Basic Medical Research

Effect of umbilical cord-mesenchymal stem cells on skin tensile strength in pressure ulcers: a rat model study

Indri Aulia[1,2], Ismail Hadisoebroto Dilogo[3,4,5], Theddeus Octavianus Hari Prasetyono[2,6], Jeanne Adiwinata Pawitan[4,5,7], Aria Kekalih[8], Nurjati Chairani Siregar[9], Yudan Whulanza[10,11], Lisa Hasibuan[12]

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Authors' affiliations:
[1]Doctoral Program in Medical Science, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, [2]Department of Surgery, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, [3]Department of Orthopedics and Traumatology, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, [4]Stem Cells Medical Technology Integrated Service Unit, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, [5]Stem Cells and Tissue Engineering Research Cluster, Indonesian Medical Education and Research Institute (IMERI), Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, [6]Medical Technology Cluster, Indonesian Medical Education and Research Institute (IMERI), Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, [7]Department of Histology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, [8]Department of Community Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, [9]Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, [10]Department of Mechanical Engineering, Faculty of Engineering, Universitas Indonesia, Depok, Indonesia, [11]Research Center for Biomedical Engineering, Universitas Indonesia, Depok, Indonesia, [12]Department of Surgery, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

Corresponding author:
Indri Aulia
Division of Plastic Reconstructive and Aesthetic Surgery, Department of Surgery, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jalan Salemba Raya No. 6, Central Jakarta 10430, DK Jakarta, Indonesia
Tel/Fax: +62-21-3162821/+62-21-3106705
E-mail: drindriaulia@gmail.com

ABSTRACT

BACKGROUND Stem cell therapy has emerged as a promising alternative for the management of chronic wounds, including pressure ulcers. Tensile strength, which reflects the biomechanical integrity of the skin, serves as an objective measure of wound healing. This study aimed to evaluate the effect of locally administered umbilical cord-mesenchymal stem cells (UC-MSCs) on the tensile strength of healing 3rd-degree pressure ulcers in a Sprague Dawley rat model.

METHODS 21 adult male Sprague Dawley rats were divided into 3 groups: normal rats without ulcers, untreated pressure ulcer as control, and pressure ulcers treated with UC-MSCs. The treatment group received locally injected 4×10^6 UC-MSCs at the ulcer site. On day-21, the tensile strength parameters (rupture point, elongation at break, and elastic modulus) of the dorsal skin were assessed using the Universal Testing System.

RESULTS When expressed relative to normal skin tensile strength, the UC-MSC group exhibited higher tensile parameters that were higher than the controls by 2.08% for rupture point, 3.29% for elongation at break, and 8.42% for elastic modulus. Although these differences between the UC-MSCs and control groups across all tensile strength parameters were not statistically significant, a clear trend toward improved tensile strength parameters were observed in the UC-MSCs group.

CONCLUSIONS Local UC-MSCs administration showed a consistent trend toward improved tensile strength in healing 3rd-degree pressure ulcers, albeit without statistically significant differences compared to controls. These findings support the further exploration of UC-MSCs as a potential treatment for promoting biomechanical restoration in healing pressure ulcers.

KEYWORDS elastic modulus, pressure ulcers, rat skin, regenerative medicine, stem cells, tensile strength

The effective management of pressure ulcers has not yet been clearly defined. Current treatment is primarily supportive, such as wound debridement, patient mobilization to reduce friction, pressure, and mechanical load, joint therapy to enhance circulation, provision of nutritional supplements with dietary regulation, and management of comorbidities.[1] According to the National Pressure Ulcer Advisory Panel (NPUAP) classification, a third-degree pressure ulcer is considered a deep ulcer, characterized by tissue damage extending into the subcutaneous tissue.[2] Continuous pressure causes repeated ischemia-reperfusion cycles, during which reperfusion may exacerbate tissue damage through the activation of reactive oxygen species (ROS) that damage

