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ORIGINAL ARTICLE

Cost-Benefit Analysis of Amniotic Membrane Transplantation for Venous Ulcers of the Legs That Are Refractory to Conventional Treatment

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KEYWORDS
Amniotic membrane;
Cost-benefit analysis;
Venous ulcern

Abstract

Background: Standard compression therapy for venous ulcers of the legs does not promote healing. Although autografting accelerates tissue repair, it is difficult to use in patients with concomitant diseases or when multiple grafts are required. The amniotic membrane has been used as a covering material and promotes epithelialization, making it a good potential treatment option when autografts are not indicated.

Objectives: To analyze the literature on the safety and efficacy of amniotic membrane grafting and compare the cost of currently available grafts (autografts, amniotic membrane grafts, and biocompatible skin substitutes) to promote tissue repair in venous ulcers.

Material and methods: A systematic review of the literature on the use of amniotic membrane grafts for the treatment of venous ulcers was performed up to 2010. A cost-minimization analysis of direct healthcare costs was then performed (at 3 and 6 months). A sensitivity analysis was performed to confirm the stability of the results.

Results: Only 1 study addressing safety and efficacy was identified. The cost-minimization analysis showed that autografts are always the least-expensive option (€ 1053 compared with € 1825 for amniotic membrane grafts and € 5767 for biocompatible skin grafts). At 6 months, however, amniotic membrane grafts would have cost € 6765 less than the use of biocompatible skin substitutes.

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Conclusions: Despite having excellent therapeutic potential for the re-epithelialization of venous ulcers that do not respond to conventional treatment, amniotic membrane transplant remains an experimental therapy. Autograft is the most efficient treatment but amniotic membrane graft is less expensive than the use of biocompatible skin substitutes.

PALABRAS CLAVE
Membrana amniótica;
Coste-beneficio;
Úlcera venosa

Estudio coste-beneficio del trasplante de membrana amniótica para úlceras venosas de extremidades inferiores refractarias a tratamiento convencional

Resumen
Introducción: El tratamiento estándar compresivo de las úlceras venosas de extremidades inferiores no promueve la cicatrizacion. El autoinjerto es uno de los tratamientos que acelera la reparación tisular, sin embargo, su aplicación es difícil en pacientes pluripatológicos o cuando se requieren aplicaciones múltiples. La membrana amniótica se ha empleado como material de cobertura y como epitelizante, por lo que podría ser una buena opción terapéutica para cuando el autoinjerto no esté indicado.
Objetivos: Analizar el estado de conocimiento científico sobre la seguridad y la eficacia de la membrana amniótica y comparar los costes de los injertos disponibles actualmente (autoinjertos, membrana amniótica y sustitutos cutáneos biocompatibles) para promover la reparación tisular de las úlceras venosas.
Material y métodos: Se realizó una búsqueda y revisión sistemática de la literatura científica hasta marzo del 2010 sobre el uso de la membrana amniótica como tratamiento de las úlceras venosas. Asimismo, se realizó un análisis coste-minimización (horizonte temporal 3 y 6 meses). Se consideraron los costes directos sanitarios. Para comprobar la estabilidad de los resultados se llevó a cabo un análisis de sensibilidad.
Resultados: Se identificó un único estudio sobre seguridad y eficacia. El análisis de costes mostró que el autoinjerto es siempre la opción más barata (1.053 € versus 1.825 € membrana amniótica, 5.767 € sustitutos cutáneos biocompatibles). A los 6 meses la membrana amniótica costaría 6.765 € menos que el uso de los sustitutos cutáneos biocompatibles.
Conclusiones: El transplante de membrana amniótica para la reepitelización de úlceras venosas refractarias al tratamiento convencional es una opción terapéutica de gran potencial, pero aún en estado experimental. El autoinjerto es el tratamiento más eficiente; pero la membrana amniótica es más económica que los sustitutos cutáneos biocompatibles.

