REVIEW ARTICLE

Grafting in Vitiligo: How to Get Better Results and How to Avoid Complications

Grafting procedures in vitiligo have become quite popular over the last one or two decades especially in India. Starting with the simplest punch grafting we have now a multitude of different grafting techniques available in vitiligo. All of these grafting procedures are associated with certain complications. In addition there are certain factors and surgical pearls that can go a long way in improving the cosmetic results achieved with any of these grafting techniques. This paper will try to address these specific factors and complications associated with these grafting techniques and the ways and means to avoid them.

KEYWORDS: Complications, cosmetic outcome, grafting, results, vitiligo

INTRODUCTION

Vitiligo is a common acquired disorder of skin pigmentation characterized by localized loss of skin pigment secondary to melanocyte damage. As most of the patients with vitiligo are managed by medical means there remains a group that is resistant to all the non-surgical means of treatment. The only possible treatment in such patients is a surgical replacement of the damaged melanocytes. In addition, there is a group of vitiligo patients in whom surgical therapy is considered to be more appropriate than medical means. These surgical techniques are collectively known as grafting procedures and they have become a popular choice among dermatologists in India and even in the rest of the world. The choice of the grafting procedure to be performed usually depends upon the extent or size of the vitiligo lesion to be treated, the site of the lesion, the age of the patient, his/her expectations and social needs, and lastly the expertise of the operating surgeon.[1,2]

In general, grafting techniques in vitiligo are divided into two main groups: Tissue grafting and cellular grafting procedures.[3,4] As the former group encompasses the different techniques of transferring skin tissue grafts as a whole to the involved recipient skin, the latter involves further separation of these skin grafts into cellular components. These cellular components are then applied on the dermabraded recipient skin either as such or after growth and multiplication in culture media. As a whole, tissue grafting procedures are simpler and easier to perform than the cellular transplantation methods.

As with any other surgical procedure, vitiligo grafting can be associated with complications. Most, if not all, of these complications can be prevented if proper precautions are taken before, during, and after the grafting procedure. In addition to the prevention of these complications there are certain other factors that have a direct bearing on the cosmetic result that is achieved with any of these procedures. What needs to be remembered is that grafting procedures in vitiligo are performed for cosmetic purposes and the ideal grafting procedure is one that gives the best cosmetic results. This paper will try to discuss the ways and means to improve the cosmetic results as well as to avoid the complications with each of the grafting procedures that we employ in vitiligo.

Before discussing the complications of each individual grafting procedure and the ways to prevent them, it is important to discuss the issue of selection of patients for vitiligo grafting. Proper selection of the patient is the most important factor for achieving a good cosmetic

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Imran Majid

Department of Dermatology, Government Medical College, CUTIS Skin and Laser Institute, Srinagar, Kashmir, India

Address for correspondence:

Dr. Imran Majid, Government Medical College, Cutis Skin and Laser Institute, Srinagar, Kashmir, India. E-mail: imran54@yahoo.com

result with any grafting procedure in vitiligo. The factors that need to be considered are the age of the patient, the site of vitiligo, keloidal tendency and most importantly, the stability of vitiligo. Stability of vitiligo simply means that the disease process is no longer active in an individual patient. Clinically, stability is manifested as absence of new lesions, absence of spread of existing vitiligo lesions, and absence of Koebner's phenomenon. The minimum duration of stability for vitiligo grafting is still a debatable issue with the recommended minimum duration ranging from 6 months to as long as 4 years in different clinical studies.[5-7] Another debatable issue in this regard is that of patient versus lesional stability but majority of researchers still favour patient stability over the lesional stability while selecting a patient for vitiligo grafting. To facilitate a consensus on the question of stability for vitiligo grafting the IADVL task force has defined stability as 'a patient with no new lesions, no progression of existing lesions and absence of Koebner phenomenon during the past 1 year'.[8] Therefore, as of now, the recommendation to be followed is to select a patient with no history of progression of lesions, no new lesions, and no history of a Koebner's phenomenon over at least 1 year before the procedure. In a recent study on the issue of vitiligo stability, a time period of '18 months of stable disease' was shown to be most suitable one for undertaking any grafting procedure.[9]

