

doi: 10.13241/j.cnki.pmb.2017.14.017

髓芯减压联合干细胞移植治疗股骨头坏死患者的临床疗效及机制研究*

付大鹏^{1,2} 覃开蓉¹ 廉皓屹² 杨 圣² 芦健民² 赵德伟^{2Δ}

(1 大连理工大学 生物医学工程系 辽宁 大连 116024; 2 大连大学附属中山医院 骨科 辽宁 大连 116001)

摘要 目的:探讨采用髓芯减压与干细胞移植联合治疗股骨头坏死患者的临床疗效及可能机制。**方法:**选择我院确诊并治疗的股骨头患者 76 例作受试者,按随机数字表法分为两组,对照组 38 例采用干细胞移植治疗,治疗组 38 例在对照组基础上联合髓芯减压疗法。观察和比较两组患者的临床疗效、髋关节 Harris 评分及治疗前后血清 PINP(I 型前胶原氨基端前肽)、CTX(I 型胶原 C 端肽)、OST(骨钙素)水平的变化情况。**结果:**治疗组总有效率及 Harris 评分均显著高于对照组($P < 0.05$);治疗组患者血清 PINP、CTX、OST 水平较治疗前明显下降,并显著低于对照组,差异具有统计学意义($P < 0.05$)。**结论:**髓芯减压与干细胞移植的联合应用可提高股骨头坏死患者的临床疗效和髋关节功能,可能与其降低患者血清 PINP、CTX、OST 水平有关。

关键词:股骨头坏死;髓芯减压;干细胞移植;I 型前胶原氨基端前肽;I 型胶原 C 端肽;骨钙素

中图分类号:R681 **文献标识码:**A **文章编号:**1673-6273(2017)14-2674-04

A Study on the Effect and Mechanism of Core Decompression combined with Stem Cell Transplantation on Patients with Femoral Head Necrosis*

FU Da-peng^{1,2}, QIN Kai-rong¹, LIAN Hao-qí², YANG Sheng², LU Jian-min², ZHAO De-weí^{2Δ}

(1 Department of Biomedical Engineering, Dalian University of Technology, Dalian, Liaoning, 116024, China;

2 Department of orthopedics, the affiliated Zhongshan hospital, Dalian University, Dalian, Liaoning, 116001, China)

ABSTRACT Objective: To investigate the effects of core decompression combined with stem cell transplantation on the serum levels of PINP, CTX and OST in patients with femoral head necrosis and its clinical efficacy. **Methods:** 76 patients with femoral head necrosis who were diagnosed and treated in our hospital were selected and randomly divided into two groups, with 38 cases in each group. The patients in the control group were treated with stem cell transplantation, while the patients in the experimental group were treated with core decompression therapy on the basis of the control group. Then the hip Harris score and the serum levels of PINP, CTX and OST of patients in the two groups were observed and compared before and after treatment. **Results:** The total effective rate and Harris score of experimental group were higher than those of the control group ($P < 0.05$). The serum levels of PINP, CTX and OST in the experimental group were obviously decreased, which were significantly lower than those of the control group ($P < 0.05$). **Conclusion:** Core decompression combined with stem cell transplantation could improve the efficacy and function of hip joint, it might be related to the reduction of serum levels of PINP, CTX and OST levels.

Key words: Femoral head necrosis; Core decompression; Stem cell transplantation; PINP; CTX; OST

Chinese Library Classification(CLC): R681 **Document code:** A

Article ID: 1673-6273(2017)14-2674-04

前言

股骨头坏死又称缺血性股骨头坏死,是一种由创伤性或非创伤性损害引发股骨头血供受损或中断,骨强度及张力下降,从而诱发股骨头结构改变、塌陷、关节功能障碍等症状发生的骨科常见疾病^[1]。股骨颈骨折复位愈合不良、骨强度及密度降低、髋关节创伤、激素滥用、乙醇中毒等原因造成的股骨头血液循环障碍是导致骨细胞缺血、变性、坏死的主要原因^[2]。以腹股沟、臀部及大腿部为主的关节持续性、间歇性或交替性疼痛、髋关节屈伸不利,活动受限、间歇性跛行、骨质疏松及局部深压痛等症状的出现往往提示股骨头坏死的发生^[3]。流行病学调查显

