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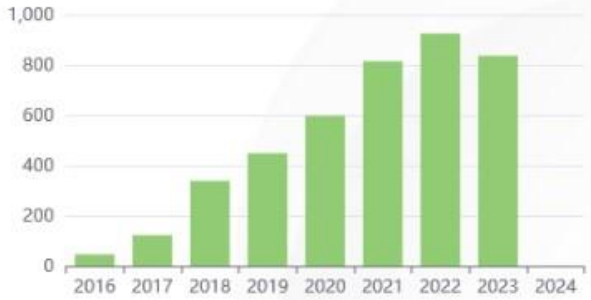

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Matrix Metalloproteinase as Predictors of Local Recurrence in Early-Stage Breast Cancer After Mastectomy and Chemotherapy A Cross-Sectional Study in Single Centre

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Quality of life of adolescent patients undergoing hemodialysis at Dr. Soetomo General Hospital, Surabaya (instrumental case study)

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Relationship between Leprosy Suspicion Questionnaire with IgM anti-PGL-1 antibody levels in household contacts of leprosy

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Temporal and severity correlation of COVID-19 with Dermatovenereological disease at Dr. Soetomo General Hospital, Surabaya, Indonesia

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Prognostic factors of peritoneal dialysis-related to peritonitis at Hasan Sadikin General Hospital, Bandung, Indonesia

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Factors influencing readiness and perceptions of Interprofessional Education (IPE) implementation at the Faculty of Medicine, Udayana University

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Low tumor-infiltrating lymphocytes (TIL) and high platelet lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), and mean platelet volume (MPV) as a risk factor of metastasis in triple-negative breast cancer (TNBC)

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Effects of Acupuncture Therapy at the Mingmen (GV4) and Zusanli (ST36) Points on the Expression of Transforming Growth Factor Beta 1 in Mice with Lupus Nephritis Model

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Effectiveness of conditioned medium mesenchymal stem cells intracutaneous for trophic ulcer due to morbun hansen

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Pro and Anti-Inflammatory Factors in Patients with Rhegmatogenous Retinal Detachment with Silicone Oil Tamponade

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GPi pallidotomy versus pallidothalamic tractotomy forel h-1 in Parkinson's disease: a systematic review in outcome and complication

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Neutrophil – Lymphocyte Ratio (NLR) predicts poor outcome in post-cardiac surgery involving aortic cross-clamping among pediatric patients with Congenital Heart Diseases (CHD): a literature review

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Hypothyroid on cardiopulmonary bypass usage in children with congenital heart disease: A literature review

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Role of platelet count, platelet indices, and immature platelet fraction as potential markers for monitoring platelet reactivity in patients with acute coronary syndrome undergoing percutaneous coronary intervention

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Single and dual limbal relaxing incisions in correcting corneal astigmatism during cataract surgery

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The autoinoculation approach for treating viral warts: a literature review

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The differences in quality of life between open thoracotomy and video-assisted thoracoscopic surgery (VATS): a literature review

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Ethnomedical entities in health law and sustainable development: a literature review

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Unrevealing the role of lacritin in eye disease: An updated systematic review

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The Effect of Erythropoietin on Cerebral Palsy Prevention in Hypoxic Ischemic Encephalopathy (HIE): A Systemic Review and Meta-Analysis

A Systemic Review and Meta-Analysis

Fadhilah Tia Nur, Harsono Salimo, Hardiono D Pusponegoro, Ari Probandari, Bambang Purwanto, Soetrisno, Naili Nur Sa'adah Nuhriawangsa

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Immune responses of COVID-19 vaccines in older adults: a systematic review and meta-analysis

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Effectivity and safety profile of oxalate decarboxylase in hyperoxaluria patient: A meta-analysis and systematic review

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Primary source of Vitamin D: sunlight or nutrition?

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Comparison of visual improvement based on the Potential Visual Test "Retinometry" in patients with Posterior Capsular Opacity Fibrotic and Regenerative types before and after Nd YAG Laser Capsulotomy

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Maternal serum docosahexaenoic acid (DHA) levels as a predictor of preeclampsia risk in urban and rural areas of developing country

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Intrauterine nephro-amniotic shunt insertion for fetal bilateral hydronephrosis and urinoma: a case report

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Costae rib resection and bypass right caroticosubclavian artery for thoracic outlet syndrome and follow up after 6 months: a rare case

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Multiple re-exploration due to excessive bleeding due to coagulopathy after aortic valve replacement in patients with chronic asymptomatic hepatitis B infection: A case report

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CASE REPORT

A case report of borderline lepromatous leprosy: a neglected tropical disease that impairs quality of life

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Management of abdominal pregnancy with placenta left in situ

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Combined ipsilesional excitation and contralesional inhibition of Repetitive Transcranial Magnetic Stimulation (rTMS) as a motor rehabilitation in ischemic stroke patient: a case report

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Mohammad Husni Thamrin, Budi Sutikno

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Cuprum insertion in Cavernous Hemangioma: a case report

I Made Candra Purnama, Dwi Hari Susilo

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Follow-up evaluation of snuffbox arteriovenous fistula as an alternative site for hemodialysis - a case series in a lower-middle country

Yunanto Kurnia, Trianingsih Trianingsih, Tandean Tommy Novenanto, Supomo Supomo, Haryo Aribowo, Yuletta Adny Ambarsari, Ihsanul Amal

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A 20-year-old man with hemopneumothorax caused by penetrating thoracic trauma: a case report

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Model prediction formulation of antibiotic type and length of treatment for pediatric typhoid fever patients at Cut Mutia General Hospital, North Aceh, Indonesia

Yuziani, Rizka Sofia, Wheny Utariningsih, Adri, Siti Ghina Faddhillah

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ORIGINAL ARTICLE

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Effectiveness of conditioned medium mesenchymal stem cells intracutaneous for trophic ulcer due to morbun hansen

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ABSTRACT

Introduction: The facts in the field that more than 50% of chronic ulcers, especially trophic ulcers due to leprosy fail to heal with usual treatment. Stem cell therapy or one of them is conditioned medium mesenchymal stem cell is a promising therapy because of its biological and physiological processes resembling the mechanism of wound healing

Methods: This research is a clinical trial research "Open Trial" Phase 2 to see the side effects caused by the intervention. Minimum sample size of 20 respondents with trophic ulcers due to leprosy that is difficult to resolve with usual treatment. The main outcome is wound healing in terms of the length and extent of the wound. The secondary outcome is treatment toxicity 4 weeks after administration. Follow-up visits will be scheduled at 2, 4, and 12 weeks post-treatment.

