

CHAPTER 9

Surgical management of vitiligo and other leukodermas: evidence-based practice guidelines

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Introduction

Both non-surgical and surgical therapies have been employed in the management of vitiligo. However, there are no uniformly agreed guidelines or recommendations available for surgical management of vitiligo and other leukodermas. Current surgical treatment practices are based on informal consensus meetings, expert opinions, results from uncontrolled clinical trials, and personal and/or institutional experiences and infrastructures [1]. There is only one randomized study available showing superiority of non-cultured melanocyte suspension over placebo [2]. In the absence of randomized clinical trials, the guidelines will be formulated on the basis of meta-analysis of published uncontrolled clinical trials.

Here a word of caution is necessary that this is only an attempt to draw some conclusions from meta-analysis of a broad variety of reports published over a long period, by different individuals. Often the results are reported as subjective observations without real measurement tools or statistical analyses. The procedures are performed using different surgical equipment and bandage materials in distinct clinical settings. The patient populations are from different parts of the world, so are genetically heterogeneous. All these factors may bias the conclusions. A Consensus Report on the definition and assessment of vitiligo has recently been worked out by the Vitiligo European Task Force. This report will be a valuable tool to make research outcomes on

this subject more uniform and comparable, but it will still take many years until a sufficient number of new publications has used the consensus assessment to make future studies more comparable and meta-analyses more appropriate. In spite of inherent biases, meta-analyses of published literature have been accepted as useful means to formulate evidence-based practice guidelines [3].

Method

We searched two databases, Medline and Embase, from 1966 to 2005 with Keywords "Vitiligo," "Leukoderma," "Transplantation," "Grafting," and "Surgery" in various combinations. A few leading researchers were contacted to retrieve reports under publication. Some Asian journals not indexed in the literature were hand-searched for relevant reports. Cross-references of some leading reviews on the subject were also studied. All the studies pertaining to transplantation procedures in vitiligo and other leukodermas were reviewed and evaluated for the data. Those studies providing inadequate data about patients or outcome or analyzing data of "patches" or "procedures" but not of "patients" were excluded. Follow-up studies of previously published case series were not included to avoid duplication of data. Data for two different subtypes of vitiligo, namely bilateral (generalized and acrofacial) and localized (segmental and focal), was compared. Data for certain "difficult to treat" sites was also analyzed. Adverse effects and total treated area were also looked into.

The successful outcome was defined as greater than 75% repigmentation, "excellent" repigmentation, repigmentation of "most" of the treated area, or "complete" or "almost complete" repigmentation. The percentage of patients with successful outcome and 95% confidence intervals (CI) were calculated. The mean number of adverse events per patient was calculated to find out which procedures have a better safety profile.

Results

A total of 96 studies were identified which were suitable for inclusion of some data in the analyses [4–99].

Procedures

The following transplantation procedures have been found to be commonly used for hypopigmentation disorders.

Tissue grafts:

- 1 Thin and ultra-thin split-thickness skin grafts (STSG)
- 2 Suction blister epidermal grafts (SBEG)
- 3 Mini-punch grafts (MPG)
- 4 Hair follicular grafts (HFG)

Cellular grafts:

- 5 Non-cultured epidermal cell suspension (NCES)
- 6 Cultured "pure" melanocytes (CM)
- 7 Cultured epithelial grafts (CE)

In addition, two procedures, namely ultrasonic abrasion and seed grafts and flip-top technique of grafting have also been tried in one study each [100,101]. In older literature, epidermal shave grafts have also been used. These studies were not included in the meta-analysis of the literature due to paucity of the data. There were 14 studies in STSG, 27 studies in SBEG, 20 studies in MPG, 12 studies in NCECS, 12 studies in cultured melanocytes, 12 studies in cultured epidermis/co-cultures, and 2 studies in follicular transplantation in patients with vitiligo.

