Use of Positron Emission Tomography to Detect Infection Around Antibiotic-loaded Cement Spacers in Patients With High C-Reactive Protein Levels

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abstract

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In patients who have antibiotic-loaded cement hip spacers in the interim period, the correct diagnosis of infection eradication is the major determinant before reimplantation arthroplasty. Diagnosis is usually based on clinical findings and serum C-reactive protein (CRP) levels. However, diagnosis can be challenging when the clinical findings are normal but the CRP level is high. From March 2007 to January 2008, fluorodeoxyglucose positron emission tomography (FDG-PET) was used to detect infection around antibiotic-loaded cement spacers in 13 patients (mean age, 60 years). Although patients’ clinical conditions were deemed suitable for reimplantation, their serum CRP levels were persistently elevated (mean, 54 mg/L) an average of 120 days (range, 28-413 days) after the first-stage operation. Reimplantation total hip arthroplasty (THA) was subsequently performed in 7 patients based on the negative findings of FDG-PET. In 6 patients, FDG-PET was positive for infection. The persistence of infection was confirmed in 3 of these patients by another debridement surgery. Staged reimplantation THA was delayed in 1 patient who underwent repeat debridement and in 3 patients who were treated with extended periods of oral antibiotics. Of the 11 staged reimplantation THAs, only 1 reinfection was noted at an average follow-up of 48 months. The success rate of 91% suggests FDG-PET could help in the differential diagnosis of infection around cement spacers, especially in patients with normal clinical findings but elevated CRP levels.

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Periprosthetic infection is difficult to treat, and the incidence ranges between 1% and 2% in primary total hip arthroplasty (THA). A 2-stage reimplantation protocol that consists of extensive debridement at the first stage followed by delayed reimplantation is currently the standard of care for chronic periprosthetic infection, with a success rate ranging from 82% to 95%.1–7

Reimplantation THA should only be performed after ensuring the complete eradication of infection to avoid devastating complications.4 However, accurately determining the eradication of infection before reimplantation remains a challenge in clinical practice. Leukocyte differential counts, erythrocyte sedimentation rate, C-reactive protein (CRP), and clinical findings including healing of the surgical wound are the most commonly used determinants for second-stage reimplantation. C-reactive protein level, although nonspecific and easily affected by underlying conditions, has been widely accepted as the indicator for second-stage reimplantation THA.8,9 In certain dilemmatic conditions in which the periprosthetic infection appears to be eradicated but the serum CRP levels are not normalized, other methods such as joint aspiration,10 amplification of bacteria-specific genes,11 serum interleukin-6 levels,12 and tissue biopsies13 can be used.

Radionuclide scintigraphy also has been used to detect periprosthetic infection, but it often is associated with low sensitivity.14,15 Recently, [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) has been reported to detect periprosthetic infection with high sensitivity (94%) and high specificity (95%).16 However, it is seldom reported to detect infection around antibiotic-loaded cement spacers. The purpose of this study was to examine the use of FDG-PET in patients with high and fluctuating serum CRP levels in the interim period before reimplantation THA.

**MATERIALS AND METHODS**

Between March 2007 and January 2008, a total of 13 patients who had antibiotic-loaded cement spacers implanted for periprosthetic infection were referred to the specialty clinic at the authors’ institute. Mean patient age was 60 years (range, 42–74 years) at the time of the first-stage operation. The Table summarizes demographic data, clinical history, bacterial cultures, and serum CRP levels.

At an average of 120 days (range, 28–413 days) after the first-stage operation, no systemic local infection signs were noted in the patients. Serum CRP levels, however, were persistently high; the mean serum CRP level was 54 mg/L (range, 16–140 mg/L), which was above the cut-off value of 5 mg/L for the criteria of reimplantation.4

To detect infection persistence around the spacers, joint aspiration was performed; however, the results were inconclusive. Combined bone and gallium scans were performed in 8 hips, but the eradication of infection could not be confirmed. Therefore, FDG-PET was performed and interpreted using the criteria suggested by Chacko et al.17 Based on the findings of the FDG-PET study, a treatment algorithm of either an immediate reimplantation or a repeat debridement was suggested. The diagnosis of infection persistence was confirmed by intraoperative cultures and pathologic findings according to the criteria described by Bauer et al.8 To detect any residual infection with the possibility of infection reactivation at a later stage, patients underwent follow-up for a minimum of 3 years. This study protocol was approved by the Institutional Review Board.

