

Surgical management of vitiligo- An approach to the patient

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Abstract

Vitiligo vulgaris is an acquired chronic pigmentary disorder with an average world wide incidence of approximately 1%. Clinical classification of vitiligo is based on the distribution and extension of lesions as localized, generalized, and universal. As vitiligo has great psychosocial implications especially in dark-skinned individuals, treatment should begin early. Current modalities of treatment include medical therapy, surgical modalities and laser. Medical treatment options include topical corticosteroids, calcineurin inhibitors, vitamin-D derivatives, phototherapy (ultraviolet A [UVA], narrowband UVB), photochemotherapy (psoralen plus UVA [PUVA]). Surgical methods used in the management of vitiligo gave cosmetically acceptable results in short periods. Successful treatment with various surgical techniques requires an appropriate selection of patients mainly focusing upon the stability of the clinical disease. The choice of the procedure always depends upon the age, the area involved, site and the cosmetic need of the patient. The nature of the procedure, expected outcome and the complications should be discussed with the patient in detail. This article mainly deals with various dermatosurgical approaches in brief available till date for the treatment of vitiligo.

Keywords: Vitiligo, Surgical treatment, Cultured and non-cultured melanocyte cell transplantation,

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Introduction

Vitiligo vulgaris is an acquired chronic pigmentary disorder characterized by white patches, corresponding to a substantial loss of functioning epidermal and sometimes hair follicle melanocytes.¹ The term vitiligo, derived from the Latin word 'vitellus' meaning veal i.e. pale pink flesh of a calf since it clinically resembled that of 'spotted calf'. It was first used by the Roman physician Celsus in the second century AD.² The world wide average incidence is estimated to be 1%.³ It mostly affects people with skin type III and IV and frequently occurs on sun exposed sites.³ Emotional stress, trauma and injury are considered as major precipitating factors. Vitiligo has great psychosocial implications especially in dark-skinned individuals. It is a symptom-free disease, but patients are usually concerned that depigmentation will interfere with their social interaction.⁴

Classification

Clinical classification is based on the distribution and extension of lesions as localized, generalized, and universal according to Nordlund⁵ (Table 1). Localized vitiligo is classified into focal and segmental forms. Generalized vitiligo can be subdivided into acrofacial, vulgaris and mixed types. Universal vitiligo involves more than 80% of the body.⁵ The natural course of the disease is generally unpredictable, but is often progressive; some degree of spontaneous repigmentation occurs in 10–20% of patients, but rarely is it cosmetically acceptable, often occurring in a perifollicular pattern.⁶

Various therapeutic options of repigmentation of vitiligo are currently available. These include medical therapy, surgical modalities and laser. Medical treatment options include topical corticosteroids, calcineurin inhibitors, vitamin-D derivatives, phototherapy (ultraviolet A [UVA], narrowband UVB), photochemotherapy (psoralen plus UVA [PUVA], laser therapy and various surgical treatments. Systemic or local administration of psoralen, either combined with UVA (PUVA) or topical corticosteroids, are

currently the most widely used.⁷ PUVA therapy is the mainstay of the medical remedies available at present for vitiligo patients, but it has its own limitations like the prolonged duration of treatment, some lesions show relative resistance to PUVA i.e. lesions on lip-tip areas and bony prominences. It has been reported that PUVA treatments result in limited success rates.⁸ Surgical methods used in the management of vitiligo gave cosmetically acceptable results in short periods which led to various dermatosurgical approaches used in cosmetic surgery, a rapidly expanding speciality. This article mainly deals with various dermatosurgical approaches available till date for the treatment of vitiligo. Successful treatment with various surgical techniques requires an appropriate selection of patients. A number of studies have shown that surgical treatments are satisfactory whenever they were used in patients with a stable type of vitiligo.^{7,9,10}

