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Surgical Treatment of Vitiligo

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Abstract:

Background: Vitiligo is an acquired depigmenting disorder characterized by the selective destruction of melanocytes, leading to the development of well-defined white patches on the skin. Although medical therapies and phototherapy remain the first-line treatment modalities, a considerable number of patients with stable vitiligo show poor or unsatisfactory response. Surgical treatment has emerged as an effective therapeutic option for stable vitiligo, particularly in refractory cases and difficult-to-treat areas. Various surgical techniques have been developed, including tissue grafts and cellular grafts, aiming to transfer functional melanocytes from normally pigmented skin to depigmented lesions. The choice of surgical modality depends on disease stability, lesion size and location, patient expectations, cost, and available expertise. This review highlights the indications, contraindications, recipient-site preparation methods, different surgical techniques, their advantages, limitations, complications, and postoperative management in vitiligo surgery.

Keywords: Vitiligo surgery, Stable vitiligo, Melanocyte transplantation, Tissue grafts, Cellular grafts, Non-cultured epidermal cell suspension, Suction blister graft, Split-thickness skin graft.

Introduction:

Surgical treatment is considered an alternative in patients with stable vitiligo resistant to medical treatment and phototherapy**.** It is based on melanocyte transfer from uninvolved skin to the stable vitiliginous patch **(1).**

Surgical treatment is indicated for segmental vitiligo (SV), as well as stable nonsegmental vitiligo (NSV) refractory to medical treatment and phototherapy. Surgery is also recommended for difficult-to-treat areas, including hands, feet, and mucosa, and lesions with leukotrichia**.** Current consensus guidelines recommend that vitiligo surgery can be safely performed across all age groups, provided that the disease is stable, with special considerations for children under 15 and elderly patients over 60 **(2).** Prior to vitiligo surgery, certain contraindications should be evaluated to ensure an optimal outcome. They include a history of unstable disease activity, keloidal tendency, hypertrophic scars, coagulopathies, active skin infections, and inflammatory dermatoses, especially in the recipient area **(3).**

There is no consensus regarding the minimum required period of stability. The recommended period of stability in different studies varies from four months to three years. Parameters for establishing vitiligo stability are the absence of new lesions, no extension of old lesions, and the absence of Koebner's phenomenon, either based on the history or by checking for positive test grafting **(4).** Test grafting includes placing six to eight punch grafts within a vitiliginous lesion and observing the repigmentation over the next 12 weeks. Unequivocal repigmentation occurring beyond 1 mm from the border of the test graft indicates a positive test and is taken as an indicator of stability **(5).**

Donor-site selection

The upper lateral aspect of the thigh is the ideal donor side. Also, the medial aspect of the forearm, arm, abdomen, and gluteal area can be used. For facial lesions, the post-auricular area is considered an ideal donor site

due to the good color match**.** Donor skin is harvested in the form of mini-punch graft, suction blister graft, split-thickness skin graft, or hair follicle graft **(6).**

Recipient-site preparation

Recipient-site preparation allows access to the underlying structures essential for melanocyte adherence and nutrition. Proper selection of the technique is crucial to generate cosmetically acceptable repigmentation**.** These techniques include dermabrasion, laser-assisted tissue ablation, electrofulguration-assisted dermabrasion, suction blister, cryoblebbing, and PUVA-induced blistering **(7).**

I. Dermabrasion

Dermabrasion represents a cost-effective and popular method for recipient site preparation. Manekshaw's dermabrader is a manual dermabrader that is available in various sizes, cheap, and doesn't require electricity. However, its disadvantages include being time-consuming with rapid user fatigue and being difficult to apply on large or concave surfaces such as eyelids, neck, axilla, and glans penis **(8).** Application of 25% trichloroacetic acid prior to the dermabrasion can make the procedure easier **(9).** Sterile sandpaper is another method for manual dermabrasion, which is very simple and cost-effective **(10).**

