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ABSTRACT

The evolution in surgical techniques for treatment of vitiligo has been producing extremely satisfying results in patients with stable vitiligo, without Köebner phenomenon and resistants to other types of treatment. Many techniques are available and should be used accordingly to the patient and to the dermatologist experience to optimize the results.

Keywords: vitiligo, surgery, transplantation, dermatologic surgical procedures

RESUMO

A evolução nas técnicas cirúrgicas do tratamento do vitiligo tem proporcionado resultados extremamente satisfatórios em pacientes com vitiligo estável, sem fenômeno de Köebner e refratários a outros métodos terapêuticos. Diversas técnicas são conhecidas e devem ser adequadas de acordo com o paciente e a experiência do dermatologista para otimizar os resultados obtidos.

Palavras-chave: *vitiligo, cirurgia, transplante, procedimentos cirúrgicos dermatológicos*

INTRODUCTION

Melanocytes transplantation procedures are therapeutic options indicated for patients bearing vitiligo in its stable phase and that has not responded to previous clinical treatments. [1] These techniques can potentially yield excellent results, even in anatomical areas that are traditionally refractory, such as distal extremities, elbows, knees, nipple areolas, eyelids and lips. [2] In recent decades, research on surgical treatment of vitiligo has increased substantially, and autologous melanocytes transplantations have become increasingly accessible to dermatologist physicians.

The disease's stability is the most important prerequisite for a successful surgical procedure. [1,3] Most authors define the stability criterion as the absence of new lesions or enlargement of pre-existing lesions within one year. [1,3,4] In cases of doubtful stability, a test can be carried out with the transplantation of four or five mini-grafts using 1.0 mm to 1.2 mm punches in the area to be treated, evaluating whether after a period of three to four months some repigmentation halo has been formed in the region. [5] Absence of the Köebner's phenomenon in candidates to undergo surgery also is of utmost importance, since the surgical manipulation of donor and receptor

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Authors:
Gerson Dellatorre[1]
Fernando Eibs Cafrune[2]

[1] Dermatologist Physician. Preceptor at the Dermatology Service, Hospital Santa Casa de Curitiba - Curitiba (PR), Brazil.

[2] Dermatologist Physician. Preceptor at the Dermatology Service, Hospital Santa Casa de Misericórdia de Porto Alegre - Porto Alegre (RS), Brazil.

Correspondence:
Gerson Dellatorre
Serviço de Dermatoloia
Pça. Rui Barbosa, 694
Cep 80010-030 - Centro
Curitiba – PR, Brazil
e-mail: dellatorre@gmail.com

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areas can induce new achromatic lesions. [1] Although it is possible to treat all types of vitiligo with good efficacy using this method, segmental vitiligo tends to yield a better response. [6] Therefore, accurate classification of the disease it is crucial, since it may influence the patient's prognosis.

Surgical modalities can to be classified into tissular or cellular techniques, according to the type of graft to be transplanted. [1,4] Most of the techniques require de-epithelization of the receptor area in order it can receive the tissular or cellular graft. This preparation is usually performed applying superficial dermabrasion, which is a simple, widely used and cost effective technique (Figure 1). Other options include the use of carbon dioxide and Er:YAG lasers, suction blisters, curettage and cryotherapy. [7,8]

In general, dressings are applied immediately after autologous transplantation surgery, and are left untouched in the treatment area over a period ranging from 7 to 14 days. Their function is to accelerate the healing of the dermabraded areas, prevent bacterial contamination, and keep transplanted tissues or cells in the receptor area. [8] To this end, it is common to use collagen-based and/or non-adherent dressings.

As a complement to the surgical treatment, phototherapy can be performed aimed at increasing the repigmentation outcome. It has been recently demonstrated that the use of narrow-band UVB phototherapy in the pre and postoperative periods is related to better repigmentation rates. [9]

