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独活寄生汤联合阿仑膦酸钠对骨质疏松症患者骨代谢指标、血液流变学以及血清炎症因子的影响*

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摘要 目的:探讨独活寄生汤联合阿仑膦酸钠对骨质疏松症患者骨代谢指标、血液流变学以及血清炎症因子的影响。**方法:**选取于2017年5月~2019年12月期间我院收治的113例骨质疏松症患者,根据随机数表法将患者分为对照组($n=56$)和研究组($n=57$),对照组患者给予阿仑膦酸钠治疗,研究组在对照组的基础上联合独活寄生汤治疗,比较两组患者疗效、骨代谢指标、骨密度(BMD)、血液流变学以及血清炎症因子水平,记录两组治疗期间不良反应发生情况。**结果:**研究组治疗1个月后的临床总有效率为91.23%(52/57),高于对照组的76.79%(43/56)($P<0.05$)。治疗1个月后两组BMD、血清碱性磷酸酶(ALP)升高,且研究组较对照组高($P<0.05$);两组治疗1个月后血清磷(S-P)、血清钙(S-Ca)组间比较无差异($P>0.05$)。治疗1个月后两组全血黏度低切、白介素-6(IL-6)、纤维蛋白原、肿瘤坏死因子- α (TNF- α)、全血黏度高切、白介素-1(IL-1)下降,且研究组低于对照组($P<0.05$)。两组不良反应发生率比较无差异($P>0.05$)。**结论:**骨质疏松症患者采用独活寄生汤联合阿仑膦酸钠治疗,疗效确切,可有效改善骨代谢、血液流变学以及血清炎症因子水平,且不增加不良反应发生率。

关键词:独活寄生汤;阿仑膦酸钠;骨质疏松症;骨代谢;血液流变学;炎症因子

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Effect of Duhuojisheng Decoction Combined with Alendronate Sodium on Bone Metabolism, Hemorheology and Serum Inflammatory Factors in Patients with Osteoporosis*

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ABSTRACT Objective: To investigate the effect of Duhuojisheng decoction combined with alendronate sodium on bone metabolism, hemorheology and serum inflammatory factors in patients with osteoporosis. **Methods:** 113 patients with osteoporosis in our hospital from May 2017 to December 2019 were selected, they were divided into control group ($n=56$) and study group ($n=57$) according to the method of random number table. Patients in the control group were treated with alendronate sodium. The study group was treated with Duhuojisheng decoction on the basis of the control group. The curative effect, bone metabolism index, bone density (BMD) and hemorheology and serum inflammatory factors of the two groups were compared. The adverse reactions of the two groups were recorded. **Results:** The total clinical effective rate of the study group at 1 month after treatment was 91.23% (52/57), which was higher than 76.79% (43/56) of the control group ($P<0.05$). 1 month after treatment, BMD, serum alkaline phosphatase (ALP) of the two groups increased, and the study group was higher than the control group ($P<0.05$). There were no significant differences between the two groups at 1 month after treatment in serum phosphorus (S-P) and serum calcium (S-Ca) ($P>0.05$). 1 month after treatment, low whole blood viscosity, interleukin-6 (IL-6), fibrinogen, tumor necrosis factor- α (TNF- α), high whole blood viscosity and interleukin-1 (IL-1) of the two groups decreased, and the study group was lower than the control group ($P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Duhuojisheng decoction combined with alendronate sodium is effective in the treatment of osteoporosis. It can effectively improve bone metabolism, hemorheology and serum inflammatory factors, and does not increase the incidence of adverse reactions.

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Key words: Duhuojiusheng decoction; Alendronate sodium; Osteoporosis; Bone metabolism; Hemorrheology; Inflammatory factors

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前言

骨质疏松症的主要特点为单位体积内骨组织量减少,表现为腰背疼痛等症状,严重者则压迫脊神经部位而产生肋间神经痛、四肢放射痛等,可诱发呼吸功能减弱、骨折等,给患者生命健康带来巨大威胁^[1-3]。目前,现代医学对于该病尚无明确的治疗手段,阿仑膦酸钠是治疗骨质疏松症的常用西药,可使骨量明显增加^[4],但不少临床实践证实^[5,6],西药长期应用,副作用较大,影响患者治疗结局、依从性,远期预后一般。近年来,中西医结合治疗骨质疏松症取得了较大的进展,独活寄生汤出自《备急千金要方》,常用于慢性关节炎、坐骨神经痛等属肝肾不足、气血两亏者的治疗,近年来将其应用于骨质疏松症的治疗中,取得了较好的疗效^[7]。鉴于此,本研究通过探讨独活寄生汤联合阿仑膦酸钠对骨质疏松症患者的临床疗效,以期为临床治疗骨质疏松症提供参考。