Introduction

Venous ulcers of the lower limbs constitute an incapacitating, chronic and recurrent condition,[1] and treatment has a considerable economic impact associated with the use of human and material resources.[2] Venous ulcers represent between 60% and 70% of all ulcers[3] and their incidence increases with age.[2] This suggests that the ageing of the population will lead to a greater prevalence of this clinical condition. When venous ulcers fail to respond to conventional treatment, one of the therapeutic options is autografting. This treatment has important limitations, however, such as limited availability of skin, particularly in elderly patients, and problems associated with harvesting from the donor region (pain, risk of infection, and unsightly scarring). These limitations make performing more than 2 autografts per year unadvisable. For this reason, the future of skin grafts is moving toward the use of biocompatible skin substitutes.

A wide range of biocompatible skin substitutes is available.[4] The main disadvantage of using these substitutes is their high cost, and this has led to the use of human amniotic membrane (Figure) being reconsidered in recent years for the treatment of venous ulcers.[5] Amniotic membrane supplied by the Transplant Service Foundation (TSF, C/ Dr. Antoni Pujadas, 42 - SSM Sant Joan de Déu - Edifici Pujadas - Sant Boi del Llobregat, Spain) is already being used in the ophthalmology department of our hospital

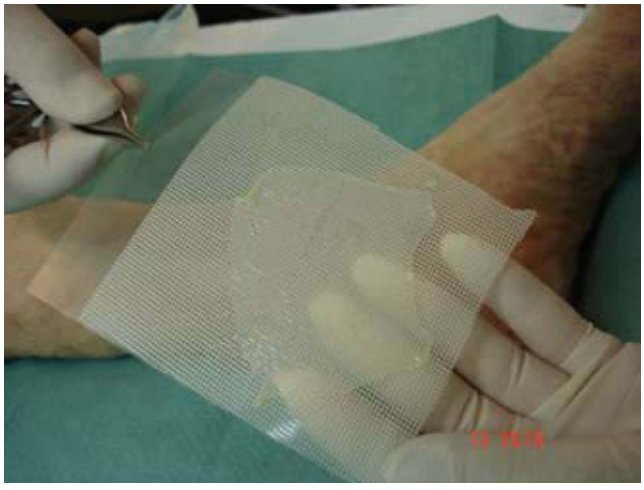

Figure 1 Amniotic membrane.

as a corneal graft[6] because of its properties and actions: it contains high levels of growth factors and cytokines, facilitates migration of epithelial cells, and promotes cell differentiation. Besides its regenerative capacity, amniotic membrane has anti-inflammatory, antiangiogenic, analgesic, and antimicrobial properties, and low immunogenicity.[7] It is permeable, thin, and flexible, and adheres easily to the contours of the ulcer, thereby facilitating patient mobility.[5] These properties and its success in treating ulcers in other areas of the body encouraged us to carry out a clinical and economic evaluation of its use as an alternative to autografting and to allografting with biocompatible skin substitutes in venous ulcers that do not respond to conventional treatment.

Material and Methods

We reviewed the scientific literature on the safety and efficacy of amniotic-membrane grafting in the treatment of venous ulcers of the leg that are refractory to conventional treatment. We also analyzed the cost of the treatment and compared it with available alternative therapies (autografting and allografts using biocompatible skin substitutes).

We performed a systematic, structured search to identify studies that used amniotic membrane in this disease. The databases queried were MEDLINE + EMBASE, PubMed, ISI Web of Knowledge, Cochrane Library Plus, CRD Databases (DARE, HTA, NHS EED), HAYES, ECRI, ClinicalEvidence.bmj.com, Tripdatabase, Clinical Trials.gov, and Google Scholar. The search included all dates up to March 2010. Finally, we considered only articles published since 2000, as current techniques for obtaining and handling amniotic membrane differ substantially from those in use before 2000 and it would therefore be impossible to extrapolate results from before this date to the current context. The key words used in the search were "amniotic membrane" and "ulcers". We used the GRADE scale[9] to analyze the quality of the studies.

