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Management of Complex Wounds with Dermal Substitute Assisted by a Negative Pressure System

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Abstract

Introduction: The standard treatment for complex wound care is autografting. The advent of dermal substitutes has provided a novel tool for the preparation of the bed to be grafted. However, most types of dermal matrices require the application of a skin graft a second time. Currently, other strategies have been developed to improve the vascularization process, such as negative pressure wound therapy (NPWT), which has been reported to reduce the time required for vascular growth and dermal matrix integration and thus achieve a shorter waiting period for autologous graft application. The present study aims to evaluate the effectiveness and safety of dermal matrix management associated with NPWT in the treatment of complex wounds. **Methods:** Seven patients with a diagnosis of complex wounds were enrolled in this study between July 1, 2015, and June 31, 2016. After debridement and having an adequate wound bed, patients who met the criteria for the application of combined therapy were treated with dermal substitutes and a negative pressure system. The percentage of graft integration into the wound bed, complications, length of hospital stay, and duration of therapy were analyzed. Results: The mean age was 42.5 ± 16 (39 - 54) years old; three women and four

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men were included in the study. The approximate size of skin loss was 120.7 ± 75 cm^2 (25 - 250 cm^2). The combined therapy of dermal matrix plus NPWT was instituted in all cases for a period of 14 days. There were no complications, with 100% graft integration in 6 of 7 cases. Patients were discharged after a mean hospital stay of 5.4 days. **Conclusions:** This study demonstrates that the utilization of combined dermal matrix plus NPWT therapy can be performed safely and effectively in patients with complex wounds with low complication rates and a short hospital stay.

Keywords

Negative Pressure Wound Therapy, Complex Wound, Dermal Matrix, Wound Therapy

1. Introduction

Various types of acute and chronic diseases can lead to skin defects. In wounds, the standard treatment is autografting, which often results in complications such as scar formation and the generation of new wounds in the donor sites. Although complex wounds have been described or mentioned in the literature, no specific criteria have been developed to classify them. The characteristics of complex wounds have been described, and one or more of the following conditions must be present for a wound to be classified as a "complex" type:

1) Extensive loss of integument (an important criteria and to be considered as the most important) in addition to whether it is an acute or chronic wound.

2) Chronic infected wound.

3) Compromised viability of superficial tissues (necrosis), or signs of impaired blood circulation, either venous or arterial; leading to extensive tissue loss.

4) Association with systemic pathologies that impede wound healing and fail to heal with simple care.

The treatment of complex wounds aims to rapidly treat the loss of the skin surface in order to reduce comorbidities and avoid complications caused by second intention healing, especially in patients with sequelae of burns [1] [2].

The introduction of dermal substitutes has provided a novel method for repairing various serious skin defects. These substitutes act as dermal regenerative templates, which facilitate dermal reconstruction and regeneration. Burns could be included in this group of complex wounds, but they are traditionally separated from this group because burns have been considered a special condition to be treated in specialized burn centers. However, they are, by definition, complex wounds [2].

The benefits and action of dermal matrices, such as Integra®, have been well documented, especially in patients with deep burns [3]-[9]. Integra®, manufactured by Integra LifeSciences in Plainsboro, New Jersey, is a dermal regeneration template that differs from other dermal substitutes in that it comprises two lay-

ers. The first layer with a "dermal" function is a synthetic material with a porous layer of cross-linked type I bovine collagen and chondroitin-6-sulfate. This layer is then covered by a second layer with an "epidermal" function, which is a semi-permeable silicone sheet. After implantation, once the dermal layer has vascularized, it is replaced with a thin autograft.

The phases of normal wound healing have been reproduced in dermal substitutes and have been best described in Integra®. Histological examination has demonstrated that Integra® integration involves the following phases: 1) imbibition, 2) fibroblast migration, 3) neovascularization, and 4) remodeling and maturation [10].

Negative pressure therapy is useful for both the first and second histological stages, in addition to stimulating the formation of granulation tissue, mitosis, and angiogenesis. It also prevents the formation of hematomas and maintains an environment without excessive humidity. Since the most common complications reported in the failure of dermal substitutes are bad beds, hematomas, and seromas, these points are of great help for dermal substitutes [11].

