EFFECT OF POSTOPERATIVE PUVA AND UVA THERAPY ON MINIGRAFTS AND MELANOCYTE TRANSPLANTATION IN VITILIGO

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Abstract

Background: The use of phototherapy (UVA) and photochemotherapy (PUVA) on surgically treated vitiligo patches has, to date, not been studied on statistical basis.

Objective: The present study was designed to compare between UVA alone, PUVA using either topical or oral psoralen on surgically treated patches.

Methods: Minigrafts (MG) and transplantation of noncultured melanocytes (MT) were concomitantly performed on 105 patients, a third patch was left as control. Patients were divided into 4 groups designated A-D 4 weeks after operation.

Results: Postoperative photo- and photochemotherapy had no significant effect on the extent of repigmentation for MG. For MT-treated areas, group B (oral PUVA) showed a significantly lower extent of repigmentation compared to other groups. Control areas of groups B and C (topical PUVA) showed positive repigmentation response, but at a slower rate compared to surgically treated patches. The most notable beneficial effect of oral PUVA and topical PUVA was a better and faster color match of grafted patches.

***Conclusion:** Surgery and photochemotherapy are complementary treatment modalities for vitiligo.*

***Key words:** vitiligo, treatment, minigraft, melanocyte transplantation, PUVA, UVA.*

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Introduction:

Minigrafting (MG) is a recognized surgical method for repigmenting vitiligo lesions refractory to medical treatment 1. Noncultured melanocyte transplantation (MT) is a procedure in which epidermal suspension containing melanocytes is prepared and later transplanted to vitiligo patches[2]. Both methods provide rapid coverage of small to medium-sized patches. Postoperative photochemotherapy (PUVA) or phototherapy (UVA) from artificial lamps or sunlight has been claimed to be effective in a number of studies employing epidermal grafting [3, 4, 5] and transplantation of cultured 6 and noncultured melanocytes [2]. Controlled studies in evaluating the efficacy of postoperative therapy are, however, lacking. The present work employs [3] modalities, namely PUVA using oral or topical psoralen, or UVA alone applied after minigrafting (MG) and transplantation of noncultured melanocytes (MT). The additive post-grafting therapy was done to examine whether it has any repigmenting enhancing activity on grafted lesions compared to the control group with no further treatment.

Patients and Methods

One hundred and five patients (66 females and 39 males) completed the present study. Sixty nine patients had stable vitiligo (6 or more months since the last appearance of activity) and 36 had moderately progressive vitiligo (2-6 months since the last appearance of activity). The age of patients ranged from 10 to 50 years with a median age of 22 years. Eleven patients had localized vitiligo and 94 had generalized type. MG and MT were performed as previously described [1, 2]. Both procedures were performed on the same patient in 100 individuals, in 5 patients only MG was done due to technical reasons. A third vitiligo patch was left as a control. Four weeks prior to surgery all types of therapy were stopped. PUVA and UVA were started after 4-5 weeks of surgey to ensure healing. Patients were divided into 4 groups, designated A, B, C and D (Table. I). Group A received no treatment and served as a control to the other groups. Phototherapy and photochemotherapy for groups B, C and D were applied to both treated and control areas.

Systemic PUVA therapy was in the form of oral 8-methoxy-psoralen (8-MOP)(Neomeladinine FR 10 mg/tablet, Memphis pharmaceutical Co., Egypt) given at a dose of 0.6 mg/kg body weight two hours before UVA exposure after a fat-poor meal (2 sessions per week).

