·论著·

双膦酸盐相关非典型股骨骨折的手术治疗

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摘要:**目的** 探讨手术治疗双膦酸盐相关非典型股骨骨折的疗效。**方法** 回顾性分析 2011 年 1 月至 2012 年 12 月手术治疗的 15 例(15 侧骨折)双膦酸盐相关非典型股骨骨折患者资料,平均年龄 76.0±6.4 岁(65~88 岁)。所有病例骨折时髋部骨密度 T 值平均为 -3.1±0.7(-1.8~-4.5)。9 病例骨折部位位于转子下,6 例位于股骨干。12 例采用髓内针固定。3 例采用钢板螺钉固定。术后观察患者的骨折愈合情况。**结果** 所有患者术后均获骨性愈合,平均愈合时间为 5.9±1.4 个月(4~8 个月)。无感染、骨折不愈合,内固定物松动或断裂,下肢深静脉血栓等并发症发生。不同固定方式骨折愈合时间无差异(t=1.56,P=0.14)。服药时间与骨折愈合时间无相关性(r=0.034,P=0.904)。**结论** 手术治疗是双膦酸盐相关非典型股骨骨折的有效方法。

关键词:股骨骨折;双膦酸盐类;非典型骨折

Surgical treatment for bisphosphonate-related atypical femoral fractures

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Abstract: **Objective** To investigate the effect of surgical treatment for bisphosphonate-related atypical femoral fractures. **Methods** The clinical data of 15 patients with bisphosphonate-related atypical femoral fractures (15 sides), who received operations from January 2011 to December 2012, aging from 65 to 88 years old, with an average age of 76.0±6.4 years old, were retrospectively analyzed. The average T-score of the hip BMD in all the cases was -3.1±0.7 (1.8~-4.5). Nine cases were subtrochanteric fractures, and 6 cases were femoral shaft fractures. Twelve cases were operated using intramedullary nail fixation. Three cases were operated using steel screws. The healing of the fractures in all patients was observed. **Results** All fractures after the operations had healed, with an average healing duration of 5.9±1.4 months, ranging from 4 to 8 months. No infection, nonunion, fixation loosening or rupture, deep vein thrombosis, and other complications occurred. No difference of healing duration in different fixation methods was observed (t=1.56, P=0.14). No correlation between the duration of fracture healing and the period of medication was observed (r=0.034, P=0.904). **Conclusion** Surgical treatment is an effective treatment for bisphosphonate-related atypical femoral fractures.

Key words: Femoral fractures; Bisphosphonates; Atypical fractures

双膦酸盐类药物自 20 世纪 70 年代应用于临床以来,因其能明显抑制破骨细胞活性,减少破骨细胞引导的骨吸收,增加骨量和降低椎体及髋部骨折而成为治疗骨质疏松症的重要药物[1]。但是近年来,一些学者报道[2-4]部分长期服用双膦酸盐的患者出现非典型股骨干或股骨转子下骨折。此类骨折与骨质疏松症所致的髋部骨折有所不同。我们回顾性分析 2011 年 1 月至 2012 年 12 月期间韩国首尔庆熙大学医疗中心骨科手术治疗 15 例与长期服用双膦酸盐相关的非典型股骨骨折患者资料,进行相应分析。

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1 资料和方法

1.1 研究对象

在2011 年1 月 ~2012 年12 月间于韩国首尔庆熙大学医疗中心骨科进行手术治疗的双膦酸盐相关股骨不典型骨折的患者。本研究双膦酸盐相关不典型骨折的诊断标准:①曾经确诊骨质疏松(T < -2.5)或骨量低下(T < -1.5),服用双膦酸盐 >4 年;②无高能量外伤史;③骨折位于股骨小转子至股骨远端的横形或短斜形骨折;④X 线上表现为骨折端内侧皮质尖锐,外侧皮质增厚。

本研究中符合标准对象共计 15 例,均为女性,左侧 7 例,右侧 8 例。平均年龄 76.0 ±6.4 岁(65 ~88 岁)。15 例患者服用双膦酸盐类药物(均为阿仑膦酸钠)6.7 ±1.9 年(4 ~10 年)。9 病例骨折部位位于转子下(骨折位于小转子下 7.5 cm 以内),6 例位于股骨干(骨折超过小转子下 7.5 cm)。5 例患者主诉骨折前出现大腿疼痛,疼痛为间断性,与活动相关。12 例患者低能量外伤造成骨折,3 例患者无明显外伤史。所有病例骨折时经双能 X 线吸收测定法测定髋部骨密度,T 值平均为 -3.0 ±0.6(-1.8 ~ -4.5)。所有病例均于入院 48 h 内手术。

