration through their differentiation in Schwann-like cells and also in the production of trophic factors. Because transplanted BM-MNCs used in this study presumably contain various kinds of cells such as bone-marrow stromal cells as previously reported, it may be speculated that transplantation of BM-MNCs might have regenerated the damaged peripheral motor nerve. Of course, we have no evidence.

Limitations of this study need to be addressed. First, this study was an observational open-label study with no placebo control group. Next, the number of patients enrolled in this

study was small. Further large sized controlled clinical study is needed to confirm our findings. Finally, we treated patients with critical limb ischemia who had undergone optimal medical and surgical treatment. Thus, it is not known whether autologous transplantation of BM-MNCs is effective for the earlier stage of patients.

5. Conclusions

In conclusion, these results suggested that cell therapy with autologous transplantation of BM-MNCs improves ischemic neuropathy with critical ischemic limb in humans.

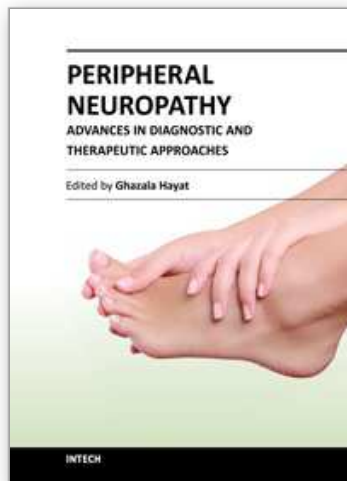
6. Acknowledgement

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Peripheral Neuropathy - Advances in Diagnostic and Therapeutic Approaches

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Over the last two decades we have seen extensive progress within the practice of neurology. We have refined our understanding of the etiology and pathogenesis for both peripheral and central nervous system diseases, and developed new therapeutic approaches towards these diseases. Peripheral neuropathy is a common disorder seen by many specialists and can pose a diagnostic dilemma. Many etiologies, including drugs that are used to treat other diseases, can cause peripheral neuropathy. However, the most common cause is Diabetes Mellitus, a disease all physicians encounter. Disability due to peripheral neuropathy can be severe, as the patients suffer from symptoms daily. This book addresses the advances in the diagnosis and therapies of peripheral neuropathy over the last decade. The basics of different peripheral neuropathies is briefly discussed, however, the book focuses on topics that address new approaches to peripheral neuropathies.

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