

骨松宝颗粒联合硫酸氨基葡萄糖治疗膝骨关节炎的临床研究

万全会, 王刘玉*

南阳市第二人民医院 骨科, 河南 南阳 473000

摘要: **目的** 探讨骨松宝颗粒联合硫酸氨基葡萄糖治疗膝骨关节炎的临床疗效。**方法** 纳入2019年10月—2020年2月于南阳市第二人民医院骨科门诊及住院治疗的86例膝骨关节炎患者作为研究对象,按照随机数表法将患者分为对照组和观察组,每组各43例。对照组患者口服硫酸氨基葡萄糖胶囊,2粒/次,3次/d。观察组在对照组治疗的基础上口服骨松宝颗粒,1袋/次,3次/d。两组各治疗6周。观察两组患者的临床疗效,同时比较两组治疗前后的视觉模拟评分(VAS)、Lysholm评分、血清炎症因子及骨代谢指标水平。**结果** 治疗后,观察组总有效率为95.34%,显著高于对照组的79.07%,差异具有统计学意义($P < 0.05$)。治疗后,两组VAS评分显著降低,而Lysholm评分显著升高,同组治疗前后比较差异具有统计学意义($P < 0.05$);治疗后,观察组VAS评分显著低于对照组,而Lysholm评分高于对照组,差异均具有统计学意义($P < 0.05$)。治疗后,两组肿瘤坏死因子- α (TNF- α)、白细胞介素-1 β (IL-1 β)、白细胞介素-6 (IL-6)水平较显著降低($P < 0.05$),且治疗后,观察组TNF- α 、IL-1 β 、IL-6水平显著低于对照组,差异均具有统计学意义($P < 0.05$)。治疗后,两组抗酒石酸盐酸性磷酸酶异构体5b (TRACP-5b)水平显著降低,而骨钙素(BGP)和骨特异性碱性磷酸酶(BALP)水平显著升高,同组治疗前后比较差异具有统计学意义($P < 0.05$);治疗后,观察组TRACP-5b水平显著低于对照组,而BGP和BALP水平显著高于对照组,两组比较差异具有统计学意义($P < 0.05$)。**结论** 骨松宝颗粒联合硫酸氨基葡萄糖治疗膝骨关节炎的临床疗效较好且安全性高,能明显改善膝关节疼痛症状及关节功能,可能机制与其能显著降低机体炎症因子水平及改善骨代谢有关。

关键词: 骨松宝颗粒; 硫酸氨基葡萄糖; 膝骨关节炎; 炎症因子; 骨代谢; 不良反应

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Clinical study of Gusongbao Granules combined with glucosamine sulfate in treatment of knee osteoarthritis

WAN Quanhui, WANG Liuyu

Department of Orthopaedic, Second People's Hospital of Nanyang, Nanyang 473000, China

Abstract: Objective To investigate the clinical effect of Gusongbao Granules combined with glucosamine sulfate in treatment of knee osteoarthritis. **Methods** A total of 86 patients with knee osteoarthritis in the department of orthopedics, The Second People's Hospital of Nanyang from October 2019 to February 2020 were included as the research objects. According to the random number table method, the patients were divided into the control group and the observation group, with 43 patients in each group. Patients in the control group were *po* administered with Glucosamine Sulfate Capsules, 2 capsules/time, 3 times daily. Patients in observation group were *po* administered with Gusongbao Granules on the basis of control group, 1 bag per time and 3 times daily. Both groups were treated for a total of 6 weeks. The clinical efficacy in two groups of patients was observed, and the VAS score, Lysholm score, serum inflammatory factors, and bone metabolism indexes of two groups before and after treatment were compared. **Results** After treatment, the total effective rate of the observation group was 95.34%, which was significantly higher than 79.07% of the control group, and the difference was statistically significant ($P < 0.05$). After treatment, VAS scores of two groups were significantly reduced, while Lysholm scores were significantly increased, with statistically significant differences between two groups before and after treatment ($P < 0.05$). After treatment, VAS score of the observation group was significantly lower than that of the control group, while Lysholm score was higher than that of the control group, with statistically significant differences ($P < 0.05$). After treatment,

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第一作者: 万全会(1984—),男,大学本科,主治医师,研究方向为骨关节炎的诊断与治疗。E-mail: quanhuw@sina.com.

