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Assessing keloid treatment efficacy: a comparison of intralesional umbilical-cord mesenchymal stem cells, their conditioned medium, and triamcinolone acetonide injection through macroscopic and microscopic examination

Anastasia Dessy Harsono[1,2*], Ismail Hadisoebroto Dilogo[3,4,5,6,7], Theddeus Octavianus Hari Prasetyono[3,4,8], Marcel Prasetyo[9], Retno Asti Werdhani[10], Sri Widia Jusman[11], Nuryati Chairani Siregar[12], Hardisiswo Soedjana[13]

[1]Department of Plastic and Reconstructive Surgery, Gatot Subroto Army Hospital, Jakarta, Indonesia;
[2]Doctoral Program in Medical Sciences Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia;
[3]ICTEC (Indonesian Clinical Training and Education Center), Cipto Mangunkusumo Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia;
[4]Medical Technology Cluster, Indonesian Medical Education and Research Institute, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia;
[5]Stem Cell Medical Technology Integrated Service Unit, Cipto Mangunkusumo Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia;
[6]Stem Cell and Tissue Engineering Research Center, Indonesian Medical Education and Research Institute, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia;
[7]Department of Orthopaedic and Traumatology, Cipto Mangunkusumo Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia;
[8]Division of Plastic and Reconstructive Surgery, Department of Surgery, Cipto Mangunkusumo Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia;
[9]Department of Radiology, Cipto Mangunkusumo Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia;
[10]Department of Community Medicine, Cipto Mangunkusumo Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia;
[11]Department of Biochemistry and Molecular Biology, Cipto Mangunkusumo Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia;
[12]Department of Anatomical Pathology, Cipto Mangunkusumo Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia;
[13]Department of Plastic and Reconstructive Surgery, Hasan Sadikin Hospital, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia.

*Corresponding author:
Anastasia Dessy Harsono;
Department of Plastic and Reconstructive Surgery, Gatot Subroto Army Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia;
anastasiadessyharsono@gmail.com

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ABSTRACT

Background: Current keloid treatment involves intralesional injection of triamcinolone acetonide (TA), which, despite its usage, is associated with high recurrence rates and adverse effects. Mesenchymal stem cells (MSCs) exhibit potent proliferative abilities and can curb fibroblast activity and proliferation within keloids. It is now known that umbilical cord mesenchymal stem cells (UC-MSCs) have been shown to have greater proliferative potential than bone marrow-derived MSCs (BM-MSCs), and other advantages of UC-MSCs include being easily accessible and less immunogenic. To assess the viability of administering umbilical cord MSC (UC-MSC) and its conditioned medium (UC-CM) via intralesional injection compared to TA in reducing macroscopic keloid volume and type 1:3 collagen ratio.

Methods: This randomized controlled trial enrolled twenty-four keloid patients by consecutive sampling. Eligible patients were required to have keloids on the chest, back, abdomen, or extremities. Patients with hypertrophic scars, a history of kidney failure, hypertension, blood disorders, malignancy, pregnancy, breastfeeding, or keloid treatment were excluded. Sociodemographic data, keloid size, and tissue biopsies were collected during scheduled visits. Bivariate analyses applied were considered significant at a p-value of <0.05.

Results: The study revealed that the most significant decrease in macroscopic volume occurred within the UC-MSC group, followed by the UC-CM group, and then the TA group (UC-MSC: 50.24% ± 3.58%; UC-CM: 43.97% ± 3.04%; TA: 33.53% ± 2.64; $p = 0.004$. The UC-CM group exhibited the most substantial decrease in the type 1:3 collagen ratios (4.80±0.26), with UC-MSC (4.60(4.15-8.05)) and TA (3.96(1.63-4.14)) following in sequence ($p=0.002$).

Conclusion: The findings of this study indicate that the use of UC-MSC and UC-CM exhibits promising superiority over TA in terms of reducing macroscopic keloid volume and type 1:3 collagen ratio.