Because we identified no head-to-head studies comparing the 3 therapeutic options (autograft, allograft using biocompatible skin substitutes, and allograft using amniotic membrane), for the economic evaluation, we assumed the hypothesis of noninferiority in terms of efficacy and safety between the therapeutic options being compared, ie, the economic evaluation assumes that all skin substitutes have similar levels of safety and efficacy when a similar number of grafts are performed. We used this hypothesis to perform a cost-minimization analysis.[9] The analysis was performed from the perspective of a health care provider (hospital) and, therefore, only the direct costs of the health care resources used are taken into account (in euros, as at 2010). Direct non-health-care costs and indirect costs were not taken into account.

The economic data included in this evaluation came from the accounting system of our hospital. We also obtained information on the frequency of grafts, time taken, and quantities of material used, based on the experience of the members of the dermatology department. The literature was also examined to determine which biocompatible skin substitute had been shown to be most effective, so that it could be included in the analysis, together with its frequency of implantation.[10] The biocompatible skin graft chosen was the bi-layered skin substitute; the price was provided directly by the company that sells the product outside Europe (Apligraf, Organogenesis Inc, Canton, Massachusetts, USA). The price of amniotic membrane was provided by the TSF, which supplies it to our hospital. The base cases in the economic model include the estimations considered to be most probable (mean values), according to sources consulted (scientific evidence and the team carrying out this health technology assessment). The model considers 2 base cases: 1 at 3 months (where the 3 alternatives [autograft, amniotic membrane, and biocompatible graft] are compared) and 1 at 6 months (comparing amniotic membrane and biocompatible graft, as there is no point in repeating an autograft if it has not worked after 3 months). To verify the stability of the results and the consistency of the estimations, an analysis of sensitivity of the values where uncertainty was considered to exist was performed, taking into account 2 extreme scenarios (maximum and minimum) (Table).

Results

The review of the literature identified only 1 prospective pilot study with no control group that showed the results of a single amniotic-membrane graft applied to 15 patients with venous ulcers of the legs. After 3 months, 3 ulcers had epithelialized, the area of 9 had shrunk by 50%, and 3 had not improved. Epithelialization ceased 30 days after implantation. The authors suggested that the properties of the amniotic membrane are lost between 2 and 4 weeks after implantation and recommended evaluating reimplantation in future studies. No adverse effects associated with use of amniotic membranes were observed.[11] According to the GRADE scale,[9] the design and characteristics of the study were poor in terms of the quality of the scientific evidence, and it is highly likely that new clinical trials will both corroborate and refute its results. We found only 1 clinical trial in progress on the efficacy of amniotic membranes for the treatment of refractory vascular ulcers.[12]

The results of the economic analysis show that, in the first base case, with 6 months of follow-up and comparison of 2 therapeutic alternatives, the mean cost per patient using amniotic membranes is estimated at €3110, compared to €9875 for artificial allografts. Thus, the cost of an allograft with biocompatible skin substitutes is more than 3 times that of implanting an amniotic membrane. Using amniotic membranes instead of biocompatible skin substitutes would lead to savings of €6765 at 6 months after the initial implant.

The mean cost per patient in the second base case, with a follow-up of 3 months and comparison of 3 therapeutic alternatives, is expected to be €5767 for an artificial allograft, €1825 for an amniotic membrane graft, and €1053 for an autograft. Thus, amniotic membrane grafting leads to savings of €3942 over allografting with biocompatible skin substitutes, whereas autografting leads to savings of €772 over the use of amniotic membranes. The cost of amniotic membrane transplantation is less than twice that of an autograft at 3 months after the initial graft. The results of

Table 1 Health Care Resources and Unit Costs Used in the Analysis of Each of the Scenarios Evaluated

