

Early Outcomes of Primary Total Hip Arthroplasty for Osteonecrosis of the Femoral Head in Patients with Human Immunodeficiency Virus in China

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Abstract

Background: Studies have reported that patients with human immunodeficiency virus (HIV) have a high incidence of osteonecrosis of the femoral head (ONFH). Total hip arthroplasty (THA) is an effective management of ONFH. However, little data exist regarding the use of THA for the HIV patients with ONFH in China. This study reviewed the outcomes of HIV-positive patients who underwent THA for ONFH, compared with HIV-negative individuals.

Methods: The patients who underwent THA for ONFH from September 2012 to September 2014 in Beijing Ditan Hospital, Capital Medical University were retrospectively studied. Twenty-eight HIV-positive patients and 35 HIV-negative patients underwent 48 THAs and 45 THAs with cementless components, respectively. Medical records and follow-up data were reviewed. Harris Hip Score (HHS) was applied to evaluate the pain and function of the hips before and after THA. Complications such as wound healing, surgical site infection, deep venous thrombosis, pulmonary embolism, sepsis, mortality, and complications from the prosthesis were reviewed. The operation time, blood loss, and hospital stay were compared between the two groups.

Results: The mean follow-up period was 19.5 ± 5.8 months (ranging from 6 to 30 months). The mean age of the HIV-positive patients with osteonecrosis at the time of surgery was 35 years old, which was significantly lower than that of the HIV-negative group (42 years old) ($P < 0.05$). The HIV-positive patients underwent surgery a mean of 2.5 years after their original symptoms, which was significantly shorter than the HIV-negatives' (mean 4 years) ($P < 0.05$). Among HIV-positive patients, the prevalence of being male and rate of bilateral procedures were significantly higher than those in the HIV-negative group ($P < 0.05$). The operation time in HIV-positive patients was significantly longer than that in HIV-negative patients ($P < 0.05$). There were no significant differences in blood loss or hospital stay between the two groups ($P > 0.05$). The HHSs of two groups significantly improved after THAs ($P < 0.05$), without significant difference between two groups. No wound complication, sepsis, mortality, prosthesis complication, and occupational exposure occurred, except for two cases of heterotopic ossification and one case of humeral head necrosis.

Conclusions: ONFH is more likely to occur bilaterally in younger HIV-positive males. The development of osteonecrosis seems faster in HIV-positive patients than in HIV-negative patients. This should be cautionary for asymptomatic HIV-positive patients with low viral RNA level and in the primary HIV stage. Despite longer operation times in the HIV-positive patients than in the HIV-negative patients, THA is still a safe and efficient approach to treat ONFH in HIV-positive patients. The incidence of complications is much lower than previously reported. However, the long-term follow-up is needed.

Key words: Arthroplasty; Harris Hip Score; Hip; Human Immunodeficiency Virus Infections; Osteonecrosis of the Femoral Head; Outcomes

INTRODUCTION

Osteonecrosis of the femoral head (ONFH) is defined by the death osteocytes and bone marrow cells, caused by an interrupted blood supply, which may subsequently lead to structural collapse, resulting in joint dysfunction. Patients often present with insidious hip pain or signs on radiographic examination.

Numerous studies since 1990 have identified that human immunodeficiency virus (HIV) infection is associated with the development of femoral head osteonecrosis.^[1] HIV-positive patients have a high incidence of ONFH, with nearly a 100-fold greater risk than the general population.^[2] Many studies focused on the risk factors in patients with osteonecrosis though the exact pathogenesis remains unclear.^[3-6]

Total hip arthroplasty (THA) is an effective treatment for advanced ONFH. Previous studies have shown a significantly

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increased risk of infection, sepsis, and other complications in implants in HIV patients.^[7-10] The sequelae of these complications can be devastating and are often managed with antibiotic therapy for several months, extended hospital stays, and additional surgical procedures.^[11] During this period, the patients' HIV status may deteriorate. Controversial results have been suggested by studies in America and Europe. However, little information about HIV/acquired immune deficiency syndrome (AIDS) and ONFH has been reported in Asia, where the prejudice and fear of HIV may potentially influence the decision to operate. The outcome of THA in HIV-positive patients, therefore, warrants further investigation. This study aimed to review the outcomes of THA for ONFH in HIV-positive patients compared with HIV-negative patients and to discuss preoperative preparations and safe operation procedures. This preliminary study preliminarily focused on the medium- and short-term outcomes of THA. Because long-term outcomes are more important, further studies on long-term outcomes of THA in HIV-positive patients will be summarized in our next study.