UVA rays were delivered from a computerized cabin (Waldmann 7001 cabin, Germany) that delivers ultraviolet light exclusively in the UVA range (315-400 nm, maximum 355 nm). Doses were delivered according to patient's skin type [7]. Considering patients with vitiligo as type I skin, the starting dose was 0.5 J/cm2 with weekly increments of 0.25 J/cm^2 until the appearance of painless erythema. The dose was sustained or slightly increased thereafter to maintain this effect [8]. Patients were instructed to avoid excessive sun exposure, to apply a broad spectrum sunscreen (UVA® LPF>3, UVB ® SPF>15) and to wear specialized UVA protective sunglasses during the whole treatment time. Topical PUVA therapy was in the form of 0.1% 8-MOP paint (Meladinine paint, Memphis pharmaceutical Co., Egypt, diluted with 70% alcohol). For the periorbital area, it was applied as 0.01%. Application of the paint was done 30 minutes before UVA exposures. UVA was given in a smaller dose, starting with 0.25 J/cm2 and increasing by 0.125-0.25 J/cm2 every week until the appearance of painless erythema, after which the dose was maintained [9]. UVA rays given to group D were delivered at a dose corresponding to patient's original skin type and increased by 50% every week for the whole observation period.

The total period of observation was 4 months. However, 59 patients were followed up for longer periods up to 1 year.

Success of MG and MT was judged after [4,8] and 12 months of surgery. The extent of repigmentation (surface area of repigmentation in relation to the original size of the patch) was recorded as excellent (75-100%), good (50-75%), fair (25-50%) and poor (0-25%)

Statistical Analysis

The clinical data were recorded on an investigative report form. These data were then transferred to IBM card using IBM-PC with statistical program "Microstat V2". P values of <0.5 were considered significant. I) Descriptive statistics:a) Mean (x), b) Standard deviation (SD), c) Range (min-max).

II) Analytical statistics: a) Student's t-test: to compare between 2 independent means, b) Paired t-test for follow-up study, c) Correlation matrix and coefficient of correlation By Pearsosn's method. Quantitative data were correlated against each other, d) Chi-square test for qualitative data.

Results

Three hundred and twenty seven (327) vitiligo sites in 105 patients were studied in the present work. 222 sites were surgically treated and 105 sites were left as control. Four weeks postoperatively, additive therapy was started. It was continued, even if MG or MT did not repigment, to compare the response of phototherapy to surgery in those patients. The clinical data of patients enrolled in this study are summarized in table II.

1. Response to MG and MT:

Out of 105 patients treated with MG, 69 patients (65.71%) showed positive repigmentation with an average extent of repigmentation of 77.2% (24.6. Repigmentation was excellent in 68.1%, good in 17.4%, fair in 13 % and poor in 1.5% of patients. MT was performed to 100 patients in which 73 patients (73%) showed positive repigmentation with an average extent of repigmentation of 56.3% (23.6. Repigmentation was excellent in 24.8%, good in 34.2%, fair in 34.2% and poor in 6.8% of patients. No significant difference between MG and MT in repigmentation response was observed ($p>0.05$), whereas extent of repigmentation was significantly better in MG ($p<0.05$) (Table III, Figure 1).

2. The effect of postoperative PUVA and UVA therapy on repigmentation:

The results are summarized in table IV and V. Our results showed no significant difference of repigmentation response in MG and MT between the groups A, B, C and D regardless of the type of postoperative treatment given ($p>0.05$). Similarly, in MG the extent of repigmentation was more or less similar in the 4 groups. Paradoxically, however, in MT group B (OrPUVA) showed significantly lower extent of repigmentation when compared with the other groups ($p\Omega<0.05$) (Table V, Figure 2 a&b).

3. Comparison of groups A, B, C & D in MG-treated with MT-treated patches:

On comparing MG with MT-treated areas in different groups, MG with or without additive postsurgical treatment was generally significantly better than MT-treated areas ($p<0.05$) (Table VI, Figure 3).

4 Comparison of control areas in each group:

In 105 sites, vitiligo lesions were left without surgical treatment but they received additive treatment. Control areas in groups A and D showed no evidence of repigmentation whereas in groups B and C the observed extent of repigmentation was less than surgically treated patches (Table VII). When each of the groups B and C

were compared 4, 8 and 12 months of surgery no significant difference was observed ($p>0.05$). However, when both groups were taken together after excluding patients not responding to medical treatment, a significant temporal response was observed ($p<0.001$) (Table VIII).

