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骨保护素对激素性股骨头坏死患者功能恢复及血清 TRAP 和 CTX-Ⅱ水平的影响 *

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摘要 目的:探讨骨保护素对激素性股骨头坏死患者功能恢复及血清抗酒石酸酸性磷酸酶(TRAP)和Ⅱ型胶原羧基端端肽(CTX-Ⅱ)水平的影响。**方法:**选取 2014 年 1 月 ~2016 年 6 月我院骨科收治的 130 例激素性股骨头坏死患者作为研究对象,采取随机数字表将其分成两组,每组 65 例。两组患者均给平卧床、患肢持续皮牵引治疗,观察组在此基础上联合使用骨保护素治疗,比较两组临床疗效、功能恢复情况以及治疗前后骨密度、血清 TRAP 与 CTX-Ⅱ水平。**结果:**观察组治疗优良率为 90.77%,相对于对照组的 72.31%明显上升(P<0.01)。两组治疗后股骨头局部骨密度均有上升(P<0.01),其中观察组上升更为明显(P<0.01);观察组治疗后腰椎平均骨密度与治疗前相比有明显上升(P<0.01),对照组无明显变化(P>0.05)。两组治疗后血清 TRAP 与 CTX-Ⅱ水平均较治疗前显著下降(P<0.01),但观察组下降更为明显(P<0.01)。**结论:**骨保护素治疗激素性股骨头坏死可有效抑制骨吸收、增强骨密度、改善患髋关节功能。

关键词:骨保护素;激素性股骨头坏死;髋关节功能;抗酒石酸酸性磷酸酶;Ⅱ型胶原羧基端端肽

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Effect of Bone Protective Hormone on the Functional Recovery and the Level of Serum TRAP and CTX-Ⅱ of Patients with Steroid Induced Avascular Necrosis of the Femoral Head*

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ABSTRACT Objective: To study the effect of bone protective hormone on functional recovery and the level of serum tartrate resistant acid phosphatase (TRAP) and C-telopeptide fragments of type Ⅱ collagen (CTX-Ⅱ) of patients with steroid induced avascular necrosis of the femoral head. **Methods:** 130 cases of steroid induced femoral head necrosis patients treated in our hospital from January 2014 to June 2016 were selected as the research subjects and divided into two groups with the method of random number table, 65 cases in each group. Both groups of patients were given conservative treatment, on the basis of which, the observation group was combined with the use of bone protective treatment. The clinical efficacy, functional recovery, bone mineral density, serum TRAP and CTX-Ⅱ levels were compared between the two groups. **Results:** The excellent and good rate of observation group was 90.77%, which increased significantly compared with 72.31% in the control group (P<0.01). The local bone mineral density of both groups both increased after the treatment (P<0.01). The observation group increased more significantly (P<0.01). The average bone mineral density of observation group significantly increased compared with that before the treatment (P<0.01). There was no significant change in the control group (P>0.05). The serum levels of TRAP and CTX-Ⅱ after the treatment in both groups significantly decreased compared with those before treatment (P<0.01), but the observation group decreased more significantly (P<0.01). **Conclusion:** Bone protective hormone could effectively inhibit bone resorption, increase bone density and improve the function of the hip joint in the treatment of steroid induced avascular necrosis of the femoral head.

Key words: Bone protection element; Steroid induced necrosis of the femoral head; Hip joint function; Tartrate resistant acid phosphatase; C-telopeptide fragments of type Ⅱ collagen