Motorized dermabrasion is a rapid alternative procedure that can save time and effort. The device 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 (**11**). In both manual and motorized dermabrasion, the end-point is pinpoint bleeding. This indicates a depth of papillary dermis has been reached. While deeper abrasion may cause scarring, superficial abrasion may lead to poor transplant uptake **(12).**

II. Laser-assisted tissue ablation

The carbon dioxide (CO_2) and Erbium-doped yttrium aluminium garnet (Er: YAG) lasers are commonly used for recipient site preparation. The wavelengths emitted by both lasers are absorbed by water, leading to tissue heating and consequent tissue vaporization. The endpoint in CO_2 laser ablation is the appearance of a "chamois" yellow skin color that is seen at the reticular dermis**.** The Er:YAG laser penetration depth is one-sixth that of CO_2 laser penetration, allowing more effective and precise tissue ablation without thermal necrosis **(13, 14).**

The advantages of this method are time-saving, lower user fatigue, and a bloodless field with a uniform depth of ablation that is effective for tendinous or concave sites**.** However, lasers are generally expensive and may increase the risk of dyspigmentation or scarring **(14).**

III. Electrofulguration-assisted dermabrasion

Superficial electrofulguration is performed, including 1-2 mm of the surrounding normal skin, and then performed over the vitiliginous patch. This method facilitates dermabrasion of concave surfaces with low cost and easy availability**.** However, its disadvantages include the absence of pinpoint bleeding leading to difficulty in depth control. Also, skip areas may be present **(15).**

IV. Suction blister

Inducing blisters using a negative pressure system with a set of syringes and three-way cannulas or a suction blister device is a commonly used technique for obtaining the donor tissue. Additionally, it has been used for recipient site preparation followed by deroofing of the blister and graft transplantation. It is considered to be superior to most of the other methods in terms of creating the near-ideal recipient site since the separation occurs precisely at the dermo-epidermal junction (DEJ)**.** Moreover, it provides a more favorable microenvironment by ensuring adequate serous drainage in the prepared areas**.** Furthermore, it has a lower incidence of complications. However, it may be unsuitable for large recipient site, as harvesting blisters for large sites is time-consuming **(16).**

Recently, **Singh et al. (17)** have reported the effectiveness of the Jodhpur technique with suction blister membrane as a biological dressing in stable vitiligo, resulting in good repigmentation with fewer side effects.

V. Liquid nitrogen-induced blister (cryoblebbing)

In cryoblebbing, a blister is induced at recipient site 24 hours after 3–6 freeze-thaw cycles with a duration of 3–5 seconds each. Although it is a relatively cost-effective and easy procedure, it may lead to several complications, such as perilesional hyperpigmentation, scarring, and hypopigmentation **(18).**

VI. Psoralen-Ultraviolet A-induced blistering

8-Methoxypsoralen (0.075%) is applied topically 10 minutes prior to UVA radiation of 10 J/cm2 per day for two consecutive days. This technique does not go beneath the reticular dermis and thus does not cause scarring, as cell apoptosis is limited to the epidermis. Moreover, the basement membrane where melanocytes reside physiologically is preserved, facilitating the attachment and survival of transplanted melanocytes. However, this method may cause eczema and pruritus **(19).**

Classification of vitiligo surgery

There are several types of vitiligo surgery, including tissue and cellular grafting techniques. The choice of surgical modality depends on patient expectations, cost, recovery time, and the location and extent of the disease. Sometimes, a combination of techniques may be required (**Table 2**) **(20).**

Table (2): Classification of surgical methods for vitiligo **(20).**

Tissue grafts	Cellular grafts
Mini-punch graft	**Cultured melanocyte graft**
Suction blister epidermal graft	**Cultured epidermal graft**
Split-thickness skin graft	**Non-cultured epidermal cell suspension**
Jodhpur technique	**Non-cultured follicular root sheath suspension**
Hair follicle graft	

