Comparative efficacy of topical Adipocyte - derived Mesenchymal Stem Cells-Conditioned Medium (ADMSC-CM) and Amniotic Membrane Mesenchymal Stem Cells-Conditioned Medium (AMSC-CM) on chronic plantar

by Medhi Denisa Alinda

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Comparative efficacy of topical Adipocyte-derived Mesenchymal Stem Cells-Conditioned Medium (ADMSC-CM) and Amniotic Membrane Mesenchymal Stem Cells-Conditioned Medium (AMSC-CM) on chronic plantar ulcers in leprosy: a randomized controlled trial

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ABSTRACT

Introduction: Chronic Plantar Ulcer of Leprosy (CPUL), one of the debilitating disabilities and complications, poses a treatment challenge. Utilization of stem cells, specifically adipocyte-derived mesenchymal stem cells-conditioned medium (ADMSC-CM) and amniotic membrane mesenchymal stem cells-conditioned medium (AMSC-CM), may serve as a novel therapeutic option. This study aims to compare the efficacy of topical ADMSC-CM, topical AMSC-CM, and farmazertin gauze dressing (FGD) only on the healing of CPUL.

Methods: In this randomized controlled trial, our study recruited 54 subjects with CPUL. Subjects were randomly assigned to topical ADMSC-CM (n = 16), topical AMSC-CM (n = 22), or FGD (n = 16) applied every three days for up to 8 weeks. Data were analyzed using SPSS version 20 for Windows.

Results: Healing percentage increased each week in all groups. Statistic differences between groups ($p < 0.05$) were observed for ulcer mean size and depth reduction from week three onwards. No adverse reactions or complications were reported. At the end of the study, based on clinically improved ulcers, topical ADMSC-CM (100.0%) were superior in improving the healing of CPULs compared to topical AMSC-CM (54.55%) and FGD only (50.0%).

Conclusion: ADMSC-CM and AMSC-CM are potential therapeutic agents in the management of CPUL, with ADMSC-CM being superior in overall ulcer improvement.

Keywords: ADMSC-CM, AMSC-CM, CPUL, Tropical Disease, Leprosy.
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INTRODUCTION

Leprosy is a chronic infectious granulomatous disease caused by *Mycobacterium leprae* (*M. leprae*).[1,2] Due to its chronicity and stigma, leprosy may go undiagnosed or untreated. Undiagnosed or untreated leprosy may progress to complications and disabilities. One of the common complications in leprosy with peripheral nerve damage is a chronic ulcer.[3] An ulcer is defined as a loss of continuity of skin tissue up to the dermis or deeper (subcutis).[1] These ulcers are usually found at the plantar pedis for Chronic Plantar Ulcers of Leprosy (CPUL), particularly in bony prominence areas. The plantar pedis is a part of the body that serves in walking; thus, the risk of experiencing trauma is more significant in this area than in other body parts.[3]

Cutaneous wound healing is a complex process involving immune and structural cells, where the secretion of growth factors, cytokines, and chemokines orchestrate the four physiological phases of healing. The classification of skin wounds into acute and chronic is based on the pathogenesis and consequences.[4,5] Acute wounds undergo a series of molecular events resulting in structural

integrity. On the contrary, chronic wounds fail to resolve and are characterized by pathological processes, such as continuous inflammation, persistent infections, and necrosis. From a molecular perspective, a chronic wound has chronic and persistent inflammation as the hallmark.[6] The inflammatory condition in CPUL can be caused by infection and ischemia due to persistent pressure on the wound from disruption of nerve functions.[3]

Stem cells are present in the human body at all stages of life, from the first development to adulthood (various adult stem cells). The primary functions of adult stem cells, such as Adipocyte-Derived Mesenchymal Stem Cells (ADMSC) and Amniotic Mesenchymal Stem Cells (AMSC), are to maintain cell homeostasis in tissues.[7] Since the early twentieth century, stem cells have emerged as a promising therapeutic option for widespread injuries, burns, chronic and deep ulcers, and surgical wounds that are difficult to close.[8-10] The growth factors and cytokines produced in the tissue medium of stem cells in *in vitro* conditions through its metabolite products favored its use as a modality in the process of cell regeneration.[7]