MINIATURE PUNCH GRAFTING

Miniature punch grafting, also known as minigrafting, is the simplest and the least expensive of all the grafting procedures in vitiligo.[1,10] The procedure involves the transfer of circular pieces or punches of skin tissue from the donor area into similar shaped pits that are made on the recipient skin. The size of these punches can range from 1 mm to 2 mm and they are spaced 5-10 mm apart on the recipient skin.[10-12] The incidence of adverse effects is the highest with this procedure and the list of these adverse effects includes cobblestone appearance, polka dot appearance, depigmentation of the grafts, perigraft halo, graft rejection, keloidal or hypertrophic scarring and variegated appearance with colour mismatch at the recipient site.[10-14] In addition, the patient can develop hypertrophic scarring at the donor site as well and there can even be a Koebner's phenomenon with development of fresh vitiligo lesions at the donor site.[10-14]

Most, if not all, of these complications can be prevented and the cosmetic outcome can be greatly improved if some minor modifications are made in the technique and proper precautions are taken.[10-14]

Cobblestoning

Cobblestoning [Figure 1] is the most common and the most distressing complication of miniature punch grafting.[10-16] Factors that can prevent or at least minimize the chances of cobblestoning include:[11,16-18]

1. Use punches of smaller size, ideally 1 mm-1.5 mm [Figures 2a and b]
2. Prevent overcrowding of grafts; keep the grafts at least 5 mm apart from each other
3. Use thinner grafts so that the upper surface of the grafts remains at the level of the recipient skin.[11] One modification that helps in obtaining such thin grafts is infiltration of the donor skin with the local anaesthetic solution at the level of the upper and mid dermis only so that the deeper dermis gets separated from the upper skin. In this manner the depth of the punch can be minimized and the graft can snugly fit in a relatively deeper punch made at the recipient area
4. If the graft taken is thicker, it is better to trim the under surface of the graft
5. Minimize tissue trauma during the procedure. Use sharp cutting instruments and non-toothed forceps to prevent damage to the graft cells
6. Use the same size of punch at both the donor and recipient sites
7. Use of silicone sheet dressings has also been claimed to prevent or minimize the chances of cobblestoning.[19]

Depigmentation of grafts

This is another important complication of miniature punch grafting and in fact any type of tissue grafting procedure. Factors that can prevent or at least minimize the chances of this complication are:

1. Proper selection of the patient before undertaking the procedure as described above
2. Perform test grafting in selected cases if there is any doubt regarding the stability of the disease. Test-grafting involves the transplantation of few mini-grafts on to the recipient area before the main surgical procedure is undertaken.[20] The test grafts are then observed over some time to see the

