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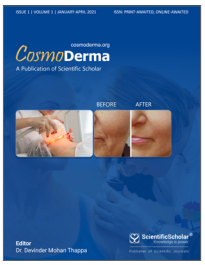

Review Article

Surgical modalities of treatment in vitiligo

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ABSTRACT

Vitiligo is an acquired disorder of depigmentation that is associated with immense stigma and psychological burden. Although there is a myriad of options available for therapy, the repigmentation is best achieved with surgical modalities for stable disease. Once the immune attack on melanocyte is halted, surgery can be undertaken. The principles of surgery may be to introduce artificial pigment, stimulate melanocyte proliferation and migration, removal of depigmented areas or repopulation of depleted melanocytes. Broadly these can be divided into grafting, non-grafting techniques, camouflage and excision. The grafting techniques are further divided into cellular and tissue grafts. The advantage of the former being a greater donor to recipient ratio, however with added cost and equipment requirement. Grafting techniques have undergone various innovations, be it in harvesting, recipient site preparation or dressing, each with their own advantages and disadvantages. New innovations continue to crop up, including the use of stem cells and regulatory T-cell modulation. A well performed surgery is incomplete if it was not done without proper patient selection, counseling and preparation. This review article briefly outlines the various techniques; pre, intra and post-operative intricacies and the innovations in each.

Keywords: Vitiligo surgery, Segmental vitiligo, Tissue grafts, Cellular grafts, Punch grafting

INTRODUCTION

Vitiligo is an acquired disorder of depigmentation affecting nearly 1–2% of the global population. Its impact is immense, and more easily noticed in darker skin types due to the visible contrast. However, its psychological impact is not bound by any phototypic restriction and affects both fair and dark.[1] The situation is further worsened by the stigma and myths that are attached with it.[2] Thus, it is important to halt the disease progression and revive the lost pigment. The principle of vitiligo therapy is to halt the ongoing autoimmune attack on melanocytes, and to repopulate the void with melanocytes.[3] Various modalities of treatment including medical and surgical methods, and phototherapy are not uniformly effective and disease is often resistant to one or more type of treatment. Surgery is often required in disease resistant to medical treatment where the aim is to repigment the vitiligo patches and indicated in stable disease only.

Patient selection

Patient selection for surgery is very important and disease stability remains one of the most important factors for the successful outcomes. Active vitiligo can have any or all of the following: appearance of new lesions, increase in size of old lesions, or presence of Koebner phenomenon. In contrast, stable vitiligo does not have koebnerization and may spontaneously re-pigment. Stability has been defined as no new lesions and no increase in the size of

pre-existing lesions, absent Koebner's phenomenon, positive minigrafting[4] and spontaneous or treatment-induced repigmentation.[5] Other methods to assess stability include vitiligo area severity index (VASI),[6] vitiligo disease activity (VIDA) score,[7] Vitiligo European taskforce assessment (VETFa).[8] The duration of stability before any surgical procedure has been described variably ranging from 3 months to 2 years, however, the 1-year duration is most accepted.[9] Another test of stability is the mini-graft test. In a patient with stable vitiligo, there is unequivocal repigmentation 1 mm beyond the graft, in 4–5 of the mini-grafts implanted in an achromic lesion. Each of these grafts must be placed 3 mm apart.[10] This is not mandatory and may be used in cases where the stability is in debate.

Pre-procedure counseling

Expectations of the patient must be assessed and surgery must not be performed when it is unrealistic. Counseling must also be done that the pigment match may not be perfect, and that it may look different from the surrounding skin. However, in majority, the pigment mismatch would normalize with time. It is essential to discuss the expected success rate and sensitize the patient on poor response of acral lesions and generalized vitiligo.[11] Although there is no age limit for surgery, younger people respond better. Outcomes are improved when concurrently medical and light-based therapies are administered.[12] Whenever feasible and resources are available, patients must be explained of all the available options and allowed to choose.

Methods of surgery

Broadly, it can be divided into grafting techniques, non-grafting techniques, camouflage techniques, and excision [**Figure 1**]**.**

Non-Grafting techniques

The techniques include chem-abrasion, dermabrasion, laser and light therapies, needling, and excimer. In these methods, the lesion is therapeutically wounded, thus melanocytes proliferate at the periphery and migrate to repopulate the depigmented area. Also, there is an influx of stimulatory cytokines.[13] Dermabrasion in addition helps in the penetration of ultraviolet radiation, which then stimulates the melanocytes.[14]

Camouflage tattooing

In this, there is introduction of artificial pigment into the mid dermis in the depigmented patch. This has a poor color match and at times imparts a bluish tinge.[15] A chalazion clamp can be utilized for providing stretch and stability, while one performs tattooing on the lips.[16]

Grafting techniques

Autologous grafting can be further divided into those techniques where tissue is transferred and those in which cells are transferred. Cells can be transferred as is or can be cultured to increase the number of melanocytes to help in wider area of coverage.[17] These methods were started in the early 1960 and since then have refined further. The basic principle in vitiligo grafting surgery is to transplant the graft as a whole in tissues grafts or through cellular suspension (cultured or non-cultured) where the recipient area can be increased. The donor to recipient ratio is briefly summarized in **Table 1**. In most of the techniques, there is a necessity to prepare the recipient site in order to promote the uptake of the transferred melanocytes. This can be done by various methods as outlined in **Table 2**. The subsequent uptake of melanocytes and thus the final pigmentation achieved has been seen to vary depending on the technique.[18]

