·临床研究·

体外冲击波联合自体骨髓间充质干细胞移植治疗早期股骨头坏死的疗效观察

张宏军 王帅 范克杰 王绍辉 张延召

【摘 要】 **目的** 观察体外冲击波联合自体骨髓间充质干细胞移植治疗早期股骨头坏死的临床疗效。**方法** 根据股骨头坏死国际骨循环研究学会(ARCO)的股骨头坏死的分期标准,选取Ⅰ期和Ⅱ期股骨头坏死患者 40 例,按随机数字表法分为治疗组 20 例(29 个髋关节),对照组 20 例(27 个髋关节)。2 组患者均采用 BMSC 移植术进行治疗,治疗组患者于 BMSC 移植术后第 2 天行 ESWT 治疗。2 组患者均于治疗前和术后 3、6、12、24 个月采用髋关节Harris评分评定患者的髋关节功能、疼痛程度和疗效,同时采用骨盆正位、蛙式位 X 线片对患者进行 ARCO 分期评定。**结果** 术后 3、6、12、24 个月,2 组的 Harris 评分以及 Harris 量表中的疼痛程度评分与组内治疗前比较,差异均有统计学意义($P<0.05$);且术后 6、12、24 个月,治疗组的 Harris 评分以及 Harris 量表中的疼痛评分与对照组治疗后比较,差异均有统计学意义($P<0.05$)。治疗 12 个月后,治疗组髋关节优 8 个,良 18 个,中 1 个;对照组髋关节优 5 个,良 13 个,中 8 个,组间差异有统计学意义($P<0.05$)。术后 12 个月,2 组换 ARCO 分期评定组间比较,差异有统计学意义($P<0.05$)。**结论** 体外冲击波联合自体骨髓间充质干细胞移植治疗早期股骨头坏死可明显缓解疼痛,改善患者的关节功能。

【关键词】 股骨头坏死; 体外冲击波; 自体骨髓干细胞移植

Extracorporeal shock wave therapy combined with autologous bone marrow stem cells transplantation for treating early-stage osteonecrosis of the femoral head

*Zhang Hongjun**, *Wang Shuai*, *Fan Kejie*, *Wang Shaohui*, *Zhang Yanzhao*. **Henan Luoyang Orthopedic Hospital*, *Luoyang 471002*, *China*

Corresponding author: *Zhang Hongjun*, *Email*: *zdzhj2000@126.com*

【**Abstract**】 **Objective** To observe the therapeutic effects of extracorporeal shock wave therapy (ESWT) combined with autologous bone marrow stem cells (BMSC) transplantation in treating early-stage osteonecrosis of the femoral head (ONFH). **Methods** Forty patients diagnosed as stage Ⅰ or Ⅱ according to the classification of osteonecrosis of the femoral head put forward by the Association Research Circulation Osseous were randomly divided into a treatment group and a control group with 20 cases in each group. Both groups were treated with BMSC transplantation, while the treatment group was further treated with ESWT the next day. Harris scores were assigned before the treatment and 3, 6, 12 and 24 months after the treatment to evaluate hip function, the degree of pain and the effects of the treatment. Frog-bit X-rays of the anteroposterior pelvis were taken to assess the stages. **Results** There were significant differences in the Harris scores and pain degree of the two groups before and at the different time points after the treatment. After 6, 12 and 24 months, significant differences were observed in the two values between the two groups. After 12 months the number of hips rated excellent, good and medium level were 8, 18 and 1 in the treatment group and 5, 13 and 8 in the control group, showing significant differences. **Conclusion** Extracorporeal shock wave therapy along with autologous bone marrow stem cell transplantation can be used to treat patients with early stage osteonecrosis of the femoral head, relieving their pain and improving their joint function.

【**Key words**】 Osteonecrosis; Femoral head; Shock waves; Bone marrow transplants; Stem cells

股骨头坏死(osteonecrosis of the femoral head, ONFH)是骨科临床常见的难治性疾病,且患者逐渐趋于年轻化,目前,在 ONFH 的治疗中,存在关节置换费用高,且年轻患者面临多次翻修等问题,因此,早期发现并及时采用有效的方法保留患者的股骨头极为重要[1]。自体骨髓间充质干细胞(bone marrow stem cell, BMSC)移植用于 ONFH 的治疗在国内外已有较多报道,且疗效较为肯定;而体外冲击波(extracorporeal shock wave therapy, ESWT)作为一种非侵入性无创治