Outcome

Vitiligo

Among all procedures, suction blister epidermal grafts and thin and ultra-thin split-thickness grafts

seem to be the most effective procedures, with overall success rates of 80.3% (CI 76.4–84.2%) and 77.9% (CI 72.2–83.6%), respectively (Fig. 9.1). The least successful method was hair grafting, with an overall success rate of 58.3% (CI 38.6–78%); however, this technique was especially useful in management of leukotrichia. Among cellular grafts, all techniques seem to be equally effective with success rates of 61.1% (CI 56.1–66.1%), 63.6% (CI 57.2–70%), and 63.6% (CI 55.8–70.6%) for non-cultured epidermal cell suspension, cultured melanocytes, and cultured epidermis, respectively. The success rates in bilateral vitiligo including generalized and acrofacial vitiligo were less than those in segmental or focal vitiligo with all the procedures. The success rates varied from 25% (CI 0–67.4%) for hair grafting to 70.4% (CI 55.1–85.7%) for thin and ultra-thin split-thickness grafts in bilateral vitiligo, while in segmental vitiligo, these ranged from 70.6% (CI 48.9–92.3%) for hair grafting to 100% (CI 100–100%) for thin and ultra-thin split-thickness skin grafts. Overall, the transplantation procedures were successful in 73.1% (CI 71.5–74.7%) of all cases of vitiligo, 84.4% (CI 81.8–87%) in patients with segmental or focal vitiligo and 58.5% (CI 54.4–62.6%) in patients with bilateral vitiligo.

Vitiligo on "difficult to treat" sites

As data pertaining to individual sites was not provided in most of the studies, the number of patients for specific sites was too small to enable us to apply methods of statistical analysis (Table 9.1).

Fingers and toes

Cultured melanocytes, thin or ultra-thin split-thickness grafts, mini-punch grafts, and suction blister epidermal grafts are all highly successful ($\geq 80\%$ success rate) on fingers and toes, which are otherwise very difficult to treat with medical therapies and excimer laser. Cultured epidermis is not as successful on this site, with a success rate of 30.8%.

Palms and soles

There is only a single case report of successful minigraft transplant on palm [68]. The donor site used for this case was the skin of sole (instep). In the literature, there are no reports of any other method used for vitiligo of this site.

