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First Clinical Experience With Thermal-Sprayed Silver Oxide–Containing Hydroxyapatite Coating Implant

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ABSTRACT

Background: Prosthetic joint infection is a serious complication of implant therapy. To prevent prosthetic joint infection, we previously reported the features of silver oxide–containing hydroxyapatite (Ag-HA), which was prepared by mixing silver (a metal with antimicrobial activity) with HA. In this study, we evaluated the potential issues of total hip arthroplasty (THA) with an Ag-HA–coated implant.
Methods: We prepared an implant for THA that was coated with Ag-HA. In this study, the implant contained silver at a maximum quantity of 2.9 mg/implant. In this prospective interventional study, we performed THA with this implant in 20 patients and investigated the effects of silver.
Results: Blood silver levels peaked at 2 weeks after THA and gradually decreased thereafter. The highest blood silver level recorded during the postoperative follow-up was 6.0 ng/mL, which was within the normal range. The Harris Hip Scores increased in all cases, and activities of daily living improved markedly after THA with Ag-HA–coated implants. Implant failure was absent on radiography. No adverse reaction to silver was noted, and argyria was not observed in any case. No patients have developed infection after surgery.
Conclusion: This is the first clinical study of Ag-HA–coated implants in THA. Our Ag-HA–coated implants markedly improved patients' activities of daily living without causing any adverse reactions attributable to silver in the human body. Ag-HA is expected to reduce postoperative infections and prevent decreased quality of life in patients undergoing prosthetic arthroplasty, thus leading to more favorable outcomes.

In orthopedic surgery, reconstruction using implants (eg, prosthetic joints, materials for internal fixation) is a standard procedure. It has become indispensable for restoration of social activities in many patients. Prosthetic joint infection (PJI) arising from implant therapy is a serious complication. The incidence of PJI has been reported to be approximately 1% [1-3]. Although the incidence is relatively rare, once an infection develops, it is difficult to treat and tends to persist for a long time. Recently, epidemiologic studies suggest that both the incidence and the prevalence of PJI may be on the rise in the United States [4]. Surgical resection and revision arthroplasty are required in severe cases, imposing heavy burdens on patients and surgeons as well as generating substantial costs. It is predicted that revision surgery after total hip arthroplasty (THA) will increase by 137% between 2005 and 2030, with the number of patients undergoing this procedure reaching 97,000 cases in 2030 [5]. Health care expenditure for revision surgery will also increase, reaching $1.6 billion in 2020, according to one estimate [6]. Given the current increasing trend in the number of patients at high risk for infection (eg, diabetes, dialysis patients), prevention of infections is becoming more important [7-9].

PIJ is attributed to adherence and proliferation of bacteria on the implant surface owing to suppression of immunity around the inserted implant [10-12]. To date, numerous studies have reported the use of implants with antibacterial activity to prevent infection [13-17]. We have paid particular attention to silver, which has a broad antibacterial spectrum, potent antibacterial activity, and low toxicity. Silver has already been used to coat

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various medical materials, and its antibacterial activity has been reported [18-21]. Meanwhile, concentrated silver is toxic and reportedly causes argyria, hepatopathy, and nephropathy [22-24]. To develop silver with satisfactorily high antibacterial activity and low toxicity, we created silver oxide–containing hydroxyapatite (Ag-HA) by combining silver with highly osteoconductive HA using the thermal spray method [25]. Ag-HA coating has markedly inhibited the adherence and proliferation of methicillin-resistant *Staphylococcus aureus* (MRSA) on the surface of implant materials *in vitro* and *in vivo* [26-29]. Furthermore, osteoconductivity of the implant inserted into the rat is not inhibited by the Ag-HA coating, and sufficient fixation was demonstrated in a direct mechanical test [30,31]. Considering these aforementioned factors, Ag-HA is therefore a promising implant material with antibacterial activity.

We prepared Ag-HA–coated implants for THA and used these implants in operations on 20 patients who gave informed consent in advance. Favorable THA outcomes with HA-coated implants have already been reported [32,33]. However, it has yet to be determined whether Ag-containing HA prevents infection and yields outcomes as favorable as Ag-free HA and whether silver results in adverse reactions or affects implant fixation. In this study, we evaluated the effects of silver and potential issues of THA with an Ag-HA–coated implant.

Materials and Methods

This prospective interventional study evaluated blood silver levels and adverse reactions. Patients were examined with the following inclusion criteria: (1) age, ≥65 years; (2) an indication for THA; and (3) the informed consent of the patients to conduct the study. Exclusion criteria were as follows: (1) the refusal of the patient to conduct the study; (2) a known allergy or hypersensitivity reaction against silver based on the medical history of the patient; (3) the existence of complete dislocation of the hip; and (4) revision THA. After full approval by the local ethical committee, patients were recruited prospectively from January 2014. A total of 20 consecutive patients were enrolled in this study. Between January 8 and April 18, 2014, all of the included patients underwent surgery at the same facility. Primary THA with an Ag-HA–coated implant was performed on 20 hips of 20 patients. Postoperative therapy was provided based on the protocol for an ordinary THA. This study was approved by the institutional review board (approval number: 0344-CT021) and registered with the University Hospital Medical Information Network Clinical Trials Registry, number UMIN000012433.