Tissue grafts

Punch graft

In this technique, small punches are harvested from normally pigmented skin and are transplanted into the depigmented recipient area [**Figure 2**]. This method relies heavily on the transplanted graft to stimulate pigment production in the surrounding depigmented skin. In a recent meta-analysis comparing various surgical methods, > 90% pigmentation was seen in 45.76% of patients after punch grafting.[19] Since most dermatologists are well versed with punch biopsy technique, it is easy to learn and perform with minimal additional equipment to be purchased. It is especially useful in areas like the palms and soles, where there is a doubtful recipient bed and the nipple areola with its irregular contour. Care should be taken that recipient punches are smaller than the donor punches by approximately 0.5 mm. A unique side effect of this technique is the cobble stoned appearance. This can be prevented by taking small size punches (1–1.5 mm), grafts kept at-least 5 mm apart, with thinner grafts and the upper surface at the level of the recipient skin. The depth of the donor graft can be minimized by injecting local anesthetic at the junction of upper and mid dermis.[20] It was recently seen in a study on vitiligo patches in rats that irrespective of the orientation of the transplanted donor graft, the repigmentation was good.[21]

Suction blister epidermal grafting [**Figure 3**].

Falabella had developed this novel technique, wherein a negative pressure is created of –200 to –500 mm Hg with the help of a syringe at the donor skin site. This causes a split at the dermoepidermal junction and forms a blister. This is deroofed and taking care as to which side is

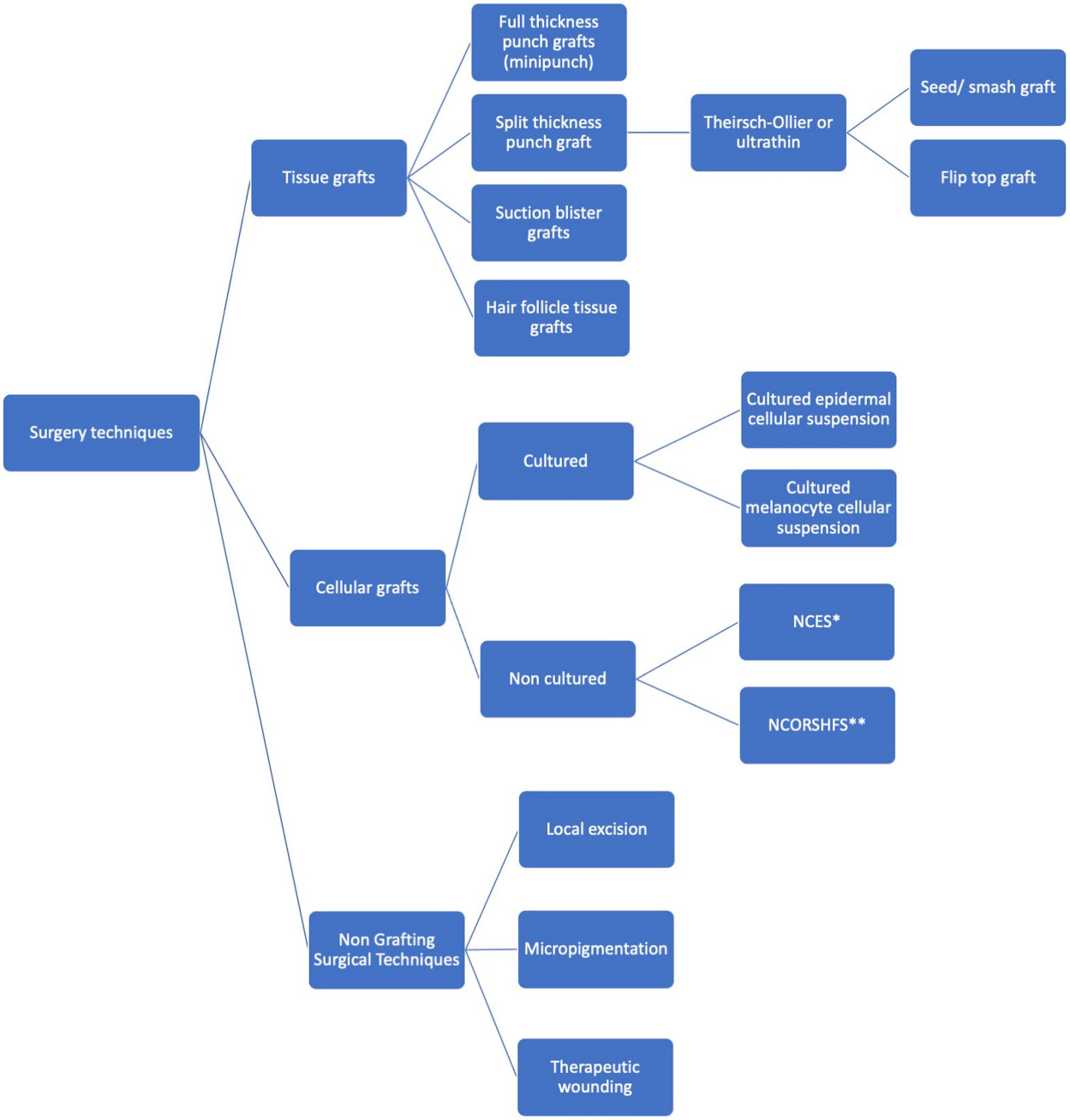

Figure 1: Flowchart of various modalities of vitiligo surgery (*non-cultured epidermal cell suspension; **non-cultured outer root sheath hair follicle cell suspension).

