ISSN: 2638-1451

Clinics of Surgery

Case Report

Negative Pressure Wound Therapy With Potential Autologous Stem Cell Therapy: The Challenge and Future of Complex Defect Healing?

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Volume 2 Issue 2- 2019
Received Date: 15 May 2019
Accepted Date: 28 June 2019
Published Date: 06 July 2019

1. Abstract

The complex wound defect always needs long-term clinical intervention and flap coverage, because of massive soft tissue loss with continuous sepsis and poorest granulation tissue with the impair healing process. Here, we report a 22-year-old male who suffered a work-related high voltage electrical burn (HVEB), resulting in extensive deep tissue damage (about 12% visible 3rd-4th degree total body surface area burns) and an abdominal wall complex defect. A series of surgical operations and medical care were taken by the trauma team, including the application of negative pressure wound therapy (NPWT) in conjunction with autologous stem cell therapy. Our results suggest that the combination of NPWT with stem cell treatment is a successful method in treating complex wound defects. This treatment was covered in observation time and wound healing was satisfactory.

2. Key words

Multiple trauma; High-voltage electrical burn; Complex wound defect; Negative pressure wound therapy; Bone marrow aspirate; Stem cell therapy

3. Introduction

Wound healing is a coordinated process involving complex mechanisms that proceed in various stages, which include blood clotting, inflammation, cellular proliferation, angiogenesis, and remodeling of the extracellular matrix. In the past few decades, the management of wound healing has evolved rapidly. Negative pressure wound therapy (NPWT) has become a standard non-invasive intervention to clinic patients with various acute and chronic wounds [1]. In recent years, the addition of stem cell therapy has become highly recommended in wound healing and is getting to be one of the most useful therapeutic methods in clinic [2].

An intractable challenge for the surgeon, the complex wound defect is infamous for its massive soft tissue loss, continuous sepsis and the presence of poor granulation tissue that impairs healing. These complications apply a challenge for the patient as well, as complex wound defects require long-term clinical invention and imposes a heavy financial burden. Additonally, the majority of complex wound defects are treated with various flap grafts and patients usually have to suffer a new round of full function loss by the reconstruction surgery required. The recent development of advanced wound healing technology has triggered the use of cell therapy to improve wound healing conditions[3]. One of the strategies is to identify and enrich the wound with functionally superior stem cell subsets, such as bone marrow extract and culture. Another approach is to optimize the stem cell delivery to the wound via bone marrow aspirate and injection[4]. Occasionally, we underwent a traditional NPWT combined with stem cell therapy would be a more efficient effect on complex defect wound healing. We will discuss the benefits of the combination therapy and their potential mechanisms.

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Citation: Fan Yang, Negative Pressure Wound Therapy With Potential Autologous Stem Cell Therapy: The Challenge and Future of Complex Defect Healing?. Clinics of Sugery. 2019; 2(2): 1-8.

4. Case and Treatments

A 22-year-old healthy male suffered a work-related HVEB, resulting in extensive deep tissue damage to the left upper limb, hypogastrium and an abdominal wall complex defect (about 12% visible 3rd-4th degree total body surface area burns) [**Figure1**]. A series of surgical operations and medical care were taken by the trauma team, including emergency debridement, fasciotomy, and laparotomy with colectomy and colostomy on the day of admission (DOA) [**Figure 2**]. Postoperatively, the patient continued to receive appropriate antibiotics and blood transfusions as required. Nutritional support in the form of amino acid infusions and oral intake of high-protein and high-calorie feeds was instituted. After performing consecutive wound observations and complete status assessment, axilla amputation and iliac osteotomy with NPWT were performed on the 3rd DOA[**Figure 3-4**]. Potential stem cell therapy of autologous iliac bone marrow aspirate (2-3 ml per time from left ilium) and injections (0.5-1 ml per site at the poor granulation tissues of defect) were performed during operation 6 times, on the 10th, 15th, 19th, 24th, 29th, 36th DOAs [**Figure 5-10**]. On the 42nd DOA, coverage of the left hypogastric wound was performed using mesh skin autografts on fresh granulation tissues [**Figure 11-12**] and wound healing was satisfactory [**Figure 13**]. The patient was discharged 18 days after grafting and was referred to the rehabilitation department for advanced rehabilitative treatment. There were no other complications during the whole inpatient treatment period.

