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臭氧油外用治疗寻常型银屑病的临床疗效

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[摘要] 目的：比较臭氧油和复方氟米松软膏外用治疗寻常型银屑病的临床疗效和安全性。方法：采用自身对照临床试验。收集40例皮损面积<30%体表面积的稳定期寻常型银屑病患者，均有左右侧躯干、四肢对称皮损。试验组选患者左侧皮损每日外用臭氧油两次，对照组选右侧皮损每日外用复方氟米松软膏两次，疗程4周。于用药后第1，2，4周观察临床疗效及安全性。结果：治疗后1周，试验组与对照组有效率分别为60.58%和72.28%，差异有统计学意义($P<0.05$)。治疗后2周，试验组与对照组有效率分别为69.84%和70.25%，第4周为70.88%和71.23%，差异均无统计学意义($P>0.05$)。试验组和对照组治疗4周后皮肤反射式共聚焦显微镜结果均显示：表皮大致正常，真皮乳头少许炎细胞浸润，炎症细胞浸润程度较治疗前明显减轻。结论：臭氧油治疗稳定期寻常型银屑病安全有效，疗效与中效糖皮质激素外用制剂相当。

[关键词] 银屑病；臭氧油；复方氟米松；临床疗效

Clinical efficacy of ozonated oil in the treatment of psoriasis vulgaris

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ABSTRACT

Objective: To compare the efficacy and safety between ozonated oil and compound flumethasone ointment in the treatment of psoriasis vulgaris.

Methods: A left/right self-controlled, parallel group study was conducted. Forty patients with stable psoriasis vulgaris were enrolled in the study, whose lesions were symmetrical and involvement areas were <30% body surface. The patients were divided into 2 groups. Patients with left lesions served as a test group were treated daily for ozonated oil twice, and patients with right lesions served as a control group were treated daily for compound flumetasone ointment twice. The

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patients in the 2 groups were treated for 4 weeks. The clinical efficacy and safety were observed at 1, 2 and 4 weeks after the treatment.

Results: After 1 week treatment, the effective rates of the test group and the control group were 60.58% and 72.28%, respectively, with significant difference between them ($P<0.05$). At 2 weeks and 4 weeks after the treatment, the efficacy in the test group was similar to that in the control group. The effective rates in the test group and the control group were 69.84% and 70.25% after 2 weeks, respectively, 70.88% and 71.23% after 4 weeks, respectively. There was no significant difference between the 2 groups ($P<0.05$). In addition, the reflectance confocal microscope results in both the test group and the control group after 4 weeks showed that the epidermis was approximately normal. There were few inflammatory cells infiltration in the dermal papilla, and the inflammatory cells infiltration was significantly reduced after treatment.

Conclusion: Ozonated oil treatment for stable psoriasis is safe and effective, and its efficacy is equivalent to the effect of glucocorticoid topical preparations.

KEY WORDS

psoriasis; ozonated oil; compound flumethasone; clinical efficacy

外用药疗法是治疗局限性寻常型银屑病的主要手段之一，糖皮质激素外用治疗寻常型银屑病具有起效快、疗效好的特点^[1]，但长期使用可能出现皮肤萎缩、毛细血管扩张、紫癜、多毛、毛囊炎等不良反应^[2]。臭氧(O_3)是由3个氧原子组成的有强氧化力的分子。臭氧具有抗感染、加速血液代谢、抗炎症^[3]及免疫调节作用^[4]，可广泛应用于如特应性皮炎、感染伤口、循环障碍、风湿、肿瘤、重症急性呼吸综合征(severe acute respiratory syndromes, SARS)和获得性免疫缺乏综合征(acquired immune deficiency syndrome, AIDS)等的治疗^[5-6]。但臭氧常温下可自行分解为氧，需将臭氧溶解在植物油中制成臭氧油才可方便使用，本研究以复方氟米松软膏为对照，探讨臭氧油治疗稳定期局限性寻常型银屑病患者的临床疗效和安全性。

