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他克莫司乳膏联合治疗白癜风的疗效评价*

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摘要 目的:通过比较自体表皮移植术联合他克莫司和传统自体表皮移植术治疗白癜风的疗效,明确他克莫司乳膏对白癜风复色的影响。**方法:**回顾性分析自体表皮移植术联合他克莫司和传统自体表皮移植术治疗的稳定期白癜风患者共 90 例,比较其均匀复色时间和疗效。**结果:**表皮移植术联合他克莫司组起效时间显著性短于单一表皮移植术组($P<0.05$),1 月、3 月的显效率和痊愈率均明显高于单一表皮移植术组($P<0.05$)。单一表皮移植术组颈部的疗效相比于头面部、躯干部、四肢更佳($P<0.05$),表皮移植术联合 0.1%他克莫司软膏外用治疗(相对于单一表皮移植术)可显著性提高位于四肢的皮损的疗效($P<0.05$)。相较于单一表皮移植术而言,表皮移植术联合他克莫司对提高节段型和局限型白癜风疗效显著($P<0.05$)。然而,他克莫司联合治疗可提高散发型和肢端型白癜风的疗效,但无统计学意义($P>0.05$)。表皮移植术联合他克莫司组和单一表皮移植术组中,男性疗效均高于女性,但无显著性差异($P>0.05$)。**结论:**自体表皮移植术联合 0.1%他克莫司软膏治疗白癜风的疗效优于单一自体表皮移植术,他克莫司可有效提高白癜风复色。

关键词:白癜风;自体表皮移植术;他克莫司;复色

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Evaluation of the Clinical Efficacy of Combined Treatment with Tacrolimus for Vitiligo*

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ABSTRACT Objective: To compare the efficacy of autologous epidermal grafting combined with tacrolimus and conventional autologous epidermal grafting for vitiligo. **Methods:** The repigmentation time and efficacy of autologous epidermal grafting combined with tacrolimus group and traditional autologous epidermal grafting in total 90 stable vitiligo patients were retrospectively studied. **Results:** The epidermal transplantation combined with tacrolimus group had significantly shorter repigmentation time than the single epidermal graft group ($P<0.05$). The efficacy in the epidermal grafting combined with tacrolimus showed significantly higher at 1 month and 3 months after treatment than that of the single epidermal graft group ($P<0.05$). The efficacy in different sites are varying, of which the neck is the best; the limbs are the worst. The combination therapy of tacrolimus and autologous epidermal grafting can improve the repigmentation at the site of limbs. The efficacy of autologous epidermal grafting combined with tacrolimus was significantly higher in segmental and localized vitiligo compared with those in single autologous epidermal grafting ($P<0.05$). However, tacrolimus combination therapy can improve the efficacy of sporadic and acral vitiligo with no statistical difference ($P>0.05$). There was no significant difference in the gender between the two groups ($P>0.05$). In autologous epidermal grafting group combined with tacrolimus group and the single epidermal graft group, the efficacy in male was higher than that in female with no significant difference. **Conclusion:** Autologous epidermal grafting combined with tacrolimus is better for repigmentation than conventional autologous epidermal grafting.

Key words: Vitiligo; Autologous epidermal grafting; Tacrolimus; Repigmentation

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前言

白癜风是临床上常见的获得性色素脱失性皮肤病,以大小

不等、数目不定的色素脱失斑为典型皮损^[1]。由于白斑常好发于颈部、头面部等暴露部位,影响患者正常社交生活,患者易产生自卑感。因此,白癜风是一种身心疾病,给患者和家人带来巨大

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压力,严重降低患者的生活质量^[1,2]。

白癜风治疗方案包含局部用药、系统用药、光疗及外科手术治疗等,目前仍缺乏特效的治疗手段^[2,3]。自体表皮移植手术治疗稳定期白癜风临床疗效确切,但受吸盘限制,术后常呈现铺路石样复色,影响美观。文献报道,0.1%他克莫司软膏可促进白癜风发病中病理性T淋巴细胞凋亡,同时刺激并诱导皮损处角质形成细胞分泌多种细胞因子,并增加黑素细胞迁移及分裂,有利于复色^[4,5]。0.1%他克莫司软膏局部外用,耐受性好、副作用少,在白癜风治疗中的疗效逐渐被认可。本研究通过分析和比较单一表皮移植手术与表皮移植术联合0.1%他克莫司软膏外用治疗白癜风的疗效,旨在评价0.1%他克莫司软膏外用治疗对单一表皮移植术疗效的影响。

