

Two-stage revision total knee arthroplasty with antibiotic-impregnated hydroxyapatite

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Abstract

Background: Antibiotic-impregnated hydroxyapatite (HA) has been used as a new drug delivery system for the treatment of periprosthetic joint infection (PJI) of the knee. The aim of this study was to evaluate the clinical results of this treatment in patients with PJI. **Methods:** Fourteen consecutive cases of PJI of the knee who were scheduled to undergo two-stage knee revision were enrolled. In the first stage, all components were removed with thorough debridement, and antibiotic-impregnated HA was inserted in the bone and joint space. In the second stage, revision total knee arthroplasty (TKA) was performed after eradication of infection. The mean period from removal of all components and treatment with antibiotic-impregnated HA to revision TKA was 3.4 months. Clinical and radiographic evaluations were performed after a mean follow-up of 5.1 years following revision TKA. Predictors of reinfection were evaluated. **Results:** Eleven patients had no recurrent infection, whereas 3 patients showed recurrent infection. No knees had osteolysis or loosening after revision TKA. The present study demonstrated no predictors for reinfection. **Conclusion:** Antibiotic-impregnated HA could be effective for the treatment of infected knee arthroplasty.

Background

Periprosthetic joint infection (PJI) remains one of the most devastating complications encountered in total knee arthroplasty (TKA), and eradication of PJI remains a surgical challenge. Two-stage revision with removal of the components and treatment with an antibiotic spacer followed by knee reimplantation is the gold standard for chronic PJI eradication [1, 2]. Antibiotic-impregnated cement is used to create the spacer of choice to deliver local antibiotics and is used in conjunction with systemic antibiotics to target any isolated organisms. Surgeons can select a static spacer or an articulating spacer [3–6]. A systematic review indicated that no specific recommendation can be made regarding the superiority of one type of spacer over the other [5], although fractures and dislocations with articulating spacers have been reported [7]. However, the second International Consensus Meeting recommended using articulating spacers whenever possible, because they provide better range of motion and fewer functional limitations to patients undergoing arthroplasty resection [2]. At the same time, antibiotic-impregnated cement is associated with certain disadvantages, including a short duration of drug release, a very low release rate, and thermal damage to some antibiotics [8–13].

To solve these problems, a new drug delivery system using antibiotic-impregnated hydroxyapatite (HA) has been used [9, 14]. This system is superior to bone cement because the porous structure allows gradual release of antibiotics for a long duration and high release rates [9, 13, 15]. In addition, antibiotics can be placed in the HA with no thermal damage to the drug.

The aim of this study was to evaluate the clinical results of antibiotic-impregnated HA used for the treatment of infected knee arthroplasty.

Patients And Methods

Fourteen consecutive cases of PJI of the knee (6 women and 8 men; mean age, 70 year; range: 52–81 years) who were scheduled to undergo two-stage revision were enrolled in this study. The following criteria were used to define PJI: sinus tract communicating with the prosthesis and/or at least two identical positive cultures.

Bone Ceram P (Olympus Terumo Biomaterials Corp, Tokyo, Japan) in cylindrical shapes was sintered at 1200 °C and had a porosity of 30–40%; the diameter of the micropores was between 40 to 150 µm. Two sizes of cylindrical blocks were used. The large size was 15 mm in diameter and 12 mm in height, and the small size was 10 × 10 mm. The small size was used for only filling narrow canal. Antibiotic powder was introduced into the cavity, and the lid was tightly sealed (Fig. 1) [13]. Our institutional review board approved this study, and all patients provided written, informed consent to participate.

Mean body mass index (BMI) was 25.0 kg/m² (range 16.2–33.1 kg/m²). The initial diagnoses were osteoarthritis in 10 patients and rheumatoid arthritis in 4 patients. Four patients (Table 1, Cases 4, 8, 11, and 14) underwent TKA revision including a polyethylene change before removal of all components. The mean period from primary TKA and removal of all components was 4.2 years (range: 0.5–8.9 years). Gram-positive microorganisms were responsible for the infection in most knees (Table 1). No bacteria were detected in 2 patients.

In the first stage, all components were removed with thorough debridement, and antibiotic-impregnated HA was inserted in the bone and joint space (Fig. 2). The knees were fixed with a brace. Patients were permitted to ambulate using crutches without weight-bearing, depending on pain tolerance. C-reactive protein (CRP) level was measured twice a week until normal ranges were reached. Systemic intravenous antibiotics were given for 2 weeks, and were continued until CRP levels normalized. Oral antibiotics were given after intravenous antibiotics were finished for 3 months. In 1 knee, persistent infection was suspected 2 months after removal, and re-debridement with antibiotic-impregnated HA exchange prior to reimplantation was deemed necessary (Table 1, Case 6).