*通信作者: 王刘玉 E-mail: dr_wangly@163.com

the levels of TNF- α , IL-1 β , and IL-6 in two groups were significantly decreased ($P < 0.05$), and levels of TNF- α , IL-1 β , and IL-6 in the observation group were significantly lower than those in the control group, the differences were statistically significant ($P < 0.05$). After treatment, TRACP-5b levels in two groups were significantly decreased, while BGP and BALP levels were significantly increased, with statistically significant differences before and after treatment in the same group ($P < 0.05$). After treatment, TRACP-5b levels in the observation group were significantly lower than those in the control group, while BGP and BALP levels were significantly higher than those in the control group, with statistically significant differences between the two groups ($P < 0.05$).

Conclusions Gusongbao Granules combined with glucosamine sulfate in treatment of knee osteoarthritis has good clinical efficacy and high safety, and can significantly improve the symptoms and joint function of the knee joint. The possible mechanism is related to its ability to significantly reduce the expression level of inflammatory factors in the body and improve bone metabolism.

Key words: Gusongbao Granules; glucosamine sulfate; knee osteoarthritis; inflammatory factors; bone metabolism; adverse reactions

膝骨关节炎也称为膝退行性骨关节炎,多好发于中老年患者,但具体发病机制不清,可能原因与炎症、骨代谢、局部免疫功能紊乱有关^[1-2]。膝骨关节炎的主要病理特征为关节软骨的退行性改变,并有一定程度的关节软骨的破坏及骨质增生,临床主要症状为关节活动受限、关节疼痛肿胀等,体征可见骨摩擦音,部分患者病情迁徙,可逐渐导致膝关节畸形,严重影响生活质量^[1]。硫酸氨基葡萄糖胶囊是治疗膝骨关节炎的一线药物,临床疗效显著^[3]。近年来,国内学者多采用中药制剂联合硫酸氨基葡萄糖胶囊治疗膝骨关节炎,中药制剂辅助治疗后能显著提高单独采用硫酸氨基葡萄糖胶囊的治疗疗效^[4]。骨松宝颗粒是常用于治疗膝骨关节炎的复方中药制剂^[5]。本研究探讨骨松宝颗粒联合硫酸氨基葡萄糖治疗膝骨关节炎的临床疗效及相关机制。

1 资料与方法

1.1 一般资料

纳入2019年10月—2020年2月于南阳市第二人民医院骨科治疗的86例膝骨关节炎患者作为研究对象,其中男44例,女42例;年龄46~57岁,平均年龄(51.22 $\pm$ 5.98)岁;病程6~14个月,平均病程(9.03 $\pm$ 2.33)个月;发病部位左侧45例,右侧41例;X线片I级37例、II级33例、III级16例。

1.2 纳入和排除标准

纳入标准:(1)膝骨关节炎诊断明确,具体标准参考骨关节炎诊疗指南(2018年版)^[1];(2)近1个月内未采用口服药物、物理疗法及局部手术治疗;(3)临床资料完善。

排除标准:(1)其他原因如骨关节结核、骨肿瘤、骨质疏松症、银屑病关节炎等导致的膝关节病变;(2)存在严重肝肾功能不全、自身免疫性疾病、恶性肿瘤及急慢性感染性疾病患者等;(3)妊娠及哺乳妇女;(4)对硫酸氨基葡萄糖胶囊及骨松宝颗