Keywords: keloid therapy, mesenchymal stem cells, keloid volume, type 1:3 collagen ratio.
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INTRODUCTION

Keloids represent an excessive growth of scar tissue that forms on incisional scars or skin trauma, extending beyond the original wound margin without regression. These formations disrupt physical appearance and induce itching, pain, and emotional distress.[1–4] The prevalence of keloids is notably higher in individuals with darker skin tones, with data indicating an incidence of 6–16% in African descent populations and elevated rates in Hispanic and Mongoloid races.[5,6]

This condition substantially impairs quality of life, and though various treatments have been attempted, recurrence rates range from 45% to 100%.[3,6,7] Various therapeutic methods have been used, from surgical to non-surgical approaches.[6] Therapeutic approaches encompass surgical and non-surgical methods, ranging from excision and grafting to triamcinolone acetonide (TA) injection, pressure garments, and laser therapy.[7,8] Despite these interventions, the quest for effective, non-invasive, and economical treatments with fewer adverse effects continues.[7,9]

Mesenchymal stem cells (MSCs) have emerged

as a promising avenue for allogeneic cell therapy due to their prolific proliferation, paracrine effects, diverse differentiation capabilities, and immunomodulatory properties[10] These versatile cells can be sourced from various tissues such as the umbilical cord, spinal cord, fat tissue, peripheral blood, and dental pulp. MSCs, aside from their ease of propagation, exhibit the ability to mitigate fibroblast activity and proliferation within keloid tissue. A study conducted by Sato et al. showcased the suppression of TGF-β-induced α-smooth muscle actin (α-SMA) and type-1 collagen upregulation in keloid fibroblasts through the administration of amnion-derived MSCs, whereas no significant impact was observed in mature fibroblasts.[11]

Researchers have turned to conditioned medium (CM) derived from MSC secretions to overcome the practical constraints and expenses tied to cell-based therapies. This metabolic byproduct contains bioactive factors like secretomes, microvesicles, and exosomes in cell culture medium. The advantages of mesenchymal stem cell conditioned medium (MSC-CM) are multifaceted; it can quell local immune reactions, diminish oxidative stress, inhibit fibrosis, promote angiogenesis, and encourage stem cell activity and differentiation in healthy tissues.[11]

It is now known that umbilical cord mesenchymal stem cells (UC-MSCs) have been shown to have greater proliferative potential than bone marrow-derived MSCs (BM-MSCs),[12] and other advantages of UC-MSCs include being easily accessible and less immunogenic.[13–15] Even with these potentials, it becomes imperative to investigate the efficacy and mechanisms underlying keloid regression facilitated by umbilical cord MSC (UC-MSC) therapy and umbilical cord MSC conditioned medium (UC-CM) in comparison to triamcinolone acetonide (TA). This study aims to evaluate the practicality of intralesional administration of UC-MSC and UC-CM for keloid treatment, relating these approaches to clinical improvements by reducing macroscopic keloid volume and type 1:3 collagen ratio.

METHODS

Research design

This research constitutes a double-blind, randomized controlled trial investigating how UC-MSC, UC-CM, and TA impact keloids. The primary focus of this study is to assess the reduction in macroscopic keloid volume and alterations in type 1:3 collagen ratio. To maintain impartiality, the laboratory team prepared the substances in indistinguishable syringes, following a randomization process, without disclosing this information to the researchers. Data analysis was performed by statisticians and clinicians not part of the research team.

Research population

The research participants for this study consisted of individuals between the ages of 18 - 55 who were diagnosed with keloids and were receiving treatment at the Gatot Soebroto Army Hospital in Jakarta from October 2021 onwards. Ethical clearance was obtained before including them in the study, and recruitment continued until the sample size of 24 participants (power=0,95) (8 of each group) was achieved by April 2022.[16]

Consecutive sampling was employed as the method for selecting subjects, followed by allocating participants using computerized block randomization with a block size of 3. The sequence for random allocation was generated by administrative personnel, participants were enrolled by one of the researchers, and their assignment to specific interventions was managed by laboratory staff. Eligible patients were required to have keloids that measured between 2 to 10 centimeters in length and had a thickness ranging from 3 to 5 millimeters. These keloids should have been on the chest, back, abdomen, or extremities. The study criteria excluded patients with hypertrophic scars, a history of kidney failure, hypertension, blood disorders, malignancy, pregnancy, breastfeeding, or previously undergone keloid treatment.