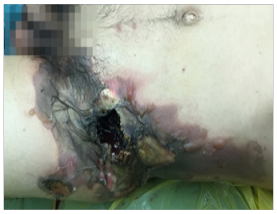

Figure 1: The patient immediately after admission, showing extensive deep tissue damage to left upper limb and hypogastrium with abdominal wall complex defect(about 10% visible total body surface area burns with 3rd degree).

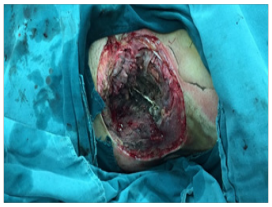

Figure 2: A series of surgical operations and medical cares had taken by the traumatic team, including emergency debridement, fasciotomy, laparotomy with colectomy and colostomy on day of admission (DOA).

Figure 3-4: Progressive tissue necrosis of the hypogastric defect. After performing a consecutivewound observation and complete status assessment, axillaamputation and iliac osteotomy with NPWT had performed on 3rd DOA.

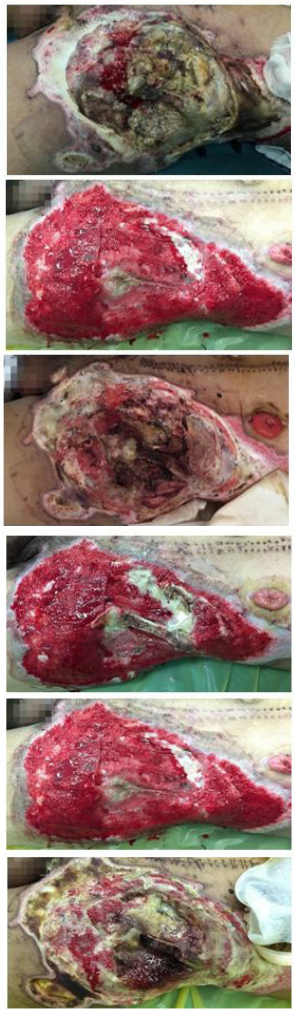

Figure 5-10: Potential stem cell therapy of autologous iliac bone marrow aspirate and injection at the poor granulation tissues had performed during the operations for 6 times, on 10^{th}, 15^{th}, 19^{th}, 24^{th}, 29^{th}, 36^{th} DOA individually, and complex defect wound was amazing healing stringendo without a flap coverage.

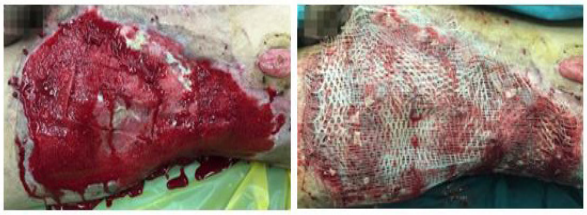

Figure 11-12: Granulation tissues were fresh and achieve the condition for mesh skin autografts on 42th DOA.

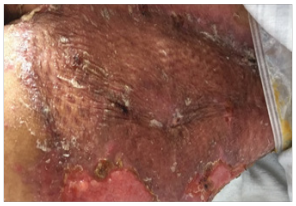

Figure 13: Wound healing satisfactorily on70th DOA.

NPWT-vacuum-oxygen partial pressure

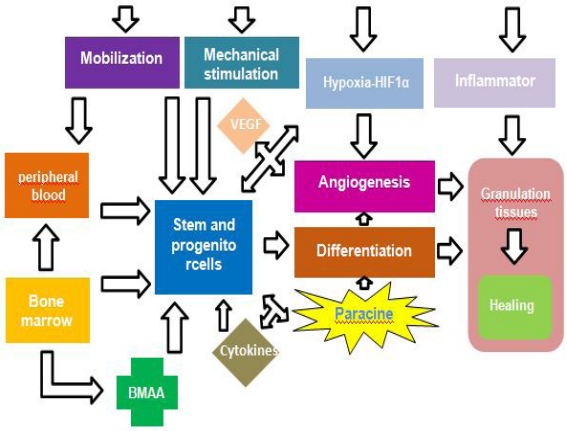

Figure 14: Potential mechanism of combinatorial therapy.

5. Discussion

5.1. Multiple trauma and HVEB

HVEBs are one of the most important etiologic factors in trauma populations and can lead to irreversible damage to different tissue types. Vessels and muscles, with the lowest resistance to HVEBs, are highly susceptible to thrombosis and muscle necrosis. The necrosis results in extensive deep tissue injury and complex defects with potentially fatal outcomes. This is one of the most challenging problems in wound healing and regenerative medicine.