I. Tissue grafts

a. Mini-punch graft

In the mini-punch grafting technique, punch biopsies of 1.2–1.5 mm size and 0.5–3 mm depth are taken from the normally pigmented donor site, mainly the lateral or inner thigh or gluteal region**.** The recipient site is prepared using a punch biopsy tool to create chambers that are placed approximately 5 mm apart; then, the healthy skin obtained from the grafting site is placed in these chambers and pressed with gauze until the bleeding stops **(21).**

Repigmentation is observed approximately 2 to 3 weeks postoperatively, and individual spots should coalesce between 4 and 6 months**.** It is suitable for challenging regions, such as the lips, palms, soles, and fingers. However, its main disadvantage is being a time-consuming method. Additionally, it may be associated with side effects such as polka dots, color mismatch and cobblestoning **(22).**

b. Suction blister epidermal graft

Suction blister epidermal graft (SBEG) is a simple surgical technique ideal for small, depigmented areas. Negative pressure of 200–350 mmHg is created by a syringe or a special device to induce separation of tissue at DEJ; then, the roof of the blister at the donor site is removed and transferred to the prepared recipient site **(23).**

Depending on the patient's age and donor site, the time required for inducing a blister varies between 30 and 180 min. Dermal injection of lidocaine or saline and heat application can hasten blister induction **(7).**

It is considered a cost-effective procedure that can even be performed as a bedside procedure in patients unsuitable for more extensive interventions**.** Undesirable side effects in the recipient area include hyperpigmentation, peri-graft halo, infection, color mismatch, and reactivation or progression of the disease. Moreover, Koebner's phenomenon and hyperpigmentation may develop at the donor site **(24).**

c. Split-thickness skin graft

Split-thickness skin graft **(**STSG) is one of the most effective surgical methods for repigmentation. A dermatome or shaving blade is used for harvesting. The donor-to-recipient size ratio is 1 to 5–10, and the thickness of the harvested epidermal graft is 0.1–0.15 mm. Abrasion of the recipient site is carried out with a CO_2 laser or dermabrasion, followed by direct placement of the graft **(25).**

This procedure showed an excellent response rate and can cover large areas in a single session with immediate results. However, complications may include graft dislodgement and failure due to seroma or hematoma formation and graft contracture leading to peri-graft halo and achromic fissures. Occasionally, the graft may develop a hypertrophic scar, milia, or become infected (**26**).

d. Jodhpur technique

In Jodhpur technique, the donor area is smeared with a thick layer of antibiotic ointment (2% mupirocin). Then, the donor site is dermabraded using the manual dermabrasion or electric motor. The smeared ointment serves to entrap the epidermal component consisting of keratinocytes, melanocytes, free melanin, fibroblasts, etc. This paste is collected with a spatula and then spread on the prepared recipient site **(27).** This technique is suitable for stable vitiligo in focal or exposed areas due to its simplicity, cost-effectiveness, and high success rates. It offers minimal donor site morbidity and uses basic equipment, making it accessible even in resource-limited settings. While it is highly effective for small, localized lesions, its application to larger areas can be more challenging **(20).**

A modification of this technique includes obtaining the graft from the perilesional pigmented skin. The whole procedure is restricted to a single site, making it an effective method for small patches and lowering the incidence of side effects at donor and recipient sites **(28).**

e. Hair follicle graft

Hair follicle grafting depends on stem cell population in the bulge region of the hair follicle that can cause repigmentation by retrograde migration**.** The donor site is usually the occipital area of scalp, and the spacing between the transplanted hair is usually 5–10 mm. It avoids donor-site complications and is considered one of the best methods to treat vitiligo with leukotrichia. However, it is difficult to be used in non-hairy areas **(29).**

II. Cellular grafts

The most significant advantage of cellular grafting methods is their donor-to-recipient expansion ratio. Cellular grafts can cover larger recipient sites than tissue grafts **(Table 3) (30).**