Materials and workflow

The research timeline is depicted in Figure 1. Initially, patients were screened by measuring the length and thickness of their keloids using a ruler. Those patients meeting the study's inclusion criteria were randomly divided into three groups. In each group, patients received an identical injection volume of 1 mL for every cubic centimeter of keloid volume, administered using a 1 mL syringe and a 27G needle. Ultrasound guidance was employed to inject the substances into the center of the keloid lesion at a 30–45-degree angle, using an in-plane technique to ensure consistent

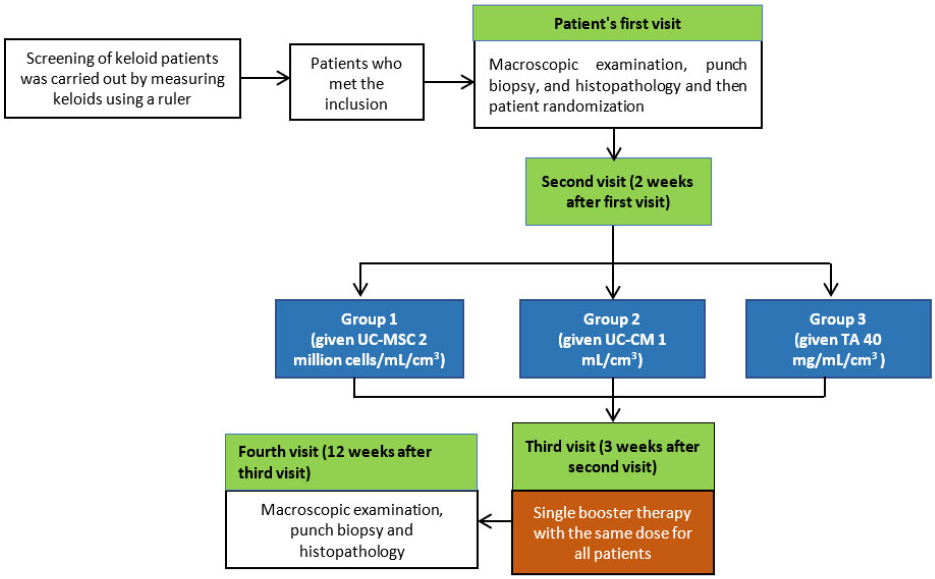

Figure 1. Research flow diagram. POSAS (Patient and Observer Scar Assessment Scale); UC-MSC (umbilical cord mesenchymal stem cells); UC-CM (umbilical cord mesenchymal stem cells conditioned medium); TA (triamcinolone acetonide).

pressure. After that, all of the samples were grouped into 3 groups. Group 1 received UC-MSC at a concentration of 2 million cells/mL/cm^3, Group 2 received UC-CM at a rate of 1 mL/cm^3, and Group 3 received TA at 40 mg/mL/cm^3.

To prepare UC-MSC and UC-CM, a ten-centimeter segment of the umbilical cord was collected in a 50 mL transport medium containing alpha minimal essential medium (MEM), amphotericin B, and penicillin/streptomycin. The umbilical cord was carefully washed with povidone-iodine and phosphate-buffered saline (PBS) to remove blood and betadine. The umbilical arteries and veins were discarded, and the remaining umbilical cord was finely minced and placed in a complete medium.[17]

UC-CM was created using alpha-MEM and Dulbecco's modified Eagle's medium (DMEM), supplemented with amphotericin B, penicillin/streptomycin, TC, L-glutamine, autologous or allogeneic cord blood serum, and human AB serum. Three explants with Wharton's jelly down were placed in each well of a 12-well plate and cultured in triplicate for all media. The cultures were incubated at 37°C and 5% CO2 and monitored daily for cell growth and contamination. Contaminated wells were removed, and when the cells reached 90% confluence, they were harvested using TrypLE Select and counted using the dye exclusion method. A new medium was added, and the plate was reincubated for subsequent cultures.[17]