Results: 24 of 27 respondents successfully followed the study until the end. Prior to intracutaneously injecting CM MSC, the mean width, length, and area of tropical ulcers in patients with Morbus Hansen were 1.1 (0.3 - 12.0) cm, 2.0 (0.5 - 9.0) cm, and 2.38 (0.25 - 108) cm square, and after intracutaneously injecting CM MSC at the first follow up were 1.0 (0 - 4.5) cm, 1.5 (0 - 8.5) cm, and 1.0 (0 - 38.25) cm. The change between the start and finish of the intervention was statistically significant (p-value 0.05). Neither systemic nor local adverse effects were observed during or up to two months after the intervention.

Conclusion: The use of intracutaneous CM MSC injection has been proven effective in accelerating the process of wound healing, especially trophic ulcers due to leprosy with side effects that are not present in this study.

Keywords: CM-MSC, stem cell, trophic ulcer, leprosy, morbun hansen.
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INTRODUCTION

Leprosy is a chronic infectious disease caused by the bacteria Mycobacterium leprae which infects the skin and causes peripheral nerve damage, with advanced complications including physical disabilities and deformities.[1–3] The case of leprosy has decreased significantly since the World Health Organization (WHO) provided a free multidrug therapy program in 1995, but the reality in the field revealed that leprosy is still the main cause of morbidity because leprosy can cause long-term disability and leave residual symptoms in around 2 million people all over the world.[4,5]

In 2016, the World Health Organization (WHO) reported a total of 214,783 new leprosy cases across 143 countries. Recognizing the significant disease burden, WHO identified 22 countries as "global priority countries," encompassing 94-96% of the overall burden and 92.3% of cases with level II disability. Globally, 12,437 cases with level II disabilities were reported in 2016. Despite a decrease in the overall number of cases from 2007 to 2016, statistical analysis revealed a consistent proportion of cases in most countries, indicating ongoing leprosy transmission.[6-8]

The Southeast Asian region exhibited the highest number of new cases and cases with disability grade II compared to Africa, America, the Mediterranean, the western Pacific, and Europe. Indonesia, Myanmar, and the Philippines played substantial roles in contributing to these figures. Indonesia, ranking among the top three countries with the highest leprosy incidence globally, reported over 10,000 new patients annually, contributing 81% of the global newly diagnosed cases.[7,9,10]

In 2016, Indonesia alone accounted for 16,826 of the 214,783 new global cases, including 1,363 cases with level II disabilities. Of these cases, 62 involved children, and 229 were relapse cases, preventing Indonesia from being declared leprosy-free. In 2017, based on the New Case Detection Rate (NCDR), 10 provinces in Indonesia were identified as having a high burden of the disease, namely Gorontalo, Southeast Sulawesi, Central Sulawesi, North Sulawesi, North Maluku, Maluku, West Sulawesi, West Papua, and Papua. Additionally, 11 provinces were identified as having a high burden for pediatric patients. These included Central Sulawesi, North Kalimantan, West Kalimantan, Banten, Riau Islands, Bengkulu, North Maluku, Maluku, Southeast Sulawesi, West Papua, and Papua.[11,12]

Persons affected by leprosy often

experience stigma and discrimination from the community. This has a negative impact on early diagnosis, treatment, and social functioning of sufferers. Stigma is a major cause of late diagnosis and increasing the spread of infection between families and the community, as well as causing complications later in life.[7]

Disability in leprosy is something that can be prevented. Physical damage associated with leprosy is usually secondary, due to chronic granulomatous inflammation of the nerves due to Mycobacterium leprae infection.[4,13] This nerve damage will cause disability, such as disability in the hands, feet and eyes, which affects the decline in physical and social function. The World Health Organization (WHO) classifies complications from leprosy due to leprosy into three classes: Grade 0, ie without peripheral nerve disorders, Grade 1, loss of sensation in the hands or feet, and Grade 2, which shows a decrease in function and the appearance of disability in organs.[4] Multidrugs (MDT) treatment is actually effective in healing wounds and preventing disability if given early. However, in reality, leprosy is often diagnosed too late and permanent disability has occurred. This disability is permanent in most patients due to irreversible nerve damage. This defect requires further treatment to prevent further secondary damage.[13]

Presentation by the World Health Organization (WHO), The proportion of new cases with second degree disability ranges from 6% to 21%. Among countries with leprosy endemic, leprosy ulceration in the legs is the most common disability.[14] Leg ulcers occur in about 10% to 20% of patients diagnosed with leprosy,[15] with ulcers generally occur in the front of the foot as much as 71% to 90% of all plantar ulcers, and the medial part is more vulnerable than the lateral part. The proximal phalanx of the big toe is the most common predilection for trophic ulcer events.[16]

Anesthesia in the foot is a major factor in the pathogenesis of plantar ulcers. The combination of anesthesia, walking barefoot, poor wound repair, excess pressure on the scar, and the focus of persistent infection are the main factors for recurrence of plantar ulcers.[16]

Ten percent of leg ulcers arise from injuries that do not get treatment or are not felt by the sufferer. This has an impact on the emergence of infection and chronic tissue damage, and 5% of cases of infection arise due to the occurrence of dry skin, anhydrotic, and hyperkeratotic on the soles of the feet or from infection in the callus through the open callus gap. The majority of plantar ulcers arise due to damage to the plantar subcutaneous tissue caused by stress and repetitive stress when walking or activity.[14]

Trophic ulcers can occur for several years even after the initial infection has resolved. The most important factor causing neuropathic leg ulcers is dynamic or static deformity that causes changes in normal anatomical structure and causes pressure to accumulate in one area and is exacerbated with low skin sensibility. Excessive pressure and stress over the specific area of the foot can explain why plantar ulcers are deeper and smaller in the plantar portion of the foot when compared to an ulcer on the ankle.[17]

Treatment should be aimed at wound management, correction of deformity, sensation recovery, normal skin recovery, removal of abnormal pressure, and eradication of deep infections.[10,18] Management of trophic ulcers due to leprosy has been widely developed and is not only limited to wound debrediment and topical antibiotic administration. Bioengineer tissue and growth factors have been used to increase ulcer healing rates, especially trophic ulcers. Some of the methods developed are ranging from artificial skin products made from fibroblasts that are cultured with a composition of a mixture of newborn skin and woven polygalacticacid mesh that triggers growth factors. Growth factors are proteins released by various types of cells during the wound healing phase and trigger cell differentiation such as basic epidermal growth factor (EGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF). Becaplermin is the first recombinant formulation that contains platelet derivative growth factor.[14]

Besides progress in technology and the persistence of a 50% non-healing rate for chronic wounds,[19] the demand for diverse wound care solutions arises. This need stems from the ineffectiveness of conventional therapies in certain situations, leading to significant expenditure of time and resources. In alignment with the evolving field of wound healing, stem cell treatment emerges as an innovative alternative to traditional methods. As a result, scientists are increasingly turning to stem cell therapy, recognizing its immense potential attributable to the presence of growth factors.[20]

Animal model data indicate that the autocrine or paracrine actions of MSC play a crucial role in wound healing.[21] According to a number of studies, MSC-CM growth factors help to the regeneration of injured organ tissue. It is also important to note that the secretome of MSCs has anti-fibrotic and angiogenic properties that, when administered early, can minimize scar tissue development and boost long-term ejection fraction.[22]