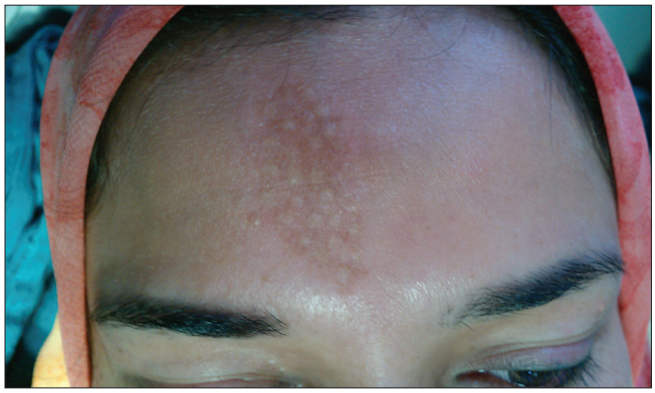

Figure 1: Cobblestoning after minigrafting with 2.5 mm punches

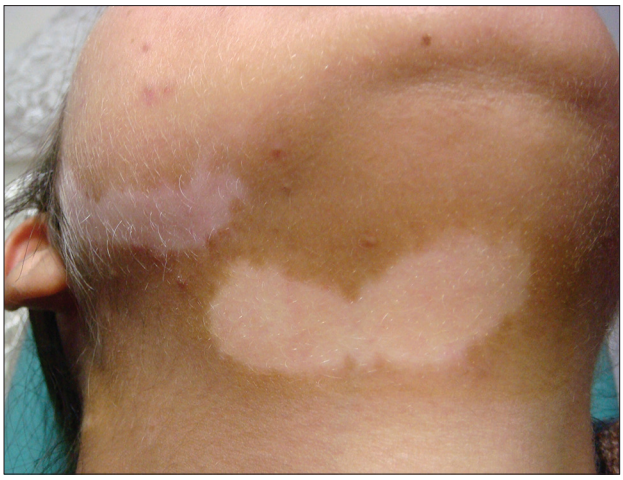

Figure 2a: Minigrafting with smaller 1.5 mm punches

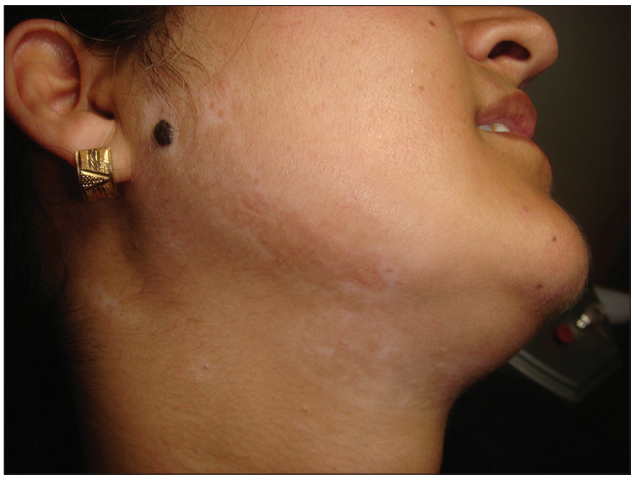

Figure 2b: Minigrafting with smaller 1.5 mm punches leading to less cobblestoning effect

repigmentation response. As a positive result with test-grafting does not always guarantee a successful result a negative result would at least avoid the complication to occur with the main grafting procedure.[21]

3. Employ a proper surgical technique and minimize tissue trauma at the donor as well as recipient sites
4. Use Narrowband UVB (NBUVB) or PUVA after the grafting procedure especially if there is a delay in the onset of repigmentation. Studies have shown that the use of NBUVB after vitiligo grafting minimizes the chances of graft depigmentation and helps graft failure cases as well.[22,23] Even other phototherapeutic methods like excimer laser has been used post-surgically to improve the clinical results.[24]

Perigraft halo

Perigraft halo means the rim of depigmentation that remains at the outer edge of the vitiligo lesion treated with cellular or tissue grafting. In case of miniature punch grafting, perigraft halo can be avoided or minimized by following a proper surgical technique. The technique involves placing the grafts along the periphery first before going towards the centre of the lesion to be treated. By placing the grafts initially all along the periphery just about 1-2 mm inside the outer border of the recipient area, the perigraft halo can be prevented to a great extent.

Rest of the complications like graft rejection, hypertrophic scarring, and Koebner's phenomenon can be minimized by preventing both clinical as well as sub-clinical infection at the recipient as well as the donor site and by selecting the patients properly before undertaking the procedure.

Split-thickness skin grafting

Split thickness skin grafting is nowadays considered to be the surgical method of choice for stable, non-responding vitiligo. The procedure is claimed to be the most successful of all the tissue grafting procedures in vitiligo at present.[1,25]

The list of possible complications includes stuck-on appearance [Figure 3], curling of the graft with beaded appearance, displacement of the grafts, cosmetically mismatched pigmentation, milia formation, perigraft halo of depigmentation [Figure 4], and scarring at recipient or donor areas.[24-26]

Points that need to be kept in mind to minimize these complications and to improve the cosmetic results are:[25,27-29]

1. Use ultra-thin grafts of uniform thickness that are free of any dermal tissue. This is undoubtedly the most important factor determining the cosmetic outcome at the recipient site. In fact, a specific term is used to describe this type of split-thickness skin grafting wherein the grafts used are purely epidermal in nature [Figure 5a and b]. The procedure has been termed as 'ultra-thin skin grafting' in some clinical studies.[28,29] The procedure differs from a traditional split-thickness skin grafting in that the graft that is used is totally translucent, without any whitish tissue on the undersurface. Another difference is that the graft in case of ultra-thin skin grafting usually falls off within 10-14 days. After the graft has fallen off, gradual uniform repigmentation is achieved at the recipient site. Therefore, the cosmetic results obtained with ultra-thin skin grafting are usually excellent and the colour matching is ideal.
2. Dermabrade the skin 1-2 mm beyond the margins of the vitiligo lesion and place the grafts beyond the dermabraded margins to minimize the chances of perigraft halo formation [Figure 4].
3. Secure the grafts firmly at the recipient area with proper dressings and immobilization of the grafted area if needed.

