

· 临床研究 ·

穴位贴敷疗法对绝经后骨质疏松患者血清 OPG、RANKL 和髋部骨密度的影响

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摘要: **目的** 观察穴位贴敷疗法对绝经后骨质疏松患者骨代谢、髋部骨密度的影响, 以评价其有效性和安全性。**方法** 将符合要求的 80 例绝经后骨质疏松患者随机分为试验组及对照组, 各 40 例。以 6 个月为一个疗程, 共两个疗程。试验组予以外用中药穴位贴敷, 内服钙尔奇 D 片和福善美片治疗, 对照组仅予内服钙尔奇 D 片和福善美片治疗, 疗程为 12 个月。比较 2 组治疗前、治疗后第 6 个月及第 12 个月血骨保护素 (osteoprotegerin, OPG)、核因子- κ B 受体激活配体 (receptor activator of nuclear factor- κ B ligand, RANKL) 含量、髋部骨密度 (bone mineral density, BMD) 及记录骨折发生情况, 所得数据进行统计学分析。**结果** 80 例中 75 例获得完整随访, 其中治疗组 37 例, 对照组 38 例。①比较治疗前 2 组患者血 OPG 含量 ($t = 1.43, P = 0.157$)、RANKL 含量 ($t = -1.84, P = 0.07$), 差异无统计学意义; 试验组治疗 6 个月后血 OPG 含量 ($t = 15.79, P < 0.01$) 与治疗 12 个月后血 OPG 含量 ($t = 21.68, P < 0.01$) 均大于对照组; 试验组治疗 6 个月后血 RANKL 含量测定 ($t = -0.35, P = 0.726$) 与治疗 12 个月后血 RANKL 含量测定 ($t = -1.15, P = 0.253$) 与对照组相比, 差异无统计学意义。②治疗前 2 组患者髋部 BMD 比较, 差异无统计学意义 ($t = 0.26, P = 0.791$); 治疗 6 个月后, 2 组患者的髋部 BMD 均增大, 试验组 BMD 与对照组相比, 差异无统计学意义 ($t = 1.06, P = 0.292$); 治疗 12 个月后, 2 组患者的髋部 BMD 仍继续增大, 试验组 BMD 增加值大于对照组 ($t = 2.22, P = 0.029$)。③试验中对照组共累计出现 2 例患者出现髋部骨折, 而试验组只出现 1 例, 经卡方检验, 卡方值为 0.320, $P = 0.572$, 差异无统计学意义, 但骨折发生率的比较中, 对照组 (5.26%) 略高于试验组 (2.70%)。**结论** 应用穴位贴敷疗法, 能有效缓解疼痛、肌痉挛等症状; 穴位贴敷使中药在局部发挥作用, 加速髋部骨密度增加; 提升 OPG 的血清含量, 促进骨骼成骨作用, 提高髋部骨量, 从而达到防治骨质疏松性髋部骨折的目的。

关键词: 绝经后骨质疏松; 髋部骨折; 骨密度; 骨代谢

The effect of acupoint application on serum OPG, RANKL, and BMD of total hip in postmenopausal osteoporosis women

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Abstract: **Objective** To observe the effect of acupoint application on bone metabolism and bone mineral density in postmenopausal osteoporosis patients, and to evaluate its effectiveness and safety. **Methods** Eighty postmenopausal osteoporosis patients were randomly divided into experimental group and control group, with 40 cases in each group. Six-month was a treatment course, and two consecutive courses were conducted. The patients in the experimental group were treated with external application of Chinese medicine acupoints, combined with oral administration of calcium D and alendronate. The patients in the control group received oral administration of calcium D and alendronate only for consecutive 12 months. The levels of osteoprotegerin (OPG),