Definition of stability in vitiligo

Stability of vitiligo has been variably defined by various authors. In their consensus recommendations, the IADVL Task Force for standard guidelines of care for dermatosurgical procedures tried to provide a clear definition of stability as 'a patient reporting no new lesions, no progression of existing lesions, and absence of Koebner phenomenon during the past one year'.¹¹ Njooet *al* proposed the VIDA as another method of establishing objective criteria for case selection. It is a six-point scale on which the activity of the disease is evaluated, gauged during a period ranging from less than 6 weeks to one year. It is suggested that surgery may be performed only in patients with VIDA scores of -1 or 0 (Table 2).¹² Before performing any surgical treatment, it is necessary to perform a minigraft test.⁹ Detailed history and physical examination should be carried out in all the patients being planned for surgical approach in vitiligo as has been proposed in the criteria for selection of cases for dermatosurgery in vitiligo (Table 3).¹³ Various surgical modalities of treatment for vitiligo have been described (Table 4). These are being discussed in detail in this article.

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Tattooing (Camouflage)

Micropigmentation used to be a common mode of camouflage in recalcitrant lesions of vitiligo, especially over distal digits, lips, hands, wrists, axillae, elbows, perianal areas, lower legs, mucosae and mucocutaneous junctions. The best results are obtained in darker skin types.¹⁴ The pigment should ideally be implanted between the superficial and middle dermis. Iron oxide is the most common pigment used. Various pigments have been used in tattooing (Table 5).¹⁵ After infiltrating the area with local anaesthetic, the paste is applied and deposited by hammering movements of the punch holding a bunch of needles. The treated area is covered with topical antibacterial. Initially the color may appear a bit darker due to ecchymosis but the skin color matches within 6-8 weeks.¹³

Advantages

It is a simple day care procedure, inexpensive and not time consuming. The results are rapid and this procedure can be used for areas like the eyelid margin where other modalities are difficult.¹⁴

Disadvantages

The cosmetic acceptability is poor because of difficulty in getting an exact color match. Color also tends to fade gradually and in some patients, bluish discoloration is seen because of the black pigment dropping down to deeper dermis. Similarly, tattoos containing certain metal oxides can become oxidized and turn black. Reactions to tattoos can include granulomatous, lichenoid and pseudolymphomatous types of histopathologic reactions. Ecchymosis, crusting and edema can last for a few days. Reactivation of herpes simplex virus infection can occur. The risk of transmission of infective diseases including HIV and Hepatitis B is always present, which can be avoided by adopting proper sterilization procedure. Micropigmentation can be effectively used only for small, localized lesions of vitiligo.¹⁴

Punch grafting

Surgical punch is the commonest instrument used by dermatologists however its precise origin is

not known. Watson (1878) and Keyes (1879) used them to remove accidental gun powder tattoos from the face.¹⁶ E L Keyes in 1887 first established the importance of the punch instrument in dermatology.¹⁷ Mini-punch grafting has been shown to be one of the cheapest, fastest, and easiest approaches of all surgical treatments available. Some authors use the term 'minigrafting' interchangeably with 'punch grafting'.¹⁰ The difference being the size of the punches used i.e. if the diameter is less than 1.2mm, it is called a 'minigraft'.⁹ It is performed with the use of 1mm, 1.5mm, 2mm or 2.5mm punches.¹³ Grafts are taken from a normally pigmented donor site of similar thickness and adnexal makeup to the recipient vitiliginous site. The recipient site is also prepared by taking multiple punch biopsies that are the same size or 0.25 to 0.5 mm smaller than those taken from the donor site.¹⁸ Most of the authors prefer the use of similar size of punch grafts from both the sites. The grafted tissue from the donor site is then secured into the vitiliginous areas. Immobilization of the recipient site is critical and can be ensured by application of a petrolatum impregnated pressure bandage for approximately 1 week. Tissue glue has also been successfully used in immobilization of tissue grafts at the recipient site.¹⁹

