Original Article

Diagnosis of bone infection by complementary role of technetium-99m MDP and technetium-99m hexamethylpropylene-amineoxime-leukocytes

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ABSTRACT

Purpose: Valuate complementary role of ^{99m}Tc-MDP bone scan and ^{99m}Technetium hexamethylpropylene-amineoxime (^{99m}Tc-HMPAO) labeled leukocyte scintigraphy in diagnosis of bone infection. **Patients and Methods:** Ninety one sites suspected to have bone infection were divided in to two groups: Group I 49 sites with current endo-prothesis; and group II 42 sites with no prosthesis. All patients were subjected to serial images of ^{99m}Tc-HMPAO labeled leukocyte (^{99m}Tc-white blood cells (WBCs)), triple phase bone scan (^{99m}Tc-MDP) and plain X-ray, in addition to clinical and bacteriological assessment, together with follow-up. **Results:** The overall sensitivity (Sn) was found to be 34.9%, 95.4%, and 86% for plain X-ray, ^{99m}Tc-MDP, and ^{99m}Tc-WBCs respectively. Concerning specificity (Sp) was found to be 47.9%, 45.8%, and 91.7% respectively for the three imaging modalities. ^{99m}Tc-WBCs showed better Sn, Sp, and accuracy in group I (95%, 93.1% and 93.9%, respectively) compared to 40%, 41.4%, and 40.8% for plain X-ray and 90%, 62%, and 73.5% respectively for ^{99m}Tc-MDP. On the other hand, ^{99m}Tc-MDP proved to have best Sn 100% versus 78.3% and 30.4% for ^{99m}Tc-WBCs and plain X-ray respectively. Yet, Sp and accuracy was found to best for ^{99m}Tc-WBCs (89.5% and 83.3% respectively) compared to 57.9% and 42.9% for plain X-ray and 21.1% and 64.3% for ^{99m}Tc-MDP. **Conclusion:** Combined imaging with ^{99m}Tc-WBCs and ^{99m}Tc-MDP proved to be effective in early detection of bone infection in the presence or absence of prosthesis.

Keywords: Bone infection, prosthesis, triple phase bone scan, ^{99m}Technetium hexamethylpropylene-amineoxime-leukocyte

INTRODUCTION

Clinical and laboratory features of skeletal infections are always present, may be confusing, and are non-specific for bone infection in its early stages; hence, several imaging modalities have been used for early detection of osteomyelitis.[1,2] Plain X-ray should always be the first step in the imaging assessment of osteomyelitis, however, bone destruction and periosteal reactions are not early findings, and are obvious only 10-21 days after the onset of disease.[1,3] The sensitivity (Sn) for X-ray radiography has been reported to range from 43% to 75%, and the specificity (Sp) from 75% to 83%.[1-4]

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The labeling leukocytes, now a routine procedure all-over the world, does not affect their chemotactic response. Usually, the majority of leukocytes labeled are neutrophils, and hence, the procedure is most useful for identifying neutrophil-mediated inflammatory processes, such as bacterial infections.[2,4,5]

In joint replacement surgery, clinical signs and symptoms, laboratory tests, radiography and joint aspiration are insensitive, non-specific, or both. Cross-sectional imaging modalities are hampered by artifacts produced by the prosthetic devices themselves.[2] Radionuclide imaging is not affected by the presence of metallic hardware and is therefore useful for evaluating the painful prosthesis. Bone scintigraphy is useful as a screening test, despite an accuracy of only 50-70%, because normal results essentially exclude a prosthetic complication. The addition of gallium-67, a non-specific inflammation-imaging agent, improves the accuracy of bone scintigraphy. It is well-known that the accuracy of combined leukocyte-marrow imaging is the highest among available radionuclide studies.[2-6]

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The aim of this study is to assess the diagnostic value, different techniques, namely plain X-ray, triple phase bone scan, and ^{99m}Tc-labeled hexamethylpropylene-amineoxime (^{99m}Tc-HMPAO) labeled leukocyte scintigraphy in diagnosis of bone infection, especially, in evaluation of infection in patients with symptomatic bone and joint prostheses.

