CASE REPORT

Combination treatment of Umbilical Cord-derived Mesenchymal Stem Cell (UC-MSC) and Umbilical Cord Mesenchymal Stem Cell-derived Conditioned Medium (UCMSC-CM) for Keloid Post Chronic Burn Injury: A Case Report

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ABSTRACT

A 44-years-old woman with hard and thick keloids after chronic mercury burn injury underwent a several times of reconstructive surgery. The patient had excised surgery and injected Umbilical Cord-derived Mesenchymal Stem Cells (UC-MSCs) and Umbilical Cord Mesenchymal Stem Cells-derived Condtioned Medium (UCMSC-CM) 9 times within 9 months. Seven times injection of UC-MSCs of $5x10^6$ cells and UCMSC-CM of 20 cc 2 times at months 4 and 9. The results of this therapy showed gradual improvement without any side effects and the size of the keloid reduced from 25x16 cm to 23x14 cm after 9 months. Keloid thickness from 12 mm to 4 mm. Keloid color becomes lighter and skin texture is more supple and soft. The cases showed that UC-MSCs and UCMSC-CM can be a potential treatment for keloids after chronic burn either alone or in combination with surgery.

Keywords: Keloid, Mesenchymal stem cells, Conditioned medium, Chronic burn injury

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INTRODUCTION

Keloid is a dermal tumor that is belonging to the fibroblasts group with immoderate deposit of extracellular matrix (ECM) components such as fibronectin, elastin, proteoglycan and collagen. These dermal tumors spread across borders of the original wound and continue to grow over time (1). Wounds appear as hard, shiny, elastic and commonly associated with pain, pruritus, deformities and joint contractures. The most common places for keloid predilection are around the shoulders, upper back, chest and auricles. Keloid sufferers can experience a functional and psychological loss that affects the quality of life (2).

Up to this point, the pathogenesis of keloid formation is not yet fully understood. It has been described that the skin's renewal process is controlled by Mesenchymal Stem Cells (MSCs) and other cell populations such as primary fibroblasts, which are obtained from various tissues containing mesenchymal progenitors and stem cells. In addition, the research also shows that fibroblast cells derived specifically from keloid tissue are clearly multipotent stem cells, which are maintained in a reproductive state and not differentiated by the presence of cytokines in the wound (2).

The common treatment used for keloids is corticosteroid injection, either as monotherapy or a combination with other treatments such as cytotherapy, 5-fluorouracil, radiotherapy, laser, surgical excision, and occlusive silicone dressings. Despite numbers of treatment options, unsatisfied results are often obtained with a recurrence rate of 45-100% (2). Recent reports show that MSCs could be a novel antifibrosis treatment strategy becaue its abillity in reducing inflammation in wounds and reprogramming resident cells to support tissue regeneration and suppress fibrosis formation. MSCs can affect resident cells throughout differentiation or paracrine signaling mechanisms.

Mesenchymal stem cells (MSCs) derived from umbilical cords (UC-MSCs) have been proven to have higher proliferative potential than MSC derived from bone marrow (BM-MSCs), which is the "gold standard" for MSC comparison, or MSCs from other postnatal (adipose tissue) and neonatal sources (placenta and amniotic membrane). However, UC-MSCs' conditioned medium differs significantly from MSCs from other sources (bone

marrow and adipose tissue). Conditioned medium of UC-MSCs do not synthesis the main proangiogenic factor VEGF-A, yet they express higher levels of angiogenic chemokines, angiogenic growth factors, neurotrophic factors, hematopoietic factors, and other important cytokines (3). This study aims to identify safety and efficacy after the use of UC-MSCs and CM UC-MSCs in subjects who developed keloids after chronic mercury burns.

CASE REPORT

A 44-years-old woman presented with hard and thick keloids covering the upper body region due to chronic mercury burn injury acquired 6 months ago. She had undergone some contractures opening (releasing) on the upper-extremities, facial, and neck region. Excision and skin grafting were not performed due to the patient's limitation. Post-operatively, the patient was injected with mesenchymal stem cells (MSCs) derived from umbilical cord (UC-MSCs) and their conditioned medium (UCMSC-CM). The UC-MSCs and UCMSC-CM therapy design was divided into 9 times of injection every once in a month. UC-MSCs injection was given 7 times, while UCMSC-CM injection was only given twice on the 4th and 9th months. The administration of UC-MSCs and UCMSC-CM were given $5x10^6$ and 20 cc respectively to the keloid area with syringe and dermapen. On 9 months follow-up, the keloid had reduced in size and thickness followed by lighter and softer skin texture. The patient underwent reconstructive surgery several times both before and after UC-MSCs and UCMSC-CM injection. Prior to stem cell injection, keloids will appear in the postoperative wound. Meanwhile, after the injection of UC-MSCs and UCMSC-CM, there was no keloid in the postoperative wound and the healing process is much faster than before injection.

DISCUSSION

The clinical parameters assessed in this study were keloid size, itchiness scale, pain scale, keloid color, keloid thickness, movement and skin texture (Table I). Based on the keloid size, the reduction of keloid area can be seen at 6th and 9th month post injection. Each keloid area was reduced by 1 cm, measured using sterile surgical ruler. Generally, keloid patients will experience symptoms of itching. Prior to the UC-MSCs and UCMSC-CM injection, the patient's itchiness scale was 9 (with a scale range of 1-10). After receiving the UC-MSCs and UCMSC-CM injection, the itchiness scale was significantly decreased into 3 at 3rd and 6th month observation. At 9th month post injection the patient's itchiness scale became 1. Apart from itchiness, keloid patients also experience pain on a scale of 7 (with a scale range of 1-10) and after injection, the pain was reduced to a scale of 1 at 3rd and 6th month follow up. Then, at 9th month observation the pain was on a scale of 0. Visual Analogue Scale (VAS) was used for itchiness and pain measurement.