METHODS

This retrospective study included 63 hospitalized patients who underwent primary arthroplasty for ONFH from September 2012 to September 2014 in Beijing Ditan Hospital, Capital Medical University. This study was approved by the Ethics Committees of in Beijing Ditan Hospital, Capital Medical University. The patients' electronic records and relevant images were reviewed. Exclusion criteria included additional diseases in the hip (such as primary osteoarthritis, rheumatoid arthritis), skin lesions around the hip, lumbar disc herniation, diabetes, tuberculosis, chronic infection, coagulation dysfunction, anemia, and leukocytopenia. HIV infection was confirmed by enzyme-linked immunosorbent assays and Western blotting analysis. The lower limit of detection of RNA assay was 20 copies/ml. The clinical stage of HIV infection was graded according to the classification system for HIV infection by the United States Centers for Disease Control and Prevention (CDC).^[12] Surgical site infection (SSI) was diagnosed according to the CDC criteria.^[13] The stage of ONFH was evaluated using Association Research Circulation Osseous (ARCO) classification.^[14]

Twenty-eight HIV-positive patients and 35 HIV-negative patients underwent 48 THAs and 45 THAs with cementless components, respectively. All patients were reviewed at 1, 3, and 6 months postoperatively and annually thereafter. Osteonecrosis in other sites was also reviewed. Recovery from hip surgery was evaluated by Harris Hip Score (HHS). Complications including deep venous thrombosis (DVT), sepsis and dislocations were reviewed. Radiographic evidence of prosthetic loosening or progressive osteolysis was also considered surgical complications.

Intravenous or oral amino acids, albumin injection, and thymopentin were administered as routine nutritional supplementation to improve nutrition and hypoalbuminemia. Infusions of red blood cell suspension and/or plasma

were administered as necessary. A second-generation cephalosporin was routinely administered within 2 h of the skin incision for all patients. In patients with allergies to cephalosporins, clindamycin was an acceptable alternative. Antibiotics were administered for 3 days and then continued as needed based on the incision condition, body temperature, white blood cell count, erythrocyte sedimentation rate, C-reactive protein level, and bacterial culture. Low molecular weight heparin and venous pressure pump were utilized postoperatively to prevent DVTs. Walking assisted by an exercise helper was allowed 1 week after the operation. The perioperative treatment, procedure, and rehabilitation were given by the same physician group.

All unilateral THAs were performed through the Marcy approach with lateral position under general anesthesia. Bilateral THAs were performed in two stages. The second-stage THA was 3 months after the initial operation and was performed with patients in the supine position using an anterolateral approach. Drainage tubes were set routinely. All prostheses were made by LINK Co, Ltd., Germany. To avoid occupational exposure, surgeons were equipped with waterproof gowns, caps, masks, two pairs of sterilized gloves, and protective boots [Figure 1].

Quantitative variables were shown as the mean \pm standard deviation (SD). Qualitative variables were described by absolute frequencies and percentages. The Fisher's exact test and Student's *t*-test were used for statistical analyses to compare the two groups. All analyses were performed with SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $P < 0.05$.

RESULTS

Twenty-eight HIV-positive patients (44.4%) and thirty-five HIV-negative patients were enrolled in the study. There was a higher prevalence of HIV in patients with osteonecrosis. There were 42 THAs in 24 men (18 bilateral) and 6 THAs in 4 women (2 bilateral) in HIV-positive patients. In the HIV-negative group, there were 26 THAs in 20 men (6 bilateral) and 19 THAs in 15 women (4 bilateral). The difference of sex ratio between the two groups was statistically significant ($\chi^2 = 6.03$, $P < 0.05$). HIV status also significantly increased the rate of bilateral procedures ($\chi^2 = 11.45$, $P < 0.05$). The mean age of the HIV-positive patients with osteonecrosis at the time of surgery was 35 years old, which



Figure 1: Surgeons equipped with protective outfits during surgery.

was significantly younger than that of the HIV-negative group (42 years old) ($t = -4.23, P < 0.05$).

Human immunodeficiency virus transmission routes included blood product transfusion, intravenous drug use, and unprotected sex. The patients had been diagnosed with HIV at a mean of 3.4 years before surgery. The HIV-positive patients underwent surgery at a mean of 2.5 years after their original symptoms, a significantly shorter timeframe than that of HIV-negative patients (4 years) ($t = -3.08, P < 0.05$).