粒过敏患者;(5)治疗中断而失访患者。上述所有研究对象均知情同意且签订知情同意书。

1.3 分组及治疗药物

按照随机数表法将患者分为对照组和观察组,每组各43例。其中对照组男20例,女23例;年龄47~57岁,平均年龄(50.0 $\pm$ 25.33)岁;病程6~14个月,平均病程(9.45 $\pm$ 1.23)个月,左侧25例,右侧18例,X线片I级18例、II级17例、III级8例。观察组男24例,女19例;年龄46~57岁,平均年龄(49.86 $\pm$ 6.15)岁;病程6~13个月,平均病程(8.79 $\pm$ 2.04)个月;左侧20例,右侧23例;X线片I级19例、II级16例、III级8例。两组患者在性别、年龄、病程、发病部位、X线片分级等基线资料上比较均无显著差异。

对照组患者口服硫酸氨基葡萄糖胶囊(浙江海正药业股份有限公司,国药准字H20041316,规格:0.314 g/粒,生产批号:20190512),2粒/次,3次/d。观察组在对照组治疗的基础上口服骨松宝颗粒(贵州富华药业有限责任公司,国药准字Z52020005,规格:5 g/袋,生产批号:20190718),1袋/次,3次/d。两组共计治疗6周。

1.4 临床疗效评估标准^[6]

显效:膝关节活动基本正常,无疼痛感和僵硬感;有效:膝关节活动得到明显改善,有轻微疼痛感和僵硬感;无效:膝关节活动受限,疼痛感和僵硬感明显,严重影响生活习惯。

总有效率=(显效+有效)/总例数

1.5 观察指标

1.5.1 视觉模拟评分(VAS)^[7]和Lysholm评分比较^[8] 采用视觉模拟法对两组患者治疗前后进行疼痛程度评分,其中VAS评分为0~10分,0分表示无疼痛,10分表示难以耐受的疼痛,VAS评分越高,说明疼痛越明显。Lysholm评分是用于反映膝关节功

能的一项指标,主要由8个维度构成,分值为0~100分, Lysholm评分越高,说明膝关节功能越好。

1.5.2 血清炎症因子 两组患者治疗前后均空腹抽取外周静脉血5 mL,离心并获取上层血清备用。血清炎症因子如肿瘤坏死因子- α (TNF- α)、白细胞介素-1 β (IL-1 β)和白细胞介素-6(IL-6)水平采用ELISA试剂盒检测,试剂盒购买自泉州市睿信生物科技有限公司。所有操作步骤均按照试剂盒说明书步骤进行。

1.5.3 骨代谢指标的变化 观察两组治疗前后检测骨代谢指标的变化,主要为抗酒石酸盐酸性磷酸酶异构体 TRACP-5b、骨钙素(BGP)和骨特异性碱性磷酸酶(BALP),由医院检验科采用放射免疫法测定BGP含量,TRACP-5b和BALP采用ELISA法测定,ELISA试剂盒购买自泉州市睿信生物科技有限公司。所有操作步骤均按照试剂盒说明书步骤进行。

1.6 不良反应

记录两组患者治疗期间出现的消化道症状如恶心、呕吐及皮肤过敏症状等发生情况。

1.7 统计学处理

采用SPSS 22.0统计学软件进行数据处理。计量资料符合正态分布,以 $\bar{x} \pm s$ 表示,两组间比较采用 t 检验;计数资料采用频数或百分比表示,采用 χ^2 检验。

2 结果

2.1 两组临床疗效比较

治疗后,观察组总有效率为95.34%,显著高于对照组的79.07%,差异具有统计学意义($P < 0.05$),见表1。

2.2 两组VAS评分和Lysholm评分的比较

治疗后,两组VAS评分显著降低,而Lysholm评分显著升高,同组治疗前后比较差异具有统计学意义($P < 0.05$);治疗后,观察组VAS评分显著低于对照组,而Lysholm评分高于对照组,差异均具有统计学意义($P < 0.05$),见表2。

