Original Article

Diagnostic Efficacy of UBI Scan in Musculoskeletal Infections

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Abstract

Background: Limited recent studies have demonstrated that ^{99m}Tc-UBI scan can be a helpful method in precise diagnosis of infection. In the current study, we aimed to investigate the diagnostic efficacy of ^{99m}Tc-UBI scan in detection of musculoskeletal infections.

Methods: Fifty patients with suspected musculoskeletal infections (painful THA, TKA, implant and nonunion) were enrolled in this study. After injection of ^{99m}Tc-Ubiquicidin 29-41, up to 30 minutes, dynamic imaging was performed every 1 minute. Whole body anterior and posterior images were acquired at 60 and 120 min (5 min/frame). A polygonal region of interest (ROI) was drawn manually around the area of increased accumulation of tracer (lesion) and anatomically similar area on the contralateral side (background) and the lesion to background ratio (LBR) was calculated. Then, patients underwent surgical procedures to assess infection by tissue sampling and histopathologic studies as gold standard. The receiver operating characteristics (ROC) analysis was performed to find a cut-off value for LBR and determining the diagnostic efficacy of UBI scan in musculoskeletal infections.

Results: Histopathologic studies revealed infection in 38 patients. The mean LBR was significantly higher in infected patients (2.05 ± 0.41 vs. 1.52 ± 0.22; $P < 0.001$). ROC analysis showed that a cut-off point of 1.74 for LBR will have 94.7% sensitivity, 83.3% specificity and 92% accuracy for diagnosis of musculoskeletal infections.

Conclusion: UBI scan is a useful diagnostic tool for evaluation of patients with suspected musculoskeletal infection. However, UBI imaging has some limitations which result in some incorrect diagnoses. It is important to interpret the results of the scan with regard to the clinical findings.

Keywords: Infection, musculoskeletal system, ubiquicidine

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Introduction

Since consequences of orthopedic infections deeply affect treatment outcome and approach to it is challenging for most surgeons, discrimination of infection from sterile inflammation is crucial for selecting treatment options in which detection of microorganism plays the main role. Although several noninvasive methods have been introduced for addressing this problem, none of them have been so far able to confirm it definitely and the diagnosis is made based on studying samples achieved through invasive methods. Current noninvasive tools such as clinical data, biologic criteria and radiologic studies do not have adequate diagnostic efficacy for revealing infection.[1–3] Since morphologic changes occur in late stages of infection, it is reasonable to investigate physiological changes which occur in early stages of infection using scintigraphic studies.[4,5] In addition, the advantage of whole body imaging enables us to recognize other concurrent infection foci.[4] Because, usual scintigraphic techniques do not target microorganisms directly and often show natural body reactions to insults, they cannot differentiate sterile inflammation from infection.[6] ^{99m}Tc-labeled antibiotics which directly target the infectious agents in some circumstances such as antibiotic resistance and in immune-deficient patients mislead clinicians to improper results.[7–10] In addition, failure in diagnosis of infection has been reported using ^{99m}Tc-labeled ciprofloxacin.[10]

Antimicrobial peptides (AMPs) are the new generation of pharmaceuticals which have shown interesting results in detection and treatment of infection. These peptides are produced by several types of cells and compose an important component of innate immune system against infection.[4,11–13] Electrostatic attraction is the basic mechanism of action of AMPs. In contrast to eukaryotic cells, the outer surface of the bacterial cell membrane is charged negatively, thus attracting the AMPs which have positively charged domains.[12–15] Following this interaction, AMPs bind to the microorganism surface and insert into membrane via several suggested methods.[12] Ubiquicidin (UBI), a synthetic AMP, was originally derived from murine macrophages[16] and is well known to be naturally produced in human cells.[17,18] In limited recent studies, promising results have been reported and using ^{99m}Tc-UBI scan seems to be a helpful method in precise diagnosis of infection.[4,16,19–30] In the current study, we aimed to investigate the diagnostic efficacy of ^{99m}Tc-UBI scan in detection of musculoskeletal infections.

Materials and Methods

Patients

Fifty patients with suspected musculoskeletal infections, who

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were admitted to our referral orthopedic hospital between 2011 and 2013, were enrolled in this study. Before the study, the ethical committee approval was obtained and all of the patients signed informed consent. Patients with antibiotic treatment, history of allergy, pregnant or lactating women, and patients with known hepatic or renal insufficiency were excluded. The suspected musculoskeletal infective conditions included painful uncemented total hip or cemented total knee arthroplasty, asymptomatic loosening and nonunion cases that were highly suspected for infection. In all of the selected patients, precise diagnosis of infection was crucial and surgical sampling was necessary.