Previous research from Natalyya et al stated that healing of chronic plantar ulcer wounds caused by leprosy using secretome gel treatment from human amniotic cell stem cells, showed that hAMSC secretome gel increased the rate of chronic plantar wound healing. In the majority of respondents (72.7%), ulcers were completely healed; in 18.2% of the subjects, ulcers partially recovered; and in one subject, plantar ulcers persisted. In this study, there were no patients with ulcers that worsened after the intervention. In addition, no subject experienced side effects or complications.[23]

To boost wound healing rates, researchers continue to investigate alternative therapies and administration methods. Current study indicates that intramuscular and intracutaneous delivery is preferable to intravenous and topical administration. In vitro and in vivo studies have demonstrated that local injections of MSC, such as intramuscularly, can promote wound healing by promoting angiogenesis and modulating the local immune system. Studies on mice indicate that MSC administered intramuscularly enhances neovascularization following femoral artery occlusion (a model of ischemic back limb).[24] The potential of Mesenchymal Stem Cells (MSC) in vivo is demonstrated through the orchestration of vascular endothelial growth factor, basic

fibroblast growth factor, and chemokines in murine hind limb ischemia tissue repair models. MSCs, operating via paracrine mechanisms, facilitate interactions with a range of cells, including immune cells, fibroblasts, endothelial cells, and others, thereby modulating the process of wound healing.[25,26] Further studies conducted in vitro have pinpointed direct cell-to-cell interactions involving MSCs, local tissue cells, and various immune cells, with regulation facilitated by secretion factors produced by MSCs.[27-31] Additionally, in vivo administration of MSCs results in the migration of macrophages and endothelial cells, along with a reduction in effector T cells. This sequential process triggers angiogenic and regenerative mechanisms facilitated by MSCs.[32-35]

This preliminary Phase II trial aims to assess the safety, feasibility, and potential efficacy of Mesenchymal Stem Cells (MSC) administered intracutaneously in treating trophic ulcers resulting from leprosy. Should the outcomes of this study affirm the safety, feasibility, and demonstrate potential beneficial effects, the research will progress to mini–Randomized Controlled Trials (RCTs) and potentially expand to large multicenter RCTs. The emphasis will be on advancing evidence-based medicine by exploring the use of intracutaneous MSC for treating trophic ulcers.

MATERIAL AND METHODS

Research Design and Subject

This study represents a phase II clinical trial employing the "non-randomized controlled trial" and "open trial" methodologies. The planned minimum sample size for this preliminary phase II trial was 20 participants. Inclusion criteria encompassed individuals aged 18-80 with chronic ulcers in Morbus Hansen's patients that had not responded to routine therapy for at least one month, presenting trophic ulcers at degrees 2 and 3, expressing willingness to participate, and maintaining good health for study participation. Exclusion criteria involved individuals taking anticoagulants, having hypertension, experiencing any stage of kidney failure, possessing a history of blood disorders, or being pregnant.

The research was carried out at the Leprosy Hospital of Alverno in Singkawang in March 2020. Before intervention, patients underwent a comprehensive screening involving a detailed history, physical examination, and laboratory tests to ensure safety and identify potential side effects during and after the intervention. The thorough physical examination covered vital signs and a head-to-toe assessment. Laboratory tests utilized in the study included fasting blood sugar level assessments and complete urine examinations.

Human Umbilical Cord Isolation

After receiving parental approval, fresh umbilical cords were harvested. Before isolation, the umbilical cords were washed in phosphate-buffered saline with an antibiotic-antimycotic (Ab-Am) solution. The umbilical cord's veins and arteries were carefully removed. The umbilical cord Wharton jelly was then carefully cut into small pieces and placed on a 100-mm culture dish filled with cell culture medium made up of alpha minimum essential medium (MEM; Gibco by Life Technologies, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS; Gibco by Life Technologies) and 1% Ab-Am. (Gibco by Life Technologies). MSC were migrated out of umbilical cord tissue and retrieved for continued expansion after 21 days.

Identification of MSCs

Immunophenotyping was used to determine that the MSC characteristics adhered to the International Society for Cell and Gene Therapy (ISCT) criteria. MSCs were labeled with phycoerythrin-conjugated surface antigens CD73, CD105, and CD90 (Systems R and D). For analysis, flow cytometry (FACS Calibur, BD, USA) and CellQuest Pro software were utilized. A positive marker must meet a 95% acceptance threshold.[36]

hUC-MSC CM production

MSCs were extracted from the umbilical cord and cultured in T175 vials till passage 6 (P6). When the confluence reached 70%-80%, the culture medium was withdrawn and replaced with basal media containing no additives. After that, cells were cultured at 37°C in a 5% CO2 incubator under hypoxic condition (5% O2). After 72 hours of incubation, hUC-MSC CM were collected and stored in a deep freezer (80 °C) for long-term storage.

Measurement of levels of pro-collagen 1, vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF)

Enzyme-linked immunosorbent assay (ELISA) was utilized to measure paracrine factors linked with wound healing, such as pro-collagen 1, VEGF, dan bFGF (R and D Systems). The operation was carried out in accordance with the manufacturer's instructions, and four-parameter logistic software was employed for the analysis.

Study Protocol and Outcome

The interventions administered in this study were Wharton's Jelly-derived mesenchymal stem cells (WJMSCs) Conditioned Medium (CM-WJMSCs) at a volume of 0.1cc/1cm intracutaneously using a flexpen device in the wound area every 2 weeks. The variables in the study were categorized into two groups: the independent variable being the intracutaneous administration of CM-WJMSCs, and the dependent variables being wound healing and any side effects resulting from the interventions. Wound healing was assessed based on granulation tissue growth, reduced edema, decreased erythema, and improvements in wound size, including length, width, and area measured with a standard ruler and digital photos.

The study lasted for 1 month, with measurements of dependent variables conducted three times: before the intervention, 2 weeks after the intervention (first follow-up), and 1 month after the intervention (second follow-up). The researcher provided a contact number for personal consultations in case of side effects during the intervention period.

Data were evaluated using the intention-to-treat approach, and the research variables were presented in univariate and bivariate tables. Analytic statistical tables were used to showcase changes in wound characteristics, while descriptive statistics presented population characteristics. Generalized linear methods were employed for normally distributed

data, the Wilcoxon Signed Ranks Test for non-normally distributed data, and the Fisher exact test for categorical data related to wound features and side effects, if applicable. The Shapiro-Wilk test was used to determine the normality of data distribution. If significant adverse effects were experienced, a Number Needed To Harm analysis was conducted. Additional analyses, such as Generalized mixed models or Kaplan-Meier curves and the log-rank test, were performed if possible.