1 资料与方法

1.1 临床资料

收集2016年4月至2017年4月在中南大学湘雅三医院门诊就诊的银屑病患者40例，其中男22例，女18例。年龄19~68(42.6±12.5)岁，病程5~36(11.6±9.3)个月。入选标准：年龄18周岁或以上；符合寻常型银屑病(稳定期)临床诊断标准，皮损面积占全身体表面积<30%；身体左右侧皮损分布对称且四肢有皮损的患者。排除标准：1)当前诊断为点滴型、脓疱型、红皮病型活动性银屑病患者；2)皮损面积占全身体表面积>30%者或银屑病病情严重需系统治疗者；3)皮损局部并发细菌、病毒、真菌或寄生虫感染者；4)已知

或怀疑对研究药物的成分超敏；5)已知或怀疑肾功能不全或肝疾病或重度心脏病；6)有神经精神疾病及严重内分泌疾病患者；7)治疗前4周内系统治疗或治疗前2周内局部应用糖皮质激素或其他治疗银屑病药物者；8)研究期间妊娠或具有生育能力并希望妊娠的女性，或处于哺乳期的女性。患者自愿参加，并签署知情同意书。

1.2 方法

1.2.1 治疗方法

采用自身对照试验，将患者左侧皮损选为试验组，右侧皮损选为对照组。试验组每天早晚2次外用臭氧油(商品名海费油，15 mL/瓶，湖南海费医疗科技有限公司赠送)。对照侧每天早晚2次外用复方氟米松软膏(15 g/支，含氟米松0.2 mg/g，澳美制药厂生产，购自中南大学湘雅三医院药房)，疗程均为4周。

1.2.2 疗效与安全性分析

根据患者治疗部位皮损的面积(A)、红斑(R)、浸润(T)、鳞屑(S)的轻重程度进行疾病严重程度指数(psoriasis area and severity index, PASI)评分。采用矫正PASI评分法，分别计算上肢(u)、躯干(t)、下肢(l)对称受测部位的皮损面积，红斑、浸润和鳞屑的程度(0为无、1为轻、2为中、3为重、4为特重)，并用受累的区域系数(上肢0.2、躯干0.3、下肢0.4)加以校正后，得到每个受损区域的总分，公式为 $PASI=0.2(R_u+T_u+S_u)A_u+0.3(R_t+T_t+S_t)A_t+0.4(R_l+T_l+S_l)A_l$ 。于治疗前和治疗后1, 2, 4周进行PASI评分，并比较患者对称部位治疗1, 2, 4周后靶皮损PASI百分比下降值。对治疗4周后PASI评分较基线下降≥

50%, ≥75%和≥90%的患者进行频数分析, 以治疗后PASI评分下降≥75%为有效。同时用皮肤反射式共聚焦显微镜(reflectance confocal microscope, RCM)观察靶部位皮损治疗前后的变化。

1.2.3 不良反应观察

观察并记录试验期间发生的不良反应, 包括局部治疗后出现的药物不良反应, 如红斑、皮肤萎缩、毛细血管扩张、色素改变、毛囊炎等刺激症状、过敏症状及全身症状和体征。

1.3 统计学处理

采用SPSS 17.0统计软件进行分析, 计量资料用均数±标准差($\bar{x} \pm s$)表示, 两组不同时间点的资料采用重复测量方差分析, 两组治疗4周后PASI评分较基线下降≥50%, ≥75%, ≥90%患者频数比较, 采用 χ^2 检

验, 以 $P < 0.05$ 为差异有统计学意义。

2 结 果

2.1 临床疗效

部分患者治疗前上肢、外阴、股内侧、额部等部位均有较对称分布的明显红斑、斑块、浸润、鳞屑等表现, 治疗4周后, 试验侧和对照侧红斑、斑块、浸润、鳞屑均基本消退, 部分留有色素沉着(图1~3)。部分患者治疗前RCM示: 皮损区棘层肥厚, 真皮乳头顶部、血管周围炎细胞浸润, Munro微脓肿或海绵状脓疱形成。治疗4周后试验侧及对照侧RCM示: 皮损区表皮大致正常, 真皮乳头少许炎症细胞浸润, 较治疗前浸润明显减轻(图4~6)。

