

· 临床研究 ·

地黄饮子与阿仑膦酸钠治疗原发性骨质疏松症的病例对照研究


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【摘要】 目的: 研究并对比分析服用中药汤剂地黄饮子与口服阿仑膦酸钠治疗原发性骨质疏松症的临床疗效差异。方法: 回顾自 2016 年 1 月至 2017 年 12 月骨质疏松专科门诊就诊的患者, 筛选口服地黄饮子及阿仑膦酸钠规律用药满 1 年以上的原发性骨质疏松患者 72 例作为观察对象, 将其分成两组, 即试验组和对照组。试验组 36 例, 男 14 例, 女 22 例; 年龄(63.97±3.70)岁; 服用中药汤剂地黄饮子, 每次 1 剂, 早晚各 1 次, 每周 2 次。对照组 36 例, 男 16 例, 女 20 例; 年龄(63.36±3.07)岁; 口服阿仑膦酸钠 70 mg, 每周 1 次。两组患者抗骨质疏松的基础治疗不变(每日口服碳酸钙 D3 片 600 mg/d, 以及骨化三醇胶丸 0.5 μg/d)。采用双能 X 线骨密度仪检测两组患者治疗前和治疗 1 年后的股骨颈骨密度、腰椎骨密度, 检测两组患者治疗前和治疗 1 年后的血清 I 型胶原 C 末端肽(β-CTX)及血清硬骨素(SOST)含量并进行统计分析。结果: 抗骨质疏松治疗前两组患者的年龄、骨密度、SOST 与 β-CTX 基线值比较, 差异均无统计学意义($P>0.05$)。两组患者在接受抗骨质疏松治疗 1 年后, 股骨颈及腰椎骨密度均较治疗前增加, 差异均有统计学意义($P<0.001$)。血清 β-CTX 检测值均较治疗前明显降低, t 值分别为 52.002 和 50.071; 血清 SOST 值均较治疗前增加, t 值分别为 -29.242 和 -30.807, 差异均有统计学意义($P<0.001$)。比较两组患者治疗后股骨颈和腰椎骨密度, P 值分别为 0.294 和 0.478, 差异无统计学意义。两组患者接受治疗后的血清 β-CTX 值比较, $P=0.908$; 两组患者治疗后的血清 SOST 值比较, $P=0.888$, 差异无统计学意义。结论: 将传统中药地黄饮子用于治疗骨质疏松, 研究发现其与阿仑膦酸钠均有较好的疗效, 地黄饮子可作为治疗原发性骨质疏松症的中药选择。

【关键词】 骨质疏松; 植物药疗法; 骨密度; 病例对照研究

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Comparison of the clinical effects between *Dihuang* Decoction (地黄饮子) and alendronate sodium in the treatment of primary osteoporosis WAN Jun-ming, ZHANG Jian-fang, HUANG Kai, ZHANG Peng-li, and ZHU Shao-yu. Department of Orthopaedics, Tongde Hospital of Zhejiang Province, Hangzhou 310002, Zhejiang, China

ABSTRACT Objective: To study and compare the clinical effects of *Rehmannia* Decoction and alendronate sodium for the treatment of primary osteoporosis. **Methods:** From January 2016 to December 2017, 72 patients with primary osteoporosis who took *Dihuang* Decoction (地黄饮子, DHD) orally and alendronate regularly for more than one year were randomly divided into 2 groups: experimental group and control group. The experimental group consisted of 14 males and 22 females, with an average age of (63.97±3.70) years old. The patients in the experimental group took Chinese medicine DHD, one dose each time, one time in the morning and one time in the evening, twice a week. The control group consisted of 16 males and 20 females with an average age of (63.36±3.07) years old. Patients in the control group were given alendronate 70 mg orally once a week. The basic treatment for osteoporosis remained unchanged in both groups (600 mg of calcium carbonate D3 and 0.5 μg of calcitriol capsules were taken daily). Bone mineral density (BMD) of femoral neck and lumbar vertebrae was measured by dual energy X-ray absorptiometry before and after treatment for one year. The levels of serum collagen type I C-terminal peptide (beta-CTX) and serum osteoclast (SOST) were measured before and after treatment for two groups. **Results:** The age, bone mineral density, SOST and beta-CTX baseline values between the two groups before and after anti-osteoporosis treatment were compared. The difference was not statistically significant ($P>0.05$). Compared with the two groups, the BMD of femoral neck and lumbar vertebrae were increased after 1 year of anti-osteoporosis treatment. The differences were statistically significant ($P<0.001$). The value of serum beta-CTX was significantly lower than before. The t values were 52.002 and 50.071 respectively.