DOI:10.3760/cma.j.issn.0254-1424.2015.04.013

作者单位:471002 洛阳,河南省洛阳正骨医院,河南省骨科医院,组织工程国家工程研究中心(张宏军、范克杰、王绍辉);福建中医药大学骨伤学院(王帅);安徽中医药大学(张延召)

通信作者:张宏军,Email:zdzhj2000@126.com

疗技术,在治疗骨科慢性疾病方面也取得了一定的临床疗效[2]。本研究将 ESWT 与自体 BMSC 移植联合应用治疗早期 ONFH,取得了较为满意的临床效果。现报道如下。

资料和方法

一、一般资料

纳入标准:①符合 ONFH 国际骨循环研究学会(Association Research Circulation Osseous, ARCO)分期[3]中Ⅰ期或Ⅱ期的患者;②年龄 20 ~ 55 岁;③试验经医院医学伦理委员会批准,且患者签署知情同意书。

排除标准:①ONFHⅢ期或Ⅳ期的患者;②严重认知障碍和精神疾病患者;③合并严重的心、肝、肾及造血系统疾病及其他感染性病变不适合手术者;⑤不能坚持治疗或难以随访者。

选取 2009 年 1 月至 2012 年 12 月在我院住院治疗且符合上述标准的 ONFH 患者 40 例,按随机数字表法分为治疗组 20 例(29 个髋关节)和移植组 20 例(27 个髋关节)。2 组患者的年龄、性别、病因、ARCO 分期、坏死侧别等一般资料经统计学分析比较,差异均无统计学意义($P>0.05$),详见表 1。

二、治疗方法

2 组患者均采用 BMSC 移植术进行治疗,治疗组患者于 BMSC 移植术后第 2 天行 ESWT 治疗。

(一)BMSC 移植术

1. BMSC 分离和培养:术前在患者左或右髂后上棘多方向、多层次采用骨髓穿刺针抽取骨髓血,每 10 ml中含肝素盐水 2 ml,单侧采集骨髓血 100 ml,双侧采集 200 ml。干细胞分离提取采用人类骨髓干细胞体外分离纯化试剂盒(中联达盛生物科技公司),按说明书操作,分离提取有核细胞(1 ~ 3) × 10^9 个,单侧制备成细胞悬液 2 ml、双侧 4 ml,采用流式细胞法测定 CD34、CD133、CD166, CD90[4],经检测表明,CD34 和 CD133(二者为造血干细胞标记物)均为低表达,CD90 和 CD166(二者为 BMSC 标记物)均为高表达,即本研究所采用的骨髓间充质干细胞达到高纯度标准[5]。

2. BMSC 移植术:患者取平卧位,结合术前 X 线、MRI 等影像资料,确定坏死范围及大小。麻醉成功后,在股骨大粗隆下 1.5 cm 和 3.0 cm 处分别进针,于 C 臂透视监控下用直径 2 mm 克氏针向股骨头坏死区钻孔直达软骨下骨,以克氏针为引导用直径 3 mm 空心钻扩大骨孔后退出克氏针,用长针头注射器经钻好的骨孔向坏死区内注入已准备好的 BMSC,然后医用蛋白胶封闭骨道,无菌敷料包扎。术后常规口服抗生素 3 d。

(二)ESWT 治疗

ESWT 治疗采用 HK-ESWO-AJII 型骨科冲击波治疗仪(深圳市慧康医疗器械有限公司),患者取仰卧位,结合患者术前 X 线、MRI 等影像资料,以坏死区域及其周围骨质为靶点进行 ESWT 治疗,能流密度为 0.16 mJ/mm^2(9 kV),每个靶点冲击 3000 次,隔日 1 次,5 次为 1 个疗程,共治疗 1 个疗程。

三、疗效评价标准

2 组患者均术后每 3 个月随访 1 次,共随访 2 年,且均于治疗前和术后 3、6、12、24 个月采用髋关节 Harris评分[6](该量表包括疼痛、功能和活动范围共 3 项,总分 100 分,其中疼痛 44 分,功能 51 分,活动范围 5 分,得分越高则髋关节功能越好。总分 90 ~ 100 分为优,80 ~ 90 为良,70 ~ 90 为中,<70 分为差)评定患者的髋关节功能、疼痛程度和疗效;同时采用骨盆正位、蛙式位 X 线片对患者进行 ARCO 分期评定[3]。