示^[4]股骨头坏死是致残致死率较高的骨科疾病之一,其发生多集中在 30~60 岁成年人群中,约占总发生率的 75%以上。手术疗法是目前股骨头坏死治疗的主要手段,干细胞移植是指通过自身干细胞的植入增加股骨颈及股骨干坏死区域附近骨髓干细胞数量,激发坏死区周边细胞活性,加快坏死骨吸收后的修复进程,促进骨、软骨等组织分化及愈合,防止骨塌陷形成^[5,6]。髓芯减压是一种通过清除坏死组织、释放股骨头髓腔内压力,改善静脉回流,刺激血管再生,从而促进股骨头修复,尽早恢复血液供应的一种手术方式^[7]。本实验通过观察治疗前后患者血清 PINP、CTX、OST 浓度及 Harris 评分变化情况,探讨髓芯减压术与干细胞移植的联合应用在股骨头坏死的治疗中的作用

* 基金项目:辽宁省自然科学基金项目(201020214)

作者简介:付大鹏(1979-),男,硕士研究生,主治医师,研究方向:生物医学工程

Δ 通讯作者:赵德伟(1955-),男,博士,主任医师,电话:13236920515

(收稿日期:2016-10-16 接受日期:2016-11-12)

及其可能机制。

1 资料与方法

1.1 临床资料

选取于2013年6月~2014年6月入住我院的符合诊断标准的股骨头坏死Ⅰ、Ⅱ患者76例作为本次研究对象。按照随机数字表法进行分组,对照组38例予以干细胞移植进行治疗,其中男性16例,女22例;年龄为23-62岁,平均年龄为(40.38±2.86)岁;治疗组38例在对照组基础上予以髓芯减压术联合治疗,其中男性20例,女18例;年龄为23-62岁,平均年龄为(38.29±2.91)岁;两组未有脱落,且两组间平均年龄、性别、病情发展状况等基本资料选择无偏倚性($P>0.05$)。患者自愿参与本次研究,与家属确认无异议后,自主签署知情同意书,积极配合此次研究。本次研究获得批准,并在市伦理委员会的追踪监督下完成。

1.2 纳入标准

①研究对象符合我国2012年颁布的《股骨头坏死诊疗标准专家共识》的诊断标准,并根据世界股循环研究学会的国际骨坏死分期标准,选取Ⅰ、Ⅱ期股骨头坏死患者;②术前患者空腹血糖控制在8 mmol/L以下、血压水平不超过160/100 mmHg;③患者主诉有髋部关节疼痛或伴有膝关节疼痛、关节活动受限、间歇性跛行等临床表现;④患者意识清醒,无手术禁忌症。

1.3 排除标准

①排除心肝肾功能严重损伤、消化系统异常、中风、严重高血压、妊娠期及哺乳期患者。②排除有下肢关节置换手术史及腰部损伤史的患者;③排除患有凝血功能障碍疾病的患者。④排除有过敏史及近3个月内服用利尿剂、钙制剂、维生素D类似物的患者。

1.4 治疗方法

入院后,所有患者进行血常规、尿常规、血糖及血压等一般

检查,同时给予患者X线、MRI等影像学检测,患者评估患者一般身体状态。确认所有患者均无手术禁忌症后,采用硬膜外麻醉。对照组:患者进行干细胞移植手术。治疗组:在对照组的基础上,对患者进行髓芯减压手术,两组患者手术均为同一组医务人员实施。术后患者去枕平卧,监测呼吸、脉搏、血压等一般体征,3个月内不得负重,定期X线检查。

1.5 观察指标及检测方法

1.5.1 观察记录 Harris 评分及临床症状改变 对患者治疗前及治疗后1个月、3个月、6个月、12个月的Harris评分情况进行追踪并比较,观察患者临床症状改变情况。

1.5.2 血清 PINP、CTX、OST 水平 患者治疗前后血清 PINP、CTX、OST 水平的测定采用电化学发光免疫分析法。

1.6 疗效评价标准

股骨头坏死患者的选取符合《股骨头坏死诊疗标准专家共识(2012版)》及国际股骨头坏死诊断标准,记录所有患者Harris评分及影像学变化情况,综合评定治疗效果。显效:治疗后患者腹股沟、臀部及大腿部关节疼痛、关节活动受限、间歇性跛行等临床症状消失或明显改善,Harris评分不低于75分。有效:患者腹股沟、臀部及大腿部关节疼痛、关节活动受限、间歇性跛行等临床症状得到改善,Harris评分大于60分。无效:患者临床症状无改善或进展,Harris评分低于60分。总有效率=[(显效例数+有效例数)/本组患者例数]×100%。