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nuclear factor-activated receptor ligand (RANKL), hip BMD and recorded fractures were compared between the two groups before and after 6 months, 12-month of the treatment, respectively. The data were statistically analyzed. **Results** 75 cases of 80 cases were followed up, including 37 cases in the treatment group and 38 cases in the control group. There was no significant difference in the levels of serum OPG ($t = 1.43$, $P = 0.157$) and serum RANKL ($t = -1.84$, $P = 0.07$) between the two groups before the treatment. The levels of serum OPG after 6 months ($t = 15.79$, $P < 0.01$) and after 12 months ($t = 21.68$, $P < 0.01$) in the experimental group was significantly higher than that in the control group ($P < 0.01$). The levels of RANKL after 6 months ($t = -0.35$, $P = 0.726$) and after 12 months ($t = -1.15$, $P = 0.253$) in the experimental group was not statistically different compared with the control group. There was no significant difference in hip BMD between the two groups before and after treatment ($t = 0.26$, $P = 0.791$). After 6 months of the treatment, the BMD of the hip increased in the both groups, but was not different between the two groups ($t = 1.06$, $P = 0.292$). After 12 months of the treatment, the BMD of the hip in the two groups continued to increase, and the BMD in the experimental group was higher than that in the control group ($t = 2.22$, $P = 0.029$). During the treatment, there were 2 cases of hip fractures in the control group, but only 1 case in the experimental group. The chi-square test showed a chi-square value of 0.320 and a P value of 0.572, which was not statistically significant. The incidence of fracture was 5.26% in the control group, which was slightly higher than that in the experimental group (2.70%). **Conclusion** Application of acupoint application can effectively relieve pain, muscle spasms, and other symptoms. It plays a role in increase of hip bone mineral density, serum OPG content, and bone osteogenesis. It improves bone mass in the hip, so as to achieve prevention and treatment of osteoporotic hip fractures.

Key words: Postmenopausal osteoporosis; Hip fractures; Bone mineral density; Bone metabolism

随着世界人口老龄化的到来,骨质疏松已成为经济发达国家及地区关注的健康问题^[1-2]。而女性因其独特的生理结构,绝经后骨质疏松发病率可高达 25%~50%,骨质疏松性骨折作为最为严重的并发症给家庭和社会增添了沉重的负担,其中以髌部骨折发生率(16%~20%)最高,且极易使高龄患者发生其他并发症^[3-6]。为探讨防治老年妇女骨质疏松性髌部骨折更为有效的治疗方式,避免相关药物从剂型、疗程、使用方式及毒副反应等不便^[7],所以在 2013 年 8 月至 2013 年 11 月,笔者对 80 例绝经后骨质疏松患者随机分组,分别从骨代谢情况、骨量及骨折发生率等方面进行了应用穴位贴敷疗法的效果观察,现将观察结果总结报告如下。

1 材料与方法

1.1 一般资料

在浙江省中山医院骨科门诊及骨质疏松研究防治中心筛选原发性 I 型骨质疏松患者 80 例,年龄(75.38 ± 2.38)岁,绝经年限(24.68 ± 2.31)年,体重指数(body mass index, BMI)为(19.90 ± 3.09) kg/m²。采用随机数字表将病例分成试验组和对照组,各 40 例。

1.2 诊断标准

参照 WHO 制定的骨质疏松症诊断标准^[8],经双能 X 线骨密度测量仪测定腰椎正位(L₁₋₄)骨密度或者髌关节骨密度,根据骨密度(bone mineral density, BMD)值对骨质疏松症进行诊断,规定以正

常健康成年人的 BMD 为依据,低于其 2 个标准差则定义为骨质疏松症。

1.3 纳入标准

符合上述骨质疏松症诊断标准;年龄 50~80 岁,绝经 1 年以上;同意参与本研究并签署知情同意书。

1.4 排除标准

体质过敏及对试验用药过敏者;不符合骨质疏松症诊断者;经常服用其他有关治疗药物,嗜酒、嗜烟者;3 个月内参加过其他药物试验(包括中西补药)或曾作过大手术者;甲状腺功能亢进、糖尿病、类风湿性关节炎,多发性骨髓瘤等继发性骨质疏松患者;有心、脑、肝、肾及内分泌等严重器质性疾病者。