1 资料与方法

1.1 临床资料

选取于2017年5月~2019年12月期间我院收治的骨质疏松症患者113例,纳入标准:(1)西医诊断标准参考《中国骨质疏松性骨折诊疗指南》^[8],中医诊断标准参考《中医内科病证诊断疗效标准》^[9],辨证分型为肝肾不足型,主证:腰痛或全身骨痛,次证:椎体压痛,下肢酸软、眩晕耳鸣、舌质偏红或淡脉沉细;(2)患者及其家属知情本研究且签署了同意书;(3)均为首次确诊,入组前未接受其他治疗者;(4)对本次研究用药无禁忌者。排除标准:(1)合并心肝肾等功能障碍者;(2)精神意识障碍患者;(3)既往有腰椎间盘突出、肿瘤骨转移者;(4)妊娠或哺乳期妇女;(5)治疗依从性差,中途退出者。根据随机数表法将其分为研究组(n=57)和对照组(n=56),其中对照组女34例,男22例;年龄45~69岁,平均(52.68±3.49)岁;病程1~6年,平均(3.52±0.83)年;体质指数21~26 kg/m²,平均(23.86±0.87) kg/m²。研究组女35例,男22例;病程1~7年,平均(3.46±0.76)年;年龄44~71岁,平均(52.16±3.52)岁;体质指数20~26 kg/m²,平均(23.75±0.82) kg/m²。两组患者一般资料比较无差异(P>0.05),具有可比性。此次研究已通过我院医学伦理学委员会批准进行。

1.2 方法

两组入院后给予合理营养膳食、适量运动等,在此基础上,

对照组予以阿仑膦酸钠(石药集团欧意药业有限公司,国药准字H20110079,规格:70 mg)治疗,70 mg/次,1次/周。基于对照组,研究组给予独活寄生汤,组成如下:独活、牛膝、桑寄生、杜仲各20 g,熟地黄、当归、补骨脂各15 g,细辛、肉桂、茯苓、白芍、秦艽、川芎、防风各10 g,甘草6 g。阴虚者加女贞子、枸杞子各10 g,气虚者加黄芪30 g,疼痛症状极为严重者另加地龙、延胡索各10 g,阳虚者加续断、巴戟天、骨碎补各10 g。上述药方加水熬煮至300 mL,早晚温服各150 mL。两组疗程1个月。

1.3 观察指标

(1)记录两组临床总有效率。疗效判定依据如下:无效:骨密度(BMD)以及疼痛症状无改善或加重。有效:BMD有所改善,疼痛明显减轻。显效:BMD明显升高,疼痛基本消失。总有效率=显效率+有效率^[10]。(2)记录治疗期间两组不良反应。(3)于治疗前、治疗1个月后采用EXPERT-XL 双能X线骨密度仪(美国LUNAR公司生产)检测患者BMD。(4)于治疗前、治疗1个月后采集患者4 mL肘静脉血,经常规离心后取上清,置于冰箱中待测。采用AU2700全自动生化分析仪(日本奥林巴斯公司生产)检测骨代谢指标:血清磷(S-P)、血清钙(S-Ca)、血清碱性磷酸酶(ALP)。采用SA6000自动血液流变仪(北京赛科希德发展有限公司生产)检测血液流变学指标:全血黏度高切、全血黏度低切、纤维蛋白原。参考试剂盒(北京百泰克生物技术有限公司)说明书步骤,采用酶联免疫吸附法检测炎症因子水平:肿瘤坏死因子- α (TNF- α)、白介素-1(IL-1)、白介素-6(IL-6)。

1.4 统计学方法

采用SPSS21.0软件处理数据,以($\bar{x} \pm s$)表示计量资料,采用t检验,以率表示计数资料,采用 χ^2 检验, $\alpha=0.05$ 为检验水准。