A study reported by Martin-Piedra MA et al., used ADMSC, dental pulp-derived mesenchymal stem cells, Wharton's jelly-derived mesenchymal stem cells, and bone marrow-mesenchymal stem cells for epidermal regeneration by tissue engineering and surgical grafting in animal models illustrated the use of the mentioned stem cells to generate bioengineered human skin substitutes for epidermal repair.[11] A study conducted by Prakoeswa CRS et al., comparing the effects of topical human AMSC-conditioned medium (AMSC-CM) and a mixture of topical human AMSC-CM + vitamin C and topical human AMSC-CM + vitamin E on CPUL applied every three days for up to 8 weeks on the healing of CPUL reported an excellent outcome of AMSC-CM as a therapeutic option in each group, with topical human AMSC-CM + vitamin E giving the best outcome.[9] However, the comparative effects of topical ADMSC-conditioned medium (ADMSC-CM) and AMSC-CM in the healing of CPUL have yet to be evaluated.

Considering the facts, this present study aimed to compare the efficacy and effect of topical ADMSC-CM (Group 1) in gel preparation, AMSC-CM (Group 2) in ointment preparation, and farmazertin gauze dressing (FGD) only (Group 3) applied on the healing of CPUL. Based on those mentioned above, this study aims to evaluate a comparative efficacy of topical ADMSC-CM and AMSC-CM on chronic plantar ulcers in leprosy.

MATERIAL AND METHODS

Study design and patients

This experimental randomized controlled clinical trial was performed using parallel designs involving 54 subjects (16 subjects, 22 subjects, and 16 subjects in group 1, group 2, and group 3, respectively) to ensure a simultaneous follow-up and structured observation. The study utilized consecutive sampling, i.e., enrolling any patients with CPUL who met the inclusion criteria for admission samples at the Dermatology and Venereology outpatient clinic, Dr. Soetomo Teaching Hospital, Surabaya, Indonesia. Randomization was done through computerization.

Inclusion criteria were leprosy patients with CPUL of > 6 weeks, an ulcer depth of < 0.5 cm, and a maximum injury area of 9 cm^2 who did not consume systemic corticosteroid in the last two weeks. The subjects also had no history of diabetes mellitus, blood clotting disorder, antiplatelet use, and hypersensitivity to transparent film dressings or adhesive plasters.

Treatment intervention

After initial history taking and physical examination, subjects who met the inclusion criteria underwent surgical debridement before intervention to remove callus and necrotic tissue and return all ulcers to the initial healing phase, i.e., the coagulation and inflammatory phase. The drug was applied every three days until the ulcer closed or for a maximum of 8 weeks. In cases where CPUL has not resolved within 8 weeks, the subjects will continue with the assigned therapy until complete resolution is achieved with a monthly follow-up. An extensive and deep ulcer measurement and evaluation of side effects and complications of both drugs were monitored weekly. Off-loading was not performed in any subject. However, subjects were advised to reduce standing and walking activities.

Laboratory Testing

The extraction of ADMSC-CM followed the standard procedure of 1) fat tissue sample preparation, 2) MSCs isolation from fat tissue process, 3) propagation of MSCs from isolated fat tissue, 4) characterization of MSCs from fat tissue, and 5) harvesting metabolites. The extraction of AMSC-CM followed the standard procedure of 1) screening of sample, 2) AMSC isolation from amniotic membrane, 3) culture of AMSC in a conditioned medium, 4) characterization of AMSC from amniotic membrane tissue, and 5) process and preparation of topical AMSC. The extraction and preparation of ADMSC-CM and AMSC-CM were determined further in Supplemental Material 1.