Table 1: Donor to recipient ratio of various surgical techniques.[35]

Split thickness skin graft	1:1 to 1.5:1
Suction blister epidermal graft	1:1
Mini-punch grafting	1:3
Non-cultured epidermal cell suspension	1:10
Cultured epidermal suspension/Cultured melanocyte suspension	1:60 to 1:100

Table 2: Various methods of recipient site preparation.

Dermabrasion
Manual dermabrader (Manekshaw's)
Motorised dermabrader
Electrofulguration assisted dermabrasion
Liquid nitrogen/cryo-blister
Suction blistering
PUVA
Dermaroller/Microneedling
Laser
CO_2
Er-YAG

Abbreviation: Er-YAG - erbium–yttrium aluminium garnet; PUVA – Psoralen + UVA

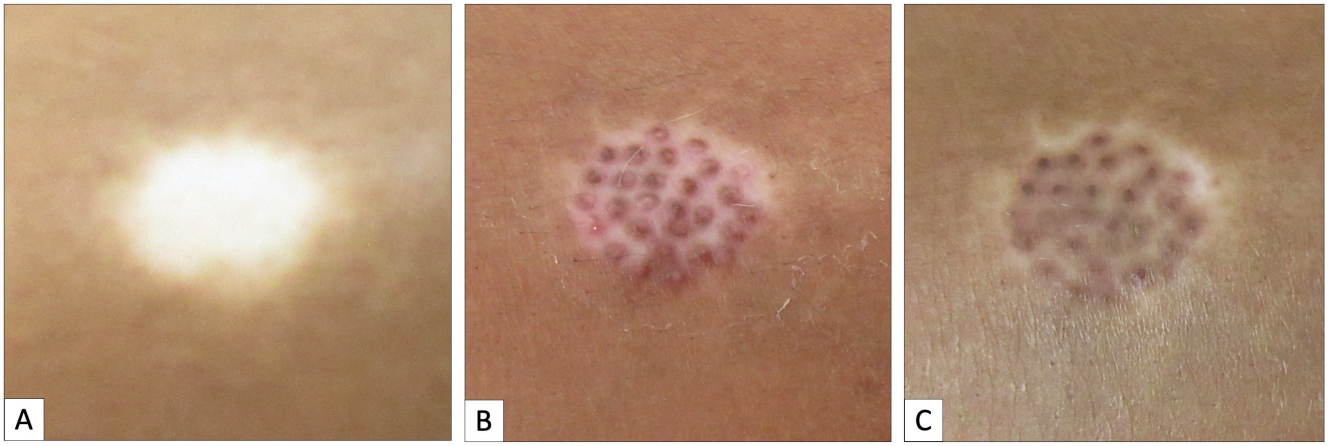

Figure 2: Punch grafting (a) patch of vitiligo (b) punch grafting after 1 week and (c) after 6 months showing almost complete repigmentation.

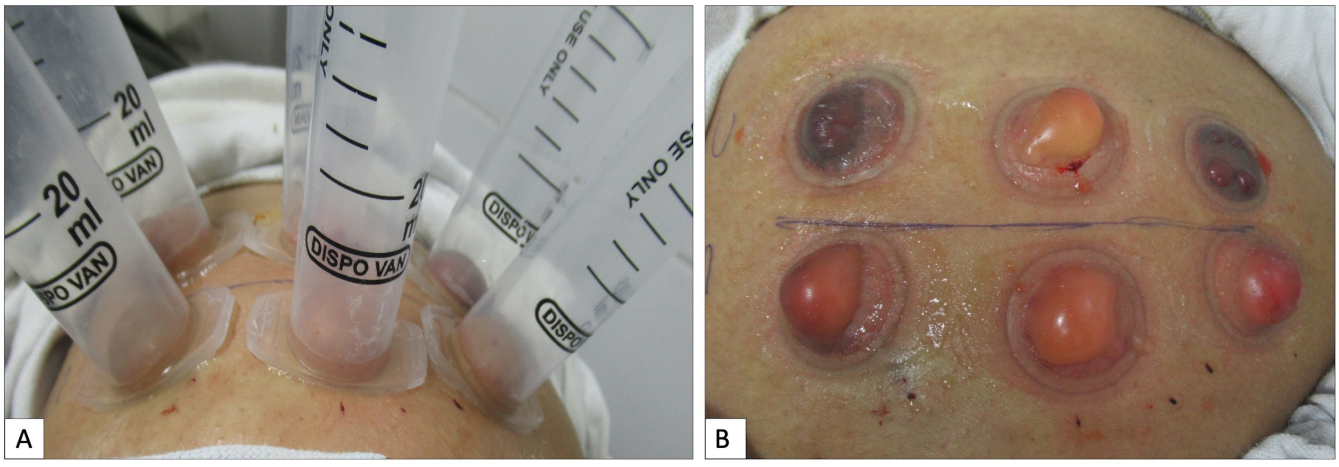

Figure 3: Suction blister technique with (a) negative pressure applied with disposable syringes and (b) suction blisters after 4 hours.

