

复方苔藓片对实验性口腔白斑癌变影响的初步研究

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摘要 应用仓鼠颊囊癌动物模型系统观察活血化瘀中药复方苔藓片对口腔白斑癌变的影响。结果表明：实验组与肿瘤对照组比较，9周时恶变率降低，12周时肿瘤体积明显减小($P < 0.01$)；组织学检查发现9周时实验组动物病变上皮及固有层有大量炎性细胞呈灶性浸润，而肿瘤对照组则仅见少许炎性细胞。12周时这两组动物颊囊病变呈高分化鳞癌，但所有动物颈淋巴结及脏器(肺、肝、脾等)检查无异常发现。实验表明复方苔藓片具有抑制白斑癌变的作用。

关键词 复方苔藓片 口腔白斑 癌变 抑制作用 7,12-二甲基苯并蒽

复方苔藓片是华西医科大学口腔医学院研制的以活血化瘀为主的复方中药制剂，临床上用于治疗口腔白斑和扁平苔藓有较好的效果。口腔白斑和扁平苔藓具有恶变倾向¹。关于活血化瘀中药抗肿瘤作用尚有争论，大多数研究认为有抗肿瘤作用，少数研究发现可促进移植瘤的转移²。为探讨复方苔藓片对口腔癌前病变恶变的影响；并评价其临床应用的安全性，作者利用仓鼠颊囊癌模型系统对此进行初步研究。

1 材料和方法

1.1 实验动物及分组

80只，6~8周龄，75~90g，雌雄各半的叙利亚仓鼠(成都生物制品研究所提供)。随机分为4组，每组20只，第I组为实验组，第II组为肿瘤对照组，第III组为复方苔藓片组，第IV组为空白对照组。饲以华西医科大学动物中心提供的小鼠颗粒料，不喂水，每日给青菜补充水分，雌雄分开分笼饲养，每笼1~2只，温度18~24℃，相对湿度50% (由华西医科大学口腔医学研究所动物实验室提供实验场所)。

1.2 实验药品

7,12-二甲基苯并蒽(DMBA)，为美国Sigma公司产品，用分析纯丙酮配成0.5% (W/V)溶液，避光密封保存。复方苔藓片(主要含川芎、丹参、赤芍、鸡血藤等)，由四川广汉制药厂生产。批号：920617，每片0.3g，每次用前与蒸馏水配成混悬液。

1.3 实验方法

致癌剂涂抹 将动物固定于自制的鼠夹上，牵开颊囊，用四号油画笔蘸DMBA溶液，在瓶口挤掉多余药液，在预先确定的I、II组动物右侧颊囊中央靠近前静脉处的涂抹

范围内做圆周运动，约4~5次，空气吹干，每周3次。

中药灌喂 涂DMBA的第二天开始，I、III组动物每日上午用自制灌喂器，每只动物灌喂复方苔藓片混悬液1.5ml(相当于片剂0.45g)，给药前后2h禁食，直至实验结束。

1.4 观察指标

每日检查动物的活动，毛色，进食及涂药区颊囊色形质改变。每周称重1次，记录肿瘤出现时间。

9周末每组随机处死10只动物，12周末全部处死余下动物，记录肿瘤大小(长、宽、高以mm计算)。切取右侧病变颊囊粘膜和颈淋巴结、肝、肺、脾、肾进行常规组织学评价。将9周时恶变率，12周时肿瘤体积 $V = 4/3 \pi r^3$ ， $r = (长 + 宽 + 高) \times 1/6 \text{ mm}^3$ ，进行统计学分析。

2 结果

2.1 大体观察结果

I和II组各有1只动物6周前死亡，排除观察。各组动物毛色、进食及活动差异不大。12周时I、III、IV组体重接近，II组下降。9周末，I组动物右侧颊囊致癌区呈白色斑块及散在粟粒大小的突起。II组动物颊囊致癌区白斑增厚明显，有4只动物出现1~3个1~4mm乳头状瘤。12周时I、II组动物颊囊诱癌区均见外生型肿瘤，表面出血或坏死不明显。III、IV组动物颊囊外观正常。

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2.2 组织学观察

9周观察结果 I组:3只动物致癌区呈重度异常增生,7只为单纯增生或轻、中度异常增生,6只(包括3只重度异常增生)上皮及固有层见大量炎性细胞呈灶性浸润。II组:致癌区2只为轻或中度异常增生,8只为重度异常增生或原位癌,早期浸润癌,上皮及固有层炎性细胞较少。I组恶变率(组织学出现重度异常增生、原位癌或早期浸润癌)为30%,II组为80%,两组间有统计学差异($P < 0.01$)。

