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The Optimized Evaluation of Diabetic Foot Infection by Dual Isotope SPECT/CT Imaging Protocol

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A B S T R A C T

Sequential Tc-99m hydroxymethylene-diphosphonate (HDP) 3-phase bone (BS) and In-111 leukocyte scanning (WBCS) have been frequently used to evaluate the diabetic foot, as nonosteomyelitis BS uptake is repeatedly observed and osteomyelitis (OM) in WBCS is often uncertain without BS correlation. Additionally, both modalities are limited in lesion localization because of low resolution and lack of anatomic details. We investigated a method that combined BS/WBCS, and if needed, WBCS/bone marrow scanning (BMS) using SPECT/CT to accurately diagnose/localize infection in a practical protocol. Blood flow/pool images were obtained followed by WBC reinjection and next day dual isotope (DI) BS/WBCS planar and SPECT/CT. BMS/WBCS SPECT/CT (step 2 DI) was obtained on the following day when images were suspicious for mid/hindfoot OM. Diagnosis accuracy and confidence were judged for the various imaging combinations. Diagnosis was classified as OM, soft tissue infection (STI), both OM/STI, and other/no bony pathology by microbiology/pathology or follow-up. Distinction between various diagnostic categories and overall OM diagnostic accuracy in 213 patients were higher for DI than WBCS or BS alone, and for DI SPECT/CT than DI planar or SPECT only. Diagnostic confidence/lesion site was significantly higher for DI SPECT/CT than other comparative imaging methods. In a group of 97 patients with confirmed microbiologic/pathologic diagnosis, similar results were attained. Step 2 DI SPECT/CT performed in 67 patients further improved diagnostic accuracy/confidence. DI SPECT/CT is a highly accurate modality that considerably improves detection and discrimination of STI and OM while providing precise anatomic localization in the diabetic foot. This combined imaging technique promises to beneficially impact diabetic patient care.

The current armamentarium of noninvasive diagnostic imaging modalities for diabetic foot infection with suspected underlying osteomyelitis has several limitations (1). Changes on radiographs are both nonsensitive, as they require several weeks to be visualized, and are frequently nonspecific because of commonly coexisting bony distortion (2). Magnetic resonance imaging (MRI) has excellent bone and soft tissue contrast, which aids the assessment of infectious bone and soft tissue involvement (3), and although it is quite sensitive, its specificity is decreased in patients with diabetic neuroarthropathy, and other pathology (4–7). Three-phase bone scintigraphy (BS) with delayed 24-hour imaging also has been shown to be a very sensitive test (8, 9) but is not specific for osteomyelitis (OM) of the foot; however, improvement in diagnostic accuracy has been obtained when BS was supplemented with leukocyte-labeled scintigraphy (WBCS) (10, 11). On the other hand, the specificity of WBCS could be compromised by the inflammatory process that accompanies a healing fracture or a neuropathic joint, particularly in the mid/hindfoot. In the latter cases, it was shown to be virtually impossible to determine whether or not a WBCS focus of activity represents an infection or an atypical site of hematopoietically active bone marrow (12). Combined WBCS and bone marrow scintigraphy (BMS) was shown to facilitate a more accurate interpretation of OM than BS/WBCS alone (13).

The aforementioned scintigraphic modalities used conventional planar imaging, which posed a limitation in identifying the precise site of OM or even determining whether or not an infection is within

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bone or soft tissues, owing to their relatively low spatial resolution and lack of anatomic specificity. The fusion of scintigraphic and morphologic images using hybrid single-photon emission computed tomography/computed tomography (SPECT/CT) was introduced to overcome the lack of anatomic landmarks in nuclear medicine and has, in fact, significantly improved diagnostic accuracy over imaging performed with SPECT alone in many scintigraphic procedures (14), despite low spatial resolution of SPECT itself.

In this study, we investigated a method that combines the imaging of multiple radiopharmaceuticals using SPECT/CT fusion for an accurate diagnosis and precise localization of diabetic foot infection.