Statistical Analysis

All enrolled patients were evaluated. Statistical analyses were performed using a Statistical Packages for Social Sciences (SPSS) version 20.0 (USA). Descriptive data were presented as number (%) or mean ± SD/median (min-max), as appropriate. Statistical analyses were performed with the non-parametric Kruskal Wallis to determine significant differences between samples before and after treatment within the same group and between two/three groups. A P-value of < 0.05 was considered statistically significant.

RESULTS

The average age of subjects in all groups was 44.57±6.85 years old. At the start of the study, subjects had ulcers with an average size of 1.38±1.19 cm, 1.99±1.19 cm, and 1.97±1.84 cm with an average width of 0.62±0.85 cm, 0.37±0.11 cm, and 0.79±1.06 cm in group 1, group 2, and group 3, respectively. There was no dropout in the study. All the patients who were included completed the study protocol. Patient demographics at the start of the study are listed in Table 1.

The patients were evaluated weekly for the progress of ulcer size and depth and evaluation of side effects and complications

Table 1. Baseline characteristic of respondents

Variables	Group 1 (N=16)	Group 2 (N=22)	Group 3 (N=16)	p
Sex, n (%)				
Male	9 (56.20)	12 (54.50)	10 (62.50)	0.882
Female	7 (43.80)	10 (45.50)	6 (37.50)	
Age (years) (mean±SD)	45.19±7.22	43.27±7.77	45.75±4.97	0.612
Occupation, n (%)				
Requires long-standing	7 (43.80)	12 (54.50)	7 (43.80)	0.738
Not require long-standing	9 (56.20)	10 (45.50)	9 (56.20)	
Ulcer location, n (%)				
Forefoot	10 (62.50)	13 (59.10)	11 (68.80)	0.524
Midfoot	2 (12.50)	3 (13.60)	2 (12.50)	
Hindfoot	4 (25.00)	6 (27.30)	3 (18.80)	
Ulcer average size (cm) (mean±SD)	1.38±1.19	1.99±1.19	1.97±1.84	N/A
Ulcer average width (cm) (mean±SD)	0.62±0.85	0.37±0.11	0.79±1.06	N/A

*Kruskal-Wallis test: statistically significant if p-value less than 0.05; N/A: Not assessed

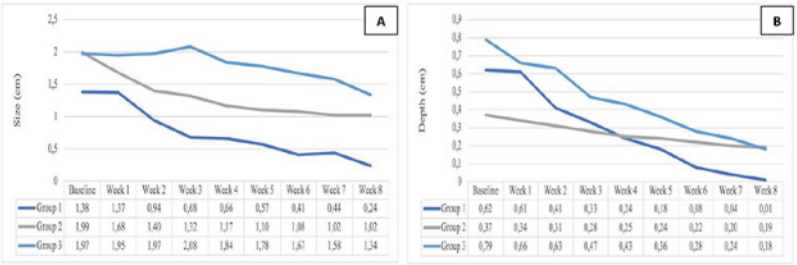

Figure 1. The weekly (A) mean size reduction and (B) mean depth reduction of ulcers between three groups

Table 2. Mean reduction of ulcer dimension (size and depth)

Variables	Group 1 (n = 16)	Group 2 (n = 22)	Group 3 (n = 16)	P
Ulcer size reduction (cm) (mean±SD)				
Week 1	1.37±1.20	1.68±1.20	1.95±1.81	0.451
Week 2	0.94±1.06	1.40±1.14	1.97±1.89	0.085
Week 3	0.68±0.88	1.32±1.14	2.08±1.94	0.021*
Week 4	0.66±1.02	1.17±1.23	1.84±1.92	0.039*
Week 5	0.57±0.94	1.10±1.19	1.78±1.96	0.033*
Week 6	0.41±0.79	1.08±1.22	1.67±1.95	0.015*
Week 7	0.44±0.77	1.02±1.24	1.58±1.95	0.047*
Week 8	0.24±0.55	1.02±1.29	1.34±1.82	0.019*
Ulcer depth reduction (cm) (mean±SD)				
Week 1	0.61±0.81	0.34±0.13	0.66±1.03	0.279
Week 2	0.41±0.70	0.31±0.13	0.63±1.03	0.087
Week 3	0.33±0.63	0.28±0.15	0.47±0.78	0.045*
Week 4	0.24±0.50	0.25±0.17	0.43±0.65	0.058
Week 5	0.18±0.35	0.24±0.18	0.36±0.65	0.083
Week 6	0.08±0.25	0.22±0.18	0.28±0.47	0.002*
Week 7	0.04±0.13	0.20±0.17	0.24±0.48	0.002*
Week 8	0.01±0.03	0.19±0.18	0.18±0.46	0.001*