Viral load and CD4 T-cell count were available for all HIV-positive patients. The mean HIV RNA level was 2356 copies/ml. Of 28 HIV-positive patients, viral RNA was undetectable in 20. The mean CD4 T-cell count was 393 cells/mm³. All patients were in World Health Organization (WHO) clinical stage A. Eight patients were in CD4 T-cell category 1, 18 patients were in CD4 T-cell category 2, and 2 were in CD4 T-cell category 3. Half of patients were taking highly active anti-retroviral therapy (HAART) at the time of surgery.

All HIV-positive patients who underwent THA suffered from pain, mobility limitations, and difficulty in their working and social lives. All hips undergoing THA were at ARCO stage 3 or 4 [Figure 2]. The mean preoperative HHSs were 25.2 ± 13.6 and 28.9 ± 9.5 in the HIV-positive and HIV-negative groups, respectively. This difference between the two groups was not statistically significant ($\chi^2 = -1.51, P > 0.05$). One year after operation, the mean HHSs in the HIV-positive and HIV-negative groups were 82.5 ± 4.3 and 84.3 ± 7.5 respectively. The difference was not statistically significant ($\chi^2 = -1.43, P > 0.05$). In patients who underwent THA, the HHS was significantly improved at follow-up evaluation compared to the preoperative

score ($P < 0.05$). No significant difference was found between the HIV-positive and HIV-negative groups.

The THA operation time of THA was longer for the HIV-positive group than for the HIV-negative group ($P < 0.05$). The differences in blood loss and hospital stay were not statistically significant between the two groups ($P > 0.05$). All HIV-positive patients and 10 HIV-negative patients received postoperative blood transfusions. The difference was not statistically significant ($P > 0.05$) [Table 1].

Operations were performed successfully without occupational exposure. The femoral components were cementless in all HIV-positive patients [Figure 3]. There were no complications such as DVT, pulmonary embolism, early sepsis, or late sepsis. There was no mortality due to AIDS-related complications. All patients were followed up for an average of 19.5 ± 5.8 months (ranging from 6 to 30 months). All incisions achieved primary healing [Figure 4]. There was no evidence on X-ray of aseptic loosening, axis shift of the hip prosthesis, periprosthetic fracture or dislocations. During follow-up, two patients suffered from heterotopic ossification.

Table 1: Comparison of HIV-positive and HIV-negative groups

Items	HIV-positive group (n=28)	HIV-negative group (n=35)	χ^2	P
Operation time, h	1.9 ± 0.4	1.6 ± 0.4	3.61	<0.05
Blood loss, ml	260 ± 96	238 ± 75	1.23	>0.05
Hospital stay, days	19.2 ± 5.0	18.0 ± 3.6	1.32	>0.05

HIV: Human immunodeficiency virus.

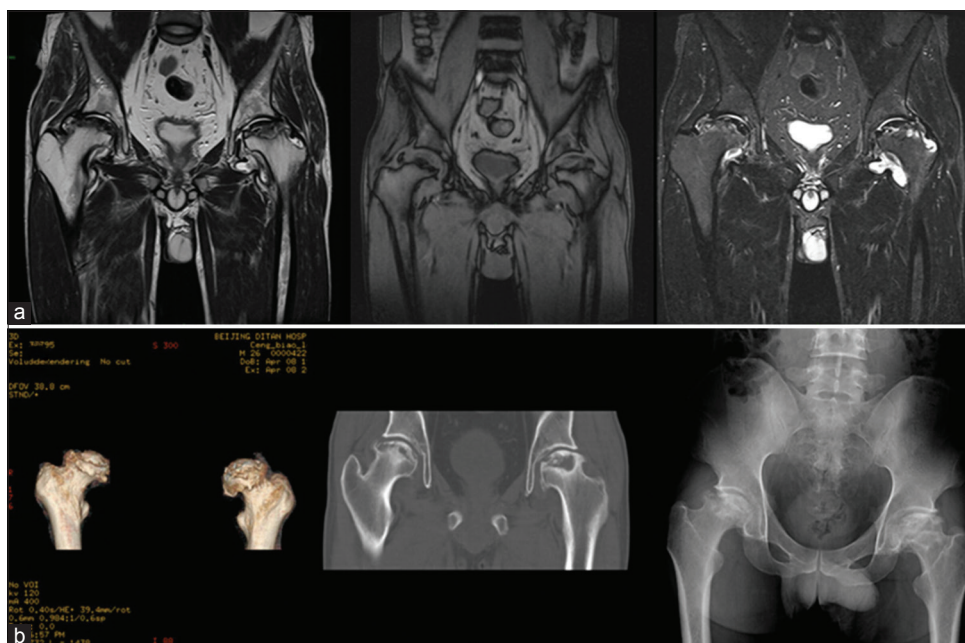


Figure 2: (a) Coronal magnetic resonance images demonstrate low-intensity in T1 and high-intensity edema in T2 in bilateral femur head, collapse head and rough articular surface; (b) computed tomography reconstruction shows the shape of collapse and cavitation in bilateral femur head. Plain radiograph demonstrates the collapse in bilateral femur head.