Methods

Study Population

We retrospectively evaluated 272 consecutive adult patients with diabetes mellitus, peripheral neuropathy, and high clinical suspicion of foot OM, who were referred for clinically indicated nuclear medicine imaging examinations between September 2006 and December 2009. This study was approved by the Institutional Review Board of the Mount Sinai School of Medicine. All patients had foot ulcerations. The final diagnosis was established in 1 of 2 ways. The first method used surgical specimens of excised or biopsied tissue. These results were considered definitive for documenting presence of OM and/or soft tissue infection (STI) if (1) the bone or tissue culture confirmed and isolated the pathogenic organism, and inflammatory changes were seen in the pathologic examination; or (2) tissue histology showed pathologic changes consistent with acute (or chronic) OM and/or STI, if tissue culture was not conclusive (owing to contamination or mixed growth or no growth, despite presence of white blood cells [WBCs] and organisms). The second method was used in subjects with no microbiology or histopathology confirmation, predominantly in patients who had no OM, with or without STI by dual isotope (DI) imaging. The final diagnosis in this group of patients was based on follow-up, which included clinical examination and other imaging procedures (CT and MRI).

Imaging Protocol

The blood flow phase of BS was started immediately after bolus injection of 925 to 1110 MBq (25 to 30 mCi) technetium-99m (Tc-99m) HDP at 1 second per frame for 60 seconds, followed by a planar blood pool image with a 120-second acquisition time. After obtaining a blood sample, the leukocytes in the sample were isolated and labeled with Indium 111 (In-111) oxine. The average labeling yield was over 90%. The labeled cells were reinjected into each patient. The administrated activity ranged from 13.0 to 18.5 MBq (0.35 to 0.50 mCi). Combined DI-delayed BS/WBCS images were performed approximately 24 hours later. A plantar view of the feet and if needed by clinical examination and location of foot ulceration, lateral and medial views of the feet, were acquired for 10 to 15 minutes each, using a 256 × 256 matrix. A 19% energy window with a negative 1% offset was used for the 140 keV Tc-99m images. Both a 20% energy window for the 247 keV energy peak and a 16% energy window with a positive 2% offset for the 173 keV energy peak were used for the In-111 images. DI SPECT/CT studies (same energy windows) were performed after planar imaging using a dual-head large field-of-view gamma camera equipped with medium-energy collimator and a low-power x-ray transmission system mounted on the same gantry with 4 sets of detectors fixed on the opposite side of the gantry (Infinia Hawkeye4; GE Medical Systems, Milwaukee, WI). The patient's feet were immobilized using an orthopedic plastic foot holder to ensure proper registration between CT and SPECT. Emission imaging with a 360° SPECT acquisition with matrix size of 64 × 64 in 3° angle steps at 60 seconds per frame, and transmission CT data over a 360° arc with a slice thickness of 5.0 mm using x-ray energy of 140 kV and 2.5 mA with an axial interval 5.0 mm, velocity 2.6 mm, 512 × 512 matrix, 1.1 mm pixel size, and a standard filter were sequentially acquired and fused on a nuclear medicine workstation (Xeleris; GE Medical Systems). When step 2 DI imaging was carried out, the patient was injected with approximately 370 MBq (10 mCi) Tc-99m sulfur colloid intravenously on the following day and a DI SPECT/CT BMS/WBCS (step 2 DI SPECT/CT) imaging was performed approximately 30 minutes later using the previously mentioned acquisition parameters except for an increase in SPECT imaging time per frame from 60 to 75 seconds. The GE Xeleris Volumetrix for Hawkeye was used for SPECT reconstruction using the ordered-subset expectation-maximization/maximum-likelihood expectation-maximization (OSEM/MLEM) method. Measured attenuation correction factors were applied. A Hanning prefilter of 0.45 was used. The 3-dimensional post filter used was a Butterworth filter with a cutoff of 0.5 and order 10. Transverse, sagittal, and coronal slices were generated.