In recent years, the use of negative pressure systems has been used to improve the integration of skin grafts. It can be used not only to prepare the wound bed but also directly on skin grafts or dermal substitutes to improve integration [12]. A significant increase in granulation tissue has been observed in wounds treated with negative pressure systems [13], as well as an improvement in wound perfusion demonstrated by Doppler ultrasound [14]. This suggests that negative pressure systems can stimulate perfusion and angiogenesis.

In the present study, the efficacy of the treatment of complex wounds will be analyzed with the use of Integra® dermal matrix, which will be removed before the definitive autograft is performed, together with the use of negative pressure systems. Although this dermal substitute already exists on the market in commercial form, no studies have been carried out to analyze the possible synergic effect of the negative pressure system.

2. Methods

This is a cohort study that was conducted at the South Central High Specialty Hospital PEMEX during the period from July 1, 2015 to June 31, 2016. Patients who met the criteria for dermal substitute were included, and the use of a negative pressure system was added for analysis.

Patients with non-infected complex wounds with the following characteristics were included:

1) Third-degree burns.

2) Wounds with deep dermal involvement, or exposing deep tissues.

3) Wounds with a history of chronicity (3 months or more) due to vascular or infectious complications.

4) Wounds in patients with comorbidities that limit the alternative treatment of local or distal free flaps.

Through non-probabilistic convenience sampling, a total of 10 patients who met the inclusion criteria were identified. However, one of them was eliminated because they did not have a complete registry and two others were excluded due to lack of follow-up. Finally, 7 patients participated in the study. As a dermal substitute, we used Integra®, and the negative pressure system was placed to evaluate them at 14 days after we proposed definitive graft placement, and we determined the success rate of placing such an autologous epidermal graft early. The decision to place such a graft was made by observing the patient's bed and classifying it as adequate. The latter was determined by observing granulation tissue in the wound bed, as well as its coloration and the absence of necrotic or infected tissues. After the observation and placement of the graft had been carried out, the outcomes obtained were analyzed. Afterward, the success rate and viability of the graft placed were evaluated individually. This was analyzed as a percentage of integration of the graft to the prepared bed, as well as the description of the complications presented and unexpected results in each case performed.

The participation of patients in this study entails one type of risk in accordance with the ethical standards of the Declaration of Helsinki and article 17 of the Regulations of the General Law of Health on Health Research.

The Pemex ethic and bioethics commit endorsed the protocol. The data will be kept in a database and it will stay password-protected. Using the data gathered, this study will be conducted, and it is planned to save this data for other studies, so that it won't be lost and can be finished with new research subjects. Given that it is a descriptive study using information from the electronic clinical record, informed permission is not necessary.

As for the statistical analysis, a descriptive analysis was performed for the nominal variables and an inferential analysis for the numerical variables, Shapiro Will normality tests were applied and then the relevant statistical test was selected. The jamovi program version 2.3.18 was used to perform the analysis. The writing of the article was based on the STROBE guidelines for objective reports. A search for articles was carried out in PubMed, Cochrane Library, Google Scholar and a synthesis of current knowledge.

3. Results

Seven patients were admitted to the study, all of whom met at least one of the inclusion criteria for complex wounds and were suitable for this treatment. The characteristics of the wounds varied greatly, with very little tissue involvement manifested by tendon, muscle, or bone exposure in all of them. The approximate size of skin loss ranged from 25 cm^2 to 250 cm^2, presenting a mean with a standard deviation of 120.7 ± 75 cm^2. Within these 7 patients were four males and three females, ranging in age from 9 years to 57 years old, with a mean of 42.5 ± 16 years and a median of 50 years. Three male patients were active workers in the company, and another one was retired. He is presented as the only patient

with chronic degenerative disease in the study, with hypertension. The three female patients, two adults and one minor, aged 9 years, had no associated comorbidities. Their diagnoses included trauma to the left foot following a car accident in the 9-year-old patient; fasciitis in the right hand and forearm in the dorsal region following an injury in a 50-year-old patient; and another 54-year-old patient with septic arthritis in the left knee, which was managed with healing following debridement, for which she was admitted to the study.