Each patient received an initial dose and a booster dose. The percentage of keloid volume regression in each treatment group was calculated by measuring the difference in volume before and after therapy using a ruler, expressed as a percentage. The keloid tissues' volume measurements and punch biopsies were performed on two occasions: initially during the first meeting and subsequently 17 weeks later. Anatomical pathology assessments included Sirius red staining to examine collagen structure when observed through a polarizing lens. To calculate changes in the ratio of type 1 to type 3 collagen levels, the ratio of collagen before treatment was divided by the ratio of collagen after each treatment. Under a polarizing lens, type-3 collagen exhibits a green birefringence, while type-1 collagen displays a yellow birefringence (Figure 2). The collagen ratio was determined by analyzing the composition of type 1:3 collagen in Sirius red staining under polarizing lenses using the ImageJ program.

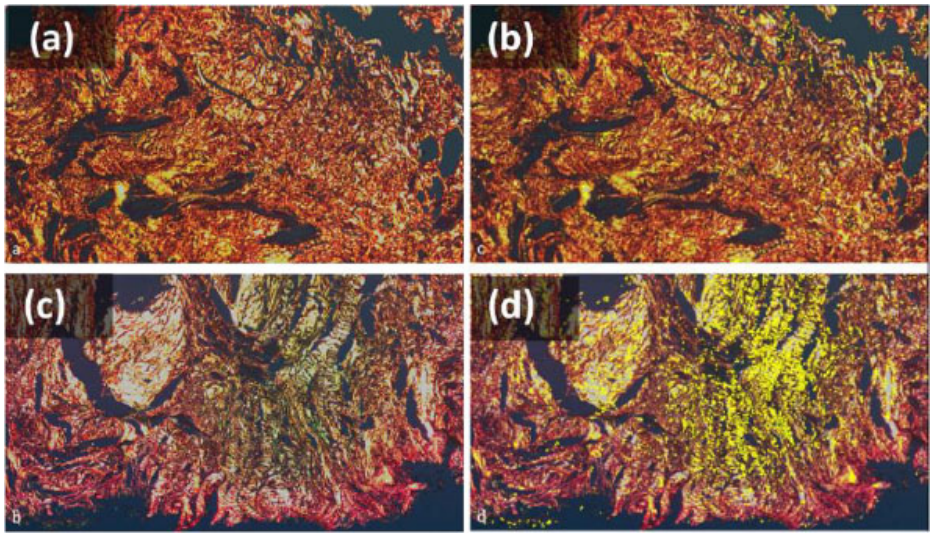

Figure 2. Examine keloid tissue using Sirius Red histopathology staining when observing through a polarized lens. (a) Before treatment, the prevailing collagen type was predominantly type-1, appearing as an orange-yellow hue when viewed through a polarizing lens. (b) Following the administration of UC-MSC treatment, regions exhibiting type-3 collagen appeared in green (center). (c) (d) The chosen regions appeared yellow After identifying and selecting type-3 collagen areas using the ImageJ application.

Research ethics and funding

The research protocol has received approval from the Health Research Ethics Committee at the Faculty of Medicine, University of Indonesia, denoted by the reference number KET-1206/UN2.F1/ETIK/PPM.00.02/2021. To protect the confidentiality of subjects, their identities were kept confidential, and informed consent was obtained from all participants. This trial is registered on clinicaltrials.gov under the identifier NCT05887804. The study was conducted at a single center, specifically at the Jakarta Gatot Soebroto National Army Hospital. Funding for the trial was provided through a research grant from the Directorate of Research and Development at the University of Indonesia under the International Indexed Publication program.