5 Comparing treated areas with their controls:

This comparison was made for groups B and C at 4, 8 and 12 months for patients who were followed up for one year. After 4 months, MG and MT-treated areas showed significantly higher extent of repigmentation than their control areas ($p<0.001$). The same difference was also present after 8 months for both groups, denoting a more rapid response rate with surgical procedures. After 12 months, MG treated areas showed significantly higher extent of repigmentation to their control areas ($p<0.001$). MT-treated areas were also significantly better than their control areas ($p<0.05$) (Table IXa & IX b & Figure 4a & b).

6 Effect of postopertive treatment on graft color:

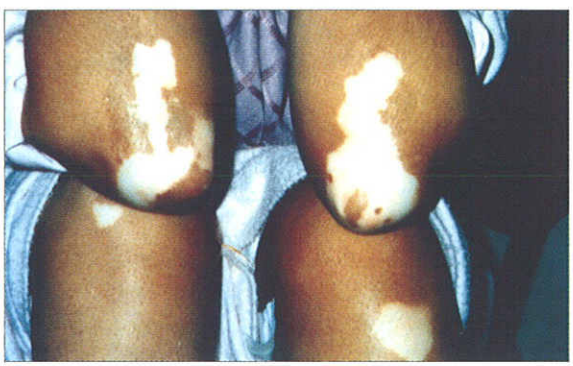
Oral and topical PUVA (groups B&C) led to a faster and better color match in both MG & MT treated patches (4-6 months) compared to those groups receiving no treatment (A) or UVA alone (D) (6-12 months) (Figure5).

Discussion

Sixty-nine out of 105 patients (65.71%) treated with MG showed positive repigmentation. The extent of repigmentation obtained in patients showing a positive response was 77.2% (24.6, indicating that most patients attained good to excellent repigmentation of the treated patches. Similarly, 73% of MT-treated patches of the same patients showed a favorable repigmentation response. This difference in response between MG and MT was, however, statistically insignificant. Nevertheless, the extent of repigmentation acquired with MT was found to be significantly lower than that attained with MG, accounting to only 56.3% (23.6 with the majority of the patients showing good to fair coverage of the vitiliginous patches.

Surprisingly, repigmentation in MG and MT was not affected by the postsurgical treatment. This may be because phototherapy was started 4-5 weeks after surgery, by which time the outcome of surgery was established. A further support of this assumption was the absence of any change in the repigmentation response 4 months after surgery. That is, areas failing to repigment remained white, and areas, which started repigmentation, continued. The only incidence when pigment developed later was in patients receiving and responding to PUVA, in which condition patients showed follicular repigmentation in surgically treated as well as control areas.

For MG-treated areas, there was a statistically insignificant difference in the extent of repigmentation between groups A, B, C & D, indicating that additive treatment did not affect the outcome of pigmentation. In MT-treated areas, group B (OrPUVA) showed a lower extent of repigmentation as compared to the other groups suggesting that OrPUVA has a detrimental effect on transplanted melanocytes. The presence of epidermis and dermis in MG may provide melanocytes with several growth factors from keratinocytes and fibroblasts under



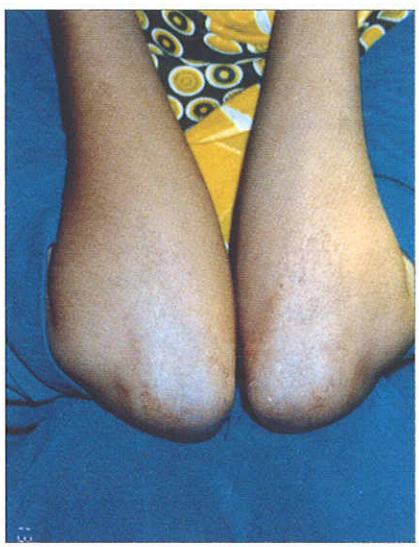


Figure 5: Patient with generalized vitiligo affecting elbows:
(i) Before treatment
(ii) After minigrafting and oral PUVA, note good color match

the effect of OrPUVA. Melanocytes in suspension are probably more vulnerable to early administration of OrPUVA. It has been shown that high doses of UVA decrease the number of melanocytes when cultured alone, while increase their number when co-cultured with keratinocytes and fibroblasts [10, 11]. Psoralens are known to intensify the effects of UVA and this may, therefore, be the cause of loss of melanocytes in MT following OrPUVA [12, 13]. Further studies are needed to examine the effect of OrPUVA when started later than 4-5 weeks, since the extent of repigmentation acquired in group B eventually improved with time.