epidermal and which one is dermal, is transplanted into a prepared recipient site. This has shown to achieve excellent pigment match. However, this is much more difficult to learn, is not feasible in cold weathers, not suitable for large areas, and patient has to wait for a long time until the blister forms.[22] A recent study found SBEG superior to the punch grafting over acral areas and bony prominences.[23] Modifications are available to speed up the formation of blister, these include heat application, normal saline injected intradermally, use of smaller syringes, and greater

negative pressure.[24] An exploitation of alternative system of medicine includes the use of Hijama cups for the creation of negative pressure and blister.[25] These are used in cupping therapy and consist of cups ranging from 2 to 7 cm with a provision for the attachment of a syringe to the valve on top of each.

Split-skin grafting

In the early 1970s, Dr. P.N. Behl demonstrated efficient repigmentation of vitiligo skin lesion with the help of split thickness skin graft.[26] Although initially thicker grafts of 0.1–0.2 mm were used, the trend now is to use ultra-thin grafts of 0.08 mm.[27] It must be kept in mind that the graft shrinks when transferred to the recipient site and thus must be 10–20% larger than the defect to be covered. Larger lesions can be covered by meshing the graft, which allows for expansion.

Seed grafts/Smash grafts

This is a variant of ultrathin and split thickness skin graft, wherein the sheets of tissue are minced to fragments less than 1 mm with the help of sterile scissors. This paste is applied to the prepared recipient site. The smaller the particles, the better will be the result.[28] A modification of this is to insert the minced grafts with the help of needling into the dermis. The results of this novel method were better than conventional dermabrasion alone.[29]

Flip top grafting

A hinge of tissue is raised in the epidermis at the recipient site and small pieces of donor tissue are slid underneath. This provides a cheap, natural yet effective dressing. It also serves as a window, allowing one to see the extent of repigmentation and thus determine the success of the procedure.[30]

Hair follicle grafting

This method is akin to follicular unit extraction or strip follicular transplant of hair transplant, wherein hair follicles are harvested and transplanted into another area. The donor site is usually the hair on the occipital area of scalp. The spacing between the transplanted hair is usually 5–10 mm.[31] Modifications of this technique include eyelash transplantation for leucotrichia and vellus hair transplantation.

Cellular grafting

Cultured melanocyte transplantation

In this method, a split thickness skin graft is harvested, and melanocytes are separated. Their numbers are increased with the help of cellular culture techniques to cover a larger area. The donor:recipient ratio is 1:60. The melanocytes can also be co-cultured with keratinocytes. Co-culturing with keratinocytes is advantageous due to the presence of melanocyte stimulatory growth factors secreted by them.[32] Although this technique dramatically increased the area that can be covered, the cost is higher.[33]

Non-cultured epidermal cell suspension (NCES)

The pioneer of this method was Gauthier, which was similar to the cultured melanocyte transplantation.[34] However, it can be performed even in places without cell culture facilities. It however has a lower donor to recipient ratio of 1:5 to 1:10.[35] This does not limit its application as the ratio is still quite large and a greater number of donor sites can be used if one needs to cover larger areas. The trypsinization of harvested split thickness graft can be done by cold or by warm method to separate the cells. In the conventional cold method, the trypsin acts for 18 hours, on the tissue at a temperature of 4°C. This was modified by Olsson and Juhlin in 1998, in which the digestion time was cut down to 60 minutes at a temperature of 37°C.[36] Warm trypsinization, while quicker, has shown to be inferior to cold one, with a lower yield of viable cells.[37] Newer methods such as room temperature trypsinization has shown efficacy comparable to other methods.[38]

There has been various modification of this technique, such as addition of hyaluronic acid to increase the viscosity (Van Geel et al.),[39] substitution of melanocyte culture media with phosphate buffered saline (Holla et al.).[40] Platelet-rich plasma when used as a suspension medium improves pigmentation due to its various growth factors.[41]

Methods have also been devised to make the procedure simple including battery devices[42] and welled plates.[43,44] These techniques eliminate the need for sophisticated instruments and lab set up, with just as good outcomes. Also the need for incubator for warm trypsinization can be bypassed by taping the donor epidermal tissue in an Eppendorf tube to the axillary vault for 50 minutes.[45] The Jodhpur technique is a modification in which there is no trypsinization step. It has been shown to have slightly better repigmentation compared to follicular unit transplantation.[46] In order to retain the transplanted material on uneven contours, a putty material can be used as a scaffold.[47] Advantages of NCES include coverage of large areas in single sitting, good cosmetic outcomes, and excellent color match [**Figure 4**].