Figure 3: Plain radiographs of total hip arthroplasties in bilateral hip joint, without loosening, axis shift, dislocation or fracture.

No revision surgery was required in any patient. No osteonecrosis in other sites was found, except one case of humeral head necrosis.

DISCUSSION

By 2012, approximately 35.3 million people globally were living with HIV. By September 2013, 43,400 people were living with HIV in China.^[15,16] HAART reduced mortality and concomitantly increased life expectancy in HIV/AIDS patients, indicating a likely increase in the number of patients presenting for arthroplasty surgery. Moreover, previous studies suggest osteonecrosis has a higher prevalence in HIV-infected patients than in HIV-negative patients. Keruly *et al.*^[17] reported a 1% annual incidence of symptomatic osteonecrosis in HIV-positive patients. Miller *et al.*^[18] reported 4.4% of HIV-positive patients were diagnosed with osteonecrosis in a study of 339 asymptomatic patients. In our study, 44.4% (28/63) of the osteonecrosis patients were HIV-positive, significantly higher than the reported prevalence, indicating that HIV may be associated with osteonecrosis of the hip. Our institute, Beijing Ditan Hospital, Capital Medical University, is the only AIDS treatment center collaborating with the WHO in China. Our department is the only Orthopedic Department in the hospital treating infectious diseases, affording us the opportunity to treat HIV patients and accumulate relevant prevalence data. As prejudice and fear of HIV make it difficult for HIV-positive patients to access adequate have treatment, they often present to our hospital. These factors contribute to the high prevalence of HIV-positive patients in the study as we accept patients from all over the country. A significantly greater proportion of bilateral osteonecrosis occurred in HIV-positive patients. As previously suggested, screening for HIV preoperatively may be beneficial to surgeons' safety.^[19] Routine preoperative screening for HIV in patients with osteonecrosis may also be necessary to help reduce the operative risk and analyze ONFH etiology.

Risk factors for ONFH are stratified as traumatic and nontraumatic. Etiology and pathogenesis of ONFH in HIV-positive patients remain controversial. Studies suggest that ONFH is caused by the combined effects of multiple risk factors including the above general risk factors. However, some propose that HIV infection and HAART play an important role in ONFH in HIV-positive patients, which differs from HIV-negative patients.^[6,20] HAART may produce



Figure 4: The incision achieved primary wound healing without complications.

autoantibodies predisposing patients to thrombosis as well as infection-related vasculitis, which has been suggested as a possible mechanism of ONFH.^[21] Sighinolfi *et al.*^[22] believed avascular necrosis of the femoral head is a side effect of HAART in HIV patients. Whether it is a direct cause of osteonecrosis has been debated. Gutiérrez *et al.*^[23] alluded to an association with HAART, and more specifically protease inhibitors. They suggested the mechanism of protease inhibitors inducing ONFH may be hyperlipidemia. Scribner *et al.*^[24] found saquinavir to be associated with the development of ONFH. Ries *et al.*^[6] support the concept that HIV infection alone may be a risk factor for ONFH. They found a significantly greater portion of HIV-positive patients with nontraumatic osteonecrosis had no known associated risk factors for osteonecrosis, compared with HIV-negative patients. Lubega *et al.*^[25] suggested it is unclear whether an association between ONFH and HIV is intrinsic to HIV disease or HAART or both.

Mahoney *et al.*^[26] found there was a significant difference in the length of HIV-positive status between those with osteonecrosis and asymptomatic HIV-positive patients. In our study, the duration of HIV infection in patients with osteonecrosis was shorter than that in patients without osteonecrosis, which was consistent with previous reports, indicating an association between a short time since HIV diagnosis and ONFH. Studies have suggested that osteonecrosis can occur at any level of immunosuppression.^[23] In our study, 71% (20/28) of the HIV-positive patients had a viral RNA level <20 copies/ml. The mean HIV RNA level was 2356 copies/ml. Therefore, the HIV-positive patients with a low viral RNA level WHO stage A were most likely to suffer from ONFH. Moreover, our results imply that femur head necrosis is likely to occur in younger HIV-positive patients. The development seems faster than in HIV-negative patients. HIV-positive patients with low viral RNA and primary HIV stage should be closely monitored for ONFH.