As for the male patients, all within the company's staff, three active and one retired, there was a diagnosis of burns in two patients; one of electrical type in a 57-year-old patient, with involvement in both hands, being a candidate for our study a wound in the left wrist, with exposure of flexor tendons; and another 38-year-old patient with direct fire burn, with deep involvement in the back of the right hand, which merited the treatment of our study.

Two additional male patients were identified with complex wound injuries in the lower limbs. One patient, aged 51 years, was found to have involvement in the middle third of the right leg, in the posterior region, due to a complicated exposed fracture. Additionally, another patient aged 39 years was found to have involvement in the distal third of the right leg due to a history of exposed fracture injury (Table 1).

Once the patients were admitted to the study, they were offered treatment with this synergy of acellular dermal matrix plus negative pressure in order to improve the preparation time for an adequate bed for the reception of a definitive autologous graft. Informed consents were signed by the patients, their parents (in the case of minors), and witnesses. After completing the above, the Integra® plate was placed in a sterile condition in the operating room. This was performed on a debrided surgical bed without any evidence of infection. In none

Table 1. Distribution of study patients. F = female, M = male.

Patient	Age (years)	Gender	Diagnosis	Anatomical site	Wound evolution
1	54	F	Septic arthritis	Left knee	2 years
2	50	F	Fascitis	Right hand and forearm	1 week
3	57	M	Electrical burn	Left wrist	1 month
4	9	F	Friction wound	Left foot dorsum	3 months
5	38	M	Burn by direct fire	Right hand dorsum	1 year
6	51	M	Exposed fracture	Middle third of right leg	1 year
7	39	M	Exposed fracture	Distal third of right leg	5 months

of the cases presented, the surgical bed had granulation tissue, and in all of them there was tendon or fascia exposure, and in one of them there was bone exposure of less than 1 cm^2.

The dermal substitute plate was placed over the wound edge by no more than 2 mm and was fixed with sutures. The Integra® plates were randomly cut between 5 and 7 mm in order to optimize the distribution of the negative pressure and enhance adhesion of the acellular dermis plate to the wound bed. Subsequently, a sterile microporous sponge was placed for the subsequent placement of the negative pressure system; VAC® was the brand used for this purpose. The hermeticism was assessed using self-adhesive patches, and intermittent negative pressure was applied at a pressure of 100 mmHg continuously for a duration of 14 days. The patient was discharged in five cases the day after placement with a portable negative pressure device, with evaluation of the good functioning of the system every week. In two of the cases, due to associated comorbidities, the patient remained hospitalized for those 14 days.

Afterward, once the proposed time for bed preparation was completed, the negative pressure system was removed, also in the surgery room, and the quality of the surgical bed was evaluated at that moment, after removing the outermost layer of silastic from the dermal substitute plate, for the subsequent placement of the definitive autologous graft. In the 7 patients selected, an adequate graft recipient bed was obtained, characterized by granulation tissue and a bright red coloration of the bed, which speaks of good vascularity of the bed. In addition to the clinical parameters of a suitable recipient bed, the absence of infection, hematoma, or a high number of fibrin creations was also assessed. The surgical bed was qualified as adequate in the 7 selected cases, giving a bed preparation success rate of 100%.

In the operating room, at that moment, after discovering the wound bed and observing in each of the 7 patients the good conditions of the same, a thin partial thickness graft (0.006 - 0.008 inches) was taken with a pneumatic dermatome, the donor site being the anterolateral side of the thigh. Afterward, the partial-thickness graft was placed in the wound bed site and fixed to the wound edges. The negative pressure system was placed again with a microporous sponge, with an intermittent pressure of 100 mmHg.

The last graft was removed 5 days after the placement of the graft and the negative pressure system. The removal of the last graft was performed in the outpatient clinic, resulting in graft success with 100% graft integration in 6 of the 7 patients. In a female patient who presented with a diagnosis of fasciitis of the dorsum of the right hand and forearm, a lysis of the graft was observed in the central region of the defect in the dorsum of the hand, measuring 2 cm in diameter, accompanied by the exposure of the extensor tendons. In this case, the graft was integrated into 90% of the wound (**Table 2**). This complication was treated by removing the lysed graft area and repositioning a dermal substitute plate. The patient underwent conventional treatment, involving occlusion of the

Table 2. NPWT/AD synergy treatment results.