1.5 方法

1.5.1 临床干预方法:试验组:为原发性 I 型骨质疏松患者口服钙尔奇 D 片(惠氏制药有限公司, H10950029)600 mg/d,福善美片(杭州默沙东制药有限公司, J20130085)70 mg/w,6 个月为一个疗程,一个疗程结束后经检查安全后进入下一个疗程,共两个疗程,12 个月。治疗组:为原发性 I 型骨质疏松患者规定穴位上给予药贴贴敷,该药贴由三味中药(肉桂、狗脊、淫羊藿)组成,将以上三味药材粉末进行提取,以提取物制成巴布膏剂,将其贴服相应穴位上,每 1~2 日换药一次。并配合对照组基础治疗药物,共两个疗程,12 个月。选取穴位:命门、肾俞、三焦俞、大肠俞、气海、关元、腰阳关、膀胱俞、气海

俞。该研究已通过医院医学伦理委员会批准。

1.5.2 观察指标测定:于治疗前、治疗后第 6 个月及第 12 个月,采集清晨空腹血液样本,检测血清骨保护素(osteoprotegerin, OPG)、核因子- κ B 受体激活配体(receptor activator of nuclear factor- κ B ligand, RANKL)含量;使用法国 Medilink 公司 OSTEOCORE2 双能 X 线骨密度仪扫描,测定髋关节骨密度;定期电话回访记录骨折发生率。

1.5.3 统计学方法:采用 SPSS 19.0 统计软件对收集到的数据进行分析,2 组患者年龄、髋部 BMD、血

清 OPG/RANKL 含量组间比较采用 t 检验,髋部骨折发生率采用 χ^2 检验,检验水准 $\alpha = 0.05$ 。

2 结果

研究中试验组中有 3 例患者中药敷贴出现皮肤过敏现象,不能坚持试验而退出,对照组中有 2 例因不满意治疗效果中断试验,最终获得完整随访信息共 75 例,其中试验组 37 例,对照组 38 例。两组年龄、身高、体重、BMI 及绝经年限比较,差异无统计学意义($P > 0.05$),见表 1。

表 1 两组患者基线资料比较

Table 1 Comparison of baseline information between the two groups

组别 Group	年龄(岁) Age	身高(cm) Height	体重(kg) Weight	BMI (kg/m ²)	绝经年限(年) Years since menopause
试验组 Treatment group	75.81 $\pm$ 2.34	151.94 $\pm$ 5.37	45.18 $\pm$ 5.51	19.62 $\pm$ 2.56	24.89 $\pm$ 2.33
对照组 Control group	74.97 $\pm$ 2.38	153.67 $\pm$ 4.80	47.13 $\pm$ 6.97	20.17 $\pm$ 3.54	24.47 $\pm$ 2.31
t 值 t value	1.532	-1.392	-1.477	-0.776	0.780
P 值 P value	0.130	0.168	0.144	0.440	0.438

2.1 骨代谢生化指标变化情况比较

两组治疗后骨代谢生化指标变化情况见表 2。血清 OPG 含量在试验组和对照组中均有提升,在治疗后 6 个月和 12 个月与对照组相比较(t 检验),差

异有统计学意义($P < 0.01$);而血清 RANKL 含量呈上下波动的稳定态势,较治疗前轻度提升($P < 0.05$),但与对照组相比,差异无统计学意义($P > 0.05$)。

表 2 两组患者血清骨转化指标比较($\bar{x} \pm s$, pg/mL)

Table 2 Comparison of bone turnover markers between the two groups($\bar{x} \pm s$, pg/mL)

组别 Group	OPG			RANKL		
	治疗前 Pre-therapy	治疗后 6 个月 6 months later	治疗后 12 个月 12 months later	治疗前 Pre-therapy	治疗后 6 个月 6 months later	治疗后 12 个月 12 months later
试验组 Treatment group	98.31 $\pm$ 3.49 ^{ab}	124.08 $\pm$ 5.25 ^a	140.06 $\pm$ 4.81 ^b	10.71 $\pm$ 1.68 ^{cd}	23.18 $\pm$ 7.11 ^c	17.65 $\pm$ 7.09 ^d
对照组 Control group	97.26 $\pm$ 2.82	106.61 $\pm$ 4.28	117.19 $\pm$ 4.31	11.40 $\pm$ 1.54	23.80 $\pm$ 8.02	19.42 $\pm$ 6.19
t 值 t value	1.430	15.790	21.680	-1.840	-0.350	-1.150
P 值 P value	0.157	<0.01	<0.01	0.070	0.726	0.253

