The Clinical Usefulness of ^{99m}Tc HMPAO Leukocyte/ ^{99m}Tc Phytate Bone Marrow Scintigraphy for Diagnosis of Prosthetic Knee Infection: A Preliminary Study

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Abstract

Purpose The preferred radionuclide imaging procedure for diagnosing prosthetic joint infection is combined radiolabeled leukocyte/ ^{99m}Tc sulfur colloid bone marrow scintigraphy, which has an accuracy of over 90 %. Unfortunately, sulfur colloid is no longer available in South Korea. In this study, we evaluated the usefulness of ^{99m}Tc phytate, a substitute for ^{99m}Tc sulfur colloid, when combined with radiolabeled leukocyte scintigraphy in suspected prosthetic knee infections.

Methods Eleven patients (nine women, two men; mean age 72 ± 6 years) with painful knee prostheses and a suspicion of infection underwent both ^{99m}Tc HMPAO leukocyte scintigraphy (LS) and ^{99m}Tc phytate bone marrow scintigraphy (BMS). The combined images were interpreted as positive for infection when radioactivity in the LS at the site of clinical interest clearly exceeded that of the BMS (discordant); they were interpreted as negative when the increased activity in the LS was consistent with an increased activity in the BMS (concordant). The final diagnosis was made with microbiological or intraoperative findings and a clinical follow-up of at least 12 months.

Results Five of eleven patients were diagnosed as having an infected prosthesis. The overall sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of the combined LS/BMS were 100 %, 83 %, 83 %, 100 % and 91 %, respectively.

Conclusion We find that combined ^{99m}Tc HMPAO LS/ ^{99m}Tc phytate BMS shows comparable diagnostic performance

to other studies utilizing sulfur colloid. Combined ^{99m}Tc HMPAO LS/ ^{99m}Tc phytate BMS is therefore expected to be an acceptable alternative to combined radiolabeled LS/ ^{99m}Tc sulfur colloid BMS for diagnosing prosthetic knee infections.

Keywords Prosthetic knee infection · ^{99m}Tc HMPAO leukocyte scintigraphy · Bone marrow scintigraphy · ^{99m}Tc phytate

Introduction

In recent years, there has been a significant increase in the number of knee joint prosthesis replacements. Prosthetic joints improve the quality of life, but they may fail, necessitating revision or resection arthroplasty.

Complications such as heterotopic ossification, fracture, and dislocation are now relatively rare and easily diagnosed. Infection, although uncommon, is the most serious complication, and it occurs in 0.8 to 1.9 % of knee arthroplasties [1, 2]. Approximately one third of prosthetic joint infections develop within 3 months, another third develop within 1 year, and the remainder develop more than 1 year after surgery [3]. Differentiating aseptic loosening, the most common cause of prosthetic joint failure, from infection is important, because these conditions are treated very differently. The former requires a single-stage revision arthroplasty, while an infected prosthesis requires excisional arthroplasty and a protracted course of antimicrobial therapy [4]. Unfortunately, the differentiation of these two entities can be challenging. Clinical signs of infection are often absent. Increased peripheral blood leukocytes, erythrocyte sedimentation rate, and C-reactive protein levels are neither sensitive nor specific for infection. Gram stain and culture is

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the definitive diagnostic test. Its specificity is in excess of 90 %; however, its sensitivity is variable, ranging from 28 % to 92 % [5, 6].

Plain radiography has low sensitivity and low specificity for detecting infections associated with the prosthetic joint. Periprosthetic radiolucency, osteolysis, migration, or a combination of these features may be present on radiographs in patients with either infection or aseptic loosening of the prosthesis. Computed tomography and magnetic resonance have a diagnostic limitation in these patients, due to the presence of artifacts created by the metallic components of the prostheses [6].

Various approaches have been developed to visualize inflammation and infection using nuclear medicine techniques. Bone scans obtained after the administration of ^{99m}Tc -labeled methylene diphosphonate are sensitive at detecting failed implants, but are nonspecific for detecting infection due to persistent periprosthetic osteoblastic activity that continues for more than a year after implantation [7, 8]. Combined bone/gallium (Ga) imaging has also been studied for diagnosing infected prosthesis, with an accuracy of 65–80 % [9, 10]. However, ^{67}Ga is expensive and cannot be acquired easily.