Side effects of MSC treatment at 4 weeks were defined, including local effects like signs of inflammation and other effects according to the "Common Terminology Criteria for Adverse Events, Version 4.0." Secondary safety outcomes included substantial adverse effects occurring four weeks to two months after the intervention, requiring hospitalization, causing chronic or significant mortality, or impairing the respondent.

Wound healing was assessed through clinical observation and a series of digital images, captured in the normal mode. Digital photographs with reference scales were deemed a reliable method for objectively describing ulcers, as manual and single ulcer measurements were considered unreliable.[37,38]

Ethical Approval

Approval for this study was granted by the Universitas Tarumanagara Human Research Ethics Committee Institute of Research and Community Engagement (Registration Number: PPZ20192072 and Letter Number: 1007-Int-KLPPM/Untar/VI/2020). The study is also registered on ClinicalTrials.gov under the ID number NCT04134676.

RESULTS

hUC-MSC characteristics

Human MSCs were isolated from the umbilical cord (1×10^5 cells) and multiplied from passage 0 to passage 6. The seeding concentration threshold for culture expansion was set at $7x10^3$ cells/cm2. hUC-MSCs had the appearance of a spindle-shaped fibroblast (Figure 1) and were around 120 µm in size. The morphology of MSCs did not change much during culture.

MSCs and did not express hematopoietic markers such as CD19, CD14, CD45, but expressed markers CD90, CD73, and CD105. Flow cytometry revealed the cells were MSCs, with positive marker values above 95% and negative marker values less than 2%. (Table-1). Surface epitopes are MSC-specific indicators, according to the ISCT.[36]

Table 1. The results of a marker analysis of human umbilical cord-derived mesenchymal stem cells (MSCs)

Markers	Population Percentage (%)
CD 19	1.47
CD 14	0
CD 45	0.26
CD 90	99.52
CD 73	99.26
CD 105	99.47

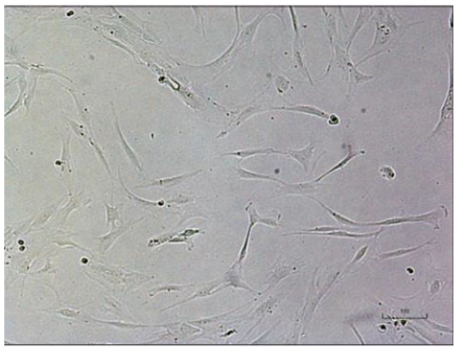

Figure 1. Microscopic 400 magnification of human umbilical cord mesenchymal stem cells (passage 5) appearance. Scale bar: 100 µm.

Results Measurement of levels of pro-collagen 1, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF)

We employed passage six cells to produce Conditioned Medium (CM) due to their distinct Mesenchymal Stem Cell (MSC) characteristics. When the MSC cells reached 70-80% confluence, they were cultured in MEM-Alpha without the addition of a growth supplement. The MSC cells were then incubated for an additional 72 hours to allow for the secretion of the secretome. To identify the optimal conditions for secretome secretion, we exposed MSCs to a hypoxic environment [5% O2]. The CM was stored in a deep freezer to maintain the stability of its protein content for long-term storage. ELISA examination revealed that the pro-collagen 1 level was 655,100.00 pg/mL, the vascular endothelial growth factor (VEGF) level was 21.42 pg/mL, and the basic fibroblast growth factor (bFGF) level was 34.64% pg/mL.

Primary Outcome for Wound Healing

The study included 27 participants who were willing to participate and met the inclusion criteria. Three (11.1%) of the 27 participants dropped out or did not get therapy during the trial, as 2 participants were absent at the first follow-up and 1 participant was absent at the second follow-up (Figure 2).

Total of 24 respondents who took the study to completion, found that the characteristics of respondents were dominated by female sex (75%) with an average age of 61.17 (14.53) years, height was 159.88 (8.19) cm, body weight was 54.33 (6.62) kg, Body Mass Index is 21.29 (2.54) kg / m2, and ulcer age is 3.28 (1.70) years. The comorbid and patient characteristics are described in table 2.

The average length of the wound was 2.0 (0.5-9.0) centimeters at baseline, 1.5 (0.0-8.5) centimeters at the first follow-up, and 1.50 (0.0-8.5) centimeters at the second follow-up (p-value 0.05). The Shapiro-Wilk normality test revealed an atypical data distribution for the varied length of the wound at baseline, first follow-up, and second follow-up. Therefore, the Non-Parametric Wilcoxon Signed Ranks Test is used to assess statistical significance. The Wilcoxon test revealed statistically significant differences in length between baseline and first follow-up (p 0.001), baseline and second follow-up (p 0.001), and first follow-up and second follow-up (p 0.001). (p 0.001). (Table 3 and Figure 3)

The average wound width was 1.1 (0.3 - 12.0) centimeters at baseline, 1.0 (0.0 - 4.5) centimeters at the first follow-up, and 0.5 (0.0 - 4.5) centimeters at the second follow-up. The Shapiro-Wilk test for normality

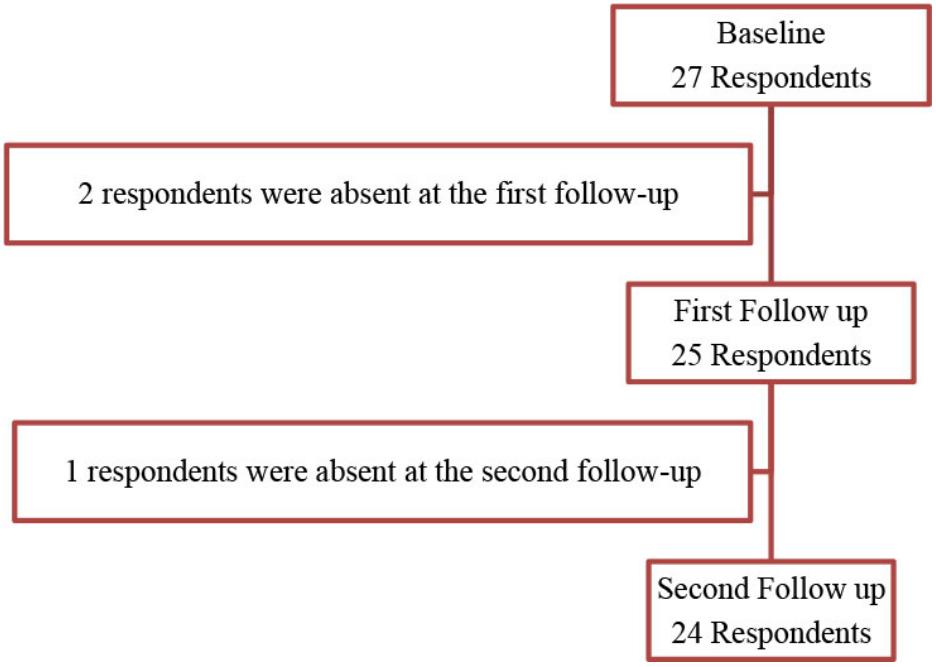

Figure 2. Sample researches allocation.

uncovered an abnormal data distribution for the variable wound width at baseline, first follow-up, and second follow-up (p-value 0.05). Therefore, the Non-Parametric Wilcoxon Signed Ranks Test is used to assess statistical significance. The Wilcoxon test demonstrated a significant difference in width between baseline and first follow-up (p 0.001), baseline and second follow-up (p 0.001), and first follow-up and second follow-up (p 0.001). (p 0.001) (Table 4 and Figure 4).