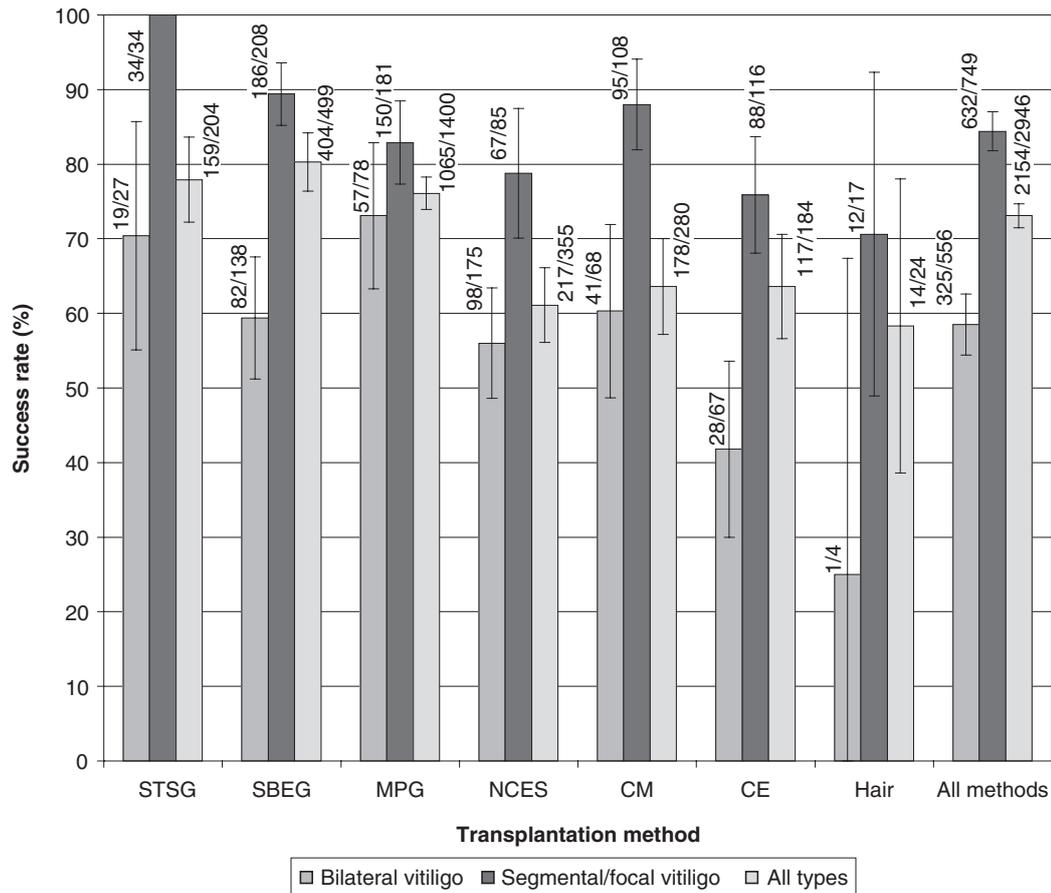


Fig. 9.1 Success rates of various transplantation methods in vitiligo, including its subtypes. The values given on each bar represent number of successful patients/total number of patients. Error bars represent 95% CI.

Table 9.1 Summary of the outcome of literature analysis for surgical treatment of vitiligo at “difficult to treat” sites.

Site	STSG (successful/total)	SBEG (successful/total)	MPG (successful/total)	NCES (successful/total)	CM (successful/total)	CE (successful/total)	All methods (successful/total)
Fingers and toes	15/16	13/15	24/27	15/25	6/6	4/13	77/102
Lips	2/2	40/45	102/132	6/14	–	–	150/193
Eyelids	7/9	14/14	1/2	8/10	–	–	30/35
Nipples and areolas	–	2/2	–	2/4	–	–	4/6
Elbows and knees	1/1	–	4/6	39/78	12/27	1/1	57/113
Genitals	0/1	1/1	1/1	3/3	1/1	–	6/7

Lips

Thin or ultra-thin split-thickness grafts and suction blister epidermal grafts are most successful in treatment of vitiligo of the lips, though very few cases treated with the former procedure have been reported in the literature. There is also a risk of mismatch in texture with dermo-epidermal grafts; therefore, presently the simplest and the most suitable procedure for this limited mucocutaneous transition area is pure epidermal grafts obtained through suction blisters. In terms of repigmentation, minigrafts are also successful at this site, but high complication rates in the form of cobblestoning which are associated with that method make it less desirable for this cosmetically highly prominent site. Non-cultured melanocyte suspension is less effective than tissue grafts on lips (42.9% success rate). Concerning cultured cellular grafts no published data for procedures on lips are available but sometimes the lips and eyelids are included in the data of face as a whole, which makes it difficult to analyze when scrutinizing the reports.

Eyelids

Suction blister epidermal grafts, thin or ultra-thin split-thickness grafts, and NCEC are among the most effective surgical treatments for eyelids [51]. No data for cultured cellular grafts are available for this specific site.

Nipples and areolas

Suction blister epidermal grafts are reported to be successful on the nipple and areola, though data from very few patients is available. Non-cultured melanocyte suspension has been found to be successful in about half of the patients.

Elbows and knees

These sites are difficult to treat because of their mobility. Inadequate data are available for thin and ultra-thin split-thickness skin grafts, SBEG, and cultured epidermis. Minigrafts and non-cultured melanocyte suspension appear to be successful in about half of the patients.

Genitals

Suction blister epidermal grafts, non-cultured cellular suspension and cultured melanocytes are reported to

Table 9.2 Repigmentation of leukotrichia in vitiligo after transplantation.

Transplantation method	Total number of patients	Number of patients with successfully repigmented white hair	Success rate (%)
STSG	10	8	80
SBEG	28	27	96.4
MPG	63	16	25.4
NCES	1	1	100
CM	–	–	–
CE	1	1	100
Hair	13	6	46.2

be successful on genitals, though data from very few patients is available [70,81].

Leukotrichia in vitiligo

The course of leukotrichia after transplantation has been specifically studied in only a few studies (Table 9.2) [13,14,43]. STSG and SBEG appear to be more successful in repigmentation of leukotrichia than MPG. Sufficient data is not available for cellular grafts. Transplantation of hair has been found to be successful in about half of the patients in the treatment of leukotrichia.