*Kruskal-Wallis test: statistically significant if p-value less than 0.05; N/A: Not assessed

of the drugs. The mean percentage of ulcer size and depth healing per week between groups is shown in Figure 1. The percentage of healing, measured by the percentage size reduction of ulcers, increased every week. The average reduction at the end of the study for ulcer size was 1.13±0.65 cm, 0.97±0.10 cm, and 0.63±0.03 cm with an average reduction of the ulcer depth of 0.79±0.82 cm, 0.19±0.05 cm, and 0.62±0.59 cm for group 1, group 2, and group 3, respectively (Table 2).

A significant improvement in ulcers at the end of the study for group 1 and group 2 was remarkable. Comparison between groups yielded statistically significant results from week III to week VIII for mean ulcer size and depth reduction ($p<0.05$). Clinical improvement in the ulcers at the end of the study for group 1 was outstanding, followed by groups 2 and 3 (Table 3 and Figure 2-4).

DISCUSSION

Management of CPUL is challenging due to its chronicity, the nature of the treatment affecting patients and their families socioeconomically, and the mental aspect to the patients.[12] Therapeutic options for CPUL start with prevention, such as daily inspection of the feet, cleaning and drying of the interdigital, straight nail cutting, hydration, callus removal, examinations of the deformities of the feet, and others.[13] However, in patients with CPUL already ongoing, the approach must be multidisciplinary. Other than the standardized leprosy chemotherapy, novel treatment such as applying Stem Cells (SC) could be an option as described in this study.

Stem cells are unspecialized cells that can self-renew and differentiate into one or more developmental fates (totipotent/omnipotent, pluripotent, and multipotent SC). SC is crucial in tissue homeostasis and repair. The differentiation potential of stem cells varies among stem cells and depends mainly on their origin.[14] In this study, we investigated the topical use of ADMSC-CM and AMSC-CM on the healing of CPUL.

ADMSCs are mesenchymal stem cells of mesodermal origin with low oxygen consumption and a considerable proliferation rate that differentiate into

endodermal, mesodermal, and ectodermal cell lines. In recent years, they have been an alternative option to bone marrow-derived stem cells. Naturally, ADMSCs are a subcutaneous adipose tissue component that lies in immediate proximity to cutaneous wounds and can foster wound repair through their migratory ability. Abundant secretome of ADMSCs may orchestrate wound healing in a paracrine fashion, such as the keratinocyte growth factor (KGF), epidermal growth factor (EGF), members of the vascular endothelial growth factor (VEGF) family, platelet-derived growth factor, to name a few. The formerly mentioned growth factors promote fibroblast and keratinocyte migration, proliferation, and differentiation. Moreover, ADMSCs were found to be anti-inflammatory through the secretion of soluble factors, such as interleukin-10.[15-17]

Table 3. Clinical improvement of the ulcers at the end of the study

Variables	Group 1 (N=16)	Group 2 (N=22)	Group 3 (N=16)
Clinical Status, n (%)			
Improved	16 (100.00)	12 (54.55)	8 (50.00)
Persisted	0 (0.00)	10 (45.45)	8 (50.00)
Worsened	0 (0.00)	0 (0.00)	0 (0.00)