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The value of serum SOST was increased than that before treatment. The *t* values were -29.242 and -30.807 respectively. The differences were statistically significant ($P < 0.001$). BMD of the femoral neck and lumbar spine was compared between the two groups after treatment. The *P* values were 0.294 and 0.478 respectively. The difference was not statistically significant ($P > 0.05$). The serum beta-CTX values were compared between the two groups after treatment. The *P* value was 0.908. The serum SOST values were compared between the two groups after treatment. The *P* value was 0.888. The difference was not statistically significant ($P > 0.05$). **Conclusion:** In this study, traditional Chinese medicine DHD is used to treat osteoporosis. It is found that DHD and alendronate have a good effect. The DHD can be used as a choice of Chinese medicine in the treatment of primary osteoporosis.

KEYWORDS Osteoporosis; Phytotherapy; Bone density; Case-control studies

原发性骨质疏松症是一种以骨量低下、骨小梁的超微结构退变破坏而引起骨的脆性增加、易于发生骨折的全身性骨病^[1]。阿仑膦酸钠作为双膦酸盐类药物的代表,已是骨质疏松症预防和治疗的一线药物,其临床疗效确切,已得到广泛使用^[2]。传统中医理论认为骨质疏松症属于“骨萎”的范畴,主要致病因素为血瘀、脾虚、肾虚等。《圣济总录》详细记载了地黄饮的功能主治,《黄帝素问·宣明论方》在原方的基础上加入了少许薄荷,名为“地黄饮子”。已有基础研究证实地黄饮子可通过抑制破骨细胞,改善骨小梁的形态,从而增加骨量,达到防治骨质疏松的作用^[3]。本研究对比分析传统中药地黄饮子与阿仑膦酸钠在治疗原发性骨质疏松症的疗效差异,以进一步阐明中药地黄饮子在治疗原发性骨质疏松症方面的优势,为临床上采用中药治疗骨质疏松症提供参考。

1 资料与方法

1.1 一般资料

回顾自 2016 年 1 月至 2017 年 12 月在我院骨质疏松专科门诊就诊的患者,筛选口服地黄饮子及阿仑膦酸钠规律用药满 1 年以上的原发性骨质疏松患者 72 例作为观察对象,将其分成两组,即试验组和对照组。试验组 36 例,男 14 例,女 22 例;年龄(63.97±3.70)岁。对照组 36 例,男 16 例,女 20 例;年龄(63.36±3.07)岁。平均随访时间 1 年以上。两组患者治疗前的基线数据比较,差异无统计学意义,具有可比性(表 1)。本研究已通过我院伦理委员会批准(伦理批号: XMSB2016039)。

1.2 病例选择

1.2.1 纳入标准 年龄 50~75 岁,其中男性>60 岁,女性>55 岁;符合原发性骨质疏松症的诊断;股骨颈以及腰椎的骨密度测量值<-2.5 SD;自愿接受临床试验并签署知情同意者。

1.2.2 排除标准 (1)近半年来使用过可能导致骨代谢指标受影响的药物者,如钙剂、骨化三醇、糖皮质激素、甲状旁腺激素、双磷酸盐等。(2)患有影响骨转换的继发性骨质疏松相关疾病,如糖尿病、甲状腺功能亢进、甲状旁腺功能亢进、多发性骨髓瘤、原发及转移性骨肿瘤等疾病。(3)不愿意配合足疗程的骨质疏松治疗,或严重基础疾病、精神疾病者。

1.3 治疗方法

两组患者基础治疗方案相同,口服碳酸钙 D3 片 600 mg(惠氏制药),每日 1 次;口服骨化三醇胶丸(罗氏制药),每次 0.25 μg,每日 2 次。试验组:患者服用传统中药地黄饮子,方剂组成为熟地黄 12 g,巴戟天 15 g,山茱萸 15 g,肉苁蓉 15 g,附子(炮)9 g,五味子 15 g,肉桂 9 g,白茯苓 15 g,麦门冬 15 g,远志 15 g,石菖蒲 15 g。水煎服,每次 1 剂,早晚各 1 次,每周 2 次。对照组:口服阿仑膦酸钠(默沙东制药),每次 70 mg,每周 1 次。两组患者服药周期均为 1 年。