^{99m}Tc-UBI scanning

Patients were referred to nuclear medicine center for UBI imaging using single head E-CAM (Siemens, USA). A dose of 20 mCi (740 MBq) ^{99m}Tc-Ubiquicidin 29-41 was injected intravenously. Up to 30 minutes, dynamic imaging was performed every 1 minute. Whole body anterior and posterior images were acquired at 60 and 120 min (5 min/frame). A polygonal region of interest (ROI) was drawn manually around the area of increased accumulation of tracer (lesion) and anatomically similar area on the contralateral side (background). Quantitative analysis was performed by calculating the ratio of mean count in pixel of lesion to background (LBR) in 60 and 120 min images.

Histopathological analysis

After UBI scan was performed, the patients underwent surgical procedures to confirm infection by tissue sampling. Histopathological analysis was performed on samples to counting polymorph nuclear (PMN) cells: the test was considered positive if more than five neutrophils were found per high-power field in five high-power fields (×400).[31]

Statistical analysis

All data were analyzed using Statistical Package for Social Sciences (SPSS) software version 20. The mean LBR between infected and non-infected patients was compared by Mann-Whitney U test. *P* values less than 0.05 were considered as statistically significant. A receiver operating characteristics (ROC) analysis, followed by Youden's J statistic (Youden's index), was performed to determine a cut-off value for LBR distinguishing between infected and non-infected patients.

Results

The characteristics of the patients are presented in Table 1. Based on either histopathological studies or UBI scanning, 38 patients were diagnosed with musculoskeletal infections. However, considering histopathological results as gold standards, the UBI technique yielded 36 true positive, 10 true negative, 2 false positive, and 2 false negative results. Thereby, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy (ACC) of UBI were calculated as 94.74%, 83.33%, 94.74%, 83.33%, and 92%, respectively. In addition, positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were calculated respectively as 5.68 and 0.063. The means of LBR for infected and non-infected patients were calculated as 2.05 ± 0.41 and 1.52 ± 0.22, respectively; the mean of LBR for infected patients was significantly higher than that of non-infected patients ($P < 0.001$). The ROC curve demonstrated an area under the curve of 0.91 for LBR to predict the infection (Figure 1). Youden's J statistic showed that a cut-off point of 1.74 for LBR will have 94.74% sensitivity and 83.33% specificity to detect musculoskeletal infection.

Discussion

Although many pharmaceuticals have been used to distinguish infections from inflammatory processes with interesting results, the specificity of these tools remains low and unfavorable.[32] Antimicrobial peptides are produced by several cell types against infection as a component of innate immunity[11–13] and because of their characteristics, it seems radiotracing them may be promising in definite diagnosis of infection. Experimental studies on animal models showed that a Tc-^{99m}-labeled peptide derived from ubiquicidine, ^{99m}Tc-UBI 29-41, targets bacterial and fungal infections, but not sterile inflammatory processes.[20] Also, there are some limited human studies supporting these findings. Akhtar, *et al.* evaluated the ability of ^{99m}Tc-UBI 29-41 in detecting infection in 18 patients with suspected bone, soft tissue or prosthesis infection and found that the sensitivity, specificity and accuracy were 100%, 80% and 94.4%, respectively.[4] In two recent studies, Assadi, *et al.* and Aryana, *et al.* demonstrated that ^{99m}Tc-UBI Scintigraphy provides complete (100%) diagnostic efficacy for musculoskeletal infections.[21,22] In another study, Dillman-Arroyo, *et al.* investigated the ability of ubiquicidine 29-41 scans in diagnosis of pyogenic vertebral osteomyelitis in 27 patients and found that the sensitivity, specificity, positive predictive value, negative predictive value and inter- and intra-observer reliability were 100%, 87.5%, 95%, 100% and 1.[23] Gandomkar, *et al.* evaluated the potential of ^{99m}Tc-UBI 29-41 scan as an infection imaging agent in seven patients and found that it was completely able to diagnose infection and roll out infection in non-infected patients.[24] Recently, Saeed, *et al.* demonstrated that the sensitivity, specificity and accuracy of ^{99m}Tc-UBI 29-41 in detection of infection in diabetic foot are 100% for bone and soft tissue infection.[28] Sepúlveda-Méndez,

Table 1. Characteristics of the patients in current study.