In cases with HVEB, electric current flows along muscle, nerve and blood vessels and causes severe heat injury in high resistant structures attached to vessels such as skin, ligament, and bony tissue. In this situation, muscle, skin, tendon, fat, and bone are all susceptible to irreversible injury. Additionally, the entry and exit sites tend to produce more extensive tissue damage[5] so the severity of the injury is not reflected in the appearance of the external lesion. HVEBs are devastating injuries associated with a vast array of serious and inevitable complications. The prognosis for these patients depends on the degree of the initial burn as well as the severity of any subsequent complications[6]. Accordingly, the delayed thrombosis of major vessels of upper extremities was found to be more frequent than lower extremities[7]. Clinical presentations are variability and leading to non-viable extremity amputation and intractable complex defect with sepsis and increased mortality, that a prolonged serial of debridements should be revised until all the wound acquires a bed of fresh granulation tissue for the flaps or skin grafts. Early intervention is the goal of resuscitation and surgery being the mainstay of management.

5. 2. NPWT for wound healing

NPWT is a non-invasive treatment that uses a vacuum to increase blood supply to the wound, stimulating angiogenesis, formation of granulation tissue, the proliferation of fibroblasts and endothelial cells[8], decreases the bacterial load, reduces swelling and decrease exudate all while maintaining a moist environment that facilitates wound healing[9].

The systemic mobilization of various cells during NPWT may be a mechanism for healing intractable wounds with infections or skin defects. This may occur through the formation of increased granulation tissue along with numerous small blood vessels[10]. Oxygen partial pressure of wound surface could also be reduced significantly by NPWT, leading to better vascularization by HIF-1α and VEGF[11].NPWT also promotes the expression of VEGFR2 and VEGFR3, which increases VEGF receptor combination to accelerate wound healing[12].NPWT reduces the bacterial burden in wounds with moderate or high levels of colonization. The authors' findings suggest a bacteria- and-fungi-binding mesh (BFBM) dressing may be a wound contact layer (WCL) of choice during the treatment of chronic wounds[13].NPWT may increase the cellular antioxidative stress reaction and inhibit the reactive oxygen species as well as the inflammatory mediators to degrade the inflammatory response[14].

5. 3. Bone marrow and bone marrow aspirate

Various adult organs and tissues harbor stem cells and progenitor cells that could potentially be used to repair, regenerate, and restore a variety of different tissues following acute injury or tissue destructive diseases. Bone marrow and peripheral-blood are both regular transplantation sources for stem cell therapy[15]. These cells not only participate in the regeneration process by differentiating into tissue-specific cell types but also promote endogenous tissue repair by secreting a multitude of trophic factors[16].

The bone marrow is an important source of hematopoietic stem cells that regularly regenerate components of blood, and non-hematopoietic stem cells, including mesenchymal stem cells (MSCs). There have been reports proving the plasticity of stem cells harvested from bone marrow and its ability to convert into

many cell lines. There were no statistically significant differences in cell characteristics between MSCs cultured from the sternum and the ilium under any circumstances[17].Many evaluations and clinical applications on bone marrow aspirate have emerged. A crucial one is the discovery that application of autologous bone marrow aspirate and cultured bone marrow cells had significantly higher percentage reduction of wound size compared to those applied with freshly applied bone marrow aspirate[18]. The ilium is the preferred donor site for obtaining autologous stem cells at the point of care. The tibial plateau yielded only half as much bone marrow multipotent or progenitor stem cells as did the anterior and posterior ilium[19], and the yield of colony-founding connective-tissue progenitors was 1.6 times greater in the posterior compared with the anterior iliac crest[20]. Only 5-10 ml aspirates is enough for adequate numbers of MSCs[21, 22]. There will be an easier and safer way for the clinical application of fresh iliac autologous bone marrow aspirate and injection than those cells from peripheral-blood, sternal and cultured under the protocol[23, 24]. By using this similar technique, adult stem cells will be easily harvested through fairly non-invasive procedures, not just musculoskeletal tissues[25].