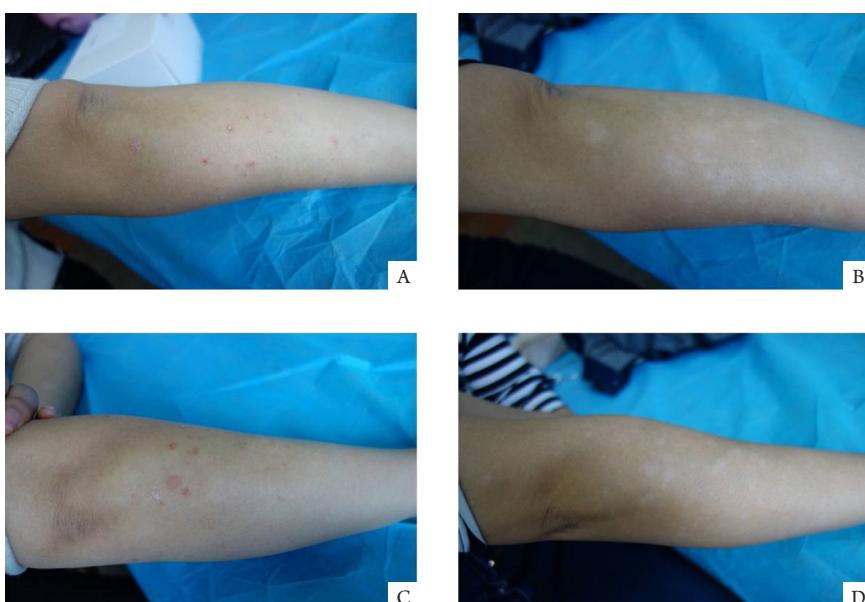


图1 治疗4周前后上肢皮损变化

Figure 1 Changes of upper limb lesions before and after 4-week treatment

A: Left upper limb before the treatment; B: Left upper limb after the treatment; C: Right upper limb before the treatment; D: Right upper limb after the treatment

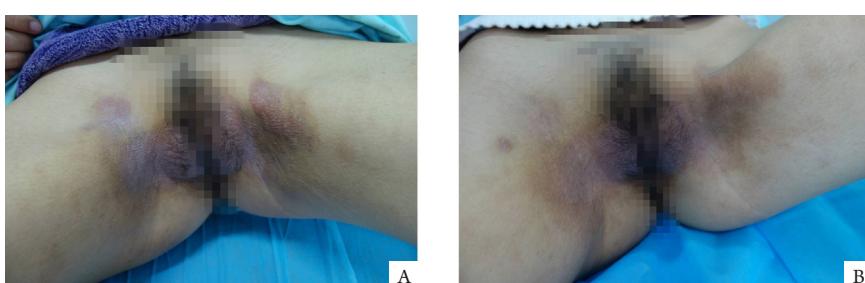


图2 治疗4周前后外阴和股内侧皮损变化

Figure 2 Changes of genital and inner thigh lesions before and after 4-week treatment