注:a,b:与治疗前相比, $P < 0.05$;c,d:与对照组相比, $P < 0.05$ 。

2.2 髋部骨密度变化情况比较

试验组及对照组中髋部骨密度均有提升,在治疗 6 个月后试验组与治疗组比较,差异无统计学意义($P > 0.05$)。治疗后 12 个月后试验组与对照组

比较,髋部骨密度有明显的上升($P < 0.05$)。试验组治疗前后比较,髋关节骨密度上升明显($P < 0.05$)。见表 3。

表 3 两组患者髋关节 BMD 比较($\bar{x} \pm s, g/cm^2$)Table 3 Comparison of bone mineral density of total hip between the two groups ($\bar{x} \pm s, g/cm^2$)

组别 Group	BMD		
	治疗前 Pre-therapy	治疗后 6 个月 6 months after treatment	治疗后 12 个月 12 months after treatment
试验组 Treatment group	-2.89 ± 0.21^{ab}	-2.46 ± 0.19^a	-2.20 ± 0.18^b
对照组 Control group	-2.90 ± 0.21	-2.51 ± 0.21	-2.31 ± 0.22
t 值 t value	0.260	1.060	2.220
P 值 P value	0.791	0.292	0.029

注:a,b:与治疗前相比, $P < 0.05$ 。

2.3 髋部骨折发生情况比较

治疗 12 个月后,对照组中共累计出现 2 例患者出现髋部骨折,而试验组只出现 1 例,经卡方检验,差异不具统计学意义($P > 0.05$);但骨折发生率的比较中,对照组(5.26%)略高于试验组(2.70%)。见表 4。

表 4 两组患者髋部骨折发生率比较

Table 4 Comparison of the rate of hip fractures between the two groups

组别 Group	髋部骨折 Hip fracture occurred	未发生髋部骨折 No hip fracture occurred	骨折发生率(%) Ratio(%)
治疗组 Treatment group	1	36	2.70
对照组 Control group	2	36	5.26
卡方值 Chi-square value	0.320		
P 值 P value	0.572		

3 讨论

70~89 岁为脆性髋部骨折的高发年龄段,绝经后女性 65 岁以后,髋部 BMD 虽然降低速率变慢,但是骨丢失主要集中在皮质骨,而皮质骨对骨强度起着主要作用,皮质骨变薄会引起骨强度的显著降低,这也就是老年人跌倒时发生髋部骨折的重要原因^[9-11]。

透皮给药系统具有疗效好、药物毒副作用小、无肝首过效应、有效血药浓度恒定、给药次数少、给药时间长、临床应用方便等优点^[12]。“经皮给药”是一种古老的给药方式,我国医典《内经·素问》、宋代《太平惠民和剂局方》中已有可用于局部治疗或透皮吸收的膏药^[13]。此外,研究表明靶向经穴给药可

明显提高补肾方药的归经调节作用,至少在骨和性腺两个靶点起作用^[14]。依据中医的经络理论,在人体的腰背部位集中了较多的经络穴位,取穴常用经脉有:足太阳膀胱经、督脉、足太阴脾经、足少阴肾经、任脉等。其中对肾、脾等脏器有较大影响的穴位有命门、肾俞、三焦俞、志室、气海、关元、腰阳、关元俞、气海俞、关元俞等。本研究针对特定部位持续给药,将起到补肾壮骨、调补肝脾的效果,对绝经后骨质疏松的防治将有一定的指导意义。

BMD 虽作为诊断骨质疏松症的金指标,但短期内灵敏度欠佳,故结合骨转化指标 OPG 和 RANKL 应用于疗效评价^[15]。研究显示破骨细胞的功能及其分化状态受成骨细胞的调控作用影响,成骨细胞分泌信号分子 OPG 和 RANKL,与破骨细胞膜上的 RANK 形成 OPG-RANKL-RANK 信号轴,对破骨细胞的分化、成熟及信号传递起着重要的调节作用^[16]。

本研究的结果提示,应用穴位贴敷疗法不仅能有效缓解疼痛、肌痉挛等症状,而且可通过提升 OPG 的血清含量,促进骨形成,提高骨量,达到防治绝经后骨质疏松性髋部骨折的目的。

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