The mean wound area was 2.38 (0.25 - 108) square centimeters at baseline, 1 (0 - 38.25) square centimeters at the first follow-up, and 0.75 (0 - 38.25) square centimeters at the second follow-up. The Shapiro Wilk test for normalcy revealed an uneven distribution of wound area data at baseline, the first and second follow-ups (p-value 0.05). Therefore, the Non-Parametric Wilcoxon Signed Ranks Test is used to assess statistical significance. There were statistically significant differences between baseline and first follow-up (p = 0.001), baseline and second follow-up (p = 0.001), and first follow-up and second follow-up (p = 0.001). (p-value 0.001). (Figure 5 and Table 5)

The study ended after the intervention lasted for 1 month. During the intervention period up to 2 months post intervention there were no side effects caused during the intervention of Conditioned Medium Wharton's Jelly-derived mesenchymal stem cells (CM-WJMSCs) intracutaneously.

DISCUSSION

Limb trophic ulcers are a significant consequence of leprosy and are classified as a handicap of category 2 by the World Health Organization.[39] Leg trophic ulcers are a severe health concern due to the fact that wound recovery is typically sluggish and frequently results in persistent ulceration. Chronic ulcers are caused by a combination of recurrent trauma, sensory problems, paralysis of the muscles, autonomic nerve disorders, superinfection and callus formation.[40,41] One factor of slow healing in chronic ulcers is exacerbated by the lack of growth factors and blood supply to the wound as a result of damage to the autonomic nerve by the Mycobacterium germ.[23,42,43] Wound healing is a collection of dynamic processes that require coordination between cells, growth factors, cytokines and extracellular matrix[44]. The management of wound care that is commonly done in daily practice does not seem to provide satisfactory results because of insufficient supply growth factors and cytokines. That's why in our research, we pay special attention adding this point in chronic wound management.

Stem cell treatment has therapeutic promise. In stem cell treatment, stem cells grow into damaged tissue and develop into specialized cells while secreting multiple growth factors and cytokines; these factors are referred to as stem cell secretomes. Stem cell secretions can be extracted in vitro from stem cell growth media. The use of stem cell secretions in regenerative medicine, particularly chronic wound therapy, is becoming widespread.[45,46] In this study we used pure secretom from human Umbilical cord Mesenchymal stem cell, without containing the medium from stem cell culture.

Several earlier research have demonstrated that MSC has the potential to improve wound healing by speeding wound closure.[29,47,48] Walter et al. demonstrated that MSC produced from human bone marrow accelerated wound healing in vitro by promoting the migration of fibroblasts and keratinocytes. Similar findings were reported by Smith et al. and Jeon et al.[44]

The potential of the MSc in increasing wound healing rates through various complex and systematic processes to support ideal conditions in the process of cell regeneration. Various forms of MSc mechanisms to improve cure rates are to increase angiogenesis, immune system immodulation, remodeling extracellular matrix, and skin regeneration.[44] Skin regeneration were also seen in our study, showed by decreasing of the width and length after 2 weeks of treatment.

Angiogenesis is described as the process by which new blood vessels are formed from preexisting blood vessels. During the wound healing process, normal angiogenesis is essential. Numerous studies have demonstrated the effect of MSC secretome on crucial phases of angiogenesis. In vitro, many MSC populations (e.g., adipose, amniotics, bone marrow (BM), and umbilical veins of Wharton jelly) encourage the proliferation and migration of endothelial cells that promote tube formation and inhibit the apoptosis of endothelial cells. Given the wide range of clinical disorders associated with inadequate or aberrant blood vessel growth, such as atherosclerosis and delayed wound healing, the involvement of MSC in angiogenesis is extremely intriguing. In numerous animal models of cerebral

Table 2. Characteristics of research respondents' demographics

Parametric	Sum (%)	Mean (SD)	Med (Min -Max)
Sex			
• Male	6 (25%)		
• Female	18 (75%)		
Age (years)	-	61.17 (14.53)	60.5 (40 – 89)
Height (cm)	-	159.88 (8.19)	159 (145 – 170)
Weight (Kg)	-	54.33 (6.62)	54 (43 – 65)
Body Mass Index	-	21.29 (2.54)	21.01 (17.22 – 28.89)
Age of ulcer	-	3.29 (1.70)	3 (0.50 – 7.00)
Pus		-	-
• No	24 (100%)		
• Yes	-		
Erythema		-	-
• No	2 (8.3%)		
• Yes	22 (91.7%)		
Hyperpigmentation		-	-
• No	21 (87.5%)		
• Yes	3 (12.5%)		
Erosion		-	-
• No	-		
• Yes	24 (100%)		
Moist Skin		-	-
• No	7 (29.2%)		
• Yes	17 (70.8%)		
Edema on wound		-	-
• No	24 (100%)		
• Yes	-		
Granulation		-	-
• No	-		
• Yes	24 (100%)		
Drug use		-	-
• No	22 (91.7%)		
• Yes	2 (8.3%)		
Type of Treatment		-	-
• Metronidazole	1 (4.2%)		
• Rifampisin, Dapson, Clofazimine, Prednison	1 (4.2%)		
Comorbid		-	-
• No	24 (100%)		
• Yes	-		
Pain on Wound		-	-
• No	24 (100%)		
• Yes	-		
Systolic Blood Pressure	-	121.33 (11.15)	120 (100 – 140)
Diastolic Blood Pressure	-	75.83 (7.17)	80 (60 – 90)
Heart Rate	-	77.38 (6.24)	77 (68 – 82)
Random Blood Glucose	-	86.25 (6.17)	87 (77 – 98)
Location		-	-
Left Calf	1 (4.2%)		
Left butt	1 (4.2%)		
Left hook	1 (4.2%)		
Left thumb	1 (4.2%)		
Right foot	7 (29.2%)		
Left Foot	5 (20.8%)		
Left ankle	1 (4.2%)		
Left elbow	1 (4.2%)		
Right foot	3 (12.5%)		
Left foot	3 (12.5%)		
Width (Baseline)	-	1.90 (2.31)	1.1 (0.3 - 12.0)