The timing of the second stage of surgery was dependent on the control of infection and clinical symptoms. The criteria for implantation of TKA were healing of the wound, normal CRP level, and negative culture results from a joint aspiration sample. After removal of antibiotic-impregnated HA, tissue samples were obtained for culture and biopsy. Eradication of infection was evaluated by intraoperative frozen section analysis [16]. Revision TKA was performed using the NexGen system (Zimmer; Warsaw, IN) with inserting antibiotic-impregnated HA in the canal (Fig. 3) The mean period from removal of all components and treatment with antibiotic-impregnated HA to revision TKA was 3.4 months (range: 1–6 months).

Clinical evaluations were performed using flexion angle of the knee, as well as ratings according to the system of the Knee Society before removal and at last follow-up. These ratings included a knee score and a function score [17]. The mean follow-up was 5.1 years (range, 1–15 years) following reimplantation.

Radiographs were assessed for the presence of osteolysis around the components, the presence of radiolucent lines at the bone-cement interface, and component loosening.

Local Vancomycin Hydrochloride (VCM) concentrations were measured using joint fluid obtained after removal of the components and treatment with antibiotic-impregnated HA using indwelling drains and joint puncture samples in 4 patients.

Statistical evaluation

The Wilcoxon signed rank test was used to compare flexion angle, Knee Society knee score, and function score before removal and at last follow-up. Various predictors of reinfection were evaluated. The Mann-Whitney U test was used to compare age, BMI, interval between primary TKA and removal, and period from removal and revision TKA. The chi-square test and Fisher's exact test were used to compare sex, initial diagnosis, antibiotic-resistant organism, and polyethylene change before removal of all components. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using SPSS version 22 (SPSS, Inc., Chicago, IL).

Results

There was no evidence of a recurrent infection in 11 patients. The remaining 3 patients showed recurrence of infection (Table 1, Case 4, 5, 7). The organism in these 3 patients was methicillin-resistant *Staphylococcus epidermidis*. Two of these patients were treated with repeat resection and 2-stage revision (Table 1, Case 4, 5). The other patient had end-stage lung cancer with brain metastasis, and no further surgery was performed (Table 1, Case 7).

The mean (standard deviation) flexion angle of the knee improved from 82.1° (35.2°) before removal to 107.5° (21.3°) at last follow up ($p = 0.006$). Both knee scores and function scores improved significantly postoperatively ($p = 0.001$, $p = 0.002$, respectively) (Fig. 4).

No knees had osteolysis or loosening after revision TKA. In addition, no knees showed radiolucent lines > 1 mm or progressive radiolucent lines.

The present study demonstrated no predictors of reinfection, including age ($p = 0.815$), sex ($p > 0.999$), BMI ($p = 0.060$), initial diagnosis ($p = 0.505$), antibiotic-resistant organism ($p = 0.205$), interval between primary TKA and removal ($p = 0.311$), period from removal and revision TKA ($p > 0.999$), and polyethylene change before removal of all components ($p > 0.999$).

Local VCM concentrations showed high trough levels (5–10 $\mu\text{g/ml}$) for at least 3 weeks (Fig. 5).

Discussion

The present study demonstrated an overall rate of recurrence of infection of 21% at a mean follow-up of 5.1 years. Kubista et al [18] reported that 16% of patients developed reinfection after 2-stage

reimplantation using antibiotic-loaded cement spacers and undergoing revision surgery. Mortazavi et al [19] reported that 28% of patients required reoperation for infection. A meta-analysis by Kunutsor et al [20] showed the re-infection rate for two-stage revision was 8.8%.

In our previous report of treatment of infected hip arthroplasty with antibiotic-impregnated HA, 6 of 7 patients showed no evidence of a recurrent infection used antibiotic-impregnated HA in two-stage reconstruction surgery for 20 periprosthetic hip joint infections at a mean of 38 months follow up [12]. Antibiotic-impregnated HA has been applied in the hip [12, 13]. However, no reports were found in the knee application. To our knowledge, the present study is the first to use antibiotic-impregnated HA in two-stage revision TKA.

The in vitro duration of the active effect of VCM released from antibiotic-impregnated HA was longer than that from antibiotic-loaded polymethylmethacrylate cement (ALAC) [9]. An in vitro study showed the active antibacterial effect of VCM in the HA was found up to 21 days, although it only continued up to 7 days with ALAC [13]. This result regarding antibiotic-impregnated HA was confirmed by the present in vivo study.

Four patients were conducted before undergoing removal of all components and treatment with antibiotic-impregnated HA; these patients had intractable infection after several attempts of antibacterial administration and surgical debridement with polyethylene change. Petis et al [21] identified elevated BMI, previous revision surgery, and compromised host status as predictors of reinfection. However, elevated BMI and previous revision surgery were not risk factors for reinfection in the present study.

Infection with antibiotic-resistant organisms may impair the successful eradication of an infection. Earlier studies suggest a higher failure rate in periprosthetic infection treatment when methicillin-resistant bacteria are present [18, 19].