Size of the treated area

Cases with more extensive vitiligo vulgaris, involving greater than 30% body surface area, are generally considered unsuitable for transplantation procedures as chances of retention of the pigment are less [102]. This is not the case in segmental vitiligo, which seems to respond equally well regardless of the size of the involved area. Extensive areas may be best treated with cellular grafts – theoretically, culture methods would provide an unlimited number of cells/tissue for transplantation, while NCEC would provide up to 8–10 times donor-to-recipient expansion. Among tissue grafts, minigrafts are also based on the principle of pigment spread and a 1.25-mm

graft is expected to provide a pigmented halo of 5–10 mm, depending on the skin type of the patient (more in darker skin type). This means a grafted area of approximately 5 mm² (or a graft of 1.25 mm) will result in repigmentation of approximately 20 mm² (pigment spread of 5-mm diameter) to 80 mm² (pigment spread of 10-mm diameter) – 4–15 times donor-to-recipient expansion. Therefore, moderately large areas may be treated with NCEC, thin split-thickness grafts, and minigrafts. Small areas do not require donor skin expansion through cultures or suspension, and therefore should be treated with less complex tissue grafting procedures such as suction blister epidermal grafts or thin split-thickness grafts.

In literature, the mean area treated with each procedure is as follows: STSG: 69.3 cm², SBEG 4 cm², MPG 21 cm², NCEC 31.6 cm², CM 34.7 cm², and CE 161.5 cm². In SBEG, data was available from only one study. Therefore, it seems that larger areas may be treated with cellular grafts and thin and ultra-thin split-thickness grafts and moderate areas may be treated cellular grafts and minigrafts. Smaller areas may be easily treated with suction blister epidermal grafts which gives good esthetic results and is technically less challenging.

Adverse events

No serious adverse events have been reported with any of the transplantation methods. Cellular grafts appear to have the least frequency of adverse events. Cultured melanocytes, cultured epidermis, and NCEC have a mean of 0, 0.02, and 0.08, respectively, adverse events at recipient site, and 0.01, 0, and 0.009, respectively, at the donor site (Tables 9.3 and 9.4). Tissue grafts are reported to be associated with more adverse effects and the maximum number of adverse events on the recipient site are seen when MPG and STSG methods are used.

Other leukodermas/hypopigmentation disorders (Table 9.5)

Lip leukoderma due to recurrent herpes labialis

It was found to be manageable with thin or ultra-thin split-thickness grafts. Minigrafting has been reported

Table 9.3 Mean number of adverse events per patient.

	Recipient	Donor
STSG	0.5	0.5
SBEG	0.2	0.3
MPG	0.7	0.05
NCEC	0.08	0.009
CM	0	0.01
CE	0.02	0

to be unsuccessful for this condition and reactivation of herpes simplex virus infection has been thought to be responsible for graft rejection [103]. Even when minigrafts were successfully transplanted with the help of concurrent acyclovir therapy, there was no pigment spread from the grafts, which soon also became depigmented. Micropigmentation (tattooing) has been successful in such cases [104].

Piebaldism

In piebaldism, thin and ultra-thin split-thickness grafting, NCEC, cultured melanocytes, and cultured epidermis have been tried and all these methods yielded 100% success rates.

DLE leukoderma

In discoid lupus erythematosus (DLE) leukoderma, thin split-thickness grafts, suction blister epidermal grafts, and minigrafts gave 100% success rates [48]; however, the number of treated patients were few (1, 4, and 1, respectively). These patients were given antimalarial therapy to prevent reactivation of disease or köbnerization.

Halo nevus

Recent studies have shown evidence that halo nevus is a different entity from vitiligo [105]. Three-quarters (75%) of patients with halo nevus will show successful outcome with transplantation procedures. Non-cultured melanocyte suspension, cultured melanocytes, and cultured epidermis have been found to be successful in the treatment of halo nevi.

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Table 9.4 Nature of adverse events in transplantation procedures.