表1 两组临床疗效比较

Table 1 Comparison of clinical efficacy between two groups

组别	n/例	显效/例	有效/例	无效/例	总有效率/%
对照	43	19	15	9	79.07
观察	43	24	17	2	95.34*

与对照组比较: * $P < 0.05$

* $P < 0.05$ vs control group

表2 两组VAS评分和Lysholm评分比较($\bar{x} \pm s$)

Table 2 Comparison of VAS scores and Lysholm scores

between two groups ($\bar{x} \pm s$)

组别	n/例	VAS评分		Lysholm评分	
		治疗前	治疗后	治疗前	治疗后
对照	43	8.02 $\pm$ 2.31	6.35 $\pm$ 1.02*	29.36 $\pm$ 5.22	62.05 $\pm$ 4.31*
观察	43	7.89 $\pm$ 1.14	3.27 $\pm$ 1.63**	30.18 $\pm$ 4.87	80.49 $\pm$ 5.69**

与同组治疗前比较: * $P < 0.05$; 与对照组治疗后比较: ** $P < 0.05$

* $P < 0.05$ vs same group before treatment; ** $P < 0.05$ vs control group after treatment

2.3 两组血清炎症因子水平比较

治疗后,两组TNF- α 、IL-1 β 、IL-6水平较显著降低($P < 0.05$),且治疗后,观察组TNF- α 、IL-1 β 、IL-6水平显著低于对照组,差异均具有统计学意义($P < 0.05$),见表3。

2.4 两组骨代谢指标比较

治疗后,两组TRACP-5b水平显著降低,而BGP和BALP水平显著升高,同组治疗前后比较差异具有统计学意义($P < 0.05$);治疗后,观察组TRACP-5b水平显著低于对照组,而BGP和BALP水平显著高于对照组,两组比较差异具有统计学意义($P < 0.05$),见表4。

2.5 两组不良反应发生率的比较

对照组治疗期间出现恶心、呕吐3例,皮疹4例,不良反应发生率为16.28%,观察组治疗期间出现恶心、呕吐4例,皮疹5例,不良反应发生率为20.93%,两组不良反应发生率相比无显著差异。

3 讨论

膝骨关节炎多好发于中老年患者,不仅导致膝

表3 两组血清TNF- α 、IL-1 β 和IL-6水平比较($\bar{x} \pm s$)

Table 3 Comparison on the levels of TNF- α , IL-1 β , and IL-6 between two groups ($\bar{x} \pm s$)

组别	n/例	TNF- α /(pg·mL ⁻¹)		IL-1 β /(pg·mL ⁻¹)		IL-6/(mg·L ⁻¹)	
		治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
对照	43	165.28 $\pm$ 20.36	98.88 $\pm$ 16.21*	275.66 $\pm$ 27.48	120.36 $\pm$ 12.29*	97.47 $\pm$ 10.02	63.37 $\pm$ 8.42*
观察	43	168.02 $\pm$ 24.84	42.42 $\pm$ 13.51**	280.25 $\pm$ 30.06	63.99 $\pm$ 9.36**	100.39 $\pm$ 8.54	42.22 $\pm$ 6.39**

与同组治疗前比较: * $P < 0.05$; 与对照组治疗后比较: ** $P < 0.05$

* $P < 0.05$ vs same group before treatment; ** $P < 0.05$ vs control group after treatment

表4 两组血清TRACP-5b、BGP和BALP水平比较($\bar{x} \pm s$)Table 4 Comparison of serum TRACP-5B, BGP and BALP levels between two groups ($\bar{x} \pm s$)

组别	n/例	TRACP-5b/(U·L ⁻¹)		BGP/(μg·L ⁻¹)		BALP/(U·L ⁻¹)	
		治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
对照	43	8.32±1.43	5.78±0.95*	6.78±1.05	9.45±2.03*	35.85±6.39	42.05±7.28*
观察	43	8.19±1.25	2.43±0.84*#	7.02±1.22	12.25±2.48*#	34.18±5.97	58.26±7.44*#