Coating and Implants

The AMS HA Cup and 910 PerFix Fullcoat D stem (KYOCERA Medical, Osaka, Japan), currently used clinically, were used as the base material. This implant is a cementless-type THA implant. The cup's surface facing the bone and the part of the stem for intramedullary insertion is coated with HA. The cup's surface facing the joint and neck is uncoated. Ag-HA was prepared by adding Ag_2O powder (Kanto Chemical, Tokyo, Japan) to HA powder (KYOCERA Medical, Osaka, Japan). Ag-HA was thermal sprayed as a coating material to prepare an Ag-HA–coated implant (Fig. 1).

Blood Serum Analysis

The serum concentration of silver was determined by inductively coupled plasma mass spectrometric analysis at Mayo Medical Laboratories (PerkinElmer, Waltham, MA). The normal blood silver range as assessed with the inductively coupled plasma mass spectrometric analysis is <15 ng/mL [34]. Complete blood count (CBC), C-reactive protein (normal range, 0.00-0.30 mg/dL), liver function, and kidney function tests were conducted as routine tests before and after surgery. For liver function, levels of γ-glutamyltransferase (normal range, 10-50 U/l), glutamic-oxaloacetic transaminase (normal range, 10-35 U/l), and glutamic-pyruvic transaminase (normal range, 5-40 U/l) were measured. For kidney function, levels of blood urea nitrogen (normal range, 8-20 mg/dL) and creatinine (normal range, 0.6-1.1 mg/dL) were measured. The CBC included leukocyte count (normal range, 3.9-9.8 × $10^3/\mu L$) and hemoglobin level (normal range, 13.5-17.6 g/dL). A routine blood test was performed 1 day after surgery, whereas blood tests for silver were carried out 3 days, 1 and 2 weeks, 3 and 6 months, and 1 year after surgery. All data are presented as median values (range).

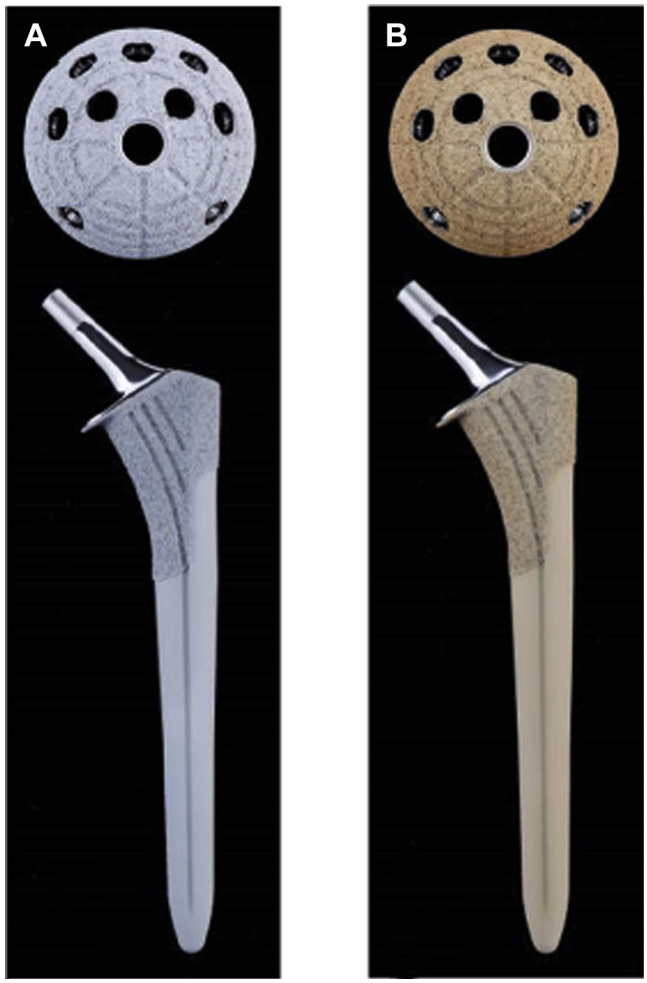

Fig. 1. (A) Conventional hydroxyapatite coating implant. (B) Silver-containing hydroxyapatite coating implant.

Clinical Assessment for Outcomes of Total Hip Arthroplasty

The hip joint status before and after surgery was evaluated using the Harris Hip Score. Evaluations were conducted immediately before, 3 and 6 months, and 1 year after surgery. Scores are presented as means ± standard deviation. SPSS version 21 (IBM Corp, Armonk, NY) was used to perform statistical analyses. The comparison between preoperative and postoperative Harris Hip Scores was compared using paired *t* tests. A value of $P < .05$ was considered as statistically significant.