TISSULAR TECHNIQUES

Punch grafts

Punch grafting (PG) is a simple, low cost, and widely used technique for the surgical treatment of vitiligo. It consists in obtaining multiple circular grafts from the donor area, taken with 3 mm punches, for subsequent transplantation to the receptor area, which in turn is prepared with punches of the same size (or slightly smaller), in a layout whose spacing corresponds to 2,5x the size of the graft (Figures 2 and 3). [10-12] As an adverse effect, the technique can produce undesirable cosmetic effects known as "cobblestone " appearance, meaning that the graft becomes slightly more elevated than the neighboring receptor area. This is mainly observed when grafts with greater diameters are used. This effect can resolve spontaneously or be treated using electrofulguration. [13] Due to the long time needed to obtain grafts, PG is typically reserved for the treatment of small areas. However, the use of devices with motor driven punchs can reduce this time, allowing the treatment of greater areas. [10]

Regarding its effectiveness, a study that included 880 patients showed that 90-100% repigmentation was achieved in 74.55% of patients during a two-year follow-up period. [11]

SUCTION BLISTER BASED EPIDERMAL GRAFTING

This procedure involves the induction of subepidermal suction blisters in the donor area (usually thighs or arms) by prolonged application of vacuum, with the subsequent transplantation of its roof ? to the receptor area. [1] The vacuum is normally applied with the aid of a syringe or a device specifically used for this purpose (Figure 4). This technique has some advantages over PG, since the donor area heals leaving only a minimal post-in-

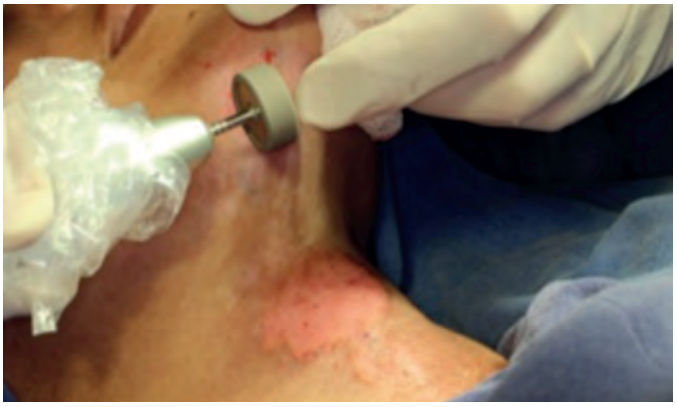

Figure 1: Dermabrasion of the receptor area using motor-driven dermabraser with diamond sandpaper

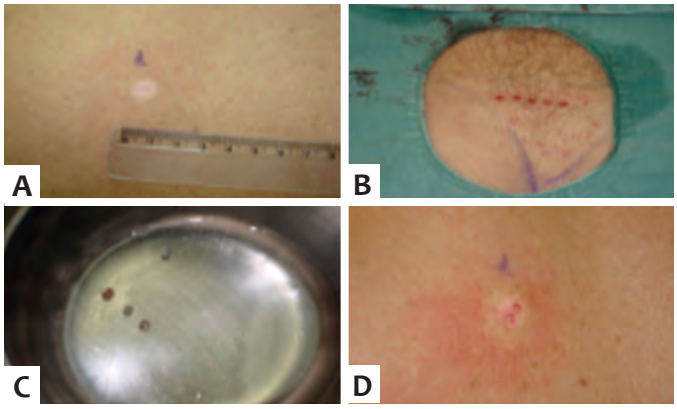

Figure 2: Punch grafting. **A.** Stable and recalcitrant achromic lesion after clinical treatment; **B.** Harvesting of the grafts from the sacral donor area; **C.** Harvested grafts; **D.** Grafting of the receptor area

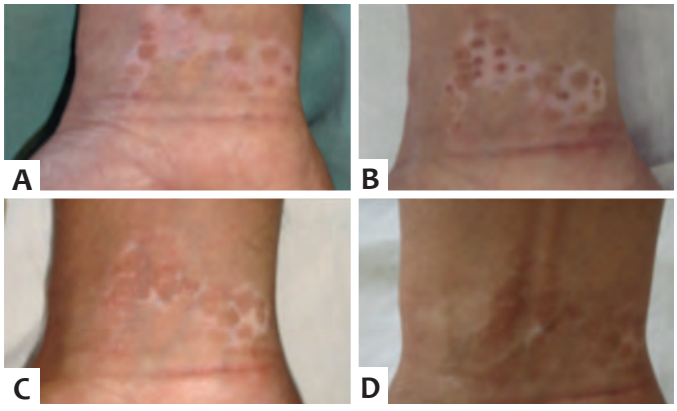

Figure 3: Punch grafting. Six-month development of repigmentation halos, with more than 90% repigmentation. This image was kindly supplied by Dr. Gustavo Braz Tha - Dermatology Service of the Hospital Santa Casa de Curitiba

flammatory hyperpigmentation. [14] Moreover, the "cobblestone" effect described for the previous technique does not occur due to the fact that the graft is purely epidermal. [15]