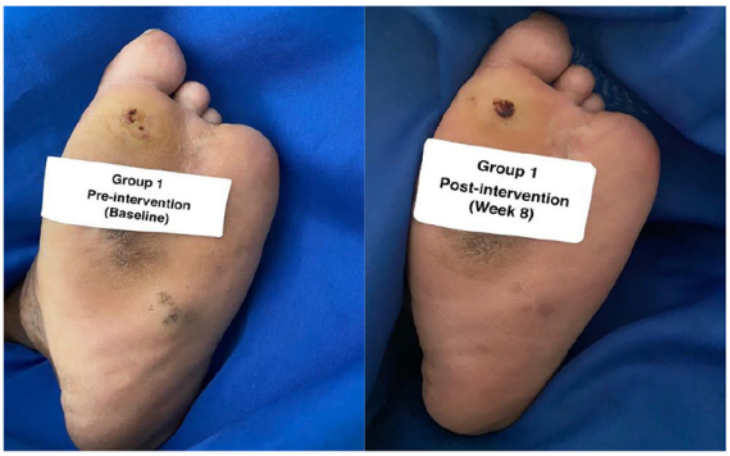

Figure 2. (A) Chronic ulcer before application in group 1 and (B) improved ulcer at week 8 after topical application.

In wound healing, ADMSC helped to restore homeostasis through several evidence: 1) In the inflammatory phase, a study conducted by Li et al. on ADMSC-exosomes (AME) conferred a protective effect by the overexpression of Nrf2 that could significantly stimulate the healing of foot wounds in diabetic rats model by inhibiting the inflammatory proteins expression and reactive oxygen species production; and 2) In cell proliferation and migration phase when various growth factors in the traumatic microenvironment regulate angiogenesis, cell proliferation and migration.[18,19] A study conducted by Yang T et al., reported a positive effect of the labeled AME after two weeks and participated in vascularization in a rat and mice model.[20] MSCs are also reported to manipulate macrophages to recruit keratinocytes and fibroblasts. Macrophages release EGF and transforming growth factor (TGF)-α to stimulate the migration and proliferation of keratinocytes. Fibroblasts increase the migration and proliferation of keratinocytes via EGF, fibronectin, and KGF.[21] Lastly, in the remodeling phase, a study conducted in mice with dorsal skin incisions *in vivo* or human dermal fibroblast *in vitro* by Wang L et al., found that AME promotes extracellular matrix reconstruction in cutaneous wound repair by regulating the ratios of collagen type III to type I, TGF-β3 to TGF-β1, and Matrix Metalloproteinase-3 (MMP-3) to Tissue Inhibitor Of Matrix Metalloproteinase-1

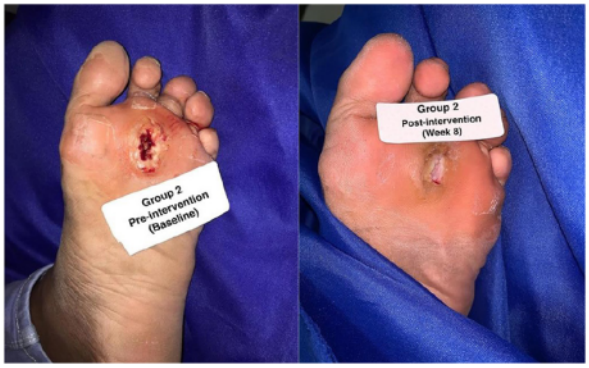

Figure 3. (A) Chronic ulcer before application in group 2 and (B) partially improved ulcer at week 8 after topical application

