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Available online at: http://www.iajps.com ***Research Article***

SAFETY AND EFFICACY OF AMNIOTIC MEMBRANE IMPLANT IN VENOUS LEG ULCERS

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Abstract:

The basic objective of the research is to evaluate the safety and effectiveness of amniotic membrane (AM) application in venous leg ulcers (VLU).

In a specific design of non-controlled pre-post clinical trial, a specialized AM fragment was subjected to the ulcer in rigorous sterility conditions. Principal result strategies: the rate of total healing, ulcer is reduction percentage and diurnal and nocturnal pain assessment. Control visits: at primary and 1, 2, 3, 4 and 8 weeks immediately after treatment.

Ten patients were employed (79.6 years). Three weeks after AM implant, pain had entirely vanished and ulcer area had lowered to just about halved and, 2 months immediately after AM implant, ulcer area was lower in significantly more than 80% along with two thirds of individuals the ulcer had been completely recovered. No significant adverse reactions were noticed.

The current research produces emerging information reinforcing the concept that AM dressing is a safety and reliable alternative to heal VLU

Keywords: *Venous leg ulcers; Amniotic membrane; Ulcer healing; Pain; Effectiveness; Safety*

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INTRODUCTION:

Venous leg ulcer (VLU) is known as a acute state which includes a prevalence rate of 3-5% and a yearly incidence rate of 2-4 emerging cases/1000 residents in the ≥ 60 year old populace. Around 40 and 50% of these ulcers continue being active for intervals for at least half a year and 10% of them can possibly achieve intervals of 5 years. Furthermore, once primarily recovered, 1/3 of them reoccur in just one year interval. VLU also have an appropriate impact on wellbeing, especially due to pain (Wu et al., 2018).

A variety of techniques can be found relating to the therapy of VLU including different medical products, but a majority of them have not exhibited its usefulness. Compression therapy is the central component of its administration along with the therapeutic option with improved research on its efficiency. However their benefits are normally inferior and considered as the impracticality of effective adherence. Remedy for VLU remains a major clinical concern due to its' high prevalence, refractory nature, quality of life influence and economic repercussions (Wu et al., 2018).

It is clear that the amniotic membrane (AM), a lot of internal placental membrane, demonstrates some physiological components which render it a good prospect towards the treatment of venous ulcers. AM fails to express HLA-A,B,C and DR antigens, so it does not induce immunological responses, likewise has bacteriostatic properties, anti-adhesive consequence and the ability to inhibit the metalloproteases in the biofilm of the ulcer agitating a rapid apoptosis of the inflammatory cells. Some in vitro studies have shown anti-fibrotic capacity of AM in the process of transformation of fibroblasts into myofibroblasts (Osman and Ahmed Elbadawy, 2016).

Furthermore, AM includes some angiogenic aspects that play a role in efficient granulation. AM constitutes a bio-therapeutic product and includes in the form of substrate for epithelial development in the management of ocular ulcers with positive results. The information about its efficiency in the therapy of VLU is increasing and encouraging, however scarce. The objective of this research was to evaluate the safety and efficacy of AM application in VLU in terms of total healing rate, reduction of the area of the ulcer and pain control (Meyer et al., 2014).

METHODOLOGY:

Design and Population

A non-controlled pre-post clinical test was performed. Study populace incorporated subjects with VLU of major or supplementary origin. Candidates to take part were adults (≥ 18 years) struggling a VLU with a granulation stage (tissue stage I or II), by having an area more than 5 $cm^{2,}$ and having more than 6 months of advancement. Everyone in the group must have to have the capability to comprehend and give, by writing, informed consent. Patients were excluded if lower limb ulcers were not of venous etiology (according to an Ankle/Arm index <0.75), in case of venous angiodysplasia, clinical signs of ulcer infection, present or past diagnosis of any neoplasm, treatment with chemotherapy and/or corticosteroids, severe liver disease, plasma levels of creatinine >1.90 mgr/dl or plasma albumin levels <2 g/l. Serological study for HIV, HBV and HCV was performed to ensure they were negative before inclusion.

Patients were enrolled in the Department of Angiology and Vascular Surgery from March 2016 to April 2017. This particular plan was considered a pilot study to be carried out in ten patients. The research protocol was authorized by the local ethical committee and by the General Direction of Health Regulation, as soon as obtained the required report of the Ministry of Health by the Pakistani Government. Almost all participants gave their consent by writing prior to recruitment.