5. 4. Stem cells therapy for wound healing

Adult stem cells have long been discussed in regards to their application in regenerative medicine. Adult stem cells have generated a great deal of excitement for treating injured and diseased tissues due to their impressive capabilities to undergo multilineage cell differentiation and their self-renewal ability. Most importantly, these qualities have made them advantageous for use in autologous cell transplantation therapies, which include the limitation of the amount of autologous stem cells available for treatment. The solution is inducible pluripotent stem cells (iPSCs), more commonly referred to as iPSCs. The iPSCs can be made from autologous donor cells and can supply an unlimited source of stem cells. The use of iPSCs have become a basic concept in regenerative medicine and are still awaiting identification on whether it can be safely and efficiently used in clinic. Tissue engineering and cell therapy approach aims to take advantage of the repopulating ability and plasticity of multipotent stem cells to regenerate lost or diseased tissue. Researchers continue to investigate stem cells in mature tissues and demonstrate the potential ability of organ-specific cells to differentiate into multiple lineages[26].

With the increasing evidence to prove the usefulness of stem cell therapy in wound healing, the focus of research is shifting toward modalities to optimize cell delivery that can promote the wound repair process through differentiation and release of pro-angiogenic factors. It is speculated that MSCs mobilize from the bone marrow niche and migrate to hypoxia and ischemic tissue through the peripheral circulation in response to cytokine signaling by injury and release factors that modulate repair indirectly by mobilizing the host cells and attracting them to the injury site in a paracrine manner. After reaching the site of injury, they differentiate into various cells for advance proliferation, angiogenesis and remodeling. Transplanted stem or progenitor cells improve tissue healing and regeneration anatomically and functionally, mostly due to their secreted trophic factors,such as VEGF stimulated human umbilical vein endothelial cell proliferation, monocyte chemoattractant protein-1 (MCP-1) elevated macrophage migration and interleukin-6 (IL-6) increased IgM production[27]. In addition to direct cell replacement using stem cells, the stem cell extracts has been discovered to improve wound healing, and reduce tissue damage and augment endogenous repair [28, 29]. This process is loosely called a 'paracrine mechanism' by stem cell secretory factors, but its effects are not necessarily restricted to the injury site[30],and studies provide direct unprecedented evidence for a paracrine lymphangiogenic action of BM-MSC via the production of VEGF-A, which acts on LEC VEGFR-2[31]. Meanwhile, both in vivo and in vitro findings demonstrate that the α6 integrin subunit in BMSCs is important for their ability to stimulate vessel morphogenesis to promote angiogenesis[32]. Not only have stem cells been shown to promote better and faster healing by paracrine, but they have also shown the ability to decreaseinflammation levels with less scar progression and fibrosis[33].

5. 5. Potential mechanism of NPWT and stem cell combinatorial therapy

Wound healing is a complex process which depends on the presence of various types of cells, growth factors, cytokines and elements of the extracellular matrix. Most of the cells that contribute to the repair process are chemo-attracted to the injury site, potentially through host neo-angiogenesis. Angiogenesis or neovascularization is a critical component of wound healing as it is necessary to supply oxygen and nutrients to and carry waste away from the damaged tissue[34]. Therefore stem cells, which give rise to their early descendants' progenitor cells and subsequently differentiated cells, play a specific role in the process of wound healing. The activity of these cells is strictly regulated by various growth factors, especially VEGF. Interestingly, transplantation of VEGF-expressing stem cells improved repair through modulation of angiogenesis, regeneration, and fibrosis[35]. Some preclinical results indicate that a short time treatment with NPWT can enhance cellular proliferation of stem cells and induce differentiation[36], and may act as an inductive role to enhance angiogenic capacity when stem cells were injected [37].

6. Microenvironment

The existence of a stem cell niche as a spatially confined regu-

latory entity relies on the notion that stem cells and progenitor cells are strategically positioned in unique bone marrow microenvironments with defined anatomical and functional features. The capability to engineer microenvironmental cues to direct a stem cell population toward multiple fates or behaviors' change. However, harsh conditions at the site of the wound, including hypoxia, ischemia, oxidative and inflammatory stress, increased fibrosis and insufficient angiogenesis, and in some cases immunological response incompatibility, are detrimental to stem cell survival[38],and most stem cells are in a partially reprogrammed state of pluripotency, which is generated by the injured microenvironment modification [39].

7. Stimulation

In vitro study findings highlight an important role for cyclic mechanical loading preconditioning of donor stem cells in optimizing transplantation. It has been shown that mechanically stimulated stem cells displayed higher VEGF expression than nonstimulated cells[40]. And, the beneficial effects of mechanical stimulation on stem cells mediated repair are lost by inhibiting VEGF[41].