Cultured epithelial grafts

This method produces a large epidermal sheet with the help of co-culture of keratinocytes and melanocytes.[48]

Non-cultured outer root sheath hair follicle cell suspension (NCORSHFS) [Figure 5]

The outer root sheath, mid-follicle region and hair bulb matrix is a rich source for melanocytes and its precursors. It is done after follicular unit extraction or by plucking hair follicle, followed by follicular unit suspension.[49,50] The trypsinization steps are similar to those of the NCES technique. There is a strong correlation between the number of melanocytes transferred and the repigmentation.[51]

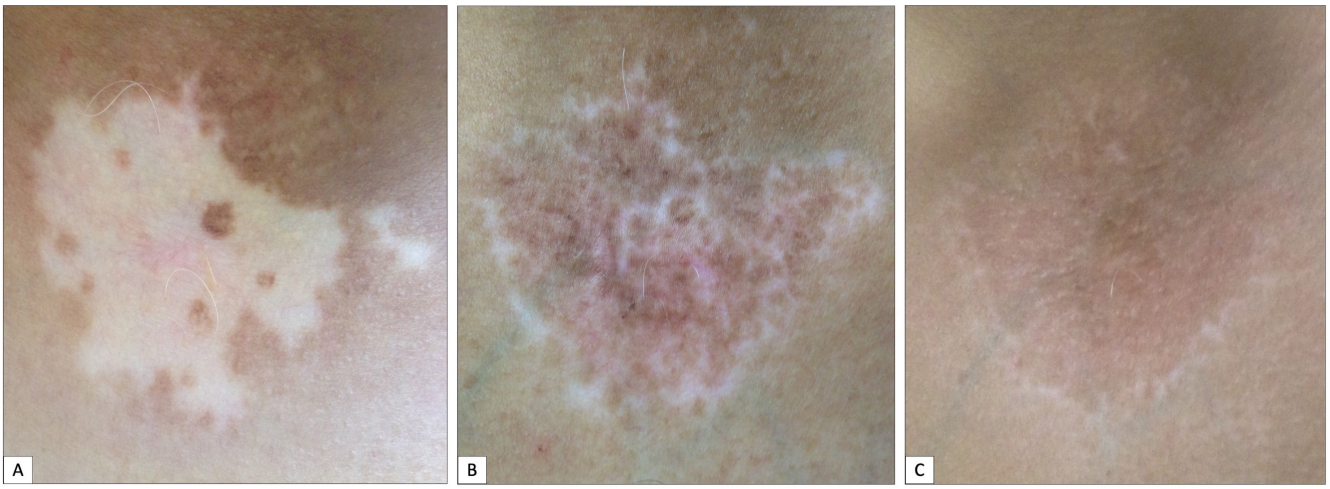

Figure 4: Repigmentation after non-cultured epidermal cell suspension in a patch of vitiligo (a) at 2 months (b) and 6 months with almost complete repigmentation and excellent color match.