2 结果

2.1 疗效比较

治疗1个月后,研究组临床总有效率高于对照组(P<0.05);详见表1。

2.2 BMD及骨代谢指标比较

两组治疗前BMD、S-P、S-Ca、ALP比较无差异(P>0.05);两组治疗1个月后BMD、ALP升高,且研究组高于对照组(P<0.05);两组治疗1个月后S-P、S-Ca组间比较差异无统计学意义(P>0.05);详见表2。

表1 临床疗效比较例(%)
Table 1 Comparison of clinical efficacy n(%)

Groups	Effective	Valid	Invalid	Total effective rate
Control group(n=56)	12(21.43)	31(55.36)	13(23.21)	43(76.79)
Study group(n=57)	17(29.83)	35(61.40)	5(8.77)	52(91.23)
χ^2				4.400
P				0.036

表 2 BMD 及骨代谢指标比较 ($\bar{x} \pm s$)Table 2 Comparison of BMD and bone metabolism indexes ($\bar{x} \pm s$)

Groups	BMD(g/cm ²)		S-P(mmol/L)		S-Ca(mmol/L)		ALP(IU/L)	
	Before treatment	1 month after treatment	Before treatment	1 month after treatment	Before treatment	1 month after treatment	Before treatment	1 month after treatment
Control group (n=56)	0.89±0.14	1.16±0.11*	1.33±0.35	1.35±0.31	2.29±0.25	2.32±0.25	62.23±7.25	71.53±6.87*
Study group (n=57)	0.91±0.17	1.54±0.12*	1.31±0.26	1.34±0.36	2.31±0.22	2.34±0.29	62.71±6.36	78.98±6.95*
t	0.682	10.154	0.345	0.158	0.452	0.392	0.374	5.730
P	0.497	0.000	0.731	0.875	0.652	0.696	0.709	0.000

Note: compared with before treatment, * $P < 0.05$.

2.3 血液流变学指标比较

两组治疗前全血黏度高切、全血黏度低切、纤维蛋白原比较无差异($P > 0.05$);治疗 1 个月后两组全血黏度高切、纤维蛋

白原、全血黏度低切下降,且研究组较对照组低($P < 0.05$);详见表 3。

表 3 血液流变学指标比较 ($\bar{x} \pm s$)Table 3 Comparison of hemorheology indexes ($\bar{x} \pm s$)

Groups	High whole blood viscosity(mPa·s)		Low whole blood viscosity(mPa·s)		Fibrinogen(g/L)	
	Before treatment	1 month after treatment	Before treatment	1 month after treatment	Before treatment	1 month after treatment
Control group (n=56)	3.89±0.43	2.96±0.32*	16.64±2.19	12.66±2.18*	4.16±0.83	3.27±0.79*
Study group(n=57)	3.82±0.42	2.09±0.25*	16.13±2.11	7.59±2.24*	4.12±0.75	2.51±0.69*
t	0.875	16.121	1.261	12.190	0.269	5.449
P	0.383	0.000	0.210	0.000	0.789	0.000

Note: compared with before treatment, * $P < 0.05$.

2.4 炎症因子水平比较

两组治疗前炎症因子水平比较无差异($P > 0.05$);治疗 1 个

月后两组 TNF- α 、IL-6、IL-1 下降,且研究组较对照组低($P < 0.05$);详见表 4。

表 4 炎症因子水平比较 ($\bar{x} \pm s$)Table 4 Comparison of inflammatory factors($\bar{x} \pm s$)

Groups	TNF- α (pg/mL)		IL-6(ng/L)		IL-1(pg/ml)	
	Before treatment	1 month after treatment	Before treatment	1 month after treatment	Before treatment	1 month after treatment
Control group(n=56)	8.57±1.32	6.49±1.49*	3.41±0.26	2.56±0.33*	345.29±28.59	264.30±23.62*
Study group(n=57)	8.53±1.26	4.10±1.32*	3.47±0.23	1.98±0.25*	344.82±23.48	176.28±24.57*
t	0.165	9.029	1.300	10.543	0.096	19.408
P	0.869	0.000	0.196	0.000	0.924	0.000

Note: compared with before treatment, * $P < 0.05$.