8. HIF-1α pathway

Hypoxia also modulates the expression of soluble mediators and cytokines, as well as that of their receptors. Hypoxia-inducible factor 1α (HIF-1α) is known to regulate the expression levels of key metabolic enzymes that favour lactic acid fermentation over mitochondrial respiration. HIF1α activity leads to the secretion of VEGF, a regulator of stem cell function. In vitro, stem cells are better maintained in hypoxic culture conditions, possibly owing to lower cycling rates. In vivo, inducible deletion of HIF1α in stem cells leads to decreased quiescence and better reconstitution ability. Thus, hypoxia might be an important step in the ontogeny of cellular niches within the bone marrow[42],but the characteristic hypoxic state of stem cells is not solely [43], it may be more benefits to stem cell applications during wound healing processes.

9. Conclusion

Wound healing without cell therapies in which complex defect won't be achieved successfully; extra cell applications are made to convert the wound bed into the environment where maximum wound healing can be achieved[44]. Autologous bone marrow aspirate therapy helps in wound bed preparation that allows the wound healing completely or easily[45]. Compared with conventional methods, the combination of NPWT and stem cell therapy appears to be a safer and more effective method for granulation tissue growth and reduces the surgical burden for complex wound defect patients. Additionally, this report describes the successful use of this method as a stand-alone treatment for both complex wound defect closure. We hypothesize that the promotion of tissue repair, occurs via neo-angiogenesis by iliac bone marrow-derived stem cells[Figure 14]. For non-vascularized tissues, such as articular cartilage, the regenerative property of the injected stem cells promotes a paracrine, or bystander, effect, which involves resident cells found within the injured microenvironment, important for stem cells survival and pluripotency.

Successful cell transplantation will require optimizing the best cell type and site for engraftment, overcoming limitations to cell migration and tissue integration, and occasionally controlling fir immunologic reactivity, as well as a number of other challenges. Collaboration among scientists, clinicians, and the industry is critical for generating new stem cell-based therapies[46]. However, the biological mechanisms behind the beneficial effect of the combination are still unclear and require further investigation using animal models and randomized, human clinical studies.

10. Future Direction Potential

We postulate on novel and future uses for NPWT in targeted drug delivery, stem cell therapy, and the prospect of combination with filtration devices, adaptable smart dressings, and remote monitoring[47]. In stem cell therapy, the new source of induced pluripotent stem cells (iPSCs) have practically unlimited proliferation potential and a capability to differentiate into any cell type in the human body as they are an attractive source of cells for regenerative medicine[48]. However, numerous ethical, technological, and regulatory complications have been hampering iPSC use in clinical applications. We need to reduce the risks associated and find possible solutions for successful use in the clinic[49].

Most of the wound healing process in mammalian adults leads to a compromise in the quality of healing and ultimately results scar formation[50]. It can cause pain and loss of function in the afflicted tissues[51]. There are also psychosocial ramifications associated with a scar formation on exposed skin, as even small changes in scar appearance can significantly impact patient quality of life[52]. Scarring results from injuries and disease. How to archive scarless healing will be a hot topic in the future.

Although we recognize the many advantages of improved musculoskeletal health, we also note that our ability to sustain this health and to maintain the quality of life in an aging population is currently deficient. However, global efforts have produced numerous advances in tissue engineering and regenerative medicine that will collectively serve to fill this deficiency in the near future[53].

Stem cells (either embryonic or induced) sometimes develop mutations in tumor-suppressor genes in vitro[54]. To ensure that the emerging field of stem-cell therapy fulfills its promise to pa-

tients, we must first understand its risks and benefits and develop therapeutic approaches based on sound science, which requires a commitment to the principles of evidence generation[55]. Researchers will have to pay close attention to evaluate which cell selection works best for a given disease. In addition, once a stem cell type has been selected for a therapeutic treatment, researchers must work to overcome any relevant obstacles, whether they are tumorigenicity, immune-rejection, or incomplete differentiation[56]. The U.S. biotechnology and pharmaceutical industries arguably lead the world in innovation while operating under stringent regulations set by the Food and Drug Administration (FDA)[57].

11. Acknowledgment

The authors thank the Bai medical team for the effective teamwork. We also thank Dr. Li's Labratory members for their valuable discussion. We sincerely apologize for any inadvertent omission of any pertinent original references.

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