Patient	Wound size	Affected skin layers	SPN/DA placement time	Bedding quality after	Integration of graft	Complications
1	50 cm^2	All	14 days	Appropriate	100%	No
2	100 cm^2	All	14 days	Appropriate	90%	Lysis of 10% of the graft
3	25 cm^2	All	14 days	Appropriate	100%	No
4	120 cm^2	All	14 days	Appropriate	100%	No
5	100 cm^2	All	14 days	Appropriate	100%	No
6	250 cm^2	All	14 days	Appropriate	100%	No
7	200 cm^2	All	14 days	Appropriate	100%	No

NPWT/AD: Negative pressure wound therapy/Acelular dermis.

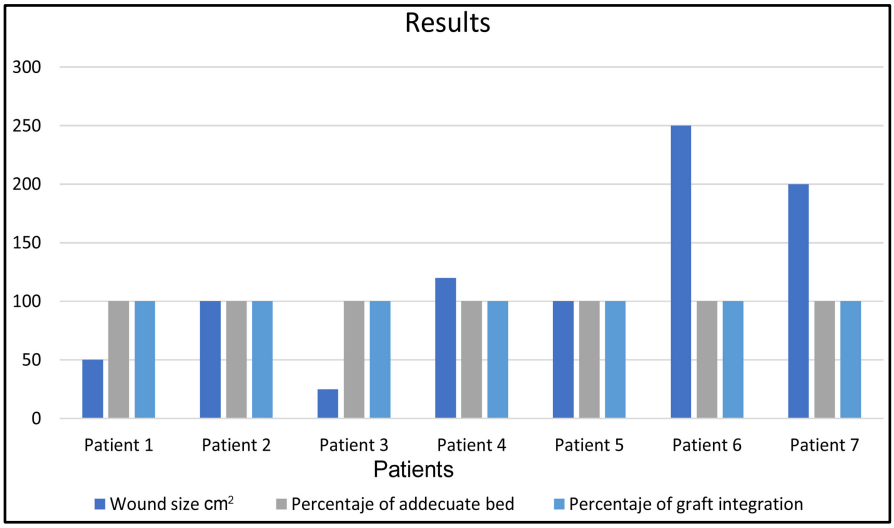

Figure 1. Summary of results found, showing a graphical comparison of wound size, percentage of adequate bed and percentage of graft integration.

same and weekly evaluation until 21 days after placement. Following this, a silastic plate was removed from the dermal substitute plate, resulting in the identification of a suitable bed with adequate coverage of the extensor tendons and good viability for the placement of an autologous graft. This bed was distinguished by granulation tissue and a favorable coloration, with no evidence of infection. After that, the graft was placed and covered with anti-adherent gauze (a negative pressure system was not used). It was reviewed 7 days later, and it was found that 100% graft integration was achieved without complications.

4. Discussion

The findings of this investigation, as described in **Figure 1**, show an encouraging synergy between these two systems, the acellular dermal substitute and the nega-

tive pressure system. The patients are a small, homogeneous population of 57% male and 43% female, with a mean age of 42.5 years and a wound size of 120.7 cm2. Regarding the medical history of comorbidities, the only case was a patient with a diagnosis of arterial hypertension, who, being an isolated case, could not be given an adequate analysis. In spite of this, it was a case in which no complications occurred.

The percentage of presentation of an adequate bed, with the clinical characteristics already described, was adequate in all cases, with a success rate of 100%. This was achieved by the synergy of dermal substitute plus a negative pressure system in intermittent mode for 14 days. Once this was done, the success of the definitive graft was not perfect due to a minor complication, which was 90% graft integration with lysis of the remaining 10% with no evidence of infection or hematoma.

The time of evolution of the initial diagnosis was very variable, ranging from 1 week (7 days) to 2 years (730 days), with a mean of 248.1 ± 240 days of evolution and a median of 150 days. In this case the complication found is in the minimum value of our range of time of evolution, of which, we did not find any clinical correlation that makes these events related, more than perhaps, the debridement prior to the placement of the treatment synergy to be studied was not adequate.