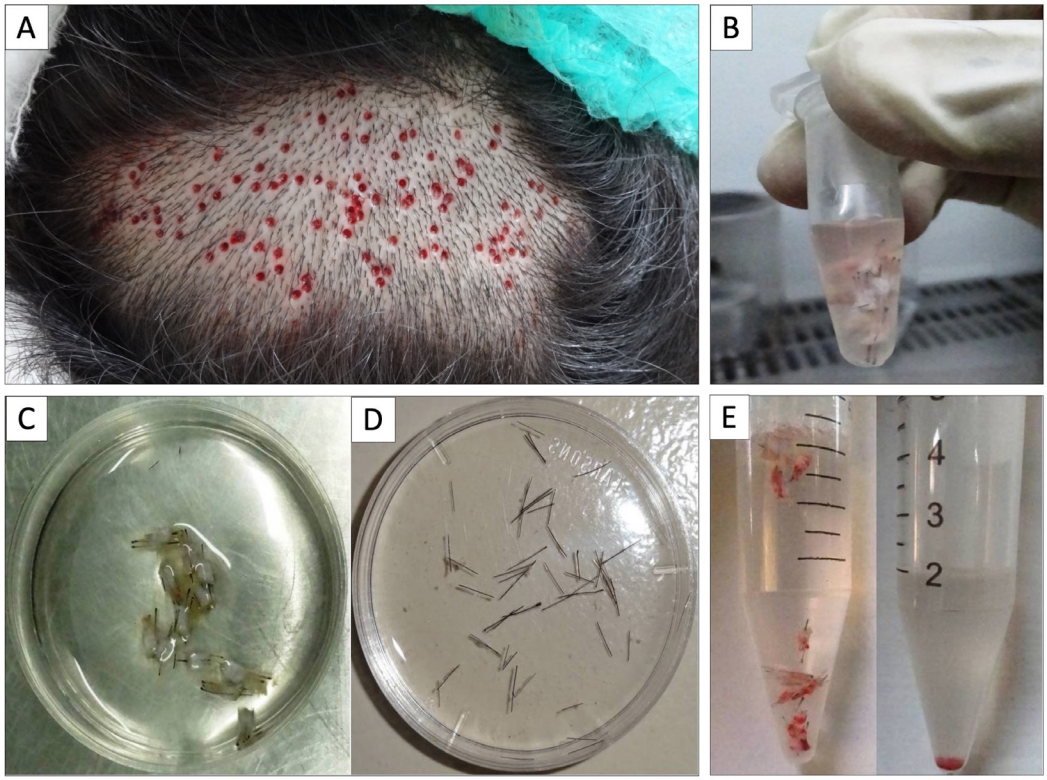

Figure 5: Procedure of non-cultured outer root sheath hair follicle cell suspension (a) hairs extracted from the occipital area using 1 mm disposable plastic punches; (b) hair follicles placed in a new tube of trypsin-EDTA after 30 minutes; (c) extracted hair follicles in Petri dish prior to trypsinisation; (d) after treating with trypsin thin keratinous hair shaft are left behind; (e) hair follicles in normal saline prior to transportation to laboratory (left) and cell pellet formed by centrifuging for 5 minutes at 1000 rpm (right).

Combined epidermal and hair follicle suspension

Combined NCES and NCORSHFS has a better result combined than either alone. This is probably due to the higher levels of melanocyte growth factors and OCT4+ stem cells.[52]

Recipient site preparation methods

Recipient site preparation is a critical step in vitiligo surgery to achieve cosmetically acceptable repigmentation and outcome of procedure significantly depends on the method of recipient site preparation. Various methods of recipient site preparation have been summarized in **Table 2**.

Dermabrasion

The most conventional method of performing this is to use a Manekshaw's dermabrader **[Figure 6]**. The device is available in various sizes and is held like a pen and with a horizontally circular motion, the recipient site is prepared. It has the advantage of being cheap, and not requiring electricity. However, it requires a greater amount of effort and time to prepare the recipient site. Also, there is a higher rate of unevenness, and requires greater dexterity while treating margins and areas with pigment in between. It is easier to perform on surface which are flat and have a concave or convex surface such as the periorbital region. An underlying bony support makes it effortless, and it becomes arduous on surfaces like the genitalia and lips. The procedure can be made easier by applying a peel with 25% trichloroacetic acid prior to the dermabrasion.[53]

The effort can be offloaded on machine with the use of a motorized dermabrader. This consists of a device which has a rapidly rotating rough surface such as a diamond fraise, wire brush, or serrated wheel. The usual setting for a diamond fraise is to set the wheel rotating at 10,000 rotations per minute.

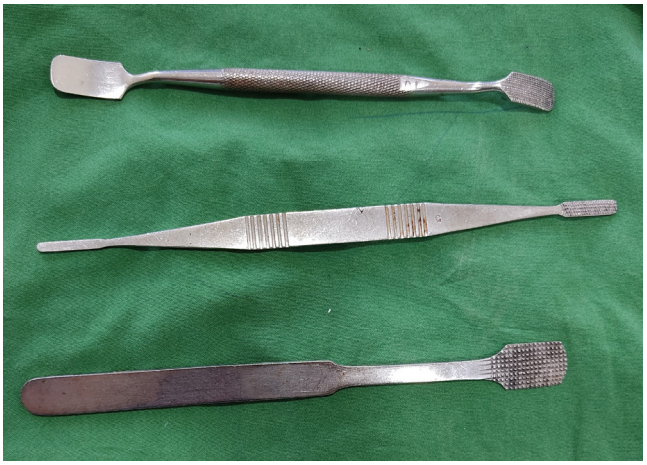

Figure 6: Manekshaw's dermabrader of different sizes.

In both, the manual and the motorized dermabraders, the end point is pin point bleeding. This indicates that the abrasion process has achieved a depth of papillary dermis. Any deeper can result in scarring and any superficial can result in poor uptake.[54]

Electrofulguration[55,56]

This technique uses electrical current alternating at a frequency of 500–4000 Hz. It has a myriad of applications based on the output waveform, in electrofulguration in particular the current is damped and in the form of a sine wave. In the method of electrofulguration, there is no contact of the electrode with the skin and the current leaps from the electrode to the target. Although a multitude of electrode shapes are available, the classical one used in the unclassical indication of vitiligo surgery is the ball shaped one. This allows for a better delineation of the margins, and does not spill over into healthy tissue **[Figure 7]**. Its independence of friction allows it to be used over sites with no underlying bony structure, as well as on convex and concave surfaces. The drawbacks however include absence of the pin point bleeding leading to difficulty in depth control. Also, there is a chance of skip areas.[57]

Cryotherapy

Liquid nitrogen is the cryogen conventionally used to prepare the recipient sites, and the donor tissue is usually obtained from a suction blister graft. The procedure produces a cryoblister at recipient site after 24 hours if 3–6 freeze thaw cycles with a duration of 3–5 seconds each are used **[Figure 8]**.[58] However, the procedure is associated with complications like perilesional hyperpigmentation, hypertrophic scarring, and hypopigmentation.[59] The hypopigmentation can be prevented by adding PUVA therapy concurrently.