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cellular proteins. These ROS induce oxidative damage to cellular proteins, including collagen, which is a major structural protein of the extracellular matrix and plays a critical role in maintaining tissue architecture and tensile strength.[3–5] This condition requires a more complex induction of wound healing due to ongoing tissue destruction caused by continuous pressure on the affected area.[6] Such extensive and prolonged management is undoubtedly exhausting and affects the patient's psychological condition.[7] In this context, regenerative therapy has emerged as a promising alternative and may represent a future strategy for the management of chronic wounds.[8]

Stem cell therapy, particularly the use of mesenchymal stem cells (MSCs), has been explored in numerous studies for the management of challenging wound cases such as pressure ulcers.[7] Umbilical cord-mesenchymal stem cells (UC-MSCs) offer several advantages compared to bone marrow-derived MSCs and peripheral blood stem cells, including a relatively straightforward harvesting process without donor-related morbidity, longer telomere lengths, higher proliferative capacity, reduced graft-*versus*-host disease, long-term storage capability, and low incidence of virus contamination.[9] Using stem cells in chronic wounds accelerates wound healing, increases wound closure rates, reduces scar formation and contractures, and promotes ideal skin regeneration. Additionally, this therapy has the potential to enhance the overall quality of the wound healing processes and enable the restoration of normal skin structure.[10] Huang et al[11] evaluated the use of UC-MSCs in diabetic ulcers and burn injuries; however, to date, no study has assessed the effectiveness of UC-MSCs alone in the treatment of pressure ulcers.

One of the most useful benchmarks for evaluating the biomechanical properties of skin is tensile strength, which is measured through three parameters: rupture point, elongation at break, and elastic modulus.[12] Evaluating the tensile strength of healing skin tissue is crucial for determining its resemblance to normal skin.[13,14] This study aimed to explore the potential of UC-MSCs to facilitate regenerative healing of third-degree pressure ulcers by enhancing the recovery of skin tensile strength, as measured through its rupture point, elongation at break, and elastic modulus. To date, no prior studies have analyzed the effects of intralesional UC-MSCs injection in rat models, emphasizing the novelty of the present study. Additionally, measuring tensile strength as a parameter for evaluating the healing of pressure ulcers has not been previously explored; therefore, further research in this area is needed.

METHODS

This study was approved by the Animal Ethics Committee, School of Veterinary Medicine and Biomedical Sciences, IPB University (No: 178/KEH/SKE/II/2024). The sample size was calculated using the resource equation formula,[15] with an additional 10% estimated for dropout, resulting in a total of seven samples in each group.

The animals underwent a 14-day acclimatization period prior to study initiation. During this period, they were administered an antiparasitic treatment to ensure that they were free from parasites. Each rat was housed individually in a plastic cage with bedding in a well-lit, open-system laboratory maintained under controlled temperature (26–27°C) and relative humidity (81%) conditions. Rats were fed (Sadewa Animal Feed, Indonesia) and supplied with drinkable mineral daily. The laboratory was sanitized 3 times per week to maintain hygienic conditions. The rats were monitored under the supervision of an attending veterinarian. Rats exhibiting signs of illness or infection before the intervention were excluded from the study.

Creation of a pressure ulcer model

Twenty-one male Sprague-Dawley rats, aged 12 months and weighing approximately 300–350 g, were bred by Taufik Rats and Mice, a certified local breeder in Bogor, Indonesia. The animals were confirmed to be healthy by an independent veterinarian and had no history of prior experimental procedures. The rats were randomly and evenly allocated into three groups: a normal model without ulcers (normal skin), a pressure ulcer model without intervention (control group), and a pressure ulcer model treated with UC-MSCs (UC-MSCs group). Both authors and analysts were blinded throughout all assessments and evaluations. During a 7 day acclimatization period, the animals were monitored for their nutritional intake and body weight. Anesthesia was administered intramuscularly using ketamine 70 mg/kg and xylazine 4 mg/kg.[16]