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前言

股骨头坏死是由多种因素引起的股骨头血液循环受损或

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中断，并由此导致骨细胞、脂肪细胞、骨髓造血细胞等凋亡，引起股骨头塌陷、畸形，最终进展为严重的骨关节炎，表现为疼痛及功能障碍等[1,2]。近年来，由于激素的广泛使用，激素性股骨头坏死的发病率明显上升，其作为最常见的非创伤性股骨头坏死类型之一，与一般股骨头缺血性坏死相比病情更为严重，具有更高的致残率，因而该类型股骨头坏死也成为骨科研究的重点[3]。研究显示[4,5]骨保护素作为一种可调节骨代谢糖蛋白，可通过骨保护素 /NF-κB 受体激活剂 /NF-κB 受体激活剂配体(OPG/RANK/RANKL)系统对破骨细胞的形成及代谢过程进行调控，故近年来常被用于骨质疏松等骨科疾病中，而在激素性股骨头坏死方面临床研究鲜少。我院在常规治疗基础上联合使用骨保护素治疗激素性股骨头坏死患者，取得了满意效果，现报道如下。

1 资料与方法

1.1 一般资料

研究对象选择我院骨科 2014 年 1 月 ~2016 年 6 月收治的激素性股骨头坏死病例共计 130 例，纳入标准：(1)符合激素性股骨头坏死诊断标准[6]，且均为单侧股骨头坏死；(2)根据国际骨循环研究学会骨坏死分期标准[7]，确定为 I~II 期，无手术指征；(3)具有明确的激素使用史；(4)存在髋关节疼痛及髋关节内旋活动受限。排除标准：(1)酒精、外伤等非激素引起的股骨头坏死；(2)合并一过性滑膜炎、骨结核、骨性关节炎、骨肿瘤；(3)合并肝肾功能不全、心脑血管疾病、血液系统疾病、代谢性疾病；(4)合并精神及神经系统疾病、认知功能障碍；(5)恶性肿瘤；(6)妊娠及哺乳期妇女；(7)对试验药物过敏。采取随机数字表将这 130 例患者分成两组，每组 65 例。观察组男 45 例，女 20 例，年龄 28~70 岁，平均 (45.0± 8.3) 岁，病程 6 个月 ~5 年，平均 (3.12± 1.25)年。对照组男 43 例，女 22 例，年龄 26~69 岁，平均 (43.8± 7.9)岁，病程 6 个月 ~5 年，平均(3.06± 1.12)年。两组资料无统计学差异(P>0.05)，存在可比性。

1.2 治疗方法

两组患者均给予平卧床，患肢持续皮牵引治疗(体重 /12)。同时指导两组患者进行功能锻炼，包括股四头肌自主收缩、髋关节屈曲、外展、内旋、内收、外旋。30 min/ 次，3 次 /d。避免负重及长距离行走。在上述治疗基础上，观察组患者联合给予重组人骨保护素(上海富纯中南生物有限公司，批号 130826)肌肉注射治疗，剂量 6 mg/kg，1 次 /d。两组均以两周为 1 个疗程，连续治疗两个疗程。用药过程中戒烟戒酒、忌食生冷辛辣刺激性食物，保持情绪稳定。

1.3 疗效评定

根据 1993 年北戴河《全国股骨头缺血性坏死专题讨论会》修订的髋关节功能标准对两组患者的髋关节功能恢复情况进行全面评估，并据此进行疗效评定[8]。该标准包括疼痛、生活能力、关节活动度、行走距离 4 项得分及 X 线标准得分，满分 100 分制，每项分 6 级，Ⅰ级最差，Ⅵ最好。疗效总评估：优：总分≥ 80 分，股骨头呈球形，囊性变消失，密度恢复正常，原坏死区骨小梁生长良好；良：总分≥ 60 分，但 <80 分，股骨头呈球形，密度恢复正常，原坏死区可见骨小梁生长；可：总分≥ 40 分，但 <60 分，股骨头呈球形，密度与正常骨质相比偏低，原坏死区仍有少量囊性变与硬化骨质；差：总分 <40 分，股骨头扁圆形，坏死区骨小梁消失，骨质硬化。总有效率 =(显效 + 有效)/ 总病例数× 100%。