According to a recent study, suction blister based epidermal grafting (SBEG) can yield results that vary from good to excellent (65-100% repigmentation) in 80% of patients. Although it is cost effective, this method is deemed as protracted, since approximately two hours are necessary to obtain a blister using a 10ml syringe. That time can be shortened using the anesthetic injections in the dermis or applying heat to the donor area before the blister is obtained. [15.16]

PARTIAL THICKNESS SKIN GRAFTING

Partial thickness skin grafts (PSG) have the advantage of treating large areas with good response (90-100% repigmentation) on a single procedure. The graft is obtained with the assistance of a dermatome, meaning the surgeon must have the proper expertise and experience to conduct the procedure. [17] Furthermore, color incompatibility in the receptor area and the potential for unaesthetic healing in the donor area are possible side effects of this technique. [4]

TISSUE FRAGMENTATION TECHNIQUES: EPIDERMAL CURETTAGE AND TISSULAR MACERATION

Different melanocyte transplantation techniques have been described using tissue fragmentation. A common characteristic to these techniques is the fact that the harvesting process of the tissue from the donor area leaves the skin macerated into small fragments to be grafted in the receptor area. In general, they are rapid and technically easy to perform methods, and can be carried out in simple and inexpensive surgical settings. They are capable of re-pigmenting areas that are four to ten times larger than the donor area. [18.19]

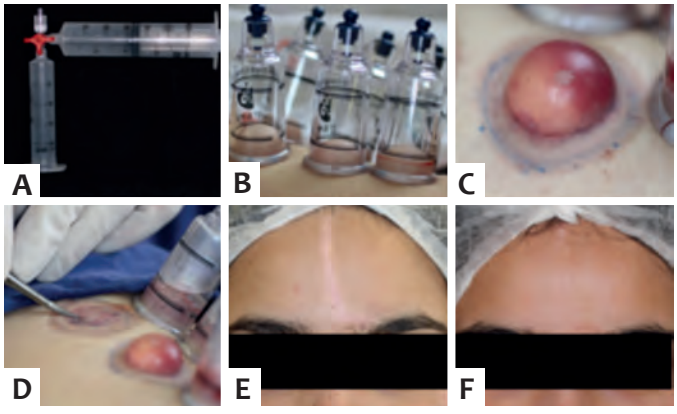

Figure 4: Suction blister epidermal grafting. **A.** Suction device using conventional syringes and a three-way tap; **B.** Differentiated suction equipment, with one-way valve; **C.** Sub-epidermal blister formed after prolonged suction; **D.** Incision of the blisters' periphery for subsequent transfer to the dermabraded area to be treated; **E.** Segmental vitiligo linear lesion in the forehead. Pretreatment; **F.** Six-month postoperative, with greater than 90% repigmentation of the lesion

The epidermal curettage (EC) technique is performed after asepsis and demarcation of the donor area (usually thigh or sacral region), where topical or injectable anesthesia is performed. With a sterile curette, the tissue is removed up until the pinpoint bleeding is visualized. The removed material is placed in a jar with saline solution, and may undergo further maceration up until a paste consistency is obtained. After dermabrasion of the receptor area, the macerated tissue is put in place observing a homogeneous distribution. Next, the area is covered with non-adherent dressing. The dressing should be kept in place with restriction of movement for one week. [18] This method leads to rapid re-epithelialization, usually without residual scarring in the donor area.