Artificial ulcers were made using circular magnetic plates, as described by Stadler et al[17] with a thickness of 5 mm and diameter of 24 mm, and strengths ranging

from 1,100 to 1,400 gauss. Two identical magnetic plates were placed on the lateral sides of the thoracic back, which were shaved beforehand. The plates were applied to induce ischemia for 12 hours, and were then removed to allow reperfusion for an additional 12 hours, repeatedly over three cycles. This ischemia-reperfusion cycle is crucial because restoration of blood flow to ischemic tissue generates oxygen-derived free radicals that disrupt normal free radical scavenging. This process triggers an inflammatory response and promotes the recruitment of inflammatory cells to the injury site. Consequently, it can alter endothelial cytokine production, delay the healing process, and contribute to ulcer formation.[17,18] Finally, two adjacent ulcers, each measuring 24 mm in diameter (Figure 1a), were formed using a minimally invasive pressure ulcer model. This "pinch" technique effectively illustrates the pathogenesis of pressure ulcers through an alternating ischemia-reperfusion cycle.

The development of pressure ulcers was evaluated both macroscopically and microscopically by the primary author (IA). Clinically, the pressure ulcers created were covered with eschar and were classified as unstageable based on the NPUAP classification (Figure 1b). Tissue damage to the pressure ulcers was confirmed by histological examination using hematoxylin and eosin staining, and the ulcers were subsequently classified as third-degree pressure ulcers (Figure 1c). Histological evaluation was performed in a blinded manner by a board-certified anatomical pathologist (NCS) with more than 40 years of experience, including expertise in stem cell research. To minimize potential confounding factors, all animals were caged under identical environmental conditions. All procedures were performed in the same sequence by the same operator and were conducted at a consistent time of day to reduce variability related to circadian influences. No additional interventions were applied outside the experimental protocol.

Injection of UC-MSCs into the pressure ulcers

UC-MSCs were obtained from human umbilical cord processed at the Stem Cell and Tissue Engineering Research Center, Indonesian Medical Education and