12周观察结果 I、II组致癌区呈高分化鳞癌,两组癌灶周围炎性细胞浸润程度差异不大。颈淋巴结、肝、肺、脾、肾未见组织学异常变化。III、IV组动物颊囊组织学正常。I、II两组12周肿瘤体积比较见表1。

表1 12周时各组肿瘤体积比较(mm³)

组别	动物数	平均肿瘤体积	总肿瘤体积
I	9	44.60	1427.75 ± 208.77
II	9	60.50	2142.90 ± 360.58
III	10	0	0
IV	10	0	0

注: I、II组间总体积比较(*t*检验) $P < 0.01$

上表显示 I组较 II组肿瘤体积明显减小。

3 讨论

中医理论认为血瘀是肿瘤形成的主要原因之一,见于病程的各个阶段;临床及动物实验也证明恶性肿瘤发生后,体内存在血液流变学及微循环障碍,通过活血化瘀或抗凝治疗,可延长生命或抑制肿瘤生长^{3,4}。研究发现活血化瘀中药单味或复方制剂可抑制移植瘤生长,防止肿瘤复发和转移作用,但也有人³认为赤芍、丹参等可促进小鼠Lew is

肺癌和静脉注入的W 256癌细胞扩散。

仓鼠颊囊癌模型系统自然状态下,肿瘤转移十分罕见,利用该系统,不仅可进行食物或药物是否有促癌或抑癌作用的观察,而且可观察是否可促进癌的转移。本研究用模拟人体口腔癌发生的实验系统,初步证实中药复方苔藓片具有抑制口腔白斑癌变的作用。

复方苔藓片是由丹参、赤芍、川芎、鸡血藤等组成,临床上主要用于治疗瘀血型口腔白斑和扁平苔藓,对其药理作用研究⁵表明具有改善循环,纠正血液流变学异常,诱导干扰素合成和抗自由基损伤作用。本实验表明还具有诱导局部免疫反应的作用,而局部免疫反应增强被认为是机体对肿瘤排斥反应增加的表现。但口腔癌发生是一个复杂过程,故复方苔藓片抑制白斑癌变的机制,尚有待进一步探讨。

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Effect of Taixian Tablet on Hamster Buccal Pouch Carcinogenesis

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Abstract

Eighty syrian hamsters were divided into 4 equal groups. The right buccal pouches of hamsters in group I and group II were painted three times weekly with 0.5% DMBA dissolved in acetone, but the hamsters in group I received 0.45g Taixian tablet daily by mouth. The animals in group III only received 0.45g Taixian tablet daily and group IV was control group. After 9, 12 weeks, animals were killed with their pouches excised, and tumors were counted and measured.

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期进行矫治会影响牙齿移动过程中的组织变化,因此怀孕期间不宜作矫治。

但作者通过上述实验,仅从孕酮对牙周组织及牙移动的影响来看,尚不能完全同意以上观点。反之,本研究显示,妊娠期牙移动后成骨活跃,新生骨增加,有利于牙齿的移动。

(本文图 2~ 4 见中心插页 6)

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Effects of Pregnancy on Orthodontic Tooth Movements: Effects of Progesterone on Orthodontic Tooth Movements in Pregnant Rats

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Abstract

This study evaluated the periodontal responses and progesterone changes to orthodontic tooth movements in pregnant rats. Adult female Sprague-Dawley rats were separated into two groups: non-pregnant and pregnant. All rats were treated with fixed orthodontic appliances that moved the upper incisors in a distal direction during 10 days. At the end of the experiment, the periodontal tissues were examined histologically and immunohistochemically (ABC method). The results showed that in the histological examination of the tension sides of the upper incisors, the bone formation was more obvious in the pregnant group than that in the non-pregnant group. In the immunohistochemical staining, the osteoblasts were positive-stained cells and they exhibited deeper stain and higher percentage in the pregnant group. In a conclusion, the progesterone influences the periodontal reconstruction on orthodontic tooth movements in pregnant rats and may be helpful in alveolar bone formation, which suggests that orthodontic treatments in pregnant patients may not be so harmful as people thought before.

Key words: pregnancy teeth movement immunohistochemical ABC method progesterone

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The results showed: Comparing with group II, the malignant rate of group I was lower after 9 weeks and the tumor volume was smaller after 12 weeks ($P < 0.01$); It was found histologically many inflammatory cells locating in the epithelial layer and lamina propria of group I after 9 weeks, while only a few inflammatory cells in group II. The high differentiated squamous cell carcinoma could be seen in group I and group II after 12 weeks, but no abnormal changes in cervical lymph nodes and organs (lung, liver, spleen, et al) of all animals in 4 groups. It suggests that Taixian tablet can restrain the development of oral carcinogenesis.

Key words: Taixian tablet leukoplakia carcinogenesis anticarcinogen DMBA