A: Before the treatment; B: After the treatment

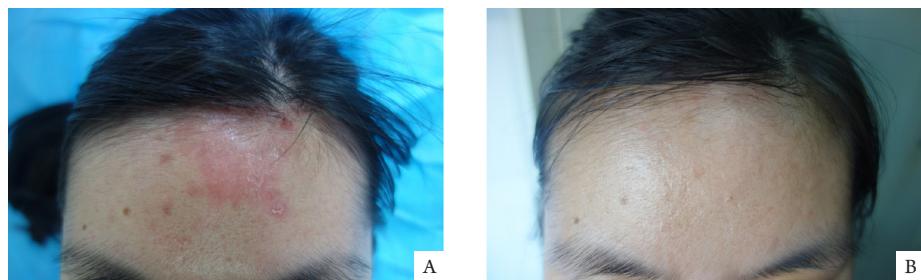


图3 治疗4周前后额部皮损变化

Figure 3 Changes of forehead lesions before and after 4-week treatment

A: Before the treatment; B: After the treatment

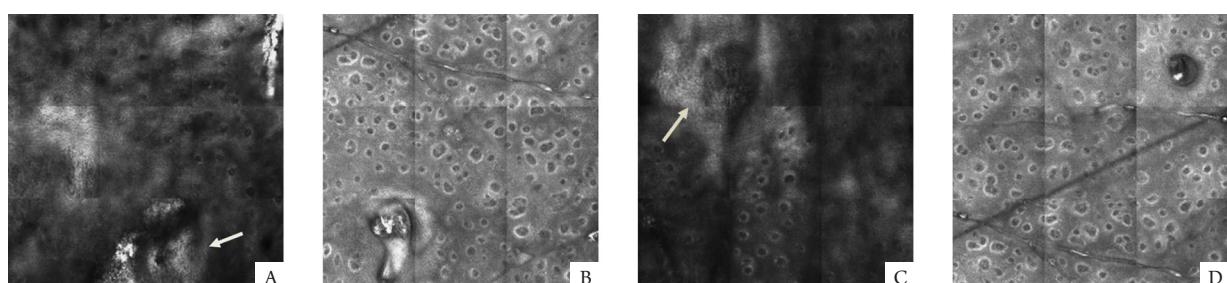


图4 治疗4周前后上肢RCM变化

Figure 4 RCM showing changes of upper limb before and after 4-week treatment

A: Left upper limb before the treatment; B: Left upper limb after the treatment; C: Right upper limb before the treatment; D: Right upper limb after the treatment

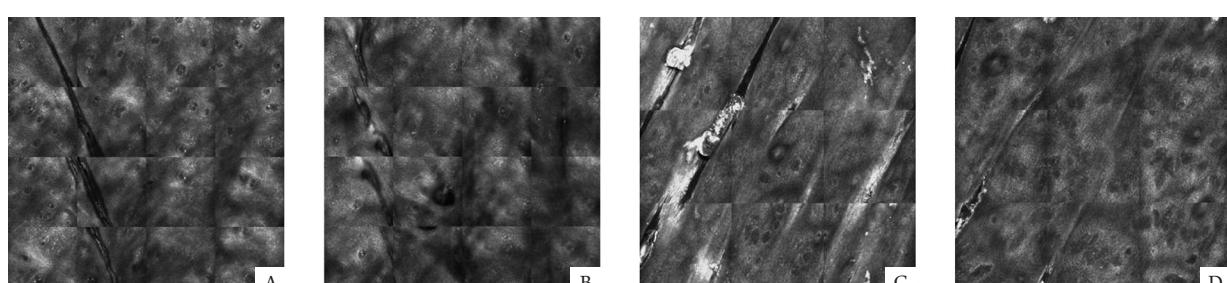


图5 治疗4周前后股内侧RCM变化

Figure 5 RCM showing changes of inner thigh before and after 4-week treatment

A: Left inner thigh before the treatment; B: Right inner thigh before the treatment; C: Left inner thigh after the treatment; D: Right inner thigh after the treatment

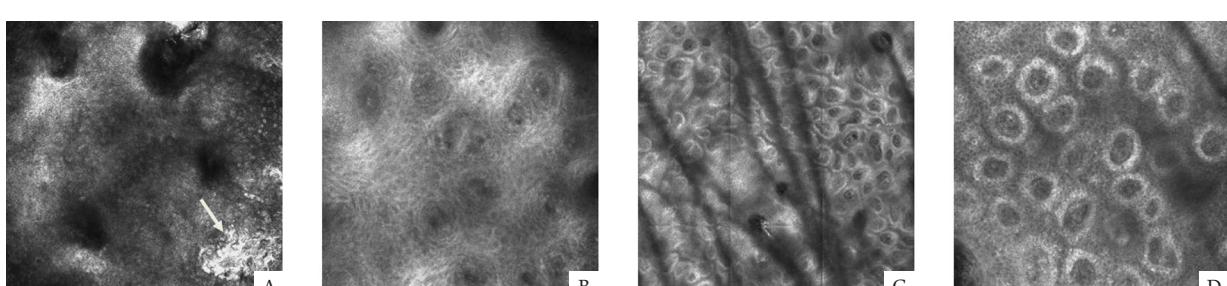


图6 治疗4周前后额部RCM变化

Figure 6 RCM showing changes of forehead RCM before and after 4-week treatment

A: Left forehead before the treatment; B: Right forehead before the treatment; C: Left forehead after the treatment; D: Right forehead after the treatment

2.1.1 PASI 评分改善情况

40例均完成了4周的观察和评价。试验组在治疗第1周末PASI评分的百分比下降值低于对照组($P<0.05$)；治疗第2周、第4周末两组的PASI百分比下降值比较，差异无统计学意义($P>0.05$ ，表1)。