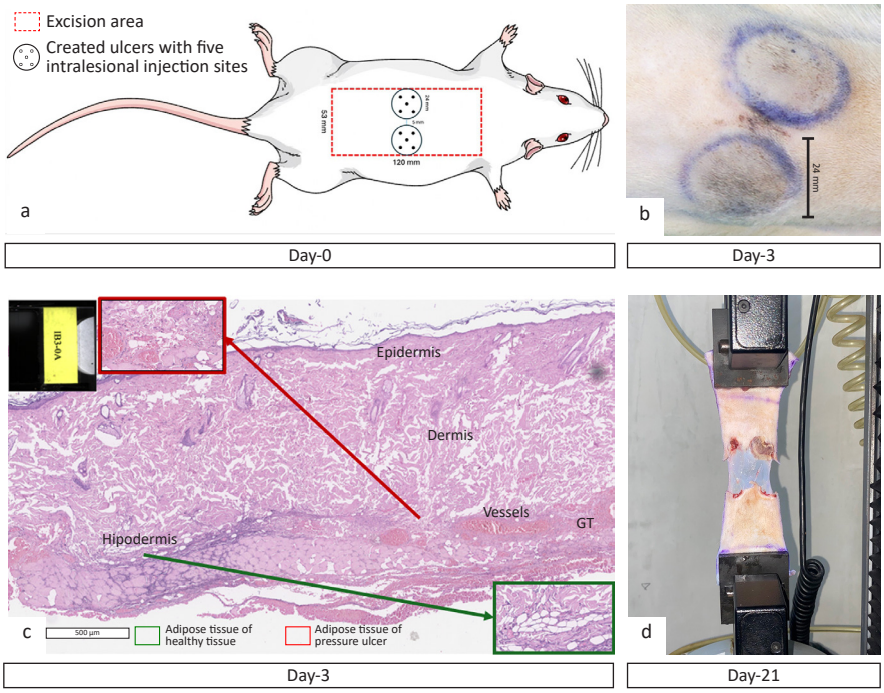

Figure 1. Rat pressure ulcer model. (a) Dorsal schematic showing placement of two 24 mm circular lesions induced with paired magnets (1,100–1,400 gauss) using 12 hours ischemia/12 hours reperfusion for three cycles. Five intralesional injection sites/ulcer are indicated (black dots). UC-MSCs (2×10^6 cells/ulcer in 0.75 ml PBS; total 4×10^6/rat) were injected 4 hours after the final reperfusion. The red dashed rectangle marks the day-21 excision coupon (≈120 × 53 mm; cranial–caudal orientation); (b) representative macroscopic appearance of two eschar-covered ulcers; (c) H&E section demonstrating full-thickness loss extending into hypodermis with granulation tissue; (d) uniaxial tensile test of the dorsal skin coupon mounted in an Instron 5944 (Instron, USA); gauge length: 85 mm, crosshead speed: 100 mm/min, cranial–caudal loading. Animals: n = 7 per group. GT=granulation tissue; H&E=hematoxylin and eosin; PBS=phosphate-buffered saline; UC-MSC=umbilical cord-mesenchymal stem cell

Research Institute, Faculty of Medicine, Universitas Indonesia. The umbilical cords were initially washed in a 0.5% povidone-iodine solution containing phosphate-buffered saline (PBS), followed by washing in PBS alone. Subsequently, the arteries and veins were removed, leaving the umbilical tissue for further processing.[19]

Anesthesia was administered intramuscularly prior to the intervention using ketamine (70 mg/kg) and xylazine (4 mg/kg). The intervention group received an injection of 4×10^6 UC-MSCs per rat, consisting of 2×10^6 cells per lesion contained in 0.75 ml PBS. The injection was administered once, 4 hours after completion of three ischemia-reperfusion cycles, using a 32G mesotherapy needle. The cells were injected intradermally into the ulcers at five predetermined points within each ulcer, with 0.15 ml administered at each point (Figure 1a). Passage five UC-MSCs with a viability of 93.29% were used to ensure optimal passage quality.[20] Meanwhile, pressure ulcers in the untreated model group were allowed to heal spontaneously and served as the control group.[17]

Tensile strength evaluation of the tissue

The euthanasia procedure was conducted on day-21 in accordance with the American Veterinary Medical Association Guidelines, using intraperitoneal ketamine (300–360 mg/kg) and xylazine (30–40 mg/kg).[21] This time point was selected because the ulcer had entered the remodeling phase of the healing process.[22] The objective was to ensure that the ulcer progressed through all stages of the healing process prior to tensile strength assessment. This is in accordance with a study by Živčák et al[14] who observed that tensile strength improved significantly within the first 24 hours of wound healing, reached a plateau between days-2 and -5, and then increased again during the maturation phase.

A rectangular pattern was drawn on the dorsum skin (12 × 5.3 cm) to be excised and used as the specimen for mechanical characterization (Figure 1a). This rectangular pattern was designed for accurate placement within the examination system and pulled in both directions at a consistent speed. The specimen geometry was standardized with a gauge length of 8.5 cm, a width of 53 mm, and an approximate thickness of 1 mm, which were measured prior to testing to enable accurate stress calculations. Tensile strength examination was performed using a Universal Testing System (Instron 5944; Instron, USA) with a system ID 5944R8335 at a speed rate of 100 mm/min, with the samples mounted vertically in the device (Figure 1d).

The tensile strength examination included quantification of rupture point, elongation at break, and elastic modulus. The rupture point represents the maximum tensile load that the skin can withstand prior to rupture. Elongation at break refers to the relative extension of the skin under tensile loading and is measured up to the point of breakage. The elastic modulus is the ratio of changes in skin tension to corresponding changes in elongation and reflects the material's elasticity.[12,23] The measured values were then used to calculate similarity percentages for each parameter by dividing the control or intervention group results by the normal skin values to determine their tensile strength relative to undamaged skin without pressure ulcers.