1.7 统计学分析

采用SPSS17.0软件将研究数据进行统计学分析,计量资料以均数±标准差($\bar{x}\pm s$)表示,采用t检验,计数资料以率(%)表示,采用 χ^2 检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者临床疗效的比较

治疗后,治疗组患者的临床有效率(89.47%)明显高于对照组(65.79%),差异具有统计学意义($P<0.05$)(表1)。

表1 两组临床疗效的比较[例(%)]

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

Groups	n	Excellent	Effective	Invalid	Clinical curative effect rate
Control group	38	11(28.95)	14(36.84)	13(34.21)	25(65.79)
Experimental group	38	18(47.37)	16(42.11)	4(10.53)	34(89.47)*

注:与对照组相比较,* $P<0.05$ 。

Note: Compared with control group, * $P<0.05$.

2.2 两组患者治疗前后 Harris 评分变化的比较

治疗后,两组患者Harris评分均较治疗前有所升高,12个月 after 评分变化明显,差异具有统计学意义($P<0.05$);与对照组相比,治疗组患者治疗后12个月的Harris评分更接近理想状态,差异具有统计学意义($P<0.05$)(表2)。

2.3 两组患者治疗前后 PINP、CTX 及 OST 水平的比较

治疗后,两组患者血清 PINP、CTX、OST 水平均较治疗前明显降低,差异具有统计学意义($P<0.05$);与对照组相比,治疗组患者血清 PINP、CTX、OST 水平更低,差异具有统计学意义

($P<0.05$)(表3)。

3 讨论

股骨头坏死是引发残疾形成的临床最常见骨科疾病之一,其发病人群多集中于成年^[8],发病机制为过量激素及酒精摄入诱发脂类代谢紊乱、骨内高压、血管内凝血的发生,造成血液循环障碍,从而引起骨质坏死、死骨吸收和新骨形成、股骨头再塑造等股骨头坏死病理过程的发生^[9]。近年来,不健康的生活习惯、饮食结构失衡、激素类药物的滥用等成为成年股骨头坏死

表 2 两组患者治疗前后 Harris 评分变化的比较

Table 2 Comparison of the change of Harris score between two groups before and after treatment

Groups	Before treatment	1 month	3 months	6 months	12 months
Control group	49.21± 8.37	52.76± 10.43	67.98± 13.65	73.76± 14.79	75.36± 15.06
Experimental group	47.75± 10.62	54.21± 12.56	72.41± 14.78	78.98± 15.31	82.75± 16.21*

注:与治疗前相比, *P<0.05。

Note: Compared with before treatment, *P<0.05.

表 3 两组患者治疗前后血清 PINP、CTX 及 OST 水平的比较

Table 3 Comparison of the serum PINP, CTX and OST levels between two groups before and after treatment

Groups		PINP(μg/L)	CTX(μg/L)	OST(ng/mL)
Control group (n=36)	Before treatment	81.67± 12.72	1.07± 0.32	37.53± 4.03
	After treatment	67.31± 8.52*	1.01± 0.29*	32.32± 2.97*
Experimental group (n=36)	Before treatment	82.01± 11.87	1.05± 0.34	37.41± 3.84
	After treatment	52.83± 7.74*#	0.73± 0.24*#	28.37± 2.03*#

注:与治疗前相比, *P<0.05;与对照组相比, #P<0.05。

Note: Compared with before treatment, *P<0.05; compared with control group, #P<0.05.

发生率增高的主要原因^[10]。目前,临床主要通过降低骨内压力、增加坏死组织周围细胞活性、加快血液循环的恢复、减少组织缺血缺氧时间治疗股骨头坏死^[11]。研究表明^[12]干细胞是一类具有自我复制能力的多潜能细胞,具有极高的自我更新、多向分化、重建长期造血潜能及损伤后自我修复的能力。采用干细胞移植手法治疗股骨头坏死能有效促进骨、软骨、肌肉、脂肪的分化,促进软骨缺损、血液供应的修复^[13]。髓芯减压术对股骨头坏死的治疗是通过清除股骨头髓腔内坏死组织、减轻骨内压力,消除水肿,增强坏死骨爬行替代,延缓股骨头坏死进展,尽快恢复血液供应来实现的^[14,15]。本组研究结果表明髓芯减压与干细胞移植的联合应用可明显提高股骨头坏死的临床疗效。