**RESULTS**

A total of 13 patients (8 women and 5 men) had chronic periprosthetic hip infection and had received antibiotic-loaded cement spacers. Seventy-seven percent of the patients had at least 1 underlying medical condition such as diabetes, liver disease, malignancy, or hemodialysis that might affect serum CRP levels. In 10 patients, the causative organisms were identified by bacterial cultures. The most common organism was oxacillin-resistant *Staphylococcus aureus*. The diagnosis of chronic infection in the 3 patients who had negative bacterial culture results was based on an open sinus tract to the hip joint and pathologic findings.

Patients underwent regular follow-up, and serum CRP levels were checked routinely. Based on our protocol, no additional antibiotics were given in the interim period before the second-stage reimplantation. The rationales for not using oral antibiotics in the interim period were: (1) high concentration of sensitive antibiotics released from the spacer should be adequate for infection control, (2) no active infection signs were seen, and (3) the higher chance for positive bacteria cultures, when concomitant antibiotic suppression was not used, if a repeat debridement were needed. These patients were selected to undergo FDG-PET because their CRP levels were high but the clinical findings did not favor active infection.

In 7 patients, FDG-PET was negative for infection. At an average of 27 days (range, 5–58 days) after undergoing FDG-PET, reimplantation THA was performed. The pathologic diagnoses at the time of reimplantation were negative for infection, and tissue cultures were negative for bacterial growth in these patients (Table; Figure 1). One patient (patient 3) with underlying uterine cervical carcinoma and radiation osteonecrosis of the pelvis underwent reimplantation THA 5 days after the negative FDG-PET study. Unfortunately, reactivation of infection was noted 4 months postoperatively.

In 6 patients, FDG-PET was positive for infection. Three of these patients underwent repeat debridement, and the persistence of infection was confirmed by tissue cultures and pathologic findings. One patient underwent a successful staged reimplantation THA after the repeat de-
bridement (Figure 2), and the other 2 patients were too ill to undergo reimplantation after the repeat debridement. The 3 patients who did not undergo repeat debridement were treated with oral antibiotics for 43 days (penicillin V), 70 days (dicloxacillin), and 149 days (dicloxacillin) until the CRP levels decreased to 1, 4, and 0.4 mg/L, respectively. These 3 patients then underwent reimplantation THA.

With a mean follow-up of 48 months (range, 43-53 months) after the reimplantation operation, only 1 of the 11 patients who underwent reimplantation THA had reactivation of the periprosthetic infection. A negative FDG-PET study helped the diagnosis of infection eradication in 6 of the 7 patients who had high CRP levels in the interim period. The FDG-PET also helped in the decision-making process in 6 patients who had high CRP levels and positive FDG-PET studies. Delayed reimplantation surgery was successfully performed in 3 patients until the normalization of CRP levels after an extended period of oral antibiotics use and in 1 patient after a repeat debridement.

**DISCUSSION**

A delayed reimplantation protocol for chronic periprosthetic hip infection has been successfully adopted in many medical institutes. The timing for the second-stage operation is a critical decision because reactivation of infection would result in greater medical losses and complica-