The recorded data encompassed the heel region of the stress-strain curve, where the tissue had passed the elasticity phase and entered plasticity, up to the starting point of the fracture region, where initial skin failure occurred.[24] Rupture point represents the maximum stress a material can endure and is calculated at the moment of material failure. Elongation at break is defined as the relative length of deformation or elongation of a material due to the applied tensile stress, measured at the point of material failure. The elastic modulus was calculated as the ratio of the change in stress to the corresponding change in strain. However, evaluation of tensile stress-strain parameters alone is insufficient to fully assess the wound healing process, as these parameters represent only one of several factors contributing to a comprehensive assessment of healing.

Statistical analysis

Data were analyzed using SPSS software version 27 (IBM Corp., USA). Normal data distribution was assessed using the Shapiro–Wilk test. Data are presented as means for normally distributed variables and as medians for non-normally distributed variables. Comparisons between groups were made using the independent *t*-test or Mann–Whitney *U* test, depending on the distribution. In addition, comparisons were conducted to determine the percentage similarity of the pressure ulcer model to normal skin tensile strength in terms of rupture point, elongation at break, and elastic modulus to illustrate its tensile strength

restoration relative to normal skin. Mean differences and standardized effect sizes were also analyzed.

RESULTS

Normal adult Sprague-Dawley rat skin tensile strength evaluation

The tensile strength of skin samples obtained from seven adult Sprague-Dawley rats without artificial pressure ulcers was evaluated to determine baseline tensile strength values. The tested dimensions, reduced by the grip area, were 8.5 × 5.3 cm with 1 mm of thickness. The mean (standard deviation) values were as follows: rupture point (9.042 [1.549] MPa), elongation at break (53.908 [5.972]%), and elastic modulus (0.214 [0.048] MPa) (Figure 2).

Pressure ulcers model tensile strength evaluation

The pressure ulcer model was divided into two groups: the UC-MSCs group and the untreated control group, each consisting of seven subjects. Histological examination revealed loss of the skin tissue layer extending to the depth of the fat tissue, along with damage to the remaining fat tissue and visible granulation tissue at the ulcer site. Dorsal skin of the rats was obtained as described previously. All subjects in both groups were also evaluated for the rupture point, elongation at break, and elastic modulus. A comparison between the normal skin and control groups showed significant differences in the rupture point, elongation at break, and elastic modulus. Similarly, comparison between normal skin and the UC-MSC group also showed significant differences across all measured variables. However, the comparison between the control and UC-MSCs groups revealed no significant differences in any of the variables evaluated (Figure 2).

To further evaluate the restoration of tensile strength relative to normal skin, a similarity percentage analysis and standardized effect size calculation were performed. The UC-MSCs group exhibited a higher similarity percentage (2.08% higher rupture point, 3.29% higher elongation at break, and 8.42% higher elastic modulus) to normal skin compared to the control group, although the difference was not statistically significant. In addition, standardized effect size analysis, performed using Hedges' correction, shows effect size values of approximately 0.5 across all tensile parameters, corresponding to a medium effect (Table 1).

DISCUSSION

In this study, the assessment of rupture point, elongation at break, and elastic modulus showed that the administration of UC-MSC for third-degree pressure ulcers did not statistically restore wound healing to levels comparable with normal skin. These results did not fully support the initial hypothesis that UC-MSCs therapy would normalize biomechanical properties. However, the injection of UC-MSCs exhibited a higher similarity percentage to normal skin than to pressure ulcers without intervention across all tensile parameters, demonstrating a clear trend of better