1.4 观察指标与方法

1.4.1 骨密度检测 采用双能 X 线吸收检测骨密度仪(美国 GE 公司)对入组的患者进行基线和治疗 1 年后的骨密度测定,检测部位为股骨颈和腰椎。

1.4.2 血液相关指标检测 检测所有患者在治疗前和治疗 1 年后的血清 I 型胶原 C 末端肽(β-CTX)

表 1 两组骨质疏松症患者治疗前临床资料比较($\bar{x} \pm s$)

Tab.1 Comparison of general data between experimental group and control group before treatment of patients with osteoporosis($\bar{x} \pm s$)

组别	例数	年龄(岁)	股骨颈骨密度(g/cm ³)	腰椎骨密度(g/cm ³)	血清 β-CTX(pg/ml)	SOST(ng/ml)
试验组	36	63.97±3.70	0.689±0.059	0.807±0.078	347.67±53.51	3.51±0.66
对照组	36	63.36±3.07	0.685±0.061	0.798±0.089	337.69±53.46	3.41±0.67
<i>t</i> 值		0.763	0.209	0.446	0.791	0.675
<i>P</i> 值		0.448	0.835	0.643	0.432	0.502

和血清硬骨素(sclerostin, SOST)等指标的变化。

1.5 统计学处理

采用 SPSS 24.0 统计软件进行分析,本研究资料属于正态分布的定量资料,患者接受地黄饮子及阿仑膦酸钠治疗前后的骨密度及血清 β -CTX、SOST 等指标的比较采用配对设计定量资料的 t 检验,两组治疗后疗效比较采用成组设计定量资料的 t 检验。检验水准 α 值取双侧 0.05,以 $P < 0.05$ 为差异有统计学意义。

2 结果

所有患者治疗并随访 1 年,由于患者主要是附近的常住居民,用药及随访的依从性很好,同时笔者建立了微信群及电话、电子邮件等回访机制,做到了良好的随访,无失访病例。

2.1 两组患者治疗前后骨密度比较

两组患者经过为期 1 年的抗骨质疏松治疗后股骨颈骨密度、腰椎骨密度均较治疗前增加,但治疗后两组股骨颈骨密度、腰椎骨密度比较差异均无统计学意义(表 2)。

2.2 两组患者治疗前后血清 β -CTX 及 SOST 检测值比较

两组患者经过为期 1 年的抗骨质疏松治疗后血清 β -CTX 及 SOST 检测值均较治疗前明显降低,但治疗后两组 β -CTX 及 SOST 检测值比较差异均无统计学意义(表 2)。

3 讨论

随着中国人口老龄化日益加重,原发性骨质疏松症患者的数量正逐年上升,而骨质疏松症导致的并发症严重威胁了老年人的生活质量及预期寿命,临床治疗的主要目的是缓解疼痛,预防骨质疏松性骨折的发生,提高患者的生存质量^[4]。

阿仑膦酸钠作为口服双膦酸盐类药物已是公认的抗骨质疏松治疗一线药物^[5],在临床上得到了广

泛的应用。该药通过作用于破骨细胞,抑制破骨细胞的形成与活化等途径达到抑制骨吸收的作用,从而升高骨密度,有效缓解骨质疏松患者的临床症状,降低骨质疏松性骨折的发生风险^[6-8]。有研究表明,无论是男性还是女性人群,口服阿仑膦酸钠治疗均能显著提高骨密度,有利于降低骨折的风险^[9-10]。基础研究证实,阿仑膦酸钠在抑制破骨细胞的同时还有促进成骨细胞的分化的作用,加强碱性磷酸酶的活性,上调骨形成蛋白(bone morphogenetic protein, BMP-2)的表达,从而促进骨钙素和 I 型胶原的形成^[11-13]。

本研究结果证实口服阿仑膦酸钠每周 70 mg 的抗骨质疏松治疗维持 1 年后,患者股骨颈和腰椎的骨密度均较治疗前得到了有效的提升,反映骨吸收活动的骨代谢指标 β -CTX 较治疗前明显下降,硬骨素也较基线数值增加,研究数据也进一步说明了阿仑膦酸钠对破骨细胞有显著的抑制作用。