The reason for the better results of TopPUVA compared to OrPUVA is another puzzling question. It is known that topical psoralen is more prone to produce erythema and burning. Burning leads to the production of a larger number of the toxic oxygen free radicals detrimental to melanocytes [12]. The finding encountered in here opposes this fact, and therefore suggests another as yet unknown mechanism.

In contrast to previous reports, our results showed no beneficial effect on response or extent of repigmentation with additive postsurgical phototherapy [3, 4, 5, 6]. Suga and coworkers [5] irradiated donor areas before transplantation and reported a favorable response of irradiated over non-irradiated grafts. Their method is different from ours, as we performed only postsurgical irradiation. In addition, these results were on a smaller number of patients without statistical evaluation.

Considering that both procedures were performed on the same patient, on comparing the extent of pigmentation of MG to MT in the different treatment groups, minigraft-treated areas were significantly better than MT in all groups. The difference in group B (OrPUVA) for MG to MT was highly significant, which emphasizes the detrimental effect of OrPUVA on transplanted melanocytes. In addition, comparing the group that received no treatment (group A) with each other, MG was also significantly better than MT, pointing to the superior results of MG.

On the other hand, we found a beneficial effect of PUVA on MG and MT. PUVA, but not UVA alone, helped in producing a better color match of the grafts to the surrounding skin. In the early repigmentation period a variegate or blotchy coloration was noted following either procedure, proper color match took 6-12 months to occur without postsurgical photochemotherapy (group A). In PUVA-treated groups (groups B&C), the color normalized in about 4-6 months; similar findings were mentioned by Skouge et al.3, Suga et al. [5] and Skouge & Morison [14], who observed the production of a rapid and good color match when epidermal grafting was combined with PUVA. Suga et al. 5 irradiated the skin first, then performed grafting, while Skouge et al. 3 performed PUVA 4 weeks after epidermal grafting and all reported a good color match.

Considering the control areas in different groups, the control areas of group A did not show any repigmentation. Similarly, control areas of group D (UVA) did not show any response, since UVA alone requires a long time to stimulate melanocytes in cases of vitiligo [15]. On the other hand, 76.9% of patients treated with OrPUVA and 90% of patients treated with TopPUVA showed positive follicular pigmentation in control areas. The repigmentation response is higher than that acquired with surgery, which reflects the superiority of photochemotherapy to surgery in treatment of generalized vitiligo. In general, not all patches repigment and certain anatomical sites, such as fingers, wrists and the dorsum of the feet remain resistant to PUVA and require surgical intervention [14, 16].

Follicular repigmentation in control areas appeared after an average of 8-10 sessions and then continued to increase throughout the obsrevation period. The extent of repigmentation in PUVA-treated areas increased progressively, as seen from the significant difference in the extent of pigmentation at 4, 8 and 12 months of observation ($p<0.001$). Repigmentation induced by PUVA required a longer time to develop than in surgically treated patches. The average extent of pigmentation with PUVA was significantly less than with surgical treatment, at [4, 8] and at 12 months of observation. The difference between the extent of pigmentation achieved with MG to PUVA was highly significant throughout the observation period ($p<0.001$). As for MT-treated areas, the difference was highly significant only at 4 and 8 months ($p<0.001$), but at 12 months the difference was only significant with $p<0.05$. This is probably because spread of pigment is rapid and complete early in minigrafts, total repigmentation is achieved at 4 months. This was not the case in the present study with transplanted noncultured melanocytes, since pigment spread progressively increased with time, being faster than PUVA at the beginning in comparison with the end. Interestingly repigmentation due to PUVA passed through phases of rapid repigmentation response followed by periods of no increase or plateau phases and then periods of rapid increase and so on, which may reflect the behaviour of melanocytes. Periods of rest may correspond to the time of proliferation before migration [17].