Some of the investigators have exposed their patients post-surgically to PUVA/ PUVASOL (Psoralen plus Sunlight) or NB-UVB (20) Successful response to mini-punch grafting, defined as repigmentation of greater than 65%, have been reported in 62% to 74% of patients.²¹ Long-term follow-up of 5 years after treatment found greater than 65% repigmentation in 50% of all patients with vitiligo and in 89% of patients with segmental vitiligo.²²

Advantages

This technique is easiest, cheapest, less expensive and does not require any special instruments. Higher success rates have been observed with very few side effects. It can be used over all parts of the body except the angle of mouth.²⁰

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Disadvantages

It is a time consuming procedure. An important side effect of punch grafting is cobblestoning at the recipient site. The risk of cobblestoning is highest with larger grafts. Thus it has been proposed that 1.5 mm should be the upper size limit for punch grafts on the trunk or extremities and 1 mm on the face.^{18,23} Lahiri and Sengupta suggested that a resistant cobblestoning may be corrected with electrofulguration.²⁴ Agarwal et al (1999) used silicone gel sheet dressings for prevention of post minigraft cobblestoning. Silicon gel sheets prevent cobblestoning by counteracting forces which tend to lift the grafts, acts as a brace preventing graft dislocation, provide a sterile environment underneath the grafts, facilitate periodic observation due to their transparency and are easily removed at the time of follow up.²⁵ Infections, hyperpigmentation and imperfect color matching are the associated side effects. Koebnerization, keloid formation and scarring are the complications seen at the donor site.¹⁸ Most of these complications can be avoided by proper selection of patients.

Blister grafting

This procedure consists of obtaining very superficial skin grafts consisting of only the epidermis. In vivo separation of epidermis from rest of the skin by the production of a suction blister was first reported by Kiistula and Mustakollio in 1964.²⁶ However, in 1971 Falabella used epidermal sheets obtained by application of prolonged suction at the donor site, to replace the depigmented epidermis.²⁷ Various alternatives have been used to produce a blister such as double-syringe devices connected to a three-way connector, a combination of syringes and a cylinder funnel, an angiostrometer, and a modified conventional gastric or respiratory suction pump.¹⁰ Rusfianti and Wirohadidjodjo used a 20-ml syringe connected to a respiratory suction pump over the lower abdominal skin to induce blisters. Blister induction took approximately 2 hours.¹⁰ The flexor aspect of the forearm and anterolateral aspect of thigh are preferred sites for blister induction.²⁷ Koga reported that the abdomen and the thighs are the

most suitable donor areas.²⁸ Gupta et al observed that the anterolateral thigh requires the least time (1.5 hours) for formation of a blister.²⁹ The mechanical split occurs at the dermoepidermal junction. In older individuals, weak adherence at dermoepidermal junction makes the separation easier and faster.¹⁰ Some techniques can reduce the time required for blister formation, such as an intradermal injection of normal saline, application of heat, increase of negative pressure by 100 mmHg when the small vesicles appear.²⁹ Lee and Jang reported that the preparation of donor sites with PUVA induces an increasing number of melanocytes, therefore improving the clinical results.³⁰

The recipient site is prepared by dermabrasion, ablation by erbium YAG laser and pulsed carbon-dioxide laser. The site is covered with saline soaked gauze to prevent dehydration. The roof of the blister at the donor site is removed and transferred to the prepared recipient site. Antibiotic ointment is recommended to be applied at both recipient and donor sites and pressure bandages are applied in order to immobilize the sites. After 1 week the bandage can be removed and the antibiotic ointment applied twice daily for another week. Post op PUVA, PUVASOL or UVB (especially narrow-band UVB) therapy have been shown to improve repigmentation and can be initiated as soon as the site is reepithelialized.¹⁸

Advantages

It is highly effective with a response rate of 83% to 90%.²¹ It shows excellent cosmetic results, which are appropriate for segmental vitiligo, and lesions on the eyelids, face, and lips. Very few side effects like hyperpigmentation and imperfect color matching have been reported. It has also shown effective results in treatment of vitiliginous areas with leukotrichia.¹³ Cobblestoning, depigmentation and scarring has not been seen. It is a relatively easy and safe procedure.