Image Analysis

In separate sessions, SPECT/CT BS, WBCS, step 1 DI, and when available step 2 DI images were jointly reviewed by 2 observers. Additional separate review sessions included DI planar, SPECT only, and SPECT/CT images. A third review of the 67 patients who had both step 1 and step 2 DI SPECT/CT images was additionally performed in separate sessions that included DI step 1 only and DI step 1 plus step 2 images together. The blood flow and blood pool images were available for review in the BS and DI but not in WBCS evaluations. Based on each review, the overall patient diagnosis was classified as OM, STI, both OM and STI (close to or distant from OM site), and other or no bony pathology. The confidence in diagnosis and exact site of lesions was categorized as uncertain, probable, or certain. Differences between observers were resolved by consensus.

Statistical Analysis

Lambda value ± standard error (SE) was used to measure association between nominal variables. In this analysis, values of the independent variable from imaging results are used to predict values of the dependent variable, which is the final diagnosis. A value of 1 means that the independent variable perfectly predicts the dependent variable. A value of 0 means that the independent variable is of no help in predicting the dependent variable. The uncertainty coefficient (error reduction) indicates the proportional reduction in error when values of one variable are used to predict values of the other variable.

To estimate various diagnostic accuracy measurements and to perform receiver-operating characteristic curve analysis for OM, the diagnosis of each scan was scaled 0 to 5 as follows: grades 0–2 = definitely, probably, and possibly no/other bony pathology or STI, respectively; grades 3–5 = possibly, probably, and definitely OM with or without STI, respectively. The sensitivity, ie, the number of true-positives divided by number of true-positives plus false-negatives; the specificity, ie, the number of true-negatives divided by number of true-negatives plus false-positives; the positive predictive value (PPV), ie, the number of true-positives divided by number of true-positives plus false-positives; and the negative predictive value (NPV), ie, the number of true-negatives divided by number of true-negatives plus false-negatives were calculated for OM, where a dichotomous call for certainty of diagnosis was defined as positive (grades 3–5) versus negative (grades 0–2). The estimate of the area under the curve (AUC) was computed using a nonparametrical model. McNemar test was used to compare paired proportions.

Noncontinuous variables were tested by a chi-square contingency table or Fishers exact test when appropriate. Values of continuous variables were shown as means ± 1 standard deviation. All statistical tests were 2-tailed and were considered to be statistically significant at a P value of .05 or less. Analyses were conducted with IBM SPSS software (version 18.0; IBM SPSS Inc., Chicago, IL).

Results

Of 272 included patients, 24 had no SPECT/CT images, as they exhibited completely no uptake in their In-111 WBC planar scans. Of the remaining 248 patients, 35 patients were excluded because of lack of follow-up, which left for analysis 213 patients with mean age 59 ± 15, consisting of 146 men and 67 women with suspected OM sites in forefoot (109), midfoot (27), hindfoot (52), and multiple sites (25). The final diagnosis in the 24 patients who had only planar DI and showed variable degree of BS uptake but negative WBCS uptake, was judged as other bony pathology mainly by clinical follow-up for 8.9 ± 2.1 months. The surgical pathologic and microbiologic examination of this group of patients was available in only 6 patients, which confirmed other bony pathology except for one false-negative scan in a patient who proved to have chronic OM of the second metatarsal bone, yielding an NPV of 96%.

The final diagnosis of the 213 patients who completed planar and SPECT/CT imaging protocol was determined as OM in 38 patients (22 with bone microbiology/pathology confirmation); both OM and STI in 66 patients (46 with microbiology/pathology confirmation); STI in 81 patients (21 with microbiology/pathology confirmation); and other or no bony pathology in 28 patients (8 with pathology confirmation). The SPECT/CT image quality was acceptable in all patients with no noticeable misregistration in the fused images.

Comparison of Imaging Scans in All Patients' Diagnoses

The accuracy of predicting the various final diagnosis categories by DI SPECT/CT was higher than WBCS SPECT/CT or BS SPECT/CT alone, as assessed by Lambda ± SE (0.90 ± 0.03, 0.54 ± 0.06, and 0.17 ± 0.07, respectively) and error reduction % (79%, 37%, and 12%, respectively). Likewise, the final diagnosis prediction by DI SPECT/CT was more accurate than DI SPECT or DI planar images, as measured by Lambda ±