Intervention and outcome measures

In every patient an AM fragment was incorporated on the ulcer in rigorous sterility environment. A distinctive AM fragment of 4.5 cm of diameter was implemented to every patient. Whenever the AM was thawed out by physiological saline at 37 degrees Celsius for 10 mins, it had been positioned on the ulcer, and it was eventually addressed through an additional silicone dressing and hydrophilic gauze. The intensity ended up being bandaged by elastic bandage of 7 meters length and 10 centimetres width up to the level of the knee. This structure was only reviewed in the course of each control visit or in the presence of signs of inflammation or infection.

All subjects had been followed-up for 8 weeks with regulatory visits at three days and at 1, 2, 3, 4 and 8 weeks after AM implantation. As part of every control visit, the perimeter of the ulcer was driven on acetate paper to approximate ulcer area in mm^2 applying the Kundin method. Healing rate in every control visit was determined using the subsequent formula: [(initial area–area at time i)/initial area]·100.

Complete ulcer healing was considered when healing rate was 100% (ulcer area was 0). Ulcer pain throughout day and at night was evaluated by a 0-10 cm visual analogue measure. Other research factors planned had been age, sex, level of education, isolation, co-morbidities, and normal remedies, duration of ulcer development, BMI (body mass index), primary or secondary etiology, serum creatinine and albumin amounts, and incidence of any side effect such as inflammation, exudation or infection. All variables were assessed in all patients by the same experienced angiologist.

Analysis

All records were authorized in an electronic system for posterior depuration and research. Numerical factors, such as recovery estimates and pain, had been characterized with means, medians, standard deviations and minimum and maximum standards, while specific ones were characterized by percentages. The time to complete recovery was determined along with the survival curve with ulcer was estimated using the Kaplan-Meier methodology. Comparison of survival curves according to sex, granulation stage (I or II), ulcer area (<or ≥ 1500 mm^2) or evolution time (≤ 18 or >18 months) were made using the log rank test. Evaluations in the section of the ulcer and pain between baseline visit (before intervention) with each control visit (1, 2, 3, 4 and 8 weeks after intervention) were made utilizing the Wilcoxon ranks test. Statistical significance was demonstrated at a p value <0.05.

RESULTS:

Ten sufferers were enrolled, 8 women and 2 men, having an average age of 79.6 years (SD 15.4). All patients other than 1, who had an unintentional fall and hip crack, had been followed during two months. Main attributes of the research sample and the ulcer are described in Table 1. At baseline, mean area of the ulcer was 2.174,92 mms2 (SD 1816, minimum 500 and maximum 5,964 mm^2).

	N (%)
Sex (female)	8 (80%)
Family support: · loneliness · live with couple	 1 (10%) 9 (90%)
Educational level: · Primary school · Secondary or superior	 8 (80%) 2 (20%)
Treatment with NSAI	3 (30%)
Etiology: · Primary VLU · Secondary VLU	 9 (90%) 1 (10%)
Ulcer location: · External face · Internal face · Dorsal face	 5 (50%) 4 (40%) 1 (10%)
	Mean (SD)
Age	76.1 (15.4)
BMI	29.1 (7.7)
Creatinine	1.05 (0.5)
Albumin	4.2 (0.26)
Time of ulcer evolution	52.8 (105.2)

Table 1: Description of main sample characteristics.

In below mentioned Table 2, there is a demonstration of the development of an area of the ulcer, the recovery level, the share of ulcers entirely recovered and diurnal and nocturnal pain throughout all research visits. It indicates that, 21 days after AM implant, pain had entirely vanished and ulcer area

had decreased to almost halved, and 2 months after AM implant, ulcer area was lower in significantly more than 80%, along with two thirds of patients VLU was entirely healed. General endurance with VLU and survival curves as reported by etiology, grade and baseline ulcer size are introduced in Figure 1.