1 材料与方法

1.1 一般资料

纳入90例白癜风患者均来自2017年4月至2018年4月在我院白癜风治疗室接受自体表皮移植手术的稳定期白癜风患者。纳入标准:①年龄16岁至60岁,成人;②无银屑病等以他自身免疫性皮肤病;③白癜风稳定期,且稳定时间超过1年。排除标准:①<16岁或>60岁;②孕妇、哺乳期及有疤痕体质者;③白癜风进展期患者;④凝血障碍、心肺疾病、肝肾功能不全以及有其他系统性疾病患者。其中,10例局限型,22例散发型,8例肢端型,40例节段型。皮损分布部位:20例头面部,35例颈部,25例躯干部,10例四肢。90例患者中,50例男性,40例女性,年龄20-55岁,平均35岁,病程2年至20年(平均5.5年)。

1.2 实验方法

单一表皮移植手术组45例(男:女=20:25),年龄25-55岁,平均年龄32岁。他克莫司联合表皮移植术组(男:女=26:19),年龄20-60岁,平均年龄37岁。两组组间在临床分型、年龄、性别、病程及皮损部位比较无统计学差异($P>0.05$),具有良好的可比性。

本项研究中,我们对表皮移植术联合0.1%他克莫司组和单一表皮移植术组术后1月、3月皮损恢复情况进行记录和评估,以评价白癜风临床疗效。我们进一步比较分析了表皮移植术联合0.1%他克莫司组和单一表皮移植术组在不同皮损部位(面部、颈部、躯干、四肢)疗效的差异、不同临床类型白癜风的疗效是否存在差异以及性别对疗效的影响。

1.3 疗效判定标准

痊愈:移植皮片全部成活,白斑基本恢复正常;显效:被移植的白斑出现色素的面积>原白斑面积的50%;有效:被移植的白斑出现色素并(或)逐渐向外扩大;无效:未出现色素或出现色素后又消失。

1.4 统计学分析

采用SPSS20.0软件进行统计学分析,计数资料的组间比较采用 χ^2 检验,以 $P<0.05$ 表示有统计学差异。

2 结果

2.1 两组临床疗效的比较

表皮移植术联合他克莫司组起效时间显著性短于单一表皮移植术组($P<0.05$,表1),1月、3月的显效率和痊愈率明显高于单一表皮移植术组($P<0.05$,表2)(典型照片见图1)。不同部位的疗效存在差异,表皮移植在颈部有效率最高,而表皮移植术联合他克莫司可能有效提高四肢复色较差的情况,不同的临床类型疗效存在差异。

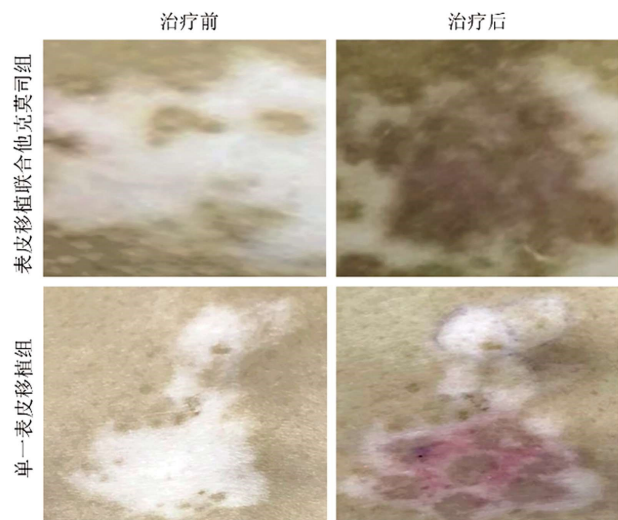


图1 表皮移植术联合他克莫司组和单一表皮移植术组疗效比较
Fig.1 Comparison of the efficacy between autologous vitiligo surgery blister grafting combined with tacrolimus and traditional autologous vitiligo surgery blister grafting

