Secreted Trophic Factors of Mesenchymal Stem Cells Support Avascular Wound Recovery in A Patient with Vascular Occlusion: A Case Report

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Abstract

Introduction: Stem cells secretome is a wide term for the complex group of chemicals produced by stem cells, including growth factors and cytokines. It promotes wound healing by it's immunomodulatory properties, stimulating angiogenesis, acceleating skin re-epithelisation and improving extracellular matrix production modelling. This is the first report of hUC-MSCs (Human umbilical cord mesenchymal stem cells) scretome application in wound management in the case of vascular occlusion after filler injection.

Case Presentation: A 49 years old gentleman had sustained vascular occlusion from filler injection over the forhead for aesthetic purposes. He suffered from ulcers, pustules and hyperpigmention over his forehead. His wound had healed well after multiple secretome injections over the course of 4 months.

Conclusion: The secretome of hUC-MSCs (Human umbilical cord mesenchymal stem cells) may be a potential therapeutic strategy for treating avascular wound.

Keywords: Platelet-Rich Plasma, PRP, Classification, Aesthetic

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The reconstruction of various cell types in the epidermal and dermal layers is a complex and well-orchestrated process during skin wound healing. In serious chronic conditions such as severe burns and diabetes, the wound healing process is delayed or fails, causing ulceration or other changes in the skin including abnormal skin structure or loss of structural functions. Hence, much effort was invested to develop novel and advanced therapeutic method such as platelet-rich plasma (PRP) therapy (Park et al., 2011), growth factor therapy (Penn et al., 2012), stem cell-based therapy (Lee et al., 2012), tissue engineering (Chen et al., 2009) and even gene therapy (Song et al., 2012). Among the aforementioned approaches, stem cell-based therapy has lately emerged as an appealing option for cutaneous wounds (Dulmovits & Herman, 2012) due to its therapeutic potential. However, despite the many promising outcomes, there are certain restrictions to consider in stem cell therapy. One of the major challenges, is the low survival rate and post administration fate of the cells following transplantation (Modo et al., 2002).

As technology in bioprocess and cell engineering advanced, stem cell secretome become an attractive option for cell-free therapy. Stem cells secretome is a wide term for the complex group of chemicals produced by stem cells, including growth factors, cytokines. The use of the stem cell secretome to treat severe cutaneous wounds could be a potential way to overcome the limits of viable replacement cell transplantation. A vast number of research on cardiovascular (Mirotsou et al., 2011), liver (Kuo et al., 2008), and renal injuries have found direct evidence that the secretome plays an important role in encouraging regeneration (Cantaluppi et al., 2013). Similarly, stem cell-conditioned media, or alternatively named secretome has been used in a number of pre-clinical investigations as a viable option to replacement cell therapies for wound healing (Walter et al., 2010; Zhou et al., 2013; Chen et al., 2014; Jun et al., 2014). This has sparked interest in using the stem cell secretome to speed up the healing process in skin wounds.

It has been proposed that MSC-S (Mesenchymal Stem Cell Secretome) can contribute to wound healing via several mechanism. Firstly, it has immunomodulatory properties as MSC-S in vitro can inhibit activation and proliferation of immune cells including T cells, B cell, NK cells, neutrophils and macrophages. Secondly, MSC-S contains proangiogenic proteins such as angiopoietin-1, angiopoietin-2, granulocyte macrophages colony-stimulating facror, platelet-derived growth factor and others. These proteins can stimulate new vessels formation, leading to accelarated wound closure. Thirdly, growth factors in MSC-S can accelerate re-epithelisation due to its ability to enhance the dermal fibroblast and epidermal keratinocyte's migration and proliferation. Lastly, these growth factors can also stimulate collagen synthesis and accelerate new tissue formation. (Ahangar P et al., 2020).

Here, we describe a work to evaluate the contribution of application of a MSC- Secretome for healing of filler induced avascular injury. As there are increasing demand to use filler as a method to improve appearrance, vascular occlusion may be a complication after or during filler injection. Adverse event associated with vascular occlusion are pain, ertythema, necrosis, scarring. Threfore wound management is important to improve patient outcome. We hope to explore further supporting treatment for wound healing after vascular occlusion other than the usual hyperbaric oxygen therapy (HBOT), Low molecular weight heparin and oral vasodilator.

Case Presentation

Patient is a 49-year-old male with underlying Ischaemic Heart Disease, Dyslipidaemia and Hypertension with defaulted medication since