In the tissular maceration (TM) method, a thin layer of skin (with little dermis) is removed from the donor area with the aid of a flexible blade. The tissue is placed in saline solution and shredded with the aid of a delicate scissors up until the fragments are substantially reduced in size. Once the material has been prepared, it is placed on the dermabraded area, followed by a dressing, just as described in the previous method. [19,20] Absence of scars in the donor area and intense repigmentation (over 90%) were observed in a study. [19]

CELLULAR TECHNIQUES

Suspension of non-cultured epidermal cells

In the non-cultured epidermal cells suspension (NECS), a thin partial thickness graft is obtained from the donor area with the aid of a razor blade or a dermatome (Figures 5A and 5B). Then the tissue fragment is incubated at 37°C in a solution of trypsin with ethylene dinitrilotetrascetic acid (EDTA), which separates the epidermis from the dermis and ungroups the epidermal cells. After centrifugation of the solution, a concentrated suspension of melanocytes and keratinocytes is obtained, re-suspended in a small volume, and transferred to the dermabraded receptor area (Figures 5C, 5D and 6).

This method has the advantage of the possibility of expanding the ration between the donor and receptor areas from five to ten times, meaning it is capable of treating large areas with satisfactory results. [1.4] Good to excellent results (75-100% repigmentation) can be achieved in 89% of patients. [21] Among this technique's disadvantages is the need for expertise and experience for obtaining the donor tissue fragment, in addition to requiring specific laboratory equipment for the trypsinization phase. [1]

Suspension of non-cultured cells from the external follicular sheath

In this procedure, a cellular suspension is obtained from hair follicles obtained using a follicle unit extraction method assisted by small punches – similar to how hairs are obtained in the hair transplant technique (Figure 7). Approximately 15 to 25 follicles are extracted per patient, depending on the area to be transplanted. Once extracted, the hair follicles are subjected to a trypsinization process similar to that of NECS, aiming at obtaining the cellular suspension. [22.23]

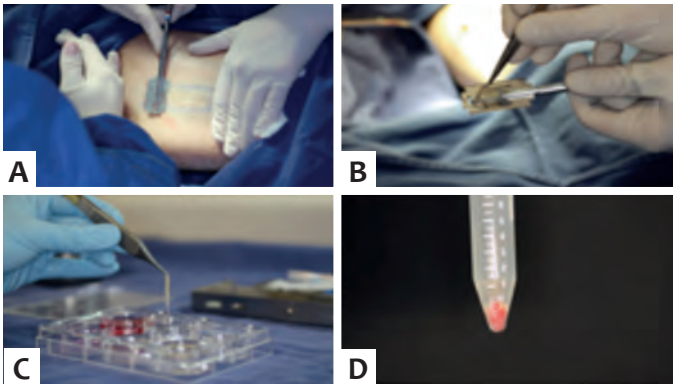

Figure 5: NECS. **A.** Preparation of the skin graft with the aid of a shaving blade, **B.** A thin graft is obtained; **C.** Graft's epidermal cells detachment phase after trypsinization; **D.** Cell pellet consisting of keratinocytes and melanocytes in the lower portion of the tube after centrifugation

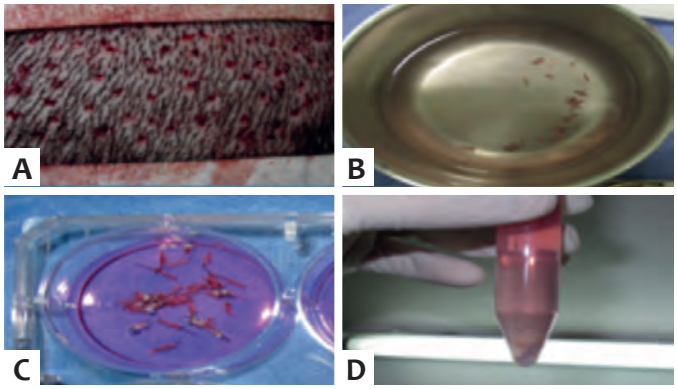

Figure 7: NECS. **A.** Preparation of the receptor area; **B.** Application of the cell suspension on the prepared area; **C.** Receptor area pre-treatment (above the dashed line); **D.** Receptor area post-treatment (above the dashed line)