Statistical analysis

Upon the completion of data collection, the subsequent steps will involve data processing, which encompasses editing, coding, tabulation, data entry, and data cleansing, employing software tools like Microsoft Excel 2016 and IBM SPSS Statistics 25. This study's data analysis methods encompass univariate and bivariate analyses. Univariate analysis was conducted to establish the frequency distribution of the research variables. Bivariate analysis, on the other hand, was performed for each hypothesis. In the case of normally distributed data, the Anova Test was utilized as the statistical test in bivariate analysis. In contrast, the Kruskal-Wallis test was used if the data did not conform to a normal distribution. Subgroup analyses were executed employing the independent T-test when the data distribution was normal; otherwise, the Mann-Whitney test was applied. The significant p-value was <0.05.

RESULTS

A total of 24 research participants were enlisted based on the predetermined inclusion and exclusion criteria, with 8 individuals assigned to each group. The recruitment phase spanned from January 6, 2022, to February 10, 2022, until the required sample size was attained. Importantly, no participants withdrew from the study, ensuring that all collected

Table 1. Basic characteristics of research subjects between groups

Characteristics	UC-MSC (n = 8)	UC-CM (n = 8)	TA (n=8)	p-value
Gender; n(%)				
Man	1 (12.5)	0 (0)	0 (0)	0.352[c]
Woman	7 (87.5)	8 (100)	8 (100)	
Age (years)	30.38±1.99	29.88±3.54	27.88±1.83	0.770[b]
BMI (kg/m^2)	21.93±0.87	24.30±1.56	24.42±1.57	0.338[a]
Smoking status; n(%)				
Yes	1 (12.5)	0 (0)	0 (0)	0.352[c]
No	7 (87.5)	8 (100)	8 (100)	
Blood pressure (mmHg)				
Systolic	112.88±2.64	114.25±3.28	114.12±3.31	0.942[b]
Diastolic	70.12±2.69	72.12±2.92	75.75±2.55	0.352[b]
Keloid location				
Trunk	3	5	5	0.511[c]
Upper extremities	5	3	3	

[a]Kruskal-Wallis test, [b]One-way Anova test, [c]Chi-square test. UC-MSC: umbilical cord mesenchymal stem cells; UC-CM: umbilical cord mesenchymal stem cells conditioned medium; TA: triamcinolone acetonide; BMI: body mass index.

Table 2. The percentages of macroscopic keloid volume regression

Treatment	Macroscopic volume regression (%)	p-value	Ratio	p-value
UC-MSC	50.24±3.58		MSC-CM	0,506
UC-CM	43.97±3.04	**0.004***	MSC-TA	**0.003***
TA	33.53±2.64		CM-TA	0.082

*significant p-value (p<0.05). UC-MSC: umbilical cord mesenchymal stem cells; UC-CM: umbilical cord mesenchymal stem cells conditioned medium; TA: triamcinolone acetonide.

Table 3. The reduction ratio of type 1:3 collagen ratio

Treatment	Reduction ratio of Type 1:3 collagen ratio	p-value	Comparison	p-value
UC-MSC	4.60 (4.15-8.05)		MSC-CM	0.529[b]
UC-CM	4.80±0.26	**0.002***[a]	MSC-TA	**0.001***[b]
TA	3.96 (1.63-4.14)		CM-TA	**0.009***[b]

[a]Kruskal-Wallis test, [b]Mann-Whitney test. UC-CM: umbilical cord mesenchymal stem cell conditioned medium; UC-MSC: umbilical cord mesenchymal stem cells; TA: triamcinolone acetonide. *significant p-value (p<0.05).

data could be included in the subsequent analysis. Before the intervention, the fundamental characteristics of the research participants are detailed in Table 1. Based on the three groups, most samples were female, with no smoking history. The UC-MSC group had the highest mean age of 30.38±1.99 years compared to the other groups. The UC-MSC group had keloids in the upper extremity area, while in the UC-CM and TA groups, most had keloids in the body area. Notably, there were no noteworthy disparities between the groups concerning age, BMI, blood pressure, and keloid location. The distribution of sex, smoking status, and age was well-balanced across the treatment groups. Furthermore, there were no statistically significant differences in the locations of the keloids among the three treatment groups.

