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Editorial

Prevention of Amputation among the Cases of Chronic Critical Limb Ischaemia with Limited Treatment Option: Current Modalities of Therapy and Future Perspectives

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Received: July 15, 2020; **Published:** July 29, 2020

Peripheral arterial disease (PAD) is a chronic vascular disease where blood flow in the limb arteries is obstructed [1,2]. The chance of PAD increases as age advances and affects a considerable proportion of the elderly population (> 20% in > 80-year old individuals) [3]. The overall prevalence of PAD among the general population has been found to be 12 - 14%, affecting up to 20% of those over 70 [4]. Worldwide, PAD was estimated as 202 million and 236.62 million in 2010 and 2015 respectively [5].

Major subtypes of PAD are Atherosclerotic Obliterans (ASO), Buerger's disease (Thromboangiitis Obliterans, TAO) and PAD due to connective tissue diseases. TAO is strongly associated with cigarette smoking. Underlying risk factors leading to ASO are older age, hypertension, cigarette smoking, hyperlipidemia and/or diabetes mellitus. According to the current recommendations, to prevent vascular damage and improve functional status, patients with PAD should receive an intensive program of guideline-based medical therapy including structured exercise and lifestyle modifications. Symptomatic PAD patients are needed to take antiplatelet therapy with either aspirin alone (range, 75 - 325 mg/day) or clopidogrel alone (75 mg/day) [6]. All patients with PAD should be treated with a statin medication [6]. Patients with PAD who smoke cigarettes or use any other forms of tobacco should be counseled at every visit to quit. For patients with symptoms of claudication, Cilostazol is an effective initial therapy to improve symptoms and increase walking distance [6]. Unfortunately, even with all conservative measures, many of those patients progress towards severe rest pain and/or limb ulceration. When severe rest pain and/or ulcerations of ischemic limbs are developed, this is defined as the state of chronic critical limb ischaemia (CLI). Chronic CLI is associated with a high risk of major amputation, cardiovascular events and death. Around 25% of the patients require amputation within a year after the onset of chronic CLI [7].

Endovascular procedures in the form of angioplasty & stenting and open surgical bypass are considered among the cases of chronic CLI. The development of a drug-eluting stent has been playing a role to reduce restenosis events. However, surgical bypass, angioplasty and stenting can be done only in major arteries and therefore cannot do optimal correction of peripheral vasculatures. Despite the poor prognosis, only half of PAD patients are suitable for the current standard of care. Due to complex vascular anatomies and/or co-morbidities, remaining patients are ineligible to receive standard treatment modalities. Those patients with chronic CLI who are selected to receive endovascular therapies, a significant proportion of them are still at risk of amputation in subsequent years. Therefore, further strategies are needed to prevent amputation among the cases of PAD with Chronic CLI.

Tateishi-Yuyama., *et al*. first reported the beneficial effects of autologous bone marrow mononuclear cell implantation (BMMNC-I) among the cases of Chronic CLI who are indicated for amputation [8]. Long term follow up study done by Therapeutic Angiogenesis by Cell Transplantation (TACT) trial in Japan shows higher major amputation free survival (MAFS) among the cases of PAD after autologous

BMMNC-I [9]. The 10-year overall survival (OS) was 46.6% in patients with ASO (n = 168), 90.5% in TAO (n = 108) and 67.6% in patients with collagen disease-associated vasculitis (CDV) (n = 69) whereas 10-year MAFS was 70.1%, 87.9%, and 90.9%, respectively [9]. PAD due to TAO patients have significantly higher limb salvage compared to ASO patients in this study. Our study similarly reveals that BMMNC-I significantly improves overall major amputation free survival (MAFS)among the cases of PAD with Chronic CLI and TAO patients have significantly higher limb salvage compared to ASO patients [10,11]. Our study additionally revealed that BMMNC-I was not effective among the PAD patients with end stage renal failure undergoing haemodialysis [10,11]. The overall MAFS were 73.0% at 5 years and 70.4% at 10 years in atherosclerotic PAD patients with Chronic CLI after BM-MNC-1 [11]. The overall MAFS at 5 years and at 10 years was significantly higher in atherosclerotic PAD patients with BMMNC-I than historical controls [11]. Studies done by Higashi Y et. al revealed that autologous BMMNC-I improved endothelium dependent vasodilatation [12] Currently BMMNC-I is an accepted mode of therapy for TAO patients with Chronic CLI under advanced insurance program in Japan.