1.2 手术方法

所有病例均为插管全麻。12 例患者行髓内针固定术。患者仰卧位,术中透视下牵引复位。在股骨大转子近侧做 2 ~3 cm 切口,在大转子尖端骨皮质内 1 ~2 cm 处植入尖端螺纹导针,沿导针扩髓,置入髓内钉。透视确认肢体对线及旋转恢复满意后,锁钉固定,如图 1、2。3 例患者行钢板螺钉固定术。患者仰卧位,外侧切口,切开阔筋膜,将骨外侧肌向前掀起,暴露骨折端,复位后使用钢板螺钉固定,如图 3。

图 1 80 岁女性,服用阿仑膦酸钠 10 年,骨折前 2 月出现左大腿痛,X 线检查见左股骨干外侧皮质增厚局限性增厚隆起。随即停用双膦酸盐。后因轻微外力导致股骨干骨折,锁定髓内针固定。6 个月后骨折愈合。

Fig. 1 An 80 years old female with 10-year medication of alendronate. Pain of the left leg occurred 2 months before fracture. X-ray showed local thickness of the cortex in the lateral left femoral shaft. The withdrawal of medication was performed immediately. Fracture of the femoral shaft occurred after slight force, and intramedullary nail fixation was used. Six months later, the fracture healed

1.3 术后处理

所有患者确诊后均停止服用双膦酸盐。术后第 2 天即开始行腓肠肌等长收缩及股四头肌功能锻炼。1 周后开始髋、膝关节的主动功能锻炼,逐渐免负重扶拐下地行走。术后 6 周开始部分负重,根据 X 线片提示的骨折愈合情况逐渐完全负重。术后改服雌激素受体调节剂类药物(雷诺昔芬)继续治疗骨质疏松。

1.4 术后随访

患者于术后每个月随访 1 次,行 X 线片检查,直至骨折完全愈合。

1.5 统计学分析

使用 PASW Statistics 21.0 统计学软件进行数据分析。计量资料采用均值 ± 标准差(最小值 ~ 最大

图 2 76 岁女性,右股骨头置换术后。服用双膦酸盐 5 年,无明显外力出现右股骨干骨折。Vancouver C 型假体周围骨折。钢板螺钉固定。8 个月后愈合。

Fig. 2 A 76 years old female after right femoral head replacement, with 5-year medication of alendronate. Fracture of the femoral shaft occurred without any force. Plate fixation was used. And 8 months later, the fracture healed

图 3 77 岁女性。服用双膦酸盐药物 6 年,转子下不典型骨折。锁定髓内针固定 8 个月愈合

Fig. 3 A 76 years old female with 6-year medication of alendronate. Subtrochanteric atypical fracture. Intramedullary nail fixation was used and 8 months later, the fracture healed

值)表示。数据采用独立样本 t 检验进行比较或采用 pearson 检验进行相关性分析。以 $P < 0.05$ 为差异有统计学意义。

2 结果

手术切口均一期愈合。所有患者均获骨性愈合,平均愈合时间为 5.9 ± 1.4 月(4 ~ 8 月)。其中采用

髓内针固定的 12 例愈合时间为 5.7 ±1.4 月;采用钉钣系统的 3 例愈合时间为 7 ±1 月,两组之间差异没有统计学意义(t =1.56,P =0.14)。所有病例未发生感染、骨折不愈合,内固定物松动或断裂,下肢深静脉血栓等并发症。服用双膦酸盐时间和骨折愈合时间相关性无统计学意义(r =0.034,P =0.904)。

3 讨论

双膦酸盐相关不典型骨折(Bisphosphonate-related atypical fractures)是指由抑制骨代谢因素造成的,在极少发生骨质疏松性骨折的部位发生的骨折[5],也有文献称为脆性骨折(fragility fracture)[6]、应力骨折(stress fracture)[7]、自发骨折(spontaneous fracture)[8]。多位于股骨转子下或股骨干,也见于椎弓根[9]、胫骨[10]等部位。不典型骨折的发生机制尚不完全清楚,大部分学者认为是由于双膦酸盐类药物抑制骨转换导致骨组织累积性的微损伤造成的[17,18]。

美国骨矿物质研究学会(American Society for Bone and Mineral Research, ASBMR)[11]和国际骨质疏松基金会(International Osteoporosis Foundation, IOF)[12]指出不典型股骨骨折有如下特点:①接受双膦酸盐治疗超过 5 年;②部分患者骨折发生前数月或数周有腹股沟或大腿疼痛(前驱痛);③无明显外力或低能量外力下发生骨折;④X 线早期主要表现为不完全骨折或仅为局部骨皮质的增厚、隆起。骨折线位于外侧骨皮质,多为横形,不累及内侧皮质。随着应力的增加可发展为完全性骨折,X 线可见股骨转子下或股骨干横形或短斜形骨折,外侧皮质断端增厚、硬化,内侧皮质可见尖锐突起。