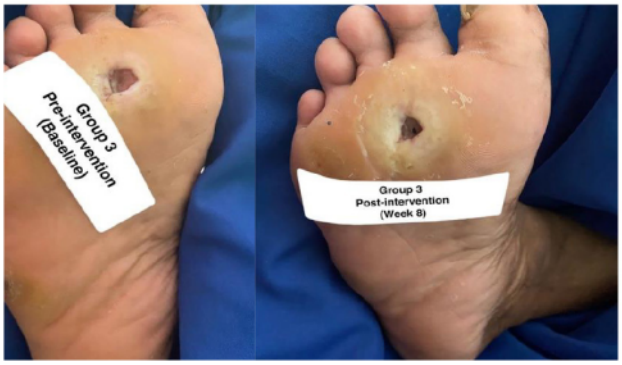

Figure 4. (A) Chronic ulcer before application in group 3 and (B) partially improved ulcer at week 8 after topical application

(TIMP-1), and by regulating fibroblast differentiation to mitigate scar formation.[22]

Amnion is the innermost fetal membrane, up to 0.5 mm thick and avascular.[23] The human amniotic epithelium is derived from pluripotent epiblasts, unlike other components of the placenta.[24] Amnion mesenchymal cells possess stem cell characteristics that indicate outstanding clonogenicity and differentiation potency. AMSCs are capable of differentiation into all three germ layers.[25] With this property, AMSCs have been utilized for post-operative and post-traumatic skin defects, burn injuries, chronic ulcers, peritoneal, intra-oral and genital reconstruction, and many more.[26]

AMSC-exosomes support wound healing through their anti-inflammatory and anti-fibrotic characteristics. It is reported that human amnion epithelial cells (hAECs) derived exosomes include various proteins involved in mitogen-activated protein kinase (MAPK) signaling and apoptotic/developmental cell signaling pathways. These exosomes also carry a remarkable range of microRNA, which control the signaling of fibrosis, including Hippo, PI3K-Akt and focal adhesion, TGF-β and Ras pathways. Human AEC exosomes exert their anti-inflammatory effect through the reduction of neutrophil myeloperoxidase activity.[25] In addition, hAECs were confirmed to express growth factors (EGF, KGF, and hepatocyte growth factor), anti-inflammatory cytokines (e.g., IL-10) and antibacterial benefits for wound-healing.[26] A study conducted by Jiang LW et al., using AEC to develop a new skin substitute successfully developed stratified epithelium on the de-epidermized dermis with main ultrastructural features, such as desmosomes, hemidesmosomes, and basement membrane zone, similar to normal skin.[27] In the highlight of our study, ADMSC-CM and AMSC-CM improved healing rates of CPUL; specifically, ADMSC-CM shows greater reductions in ulcer size and depth as well as clinical improvements compared to AMSC-CM.

Surgical debridement was performed on all patients prior to applying the gel to remove calluses and necrotic tissues. Removing calluses and necrotic tissues is critical for wound healing management because they can be a source of infection that impedes the healing process. Calluses also apply constant pressure to the ulcer, preventing epithelialization during the healing process.[12,28]

In conclusion, ADMSC-CM and AMSC-CM were beneficial in treating CPUL and presented as an alternative treatment of CPUL. There were no complications or adverse reactions observed in any subject. Additional controlled prospective clinical trials, however, will be necessary to demonstrate its efficacy definitively.

The present study has two limitations. One, the number of samples within each group was not equal. In addition, this study did not perform off-loading (reducing or removing the load on the legs through bed rest, crutches, wheelchairs, walkers, and special footwear) on any of the subjects recruited.

CONCLUSION

ADMSC-CM and AMSC-CM are potential therapeutic agents in the management of CPUL, with ADMSC-CM being superior in overall ulcer improvement.

CONFLICT OF INTEREST

The authors report no conflict of interest.

ETHICAL CONSIDERATION

This clinical study was approved by the ethical committee board of Dr. Soetomo Teaching Hospital Surabaya (Ref: 0052/LOE/302.4.2/VII/2020) prior to the study.

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None.

AUTHOR CONTRIBUTION

All authors contributed to the preparation of the manuscript from initial conceptualization, study design, intellectual content, literature search, clinical studies, data acquisition, data analysis, manuscript preparation, and review of the earliest draft of the manuscript.

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