Therapeutic angiogenesis by autologous BMMNC-I among the cases of chronic CLI is thought to be associated with paracrine effect of bone marrow cells rather than differentiation of bone marrow stem cells to vascular endothelial cells. Therefore, cells with higher regenerative potentials can be one of the options to improve cell therapy for the patients with chronic CLI. Embryonic stem cells have proven pluripotent characteristics; however, risk of malignancy, inherent allogenicity and ethical issues are major obstacles [13,14]. Induced Pluripotential (iPS) cells are another cell type with a proven capacity to differentiate into different cell lineage. Allogenicity and time consumption for the preparation of iPS cells are several hurdles in cases of urgent necessities [14]. Umbilical Cord Blood (UCB) stem cells have been used in haematology for more than four decades. UCB cells possess some degree of capability to differentiate into various cell lineage and tissue types. Due to proven safety record UCB cells could be one of the options to improve cell based therapies. Adipose tissue derived regenerative cells (ADRC) are another promising cell type that can be used in regenerative medicine and chronic CLI. Usage of UCB cells and ADRC do not need complex bone marrow harvesting procedures with the direct involvement of patients. Studies done on clinical subjects by UCB cells and ADRC showed optimism among the cases of chronic CLI [15,16], however, study with a larger number of patients and longer follow up is needed to validate the initial promising outcome.

Bone marrow derived mesenchymal stem cells (BMMSC) have been used to treat patients with chronic CLI [17]. BMSC can be used in an autologous and allogeneic manner [17]. Due to low allogenicity and expected safety and higher capabilities to produce different cell lineage, BMSC can be one of the options to improve cell therapy. Most of the cell therapy trials used once only stem cell injection protocol. The outcome resulting from repeated injection of BMMNC-I is not clear. Therefore, during the bone marrow harvesting procedure, BMMSC can be collected at the same time. And it could be interesting to use BMMNC plus BMMSC injection to improve outcomes among the cases of CLI.

Gene therapy has been explored among the cases of CLI. Various gene including fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), hypoxia inducible factor 1 (HIF-1), and hepatocyte growth factor (HGF) have been tested. The initial encouraging results showed by FGF leaded towards Phase 3 trial. However, Phase 3 TAMARIS trial failed to reveal a significant difference in MAFS compared with placebo in patients with chronic CLI (63% in the treatment group vs 67% in the placebo group) [18,19]. Several clinical trials have subjected HGF plasmid in the treatment of patients with chronic CLI and not suitable for revascularization. Although Early Phase 2 trials have shown that HGF can improve transcutaneous oxygen pressure and pain scores in patients with CLI compared with placebo, but this did not result in improved MAFS [20].

Platelet rich plasma (PRP) has been shown to be beneficial for wound healing and limb salvage [21]. PRP harbours a milieu of various growth factors and cytokines, thereby thought of directly producing benefit for those patients [21]. Further studies with a higher number of patients are needed to establish the utility of PRP among the cases of chronic CLI.

Hyperbaric Oxygen Therapy (HBOT) has been found to be effective in cases of non-healing ulcers by promoting tissue oxygen concentration, aerobic metabolism, fibroblast proliferation, collagen synthesis and inducing liberation of angiogenic factors [22]. HBOT inhibits

bacterial growth (particularly anaerobes), generates free radicals that destroy bacterial cellular structures, and improves the oxygen-dependent transport of antibiotics and thus reduce incidences of superimposed infections [23]. In 2015, a Cochrane review on the role of HBOT in healing concluded that HBOT increased the rate of ulcer healing in diabetic foot ulcers at 6 weeks but not at longer term follow-up, with no significant difference in the risk of major amputation [24].

Among the noninvasive tools to treat CLI, Low intensity pulsed ultrasound (LIPUS) is one of the recent encouraging development [25]. Ultrasound technique has been used in modern medicine for diagnostic and several therapeutic purposes for quite a long time. Recent studies reveal that LIPUS accelerates angiogenesis in the animal model. Several multicentres, double blind clinical trials are underway to evaluate the efficacy of LIPUS among the patients with PAD.

In conclusion, cell and gene based therapies along with noninvasive tools like HBOT and LIPUS produce an optimism to prevent amputation among the cases of chronic CLI. However, further studies with an increased number of patients and longer follow-up are needed to consolidate initial promise shown by those studies.

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Volume 3 Issue 8 August 2020