Table (3): Donor-to-recipient ratio in various surgical techniques for vitiligo **(26).**

Technique	**Ratio**
Split thickness skin graft	**1:1**
Split thickness skin graft with meshing	**1:1.5 to 1:3**
Suction blister graft	**1:1**
Non-cultured epidermal cell suspension- **Single confluent recipient patch**	**1:10**

Non-cultured epidermal cell suspension- few scattered large patches	**1:8**
Non-cultured epidermal cell suspension- multiple scattered small patches	**1:5**
Cultured melanocyte suspension	**1:60 to 1:100**

a. Cultured melanocyte graft

In cultured melanocyte grafting, a split-thickness skin graft is harvested, and melanocytes are separated. Their number is amplified by cellular culture techniques to cover a larger area. The donor-to-recipient ratio is 1:60. Melanocytes can also be co-cultured with keratinocytes that produce several growth factors with a stimulatory effect on melanocytes (**12**). This method has shown good clinical results and can be successfully used both in adults and children. Its main disadvantages are being expensive and time-consuming, the need for specialized equipment and a skilled team, and the concern of mitogenesis due to the usage of culture medium (**31**).

b. Cultured epidermal graft

Cultured epidermal grafting is similar to cultured melanocyte grafting. It was first described by **O'Connor et al. (32)**, who reported the potential benefit of cultured epithelium in treating severe burns. The skin harvested from the donor site is subjected to trypsinization to separate the epidermis from the dermis. After 24 hours, the cells are transferred to a culture medium, which may be supplemented with patients' sera. The epidermal membrane, produced after a few weeks and covered with collagen on one side, is placed on the dermabraded recipient site. Finally, the grafted area is protected for two weeks with a layer of Vaseline and sterile gauze (**33**).

This procedure does not cause scarring. Moreover, the repigmentation process often shows a very good color match, which may be maintained for long periods. Its main disadvantages are high cost and being time-consuming. It may be complicated by infection, bleeding, and transplant rejection (**6**).

c. Non-cultured epidermal cell suspension

Over the past years, non-cultured epidermal cell suspension (NCES) or non-cultured melanocyte-keratinocyte cell suspension transplantation has become the standard vitiligo surgery**.** It is similar to the cultured melanocyte transplantation without the need for cell culture facilities**.** It is a very simple method that can achieve excellent repigmentation and color match. A ten-fold (average 5 folds) large vitiliginous area can be treated at one time with a small-sized graft. Vitiliginous areas of any size, shape, and at any site can be treated except fingertips, toe tips, palms, and soles. Its disadvantages include the high cost and the need for specialized equipment and a skilled team. The significant run-off of the suspension from the recipient site makes it unsuccessful in difficult-to-treat areas and uneven areas **(34).**

History of non-cultured epidermal cell suspension transplantation

Non-cultured epidermal cell suspension transplantation was first described by **Gauthier & Surleve-Bazeille (35)**. The graft was harvested from the occipital area, previously anesthetized with 1% lidocaine solution. Then, it was placed in a 0.25% trypsin solution and incubated at 4°C for 18 hours to facilitate dermal-epidermal separation. Then, the epidermis was immersed in EDTA solution and then in salt solution. A cellular suspension of keratinocytes and melanocytes was injected into a blister created in the recipient site by cryoblebbing after aspiration of the blister fluid. Finally, dressing of recipient and donor sites was performed. Later on, this method has undergone several modifications to overcome its disadvantages (**36).**

In 1998, Olsson and Juhlin (37) have developed the rapid (hot) trypsinization method that consumed 60 minutes under 37°C. The melanocyte culture medium was used to stimulate cell growth. The cellular suspension was transferred directly to the dermabraded recipient site, followed by coverage with a thin collagen,

moistened gauze, and Tegaderm. There was no difference in the repigmentation rate whether hot or cold trypsinization was used **(20)**.