The exact mechanism by which PUVA stimulates repigmentation is not exactly known. PUVA stimulates melanocyte proliferation with increased formation and melanization of melansomes and melanin transfer to keratinocytes [18, 19]. In addition, PUVA may indirectly stimulate the release of melanocyte growth, proliferative and migratory factors, such as basic fibroblast growth factor, endothelin-1 or other unknown ones from epidermal or dermal cells [13, 20, 21].

The reason for the slower rate of pigmentation using PUVA in comparison with surgery is not clear. In surgically-treated areas, basal keratinocytes and keratinocytes in the suspension in addition to dermal fibroblasts may provide melanocytes with several mitogens during the healing process that speed-up pigmentation [6, 22, 23, 24, 25]. The distance traveled by melanocytes from the margins of MG and MT spots may be less than that traveled from the follicular reservoir, or PUVA may take time to stimulate dormant melanocytes to proliferate and migrate upwards then horizontally [26, 27, 28, 29]. Another speculation is that melanocytes transplanted from a healthy site are more capable to migrate and melanize than dormant melanocytes hair follicles that may also be exposed to some degree of melanocytotoxic products in a manner comparable to, but less than surface melanocytes in vitiligo areas.

It is concluded that oral and topical PUVA as well as UVA do not have any enhancing activity on the extent of repigmentation in MG and MT-treated patches. PUVA produced a better color match of grafted areas. A combination of surgery and photochemotherapy would thus give the best results. Surgery would cover PUVA resistant areas and therefore decrease doses of PUVA delivered to the patient. PUVA would give a better color match of grafted areas.

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Table I. Groups of patients included according to additive treatment

Group (number of patients)	Description
Group A (28 MT and MG+3MG only)	No further treatment
Group B (28 MT and MG)	Oral 8-MOP + UVA (OrPUVA)
Group C (20 MT and MG)	Topical 8-MOP + UVA (TopPUVA)
Group D (28 MT and MG + 2 MG only)	UVA alone

MG=minigrafts, MT= Noncultured melanocyte transplantation

Table II. Demographic data:

Item	Data
Age	10-50y (Median 22y)
Sex	66 females:39 males
Skin Type	III=12, IV=66, V=26, VI=1
Type of Vitiligo	94 Generalized:11 Localized
Duration of disease inactivity	2 months-15 years (1.9y (2.5)

Table III. Results of surgery

	MG	MT	Test
Repigmentation response	65.71%	73%	Chi sq. (p>0.05)
Extent of repigmentation	77.2% 24.6	56.3% 23.6	t-test (p<0.05)

MG=minigrafts, MT= Noncultured melanocyte transplantation

Table IV. Comparison of the percentage of patients repigmenting at 4 weeks and 4 months in groups A- D

Group	MG		p value	MT		p value
	4 weeks	4 months		4 weeks	4 months	
A	67.7%	67.7%	>0.05	67.9%	67.9%	>0.05
B	42.3%	42.3%	>0.05	46.2 %	46.2 %	>0.05
C	80%	80%	>0.05	92%	92%	>0.05
D	71.8%	71.8%	>0.05	91.7%	91.7%	>0.05

(Chi square test) MG=minigrafts, MT= Noncultured melanocyte transplantation

Table V. Extent of repigmentation attained in groups A-D

Procedure	A	B	C	D
MG	76.9% ± 23.6	79.5% ± 26.9	77.2% ± (24.8	76.4% ± 26.1
MT	60.8% ± 24.6	*42.5% ± 12.2	57.8% ± 19.5	58.6% ± 29

