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Use of an autologous bioengineered composite skin in extensive burns: Clinical and functional outcomes. A multicentric study

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ABSTRACT

Objective: We report clinical and functional outcomes obtained after application of an autologous bioengineered composite skin (ABCS) produced in a single Spanish tissue-engineering unit.

Materials/methods: Twenty-five burned patients treated with ABCS from 1999 to 2007 in five burn centres were included in the study. Mean age was 29 years (SD 11), with mean total body surface area (TBSA) burned being 74% (SD 17) and mean full-thickness injury of 61% (SD 19) of TBSA.

Results: The mean area initially engrafted with ABCS was 24% (SD 13) of TBSA, with a final take of 49% (SD 30, range 0–100%). ABCS achieved permanent coverage of a mean of 11% (SD 8) of TBSA. In subset analyses, lack of pre- and post-application wound bed infection and lack of serious acute systemic complications at the time of engraftment were significantly associated with better ABCS take.

Conclusions: Final take obtained with ABCS could be improved with the use of non-cytotoxic topical antibiotics following engraftment. The use of plasma to prepare ABCS reduces production costs: cost-effectiveness ratio is not a limitation for its use. In terms of patient satisfaction, cosmetic/functional outcomes (general appearance, texture, flexibility, sensitivity and colour) of ABCS and split-thickness autografts are not different statistically.

1. Introduction

Currently, the overall mortality rates of patients with burns have been reported between 5% and 7% (5.3% in the United States [1] and 6.9% in the Rotterdam Burn Centre [2]). Multisystem organ failure has been identified as the most frequent cause of death, with systemic inflammatory response syndrome and infection often associated with mortal-

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ity [2,3]. In patients with extensive full-thickness burns, skin wounds are a common site of infection and persistence of eschar perpetuates systemic inflammatory response [4]. Therefore, early excision of burns and rapid permanent wound closure remains a limiting factor for reducing morbidity and mortality among these patients, and has been shown to be effective in patients without inhalation injury [5]. Split-thickness skin autografts remain the gold standard for permanent closure of excised burns [6], but they have limited availability in extensive burns. Bioengineered skin substitutes (biosynthetic skin substitutes and autologous cultured/non-cultured skin engineering products) are particularly useful for extensively burnt patients, in the absence of sufficient autograft donor sites. However, most of the products currently available have not sufficiently proved as effective as autografts. For the management of full-thickness burns, the efficacy of bioengineered skin substitutes cannot be determined based on the available evidence [7].

Among the bioengineered skin substitutes, the discovery and application in the early 1980 s of cultured epithelial autografts (CEA) resulted in a great interest for the treatment of seriously burned patients, as they allow to obtain, from a small biopsy of healthy skin and in a short period of time, a large epithelium surface enough to cover the needs of a patient bearing a great surface of the body damage [8]. However, the initial optimism has been tempered by subsequent reports of CEA limitations: delay of 2–5 weeks for culture of the autologous sheets of keratinocytes; mechanical fragility and difficult graft handling; need for an appropriate wound bed; unpredictable take; poor long-term durability with loss of the epithelialisation in treated areas and formation of blistering lesions; vulnerability to infection; and high cost [9–16]. In view of these drawbacks, the exclusive use of CEA in the treatment of burns has been questioned, although they have clearly formed the basis for the development of many of the current bioengineered skin substitutes used *in vivo*. Attempts to improve CEA include incorporating fibroblasts and a dermal layer as an essential element for improving wound regeneration and functionality of the substitutes [17,18].

For the first time in Spain in 1999, an autologous bioengineered composite skin (ABCS) was used for the treatment of a burn patient. This bioengineered skin substitute was developed at the Tissue Engineering Unit of the Centro Comunitario de Sangre y Tejidos del Principado de Asturias (CCST, Spain) and the Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT, Spain), based on the use of both autologous fibroblasts and keratinocytes obtained from a single biopsy, and the use of clotted human plasma as a three-dimensional dermal scaffold in which fibroblasts were embedded [19–21].

To obtain objective data of the clinical outcomes after ABCS engraftment in burn patients, a multicentre retrospective study was undertaken. In addition, patient satisfaction was assessed by comparing cosmetic and functional outcomes with the use of ABCS vs. those obtained with the use of conventional split-thickness meshed autografts (control area). We report the results obtained with the use of ABCS in 25 patients with severe burns.

2. Materials and methods

This was a multicentre retrospective observational cohort study.

Eligibility for inclusion into the study was all patients with burns treated with ABCS from 1999 to 2007 inclusive in five Spanish burn units. Participation in the study was voluntary and participants were requested to sign an informed consent to permit use of the data obtained. Before starting the study, ethic approval was obtained from the ethical committee. A total of 69 patients treated with ABCS were identified and initially considered for inclusion. Finally, data from 25 patients were included in the analysis. The information from the other patients was discarded due to lack of informed consent or loss of follow-up.

Twenty-five patients treated with ABCS from 1999 to 2007 inclusive were therefore included in the study. The mean age was 29 (SD 11) years with a mean total body surface area (TBSA) burned being 74% (SD 17) and a mean total full-thickness injury of 61% (SD 19) of TBSA.

Five Spanish burn units participated in the study: Hospital Universitario de Getafe (Madrid), Hospital de Cruces (Bilbao), Hospital Universitario La Fe (Valencia), Hospital Vall D'Hebrón (Barcelona) and Hospital Virgen del Rocio (Sevilla).

The ABCS used in all patients was produced in similar conditions in a single Tissue Engineering Unit in the CCST in Asturias, Spain, using a small skin biopsy (range 4–8 cm^2) from the patient. In all cases, the ABCSs were transported using conventional land-based means (coach-train). Data collection included demographic and clinical characteristics, treatment and outcomes. Data were compiled from medical records, patient examination and a questionnaire on patient satisfaction with outcomes. In this questionnaire, patients were asked to compare the qualitative outcomes of paired sites of excised full-thickness burns treated with either ABCS or 3:1 split-thickness autografts (control area). These comparative sites were assessed by ordinal scoring for satisfaction with respect to colour, texture, flexibility, sensitivity and general appearance. The assessment used a five-point visual analogue scale in which '1' corresponded to 'very unsatisfied', '2' to 'unsatisfied', '3' to 'neutral', '4' to 'satisfied' and '5' to 'very satisfied'. We converted these data into a new dichotomous variable 'satisfaction' with a positive/negative scoring, considering 'positive' when the response was ''very satisfied/satisfied'' and 'negative' when the response was ''neutral/unsatisfied/very unsatisfied.'' The questionnaire also included some open-ended questions so that the patient could express problems related to the areas investigated. Before completing the questionnaire, a health-care professional indicated the body areas to be compared in each case and explained the assessment scale and the questions.

For long-term medical examination and for assessment of patient satisfaction, data from 18 cases were used. Seven patients were excluded because of ABCS coverage $\leq$5% of TBSA (five cases: patients 8, 17, 21, 22 and 23), which meant that they did not have a sufficient area for evaluating the cosmetic outcomes of ABCS and because they could not answer the questionnaire. The other two patients were excluded because of incomplete questionnaires due to lack