Parametric	Sum (%)	Mean (SD)	Med (Min -Max)
Length (Baseline)	-	2.82 (2.10)	2.0 (0.5-9.0)
Area (Baseline)	-	8.95 (21.92)	2.38 (0.25 – 108)
Exudate (Baseline)		-	-
• No	24 (100%)		
• Yes	-		
Granulation (Baseline)		-	-
• No	-		
• Yes	24 (100%)		
Necrotic tissue (Baseline)		-	-
• No	24 (100%)		
• Yes	-		
Length (First Follow up)	-	2.23 (1.98)	1.5 (0 – 8.5)
Width (First Follow up)	-	1.22 (1.07)	1.0 (0 – 4.5)
Area (First Follow up)	-	4.55 (8.58)	1 (0 – 38.25)
Exudate (First Follow up)		-	-
• No	24 (100%)		
• Yes	-		
Granulation (First Follow up)		-	-
• No	1 (4.2%)		
• Yes	23 (95.8%)		
Necrotic tissue (First Follow up)		-	-
• No	24 (100%)		
• Yes	-		
Width (Second Follow up)	-	1.00 (1.00)	0.5 (0 – 4.5)
Length (Second Follow up)	-	1.89 (1.90)	1.5 (0 – 8.5)
Area (Second Follow up)	-	3.54 (8.05)	0.75 (0 – 38.25
Exudate (Second Follow up)		-	-
• No	24 (100%)		
• Yes	-		
Granulation (Second Follow up)		-	-
• No	1 (4.2%)		
• Yes	23 (95.8%)		
Necrotic tissue (Second Follow up)		-	-
• No	24 (100%)		
• Yes	-		

Table 3. Changes in wound length from the baseline, first follow up, and second follow up

Time	Mean (SD)	Med (Min – Max)	p-value		
Baseline	2.82 (2.10)	2.0 (0.5-9.0)	< 0.001	< 0.001	< 0.001
Follow up 1	2.23 (1.98)	1.5 (0 – 8.5)			
Follow up 2	1.89 (1.90)	1.5 (0 – 8.5)			

ischemia/stroke, myocardial infarction, neurogenic bladder, peripheral artery disease, and urinary incontinence stress, MSC have been shown to successfully stimulate angiogenesis. In the MSC secretome, several angiogenic stimulators and inhibitors have been identified. Recent proteome studies of MSC-CM triggered with inflammatory cytokines revealed that metalloproteinase-1 tissue inhibitors (TIMP-1) are responsible for the antiangiogenic effects of MSC. All of these findings indicate that the numerous variables present in MSC-CM can constitute a balance that promotes angiogenesis. Moreover, multiple studies have demonstrated that the release of pro- and anti-angiogenic factors can be altered by chemokine and hypoxic circumstances. Thus, TGF has the ability to elevate the levels of many growth factors (e.g., VEGF, HGF, PDGF, IL6 and IL8). Similarly, CM of MSC with TFG stimulates the development of blood vessels in an in vivo test.[22] Secretom in our study were an hypoxic conditions too, and in this study, angiogenesis were supported also by our research as clinically seen fresher color and growing granulation formation in the base of the treated chronic wound.

MSC-CM has a variety of neurotrophic factors. Multiple studies have revealed positive benefits of MSC on experimental models of nerve damage. Modulation of the inflammatory environment in the ulcer area, increased vascularity and regeneration in the wound area, increased myelin sheath thickness, modulation of the Wallerian degeneration stage, accelerated fiber regeneration and increased cell count, reduced incidence of fibrosis scars, and increased organization fiber density are the effects observed.[22] In leprosy patients most of all are with low skin sensibility causes by peripheral

nerve damage, long term evaluation post treatment are needed to evaluation in this condition, unfortunately 2 weeks after treatment cannot support this statement, and it is a good idea for our research to evaluate this statement later.

Previous research has demonstrated that MSCs can affect the activation and proliferation of all immune cell types. Nicola et al. discovered that MSC reduced the growth of CD4+ and CD8+ T cells. In addition, MSC participates in three major phases of the immune response: the introduction and presentation of antigens, the activation, proliferation, and differentiation of T cells, and the T-cell effector phase. It is generally recognized that at least a portion of the anti-inflammatory impact of MSC-CM is mediated by dispersed immunoregulatory substances. MSC-CM contains tumor growth factor-1 (TGF-1), interleukin (IL) 13, IL18 (IL18BP) binding protein, ciliary neurotropic factor (CNTF), neurotropin 3 (NT-3), IL10, IL12p70, IL17E, IL27, and IL1 receptor antagonist (IL1RA). MSC-CM also included proinflammatory cytokines, including IL1b, IL6, IL8, and IL9. This equilibrium between anti-inflammatory and proinflammatory cytokines determines the final outcome. MSC suppresses proinflammatory cytokines, including as interferon (IFN) and tumor necrosis factor (TNF), while increasing the release of anti-inflammatory IL10.[22]

MSC also demonstrated the ability to enhance the healing process through extracellular matrix manipulation.[49–51] It has been demonstrated that the conditioned medium (CM) of human cord blood MSC inhibits the expression of matrix metalloproteinase (MMP) -1, which works to limit the degradation of collagen matrix and plays a role in fibroblast regeneration.[47] In the same study, the enhanced production of collagen and elastin by fibroblasts played a role in wound healing. MSC generated from human adipose has been proven to boost wound healing rates in vitro. Lee et al. demonstrated that MSC treatment dramatically increased the proliferation of immortalized human keratinocyte (HaCaT) cells and skin fibroblasts, leading to increased wound healing rates.[51] Extracellular matrix formation clinically also showed in granulation formation as seen in our study by decreasing of the width and length of the chronic wound, indicated progress wound healing and support the study above.

Stem cells have been widely used, both extrinsically and intrinsically. In 2004, Rasulov et al. first reported BM-SMC application in female patients with IIIB degree burns, 30% TBSA. Topical application can cause faster wound healing and actively induce new blood vessel growth.[52] The use of ASC is mostly used mainly in plastic surgery, which has been applied every day.[53] In aesthetics ASC has shown promising potential especially in antiaging and rejuvenation.[54] Stem cells have also been shown to prevent and reduce the incidence of hypertrophic scars (HTS), although the actual mechanism is still poorly understood. Liu YL believes that the paracrine mechanism decreases the regulation of p53 mRNA, and reduces the immune response and thereby inhibits the migration and activity of fibroblasts and myoblast HTS, which decreases the formation of extracellular matrix, collagen, and alpha smooth muscle (α-SMA).[55] In this study we injected only one time secretome around the trophic wounds using Secretome of human Umbilical Cord Mesenchymal Stem Cells (CM-hUCMSC), analyzed the levels of b-FGF, VEGF, and Pro-Collagen 1 using ELISA, and Fibroblast cell viability was evaluated by CCK-8 assay. The Reason we use only one time injection in this research because this is the phase 2 trial, we did it very carefully to avoid the side effect that may be happen after the injection, luckily we did not find any side effects in this study.