	Baseline visit	1 week after	2 weeks after	3 weeks after	4 weeks after	8 weeks after
Mean (SD) ulcer area (mm^2)	2175 (1817)	1470 (1501)*	1596 (1795)*	1445 (1837)*	1243 (1731)*	278 (424)*
Median ulcer area (mm^2)	1365	1092*	1047*	867*	402*	0*
Healing rate	---	29.2 (29.3)	37.6 (30.8)	46.6 (38.2)	61.8 (41.7)	84.3 (26.5)
% of complete healing	---	0%	0%	20%	50%	66,7%
Diurnal pain (VAS)	1.6 (1.8)	0.4 (0.97)	0*	0*	0	0
Nocturnal pain (VAS)	2.9 (3.5)	1.0 (2.0)*	0.2 (0.63)	0*	0*	0*

*Statistically different in comparison to the baseline value ($p<0.05$) (Wilcoxon ranks test).

Table 2: Evolution of main outcome measures.

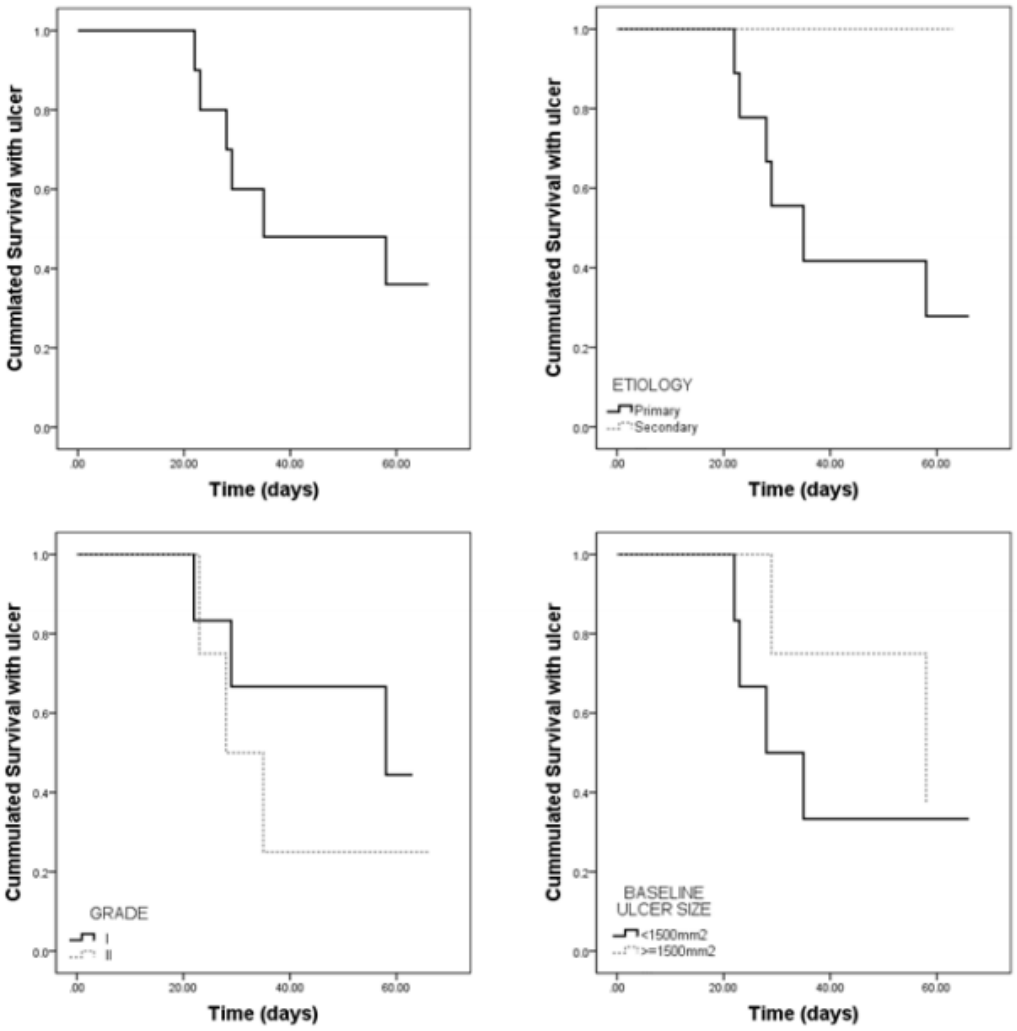

Figure 1: Overall survival with ulcer and survival with ulcer according to ulcer etiology, grade and size.