四、统计学分析

采用 SPSS 16.0 版统计学软件对研究数据进行统计学分析,计量资料均以($\bar{x} \pm s$)表示,组间比较采用两独立样本 t 检验,计数资料采用 χ^2 检验,等级资料采用秩和检验,以 $P<0.05$ 为差异有统计学意义。

结　果

本组术后无 1 例患者发生术后感染及手术、冲击波治疗相关的并发症。治疗组 18 例(27 个髋关节),对照组 19 例(26 个髋关节)获得 2 年随访。

一、2 组患者 Harris 评分结果

治疗前,2 组患者 Harris 评分以及 Harris 量表中的疼痛程度评分组间比较,差异均无统计学意义($P>0.05$);术后 3、6、12、24 个月,2 组的 Harris 评分以及 Harris 量表中的疼痛程度评分与组内治疗前比较,差异均有统计学意义($P<0.05$);且术后 6、12、24 个月,治疗组的 Harris 评分以及 Harris 量表中的疼痛评分与对照组治疗后比较,差异均有统计学意义($P<0.05$),详见表 2 和表 3。治疗12个月后,治疗组髋关节优8

表 1　2 组患者一般资料

组别	例数	性别(例)		平均年龄	髋关节 ONFH 病因(个)				髋关节 ARCO 分期(个)		单双侧(例)	
		男	女	(岁,$\bar{x} \pm s$)	激素	酒精	外伤	特发	Ⅰ期	Ⅱ期	单侧	双侧
治疗组	20	15	5	36.1 ± 6.2	8	7	4	10	8	21	11	9
对照组	20	14	6	35.5 ± 5.7	7	8	3	9	8	19	13	7

表 2　2 组治疗前、后 Harris 量表评分比较(分,$\bar{x} \pm s$)

组别	例数	治疗前	术后 3 个月	术后 6 个月	术后 12 个月	术后 24 个月
治疗组	27	61.75 ± 5.13	73.72 ± 4.81[a]	81.12 ± 5.32[ab]	84.15 ± 4.83[ab]	89.19 ± 5.53[ab]
对照组	26	62.37 ± 4.25	73.57 ± 4.14	77.74 ± 4.61	80.27 ± 4.27	82.64 ± 5.11

注:与组内治疗前比较,[a]$P < 0.05$;与对照组同时间点比较,[b]$P < 0.05$

表 3　2 组治疗前、后 Harris 量表疼痛评分比较(分,$\bar{x} \pm s$)

组别	例数	治疗前	术后 3 个月	术后 6 个月	术后 12 个月	术后 24 个月
治疗组	27	25.35 ± 3.26	29.28 ± 3.2[a]	33.24 ± 3.46[ab]	38.49 ± 3.58[ab]	41.69 ± 2.24[ab]
对照组	26	25.67 ± 3.71	28.97 ± 2.77	30.47 ± 3.67	36.33 ± 3.22	37.15 ± 2.75

注:与组内治疗前比较,[a]$P < 0.05$;与对照组同时间点比较,[b]$P < 0.05$

个,良 18 个,中 1 个;对照组髋关节优 5 个,良 13 个,中 8 个,组间差异有统计学意义($Z = -2.054$,$P < 0.05$)。

二、ARCO 分期评定

术后 12 个月,治疗组有 2 例 2 个髋关节Ⅱ B 期患者进展为Ⅱ C 期,1 例 1 个髋关节Ⅱ C 期出现塌陷,进展为Ⅲ A 期;对照组有 4 例 6 个髋关节Ⅱ B 期患者进展为Ⅱ C 期,2 例 3 个髋关节Ⅱ C 期患者出现塌陷,进展为Ⅲ A 期,2 组比较,差异有统计学意义($\chi^2 = 4.178$,$P < 0.05$)。

讨　论

本研究结果显示,2 组 ONFH 患者经 BMSC 移植术后 3、6、12 和 24 个月,其 Harris 评分以及 Harris 量表中的疼痛程度评分与组内治疗前比较,差异均有统计学意义($P < 0.05$),提示 BMSC 移植术可显著改善 ONFH 患者髋关节的功能。这与王坤等[4]和李瑞琦等[7]的研究结果一致。本课题组认为,其可能的原因是钻孔减压不仅可以减轻股骨头颈内高压,还可改善血液循环,减轻骨髓水肿[8];BMSC 的植入可增强其向成骨细胞分化,维持成骨细胞生成与凋亡之间的平衡,促进股骨头内再血管化、再骨化,从而达到改善髋关节功能的目的。有研究指出,BMSC 是一种来源于中胚层的间充质细胞,具有增殖与多向分化性、高保真性等生物学特性,在一定条件下,可分化为成骨细胞、成软骨细胞、成骨骼肌细胞等多种细胞谱系,是修复坏死股骨头组织的最理想组织工程种子细胞之一[8]。