Disadvantages

This procedure is time consuming. Blister formation requires about 2 hrs. It needs special attention as epidermal graft has a tendency to roll

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up and tear. This technique is not suitable for body areas like palms, soles and body folds.¹⁰ Large body areas cannot be treated by this method.¹¹

Thin Thiersch's Split Thickness Skin Grafting
Split-thickness skin grafting involves the free transfer of the epidermis along with a portion of the dermis from one site to another. The procedure is carried out under local anesthesia (for localized lesions) or general anesthesia (for extensive lesions). The basic principle involves three basic steps including graft uptake, revascularization and contracture.³¹ Behl (1964) was the first to report the use of thin Thiersch's skin grafts to treat vitiligo.³²

After surgical cleansing and adequate anaesthesia, a thin even split thickness graft is harvested using either a sterile razor blade mounted on a Kochers forceps or a blade holding instrument. Alternatively, a hand dermatome, Humby's knife or Silvers knife may be used, depending on the expertise of the surgeon and availability of the instruments. However, these techniques require skilled operators to harvest thin, even grafts.³³ The vitiliginous area is prepared by dermabrasion. The recipient site can also be prepared using a pulsed Erbium-YAG laser or ultrapulse CO₂ laser. The graft is carefully placed over the denuded recipient site, taking utmost care to place the dermal surface facing down. Immobilization of the graft is most important and is achieved by using surgical adhesive, octyl-2-cyanoacrylate and pressure dressing. A nonadherent dressing is then applied. The dressing is removed after 1 week.³³ In a systematic review, thin split thickness skin grafting was found to be the most successful technique among all the surgical methods, with a success rate of 78 - 91%.²¹

Advantages

The advantages of split thickness skin grafting are that they can be used for larger areas of depigmentation with a uniform pigmentation. Certain sites such as eyelids, inner canthus of eyes, areola, nipples, and genitals can also be treated. Cobblestoning is not observed.³³

Repigmentation of leukotrichia is also possible.³⁴ In addition, as compared to noncultured or cultured melanocyte suspensions, no reagents, laboratory facilities or equipment are required.

Disadvantages

Certain limitations associated with the procedure include hyperpigmentation at the recipient site which is cosmetically unacceptable. This technique requires great skill to get a uniform thickness graft. A thick graft often causes stuck on appearance at the recipient site and an ugly scar and sometimes depigmentation at the donor site.^{33, 13}

Excision and primary suturing

Excision and primary suturing is a very old method used since the time of Galen to excise various types of skin lesions and approximate by sutures.³⁵ This is simple to perform but could be applied only over the small lesions where easy approximation would be possible for marginal suture. The margins are approximated in the direction of skin lining to avoid the tension. Excision, undermining and primary closure appears to be an effective method for treating small patches of lip vitiligo.³⁶

Advantages

This procedure gives immediate result as compared to other surgical modalities which take a long time. There is neither any uncertainty of results, nor requirement of special instruments.

Disadvantages

It cannot be performed for a larger area. It may lead to alteration in the shape of the lip if there is excessive tension on the wound edges.³⁶

Therapeutic wounding

It consists of wounding lesions of stable vitiligo to induce repigmentation. Spot and regional dermabrasion, laser ablation, liquid nitrogen cryosurgery, needling or chemical wounding with 50% TCA or 88% phenol are commonly used.³⁷ In therapeutic wounding, there is acute inflammation which is known to stimulate melanogenesis. Melanocytes migrate from the

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remnants of hair follicles, eccrine glands and also from surrounding normal skin. In the hair follicles, the inactive melanocytes in the outer root sheath divide, proliferate and migrate radially to nearby epidermis to form the pigmented islands which are seen as perifollicular pigmentation. Various growth factors like endothelial growth factor and fibroblast growth factor released during wound healing are mitogenic for the melanocytes.³⁸ In addition, the inflammatory mediators like leukotriene C4 and D4 are known to stimulate the melanocyte proliferation.³⁸ Repigmentation can be further enhanced by PUVA/PUVAsoL.