2.2 皮损部位、临床类型、性别差异对疗效的影响

表皮移植术联合他克莫司组和单一表皮移植术组针对不同部位的疗效不同。皮损发生在颈部相比于头面部、躯干部、四肢在表皮移植术联合他克莫司组中,治疗3月后相较于治疗1月后疗效显著性增加($P<0.05$,表3)。单一表皮移植术组颈部的疗效相比于头面部、躯干部、四肢更佳($P<0.05$,表3)。表皮移植术联合0.1%他克莫司软膏外用治疗(相对于单一表皮移植术)可显著性提高位于四肢的皮损的疗效($P<0.05$,表3)。

我们进一步分析不同临床类型在表皮移植术联合他克莫司组和单一表皮移植术组疗效的差异。结果显示相较于单一表皮移植术而言,表皮移植术联合他克莫司对提高节段型和局限型白癜风疗效显著($P<0.05$,表4)。然而,他克莫司联合治疗可提高散发型和肢端型白癜风的疗效,但无统计学意义($P>0.05$,

表1 表皮移植术联合他克莫司组和单一表皮移植术组起效时间比较

Table 1 Comparison of the onset time between autologous vitiligo surgery blister grafting combined with tacrolimus and traditional autologous vitiligo surgery blister grafting

Groups	Number	Onset time (weeks)
Autologous vitiligo surgery blister grafting combined with tacrolimus	45	4.02± 0.74
Traditional autologous vitiligo surgery blister grafting	45	5.25± 1.88

表 4)。

最后我们分析了性别对表皮移植术联合他克莫司组和单一表皮移植术组疗效的影响。结果显示,性别对疗效无统计学

差异($P>0.05$,表 5)。在表皮移植术联合他克莫司组和单一表皮移植术组中,男性疗效均高于女性,但无显著性差异($P>0.05$,表 5)。

表 2 表皮移植术联合他克莫司组和单一表皮移植术组术后 1 月和 3 月有效率和痊愈率的比较

Table 2 Comparison of effective rate and cure rate between autologous vitiligo surgery blister grafting combined with tacrolimus and traditional autologous vitiligo surgery blister grafting

Groups	Number	Effective rate		Cure rate	
		1 month	3 months	1 month	3 months
Autologous vitiligo surgery blister grafting combined with tacrolimus	45	55.6%	77.8%	35.6%	53.3%
Traditional autologous vitiligo surgery blister grafting	45	51.1%	66.7%	33.3%	44.4%

表 3 不同部位的疗效比较

Table 3 Comparison of the efficacy between different lesion sites of repigmentation

Lesion site	Autologous vitiligo surgery blister grafting combined with tacrolimus		Traditional autologous vitiligo surgery blister grafting	
	1 month	3 months	1 month	3 months
Face	55.0%	70.0%	45.0%	65.0%
Neck	65.7%	85.7%	57.1%	77.1%
Trunk	44.0%	68.0%	40.0%	60.0%
Limb	30.0%	50.0%	20.0%	30.0%

表 4 不同临床分型的疗效比较

Table 4 The effect of different clinical types of vitiligo on the efficacy of therapy

Clinical types	Autologous vitiligo surgery blister grafting combined with tacrolimus		Traditional autologous vitiligo surgery blister grafting	
	1 month	3 months	1 month	3 months
Localized	50.0%	80.0%	40.0%	60.0%
Generalised	40.0%	70.0%	41.6%	66.6%
Acrofacial	25.0%	50.0%	25.0%	50.0%
Segmental	60.0%	87.5%	55%	75.0%

表 5 性别对疗效的影响

Table 5 The effect of gender(male/female) on the efficacy of therapy

Gender	autologous vitiligo surgery blister grafting combined with tacrolimus		traditional autologous vitiligo surgery blister grafting	
	1 month	3 months	1 month	3 months
Male	53.8%	76.9%	50.0%	70.0%
Female	52.6%	73.7%	48.0%	64.0%