		STSG (n = 76)	SBEG (n = 441)	MPG (n = 1295)	NCES (n = 318)	CM (n = 259)	CE (n = 170)	Hair (n = 21)
Recipient area	Hyperpigmentation	2	53	312	3		1	
	Hypopigmented borders	4	1	5	20			
	Cobblestoning			397				
	Contact dermatitis to topical medication		6	3				
	Inclusion cysts	20						
	Thick margins/stuck-on appearance	9						
	Variegated appearance		7	244				
	Infection	2	9	3	1			
	Scarring			19			2	
	All adverse events	37	76	983	24		3	
Donor area	Hyperpigmentation	1	131					
	Scarring	30		60				
	Köbner phenomenon		4	3		3		
	Infection			1				
	All adverse events	31	135	64		3		

Table 9.5 Summary of the outcome of literature analysis in other leukodermas.

Type of leukoderma	STSG (successful/ total)	SBEG (successful/ total)	MPG (successful/ total)	NCES (successful/ total)	CM (successful/ total)	CE (successful/ total)	All methods (successful/ total)
Lip leukoderma due to herpes	10/10	–	0/8	–	–	–	10/18
Piebaldism	14/14	2/2	4/4	10/10	2/2	7/7	39/39
DLE leukoderma	1/1	4/4	1/1	–	–	–	6/6
Contact leukoderma	–	1/1	1/1	1/1	1/1	–	4/4
Halo nevus	1/0	–	–	2/2	1/1	–	3/3
Nevus depigmentosus	–	1/1	–	1/2	–	–	2/3
Albinism	–	–	–	–	–	0/1	0/1
Post-burn leukoderma	60/60	11/11	4/4	–	–	1/1	76/76
Ideopathic guttate hypomelanosis	–	4/4	–	–	–	–	4/4

Table 9.6 Guidelines for surgical management of vitiligo and other leukodermas.

	First choice(s)	Alternative
A. Vitiligo		
<i>Site</i>		
Acral (fingers and toes)	CM, SBEG, STSG	MPG, NCES, CE
Palms	MPG	–
Lips	SBEG, STSG	MPG, NCES
Eyelids	SBEG, NCES, STSG	MPG
Nipple and areola	SBEG, NCES	
Genitals	NCES, SBEG, CM	–
<i>Area</i>		
Small	SBEG, STSG	MPG, Hair
Moderate	NCES, STSG	MPG
Extensive	CM, CE, NCES	STSG
B. Herpes lip leukoderma	STSG	–
C. Piebaldism	Any – choice depends on the size of the lesions. All are likely to be successful	
D. DLE leukoderma	SBEG, STSG, MPG	–
E. Contact leukoderma	Any – all are likely to be successful	
F. Halo nevus	NCES, CM, CE	
G. Nevus depigmentosus	SBEG	NCES
H. Post-burn leukoderma	Any – STSG, SBEG, and MPG have been tried with consistent success	–
I. Ideopathic guttate hypomelanosis	Any – SBEG has been tried successfully	–
J. Albinism	Should never be treated with autologous transplantation methods	–

Nevus depigmentosus

There were only three cases with nevus depigmentosus reported to be treated with transplantation procedures – two with melanocyte suspension and one with epidermal grafts [52,76,77]. It seems that there is no pigment spread phenomenon in these patches and the whole depigmented area needs to be replaced with normally pigmented epidermal sheets [52].

Leukoderma after partial thickness burn injuries

Post-burn leukoderma is almost always successfully managed with transplantation procedures. In the literature, reports of use of tissue grafts are available and most reported cases have been treated with split-thickness grafts [106]. This may be due to familiarity of plastic surgeons with this procedure, as most of the reported studies have been done in

that setup. Cultured epidermis has also been used in post-burn leukoderma in a single case report.

Idiopathic guttate hypomelanosis

This has been successfully treated with suction blister epidermal grafts (4/4) [45].

Albinism

Albinism should never be managed with transplantation procedures as it is not likely to be successful. Only one case of albinism has been reported in the literature, in which cultured melanocyte transplantation was tried without any success [92].

Leukoderma due to contact with chemicals

It is manageable with transplantation methods – cell suspension, suction blister epidermal grafts, and minigrafts were all found to be 100% successful in these patients.

Guidelines

Based on reported success rates, adverse events, technical complexities, anatomical location, and size of the areas, the guidelines have been developed (Table 9.6). Yet every patient should be evaluated individually to find out the best possible options. This depends on expertise of the treating surgeon, economy of the institute, infrastructure available, and patient's preference. Patient should be counseled for all possible therapeutic options and should be given liberty to choose from the available modalities.

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