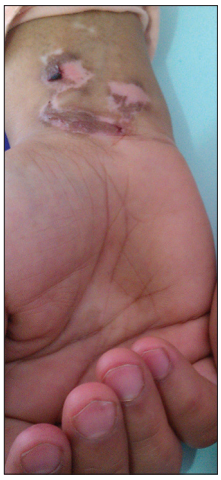

Figure 3: Scarring and poor cosmetic results with a thick split-thickness graft

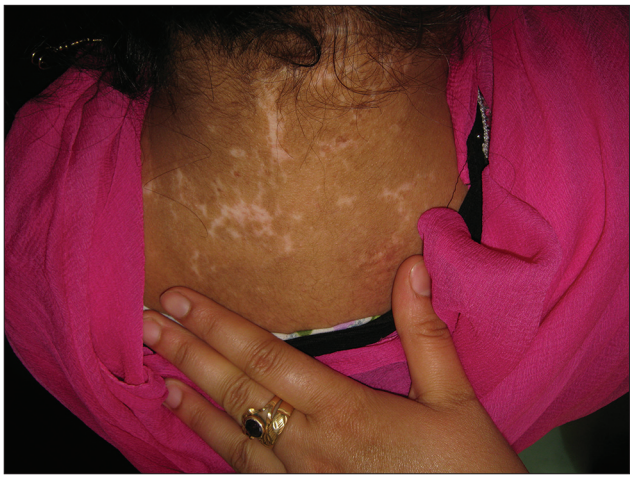

Figure 4: Perigraft halo of depigmentation after ultrathin skin grafting

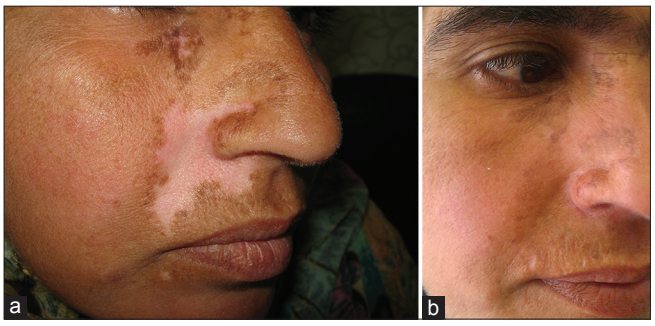

Figure 5 (a, b): Ultrathin skin grafting with NBUVB giving cosmetically acceptable pigmentation

4. Use of cyanoacrylate or surgical glue along the periphery of the graft has been shown to minimize the chances of graft displacement.[25]
5. Spread the graft fully over the recipient area and avoid wrinkling or curling of the graft at the margins.
6. Use NBUVB, PUVA, or even excimer laser after removing the dressings especially if there is a delay in the onset of repigmentation. This is helpful in preventing or minimizing perigraft halos and also improves the cosmetic outcome.[29,30]
7. Prevent overuse of topical psoralens or NBUVB as it can lead to hyperpigmentation at the recipient site. One way of doing so is to stop the use of phototherapy as soon as there is uniform pigmentation seen over the treated lesion.[13,25]
8. Infiltration anaesthesia at the donor site needs to be avoided as it can lead to an irregular surface and thus interfere with the harvesting of a uniform-thickness skin graft. A ring-block is thus preferred at this site.
9. Topical anaesthetic creams can be used as an alternate to injectable anaesthetics at the donor and even at the recipient site.

Suction blister grafting

In this procedure suction is used to obtain very thin skin grafts by causing a split at the dermo-epidermal junction. These thin grafts are then applied on to dermabraded recipient skin.[31-33] The advantages of suction blister grafting are an excellent cosmetic matching and minimal chances of scarring at the recipient or donor sites.[25,32,33] Areas like the lips and areolae respond very nicely to suction blister grafting.[33] The main disadvantages are that the procedure is time consuming and can take care of a limited area of skin in a single session.

The complications associated with the procedure are perigraft halo of depigmentation, wrinkling and displacement of the graft and graft rejection. Tips to avoid these complications are:

1. Dermabrade the recipient area 1-2 mm beyond the actual margins as in split thickness skin grafting.
2. Secure the graft nicely with the underlying dermabraded recipient area to prevent graft displacement.
3. Use cyanoacrylate glue along the margins if the graft is to be placed over mobile areas.
4. Select the patients properly as in any other form of tissue or cellular grafting procedure.
5. Supplement the procedure with post-operative use of NBUVB or PUVAsol especially if the onset of repigmentation is delayed.[34]

Other surgical pearls that have been described in this procedure are:

1. Use a 50 ml syringe as a vacuum creating device instead of the expensive and cumbersome vacuum devices. The time taken for the blister formation is the same with both these methods.[25,35]
2. Use intra-dermal saline injections by means of a 27 guage needle if there is a single small blister

inadequate for grafting or if there are multiple small blisters separate from each other. This leads to coalescence of these blisters or even enlarges the size of a single blister that is present.[25,35,36]
3. Even UVA exposure and intra-epidermal injection of anaesthetic solutions has been reported to shorten the time of blister formation.[37,38]
4. Suction blister technique can be used even at the recipient site instead of dermabrasion to create a bed for the epidermal graft.[39]