有研究指出,物理治疗可改善骨组织的氧含量,减轻水肿,减小骨内压,改善骨循环,促使缺血、缺氧组织恢复血液供应,促进坏死区的骨修复[9]。Wang 等[10-11]进行了 ESWT 治疗早期 ONFH 的研究,同时与髓芯减压、自体骨和异体腓骨移植手术进行了疗效比较,结果发现,ESWT 治疗早期 ONFH 的疗效显著优于髓芯减压和自体骨、异体腓骨移植疗法。本课题组前期采用 ESWT联合中药口服治疗早期 ONFH 取得了较好疗效,研究认为,其作用机制可能与机械应力效应、应力压电效应、空化及成骨效应、代谢激活效应等促进坏死股骨头的血管生成,改善血液循环,缓解机体的高凝状态,改善成骨细胞和血管内皮细胞的功能状态,从而加速 ONFH 的修复有关[12]。

本研究采用 ESWT 与 BMSC 移植相结合的治疗方案,结果显示,术后 6、12 和 24 个月,治疗组的 Harris 评分以及 Harris 量表中的疼痛评分与对照组治疗后比较,差异均有统计学意义($P < 0.05$),提示 ESWT 与自体 BMSC 移植联合治疗早期 ONFH,其疗效显著优于单纯的自体 BMSC 移植治疗。课题组认为,其作用机制可能为:①机械应力效应可使坏死部位不同密度的组织间产生梯度差及扭拉力,从而松解粘连,减轻股骨头内压;②细胞周围自由基的改变过程中可释放抑制疼痛的物质;③高强度冲击波可对神经轴突产生强刺激,从而破坏部分痛觉感受器的细胞膜,降低神经敏感性,缓解肌肉紧张,阻断痛觉传导通路[13-14]。

综上所述,ESWT 结合自体 BMSC 移植术治疗早期 ONFH 可以显著缓解患者的疼痛症状,改善其关节功能,提高生活质量。由于本研究样本量偏小,随访时间较短,其远期疗效需还有待进一步随访,且 ESWT 联合自体 BMSC 移植术的作用机制也有待于进一步研究。

参　考　文　献

[1] 孙伟,李子荣. 股骨头坏死:保存自身关节的治疗[J]. 中国关节外科杂志,2011,5(3):60-62.

[2] 丁志进,丁凤菲,周全胜. 体外冲击波在骨骼-肌肉疾病疼痛康复治疗中的应用[J]. 中华物理医学与康复杂志,2011,33(4):313-315.

[3] 中华医学会骨科分会纤维修复学组,中国修复重建外科专业委员会骨缺损及骨坏死学组. 成人股骨头坏死诊疗标准专家共识(2012)[J]. 中华骨科杂志,2012,32(6):606-610.

[4] 王坤,龚跃昆,李彪,等. 骨髓间充质干细胞治疗早期股骨头坏死的作用与机制[J]. 中国组织工程研究与临床康复,2011,15(10):1863-1866.

[5] 王廷华,羊惠君,Mcdonald JW. 干细胞理论与技术. 北京:科学出版社,2005:56-61.

[6] Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fractures:treatment by mold arthroplasty. An end-result study using

a new method of result evaluation[J]. J Bone Joint Surg Am,1969,51(4):737-755.
[7] 李瑞琦,张国平,任立中,等. 骨髓间充质干细胞治疗股骨头坏死的评价[J]. 中国组织工程研究,2013,17(35):6327-6332.
[8] 杨静,康鹏德,沈彬,等. 小孔径通道髓芯钻孔减压治疗早中期股骨头坏死[J]. 中华骨科杂志,2010,30(1):58-61.
[9] 郭万首,李子荣. 股骨头坏死的保存自身关节治疗[J]. 中华骨科杂志,2010,30(1):19-24.
[10] Wang CJ, Wang FS, Huang CC, et al. Treatment for osteonecrosis of the femoral head: comparison of extracorporeal shock waves with core decompression and bone-grafting. J Bone Joint Surg Am, 2005, 87(11):2380-2387.
[11] Wang CJ, Huang CC, Wang JW, et al. Long-term results of extracorporeal shockwave therapy and core decompression in osteonecrosis of the femoral head with eight- to nine-year follow-up. Biomed J, 2012, 35(6):481-485.
[12] 范克杰,张宏军,郭艳幸. 体外冲击波联合中药内服治疗股骨头坏死 60 例[J]. 中国中医骨伤科杂志,2014,22(8):44-45.
[13] 梁卫东,徐王兵,李晓芳,等. 体外冲击波治疗股骨头坏死的临床研究[J]. 实用中西医结合临床,2012, 12(6):28-29.
[14] 周宁,邵彬,陈勇,等. 冲击波治疗肩周炎的单盲研究[J]. 中国康复医学杂志,2009,24(6):537-539.