No. of patients		50
Age (year)		44.6 ± 17.9
Sex	Male	34
	Female	16
Chief complaint	Painful uncemented THA*	22
	Painful cemented TKA**	10
	Painful implant	7
	Nonunion	11

*total hip arthroplasty, **total knee arthroplasty.

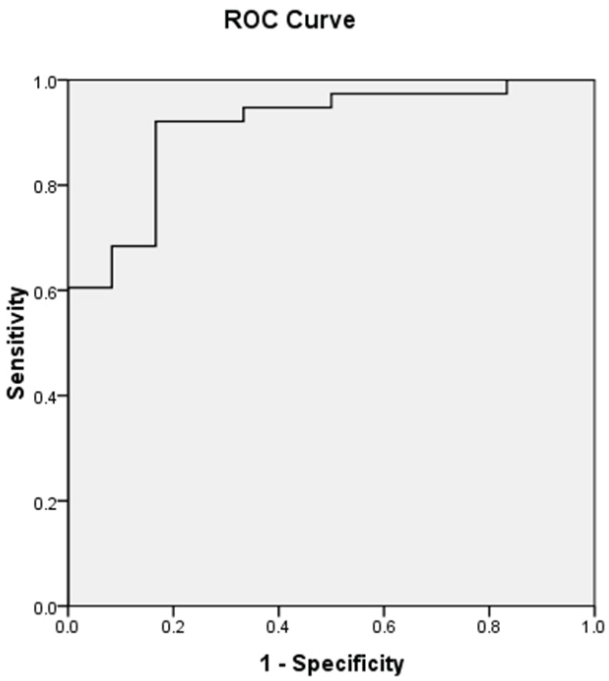

Figure 1. A receiver-operating characteristics (ROC) curve demonstrated an area under the curve of 0.91 for LBR to predict the infection.

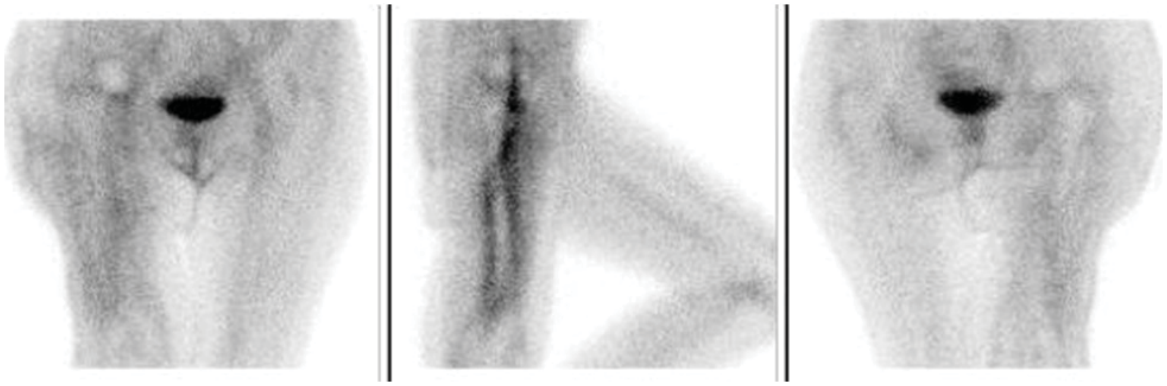

Figure 2. The UBI scan of a 60-year old woman who underwent right total hip arthroplasty secondary to hip fracture and was admitted with pain and discharge. She was under intense and prolonged antibiotic therapy (150 days). Based on the culture, the microorganism was klebsialla. As seen, in AP view, there is no significant difference between two sides while in lateral view, the difference of uptake between two sides is significant.