Macroscopic volume reduction

The results of the Shapiro-Wilk normality test indicated that the data distributions were normally distributed in all three groups. Consequently, we employed a one-way ANOVA test. Based on the analysis of therapy type on microscopic volume regression, there was a significant difference between each group (p=0.004). Of the three groups, the UC-MSC group produced the highest percentage of microscopic volume regression compared to the other groups, which was 50.24±3.58%, followed by the group that received UC-CM therapy (43.97±3.04%), and TA (33.53±2.64%). However, a significant microscopic volume regression ratio was only found in MSC-TA (p=0.003) (Table 2).

Type 1:3 collagen ratio

The Shapiro-Wilk normality test revealed abnormal data distribution in the UC-MSC group (p=0.01) and the TA group (p=0.00). Consequently, we proceeded with the Kruskal-Wallis hypothesis test, which yielded statistically significant findings. Additionally, the Mann-Whitney post-hoc test indicated a significant distinction between the UC-MSC group compared to the TA group and the UC-CM group compared to the TA group (Table 3).

DISCUSSION

This research discovered that the most substantial reduction in keloid volume, as observed through macroscopic examination, was observed in the group treated with UC-MSC. Following this, the UC-CM and TA groups exhibited decreasing percentages in sequence (UC-MSC: 50.24%±3.58%; UC-CM: 43.97%±3.04%; TA: 33.53%±2.64%; p=0.004), and these differences were statistically significant. When comparing these groups, a significant difference was evident between UC-MSC and TA (p=0.003). Still, no significant differences were observed between UC-MSC and UC-CM or between UC-CM and TA. Multiple

studies have documented the unique tumoricidal properties of UC-MSC, characterized by a high expression of tumor suppressor genes and pro-apoptosis genes.[18,19] Both UC-CM and the lysate derived from UC-MSC inhibit the growth of breast and ovarian adenocarcinomas and osteosarcoma cells in laboratory settings. Additionally, the successful treatment of congenital abdominal hernias involved the application of a baby's umbilical cord, containing Wharton's jelly, to the hernia site. This approach resulted in no scarring or keloid formation due to the tumoricidal attributes of UC-MSC.[18] There have not been any studies comparing the effect of UC-MSC, UC-CM, and TA in reducing keloid volume in humans.

The findings of this study align with a study conducted by Arjunan et al.[18], which observed a reduction in both keloid volume and weight in mice with congenital immune diseases following the injection of UC-CM compared to controls (CM derived from human skin fibroblasts) in both in vitro and in vivo experiments, conducted over 30 days. This underscores the tumoricidal properties of UC-MSC, as it hinders the growth of various cancers in both laboratory settings and living organisms. In another investigation by Liu et al. 2018, it was confirmed that UC-MSC upregulates the expression of tumor suppressor genes and anti-apoptotic genes compared to other stem cell types like human embryonic stem cells and bone marrow MSC. Additionally, UC-CM was shown to impede the growth of lymphoma cells, indicating the presence of anti-cancer substances secreted by UC-CM. Moreover, antifibrotic effects have been detected in CM derived from adipose tissue and bone marrow MSC.[19] UC-CM and UC-MSC contain tumoricidal compounds that inhibit the proliferation of keloid cells, especially considering that keloids exhibit characteristics akin to benign tumors with uncontrolled growth. [18] This observation is substantiated by the significant reduction in keloid tissue volume seen in the UC-CM and UC-MSC treatment groups. In a study focusing on keloid cells isolated from Asian populations, the tumoricidal impact of UC-CM and UC-MSC was linked to an increase in the expression of proapoptotic and autophagy-related genes (BECLIN-1, BAX, ATG5, ATG7), along with a decrease in anti-apoptotic genes (SURVIVIN), which operate during the mitotic phase, thereby restraining the proliferation of keloid cells.[18,19]