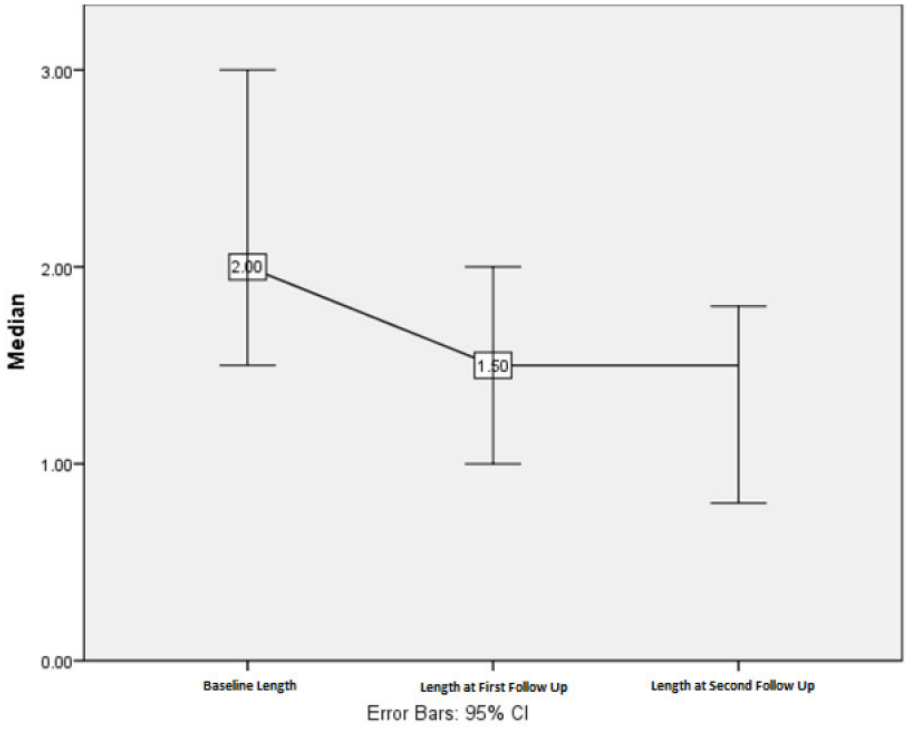

Figure 3. Changes in wound length from the baseline, first follow up, and second follow up.

Table 4. Changes in wound width from the baseline, first follow up, and second follow up

Time	Mean (SD)	Med (Min – Max)	p-value		
Baseline	1.90 (2.31)	1.1 (0.3 - 12.0)	< 0.001	< 0.001	< 0.001
Follow up 1	1.22 (1.07)	1.0 (0 – 4.5)			
Follow up 2	1.00 (1.00)	0.5 (0 – 4.5)			

Jin et al compared the characteristics and characteristics of BM-MSC, AT-MSC, and Umbilical Cord Blood-MSC, with an initial density of 2000 cells / cm2, and the final population was then calculated using the formula (t-t0)· log2 / log (N - N0), It was found that the UCB-MSC culture had longer senescent cells, longer aging. Further findings, the level of anti-inflammatory factors with Ang-1 is higher compared to other MSCs. UCB-MSC has a number of proliferation and cloning activities, and expresses p53, p21, and p16 which are much lower, which is a marker of aging. On the other hand, Xu et al compared the effect of ASC with PSC secretome on antiaging. The study used 6-8 x 106 cells, with an initial concentration of 0.389 ± 0.04 mg / ml in 100 ml and revealed a final concentration of 5989 ± 0.07 mg / ml in 70 ml after undergoing a 15x screening process. ASC secretomes consist of proteins that have a greater role in adhesion, promotion, inhibition of metalloproteinases, and plasminogen activators. Whereas PSC-CM contains more embryogenic proteins in FGF2, FGF7, CCL2, MMP1 and MMP9, FGF2 and FGF7. Overall, it has an important role in differentiation, cell division, survival, the inflammatory response, and collagen degeneration.[53]

Current study indicates that intramuscular and intracutaneous delivery is preferable to intravenous and topical administration. In vitro and in vivo studies have demonstrated that intramuscular MSC promotes wound healing by promoting angiogenesis and modulating the local immune system. Studies on mice indicate that MSC administered intramuscularly enhances neovascularization following femoral artery occlusion (a model of back limb ischemia).[24]

The intracutaneous MSC route utilized in this study is a novel method of drug administration in terms of both medication kind and method of drug delivery. There are currently no clinical studies evaluating the safety and efficacy of different routes and sites for the treatment of trophic ulcer injuries. There are signs, however, that intracutaneous administration is superior to intravascular administration and simpler to implement.

The administration of MSC by local injection has only been investigated by administering MSC intracutaneously in patients with pinky ulcers in systemic sclerosis.[35] On the basis of this study, intracutaneous administration that is almost similar to intramuscular administration is preferred because of the shallower forms of trophic ulcer wounds. In fact, local injection administration is preferred over systemic injection because local injection has been shown to be superior in providing external results. First, intramuscular administration can send cells closer to the location of the ulcer in patients with vascular complications and impaired peripheral perfusion. Second, the tissue around the wound will further the survival of MSC cells that are injected locally through the supply of oxygen and nutrients.[56] Third, in preclinical and clinical studies local injections have been performed more safely in patients when compared to intravenous administration. Fourth, a lot of evidence shows that systemic administration will cause MSC cells to be trapped in the lungs that trigger changes in lung pathology.[57,58]

Previous preclinical and clinical studies in treatment for patients with critical limb ischemia and / or ulcers that are difficult to cure show that administration of MSC by local injection (intramuscular route) shows no evidence of local or systemic toxicity.[41,43,59,60] The results of this study are in line with all clinical studies regarding the side effects arising from the administration of MSC by local injection with minimal side effects. We did intracutaneously injection carefully to shorten the chronic trophic wounds healing time as known as one of the