Follicular grafting

Follicular unit transplant (FUT) has been recently developed as a surgical approach to achieve repigmentation in cases of stable vitiligo. Its effectiveness was first evaluated in 1998 by Na et al.³⁹ This technique is based on an understanding that the hair follicle is an important reservoir of melanocyte.⁴⁰ It was demonstrated that certain inactive melanocytes migrate along with regenerated epidermis and mature gradually, thus contribute to pigmentation.⁴¹ Ortonne *et al.* postulated the existence of a melanocyte reservoir, specifically located in the lower portion of human hair follicles and they proposed that repigmentation of vitiligo was derived from the melanocyte reservoir in the hair follicles.⁴² Cui et al confirmed that during vitiligo repigmentation, the number of inactive melanocytes in the outer sheath of the hair follicle increases significantly and some active melanocytes appear in the outer root sheath, hair follicle orifices, and around the perifollicular epidermis.⁴³ Repigmentation in vitiligo usually begins in the perifollicular area in almost all the cases on treatment. Pigmentation starts appearing by 4th to 5th week and continues upto 6 months.⁴¹

Advantages³⁹

The advantages of this procedure includes absence of cobblestoning and hypertrophic scar and post operative hyperpigmentation in the grafted site. No special equipment is needed and it can be applied to small areas as well as difficult sites like eyelashes, angle of mouth. Hair follicle

melanocytes also seem to be more resistant to the vitiligo process.

Disadvantages

This procedure has certain limitations as dissection of hair is a time consuming, tedious process and needs proper training. It is not suitable for treating medium or large achromic areas. Repigmentation takes a longer time.^{10, 41}

Ultrathin Skin Grafting

It consists of securing ultrathin (<0.125 mm) split thickness skin grafts containing the epidermis and the uppermost part of papillary dermis to the laser ablated or dermabraded vitiliginous recipient sites. These were obtained using power dermatome. Kahn and Cohen successfully repigmented post-burns leucoderma and large vitiliginous areas through ultrathin grafts.⁴⁴ Olsson and Juhlin also used this technique to achieve pigmentation on dermabraded vitiligo with good results.⁴⁵ Concurrent use of NB-UVB therapy has been reported to give faster and better cosmetic results. Advantages of UTSG include minimal chances of scarring and although pigmentary changes similar to split thickness skin grafting were observed but were rarely reported.⁴⁶

Cultured and Noncultured Epidermal Cell Transplantation

Stable vitiligo can be treated by using skin cultures containing keratinocytes and/or melanocytes in the form of sheets or cell suspension. Noncultured epidermal cell suspensions containing keratinocytes and melanocytes can also be used.

Cultured skin grafts

In 1975, Rheinwald and Green described a method of growing human epidermal cells in stratified sheets in vitro without its dermal correspondent.⁴⁷ These cultured epidermal cells were known to lose all their expressions of HLA DR antigen, thus allowing them to be used as either autografts or allografts for treating various skin conditions.⁴⁸ They are used for resurfacing skin in cases like extensive burns, chronic ulcers, recalcitrant epidermolysis bullosa and stable vitiligo.^{49, 50, 51}

Review Article**a) *Cultured Epidermal Autografts Containing Keratinocytes and Melanocytes as Sheets or Cell Suspension:***

