

Application of 3D Printing Insole by Hemodynamics in Older Patients with Critical Limb Ischemia: Protocol for a Randomized Clinical Trial

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Introduction: Critical limb ischemia (CLI) is a severe condition characterized by inadequate blood flow to the lower extremities, often leading to tissue damage and amputation. CLI is characterized by microcirculatory dysfunction, muscle tissue necrosis, and inflammation. Patients may suffer from the traumatic pain and the increase of plantar pressure, and foot care for patients with CLI has become the “last mile” to improve their life quality. Traditional shoe insoles often lack individual customization, failing to address the unique anatomical needs and hemodynamic characteristics of patients. The study aims to investigate the effects of this innovative intervention on improving the clinical outcomes, and quality of life in CLI patients.

Methods and Analysis: This Critical Limb Ischemia Hemodynamic Insole Study is a randomized controlled study performed to explore the effect of a 3D printing insole on foot care of CLI patients. This study recruitment began on November 1, 2021. Patients with CLI confirmed by clinical symptoms and imaging were recruited as the research objects. Participants will be randomly assigned to either the experimental group, which will receive 3D-printed insoles customized based on their hemodynamics, or the control group, which will receive traditionally manufactured insoles. Both groups were followed up for up to 24 months after surgery, including claudication distance, claudication time, pain score, rehospitalization, etc.

Trial Registration Number: ChiCTR2100051857.

Keywords: 3D printing, insole, hemodynamics, critical limb ischemia

Introduction

Critical limb ischemia (CLI) refers to a condition in which patients with peripheral artery disease experience severe ischemia in their limbs due to inadequate blood supply. It is characterized by rest pain, ulcers, or gangrene.^{1,2} With the prolongation of life span and the increase of patients with peripheral artery diseases, patients with severe lower limb ischemia often suffer from severe pain, which leads to the loss of walking function and the decline of quality of life, causing great burden to patients, families and society.³ Foot ulcer is one of the most common chronic complications in patients with severe lower limb ischemia. Ulcer often involves fascia and tendon and is highly invasive, changes quickly, has a long course of disease, and is not easy to heal.⁴ It is an important cause of disability and death of patients.⁵ About 10%–20% of CLI patients finally underwent lower limb amputation due to severe foot ulcer. Although life was saved, normal walking ability was seriously affected.⁶ The foot care for patients with lower limb ischemia has become the “last mile” to improve CLI patients and one of the important links to reduce the health and economic burden of CLI patients. The formation of foot ulcer in patients with severe lower limb ischemia is related to many factors: vascular disease and ischemia, peripheral neuropathy and changes in plantar pressure.^{7,8}

CLI patients suffer from the trauma pain and the plantar pressure increases.⁹ In daily exercise, the plantar force is uneven, the local hemodynamics is abnormal, and the foot is damaged due to repeated friction, which eventually leads to

foot ulcer. At present, most of the nursing care for CLI patients with foot ulcers is from the aspects of diet, psychology, skin care, etc.¹⁰ A considerable number of patients failed to correct abnormal high foot pressure and conduct lower limb vascular assessment within one year after surgery. Many patients with severe lower limb ischemia had a long waiting time before intervention, which greatly affected their quality of life after surgery.¹

To enhance the quality of life of patients with foot ulcer, it is crucial to take real-time physiological indicators in to account and develop corresponding nursing strategies based on these indicators.⁸ As the most commonly used and closest nursing product for feet, accurate customized shoe insoles are an important means of nursing intervention, taking full account of the pathological characteristics and recovery of patients with foot ulcer CLI.¹¹ Therefore, for CLI patients with foot ulcer, in order to prevent or delay the occurrence and development of complications, effectively reduce the amputation rate, and improve their quality of life.¹² We need to design customized insoles that meet the requirements of personalized treatment and formulate corresponding follow-up evaluation design adjustment programs based on the basic conditions of CLI patients. Combined with the real-time postoperative dynamic evaluation of foot ischemia and ulcer pathophysiological indicators.

This protocol presents a randomized clinical trial aimed at evaluating the potential benefits of using 3D-printed insoles designed with hemodynamics in mind for patients suffering from CLI. The study aims to investigate the effects of this innovative intervention on improving the clinical outcomes, and quality of life in CLI patients.

Methods and Analysis

The 2016 AHA/ACC guidelines on the management of patients with CLI recommend that imaging be performed to assess revascularization options, such as duplex ultrasonography, computed tomography angiography (CTA), magnetic resonance angiography (MRA), or catheter-based angiography. Traditional treatment methods include endovascular intervention therapy, vasoactive drug therapy, and chronic disease management.^{13,14}

In this study, we first plan to use 3D printing technology guided by ultrasound hemodynamics. The 3D printed insole adopts double-layer printing, consisting of two layers of flexible materials: the first layer is a flexible shock absorbing material, poron foam material insole, and the second layer uses thermoplastic polyurethane (TPU) as the insole material based on hemodynamic results and wound range. Using a 3.5-inch high-definition touch screen with isun3D dual station-independent printer to control end material detection. Select appropriate materials and tailor the decompression insole for patients with severe lower limb ischemia to correct the foot ischemia of patients with severe lower limb ischemia foot ulcer. In order to meet the above requirements, it is necessary to use the patient's CTA imaging data to generate a 3D printed insole through 3D printing. By monitoring the ultrasonic hemodynamic parameters of plantar artery in patients with severe lower limb ischemia at 1, 3, 6 and 12 months after operation. Finally, the design of insole was adjusted according to the personalized parameters.