Table I: Clinical Parameter Results

Clinical Parameter	Baseline	3 months	6 months	9 months
Keloid size	25x16 cm	25x16 cm	24x15 cm	23x14 cm
Itchiness scale (1-10)	9	3	3	1
Pain scale (1-10)	7	1	1	0
Keloid color	Dark	Pink	Pink	Pale
Keloid thickness	12 mm	10 mm	6 mm	4 mm
Body movement	+	++	++	+++
Keloid texture	hard, solid	mild, solid	mild, supple	smooth, supple

After the 1st and 2nd injection, the keloid texture was still hard and thick. However, after the 3rd and 4th injections (shown by Fig. 1), the keloid began to become mild and reddish, which allows the patient to make a movement, especially on the neck. Improvements in texture and color are also supported by a reduction in the thickness of keloids (shown by Fig. 2). The thickness at the beginning was 12 mm, then after injection was reduced into 10 mm at 3 month follow up. At 6th and 9th month post injection, the keloid thickness was reduced into 6 and 4 mm. The thinning of this keloid indicates that there is an improvement shown by a visible blood vessels, and bone around the keloid begin to be felt.

Based on clinicaltrials.gov data, umbilical cord of mesenchymal stem cells (UC-MSCs) are used for many diseases such as acute myocardial infarction, cardiomyopathies, crtitical limb ischemia, bronchopulmonary dysplasia in infants, diabetes mellitus types I and II, acute liver diseases and other diseases. Only allogeneic transplantation of UC-MSCs is studied in all clinical trials. The results of all clinical studies of the administration of UC-MSCs showed no adverse events, except for a few cases of fever (4).

Mesenchymal stem cells (MSC) derived umbilical cord (UC-MSCs) have been shown to enhance cutaneous wound healing by means of the paracrine activity. Study revealed that the paracrine effect of secreted soluble factors may be the most effective way of MSCs promote wound repair. It also discussed that conditioned medium from UC-MSCs take part in stimulating macrophage and endothelial migration, therefore re-epithelialization and dermal fibroblast migration (4). Mesenchymal stem cells (MSCs) actively produce tissue reparative paracrine factors. Among the substances, there are not only growth factors, but also some anti-inflammatory and anti-microbial molecules, which accelerate the shift from inflammatory phase to proliferative phase of wound healing (5).

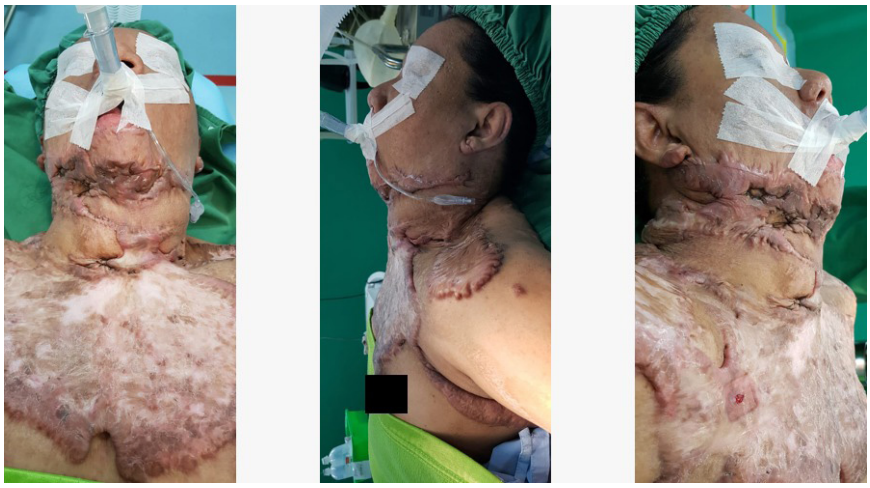

Figure 1: Patient after 4 times of stem cell injections

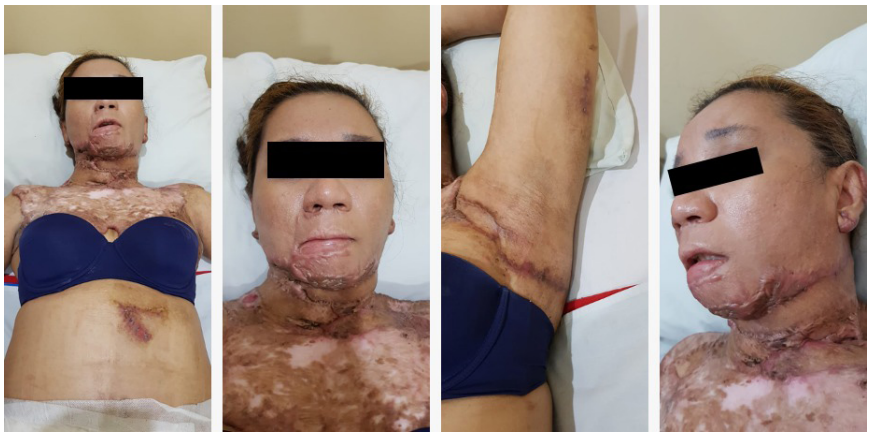

Figure 2: Patient after 7 times of stem cell and 2 times of secretome injections

CONCLUSION

In conclusion, UC-MSCs and UCMSC-CM can be a potential treatment for keloids after chronic mercury burn either alone or in combination with surgery. It is necessary to carry out further studies with more subjects and parameters.

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