With regards to security, one patient introduced inflammation signs (dermatitis) a week after AM implant however they totally vanished fourteen days later. Four patients displayed enhanced exudate after AM implant, which has been resolved in a week. It's unlikely that any of them presented clinical signs and symptoms of ulcer infection. One patient experienced a femoral fracture throughout follow-up because an accidental fall, which was considered a serious adverse event not related with the study intervention. No other side effects were observed.

DISCUSSION:

The particular results of the current research suggest an advantageous effect of AM implant through the remedy for VLU. In a decreased number of patients among the VLU with a median duration of development of twenty months, the AM implant attained a comprehensive ulcer healing in 50% of patients four weeks after therapy and in 66% of patients 2 months after treatment. These individuals had a relieving rate of 60% and 80% 4 and 8 weeks after treatment, correspondingly. Diurnal and nocturnal pain also enhanced, entirely vanishing 3 weeks after AM implant. Moreover, study interference revealed safe and without having serious negative events. It has always been assumed that AM had impressive therapeutic prospective in ulcer recovery, but only in the most recent few years scientific research supporting the explanation for its use and its safety and effectiveness has begun to appear (Kirsner, 2018).

The particular results of the current research go along with this incipient evidence about the impact of AM graft in the treating of ulcers. Even though there is

numerous scientific verification concerning the effect of AM implant to treat corneal ulcers, clinical research about its impact through the treatments for VLU is still comparatively scarce. Few non controlled trials in a limited number of patients have evaluated the effect of AM grafting in VLU refractory to usual treatments. Werber et al. performed a prospective study of 20 leg wounds treated with cryopreserved amniotic membrane and fluid allograft and showed that 18 of them (90%) healed during the 12-weeks observation period. Barr describes a series of 7 patients with refractory leg wounds in which dehydrated amniotic membrane allograft (DAMA) was used, and reported that complete wound healing was observed in 6 (85%) patients, with an average time to closure of 7.9 weeks (González-Consuegra and Verdú, 2011).

According to the reports of Lintzeris et al. a retrospective case series of eight patients also addressed with DAMA and stated that all wounds were recovered in an average time of 5.7 weeks lacking undesirable happenings. Francis et al. published preliminary outcomes of a prospective study conducted in forty patients where a single AM transfer was finished likewise determined this particular treatment solutions are protected, helpful, affordable, well-accepted by patients and having awesome prospective in treating resistant VLU. A non-randomized managed research contrasting DAMA with conventional care demonstrated a big change in opportunity to healing advocating graft treatment, recommending that DAMA may increase ulcer healing. There may also be some randomized controlled studies evaluating AM implant advantages in VLU healing (Cullum et al., 2013).

Hanumanthappa et al. released the primary randomized clinical experiment in two hundred middle age (mean age 45 years) patients with VLU. It reveals a considerably enhanced epithelialisation rate at a three week period in the intervention group as compared to the control group (80% vs 40%, respectively) and proves that AM ulcer dressing is more effective than traditional dressing in the management of varicose ulcers. Serena et al. enrolled 84 subjects in a randomized controlled test comparison DAMA and compression therapy compared to compression therapy alone, and noticed a considerable enhancement in healing rate at four weeks in the empirical group as compared to the control group. In another randomized controlled test, ElHeneidy et al. noticed a comprehensive healing in all 14 ulcers in the intervention group (33 days in mean), whilst in the control group with traditional ulcer dressing all ulcers revealed no decrease in their size (Cullum et al., 2013).

Subsequently, a recent multicentre controlled trial evaluating DAMA in venous leg ulcers randomly assigned 109 patients to receive DAMA plus compression therapy or compression therapy alone and observed that complete ulcer healing was achieved in 60% in the intervention group and 35% in the control at 12 weeks. All these studies report significant advantage of AM dressing, with complete ulcer healing in a very relevant percentage of patients in few weeks, which agree with the results of our study (Bianchi et al., 2017).

CONCLUSION:

There is a lack of an effective treatment for VLU. Apart from compression therapy, the rest of more than hundred therapeutic strategies available are considered sanitary products, and have demonstrated safety but not efficacy. In fact, it is usual in VLU patients to be treated with several different dressings in few months. There is a lack of well-designed studies comparing the effect of such strategies especially in comparison to compression therapy, considered the gold standard, and there is also an urgent need to explore for new therapeutic strategies to treat such a devastating clinical condition in terms of pain, quality of life and economical costs. AM dressing has a great potential in treating VLU and has shown positive and promising results.

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