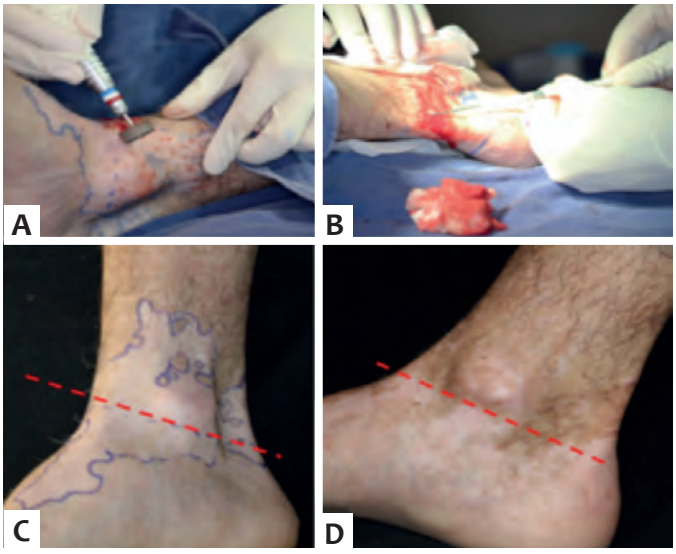

Figure 6: Figure 6: NECS. **A.** Preparation of the receptor area; **B.** Application of the cell suspension on the prepared area; **C.** Receptor area pre-treatment (above the dashed line); **D.** Receptor area post-treatment (above the dashed line)

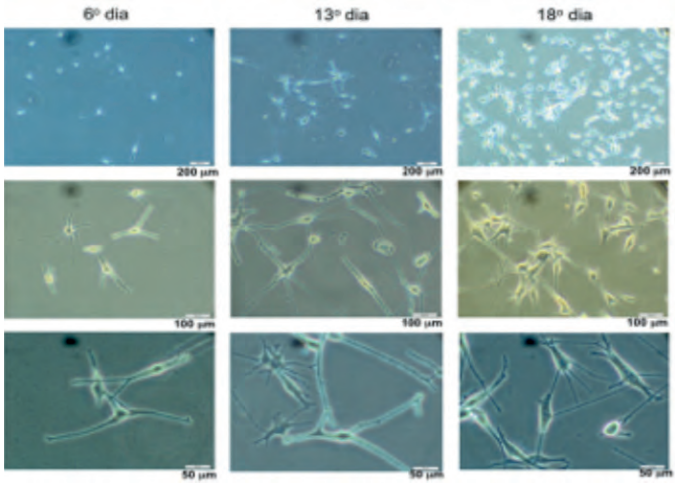

Figure 8: Optical micrographs of cultured human primary melanocytes isolated from skin specimens (4x, 10x and 20x magnification, top to bottom). Cells were previously treated with geneticin for eliminating the fibroblasts and keratinocytes. After treatment with geneticin, melanocytes were cultured for 18 days in medium supplemented with growth factors (bFGF and HGF), which allowed the maintenance and proliferation of cells. Image kindly provided by: Dr. Renata Helena Monteiro Sindeaux and Mariana Kraft Soares, Núcleo de Investigação Molecular Avançada (Advanced Molecular Research Nucleus) - NIMA, Pontifícia Universidade Católica do Paraná - PUC-PR.
6° dia = 6th day; 13° dia = 13th day; 18° dia = 18th day

Obtaining cells originated from hair follicles has some advantages. In addition to being considered an important reservoir region of melanocytes and their precursors, the scars resulting from follicular extraction are virtually invisible. [22] In a comparative and randomized study contrasting NECS and the suspension of non-cultured cells from the external follicular sheath (SNCEFS) conducted with 30 patients, repigmentation of 92% and 78% of the lesions were obtained, respectively. However the difference was not statistically significant. [24]

Suspension of cultured cells

The *in vitro* culture of melanocytes (Figure 8), combined or not with keratinocytes, can dramatically increase the number of transplanted cells. One of the greatest advantages of this technique dwells in the fact that, from a small skin fragment, it is possible to obtain sufficient cells to treat large areas. [25] This method can lead to even greater repigmentation rates when compared to techniques without culture of cells. [25,26] In a recent study, the suspension of cultured cells (SCC) was able to produce more than 90% of re-pigmentation in up to 81.3% of patients. [9]

Despite these advantages, the high cost, the dependence on a specialized team and on laboratory cell culture equipment are important disadvantages of the method. [1] Moreover, since the culture media contain mitogenic factors, prolonged follow-up of patients is recommended due to the theoretical potential post-transplantation malignant transformation. [26] Although in some countries this risk is still considered an ethic barrier for the use of the technique for therapeutic purposes, there are an increasing number of studies in the medical literature with absence of adverse events. [9,25]

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