Several substances were added to the suspension. Hyaluronic acid was added to increase the viscosity of the suspension to decrease its run **(38).** The culture medium was substituted by phosphate-buffered saline (PBS) to stimulate melanocyte survival by preventing osmosis-induced cell death and to get rid of the excess trypsin **(39).** Patient's serum was added to the suspension to improve the repigmentation response **(40).**

A battery-operated ReCell kit automatic process was developed**.** In this method, a single-use battery-operated autologous cell-harvesting device is used, which consists of a processing unit with a built-in heating mechanism and a removable insert to act as a sterile Petri dish for the separated skin biopsy **(41).**

The '6-well plate' technique is a simple inexpensive cellular grafting procedure at which the cellular suspension produced with the use of a microfilter and three reagents (trypsin, soybean trypsin inhibitor and PBS) was satisfactory with a high repigmentation rate, and unlike other methods, none of the patients required postsurgical phototherapy **(42).**

The four-compartment (4C) method was introduced to simplify the steps of NCES and to decrease its cost. It included a petri dish divided into 4 partitions in which the graft was processed. In the first partition, the graft was incubated for one hour at 37^{o}c. In the second and third partitions, the graft was immersed in PBS to get rid of extra trypsin. In the last partition, cells were detached into PBS. The separated melanocytes and keratinocytes were resuspended in PBS to prepare a homogenous cell suspension **(43).**

d. Non-cultured follicular root sheath suspension

Non-cultured follicular root sheath suspension transplantation was first described by **Mohanty et al. (44),** who have used the follicular unit extraction (FUE) procedure to obtain grafts for transplantation**.** The outer root sheath, mid-follicle region, and hair bulb matrix are rich sources for melanocytes and their precursors. This technique can be done by FUE or hair follicle plucking, followed by follicular unit suspension preparation **(45).** The trypsinization steps are similar to those of the NCES technique, with a strong correlation between the number of melanocytes transferred and the repigmentation outcome **(12).**

This technique is usually effective and gives very good clinical results, including a good color match and absence of scarring**.** Moreover, 15–25 follicular units taken during a single procedure provide a source of 300,000 to two million cells in the form of a suspension that can be used to treat about 20 cm^2 of depigmented area. Therefore, this method seems attractive, although it requires high skills **(46).**

Razmi et al. (47) have combined the non-cultured hair follicular cell suspension with NCES to improve the repigmentation outcome.

Postoperative Management

Post-operative dressing aims at keeping the transplanted tissue in place, allowing it to integrate into the recipient bed and preventing infection**.** To avoid graft loss and unequal distribution of the transplanted cells, adequate immobilization is required after all transplantation techniques for several days **(48)**.

The rate of infection in vitiligo surgery is usually low, due to adequate preparation of both the recipient and donor sites prior to surgery. Prophylactic antibiotics are advisable for 1 week after treatment**.** Antiseptic solutions and dressings used post-operatively do more harm than good, as they prevent the growth and survival of the transplanted tissue/cells**.** Also, the greenish material that develops on wound dressings may actually be harmless myeloperoxidase rather than an infection **(49).**

According to **Bhingradia et al. (20),** the most important considerations following vitiligo surgery include:

- The dressing is removed 7 days post-surgery. Care should be taken to ensure the grafts are not disturbed during this period.

- Patients should undergo regular post-operative monitoring to assess healing, repigmentation rates, color match, and any adverse events.
- Areas around the graft may show hyperpigmentation due to increased melanin production. Topical depigmenting agents such as hydroquinone or retinoids can help lighten these areas.
- For slow or incomplete repigmentation, EL or NBUVB can be used to stimulate melanogenesis. They can be started after complete wound healing (approximately 2–3 weeks post-surgery).
- If immune modulation is necessary, cyclosporine can be considered, starting 1–2 weeks post-operative.
- A subsequent second surgery, if needed, can be planned after 6 months of the previous surgery.

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