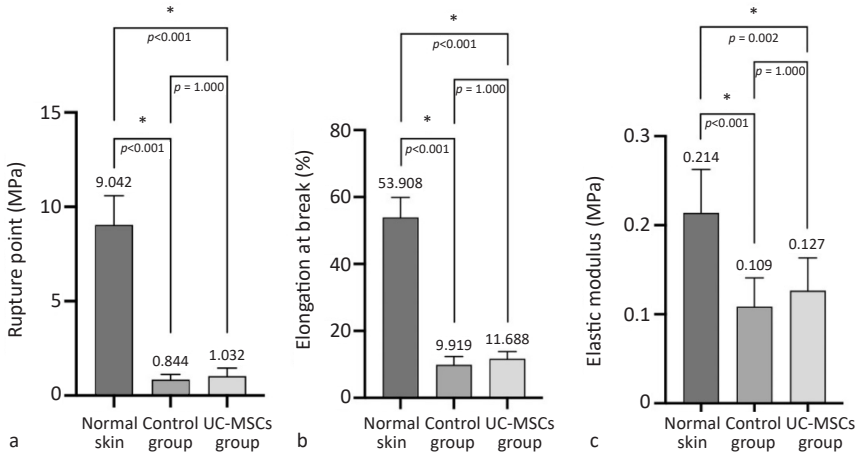

Figure 2. Tensile properties of dorsal skin at day-21 in Sprague-Dawley rats (n = 7/group). (a) Rupture point; (b) elongation at break; (c) elastic modulus. Group differences were tested by independent *t*-test. UC-MSC=umbilical cord-mesenchymal stem cell

Table 1. Day-21 similarity to normal skin (%) for tensile metrics in rat pressure ulcer model

Parameter	Control group, mean (SD) (N = 7)	UC-MSCs group, mean (SD) (N = 7)	Mean difference (95% CI) (N = 7)	Standardized effect (N = 7)
Rupture point (%)	9.34 (3.01)	11.41 (4.69)	2.08 (−2.52–6.67)	0.492
Elongation at break (%)	18.39 (4.59)	21.68 (3.93)	3.29 (−1.69–8.26)	0.719
Elastic modulus (%)	50.81 (15.15)	59.2 (17.22)	8.42 (−10.47–27.30)	0.486

CI=confidence interval; SD=standard deviation; UC-MSC=umbilical cord-mesenchymal stem cell
Standardized effect calculated using Hedges's correction. *p*-values for comparisons between the control and UC-MSCs groups were all $p = 1.000$ (independent *t*-test)

tensile strength restoration in the intervention group, despite the lack of statistically significant differences.

This study demonstrated that while the local administration of UC-MSCs in a third-degree pressure ulcer rat model did not yield statistically significant improvements in tensile strength compared to untreated controls, a consistent trend toward enhanced tensile strength was observed across all measured parameters. The rupture point, elongation at break, and elastic modulus were found to more closely resemble the tensile strength parameters of normal skin compared with the control, although they did not fully restore the tensile strength to normal baseline levels. Additionally, standardized effect size analysis using Hedges' correction demonstrated medium effect sizes for all parameters, suggesting a potentially meaningful biological effect.

Stem cell therapy is a promising modality to enhance wound healing, including in chronic wounds.[1,7,25,26] Tan et al[26] investigated the effects of stem cells on chronic wounds, such as diabetic and trophic ulcers, and demonstrated that administration of secretome from human UC-MSCs in a gel form (10% SM-hUCMSC gel) significantly accelerated wound healing, as indicated by a notable reduction in wound area. Additionally, a clinical trial by Huang et al[11] explored the use of UC-MSCs in diabetic ulcers and burns, showing potential for improving wound healing outcomes, and could be a treatment option for chronic wounds. This study examines the wound healing effects of UC-MSCs administration in a third-degree pressure ulcer model, with the expectation of achieving similarly favorable outcomes, especially in terms of tensile strength, which is a well-established method for evaluating wound healing according to previous studies.[13,14]

This lack of statistically significant findings in this study may be partly attributable to UC-MSCs exerting their effect on wound healing through paracrine effects, such as modulating inflammation, promoting angiogenesis, and stimulating cell proliferation, rather than directly integrating into the tissue to enhance mechanical strength.[8,10,27,28] While these cells can accelerate wound closure and improve epithelialization, they may not significantly influence the wound healing process. Additionally, administration of a single UC-MSC dose may not have provided the sustained biological stimulation required for optimal outcomes, and increasing the frequency of UC-MSC administration may be required to achieve optimal biomechanical restoration. Moreover, the result of medium effect sizes across tensile parameters suggests a potential treatment effect that may not have been fully captured in this study and needs further evaluation in investigations with larger sample sizes.