At present, combined radiolabeled leukocyte scintigraphy (LS)/ ^{99m}Tc sulfur colloid bone marrow scintigraphy (BMS), which has approximately a 90 % accuracy, is the radionuclide imaging procedure of choice for diagnosing prosthetic joint infection [5, 11–13]. However, ^{99m}Tc -labeled colloid agent is difficult to obtain in our country, which necessitates the identification of valid alternatives. ^{99m}Tc phytate is occasionally used as a substitute for lymphoscintigraphy [14]. To the best of our knowledge, no study has been conducted using ^{99m}Tc HMPAO LS/ ^{99m}Tc phytate BMS to diagnose infected knee joint replacements. The aim of this study was to prospectively evaluate the diagnostic efficacy of ^{99m}Tc HMPAO LS/ ^{99m}Tc phytate BMS for the diagnosis of prosthetic infection in patients with total knee arthroplasty.

Patients and Methods

Patients

From March 2010 to March 2011, a total of 11 patients (nine women, two men; mean age 71.8 ± 6.1 years) with suspected total knee arthroplasty infections were recruited. All patients had local signs of infection (pain, swelling, effusion, warmth, or erythema), and all but one had elevated laboratory parameters, such as in their erythrocyte sedimentation rate or their C-reactive protein level. The same team of surgeons performed all operations. The characteristics of the patients are summarized in Table 1.

Table 1 Patient characteristics (N=11)

Characteristics	
Age (year)	71.8 ± 6.1 (59–77)
Gender	
Male	2
Female	9
WBC count ($\times 10^9/\text{L}$)	7.2 ± 3.9
ESR (mm/h)	46.2 ± 25.3
CRP level (mg/dl)	1.9 ± 1.7
Local signs of infection	5
Time since prior arthroplasty (year)	3.4 ± 3.5
Within 3 months	0
Within 1 year	2
More than 1 year	9
Type of arthroplasty	
Primary implant	9
Revision implant	2

WBC white blood cell count;

ESR erythrocyte sedimentation rate;

CRP C-reactive protein

^{99m}Tc HMPAO Leukocyte Scintigraphy and ^{99m}Tc phytate Bone Marrow Scintigraphy

All patients underwent LS followed by BMS. Blood samples were collected for leukocyte labeling. The leukocyte fractions were labeled with ^{99m}Tc HMPAO using a dose of 740–1,110 MBq (20–30 mCi) ^{99m}Tc , using standard techniques [15, 16]. The radiolabeled leukocytes were reinjected intravenously with a delay of no more than 3 h; the administered activity ranged from 555 to 740 MBq (15–20 mCi). ^{99m}Tc -labeled leukocyte images were acquired in anterior and posterior views of the knee area at 3 h.

^{99m}Tc phytate BMS was acquired 30 min after the injection of 185 MBq (5 mCi) ^{99m}Tc phytate. Anterior and posterior views of the prosthetic area were imaged with 300 kCounts. The minimum interval from LS was 3 days.

Imaging was performed using a large-field-of-view gamma camera (Infinia; GE, USA) equipped with a low-energy and general-purpose collimator. Energy discrimination was accomplished by using a 20 % window that was centered on 140 keV.

Image Interpretation

The images were interpreted as being either positive or negative for infection using visual analysis. With the LS, the presence or absence of periprosthetic activity around each component was noted. When such activity

was present, the intensity of the activity was compared with the intensity of the activity in the corresponding region of the contralateral knee. The LS was regarded as positive when the periprosthetic uptake was greater than the activity in the surrounding bone tissue and in the contralateral knee. The combined LS/BMS results were classified as concordant if the distribution of the two radiotracers was spatially identical, and as discordant if activity was observed in the LS without corresponding activity in the BMS. Discordant images were classified as positive for infection.

Diagnosis of Infection

Infection was diagnosed when one or more of the following criteria were fulfilled: 1) isolation of the same microorganism from two or more cultures of joint aspirates or intraoperative periprosthetic-tissue specimens, 2) gross purulence in the joint space or sinus tract communication with the prosthesis, as identified by the surgeon at the time of surgery [17], or 3) positive intraoperative histological findings (at least ten neutrophils per high-power field), even in the absence of culture growth [18]. In the absence of any of the above evidence, the prosthesis was considered to be uninfected. For these cases in which no further surgery was performed ($n=6$), careful monitoring of the clinical outcomes was performed for at least 1 year after the imaging. Based on the clinical parameters, we considered those patients for whom antibiotic treatment was not required at the end of the follow-up to be uninfected, while we considered those patients who required a justified antibiotic therapy during the follow-up to be infected.

The sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were calculated by comparing the results of the combined ^{99m}Tc HMPAO

LS/ ^{99m}Tc phytate BMS with the definitive diagnostic standard.