(修回日期:2015-01-29)
(本文编辑:阮仕衡)

· 外刊撷英 ·

Nutritional supplements for pressure ulcer healing

BACKGROUND AND OBJECTIVE Malnutrition is known to be prevalent among patients with pressure ulcers, and is considered a factor contributing to the development of, as well as inhibiting the healing of these ulcers. As previous studies have demonstrated that supplementation with nutritional formulas enriched with arginine, zinc and antioxidants may having a healing effect, this study further investigated whether an oral nutritional supplement enriched with those substances can assist in healing pressure ulcers.

METHODS Subjects were long-term care residents or homecare patients with stage II through stage IV pressure ulcers, all demonstrating malnourishment, defined as a low body mass index, recent unintentional weight loss, low serum albumin levels and reduced food intake. The subjects were randomized to receive a control formula or an experimental formula enriched with arginine, zinc, and vitamins E and C. All patients received optimal wound care. Pressure ulcer areas were documented at baseline, and four and eight weeks.

RESULTS Of the screened patients, 200 were randomized. Both groups realized improved wound healing. Compared to baseline, pressure ulcer areas were decreased by an average of 60.9% in the treatment group and 45.2% in the control group ($P=0.017$). In the treatment group, 16.9% experienced complete healing, as compared with 9.7% in the control group ($P=0.097$). Withdrawals from the study included two in the experimental group and three in the control group, with gastrointestinal intolerance as the primary cause of withdrawal.

CONCLUSION This study found that, when added to optimal wound care and proper nutrition, a formula with arginine, zinc and antioxidants seems to accelerate pressure ulcer wound healing.

【摘自:Cereda E, Klersy C, Serioli M, et al. A nutritional formula enriched with arginine, zinc and antioxidants for the healing of pressure ulcers. Ann Intern Med. 2015, 3; 162(3): 167-174.】

Ultrasound assessment of steroid injections to the knee

BACKGROUND AND OBJECTIVE Osteoarthritis (OA) is a common form of arthritis, affecting up to 10% of the North American elderly population. In addition, the prevalence of radiographically established OA in the United States is estimated to be 33% among individuals over 63 years of age. This study was designed to determine whether ultrasound (US) can be effective in demonstrating a response to intra-articular corticosteroid injections to the knee.

METHODS Subjects included 35, consecutive subjects who met the American College of Rheumatology's radiologic criteria for OA. All subjects completed a symptom assessment and US examination at baseline, and returned for follow-up at 14 weeks. Of those, 19 participants were determined to be in need of a corticosteroid injection, and received 80 mg of methylprednisolone mixed with 2 mL of lidocaine one percent. The remaining subjects underwent no therapeutic intervention. All participants were asked to rate their knee pain on a visual analogue scale, and to complete the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC). The knee joints were assessed with US at baseline and at four weeks.

RESULTS At follow-up US, synovial thickness was noted to have decreased in 16 of the 19 patients in the treatment group, and in two of the 14 patients in the control group ($P=0.012$). A reduction in synovial thickness was associated with a reduction in pain greater than or equal to the predetermined minimally clinically important improvement level (>20 mm on the VAS). With both groups combined, no substantial association was seen between changes in synovial thickness and changes in pain.

CONCLUSION This pilot study suggests that US may be useful in detecting early changes in synovial pathology in response to intra-articular anti-inflammatory therapy.

【摘自:Keen HI, Hensor EM, Wakefield RJ, et al. Ultrasound assessment of response to intra-articular therapy in osteoarthritis of the knee. Rheum. 2015 DOI: 10. 1093/rheumatology/keu 529】