** Significantly lower ER in comparison with other MT-treated groups ($p<0.05$)*
MG=minigrafts, MT= Noncultured melanocyte transplantation

Table VI. Comparison of results of groups A-D

Group A MG: Group A MT	p<0.05
Group B MG: Group B MT	p<0.001
Group C MG: Group C MG	p<0.05
Group D MG: Group D MT	p<0.05

MG=minigrafts, MT= Noncultured melanocyte transplantation

Table VII. Response of control areas

	A	B	C	D
RR	0%	76.9%	90%	0%
ER at 4 mo.	0%	24.7% ± 14.6	27.3% ± 10.4	0%
ER at end	0%	42.9% ± 29.3	51.3% ± 21.9	0%

RR=repigmentation response, ER= extent of repigmentation, mo=month

Table VIII. Temporal response of control areas responding to Oral PUVA (B) & Topical PUVA (C)

Control B & C	ER at 4 mo	ER at 8 mo	ER at End	p value
	31.3% ±6	47.5% ±8.7	64.2%±17.3	<0.001

Student t-test. ER= extent of repigmentation

Table IXa. Comparison of MG-treated areas with their controls in groups B&C

Observ. Time	MG	*Control	t-test
4 mo.	87.3% (21.8	31.3% (6	p<0.001
8 mo.	89.5% (20.3	47.5% (8.7	p<0.001
End	90.5% (20.5	64.2% (17.3	p<0.001

**Control groups considered together and without zero values*
MG=minigrafts, MT= Noncultured melanocyte transplantation, mo-month(s)

Table IXb. Comparison of MT-treated areas to their controls (groups B&C taken together for MT and control)

Observ. Time	MT	*Control	t-test
4 mo.	61.5%(20.3	31.3%(6.1	p<0.001
8 mo.	70.0%(18.5	47.5(8.7	p<0.001
End	78.5%(19.9	64.2%(17.3	p<0.05

**Control groups considered together and without zero values*
MG=minigrafts, MT= Noncultured melanocyte transplantation

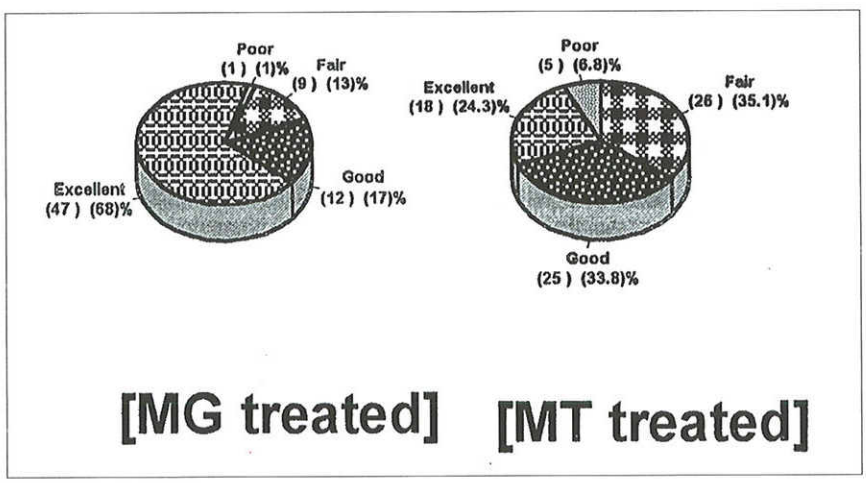

Figure 1: Extent of repigmentation achieved in both minigraft and noncultured melanocyte-treated areas