Suction blister

This method is versatile and can be used to prepare both the recipient area and the donor tissue. The technique is the same as described in donor tissue preparation. The serous discharge associated with this technique is thought to provide a better micro environment.[60]

PUVA

The phototoxic potential of psoralens can be exploited to prepare the recipient area in a large site. It can be performed with the help of 0.075% 8-methoxypsoralen, applied topically 10 minutes prior to exposure to UVA radiation of 10 J/cm^2 per day for two consecutive days.[61] This technique does not go beneath the reticular dermis and thus does not scar.[62]

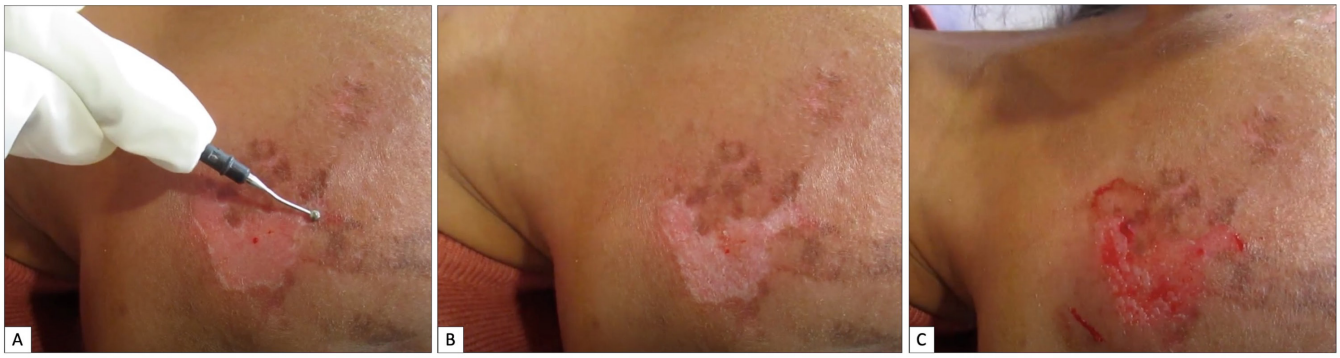

Figure 7: Dermabrasion with ball-tipped electrofulguration probe and frosting at the edges (a) complete frosting at the patch (b) and (c) after removal of the frost with saline soaked swab.

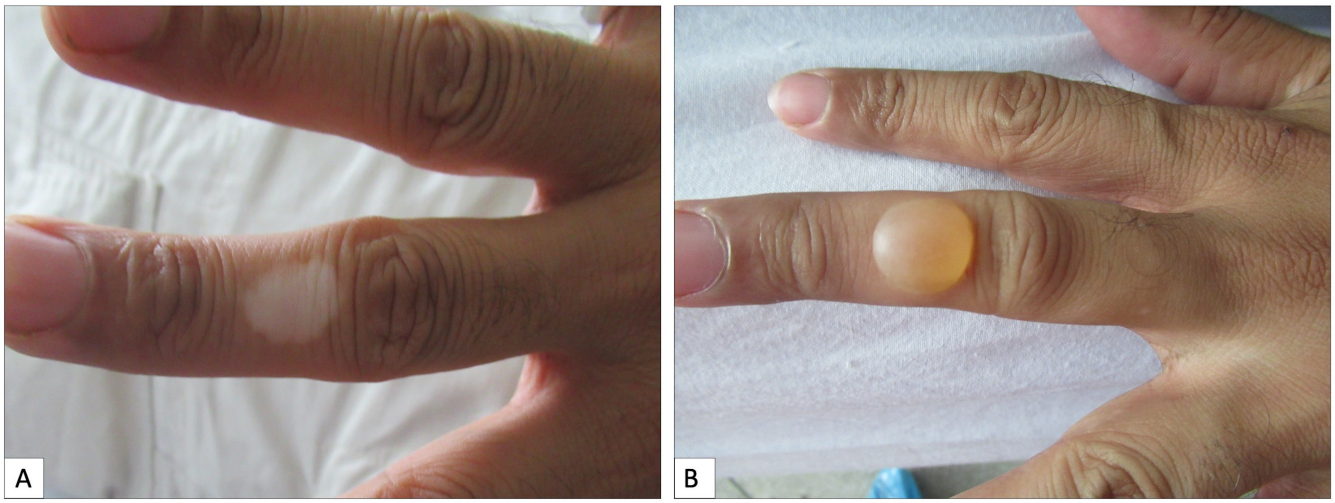

Figure 8: A patch of vitiligo over dorsum of finger (a) at day 0 and cryoblister at day 1 (b).