In this investigation, it was observed that the reduction in the type-1:3 collagen ratio was most pronounced in keloid cells treated with UC-CM injection, followed by UC-MSC and TA (UC-MSC: 4.60 (4.15-8.05); UC-CM: 4.8 ± 0.26; TA: 3.96 (1.63-4.14); p=0.002), and this difference was statistically significant. A significant difference was also noted between UC-MSC and TA and between UC-CM and TA. In contrast, the difference between UC-MSC and UC-CM was not statistically significant. The identified keloid genetic marker is TGF-β or the SMAD family, which plays a role in pathological fibrogenesis by promoting fibroblast proliferation and increasing the synthesis and deposition of type-1 collagen more than type-3 collagen.[20] In keloids, apart from increased collagen production, the ratio of type-3 to type-1 collagen is lower than in normal skin, contributing to keloids' denser and stiffer tissue characteristics.[3] While the procollagen type-1 mRNA composition in keloids is significantly higher than in normal skin, the composition of procollagen type-3 mRNA remains unchanged. Consequently, the procollagen type-1/type-3 mRNA ratio in keloids significantly increases (22.1) compared to normal skin (5.2). Conversely, in hypertrophic scars, the type-1:3 collagen ratio averages 7.73, significantly lower than in keloids (17.28).[21] In this research, it was found that the type-1 collagen to type-3 collagen ratio aligned with the theoretical expectation, which was 15.44. Researchers suggest that the reduction in this ratio in the groups treated with UC-MSC and UC-CM was attributed to the presence of IL-10 and other antifibrotic factors produced by UC-MSC. This reduction in the type-1 collagen ratio is consistent with a study by Sato et al.[11], which demonstrated that UC-CM could decrease type-1 collagen production in keloid fibroblasts by lowering TGF-β levels. No study compares the type 1:3 collagen ratio between UC-MSC, UC-CM, and TA interventions. However, this study's findings align with an analysis by Chen[22], which observed that conditioned media from adipose-derived stem cells reduced the expression of type 1:3 collagen ratio and smooth muscle actin, based on in-vitro and in-vivo experiments. This reduction serves as a preventative measure against fibrosis in human skin fibroblasts. On the other hand, conditioned media from adipose-derived mesenchymal stem cells significantly increased the expression of MMP-1 and, in a dose-dependent manner, decreased cell survival, the expression of fibrosis-related markers, tissue inhibitor of metalloproteinases-1, the production of collagen, and type 1:3 collagen ratio. These findings indicate that conditioned media from adipose-derived stem cells effectively hinder fibrosis-associated factors and regulate the remodeling of the extracellular matrix in human skin fibroblasts.[23]

This study comes with both strengths and limitations. Among its strengths, it is the first randomized, double-blind controlled trial to investigate the role of UC-MSC and UC-CM compared to TA in keloid therapy. However, there are limitations to this research. The cost-effectiveness comparison between UC-CM and UC-MSC cannot be definitively determined due to the relatively short 17-week study duration, making the effectiveness difference between UC-MSC and UC-CM statistically insignificant. UC-CM is significantly more affordable than UC-MSC, suggesting that UC-CM could serve as a cost-effective alternative keloid therapy option if, after a comprehensive cost-effectiveness analysis, it proves to be superior to UC-MSC.

CONCLUSION

This trial discovered that UC-MSC and UC-CM are considerably more effective than TA in reducing keloid volume and type 1:3 collagen ratio. Therefore, UC-MSC and UC-CM show considerable promise as potential treatments for keloids. However, further research conducted over an extended period is necessary to assess their cost-effectiveness more comprehensively.

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DISCLOSURE

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Conflict of Interest

The authors have no conflict of interest to declare.

Authors contribution

The substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data: Anastasia Dessy Harsono (ADH), Ismail Hadisoebroto Dilogo (IHD), Theddeus Octavianus Hari Prasetyono (TOHP), drafting the article or revising it critically for important intellectual content: ADH, IHD, TOHP, Marcel Prasetyo (MP), Retno Asti Werdhani (RAW), and final approval of the version to be published: ADH, IHD, TOHP, MP, RAW, Sri Widia Jusman (SWJ), Nuryati Chairani Siregar (NCS), Hardisiswo Soedjana (HS).

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