2.5 不良反应

治疗期间,两组不良反应发生率比较无差异($P > 0.05$);详见表 5。

3 讨论

骨质疏松症是老年人常见疾病,一般可分为特发性、继发性及原发性三类^[11]。骨质疏松症的发病机制目前尚不十分明确,既往认为该病发病的主要原因在于骨形成和骨吸收不足间的平衡遭到破坏,骨代谢时,破骨细胞黏附到骨表面,促进骨吸

收,成骨细胞转移至该处,分泌类骨质,促进矿化沉积形成新骨,当骨吸收超过骨形成,将导致骨质疏松^[12,13]。随着研究的深入,学者们还发现骨质疏松症的发生发展与 T 细胞功能异常及其激活所致的细胞因子参与的骨代谢调控息息相关^[14]。T 细胞通过直接作用于破骨细胞的前体细胞,可诱导破骨细胞分化,同时免疫功能激活所致的细胞因子大量分泌,导致机体处于炎性状态,可诱发破骨细胞形成^[15,16]。此外,还有不少学者认为骨质疏松的发生与生长激素、性激素、甲状腺素等有关^[17,18]。其中性激素、甲状腺素、生长激素分泌对机体血液流变学又有一定

表 5 不良反应比较例(%)

Table 5 Comparison of adverse reactions n(%)

Groups	Nausea and vomiting	Gastrointestinal discomfort	Constipation	Total incidence rate
Control group(n=56)	1(1.79)	0(0.00)	2(3.57)	3(5.36)
Study group(n=57)	1(1.75)	3(5.26)	0(0.00)	4(7.02)
χ^2				0.134
P				0.714

的调控作用,且对机体血液流变学的影响具有双重作用^[19]。

阿仑膦酸钠片是人工合成化合物,与钙亲和力高,该药物可抑制骨吸收,并在破骨细胞破骨时释放,破骨细胞可再次吸收,从而其活性被抑制,BMD 逐渐增加^[20-22]。而中医认为本病属于"腰腿痛"、"骨伤"等范畴,主要病机为痹证日久,肝肾亏虚,气血不足,治疗上应以补气养血、填精补髓为大法^[23]。独活寄生汤方中秦艽、独活、防风祛风止痛,桑寄生、杜仲、牛膝补益肝肾,川芎、当归、白芍、熟地黄养血和血,茯苓健脾补气,补骨脂滋补脾肾,细辛发散止痛,肉桂温通血脉,甘草调和诸药,共奏填精补髓、补气养血之功^[24]。本次研究结果显示,独活寄生汤联合阿仑膦酸钠治疗骨质疏松症患者,可进一步提高治疗效果。在西医治疗基础上联合中药治疗,可发挥协同作用,进一步提高治疗效果。

BMD 作为诊断骨质疏松症的金标准,具有稳定性、精确度高等优点,但存在滞后性^[25]。骨代谢标志物可反映机体短期内骨重建、骨代谢,与骨合成、骨丢失的速度联系紧密^[26]。血液流变学异常可引起血液粘滞状态,导致机体循环障碍,引起代谢产物尤其是酸性代谢产物的堆积,而钙易溶于酸,导致局部的钙、磷等骨盐减少,骨质来源缺乏,最终引起骨质疏松^[27]。此外,骨质疏松症的疾病进展与炎症因子的激活具有一定相关性,TNF- α 主要由单核吞噬细胞分泌,可通过破坏软骨基质,造成破骨细胞吸收;IL-6 是由 T 淋巴细胞分泌,可减少关节软骨糖蛋白合成,降解基质,从而进一步损伤、破坏软骨机制;而 IL-1 同样作为临床常见的炎症因子,不仅能够直接作用于软骨基质,同时还可通过介导 IL-6 抑制软骨细胞合成蛋白多糖^[28]。本研究通过观察上述三个方面指标发现,独活寄生汤联合阿仑膦酸钠治疗可有效改善骨质疏松症患者的骨代谢、血液流变学以及血清炎症因子水平。现代药理证实^[29,30],独活寄生汤具有镇痛、抗炎、改善循环、扩张血管、强筋健骨、调节免疫功能等多方面功效。另研究结果显示该联合治疗方案安全可靠,这可能与独活寄生汤为中药材组方而成,本身即具备低毒副作用有关。本次研究尚存在样本量偏少、未能观察患者复发率等远期预后这些不足,后续报道将扩大样本量、增加随访时间以获取更为准确的数据。

综上所述,独活寄生汤联合阿仑膦酸钠治疗骨质疏松症患者安全有效,可有效改善患者骨代谢、血液流变学以及血清炎症因子水平。

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