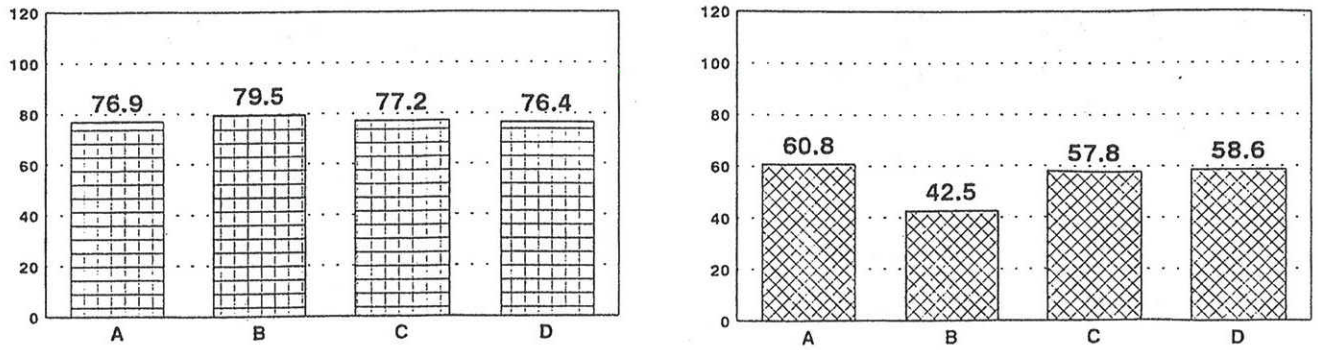

Figure 2: a) Extent of repigmentation achieved in minigraft-treated areas with additive treatment.
b) Extent of repigmentation achieved in noncultured melanocyte-treated areas with additive treatment.

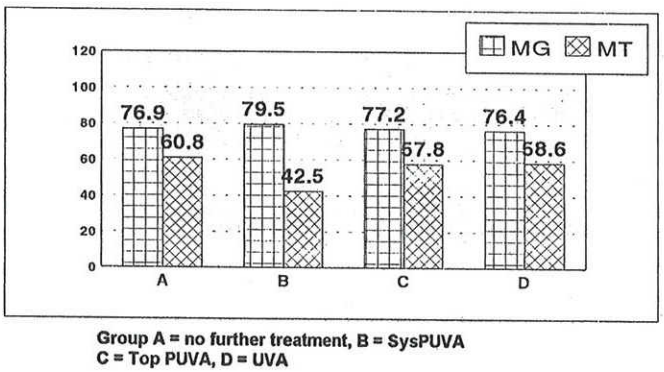

Figure 3: Comparison of the extent of repigmentation in minigraft and noncultured melanocyte-treated areas with additive treatment.

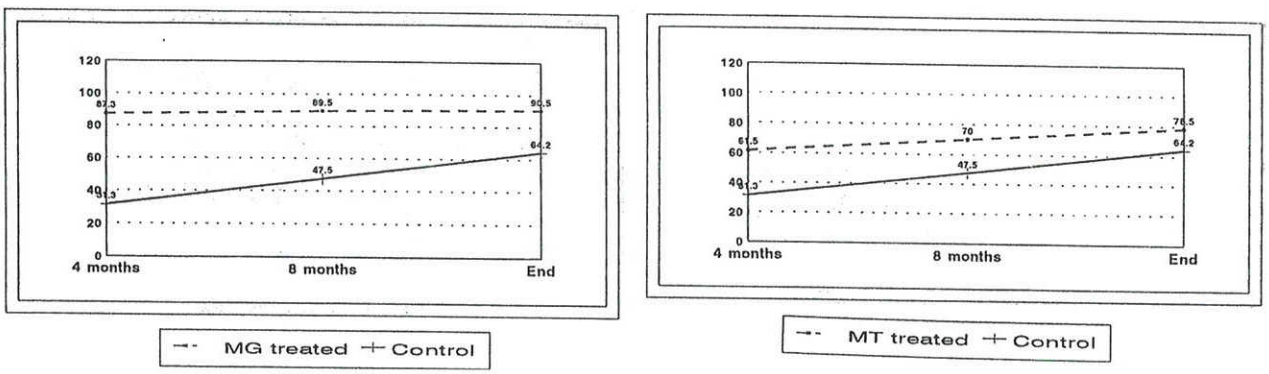

Figure 4: Follow-up study comparing: (a) MG-treated areas of groups B & C to their controls,
(b) MT-treated areas of groups B & C to their controls