1.4 观察指标

(1)骨密度：对两组患者治疗前后的骨密度进行检测，患者取仰卧位测量正位腰椎(L2~L4)骨密度。仪器选择美国 Lunar 公司的双能 X 线骨密度检测仪。所有步骤均由计算机自行定位、采集数据及处理。(2)血清抗酒石酸酸性磷酸酶(TRAP)和Ⅱ型胶原羧基端端肽(CTX-Ⅱ)水平：采用酶联免疫法(ELISA)检测两组患者治疗前后的血清 TRAP 与 CTX-Ⅱ水平。试剂盒购自北京博奥森试剂公司，操作步骤严格按照说明书进行。

1.5 统计学分析

采取统计学软件 SPSS18.0 对数据进行处理，计数资料、计量资料分别采取 x^2 检验、t 检验，以 P<0.05 为差异具有统计学意义。

2 结果

2.1 两组患者临床疗效比较

观察组优良率为 90.77%，相对于对照组的 72.31%有明显上升(P<0.01)。见表 1。

表 1 两组患者临床疗效比较

Table 1 The comparison of clinical efficacy between the two groups [n(%)]

Groups	n	Good	Fine	Pass	Poor	Total efficiency
Experimental group	65	24	35	3	3	59(90.77)
Control group	65	13	34	6	12	47(72.31)
x^2						7.359
P						0.007

2.2 两组患者治疗前后骨密度比较

两组治疗后股骨头局部骨密度均较治疗前显著上升(P<0.01)，观察组上升更为明显(P<0.01)；观察组治疗后腰椎平均骨密度与治疗前相比有明显上升 (P<0.01)，对照组无明显变化(P>0.05)。见表 2。

2.3 两组治疗前后血清 TRAP 与 CTX-Ⅱ水平比较

两组治疗后血清 TRAP 与 CTX-Ⅱ水平均较治疗前显著下降(P<0.01)，但观察组下降更为明显(P<0.01)。见表 3。

3 讨论

股骨头坏死为骨科常见病及多发病，糖皮质激素的长期大量使用是最常见的病因之一[9]。使用糖皮质激素治疗的患者中，约有 5%~25%可发生股骨头坏死，而在非创伤性股骨头坏死患者中约有 50%为激素性股骨头坏死。人体大剂量使用糖皮质激

素可导致骨组织合成减少,骨吸收增加,引起骨样组织形成发生障碍,进而导致骨质疏松以及骨小梁塌陷,造成病变处小动脉与毛细血管受压,引起局部循环不畅及骨组织坏死[10]。此外,人体大量摄入激素后可使血清脂类物质增加,当肝脏难以对其进行代谢时,即可引发高脂血症,血管中也可形成脂肪栓子,股骨头内动脉可因此栓塞,使骨组织发生缺血坏死,而动脉中脂肪栓子分解后可形成大量的脂肪酸,使白三烯 B4、血栓素 B4、前列腺素 E2 等炎性因子含量增加,上述因素均可导致骨内小血管损害以及炎症反应加重,增加血管的通透性,并阻断骨组织内出血及血供,最终引起骨缺血性坏死[11]。

表 2 两组患者治疗前后骨密度比较

Table 2 The comparison of bone mineral density before and after the treatment between the two groups($\bar{x}\pm$ s, g/cm^2)

Groups	n	Proximal femur				Lumbar vertebra			
		Prior treatment	Post treatment	t	P	Prior treatment	Post treatment	t	P
Experimental group	65	0.70± 0.16	0.98± 0.18	9.374	0.000	0.74± 0.18	0.97± 0.17	7.490	0.000
Control group	65	0.72± 0.15	0.81± 0.19	2.997	0.003	0.75± 0.20	0.79± 0.21	1.112	0.268
t		0.735	5.237			0.300	5.371		
P		0.464	0.000			0.765	0.000		

表 3 两组治疗前后血清 TRAP 与 CTX-Ⅱ水平比较

Table 3 The comparison of serum levels of TRAP and CTX-Ⅱ in the two groups before and after the treatment($\bar{x}\pm$ s)