### Table

**Patient Characteristics and Clinical Data**

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Medical Conditions</th>
<th>Culture</th>
<th>CRP &amp; Interim Length</th>
<th>PET Finding</th>
<th>CRP &amp; Second-stage Surgery</th>
<th>Culture</th>
<th>Follow-up &amp; Final Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/73</td>
<td>Cervical carcinoma, chronic pyelonephritis</td>
<td>EC</td>
<td>56 mg/L, 413 days</td>
<td>Negative</td>
<td>62 mg/L, reimplantation</td>
<td>ORSA</td>
<td>45 months, no recurrence</td>
</tr>
<tr>
<td>2/F/52</td>
<td>Hepatitis B carrier</td>
<td>ORSA</td>
<td>16 mg/L, 214 days</td>
<td>Negative</td>
<td>22 mg/L, reimplantation</td>
<td>ORSA</td>
<td>50 months, no recurrence</td>
</tr>
<tr>
<td>3/F/74</td>
<td>Cervical carcinoma</td>
<td>ORSA</td>
<td>26 mg/L, 168 days</td>
<td>Negative</td>
<td>26 mg/L, reimplantation</td>
<td>ORSA</td>
<td>52 months, reinfection (ORSA)</td>
</tr>
<tr>
<td>4/M/69</td>
<td>Diabetes, hemodialysis</td>
<td>ORSA</td>
<td>134 mg/L, 113 days</td>
<td>Positive</td>
<td>134 mg/L, Girdlestone</td>
<td>ORSA</td>
<td>53 months, acute myocardial infarction</td>
</tr>
<tr>
<td>5/F/71</td>
<td>Cervical carcinoma</td>
<td>CONS</td>
<td>140 mg/L, 71 days</td>
<td>Positive</td>
<td>138 mg/L, Girdlestone</td>
<td>CONS</td>
<td>50 months, cerebrovascular accident</td>
</tr>
<tr>
<td>6/M/60</td>
<td>Diabetes</td>
<td>OSSA</td>
<td>25 mg/L, 75 days</td>
<td>Negative</td>
<td>13 mg/L, reimplantation</td>
<td>ORSA</td>
<td>51 months, no recurrence</td>
</tr>
<tr>
<td>7/F/47</td>
<td>None</td>
<td>CONS</td>
<td>76 mg/L, 47 days</td>
<td>Positive</td>
<td>4 mg/L, reimplantation</td>
<td>ORSA</td>
<td>50 months, no recurrence</td>
</tr>
<tr>
<td>8/M/42</td>
<td>None</td>
<td>ORSA</td>
<td>16 mg/L, 30 days</td>
<td>Positive</td>
<td>135 mg/L, Girdlestone</td>
<td>ORSA</td>
<td>49 months, reimplantation at 6 months, no recurrence</td>
</tr>
<tr>
<td>9/F/66</td>
<td>Diabetes</td>
<td>No growth</td>
<td>21 mg/L, 28 days</td>
<td>Positive</td>
<td>0.4 mg/L, reimplantation</td>
<td>ORSA</td>
<td>47 months, no recurrence</td>
</tr>
<tr>
<td>10/F/47</td>
<td>Diabetes, hemodialysis</td>
<td>No growth</td>
<td>18 mg/L, 127 days</td>
<td>Negative</td>
<td>12 mg/L, reimplantation</td>
<td>ORSA</td>
<td>45 months, no recurrence</td>
</tr>
<tr>
<td>11/M/48</td>
<td>None</td>
<td>PA</td>
<td>18 mg/L, 125 days</td>
<td>Positive</td>
<td>1 mg/L, reimplantation</td>
<td>ORSA</td>
<td>43 months, no recurrence</td>
</tr>
<tr>
<td>12/F/53</td>
<td>Diabetes</td>
<td>No growth</td>
<td>102 mg/L, 32 days</td>
<td>Negative</td>
<td>2 mg/L, reimplantation</td>
<td>ORSA</td>
<td>45 months, no recurrence</td>
</tr>
<tr>
<td>13/M/72</td>
<td>Psoriasis vulgaris, alcoholic liver cirrhosis</td>
<td>CONS, PRE</td>
<td>52 mg/L, 116 days</td>
<td>Negative</td>
<td>9 mg/L, reimplantation</td>
<td>ORSA</td>
<td>43 months, no recurrence</td>
</tr>
</tbody>
</table>

**Abbreviations:** CONS, coagulase-negative Staphylococcus; CRP, C-reactive protein; EC, Escherichia coli; ORSA, oxacillin-resistant Staphylococcus aureus; OSSA, oxacillin-sensitive Staphylococcus aureus; PA, Peptostreptococcus asaccharolyticus; PRE, Prevotella sp.
The most commonly used indicators include clinical presentations (eg, decrease in pain, improvement in wound condition, absence of systemic or local infection signs) and normalization of serum CRP levels. However, serum CRP levels may fluctuate in patients with underlying inflammatory disease, malignancy, or medical conditions such as liver diseases or hemodialysis. As alternatives, tissue biopsy, joint aspiration, molecular detection of bacteria-specific genes, serum cytokine levels, or frozen tissue sections have been reported. Unfortunately, their usefulness depends on the individual laboratory’s sophistication and experience.

