

棉酚治疗功能性子宫出血等病的 临床观察和实验研究

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内容提要 用棉酚治疗功能性子宫出血、子宫内膜异位症及子宫肌瘤共192例，收到较好疗效。观察了不同累积量棉酚对雌性大鼠的性生殖轴和生命重要器官的组织形态影响，及对性腺轴的内源性阿片肽和激素水平的影响。结果提示棉酚有兴奋和抑制的双相作用，且与累积量明显相关。适当使用或可作为诱导排卵、更年期人工绝经和治疗中度高泌乳素血症的药物。

1981年起我们用棉酚治疗功能性子宫出血（功血）子宫内膜异位症（异位症）和子宫肌瘤（肌瘤），取得较好效果，并对其机理进行了较系统性研究，分别介绍如下。

临 床 观 察

一 治疗对象：192例均来源于妇科内分泌门诊，年龄25~69岁，40岁以上者128例，占67%，6例已绝经。192例中功血117例，异位症31例，肌瘤44例。141例在治疗前作内膜活检，93例治疗结束时重复检查。病理改变属无排卵型功血表现为良性者48例；癌前期者11例（包括乳头状、腺瘤样和不典型增生）；另有3例绝经后内膜乳头状增生病例，因手术禁忌症接受棉酚治疗。

二、方法：每日口服醋酸棉酚（西安油脂化工厂生产，每片20mg）1片及10%枸橼酸钾30ml分三次服。40~60天后酌情原量或减量或停药。随访3~70个月。

三、结果

1 功血：117例中显效108例（92.3%）。（1）有排卵型功血28例。18例服药后闭经，内膜萎缩；6例出血减少；4例无效。（2）无排卵型功血83例。14例服药累积量达400~1200mg时，月经正常有排卵；10例出血减少；药量大于1200mg时，54例闭经，内膜萎缩；5例无效。（3）绝经后出血6例，服药2个月后内膜萎

缩，迄今5例健在，1例死于心肌梗塞。

2. 异位症：31例均于服药3个月左右闭经。其中14例5~8个月自然复经，痛经减轻；16例9个月后复经，无痛经；另1例服药2周发现受孕。局部包块基本消失者14例，明显缩小者13例，无变化3例。其中1例闭经9个月复经，半年后受孕并足月分娩。

3. 肌瘤：44例累积药量均>1200mg，显效35例，肌瘤明显缩小；8例无变化；1例反而增大（手术证实为恶变）。所有病例治疗前子宫均相当于孕2½月大小。随访显效的35例中，11例绝经 子宫正常大小；24例又回复原来大小。

4 用药后情况：服药后闭经者142例，其发生率与累积药量呈正相关（见附表）。其中64例从此绝经，78例于1年内自然复经。有6例用药后血钾下降，4例SGPT轻度上升，停药后均恢复。

附表 累积药量与闭经的关系

累积药量(mg)	治疗例数	闭经例数(%)
600~800	192	13(6.7)
820~1200	158	45(28.4)
1220~1800	114	51(44.7)
>1800	40	33(82.6)

实 验 研 究

一、不同剂量棉酚对雌性大鼠下丘脑、垂

体、卵巢、子宫组织形态的影响：用纯种成熟大鼠，每只每天棉酚 1~4 mg 灌胃，按累积量分 7 mg、20mg、48mg、48mg 恢复和对照五组。48mg 恢复组在停药后 21 天处死，其他组均在最后一次用药 24 小时后处死。结果提示各服药组下丘脑神经元胞浆中尼氏小体有所减少；腺垂体中嗜酸性细胞数随累积药量增加而明显减少。嗜碱性细胞在 48mg 组中明显增多变大；卵巢成熟卵泡在 20mg 组中减少，48mg 组 7 只大鼠中只有 1 只见到成熟卵泡，其它卵泡也少；子宫内膜腺体在 20mg 组 10 只中有 8 只小而直，48mg 组则全呈萎缩相，且间质中结缔组织明显增生。总之，棉酚对这些器官均有直接作用，但主要作用在子宫和卵巢。以上变化在停药后均有所恢复。

二、不同剂量棉酚对雌性大鼠下丘脑、垂体内源性阿片肽及垂体、卵巢激素的影响：用成熟纯种大鼠，在连续两个动情周期后于动情期开始每天棉酚 1~2mg 灌胃，累积量分 7mg、20mg、40mg 及对照四组。结果如下：(1) 7mg 组：下丘脑亮脑啡肽(L-ENK)含量为 $106 \pm 31 \text{ pg/mg}$ ，明显低于其它各组 ($P < 0.05$)；下丘脑和垂体的 β -内啡肽(β -EP)的含量分别为 $141 \pm 91 \text{ pg/mg}$ 和 $84.33 \pm 21.63 \text{ pg/mg}$ ，明显高于其它组 ($P < 0.01$ 和 0.05)；血浆 FSH ($46.7 \pm 35.5 \text{ mIU/ml}$) 和 LH ($18.75 \pm 14.57 \text{ mIU/ml}$) 都明显高于对照组 ($P < 0.01$)；血 E_2 和 PRL 值与对照组相比无差异。(2) 20mg 组：下丘脑 L-ENK 和下丘脑、垂体的 β -EP 与对照组相比均无明显差异，而血 LH 突出地升高，血 E_2 和 PRL 明显降低。(3) 40mg 组：下丘脑、垂体的 L-ENK 与对照组的相近，而 FSH、LH 均呈下降趋势、血 E_2 和 PRL 也降低。