Nonetheless, biomechanical integrity, represented by tensile strength, is a critical endpoint in tissue repair, especially in pressure ulcer management, where the skin must withstand recurrent mechanical loading.[13,14] Most previous studies investigating UC-MSCs therapies for wound healing have focused on outcomes such as epithelialization, histological appearance, and collagen deposition, rather than directly assessing biomechanical properties. By measuring tensile strength, our study aimed to determine whether UC-MSC treatment contributes not only to faster or more complete closure but also to functional restoration of the skin's mechanical resilience. Therefore, our findings add to the body of knowledge suggesting that, while UC-MSCs support wound resolution through immunomodulatory and angiogenic pathways, they may be insufficient to restore biomechanical integrity to a significant degree under the conditions tested.

Furthermore, it is also known that tensile strength in healed skin is affected by the quality and arrangement of collagen fibers.[27,29] Although UC-MSCs have been shown to influence collagen deposition, this

effect might not be sufficient to produce statistically significant improvements in tensile strength, especially without adjunctive therapies specifically targeting collagen remodeling. Emerging evidence suggests that combining UC-MSCs with other treatments, such as platelet-rich plasma, can enhance wound healing outcomes through synergistic effects that improve both tissue regeneration and mechanical strength.[30,31] Therefore, the observed trend of positive effects of UC-MSCs injection on tensile strength in our results still demonstrates the viability of combination therapy using UC-MSCs for pressure ulcers.

This is the first study to utilize local UC-MSC injections for the treatment of artificially created pressure ulcers in an animal model. Sprague-Dawley rats, used as animal models, are also an established choice for research on pressure ulcers, since they adequately represent key aspects of human pressure ulcers. No previous studies have investigated the mechanical tensile strength testing of skin with pressure ulcers using a Universal Testing System (Instron 5944; Instron), demonstrating a novel and useful method for future studies to evaluate skin biomechanical properties as an indicator of wound healing. Furthermore, this study also emphasized the necessity of using multiple outcome domains in wound healing research, not only histological or wound closure-based outcomes, but also mechanical strength to fully characterize the efficacy of other emerging regenerative therapies. Such a multidimensional assessment will strengthen its translational relevance to clinical applications and provide a better understanding of tissue repair mechanisms.

In this study, the investigation was conducted on third-degree pressure ulcers, although fourth-degree ulcers present a more comparable clinical challenge. While creating two wounds with a magnetic plate is a feasible method to date, it may also present a limitation by potentially influencing the healing response to the administered intervention. A relatively large expense was also incurred for UC-MSCs in the small rat model, although no direct comparison with the financial demands of conservative or long-term treatment methods was performed. Despite these limitations regarding ulcer staging, model design, and cost, the study supports continued exploration of UC-MSCs, particularly in combination with adjunctive therapies, as a regenerative treatment strategy for pressure ulcer management. The observed trends toward improved tensile strength reinforce the potential role of UC-MSCs in promoting the functional aspects of wound healing, including biomechanical restoration, as described using tensile strength. Future investigations should consider multimodal outcome assessments, including histological evaluations and additional wound healing markers, to provide a more comprehensive assessment of stem cell-based therapeutic interventions.

Conflict of Interest

Theddeus Octavianus Hari Prasetyono and Jeanne Adiwinata Pawitan are the editorial board member of this journal but was not involved in the review or decision-making process of the article

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