3 讨论

白癜风是由于皮肤黑素细胞缺失引起,以进行性皮肤色素脱失为特征的自身免疫性疾病,以大小不等、数目不定的色素脱失斑为典型皮损^[6,7]。全球患病率约为 0.1%-2.9%,白癜风给患者带来沉重的经济和精神负担,影响正常社交生活^[6,8]。自身免疫、遗传因素、氧化应激、感染等共同参与了白癜风发病,其中自身免疫是参与白癜风白斑发生的主要原因^[3,9,10]。自体表皮移植术适用于治疗小面积白癜风患者,疗效确切^[11-13]。然而,自

体表皮移植术易复色不均匀,影响美观;并且单一采用自体表皮移植术复色时间较慢。为提高表皮移植的均匀复色率和缩短复色时间,联合其他治疗值得尝试和研究。本研究通过比较单一自体表皮移植术和自体表皮移植术联合 0.1% 他克莫司软膏外用治疗疗效的差异,探讨联合治疗是否更有优势和临床价值。

他克莫司是一种免疫抑制药物,既往主要用于降低同种异体器官移植后的器官排斥风险^[14]。通过减少 IL-2 的产生从而抑制 T 细胞发育和增殖^[15]。他克莫司还用于治疗其他 T 细胞介导的疾病,如他克莫司的外用剂型可用于治疗湿疹和白癜风^[16]。

0.1%他克莫司软膏通过促进角质形成细胞细胞因子的合成和分泌,促进黑素细胞及黑素干细胞增殖,并促进黑素细胞迁移^[4,17]。他克莫司穿透细胞膜进入细胞后,与他克莫司结合蛋白(FKBP12)相结合,从而蓄积于细胞质内,产生效用。FKBP12-他克莫司结合物,特异性降低钙调磷酸酶的活性,从而抑制T细胞中钙离子依赖型信号激活,最终抑制T细胞增殖和活化^[4,18]。另一方面,他克莫司分子量小,故局部外用渗透性较好,容易被白癜风皮损吸收,促进色素恢复^[4]。文献报道他克莫司乳膏适用于白癜风治疗,复色均匀^[19-21]。一项纳入57例儿童白癜风的研究表明他克莫司软膏在89%的患者的头部和颈部,63%的患者的躯干和四肢有效果,其中面部白癜风的效果最佳^[22]。本研究采用自体表皮移植术后联合他克莫司乳膏治疗稳定期白癜风患者,结果发现联合治疗组在术后3月的有效率和痊愈率分别为77.8%和53.3%,明显高于单一治疗组。并且联合运用0.1%他克莫司软膏外用缩短起效时间,提示他克莫司乳膏参与白癜风自体表皮移植术后色素扩展融合。国外研究报道他克莫司联合表皮移植术可降低术后复色后色素脱失^[23]。一项纳入110名白癜风患者的他克莫司联合NB-UVB的研究,42%出现临床可见的复色,复色效果在不同部位不同,面部效果最佳,其次是四肢和躯干。肢端和生殖部位效果差^[12,24]。治疗耐受良好自体表皮移植术结合0.1%他克莫司软膏局部外用治疗,能缩短复色时间,并且促进色素融合,使复色均匀。

白癜风一般分为非节段型和节段型两种类型^[25]。相较非节段型而言,节段型白癜风有其特殊的临床表现和自然病程:一般分布于躯体的单侧,不超过中线;发病比非节段型更早,并在快速进展后进入长期的稳定期^[26]。目前研究认为节段型白癜风,相比于其他类型白癜风病情稳定,更适合表皮移植手术治疗,并且不易复发^[27,28]。本次研究结果显示0.1%他克莫司软膏局部外用结合表皮移植术对节段型白癜风,相比于局限型、散发型、肢端型更有效。自体表皮移植术对不同部位白斑效果不同,有研究报道指出头面部复色效果较其他部位佳^[29]。本次研究发现,头颈部皮损,相比于四肢和躯干白斑,特别是手足部位白斑,0.1%他克莫司软膏联合自体表皮移植术的疗效更佳。报道指出自体表皮移植术对男性和女性疗效相似^[30]。本次研究表明无论男性女性对0.1%他克莫司软膏外用联合自体表皮移植术效果无差异,提示性别对疗效无影响。

综上所述,相比于单一的自体表皮移植术,0.1%他克莫司软膏外用联合自体表皮移植术治疗稳定期白癜风的效果更佳。

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