2.1.2 治疗后有效率比较

治疗后1周，试验组与对照组有效率分别为60.58%和72.28%，差异有统计学意义($P<0.05$)。治

疗后2周，试验组与对照组有效率分别为69.84%和70.25%，第4周为70.88%和71.23%，差异均无统计学意义($P>0.05$)。

试验组治疗4周后PASI评分较基线下降 $\geq 50\%$ ， $\geq 75\%$ 和 $\geq 90\%$ 的患者频数分别为37，30，12人，对照组分别为38，31，12人，2组差异无统计学意义($P>0.05$)。

表1 两组治疗后PASI评分较基线百分比下降值的比较(n=40, $\bar{x}\pm s$, %)

Table 1 Comparison of the decline percentage of PASI score after the treatment compared to the baseline in the 2 groups (n=40, $\bar{x}\pm s$, %)

组别	治疗1周末	治疗2周末	治疗4周末
试验组	26.89±15.32*	48.58±18.27	74.29±18.22
对照组	40.57±18.23	50.26±17.19	75.39±17.78

与对照组比较，* $P<0.05$

2.2 不良反应

试验组有2例发生瘙痒，3例发生色素减退，对照组3例发生毛囊炎，5例发生色素减退，停用药物后缓解。所有受试者均无严重不良事件发生。

3 讨论

本研究结果显示治疗后1周，臭氧油与复方氟米松有效率分别为60.58%和72.28%，差异有统计学意义($P<0.05$)。臭氧油起效较复方氟米松软膏慢，考虑与复方氟米松软膏为糖皮质激素药物，具有起效迅速的特点相关。而治疗2周后，两组有效率分别为69.84%和70.25%，4周后分别为70.88%和71.23%，差异均无统计学意义($P>0.05$)，表明臭氧油治疗银屑病与复方氟米松软膏疗效相近。经臭氧油和复方氟米松软膏药物治疗4周后RCM结果均显示：表皮大致正常，真皮乳头少许炎细胞浸润。RCM观察到炎症细胞浸润程度较治疗前明显减轻，提示臭氧油与糖皮质激素一样具有抗炎作用。且试验组仅2例出现用药物后瘙痒的局部刺激反应，无严重不良事件发生，用药相对安全。

银屑病是多种免疫细胞共同参与的慢性复发性炎症性皮肤病，其病因及发病机制复杂，但其核心是免疫功能异常，以T细胞为主的免疫功能紊乱在疾病的发生发展中起重要作用。以往的研究^[7]证实银屑病发病中存在Th1/Th2的细胞平衡失调，近年来研究^[8]发现Th17与Treg细胞在银屑病的发病中同样起重要作用。研究^[9]表明：Treg细胞功能障碍将导致其抑制功能降低，从而导致银屑病的发生。此外，临床证据

还证明银屑病的发生与感染密切相关。大量临床资料^[10-11]显示细菌能够激发银屑病，银屑病患者皮肤有金黄色葡萄菌的寄居，且其发病和加剧与链球菌感染有关。

臭氧已广泛应用于特应性皮炎、感染伤口、循环障碍、黄斑变性、风湿、肿瘤、SARS和AIDS等疾病的治疗。研究^[5]还发现臭氧具有免疫调节的作用：臭氧可以诱导IL-10，TGF-β等的释放。IL-10，TGF-β是免疫抑制性细胞因子，主要为Treg细胞分泌。IL-10和TGF-β对Th1和Th2都有抑制作用。本研究观察到臭氧油治疗银屑病有效，且RCM示炎症细胞浸润程度较治疗前明显减轻，推测臭氧油用于治疗银屑病机制之一可能为臭氧诱导Treg细胞分泌免疫抑制细胞因子IL-10，TGF-β等相关，且与臭氧抗感染、抗炎作用密切相关。

本研究采用了自身左右对照的方法，可以排除年龄、性别、病期等个体差异的影响所造成的统计学误差。本研究发现臭氧油治疗银屑病效果较好，不良反应小，用药方便；但样本量较小，尚需要更大样本量的双盲平行对照的临床研究来证实。

利益冲突声明：作者声称无任何利益冲突。

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