三、不同剂量棉酚对雌性大鼠肝、肾、肾上腺和心脏的组织形态的影响：结果 7 mg、20mg 和 40mg 组的组织形态与对照组相比无差异。

讨 论

一、本研究结果提示，棉酚对异位症和功血(尤其是更年期者)有较好疗效，与国内报道

相似^[1~3]，对女性性轴各器官的作用与用药剂量有明显关系。

二、较小剂量棉酚的作用：临床上 14 例无排卵型功血者服药 400~1200mg 时出现排卵。7 mg 组动物的下丘脑 L-ENK 含量下降及 β -EP 量上升，可能是前者的合成和后者的释放受到抑制所致。已知下丘脑内源性阿片肽对促性腺激素 (GnRH) 有抑制作用，小剂量棉酚使下丘脑 L-ENK 下降，可能就解除了它对 GnRH 的抑制而使 FSH、LH 分泌增加^[4]， β -EP 的释放减少，对 GnRH 的作用也是如此。至于垂体中 β -EP 上升，一般是对垂体起抑制作用的，但也有人认为其作用与机体 E_2 水平密切相关。7 mg 组下丘脑神经元尼氏小体有所减少，证实它对下丘脑有直接作用。

三、较大剂量棉酚的影响：卵巢和子宫呈明显退变相，血 E_2 和 PRL 明显下降，LH 则上升，腺垂体的嗜碱细胞明显增多变大，似所谓“绝经期细胞”。临床病例当所服累计量超过 1800mg 时，约 83% 发生闭经，且内膜均萎缩，可见此时对性轴呈明显抑制作用，主要在卵巢和子宫内膜。下丘脑 L-ENK 和下丘脑、垂体 β -EP 的含量和对照组相比无显著差异。

四、大剂量组动物垂体嗜酸性细胞显著减少，血 PRL 含量低至检测不出的程度，这可能是药物对嗜酸细胞直接作用的结果。由此推想，棉酚可能成为治疗中度高泌乳素血症的药物。

五、临床和动物实验所用大剂量棉酚引起的各种组织形态或功能的影响，均能在停药一定时间后得到恢复，且对生命重要器官的组织形态没有不良影响。

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Clinical Observation and Experimental Study of Gossypol in Treatment of Dysfunctional Menorrhagia, Endometriosis and Fibromyoma of Uterus

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A total of 192 cases of dysfunctional menorrhagia, endometriosis and fibromyoma of uterus were treated with gossypol (20mg/day) for 3 weeks to 3 months or more with satisfactory results, the markedly effective rates were 91.5%, 90.3% and 79.5% respectively. 142 cases (74%) became amenorrheic, and the incidental rate varies with the accumulative amount of gossypol. Menstruation resumed after a period of 3~13 months of amenorrhea in 78 cases. Permanent amenorrhea resulted in 64 menopausal patients, and 10 of them have remained to be amenorrheic for over 5 years and enjoyed good health. 400~1200 mg gossypol were given to 14 cases of dysfunctional menorrhagia (anovulatory type) with the result of the menstruation normalized with ovulation, suggesting a proper and smaller accumulative dosage might produce menstruation regulatory and/or ovulation stimulating effects. Further observation is necessary. Results of the present study showed that immediate and longterm effects displayed in the following order: dysfunctional menorrhagia, endometriosis and uterine fibromyoma, the longterm result of the latter was unsatisfactory. However, the use of gossypol for premenopausal fibroids of smaller size might bring beneficial therapeutic results. No persistent adverse side-effects have been noted during treatment.

Animal experiments were carried out to explore the mechanism with following findings: (1) Rats receiving gossypol with accumulative dosis of 7 mg in a significant drop of Leucine-enkephalin and a marked increase of β -endorphin in the hypothalamus; plasma FSH and LH increased significantly with no change for the E_2 and PRL. (2) Large dosis of 40~48 mg gossypol caused marked atrophic changes of both the ovaries and the uteri of rats. The suppressive effect on the hypothalamus-pituitary-gonadal axis appeared to vary directly with the dosage of drug administered. Acidophils of the anterior pituitary lessened or even disappeared completely while that of the basophils increased both in number and size resembling that of the so-called "postmenopausal cells". Plasma E_2 diminished markedly and PRL was hardly detectable, suggesting that gossypol might be a valuable drug in treating the medium hyperprolactinemia. (3) Spontaneous remission of the above changes took place sooner or later following cessation of therapy. (4) No histological change was observed in the vital organs after medication.

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Observation on Effect of Liangxue-Huayu(凉血化瘀) Prescription on High Coagulation Phase of DIC in Rabbits

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The model of high coagulation phase of DIC in rabbit was established in our laboratory. It was used to study the relationship between "blood heat with stasis" syndrome and high coagulation phase of DIC, and the mechanism of liangxue-huayu (LXHY, cooling blood and relieving stasis) therapy. The results indicated that the "heat flaming in blood portion" syndrome and the "stagnation of blood channel" syndrome in TCM were closely related with the pathologic changes in DIC caused by the infection. The preventive effect of LXHY prescription for high coagulation phase of DIC caused by E. Coli endotoxin in rabbits was proved. The results of examining blood coagulation, hemorrheology and conjunctiva microcirculation showed that the pathologic changes of the therapeutic group could be alleviated, which suggested that the protective effect of LXHY therapy was related to the action of improving coagulation, microcirculation and blood viscosity of affected rabbits. Thus the pathologic process might be abated and blocked, the blood flow in some viscera increased and the shock would be prevented.

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Effect of *Duchesnea indica* on Extracorporeal Esophageal Cancer Cells

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The purpose of present study was to investigate the effect of *Duchesnea indica* on human esophageal cancer cell line (Eca-109). At the concentration of 10 mg, 15 mg/ml, the growth of the cells