Regarding the analysis of the size of the skin defect, there is no statistical or clinical relationship with the complication presented, since the size of the wound with complication is approximately 100 cm^2, very close to the mean of 120.7 ± 75 cm^2.

The analysis of this complication should focus on the questioning of the true success of bed preparation at this level, as characteristic data at this level was the greatest tendon exposure of all the cases studied. As previously described, a negative pressure system has main virtues at the wound bed level, including stimulating angiogenesis, decreasing edema, and preventing infections.

Despite this premise, it should be noted that in the case of the largest skin loss presented in these cases, which was approximately 250 cm^2, there was a bone exposure of 2 cm in diameter which was completely covered by the acellular dermal matrix, in addition to presenting adequate integration of the graft at that level.

Another factor to consider is the success of definitive graft integration. The mean percentage of graft integration was 98% with a standard derivation of 3.5 and a variation coefficient of 0.0355. The only adverse event was the lysis of 10% of the graft already described.

Something important in this study was the absence of serious complications. For the acellular dermal substitute plate, there are several issues described: lack of integration to the surgical site due to poor adhesion to the site, hematoma and infection. The reason this synergy was proposed is to avoid these complications. The lack of integration is, to a great extent, a complication presented by the poor

adherence of the plate to the wound bed, this can happen due to a bad fixation of the plate, due to a shearing mechanism performed by the patient, or due to a bad occlusion to achieve a uniform pressure of the dermal substitute to the bed. With the negative pressure system, we achieve an adequate adhesion to the wound bed, this together with the perforations or cuts made to the silastic plate and to the acellular dermal substitute plate itself.

Another common complication leading to failure of dermal substitute placement is the presence of hematoma separating the adhesion of the plate to the wound bed. This was also absent in our study, with an apparent synergy of the negative pressure system to the acellular dermal plate, which through the suction exerted could have drained an eventual hematoma. And finally, no infection was present, this achieved by the mechanism of dragging and hermetic occlusion of the wound, which produces an inhospitable environment for any bacterial infection.

In addition to this, the negative pressure system maintains an adequate humidity environment, stimulates angiogenesis and, by means of dragging, keeps the wound bed free of fibroblast-inhibiting cytokines, which favors an acceleration of the healing process; all of the above, widely described in wounds at the molecular and histological level.

In general terms, a shortening of the process of closure of a complex wound was achieved which, using the same resources, the healing time could have been from 21 days for dermal substitute placement plus 7 days for graft integration, giving a total of 28 days; to a decrease of 14 days plus 5 days for graft integration, both accelerated by the aid of the negative pressure system, giving a total of 19 days.

5. Conclusions

Since this is a Pilot Study, it fulfills the objective of being an initial sampling for the advent of a larger-scale study, giving the guideline and showing the safety of the model used, and above all, giving favorable results for the motivation to conduct randomized, comparative trials with a larger universe of patients.

It should be noted that, although one patient achieved 90% integration, the rest achieved excellent results. This motivates us to reduce the placement times of the synergy mentioned in the study to 10 - 12 days. Due to the fact that the acellular dermal substitute plate utilized in our service is Integra®, which utilizes synthetically created microtunnels that stimulate the advancement of blood vessels. Furthermore, it has been reported that the timeframe for accelerated angiogenesis by negative pressure ranges from 21 to 10 - 14 days. Therefore, we do not recommend removing the suction prior to the minimum duration of 10 days for grafting placement. This study provides a good result in terms of accelerating the process of integration of the dermal substitute plate to the bed, shortening the usual times, and above all, a decrease in the most common complications. The great limitation of the study for its statistical analysis was the size of the

sample, but, with these favorable results, we will be motivated to capture a larger number of patients and perform a statistical analysis of greater impact for the benefit of our patients, to shorten their convalescence time, and to offer them a procedure with a minimum risk of complications.

Informed Consent

As this is a non-experimental clinical trial, the informed consent of the institution South Central High Specialty Hospital Petróleos Mexicanoswas used in which the benefits, risks and possible complications with this treatment are addressed, the patient, in case of not wanting to be part of this treatment will be excluded from this study, as previously commented.

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This study was conducted with resources from the authors.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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