Human immunodeficiency virus-positivity was previously considered an independent risk factor for postoperative

infection, thus the safety and benefit of performing THA procedures has been questioned in HIV-positive patients.^[6,10,27] Malnutrition always exists with HIV infection, and both influence each other, resulting in adverse consequences.^[28] Studies carried out before the widespread use of HAART in Africa showed HIV patients may be at higher risk of developing late, deep implant infection.^[10,27] A large retrospective multi-center study by Hicks *et al.*^[7] showed an increased rate sepsis after joint replacement in HIV-positive hemophiliacs. The postoperative infection rate following arthroplasties was up to 14–28.6%.^[29,30] However, some recent studies of THA in HIV-positive individuals challenged this notion. Phaff *et al.*^[31] reported patients infected with HIV were not at higher risk of delayed sepsis. Lin *et al.*^[32] identified patients who underwent primary total joint arthroplasty from the US Nationwide Inpatient Sample and found HIV infection was not an independent risk factor for the total rate of perioperative complications. HIV patients were at slightly higher risk of certain immediate postoperative complications because of a higher rate of medical comorbidities.^[32] No complications such as SSI or sepsis occurred in HIV-positive patients treated at our institution. The absence of SSI was consistent with recent studies on outcome after internal fracture fixation and THA in HIV-positive patients.^[26,33-39] The incidence of complications is much lower than previously reported. We attributed the lower incidence of complications in our study to several factors, including the use of standard surgical techniques, advances in perioperative management and the care of the HIV-positive patients. Significant improvements in pain and function were observed after THA operations in all study participants. If they are well-managed, HIV-positive patients can achieve satisfactory outcomes when undergoing THAs instead of suffering postoperative complications. Our study of early outcomes of primary THA in HIV-positive patients with ONFM revealed THA to be efficacious and safe in China.

Longer surgical duration in HIV-positive patients can be attributed to occupational exposure measures: Surgeons equipped with waterproof gowns, caps, masks, double layer gloves, and protective boots, which could reduce their comfort and flexibility. Surgeons and operating room nurses are requested to take extra precautions and compatibility, such as passing tools through a kidney basin rather than directly from hand to hand. Moreover, nontouch techniques were used in suturing. Accidental harm occurred at times due to careless use of equipment. If there was a breakage of gloves or gowns, the local area needed washing and disinfecting. When blood soaked into the gowns or splattered on caps and masks, they were immediately replaced. This cautious management taken during the procedures may be associated with the increase in operation time.

A previous epidemiological study described the risk of HIV infections in healthcare workers after transcutaneous exposure as 0.3%.^[40] Fortunately, we have no cases of HIV infection due to occupational exposure. We believe it is

important to be fully aware of the safety practices used during treatment. Special protection measures during the procedure and use of disinfectant insulation are vital in avoiding occupational exposure. The American Academy of Orthopaedic Surgeons recommended several measures to reduce iatrogenic HIV infection,^[41] including: Prompt removal of all unnecessary equipment, informing the surgeon when passing an instrument, avoiding the use of sharp instruments if possible, avoiding simultaneous suturing of the same layer by two surgical team members, the use of blunt suture needles, and always wearing gloves when handling material covered with blood. In conclusion, the safety of the surgeons can be guaranteed if infection control guidelines are thoroughly enforced. Continuing education is paramount to establishing occupational protection.

It should be noted that this study examined only patients undergoing THA for ONFH; asymptomatic osteonecrosis and symptomatic osteonecrosis without THA were not included in the study. Therefore, our findings were not extensive enough to extrapolate the prevalence of HIV-positive status in the total population of ONFH sufferers. Moreover, the accuracy of determining risk factors for ONFM may be limited by the retroactive nature of this study. A large prospective study could evaluate the role of HIV and other risk factors in developing ONFH, and the prevalence of HIV in patients with osteonecrosis. Notably, gender and age difference may create a bias. Notwithstanding its limitations, this study suggested the short and medium outcomes of THA in HIV-positive patients were not worse than that of the general population, with fewer complications than previously reported. Young HIV-positive patients with low viral RNA levels may be predisposed to developing osteonecrosis.

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