Harris 评分是一种针对患者髋关节形态、疼痛、功能、活动范围等方面进行综合评估的常用方式,能有效判定患者髋关节状态,对股骨头坏死患者的治疗有指导意义^[16]。研究证实^[17]90%的骨基质是由 I 型胶原组成的, I 型前胶原氨基端前肽(PINP)的形成来源于 I 型胶原的沉积,其浓度变化与骨胶原合成情况、骨细胞活性、成骨能力密切相关,因此临床又称其为骨形成标志物。I 型胶原羧基端肽(CTX)是 I 型胶原降解特异性产物,被誉为骨吸收标志物,能有效表达破骨细胞活性,为骨质疏松及抗吸收治疗提供诊断依据^[18]。骨钙素(OST)又称 γ-羧基谷氨酸蛋白(BGP),是一种由成骨细胞生成和分泌的对骨代谢具有调节作用非胶原蛋白,其浓度的测定为评估成骨细胞活性、骨代谢转换率提供依据。有研究表明^[19,20]股骨头坏死患者血清 PINP、CTX、OST 水平明显增高且其浓度与股骨头坏死严重程度呈正相关。本组研究结果显示对照组患者血清 PINP、CTX、OST 的水平较高,有效率较低,表明髓芯减压术与干细胞移植的联合应用提高股骨头坏死患者的联系疗效可能与其降低血清 PINP、CTX、OST 的水平有关。

综上所述,本研究发现髓芯减压与干细胞移植的联合应用可提高股骨头坏死患者的临床疗效和髋关节功能,可能与其降

低患者血清 PINP、CTX、OST 水平有关。髓芯减压术与干细胞移植的联合应用在促进坏死骨组织局部干细胞活性、尽早恢复患者股骨头血供等方面效果显著,值得推广。然而本次研究样本数、例数限制,关于髓芯减压术与干细胞移植的联合应用对股骨头坏死患者的有效性需要循证医学证据进一步证实。

参考文献(References)

- [1] Zhao C S, Xin L, Qiang Z, et al. Early Outcomes of Primary Total Hip Arthroplasty for Osteonecrosis of the Femoral Head in Patients with Human Immunodeficiency Virus in China [J]. Chin Med J (Engl), 2015, 128(15): 2059-2064
- [2] Zhao D W, Yu M, Hu K, et al. Prevalence of Nontraumatic Osteonecrosis of the Femoral Head and its Associated Risk Factors in the Chinese Population: Results from a Nationally Representative Survey[J]. Chin Med J (Engl), 2015, 128(21): 2843-2850
- [3] Zheng Hui-feng, Yang Er-ping, Peng Hao, et al. Gastrodin prevents steroid-induced osteonecrosis of the femoral head in rats by anti-apoptosis[J]. Chin Med J (Engl), 2014, 127(22): 3926-3931
- [4] Yini Jiang, Daobing Liu, Xiangying Kong. Huogu I formula prevents steroid-induced osteonecrosis in rats by down-regulating PPARγ expression and activating Wnt/LRP5/β-catenin signaling [J]. J Tradit Chin Med, 2014, 34(3): 342-350
- [5] Li Qi-zhou, Wang Yuang, 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
- [6] Cao L, Wang B, Li M, et al. Closed reduction and internal fixation versus total hip arthroplasty for displaced femoral neck fracture [J]. Chinese Journal of Traumatology, 2014, 17(2): 63-68
- [7] Dagaard 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