2005 年,Odvina 等[13]最早报告了 9 例长期服用双膦酸盐的患者发生自发性骨盆、股骨、骶骨骨折。此后关于长期服用双膦酸盐患者发生不典型骨折的病例报道越来越多[14,15]。Kwek 等[17]认为长期服用阿伦膦酸钠患者,若出现前驱性症状者需进行影像学检查,而已出现一侧应力性骨折患者,对侧股骨也应进行检查。CT 和 MRI 对于不典型骨折的早期诊断是有帮助的[18]。CT 上可以看到股骨外侧皮质局限性增厚,且增厚区域的皮质有空洞。MRI 可见皮质增厚,局限性骨髓水肿。Wang[6]指出,由于双膦酸盐的广泛使用,1999 ~2007 年间全美住院女性病例中典型髋部周围骨折下降 31.6%,而不典型转子下骨折病例增加 20.4%。Allison[20]报道连续服用双膦酸盐超过三年,在 MRI 下可以观察到的不完全不典型骨折达到 1.82%。Chang[18]认为临床上有一些转移癌或多发性骨髓瘤的患者发生的股骨病理性骨折实际上是不典型骨折,在他的研究中这一比例甚至达到了 10%。不典型骨折的发生与使用双膦酸盐时间过长(>5 年)、使用糖皮质激素、糖尿病等因素有关[11]。

不典型骨折可以单侧发生,也可以双侧同时或依次发生[21,22]。本研究中 15 例患者均为单侧。大多数学者认为内固定治疗不典型股骨骨折较为可靠,保守治疗效果不佳。Ha 等[23]报道 14 例不典型股骨骨折,10 例行内固定术,随访 12 -60 个月均愈合。4 例保守治疗,随访结束时 X 线检查未见骨折愈合。Banffy 等[24]回顾性分析 12 例非典型股骨不完全骨折资料:6 例采用髓内钉固定治疗,其余 6 例行保守治疗。结果手术治疗的患者骨折全部获愈合。而保守治疗的患者中 5 例(83%)未愈合,平均 10 个月后发展为完全性骨折,再予以手术治疗获得愈合;剩余 1 例经保守治疗 1 年后获愈合。国内对于双膦酸盐相关的不典型骨折的治疗报道较少。周耀东[25]总结了 2008 ~2012 年香港玛丽医院的病例。21 例(24 侧骨折),均使用髓内固定进行手术治疗。21 例患者(24 侧骨折)均获骨性愈合,平均愈合时间为 5.1 个月(3 ~8 个月)。Puah[26]的研究显示,不典型股骨骨折会在停用双膦酸盐后自愈,但再次服药后可复发并发生完全移位。他认为不典型骨折患者应使用特立帕肽(重组甲状旁腺素)进行治疗。

目前对于此类骨折的具体手术方式尚缺乏循证医学依据。理论上髓内固定可以比髓外固定提供骨折端更为合适的生物力学环境。而且髓内固定对局部组织损伤小,对骨折的愈合更为有利,必要时还可以动力化处理骨折不愈合。Das 等[19]回顾 12 例双膦酸盐相关非典型股骨骨折患者资料,认为髓内固定是非典型股骨骨折的首选固定方式。周耀东[25]的研究表明髓内固定治疗股骨不典型骨折疗效肯定。本研究有 12 例患者使用锁定髓内针固定,疗效满意,也表明髓内固定牢靠,是理想的固定方式。需要指出的是,即使骨折位于转子下,也应尽量使用足够长的髓内针进行固定,如图 3。因为此类患者的股骨转子下至股骨干均为不典型骨折的高发部位,如果仅仅使用股骨近端髓内针,可能会因为应力集中而增加髓内针远端区域的骨折风险。髓外固定属于偏心固定,对骨外膜破坏大,容易产生骨不愈合或延迟愈合,应力遮挡明显。此类患者骨质疏松,会增加钉钣系统固定的困难,多数学者不建议采用。在本研究中,3 例患者

为假体周围骨折,不适用髓内针固定,遂采用钢板螺钉固定,3 例患者全部愈合。髓内针组的愈合时间为 5.7 ±1.4 个月,钢板组愈合时间为 7 ±1 个月,两组差异没有统计学意义(t =1.56,P =0.14)。由于双膦酸盐能整合入骨基质,持续性抑制骨的重吸收,其半衰期长达 10 年以上。有研究认为长时间服用双膦酸盐药物会延缓骨折愈合[16]。在本研究中,术前患者服用双膦酸盐药物时间和患者骨折愈合时间没有相关性(r =0.034,P =0.904)。

综上,如果长期服用双膦酸盐类药物的患者出现大腿或腹股沟区疼痛,应排除不典型骨折的可能。对于服用双膦酸盐超过 5 年的患者,建议服用其他类型骨质疏松药物治疗。一旦出现非典型骨折,进行手术治疗是处理此类骨折的有效手段。本研究的局限性在于病例数量较少。我国骨质疏松的患者很多,发生不典型骨折的绝对数目应该不少。但是目前尚无基于国内病例资料的文献报道,这可能与我们随访机制不够完善有关。建立良好的骨质疏松病例的资料库是我们今后努力的方向。

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双膦酸盐相关非典型股骨骨折的手术治疗

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