Groups	n	TRAP(ng/mL)				CTX-Ⅱ(ng/L)			
		Prior treatment	Post treatment	t	P	Prior treatment	Post treatment	t	P
Experimental group	65	45.07± 5.32	18.12± 3.87	33.028	0.000	221.23± 17.23	185.92± 20.21	10.719	0.000
Control group	65	44.91± 4.86	34.06± 3.24	14.976	0.000	218.65± 19.54	200.35± 21.24	5.112	0.000
t		0.179	25.462			0.798	3.968		
P		0.858	0.000			0.426	0.000		

股骨头坏死机制复杂,主要与骨代谢平衡失调有关,其中成骨细胞、破骨细胞平衡与否对于维持骨骼的完整性起着重要作用。近年来,随着基因工程的快速发展,重组人骨保护素等可于人体外合成,经合成的骨保护素具有和生物体内骨保护素相同的生物功能。骨保护素为肿瘤坏死因子受体(TNFR)超家族成员,产生于成骨细胞系基质细胞,RANKL 属 TNF 配体家族成员,可由成骨细胞系与活化 T 细胞产生。骨保护素通过竞争性结合 RANKL 后,可抑制 RANKL 和破骨细胞 RANK 结合[12],对骨细胞活动起到有效的调节作用,促使骨质吸收处在动态平衡之中[13]。熊琦等[14]在破骨细胞混合培养体系中加入重组人骨保护素后,TRAP 染色阳性多核细胞计数明显减少,提示重组人骨保护素可对破骨前体细胞分化融合至破骨细胞进行抑制。Kadri 等[15]将骨保护素于小鼠骨关节炎模型腹腔内注射后,骨体积 / 组织比显著上升,骨小梁分离显著减少,指出骨保护素可防止软骨退化。实验研究显示[16]重组人骨保护素还可调节牙周炎大鼠牙槽骨骨保护素、RANKL 的表达。尽管目前已有研究证实[17],重组骨保护蛋白可对糖皮质激素性骨吸收进行抑制,使骨强度增加,对激素性骨质疏松可起到保护作用,但将骨保护素用于股骨头坏死的研究鲜少。

本研究结果显示:在常规治疗基础上联合重组人骨保护素治疗可显著改善患者的髋关节功能,改善髋关节活动受限及疼痛症状,临床治疗优良率可达 90.77%。通过对比常规治疗以及常规治疗基础上加用重组人骨保护素治疗前后患者的骨密度,可见治疗后联合使用重组人骨保护素治疗的激素性股骨头坏死患者,其股骨头及腰椎部位的骨密度与治疗前相比有明显增加,且显著高于治疗后常规治疗组的骨密度,提示重组人骨保护素可有效抑制骨吸收、增加骨密度、促进激素性股骨头坏死患者髋关节功能的恢复。在股骨头坏死的评估中,骨代谢指标应用广泛[18]。TRAP 主要存在于破骨细胞内,通过结合蛋白酶进而参与到骨代谢过程中,可有效反映骨形成 / 骨吸收平衡程度。TRAP 水平上升提示骨吸收变得严重,股骨头坏死程度也就越严重[19]。CTX-Ⅱ属于Ⅱ型胶原代谢产物,可用于评估关节软骨降解程度。CTX-Ⅱ是玻璃液与软骨中的主要胶原,也是构成软骨基质的一种主要成分,可促进软骨细胞分化,目前已成为反映骨转移和骨吸收的重要指标,坏死股骨头骨吸收越严重,则 CTX-Ⅱ水平越高[20]。本研究中,两组患者治疗后血清 TRAP 与 CTX-Ⅱ水平均较治疗前显著下降,但观察组治疗后血清 TRAP 与 CTX-Ⅱ水平明显低于对照组,提示在常规治疗基础上加用骨保护素治疗可有效抑制骨吸收,促进骨修复,进而抑制激素性股骨头坏死病情的进展。