Technetium 99m bone, gallium 67 inflammatory, and indium 111 leukocyte scans also have been used in the diagnosis of prosthetic infection. However, in this study, their use for detecting infection around antibiotic-loaded cement spacers was limited. FDG-PET has been successfully used to detect periprosthetic hip infection. In this study, it also provided better resolution by using isotopically labeled glucose molecules as radiotracers for infection around the hip spacers. By using FDG-PET, we were able to decide whether immediate reimplantation or repeat debridement would be adequate in 13 patients in whom stage-2 operation had been postponed. Of the 13 patients, 77% had miscellaneous medical conditions that might have accounted for fluctuating serum CRP levels. One of our patients (patient 1) for whom reimplantation had been deferred for 14 months because of fluctuating high CRP levels underwent successful reimplantation arthroplasty after a negative FDG-PET study.

Figure 1: A 73-year-old woman (patient 1) had an antibiotic-loaded cement spacer for her right hip infection. Because of chronic pyelonephritis, her CRP level was persistently elevated (56 mg/L) despite percutaneous nephrostomies (arrows) (A). Bone and gallium scans showed equivocal uptake of radioisotopes around the cement spacer (B). A FDG-PET study showed no uptake of the radiolabeled glucose molecules around the cement spacer (C). Reimplantation THA was performed, and no reactivation of infection was found in 39 months of follow-up (D).

Figure 2: A 42-year-old man (patient 8) had a chronic periprosthetic infection in the left hip. Thirty days after first-stage surgery, he had a mildly elevated CRP level (16 mg/L) and a normal wound condition (A). He was considered a candidate for early reimplantation surgery, but FDG-PET demonstrated marked increase of the radioisotope signals around the cement spacer (arrow) (B). Reimplantation was halted, and he underwent repeat debridement with a new antibiotic-loaded cement spacer (C). Reimplantation THA was performed 6 months later (D).
In this study, FDG-PET proved to be a feasible tool in the decision-making process for patients with normal clinical findings but high CRP levels. Of the 7 patients who had a negative FDG-PET study, only 1 patient had reactivation of periprosthetic infection after an immediate reimplantation. In the 6 patients who had a positive FDG-PET study, persistence of infection around the spacer was confirmed in 3 by repeat debridement. The growth of bacteria by tissue cultures revealed similar organisms to the first-stage operation. Reimplantation was halted in the remaining 3 patients with a positive FDG-PET study. Although repeat debridement was recommended, they chose to use an extended period of oral antibiotics until their CRP levels finally normalized.

This study had several limitations; the number of patients was small, and the study design was not randomized. However, our intention was not to investigate the sensitivity, specificity, or predictive values of FDG-PET in the diagnosis of periprosthetic infection. We are reporting the possible implications of using FDG-PET to detect residual infection around antibiotic-loaded spacers in cases with a clinical dilemma. We found FDG-PET helped with the clinical decision-making process in such patients. However, FDG-PET should be reserved and should not be performed as a routine screening study. Other diagnostic measures such as joint aspiration, molecular diagnosis, or frozen tissue sections should not be dispensable if reimplantation surgery is anticipated in patients with high CRP levels.

This study demonstrated that FDG-PET was a feasible tool to help in detecting infection around an antibiotic-loaded cement spacer. It can be reserved for patients with dilemmatic conditions when other diagnostic measures are inconclusive. A negative FDG-PET study could be used as an important reference for second-stage reimplantation, whereas a positive FDG-PET study should encourage further treatment to eradicate infection before reimplantation.

REFERENCES