This technique involves co-culturing the patient's melanocytes and keratinocytes on a collagen coated membrane which is then grafted on to the dermabraded or liquid nitrogen denuded vitiliginous skin. Most tissue culture laboratories follow Rheinwald-Green technique or its modification.⁴⁷ Split thickness skin sample of size 2-4 sq cm is obtained from the patient. It is then transported to tissue culture laboratories in special transport media containing antibiotics and antifungals. After trimming the dermis, specimen is trypsinized and disintegrated to obtain single cell suspension containing both keratinocytes and melanocytes. Thin epidermal sheets are obtained 3 weeks later, removed from the culture vessel and finally transferred to the previously denuded recipient site. Cultured epidermal autografts were found to be difficult to handle at laboratory level and in the clinical setting due to their fragility. This problem was overcome by using cultured epidermal autografts in cell suspension form. Successful repigmentation by epidermal transplants to the vitiliginous area has been achieved. Repigmentation was visible within 6 to 8 months. Histochemical examination revealed dopa positive melanocytes 12-17 days after grafting in the basal layer of epidermis and the dermis. Melanocytic granules were visible in keratinocytes in 1.5 months. A normal number of dopa-positive melanocytes and melanocytic granules were seen in approximately 8 months.⁵² Tsukamoto et al (2002) used cultured epidermal cell suspension to spread over the denuded vitiligo area. They called it as epidermal seed grafting and found it superior to cultured autografts sheets for repigmentation as it could cover large areas.⁵³ Studies have shown a good repigmentation in 33% to 54% of treated patients.^{54,55} This technique has the advantage that a large area can be treated. Hyperpigmentation is an observed side effect which tends to disappear after a few months. Another disadvantage is the cost of the procedure and failure of culture.⁵⁶

b) *Cultured Epidermal Autografts containing only Melanocytes*

Lerner and colleagues successfully achieved repigmentation by transplanting autologous cultured melanocytes for the treatment of vitiligo in 1987. Cultured melanocytes were washed several times with PBS (phosphate buffered saline), suspended in 200 ml PBS and injected into suction blisters induced at vitiliginous areas. To grow cells in culture, they used 12-O-tetradecanoyl-phorbol-13-acetate (TPA) as well as cholera toxin and isobutylmethyl xanthine. The culture media used by Lerner et al contained TPA which has harmful effects such as altered cells and unwanted clone (tumor promoting mutagenic potential). Hence, this was replaced by TPA free media containing supplements of basic fibroblast growth factor (bFGF), as it is the putative natural growth factor for human melanocytes.⁵⁷ Jha et al (1992) studied the comparative evaluation of various therapeutic regimens in the treatment of depigmentary skin disorders. The results were best with inoculation of cultured autologous epidermal suspension followed by punch grafting.⁵⁸ Lontz et al (1994) and Guerra et al (2000) compared cultured epidermal autografts containing both keratinocytes and melanocytes, with pure melanocyte in treating vitiligo. They reported that cultured epidermal autografts sheets were better than pure melanocyte culture as presence of keratinocytes helps in regulating melanocyte growth and differentiation.^{59,60}

c) *Noncultured Epidermal Cell suspension*

The melanocyte transplantation technique has now been modified to a one-time day care procedure in the form of transplantation of non-cultured melanocyte-keratinocyte suspension. It is a simple technique in which cell culture is not needed and skin harvesting from the donor area, preparation of cell separation by trypsinization and transplantation of melanocytes can all be undertaken in a single day procedure. This method was introduced for the first time by Gauthier and Surleve-Bazeille in 1992, who obtained a split

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thickness skin sample from the occipital region by superficial shave with a razorblade dermatome.⁶¹ In 1997, Olsson and Juhlin used a basal layer enriched epidermal cell suspension that achieved an 85% rate of success.⁶² Bhura et al in 2000 calculated the optimum number of cells needed to produce pigmentation. They inferred that if the cell concentration in the inoculum is above 50×10^3 cells/ml, fairly good cosmetic results are observed.⁶³ Geel et al has used modified technique with good results.⁶⁴