综上所述,在常规治疗基础上联合骨保护素治疗激素性股骨头坏死可有效缓解临床症状,抑制骨吸收,促进骨修复,增强骨密度,改善髋关节功能,进而提高患者的生活质量。

参 考 文 献(References)

[1] Zhang Hui, Liu Jun-feng, Huang Jun-hua, et al. Effect observation of Simvastatin therapy for patients with glucocorticoid-induced avascular necrosis and the effects on the function of circulating endothelial progenitor cell[J]. China Medical Herald, 2013, 10 (22): 67-69

[2] Wang Tian-sheng, Teng Shou-fa, Zhang Ying-xia, et al. The mechanism of bone marrow stromal cell transplantation in the treatment of steroid induced avascular necrosis of the femoral head [J]. Journal of Clinical and Experimental Medicine, 2015, 14 (1): 10-12

[3] Liu Bin, Li Gang, Xu Bo, et al. Glucocorticoids-induced osteonecrosis of the femoral head: adipogenic differentiation and treatment progress [J]. Chinese Journal of Tissue Engineering Research, 2014, 18 (29): 4730-4735

[4] Jiang chuan, Shang Jiang-yinzi, Li Zhe, et al. Lanthanum chloride attenuates osteoclast formation and function via the downregulation of rankl-Induced nf-κb and nfatc1 activities[J]. J Cell Physiol, 2016, 231 (1): 142-151

[5] Zheng Hong, He Bing, Zeng Rong, et al. Effect of Recombinant Human Osteoprotegerin on the Polyethylene Particles-Induced Peripheral Serum IL-6 and TNF-α Expression of Patients after Artificial Joint Replacement [J]. Progress in Modern Biomedicine, 2013, 13 (23): 4467-4469

[6] ARCO (Association Research Circulation Osseous). Committee on Terminology and Classification[J]. ARCO News, 1992, 4 (1): 41-46

[7] Mont MA, Hungerford DS. Non-traumatic avascular necrosis of the femoral head [J]. J Bone Joint Surg (Am), 1995, 77(3): 459

[8] Zhao Fu-tao, Han Xing-hai, Guan Jian-long. Ameliorative effect of hip X-ray radiotherapy on the tip involvement in patients with ankylosing spondylitis: 3-year follow-up[J]. Chinese Journal of Clinical Rehabilitation, 2005, 9(34): 88-91

[9] Wang Xing-shan, Zhuang Qian-yu, Weng Xi-sheng, et al. Etiological and clinical analysis of osteonecrosis of the femoral head in Chinese patients[J]. Chin Med J (Engl), 2013, 126(2): 290-295

[10] Wang Jian-zhong, Wu Yong-gang, Dong Hui-zhen. Effects of atorvastatin on the expression levels of tissue inhibitor of metalloproteinases timps / matrix metalloproteinases in bone tissues of femoral head necrosis induced by glucocorticoid [J]. Chinese Journal of Bone and Joint, 2014, 3(11): 865-870

[11] Busillo JM, Cidlowski JA. The five Rs of glucocorticoid action during inflammation: ready, reinforce, repress, resolve, and restore [J]. Trends Endocrinol Metab, 2013, 24(3): 109-119

[12] Ponnapakkam T, Katikaneni R, Sakon J, et al. Treating osteoporosis by targeting parathyroid hormone to bone [J]. Drug discovery today, 2014, 19(3): 204-208

[13] Li Yi-zhou, Wang Yuan, Chen Jun-yu, et al. Correlation between OPG/RANK/RANKL and steroid induced avascular necrosis of the femoral head [J]. Chinese Journal of Bone and Joint Injury, 2015, 30 (8): 892-893