Based on literature reports and our previous retrospective research results, it is estimated that the average SF-36 score for CLI in the control group is 64 points. Through the preparation and application of 3D personalized insoles, the average 36-SF score for severe lower limb ischemia foot ulcers is 78 points, with a first class error of 0.05 and an efficiency of 80%. Considering a 10% loss of follow-up rate, a total of 68 cases were included in the study group and the control group were allocated 1:1.

The Critical Limb Ischemia Hemodynamic Insole Study is a randomized controlled study performed by nursing department of Shanghai Ninth People's Hospital Affiliated to Shanghai JiaoTong University School of Medicine. This study recruitment began on November 1, 2021. Patients with CLI confirmed by clinical symptoms and imaging (ultrasound, computed tomography angiography (CTA), or digital subtraction angiography (DSA)) were recruited as the research objects.

Randomized grouping was used to divide them into intervention group given 3D insole and routine nursing group. Both groups were followed up for up to 24 months after treatment, including claudication distance, claudication time, pain score, SF-36 score, AOFAS score, and rehospitalization rates after surgery, etc. As the protocol differs slightly for the two groups, some study procedures are described separately by group.

Eligibility Screening

The screening process for both study groups takes place when an eligibility checklist and screening log form is completed by study personnel while screening the patient's electronic medical record for verification of eligibility criteria (Table 1).

Table 1 Eligibility Criteria for Study

Randomized Control Group/ Routine Group	Inclusion Criteria	Exclusion Criteria
Patients with CLI confirmed by clinical symptoms and imaging (ultrasound, CTA, or DSA)	• ABI index ≤ 0.4 or ankle pressure $< 40-50$ mmHg, with or without severe lower limb ischemia; • Able to walk independently; • Age: 60–80 years old, regardless of gender; • Those who are willing to participate in the research of this project and sign the informed consent form.	• Walking instability caused by central diseases and other reasons; • CTA and DSA confirmed that there was no occlusion of the lower limb arteries; • Have amputation history; • Severe heart and lung insufficiency, affecting walking; • Those who participate in other projects at the same time or are unwilling to participate in this project or to sign the informed consent form; • Those who cannot complete follow-up.

When the patient was admitted to the hospital, he received various basic data collection and completed ABI examination. Qualification check form and screening form shall be filled in by researchers. Each enrolled patient will create a CRF table, generate a study ID number, and create a study record. Eligibility status for consented participants is reviewed and certified by the principal investigator within 1 month of consent (Figure 1).

Overview of Study Protocol

The foot model was obtained by CT foot scanning and 3D reconstruction scanning data of the foot, and the foot hemodynamic parameters were collected to complete the preparation of 3D printed insole. In a prospective randomized controlled study, participants will be randomly assigned to either the experimental group, which will receive 3D-printed insoles customized based on their hemodynamics, or the control group, which will receive traditionally manufactured insoles.

In the chronic recovery phase of patients with lower limb ischemia, the former group received personalized treatment with 3D printed insoles guided by hemodynamic monitoring, along with nursing care management. In contrast, the latter

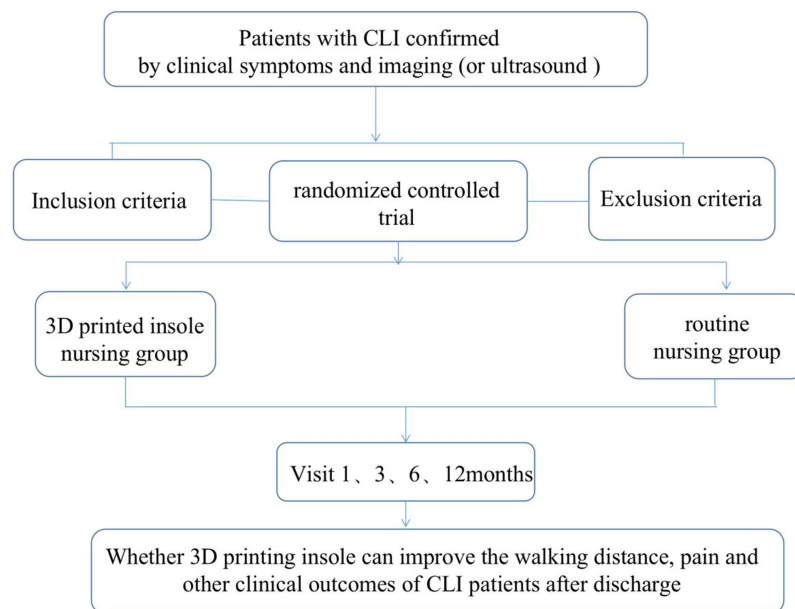


Figure 1 Clinical experiment process: patients were divided into two groups according to screening after admission, and follow-up in 1, 3, 6 and 12 months.

group received routine nursing care management in the chronic rehabilitation period after discharge of lower limb ischemia patients.