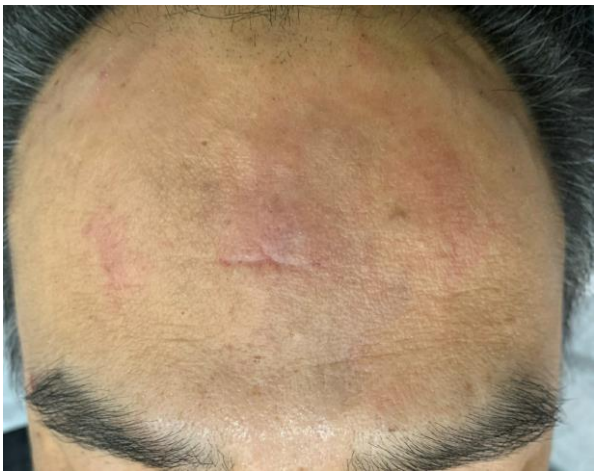

Figure 1: Photographic image, Day one (D1), after filler injection

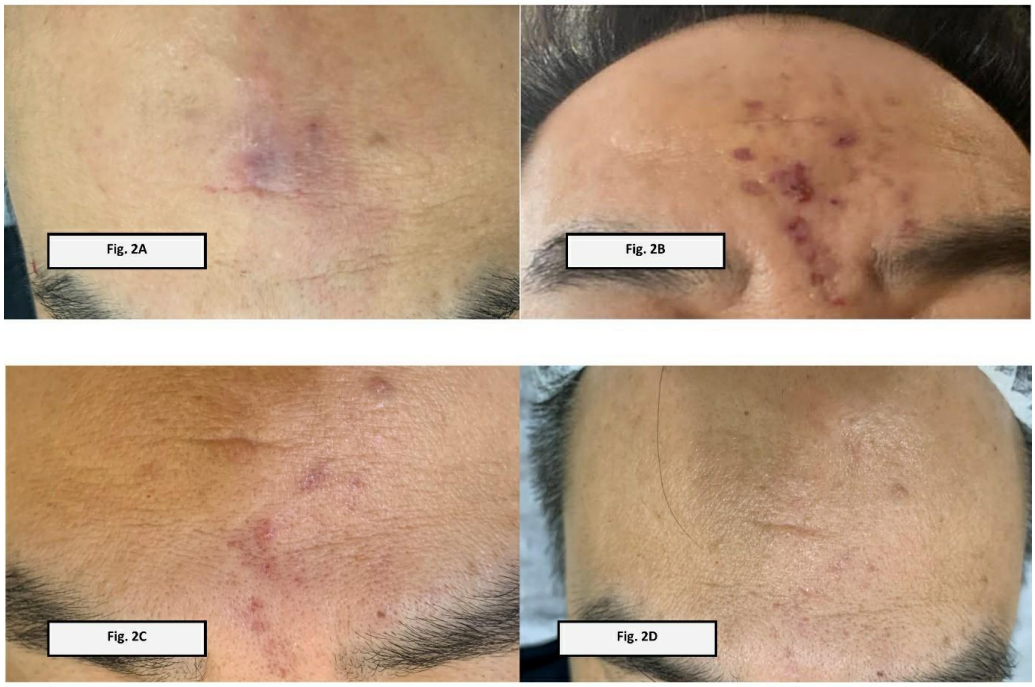

Fig. 2A. Photographic image, Day two (D2) days, after Hyaluronidase correction.

Fig. 2B. Photographic image, Day seven (D7).

Fig. 2C. Photographic image, Day thirty-nine (D39).

Fig. 2D. Photographic image, Day one-hundred and twenty-two (D122).

March 2021. On 1st of July 2021, 0.35 ml of hyaluronic acid based injectable filler (Juvederm Volift, France) was injected on the sunken area at the subject's forehead for volumization. Within minutes, we noticed some grey hue over the left forehead extending to eyebrow, while capillary refill time (CRT) was about 2-3 seconds in certain part. No pain or discomfort was mentioned during the procedure.

Approximately 300 IU of hyaluronidase (SRS International, Spain) was administrated all over the glabellar region and initial injection site respectively as management procedure. CRT then improved (< 2 seconds) over the forehead region.

Subject mentioned about slight discomfort

at the injection site, however no sign of inflammation or ulcers was detected 24 hours after procedure. Unfortunately, inflammation, pustules and new ulcers were observed at during subsequent monitoring over four days. Additional 500 IU of hyaluronidase (SRS International, Spain) were administrated at the redness region and glabellar region respectively. Upon further investigation, we found out that the subject punctured the pustules with unsterilized needle which may trigger the inflammation and adverse effect.

Widths and depths of the ulcers were recorded and photographed. We injected 2 ml of stem cells secretome for 3 consecutive days (Day 5, 6 and 7 Post injection respectively) with 25G cannula over the affected region in the subcutaneous layer. Upon completion of 3 days of IV antibiotics, he was then started on 5 days of T Unasyn 375mg BD.

Day 8 post injection, his wound had started to dry up with no new pustules/ulcers seen. Subject score 0 during pain scoring survey. We reviewed him again on Day 11 post injection, noted hyperpigmentation over forehead. There was no pain or new ulcers developed. We toned the hyperpigmented area with laser wavelength 1064nm (TRI- BEAM,Jeisys,Korea). Approximately 3 ml of stem cells secretome was administrated on the Day 11. On Day 12 post injection, we administrated another 1 ml of stem cells secretome and sprayed another 1 ml over the affected area.

During the subsequent follow up, 5 ml of stem cells secretome was injected at 1.5 months and 4 months after that incident. His wound had recovered well.

Discussion

Avascular ulcer management is difficult because ulcers take a long time to heal, the therapy has a financial impact on patients and their families, and it is frustrating for patients. To address these issues, a variety of wound treatment techniques have been developed, including the use of stem cell secretome, as described in this article.

The stem cell secretome increased the healing rate of chronic ulcers with little side effects or problems, according to our findings. Chronic ulcers can be caused by a variety of factors, including extended inflammatory conditions, high protease activity, and low growth factor levels. The secretome of stem cells contains a variety of paracrine substances, such as growth factors and cytokines (Vizoso et al., 2017).

The stem cells secretome may help to improve the wound microenvironment and so promote healing, especially during the inflammation phase of wound healing. Proinflammatory cytokines will treat any infection in the wound, while anti-inflammatory cytokines will lessen the inflammation process. Simultaneously, growth factors will aid wound healing by inducing angiogenesis and encouraging cell proliferation for the epithelialization process (Nuschke, 2014; Anandan et al., 2016; Park et al., 2017).

Conclusion

The secretome of hUC-MSCs (Human umbilical cord mesenchymal stem cells) may be a potential therapeutic strategy for treating avascular wound. Futher clinical studies are needed to prove treatment efficacy.

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