地黄饮子出自古代著名的医家刘完素的《黄帝素问宣明论方》,该药具有补肾阳、滋肾阴、化痰开窍等作用。近些年来随着我国中医药研究的不断深入与拓展,地黄饮子在循环系统、神经系统、内分泌系统、骨科、老年科等疾病领域有着广泛研究与临床应用。经过国内专家学者大量的临床观察和实验研究证实地黄饮子对全身多系统各个器官的多种疾病都有确切的临床疗效,目前在中医临床的应用范围已完全超越古籍所记载的传统治疗范围,有学者通过基础实验观察地黄饮子汤药对去势大鼠造模骨质疏松模型的骨密度、骨代谢指标、生物力学指标及股骨形态学的变化,结果表明地黄饮子可以使骨质疏松模型的骨小梁数量增多、增宽且排列非常规则^[14-16]。这些研究结果也证实了地黄饮子能够提高绝经后骨质疏松模型的骨密度值,抑制骨吸收,促进骨形成。

本研究给予患者服用地黄饮子,经过为期 1 年

表 2 两组骨质疏松症患者治疗前后各项指标比较($\bar{x} \pm s$)

Tab.2 Comparison of indexes of patients with osteoporosis between two groups before and after therapy($\bar{x} \pm s$)

组别	例数	股骨颈骨密度(g/cm ³)		腰椎骨密度(g/cm ³)		β -CTX(pg/ml)		SOST(ng/ml)	
		治疗前	治疗后	治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
试验组	36	0.689±0.059	0.700±0.064 ^{a1}	0.807±0.078	0.867±0.008 ^{a2}	347.67±53.51	59.17±21.30 ^{a3}	3.51±0.66	5.53±0.95 ^{a4}
对照组	36	0.685±0.061	0.715±0.060 ^{b1}	0.798±0.089	0.854±0.079 ^{b2}	337.69±53.46	59.75±21.19 ^{b3}	3.41±0.67	5.50±0.96
t 值		0.209	-1.058	0.446	-0.713	0.791	-0.116	0.675	-0.142
P 值		0.835	0.294	0.643	0.478	0.432	0.908	0.502	0.888

注:与治疗前比较,^{a1} $t=-9.302, P < 0.001$; ^{a2} $t=-30.828, P < 0.001$; ^{a3} $t=52.002, P < 0.001$; ^{a4} $t=-29.242, P < 0.001$; ^{b1} $t=-9.194, P < 0.001$; ^{b2} $t=-9.194, P < 0.001$; ^{b3} $t=50.071, P < 0.001$; ^{b4} $t=-30.807, P < 0.001$

Note: Compared with preoperative results, ^{a1} $t=-9.302, P < 0.001$; ^{a2} $t=-30.828, P < 0.001$; ^{a3} $t=52.002, P < 0.001$; ^{a4} $t=-29.242, P < 0.001$; ^{b1} $t=-9.194, P < 0.001$; ^{b2} $t=-9.194, P < 0.001$; ^{b3} $t=50.071, P < 0.001$; ^{b4} $t=-30.807, P < 0.001$

的抗骨质疏松治疗, 研究结果证实传统中药地黄饮子能较治疗前显著提高患者股骨颈和腰椎的骨密度, 骨代谢指标 β -CTX 较治疗前明显下降, 硬骨素较前明显升高。这些研究数据也进一步说明了地黄饮子对原发性骨质疏松症患者破骨细胞的抑制作用较明显, 同时具有一定的成骨作用。通过比较两组患者治疗前、后各指标的差值, 笔者发现地黄饮子与阿仑膦酸钠在治疗原发性骨质疏松方面的疗效并无显著差异。地黄饮子组方中使用的中草药具有资源丰富、价格低廉、疗效肯定等优势, 应用在治疗原发性骨质疏松症方面或许会有良好的应用前景。

综上所述, 阿仑膦酸钠作为抗骨质疏松的一线经典药物, 临床疗效和长期随访结果均非常稳定可靠, 而药物价格及部分副作用可能会影响一部分患者的用药依从性。传统中药地黄饮子, 已经在全身各系统多领域的疾病治疗方面发挥了良好的功效, 研究结果也证实了其在原发性骨质疏松症方面具备的优势, 但长期用药及随访数据还需要大样本、多中心的随机对照临床研究来验证, 这些还有待进一步的深入研究。

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