The daily number of steps walked, ultrasound foot hemodynamic indexes, and the number, location and area of foot ulcers of the two groups were recorded in the follow-up 30 days $\pm$ 7 days, 90 days $\pm$ 10 days, 180 days $\pm$ 30 days and 360 days $\pm$ 30 days after discharge to clarify the effect of preventing and treating foot ulcer in patients with severe lower limb ischemia.

Follow-Up

The current situation of patients with CLI after operation was investigated. Improve data collection and follow-up. Record the plantar pressure and hemodynamic data during each follow-up, observe the ulcer and adjust the insole in time. Before discharge, the nursing management team establishes a WeChat group to communicate through voice messages, pictures, videos, and other means. Every Monday and Thursday at a fixed time, disease-related content will be pushed to the WeChat official account. If patients encounter any issues, the nursing management team can communicate and resolve them on WeChat at any time. They also request patients to continue recording the wound care situation in the self-care management manual after discharge. After discharge, the nursing management team will conduct a weekly phone follow-up to promptly address any issues the patient may have, provide psychological support, strengthen communication with the family, and encourage family members to participate. The routine nursing group was followed up according to the clinical routine. After the patients were discharged from the hospital, they were reminded of the matters needing attention by telephone at 1 month, 3 months, 6 months and 12 months.

Data Analysis

The registered case data and follow-up data shall be timely entered into the clinical trials and MedRIS system to ensure consistency with the original data, so as to facilitate verification and inspection by the superior department. In view of the particularity of intervention measures, it is impossible to achieve double blindness, that is, researchers and subjects are not aware of the group of patients, and single blindness is often the most common, that is, blind evaluation is achieved, that is, data statistics analysts are not aware of the grouping of patients.

Statistical Analysis

The incidence of CLI was analyzed by K-M survival curve, and log rank test was used for comparison between groups. The paired *t*-test is used for comparison within the measurement data group of normal distribution, and the Wilcoxon Sign Rank test is used for comparison within the measurement data group of nonnormal distribution. CMH (Cochran Mantel Haenszel) with adjusted central effect was used for comparison among counting data groups χ^2 inspection. Cox model was used for multifactor analysis.

Patient and Public Involvement

The research questions were designed by the team of nurses in our center based on clinical practice and literature review and audited by the Clinical Research Center of Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine. Neither patients nor the public were directly involved in the selection of outcome measures, design and implementation of the study. Patients will be informed of the study flow and provided feedback on reducing burden. The main results of the study will be disseminated to participants who are interested in their results from baseline and end-of-study assessments.

Discussion

This protocol presents a randomized controlled trial aimed at evaluating the potential benefits of using 3D-printed insoles designed with hemodynamics for patients suffering from CLI.^{15–17} In this study, we plan to assess patients' ultrasound hemodynamic characteristic, use 3D printing technology and appropriate materials to tailor the decompression insole for patients with CLI.^{18–21} The design of insole was adjusted according to the personalized parameters.^{22–24} In order to meet the requirements, it is necessary to use the patient's CT imaging data to generate a 3D printed insole through 3D

printing.^{25–27} The CLI patients' ultrasonic hemodynamic parameters of plantar artery would be monitored at 1, 3, 6 and 12 months after treatment.

This personalized insole, which takes into account both hemodynamics and the shape of the patient's foot,^{28–30} is expected to provide a new idea for foot care of CLI patients, and provide an economical and effective way to prevent and treat the occurrence of foot ulcers due to severe lower limb ischemia.^{31,32}

Therefore, for patients with CLI, we can enhance traditional 3D modeling techniques by incorporating real-time data on foot hemodynamics. By collecting foot shapes and designing a combination partition insole, we can improve blood perfusion in the feet, reduce the incidence of foot ulcers, lower amputation rates, and ensure a better quality of life for CLI patients.

Strengths and Limitations of This Study

This prospective randomized controlled study collected data of patients with CLI.

This study represents multidisciplinary cooperation of clinical researchers in peripheral blood vessels, including medicine, ultrasound and 3D technology.

This is a single-center pilot study with limited follow-up, comparing whether the symptoms of the two groups have improved under the intervention of 3D insole.

Ethics Approval and Informed Consent

The study protocol and informed consent form have been reviewed and approved by the Institutional Review Board of Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine (SH9H-2021-T233-2). This study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and the Guideline for Good Clinical Practice. Written informed consent will be obtained from each adult participant. Yong Cheng is the supervisor of this study. The interim and final results will be published in peer-reviewed journals.

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Disclosure

The authors declare that they have no competing interests.

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