与同组治疗前比较: * $P < 0.05$; 与对照组治疗后比较: # $P < 0.05$ * $P < 0.05$ vs same group before treatment; # $P < 0.05$ vs control group after treatment

关节疼痛、肿胀、僵硬及功能障碍,严重者可引起关节畸形,临床治疗原则主要为止痛及改善关节功能为主。硫酸氨基葡萄糖胶囊主要成分为氨基葡萄糖,能够刺激关节软骨细胞的增殖及改善骨代谢,此外,也具有一定的止痛作用及缓解机体的炎症状态^[4, 9-10]。骨松宝颗粒是由淫羊藿、续断、知母、地黄等多种中药制成的中药制剂,主要用于治疗骨关节炎、骨折、骨痛等^[5, 11]。因此,本研究探讨骨松宝颗粒联合硫酸氨基葡萄糖治疗膝骨关节炎的临床疗效和相关机制。

本研究结果发现,与对照组比较,治疗后观察组总有效率、Lysholm评分显著升高,而VAS评分显著降低,提示骨松宝颗粒能够显著提高单独采用硫酸氨基葡萄糖治疗膝骨关节炎的疗效,能够使患者的疼痛程度和关节功能得到显著改善。研究证实,膝骨关节炎患者血清TNF- α 、IL-1 β 、IL-6水平显著升高,且TNF- α 和IL-6水平与关节损伤的严重程度具有显著正相关性^[3, 12]。TNF- α 、IL-1 β 、IL-6与膝骨关节炎的发病机制密切相关,TNF- α 主要由纤维母细胞分泌,主要介导关节软骨基质的降解,也能通过刺激前列腺素的分泌而诱导关节软骨细胞发生过氧化反应,最终引起关节骨和软骨的破坏^[13];IL-1 β 属于IL-1家族中的一种促炎介质,关节内注射IL-1 β 可以诱导膝骨关节炎样改变^[14-15];IL-6与关节软骨细胞的炎症状态有关,郭静等^[16]研究结果显示,骨关节炎患者关节软骨和滑膜组织中IL-6蛋白表达水平显著升高,且膝骨关节炎患者关节液中IL-6浓度与胶原酶呈现显著正相关性,而胶原酶是破坏软骨细胞的主要活性酶之一^[17]。本研究中治疗后观察组血清TNF- α 、IL-1 β 、IL-6水平显著低于对照组,因此,本研究结果提示骨松宝颗粒的临床疗效可能与其能够显著降低膝骨关节炎患者的炎症状态有关。淫羊藿是骨松宝颗粒中的主要成分之一,研究显示^[18],淫羊藿的抗炎机制主要涉及到抑制NF- κ B信号通路的激活、抑制NLRP3/caspase-1/IL-1 β 、STAT和MAPK介导的信号传导通路,上调

Nrf2/ARE/HO-1信号通路等。TRACP-5b水平主要用于反映破骨细胞及骨吸收活性指标之一,而BGP和BALP水平主要用于反映成骨细胞活性及骨形成能力的指标^[19],本研究中发现,骨松宝颗粒治疗后能显著降低TRACP-5b水平及提高BGP和BALP水平,说明骨松宝颗粒能显著改善患者的骨代谢进程。

中药制剂治疗的安全性也一直是临床上关注的重点,本研究中两组的不良反应均为消化道症状和皮肤过敏症状,但不良反应症状较轻微,给予对症处理后能明显缓解,且两组不良反应发生率相比较无显著差异,说明骨松宝颗粒的安全性较高。

综上所述,骨松宝颗粒联合硫酸氨基葡萄糖治疗膝骨关节炎的临床疗效较好且安全性高,能明显改善膝骨关节炎疼痛症状及关节功能,可能机制与其能显著降低机体炎症因子的水平及改善骨代谢有关。

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