In terms of the use of non-articulating or articulating spacers for the treatment of PJI in the knee in between two-stage exchange arthroplasty, articulating spacers provide better function than non-articulating spacers [22]. A systematic literature review by Voleti et al [23] demonstrated articulating spacers provided improved knee motion following reimplantation (105°) compared with static spacers (92°). Another review by Guild et al [4] showed articulating spacers increased range of motion (100° vs. 83°). Another study showed there was a non-significant trend in range of motion improvement with articulating compared to non-articulating spacers at a minimum of 2 years after reimplantation [22].

One of the disadvantages of antibiotic-impregnated HA for two-stage reconstruction surgery is that it is not an articulating spacer. However, the mean flexion angle at last follow up was 107.5° in the present study, similar to previous studies with articulating spacers. The limitations of the present study include its small sample size and lack of long-term results.

Conclusions

Successful infection control in 11 of 14 patients treated with antibiotic-impregnated HA compares favorably with historical infection control rates with ALAC. Antibiotic-impregnated HA could be effective for the treatment of infected knee arthroplasty.

Abbreviations

HA: hydroxyapatite; PJI: periprosthetic joint infection; TKA: total knee arthroplasty; CRP: C-reactive protein; BMI: body mass index; VCM: Vancomycin Hydrochloride; ALAC: antibiotic-loaded polymethylmethacrylate cement

Declarations

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Authors' contributions

MH was the main investigator and wrote the manuscript. ST, YN, and WH helped with data analysis. AS helped with the interpretation of the data and results. All authors read and approved the final manuscript.

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Availability of data and materials

All data related to this case report are contained within the manuscript.

Ethical approval and consent to participate

The study was approved by the ethical committees, and all participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Table 1

Due to technical limitations the Table is available as a download in the Supplementary Files.

Figures



Figure 1

Hydroxyapatite block with cavity and lid.



Figure 2

Radiograph showing antibiotic-impregnated hydroxyapatite in the bone and joint space after removal of all components.



Figure 3

Radiograph showing revision total knee arthroplasty with a constrained condylar knee.

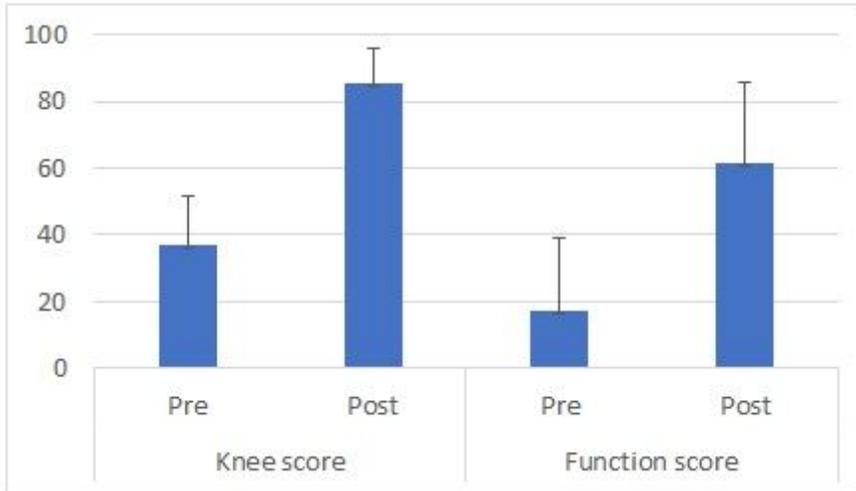


Figure 4

Knee scores and function scores.

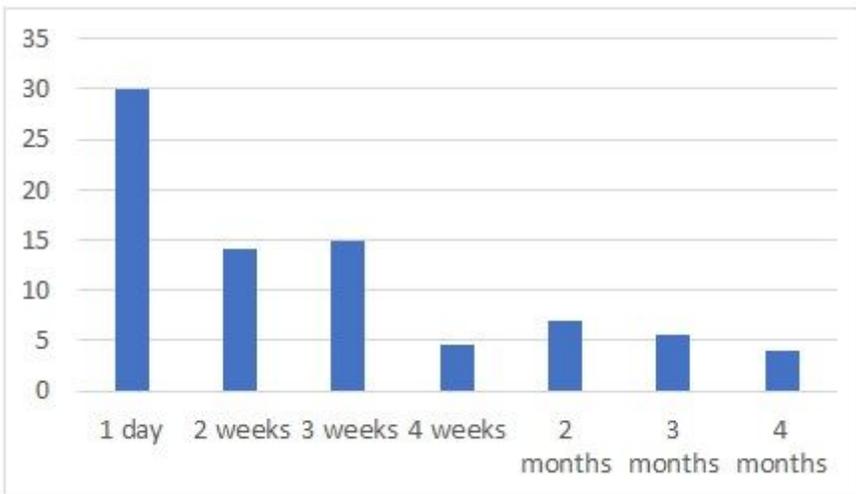


Figure 5

In vitro Vancomycin Hydrochloride (VCM) concentration.

Supplementary Files

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- [Table1.xlsx](#)