Non-culture epidermal suspension transplant

This is a type of cellular grafting which involves separation of different cellular components of a split-thickness skin graft. The cellular suspension which consists of a mixture of epidermal keratinocytes and melanocytes is then applied on to a dermabraded recipient area.[40,41] The procedure is also known by certain other names like non-culture melanocyte transplant, 'basal cell suspension technique' and 'non-culture cellular transplant'. The procedure offers certain advantages over the tissue grafting techniques in that a relatively larger area can be treated in a single session and with a much smaller size of donor graft.[40-42] In addition, the repigmentation achieved matches the recipient skin closely leading to a better cosmetic result. The main disadvantage is that the procedure involves the use of reagents that are relatively expensive and that need to be stored in subzero temperatures. However, with the use of commercial kits (Hi-media, Re-cell), this storage facility is not required. Additionally, the procedure is relatively more time consuming and involves a learning curve for the operating surgeon.[43]

Adverse effects reported with the procedure are a mild textural change at the donor site and cosmetic mismatch at the recipient site.[44] This colour mismatch can be in the form of hyperpigmentation or hypopigmentation.[45]

Tips to achieve better results in non-culture melanocyte transplant are:
1. Ensure that the trypsinization is complete. For this purpose both the time of incubation and maintenance of a proper temperature in the incubator is important. If trypsinization is not complete, it is better to re-incubate the donor graft for some more time.[43] Two types of trypsinization have been described in the literature-cold and hot trypsinization. As the former is claimed to give a better yield of cellular constituents, the latter is more commonly followed in India as it is less time consuming.[46]
2. Ensure that the graft suspension is not too 'fluidy'. Use of hyaluronic acid gels has been recommended in such situations to increase the viscosity or thickness of the graft suspension.[47,48]
3. Spread the solution evenly and uniformly over the dermabraded area to minimize the chances of a non-uniform repigmentation.
4. The cellular component in the suspension needs to be maintained at an ideal level to prevent hyper- or hypo-pigmentation at the recipient area. A donor to recipient ratio of 1:10 has been considered ideal to prevent this complication but the same is yet to be scientifically validated.[48]
5. Both NBUVB as well as PUVA can be used after the procedure to cause a rapid onset of repigmentation. However, some authorities use this supplemental treatment only if there is a delay in the onset of repigmentation.[43,48]
6. Use of collagen dressings is also encouraged to improve the pigmentation achieved with the procedure.
7. Another way to know the size of the graft needed is to measure the number of melanocytes in the cellular suspension; a count of 210-250 cells per mm^2 has been seen to be ideal for the procedure.[49]

Some more points that can be considered as pearls in this procedure are:
1. Use of trypsin inhibitor can be avoided by washing the grafts after trypsinization in DMEM or any other suitable medium twice or thrice. This cuts down the cost of the procedure to a great extent as the most expensive reagent in the whole procedure is the trypsin inhibitor only.[42]
2. Even patient's own serum can be used as an alternate to DMEM medium with equally good results. This modification has even been claimed to improve the viscosity of the cellular suspension.
3. Another technique that has been described is the 'six-well plate' technique that uses a microfilter, trypsin, trypsin inhibitor and phosphate buffer saline.[50]

Cultured melanocyte transplantation

In this technique, after separation of epidermis by trypsinization, the melanocytes and keratinocytes are dissociated and then the melanocytes are seeded in a proper melanocyte medium containing certain growth factors. The melanocytes are thus cultured over 15-30 days and then transplanted as free suspension or as epidermal sheets on to dermabraded recipient skin.[43,51]

The most important advantage of the procedure that a large area can be treated in a single session with a donor to recipient ration of 1:20-1:30. However, the procedure provides no advantage over the non-culture technique as far as the repigmentation response is concerned. Moreover, melanocyte culture technique is associated with certain drawbacks which are listed below:
1. The procedure needs an expensive laboratory support and set-up.

2. There are concerns of mutagenicity of certain ingredients of the culture media especially tetradecanoylphorbol acetate (TPA) used in melanocyte culture.
3. The cost of the procedure is too high for the patient.
4. The procedure provides no significant advantages over the non-culture technique.

Factors that can obviate at least some of these drawbacks include:

1. Use of TPA-free and serum-free culture media can minimize the chances of a possible mutagenic effect.
2. Beta fibroblast growth factor can be a useful substitute and provides equally good results.[52]

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