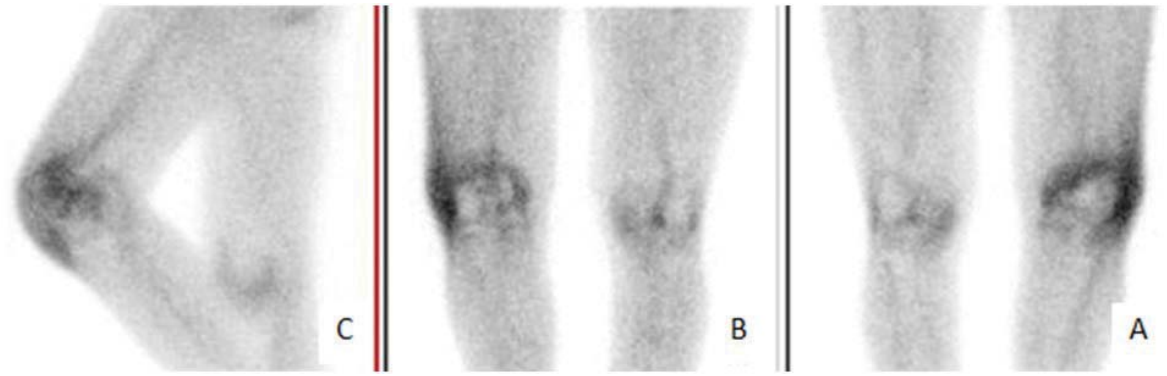

Figure 3. The anterior **(A)**, posterior **(B)**, and lateral **(C)** images of a patient which demonstrate the heterogenic distribution of the infection.

et al. found that ^{99m}Tc-UBI 29-41 scintigraphy can detect infection in patients with fever with sensitivity, specificity, accuracy, positive predictive value and negative predictive value of 97.52%, 95.35%, 96.62%, 96.72%, and 96.47%.[29]

In spite of good results in previous studies, our findings demonstrated the acceptable sensitivity (94.7%) but to some extent low specificity (83.3%) of ^{99m}Tc-UBI 29-41 scintigraphy in diagnosis of musculoskeletal infection with a cut-off point of 1.74. We performed a vast literature review to explain these findings. It seems that the number of micro-organisms can affect the ability of ^{99m}Tc-UBI 29-41 imaging in discriminating between sterile inflammation and infection like other nuclear medicine techniques. In an experimental study, Akhtar, *et al.* addressed the relation between bacterial number and uptake of ^{99m}Tc-UBI 29-41 and demonstrated that it is difficult to discriminate between 2×10^4 and 2×10^6 bacteria. They also found that it is probably difficult to image fewer than 2×10^4 bacteria, at least in mice.[33] It is assumed that limitation of ^{99m}Tc-UBI 29-41 scanning with numbers of bacteria has resulted in incorrect findings in some of our cases. In addition, it is probable that previous long term antibiotic therapy can increase the risk of false negative results through suppression of bacterial growth. In our study, two infected patients who tested negative on scan were treated with ciprofloxacin for a long period before scintigraphic evaluation. Furthermore, in another experimental study, Akhtar, *et al.* found relatively low target to non-target ratio in *Escherichia coli* infections compared with those of the *Staphylocucus aureus* and suggested that the virulence of micro-organism may affect the scintigraphic results.[6] In our study, microbiological analysis in one the two previous false negative patients showed the presence of Klebsiella as the major micro-organism. Also, in this patient with hip prosthesis, the LBR was less than 1.74 in anteroposterior image while it was > 1.74 in lateral image which was not studied in our study (Figure 2). Based on this finding, it is reasonable in patients with metal implants who are suspected for infection to investigate the lateral images in addition to anteroposterior images. Due to the heterogenic distribution of infection (figure 3), it is possible that tissue sampling was not performed exactly from the region of interest which is the most probable site of infection. Then, to increase the accuracy of tissue sampling, ^{99m}Tc-UBI 29-41 images may be helpful. Since definitive diagnosis of infection was made based on the histopathologic characteristics in our study, we selected highly suspected patients who had been scheduled for surgery to be evaluated using ^{99m}Tc-UBI 29-41 imaging. This selection bias decreased the number of true negative patients and consequently decreased specificity. Our study was limited by the small sample size and short-term follow up of the patients. Also, the limited sample size prevented us from investigating the results of the UBI scan in separate groups based on the type of the operation.

In conclusion, ^{99m}Tc-UBI 29–41 scan is a sensitive and to some extent specific agent for localizing bone and soft tissues infection in human. The optimum time for imaging is 60 min after tracer injection. For more accurate interpretation, the scan findings should be considered in association with pathogenicity of suspected microorganisms and in concordance with history and physical examination and other findings to find every confounding factor. Our findings need to be elucidated in further investigations.

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