	Mean Values		Sensitivity Analysis	
Items	Base Case at 6 Mo	Base Case at 3 Mo	Minimum	Maximum
Conventional Treatment (CT)				
Material cost of application of CT	€8.11	—	—	—
Application time for CT	30 min	—	—	45 minutes
Cost of nursing staff	€26.20/h	—	—	—
Frequency of application of CT	2/wk	—	1/wk	—
Cost of material for debriding	€3.22	—	—	—
Debriding time	15 min	—	—	—
Debriding frequency	Once per ulcer	—	—	—
Prevalence of debriding	30% of patients	—	—	—
Time frame	6 mo	3 mo	3 mo	6 mo
Amniotic-membrane allograft				
Cost of a graft from the TSF	€425	—	—	—
Frequency of reimplantation	3	2	1	4
Nursing time per graft	10 min	—	—	—
Allograft of biosynthetic tissue				
Cost of 1 biosynthetic allograft	€2000	—	—	—
Frequency of reimplantation	3.34	2	1	5
Nursing time per graft	10 min	—	—	—
Autograft (noncultured)				
Cost of material for harvesting of skin	€4.17	—	—	—
Cost of tissue for autograft	€0	—	—	—
Frequency of reimplantation	N/A*	1	1	N/A
Physician time per graft	50 min	—	—	—
Cost of physician	€45.14/h	—	—	—
Healing of donor site	4 wk	—	—	—
Cost of treatment of donor site	= CT of ulcer	—	—	—

The table includes the mean values used in the cost per process. The costs associated with administrative support for each visit to the day hospital have also been included (costs associated with the application of conventional treatment), as have costs due to maintenance of the physical hospital structure (overheads) and costs due to fees. The data for the sensitivity analysis were taken from the literature (for biosynthetic allografts) and from our own clinical experience.

*Not applicable, as performance of more than 2 autografts in a year is not clinically recommended.

Abbreviation: TSF, Transplant Service Foundation, Barcelona.

the sensitivity analysis confirm the stability of both base cases in all scenarios. In conclusion, at current prices, the autograft option is always more economical, but amniotic membrane grafting is always the most economical option after 6 months compared to allograft using biocompatible skin substitutes (Table).

Discussion

Although transplantation of amniotic membranes for the treatment of venous ulcers has considerable potential, scientific evidence regarding its safety and efficacy is currently scarce and of poor quality. In terms of safety, the risk of transmission of disease is minimal due to current donor controls, although it cannot be ruled out with absolute certainty in products of human origin. Given the considerable potential of amniotic membranes in terms of the associated benefits at minimal risk and considering the limitations of autografts, we believe that, on balance, its clinical use should be recommended.[5]

Our study's estimation of the costs associated with each treatment option shows that the use and cost of health care resources aimed at promoting healing of chronic ulcers is substantial. The results suggest that the option that provides the fastest rate of healing will have a clear advantage over competing strategies, provided that the cost per graft is not excessive.

This study shows autografting to be the most efficient option, particularly when micrografting techniques such as postage-stamp grafts are used. However, in elderly patients or patients with multiple diseases, autografting is subject to some adverse effects and risks associated with harvesting and healing of the donor site; these risks and adverse effects have not been taken into account in the economic evaluation. Inclusion of these factors may bring the results closer to those obtained for amniotic-membrane grafts, provided that this new technique continues to be shown to be safe over the long

term. Furthermore, the other alternative to autografting—allografting with biocompatible skin substitutes—is associated with an excessively high cost that makes its regular use in routine clinical practice difficult at present. As knowledge of the efficacy of amniotic membrane in venous ulcers that are refractory to conventional treatment increases, the assumption of noninferiority may vary (positively, in terms of greater efficacy or negatively, in terms of lesser efficacy), which, in this case, would cause the cost-effectiveness results to vary.

In conclusion, amniotic-membrane transplantation to heal venous ulcers that are refractory to conventional treatment is a therapeutic option with considerable theoretical (given the properties attributed to it) and practical (the only existing study shows promising results) potential. Moreover, the foreseeable increase in demand for amniotic membranes to be used in different clinical applications may reduce the acquisition cost, thereby making these grafts more cost-effective. Nevertheless, transplantation of amniotic membranes in venous ulcers should be considered experimental and the results of clinical trials currently in progress should be awaited before its widespread use is recommended.

Conflict of Interest

Dr M Alsina is currently the director of the Hospital Clínic-TSF skin-tissue bank. The other authors declare no conflict of interest.

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