- [8] CongLiu, Meng-TingLiu, PengLi, et al. Efficacy Evaluation for the Treatment of Subcapital Femoral Neck Fracture in Young Adults by Capsulotomy Reduction and Closed Reduction[J]. Chin Med J (Engl), 2015, 128(4): 483-488
- [9] Ünal MB, Cansü E, Parmaks ızo ğ lu F, et al. Treatment of osteonecrosis of the femoral head with free vascularized fibular grafting: results of 7.6-year follow-up [J]. Acta Orthopaedica Et Traumatologica Turcica, 2016, 50(3): 185-196
- [10] Chen D, Chen X, Bai Y, et al. Mechanism of Tongluo Shenggu Capsules on Glucocorticoid-induced Osteonecrosis of Femoral Head in Rabbits [J]. Traditional Chinese Drug Research & Clinical Pharmacology, 2016, 15(8): 25-78
- [11] Ning Y, Wei T, Lei S, et al. Neural stem cell transplantation in a double-layer collagen membrane with unequal pore sizes for spinal cord injur y repair [J]. Neural Regeneration Research, 2014, 9(10): 1014-1019
- [12] Wojciech P, Philip K, Beckmann N A, et al. Core Decompression and Autologous Bone Marrow Concentrate for Treatment of Femoral Head Osteonecrosis: A Randomized Prospective Study[J]. Orthopedic Reviews, 2016, 8(1): 47-52
- [13] Yang Z, Nan W, Yang L F, et al. Bone marrow mesenchymal stem cell transplantation combined with core decompression and bone grafting in the repair of osteonecrosis of femoral head [J]. Int J Clin Exp Med, 2015(6): 883-890
- [14] Yan Y, Ma T, Kai G, et al. Adipose-derived mesenchymal stem cell transplantation promotes adult neurogenesis in the brains of Alzheimer's disease mice [J]. Neural Regeneration Research, 2014, 9(8): 798-805
- [15] Ye-ming, GUAN, Hai-li, et al. Human umbilical cord blood mesenchymal stem cell transplantation suppresses inflammatory responses and neuronal apoptosis during early stage of focal cerebral ischemia in rabbits [J]. Acta Pharmacologica Sinica, 2014, 35(5): 585-591
- [16] Yang J H, Kim J H, Lim D S, et al. Effect of combined sex hormone replacement on bone/cartilage turnover in a murine model of osteoarthritis[J]. Clinics in orthopedic surgery, 2012, 4(3): 234-241
- [17] Wojciech P, Philip K, Beckmann N A, et al. Core Decompression and Autologous Bone Marrow Concentrate for Treatment of Femoral Head Osteonecrosis: A Randomized Prospective Study[J]. Orthopedic Reviews, 2016, 8(1): 256-266
- [18] Wang Z, Zhou X, Liang D, et al. Clinical Randomized Controlled Trial on Needle- Knife and Marrow Core Decompression Therapy for Early and Middle Avascular Necrosis of Femoral Head [J]. Liaoning Journal of Traditional Chinese Medicine, 2016, 77(52): 25-54
- [19] Shi Y, Zhou S, He X, et al. Autologous hematopoietic stem cell transplantation in chemotherapy-sensitive lymphoblastic lymphoma: treatment outcome and prognostic factor analysis [J]. Chin J Cancer Res, 2015, 27(1): 66-73
- [20] Dong Y, Yang L, Lin Y, et al. Transplantation of neurotrophin-3-transfected bone marrow mesenchymal stem cells for the repair of spinal cord injur y [J]. Neural Regeneration Research, 2014, 9(16): 1520-1524

(上接第 2785 页)

- [71] Zhou X, Murphy FR, Gehdu N, et al. Engagement of alphavbeta3 integrin regulates proliferation and apoptosis of hepatic stellate cells [J]. J Biol Chem, 2004, 279(23): 23996-24006
- [72] Xu X, Shi F, Huang W, et al. Metallothionein gene transfection reverses the phenotype of activated human hepatic stellate cells [J]. J Pharmacol Exp Ther, 2013, 346(1): 48-53
- [73] Jiang YF, Sun HL, Zhang JJ, et al. Effect of shRNA-mediated silencing of CTGF and TIMP-1 on mRNA expression of CTGF, TIMP-1, and PC I and secretion of extracellular matrix in rat hepatic stellate cells [J]. Chinese Journal of Hepatology ISSN, 2012, 20(8): 576-580
- [74] Murphy FR, Issa R, Zhou X, et al. Inhibition of apoptosis of activated hepatic stellate cells by tissue inhibitor of metalloproteinase-1 is mediated via effects on matrix metalloproteinase inhibition: implications for reversibility of liver fibrosis [J]. J Biol Chem, 2002, 277(13): 11069-11076
- [75] Pellicoro A, Ramachandran P, Iredale JP. Reversibility of liver fibrosis[J]. Fibrogenesis Tissue Repair, 2012, 5(Suppl 1): S26
- [76] Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs[J]. Mol Cell, 2011, 43(6): 904-914
- [77] Du Y, Kong G, You X, et al. Elevation of highly up-regulated in liver cancer (HULC) by hepatitis B virus X protein promotes hepatoma cell proliferation via down-regulating p18[J]. J Biol Chem, 2012, 287(31): 26302-26311
- [78] He Y, Wu YT, Huang C, et al. Inhibitory effects of long noncoding RNA MEG3 on hepatic stellate cells activation and liver fibrogenesis [J]. Biochim Biophys Acta, 2014, 1842(11): 2204-2215