Conclusion

Surgical treatment has an important role in the management of vitiligo not responding to medical therapy and is a continuous field of research. The

choice of the procedure always depends upon the age, the area involved, site and the cosmetic need of the patient (Table 6). The nature of the procedure, expected outcome and the complications should be discussed with the patient in detail (Table 7). The future aspect of the treatment mainly relies upon mesenchymal stem cell therapy and is still hypothetical. Recent advances in the surgical treatment of vitiligo has enabled us to treat localized areas with great success and are accepted cosmetically both by dermatologists and patients. Due to the simplicity and less infrastructure requirements, non-cultured melanocyte transplantation seems to be the therapy of the future but more randomized controlled trials are required to establish it.

Table 1: Clinical classification of vitiligo according to Nordlund

Localized	a. Focal b. Unilateral c. Mucosal	One or more macules with casual distribution One or more macules are localized in a unilateral body region, with a dermatomeric distribution; a typical feature is an abrupt stop of the lesions at the midline Unique involvement of mucous membranes
Generalized	a. Vulgaris b. Acrofacialis c. Mixed	Presence of scattered stains extensively disseminated Patches are localized on distal extremities and face Co-existence of acrofacialis and vulgaris forms
Universalis		Depigmented lesions interest completely or almost completely the skin surface

Table 2: VIDA 6 point score

Disease activity	VIDA score
Active in past 6 weeks	+4
Active in past 3 months	+3
Active in past 6 months	+2
Active in past 1 year	+1
Stable for at least 1 year	0
Stable for at least 1 year and spontaneous repigmentation	-1

Table 3: Criteria for selection of cases for surgery

1. No signs of activity = Stable vitiligo <ul style="list-style-type: none"> • Size of the macule or patch should be stationary for more than 3 years. • No recent development of new lesions
2. Minigrafting test is negative for activity
3. Lesions are refractory to medical treatment
4. Stable segmental vitiligo with leukotrichia
5. Skin over the lesion should not be thickened/lichenified

Review Article**Table 4:** Surgical modalities of treatment in stable vitiligo

1. Tattooing (Calmouflage)
2. Punch grafting
3. Blister grafting
4. Excision and primary suturing
5. Therapeutic wounding
6. Follicular grafting
7. Thin Thiersch's Split Thickness Skin Grafting
8. Ultrathin Skin Grafting (Melanocyte transfer)
9. Cultured and Noncultured Epidermal Cell Transplantation

Table 5 : Various chemicals and the colors produced in tattooing

Chemicals used	Colors produced
1. Iron oxide	Black, camel yellow, light and dark brown
2. Titanium dioxide	White
3. Cadmium sulfide	Yellow
4. Mercuric sulfide	Red

Table 6: Choice of method according to area and site

Area	Preferred	Alternative
	Area	Area
Small area	SBEG, STG	PG
Moderate area	NCES, STG	PG
Relatively large area	CM, CE, NCES, STG	
Site	Site	Site
Fingers and toes	PG, SBEG	NCES
Palms and soles	PG	
Lips	SBEG	PG
Eyelids	SBEG, NCES, STG	MPG
Nipple and areola	SBEG, NCES	
Genitals	NCES, SBEG, CM	

SBEG - suction blister epidermal grafting

STG - split thickness grafting

PG - punch grafting

NCES - noncultured epidermal suspension

CM - cultured melanocytes

CE - cultured epidermis

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Method	Complications
Tattooing	Leaching, color mismatch, change in shade over time
Thiersch's split thickness skin graft	Graft rejection, stuck-on tyre patch, perigraft halo, scarring of donor site
Suction blister grafting	Ecchymosis, post-inflammatory hyperpigmentation
Miniature punch graft	Cobblestoning, polka dot appearance, depigmented junctional zone, graft rejection, scarring of donor site
Therapeutic wounding (phenol)	Scarring
Ultra-thin skin grafts	Skip areas and depigmented junctional line
Non-cultured epidermal cell transplantation	Milia, scarring, koebnerization

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