Results

Eleven patients (nine women, two men; mean age 71.8 ± 6.1 years) with painful knee prostheses and a suspicion of infection were included in the study. The time from the replacement surgery was less than 1 year in two patients, 2–5 years in five patients and more than 5 years in the remaining four patients. Additionally, nine patients underwent primary operations, and the remaining two patients received revision operation.

Five patients of eleven were diagnosed as infected. One patient was verified by two intraoperative positive cultures (*Candida* species, not *albicans*); one patient was diagnosed by intraoperative histological findings (at least ten neutrophils per high-power field); one patient was diagnosed by positive cultures (*Enterococcus faecalis*) from their joint aspirates and their intraoperative appearance, including the sinus tract communicating with the prosthesis; and the remaining two patients were diagnosed by their intraoperative appearance, including gross purulence in the joint space or the sinus tract communicating with the prosthesis. Six patients were diagnosed as uninfected; they had negative cultures for their joint aspirates and completed a minimum follow-up of 12 months after the scintigraphy, without evidence of the development of an active infection (Table 2).

Figure 1 presents a true positive case in which the infection was diagnosed by an intraoperative finding, such as gross purulence. A discordant LS/BMS pattern is shown. Figure 2 shows a true negative case with a spatially concordant pattern of the combined LS/BMS. This patient was diagnosed by their negative joint aspirate cultures and the completion of a minimum follow-up of 12 months after the

Table 2 The scintigraphic results and final diagnosis

Patient	Scintigraphic finding	Final diagnosis	Method of confirmation
1	Concordant	Non-infection	Clinical follow-up
2	Concordant	Non-infection	Clinical follow-up
3	Concordant	Non-infection	Clinical follow-up
4	Concordant	Non-infection	Clinical follow-up
5	Concordant	Non-infection	Clinical follow-up
6	Discordant	Non-infection	Clinical follow-up
7	Discordant	Infection	Intraoperative appearance
8	Discordant	Infection	Intraoperative appearance
9	Discordant	Infection	Intraoperative cultures
10	Discordant	Infection	Intraoperative appearance and cultures of joint aspirates
11	Discordant	Infection	Intraoperative histologic finding

Fig. 1 A representative image of a true positive case. ^{99m}Tc -HMPAO leukocyte scintigraphy (a), ^{99m}Tc -phytate bone marrow scintigraphy (b). There is focal uptake around the left knee prosthesis on the ^{99m}Tc -HMPAO leukocyte scintigraphy, and the spatially discordant activity on the ^{99m}Tc -HMPAO leukocyte scintigraphy/ ^{99m}Tc -phytate bone marrow scintigraphy is consistent with infection at the left knee prosthesis. This patient was proven to have an infection via intraoperative culture

scintigraphy without evidence of the development of an active infection. Figure 3 shows a representative image of a false positive case. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of the combined LS/BMS to diagnose the prosthetic infection were 100 %, 83 %, 83 %, 100 % and 91 %, respectively (Table 3).

Fig. 2 A representative image of a true negative case. ^{99m}Tc -HMPAO leukocyte scintigraphy (a), ^{99m}Tc -phytate bone marrow scintigraphy (b). There is mild uptake around the left knee prosthesis on the ^{99m}Tc -HMPAO leukocyte scintigraphy, and the spatially concordant activity on the ^{99m}Tc -HMPAO leukocyte scintigraphy/ ^{99m}Tc -phytate bone marrow scintigraphy is consistent with non-infection. There was no evidence of infection as there was no antibiotic treatment used in the clinical follow-up

Discussion

The detection of prosthetic joint infection and its differentiation from aseptic loosening is important because it is necessary to differentially treat and manage these TKR complications. Although radiolabeled LS is a useful tool for diagnosing bony infection [19], Park et al. reported

Fig. 3 A representative image of a false positive case. ^{99m}Tc -HMPAO leukocyte scintigraphy (a), ^{99m}Tc -phytate bone marrow scintigraphy (b). There is mild uptake around the right knee prosthesis on the ^{99m}Tc -HMPAO leukocyte scintigraphy, and the spatially discordant activity on the ^{99m}Tc -HMPAO leukocyte scintigraphy/ ^{99m}Tc -phytate bone marrow scintigraphy is a suggestive finding supporting infection at the right knee prosthesis; however, she was finally diagnosed as non-infected during the clinical follow-up

several false positive cases even when investigating asymptomatic prostheses [20]. However, Palestro et al. reported that the combined analysis of radiolabeled leukocyte and marrow scintigraphy showed a satisfactory result, with more than 95 % accuracy to diagnose hip and knee replacement infections [21, 22]. Radiolabeled leukocytes accumulate not only in the infection site, but also in the hematopoietically active bone marrow. The generalized and localized expansion of hematopoietically active marrow as a response to orthopedic hardware complicate the interpretation of leukocyte images, because it is difficult to determine whether leukocyte accumulation represents infection or hematopoietically active marrow in the periprosthetic region [23]. The combined analysis of radiolabeled LS and BMS has been introduced as an effective method to distinguish between infection and altered marrow distribution. The basis