CO_2 laser

Conventionally, the CO_2 laser is used for ablative resurfacing in a defocussed mode. Since long pulse has a risk of uncontrolled tissue damage and potential for scarring, the ultra-pulse mode and short-pulse mode can be used in vitiligo recipient site preparation. Coupled with scanning devices, it can provide uniformity in depth of ablation along with precision and greater speed. The main drawback with this method is the high cost.[63] The parameters that can be used are 4.5 W, 0.2 sec pulse duration, 0.4 sec rest duration, 3-mm laser spot size with an attached scanning device.[64]

Er-YAG laser

The higher affinity of this laser for water and lesser depth of penetration both make it suitable for resurfacing in vitiligo lesions. It can be applied on larger areas and provides the advantage of a blood-less field. Another advantage offered is the lack of need of anesthesia. The parameters that can be used are spot size 2 mm, 200–500 mJ with a fluence of 6.37–15.92 J/cm^2.[65]

Post-operative dressings [Figure 9]

Post-operative dressings aim at keeping the transplanted tissue in place, allowing it to integrate into the recipient bed, while preventing infection. The requirements of the wound milieu vary according to the stage. In the phase of imbibition, a moist environment is required. This is achieved with the help of occlusive dressings, which prevent evaporative water loss. The occlusion also acidifies the pH and stimulates angiogenesis due to a relative state of hypoxia. During and after the inoculation phase, trauma and traction has to be kept minimal to prevent the loss of transplanted tissue. Post re-epithelisation, the dressings can be switched over to non-occlusive ones. Continued protection from physical trauma is required for up to 2 weeks post-surgery.[66]

The rate of infection in vitiligo surgery is usually low, due to adequate preparation of both the recipient and donor site prior to surgery. Antiseptic solutions and dressings used post-operatively do more harm than good, as they prevent the growth and survival of the transplanted tissue/cells.[67]

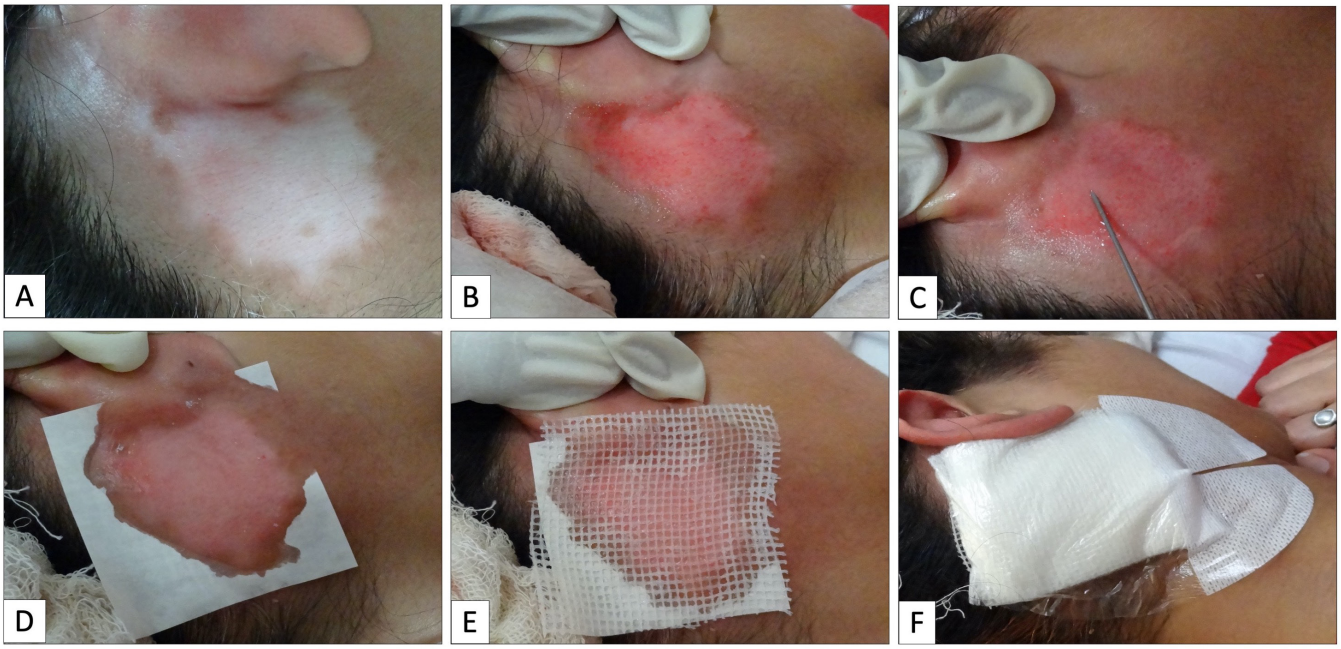

Figure 9: Different stages of cellular grafting; lesional skin over retro auricular area (a) dermabrasion of the lesional skin till pinpoint bleeding spots are seen (b) placement of cellular graft by a tuberculin syringe (c) first layer dressing by fish collagen and chlorhexidine gauze (d and e) second layer dressing by cotton pad and third layer dressing by a transparent dressing film (f).

Also the greenish material that develops on wound dressings may actually be harmless myeloperoxidase rather than an infection.[68]

Future prospects

Multi-lineage differentiating stem cells (Muse) are located in mesenchymal tissue such as the dermis and serve as a potential source for re-pigmenting vitiligo lesions apart from having immunomodulatory actions, thus can be used in vitiligo lesions with stability < 1 year.[69] These have an added advantage that they do not undergo tumorigenesis. T regulatory cells (T-regs) act as breaks on overactive immune system and these are found to be deficient in vitiligo lesions. Thus, replenishing these can serve as a new horizon to therapy.[70]

Declaration of patient consent

The written informed consent has been obtained from the patients.

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Conflicts of interest

There are no conflicts of interest.

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