[14] Xiong Qi, Zhang Li-cheng, Zhang Li-hai, et al. Effects of recombinant human osteoprotegerin and recombinant RANK protein on the differentiation of osteoclast precursors [J]. China J Orthop Trauma, 2013, 26(4): 324-327

[15] Kadri A, Ea HK, Bazille C, et al. Osteoprotegerin inhibits cartilage degradation through an effect on trabecular bone in murine experimental osteoarthritis [J]. Arthritis Rheum, 2008, 58(8): 2379-2386

[16] Zhong Wen-yi, Wu Qi-shan, Gao Li, et al. Effect of recombinant human osteoprotegerin on RANKL, OPG protein expression in alveolar bone tissue of rat with periodontitis [J]. Chongqing Medicine, 2015, 44 (14): 1879-1881

[17] Daugaard H, Elmengaard B, Andreassen T T, et al. Systemic intermittent parathyroid hormone treatment improves osseointegration of press-fit inserted implants in cancellous bone: A canine study [J]. Acta orthopaedica, 2012, 83(4): 411-419

[18] Gao Fei, Zhang Yu, Wang Hong-wei, et al. Correlations of osteoporotic vertebral deformation to bone mineral density and bone metabolic levels [J]. Chin Orthop J Clin Basic Res, 2015, 7 (3): 133-140

[19] Zhang Meng-meng. Bone metabolism indexes in bone remodeling[J]. Chin J Osteoporos, 2013, 19(8): 866-873

[20] Yao Li, Zhao Jing, Zhou Qiang, et al. The Effect of Qutanhuayulishi Decoction on Synocial IL-1β, MMP-1 and Serum IL-1β, MMP-1, COMP and CTX-Ⅱ in Rats with Knee Osteoarthritis [J]. Chinese J Trad Med Traum & Orthop, 2015, 23(11): 5-8, 14

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[11] Ego A, Preiser J C, Vincent J L. Impact of diagnostic criteria on the incidence of ventilator-associated pneumonia [J]. CHEST Journal, 2015, 147(2): 347-355

[12] Valachis A, Samonis G, Kofteridis D P. The role of aerosolized colistin in the treatment of ventilator-associated pneumonia: a systematic review and metaanalysis [J]. Critical care medicine, 2015, 43 (3): 527-533

[13] Nair G B, Niederman M S. Ventilator-associated pneumonia: present understanding and ongoing debates[J]. Intensive care medicine, 2015, 41(1): 34-48

[14] Damas P, Frippiat F, Ancion A, et al. Prevention of ventilator-associated pneumonia and ventilator-associated conditions: a randomized controlled trial with subglottic secretion suctioning [J]. Critical care medicine, 2015, 43(1): 22-30

[15] El-Rabbany M, Zaghlol N, Bhandari M, et al. Prophylactic oral health procedures to prevent hospital-acquired and ventilator-associated pneumonia: A systematic review [J]. International journal of nursing studies, 2015, 52(1): 452-464

[16] Younan D, Lin E, Griffin R, et al. Early trauma-induced coagulopathy is associated with increased ventilator-associated pneumonia in spinal cord injury patients[J]. Shock, 2016, 45(5): 502-505

[17] Leonard K L, Borst G M, Davies S W, et al. Ventilator-Associated Pneumonia in Trauma Patients: Different Criteria, Different Rates[J]. Surgical infections, 2016, 17(3): 363-368

[18] Dimopoulos G, Matthaiou D K. Duration of therapy of ventilator-associated pneumonia [J]. Current opinion in infectious diseases, 2016, 29(2): 218-222

[19] Chastre J. Ventilator-associated pneumonia and ventilator-associated conditions: apples are not oranges (mix only in a salade de fruits!)[J]. Critical care medicine, 2015, 43(1): 227-229

[20] Lutmer J E, Brilli R J. Unanswered Questions and Consternation: The Ventilator-Associated Pneumonia Diagnostic Challenge Continues[J]. Pediatric Critical Care Medicine, 2016, 17(2): 175-176