for this combined test is the fact that both leukocytes and sulfur colloid accumulate in the marrow regardless of its location, whereas leukocytes accumulate in the infection but sulfur colloid does not. The combined analysis of radiolabeled LS/BMS is positive for infection when there is activity in the leukocyte image without corresponding activity in the bone marrow image; in other words, the images are spatially incongruent. When any other pattern is present, the study is negative for infection [23]. The current radionuclide gold standard has been combined radiolabeled LS/ ^{99m}Tc sulfur colloid BMS, but the radiolabeled sulfur colloid is no longer available in our country.

^{99m}Tc phytate is a technetium complex of inositol hexaphosphate, which was developed as a radiopharmaceutical for imaging the reticuloendothelial (RE) system. The uptake mechanism of ^{99m}Tc phytate is believed to rely upon in vivo colloid formation via chelation with the divalent ion Ca^{2+} in the blood in a manner that is similar to the free ligand; thus, it behaves as an RE agent [24]. The ^{99m}Tc phytate has been used for visualization of the RE system, mainly the liver [25], and for sentinel lymph node mapping in melanoma, breast cancer [14], vulvar cancer [26] and lung cancer [27]. The accumulation of the radiopharmaceutical by select organ systems depends on the chemical characteristics and the pathophysiological status of the subject under investigation. Noronha et al. reported that ^{99m}Tc phytate and ^{99m}Tc sulfur colloid have different biodistributions and excellent localizing properties in the liver, but their dispositions in other tissues differ to varying extents [28]. Although some reports showed the limited role of ^{99m}Tc phytate as a bone marrow

Table 3 Diagnostic value of combined ^{99m}Tc HMPAO leukocyte/ ^{99m}Tc phytate bone marrow scintigraphy

	Infection	Non-infection
Concordant	0	5
Discordant	5	1
Sensitivity (%)	100	
Specificity (%)	83	
PPV (%)	83	
NPV (%)	100	
Accuracy (%)	91	

PPV positive predictive value, NPV negative predictive value

imaging agent because of its different biodistribution, preferring compact bone to bone marrow [29, 30], Subramanian et al. [24] elucidated the localization of ^{99m}Tc phytate in the functioning marrow of mouse. We therefore thought it worthwhile to study ^{99m}Tc phytate as a potential substitute for radiolabeled sulfur colloid to diagnose prosthetic infection in our country.

In their work with ^{99m}Tc sulfur colloid, Love and coworkers reported that the sensitivity, specificity, PPV, NPV and accuracy of the leukocyte/marrow imaging to diagnose knee prosthetic infections were 100 % [31], and Palestro et al. reported that the sensitivity, specificity and accuracy were 100 %, 94 %, and 96 %, respectively [32]. In our work, the sensitivity, specificity, PPV, NPV and accuracy were 100 %, 83 %, 83 %, 100 % and 91 %, respectively. Careful consideration should be given when comparing to other studies for the following reasons. First, our study was performed using ^{99m}Tc HMPAO leukocytes, but other studies were performed using ^{111}In leukocytes. To our knowledge, there have been few or no studies on the application of combined ^{99m}Tc HMPAO LS/radiolabeled colloid BMS to prosthetic infections. Second, there was one false positive case out of 11 patients. This patient was categorized as uninfected through clinical follow-up, but the possibility of an indolent prosthetic infection also should be considered.

Our study had some limitations. Guidelines for the labeling of leukocytes with ^{99m}Tc HMPAO recommended the routine measurement of the labeling efficiency, which was expected to be between 40 % and 80 %, and further quality control if the labeling efficiency fell below 40 % [33]. In our work, the labeling yield of the leukocytes was not measured. However, the biodistribution of the radiolabeled leukocyte was normal, and in the thyroid or gastric uptake, free technetium was not found in the scintigraphic images. The second limitation is the small sample size. In the future, a study with a larger sample size will be needed.

In conclusion, our result for combined ^{99m}Tc HMPAO LS/ ^{99m}Tc phytate BMS shows comparable diagnostic performance to other studies that utilized sulfur colloid. Combined ^{99m}Tc HMPAO LS/ ^{99m}Tc phytate BMS is expected to perform well as an alternative to combined radiolabeled LS/ ^{99m}Tc sulfur colloid BMS to diagnose prosthetic knee infections.

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