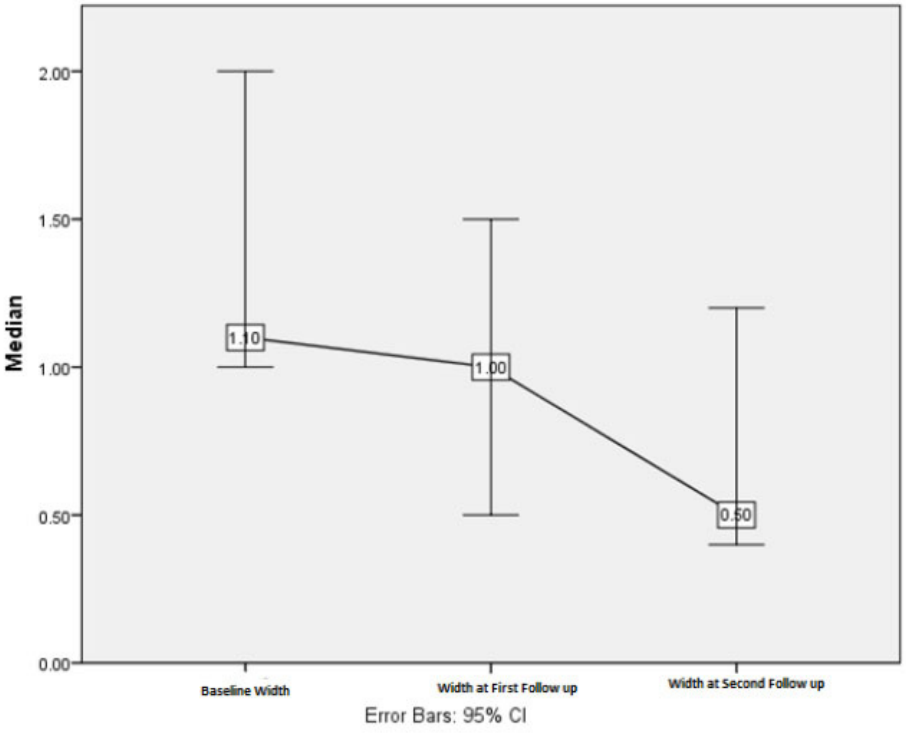

Figure 4. Changes in wound width from the baseline, first follow up, and second follow up.

Table 5. Changes in wound area from baseline, first follow up, and second follow up

Time	Mean (SD)	Med (Min – Max)	p-value		
Baseline	8.95 (21.92)	2.38 (0.25 – 108)	< 0.001	< 0.001	< 0.001
Follow up 1	4.55 (8.58)	1 (0 – 38.25)			
Follow up 2	3.54 (8.05)	0.75 (0 – 38.25			

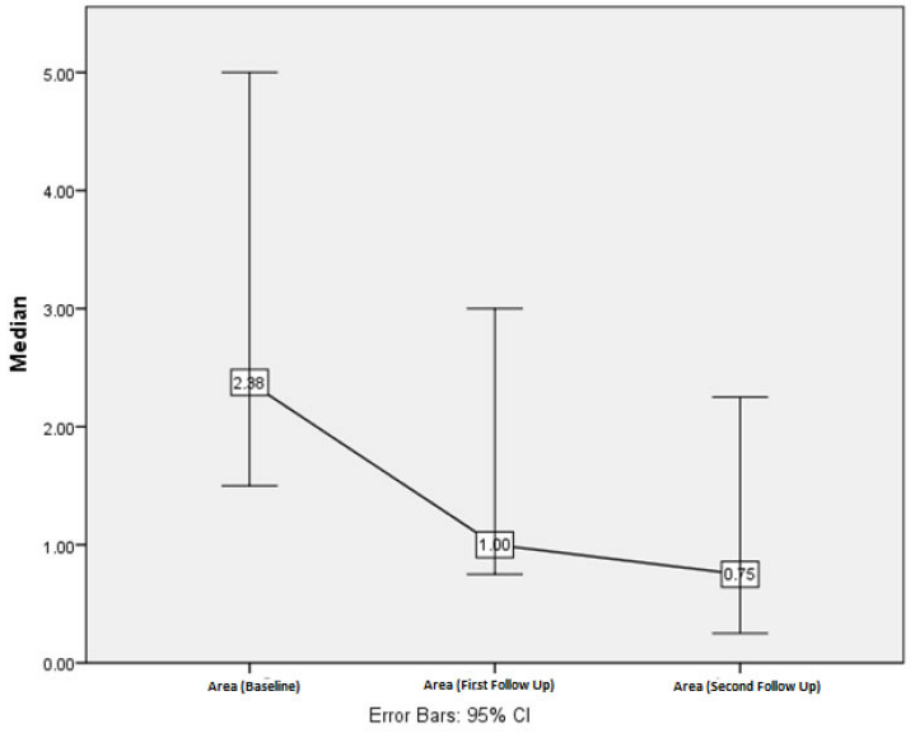

Figure 5. Changes in wound area from baseline, first follow up, and second follow up.

very difficult wound healing processes, hopefully we can solve these problems easier and can improve quality life of the leprosy patients. Intracutaneously injection in this study done after we passed the same study in diabetic wound healing in mice, showed good results and we did also in topical treatment in chronic wound healing using 10% secretom of hUC-MSC gel. Secretome we are using is the same product as we used in all of our research. Compared to applying gel in the chronic wound treatment, some benefits in intracutaneously injection are more effective and efficient, cheaper, easier, less time, sterilized and less contamination product. The results of this study show promising evidence for the Secretome of hUC-MSC use of intracutaneously injection around the wound in chronic trophic wound healing process due to leprosy. The results of this study are expected to be continued into a phase 3 clinical trial with better research methods in order to increase clinical evidence of treatment of trophic wound healing and improve the quality of life due to leprosy patients.

There are several limitations in this research which can then be carried out further. These limitations include the focus of this research which is only pre-post therapy without comparative therapy. It becomes important to compare the effectiveness of test therapy versus standard therapy. There are also shortcomings regarding the minimum dose of secretome used for the treatment of chronic wounds or trophic ulcers. This is important to study further in terms of minimum and optimal doses for efficient therapy. The test parameters in this study focused on clinical and macroscopic parameters. This is a further limitation because there are no markers for wound healing at the molecular level such as VEGF, TGF, and others.

CONCLUSION

The intracutaneous use of "Secretome of human Umbilicord Stem cell or SC-hUC MSC" has been proven effective in spurring the wound healing process especially trophic ulcers due to leprosy. This can be seen from the significant decrease in length, width, and area of the wound between before and after intervention by intracutaneously injection with Secretome of human Umbilicord Stem cell. The use of this intervention has also been tested for safety in phase 2 clinical trials in the absence of evidence of side effects both local and systemic side effects. Suggestions for further research are to conduct further clinical testing (Phase 3) involving larger samples and the use of control media such as antibiotics or placebo in order to increase the evidence base for using Secretome of human Umbilicord Stem cell or SC-hUC MSC intracutaneous healing of trophic ulcers due to leprosy.

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CONFLICT OF INTEREST

The authors declared that they have no conflicts of interest. This research received a grant from Tarumanagara University which is engaged in the field of Education and Science Development. All products and results are not related to any particular group or personal interests.

ETHICAL CONSIDERATION

Approval for this study was granted by the Universitas Tarumanagara Human Research Ethics Committee Institute of Research and Community Engagement (Registration Number: PPZ20192072 and Letter Number: 1007-Int-KLPPM/Untar/VI/2020). The study is also registered on ClinicalTrials.gov under the ID number NCT04134676.

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of this research have been documented in the Tarumanagara University repository.

AUTHORS' CONTRIBUTIONS

Sukmawati Tansil Tan and Siufui Hendrawan designed and managed the project. Sukmawati Tansil Tan, Putri Bennya Aisyah, and Kelvin Cristian Halim performed sample collection.. Yohanes Firmansyah did data collection and analysis. Sukmawati Tansil Tan and Yohanes Firmansyah wrote the manuscript. All authors participated in the revision of this manuscript and approved the submission.

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