PATIENTS AND METHODS

Patients

In this study, all patients with suspected bone infection, referred to the orthopedic and nuclear medicine departments in Al-Hada Military and King Abd Al-Aziz hospitals during the period from February 2010 to October 2011 were included.

Exclusion criteria

Patients below 18 years old, suspected vertebral osteomyelitis, and those with administration of antibiotics.

On the basis of localization and the presence of endo-prosthesis, the patients were classified into two groups: Group I with 49 sites with endo-prostheses, and group II including, 42 sites with suspected infection in different parts of the appendicular skeleton. Of these patients, 35 had an underlying pre-existing condition such as trauma or previous orthopaedic surgery, and bone violation.

Methods

Clinical assessment

Symptoms (pain, fever, warmth, erythema or swelling, sinus track) – mainly pain on motion or at rest, leading to a suspicion of infection – were the typical reason for performing the study.

In the 69 sites investigated, the results of the nuclear studies were correlated with tissue culture either withdrawn during surgery or by biopsy, which allowed comparison of the performed studies with the samples obtained for bacterial culture. The sites were considered infected if tissue cultures grew bacteria or in case of a grossly purulent finding at surgery, and they were considered uninfected in the absence of purulence at surgery samples.

In those cases in which no further surgery or biopsy was performed (22 sites out of the 91 sites), the clinical outcome was carefully monitored for about 6 months after the imaging procedures. On the basis of clinical parameters, we considered those patients for whom antibiotic treatment was not required through-out the time of follow-up as not infected. On the other hand, we considered those patients who required a justified antibiotic therapy during follow-up as infected.

Laboratory parameters

We evaluated laboratory parameters (white blood cells (WBCs)) count, percentage of neutrophils and erythrocyte sedimentation rate (ESR) in all patients before scanning.

Plain X-ray films

Plain X-ray films were obtained for all sites studied. The conventional radiographs of the region of interest were reviewed by an experienced radiologist who was unaware of the clinical and scintigraphic findings. The radiographs were assessed for osteomyelitis using criteria as given by Resnick and Niwoyama,[7] (in ascending order of relevance: Soft-tissue swelling, osteoporosis, osteolysis, cortical or medullary destruction and sequestration).

Nuclear medicine studies

This included, triple phase bone scan (^{99m}Tc-MDP), and ^{99m}Tc-HMPAO labelled WBCs (WBCs) with complementary ^{99m}Tc-tin colloid marrow imaging.

^{99M}TC-HMPAO-LEUKOCYTE SCINTIGRAPHY (WBCS)

Technique used for white blood cell labeling

A 50 ml sterile syringe containing 2-3 ml of anticoagulant was used and 30-50 ml of patient's blood was withdrawn via "Acid citrate dextrose solution (ACD)." The sample was allowed to stand for 30-60 min to separate plasma rich in WBCs from bulk of the red blood cells (RBCs). One milliliter of hetastrach (hespan) was used to accelerate the sedimentation process of RBCs.[8-10]

The resulting plasma was separated from RBCs in a sterile test tube (30 ml phalcon tube). The later was centrifuged at 150 g for 5 min to separate WBCs from the rest of remaining blood components, the former would appear after centrifugation as a pinkish pellet (button) in the bottom of the tube.

The excess of plasma and RBCs was then removed and the removed solution would be platelet rich plasma (PRP). PRP was centrifuged at 1500 g for 5-10 min to obtain cell free plasma (CFP).

Preparation of ^{99m}Tc-HMPAO

This was carried out by adding 740-1110 MBq (20-30 mCi) of free ^{99m}Tc to HMPAO vial (Ceretec; Amersham).

The prepared ^{99m}Tc-HMPAO was added to the formed WBCs pellet, and they were incubated together in normal atmospheric conditions for 2-3 min. Afterwards 2 ml of CFP were then added, and then centrifuged again at 150 g for 5 min to separate free ^{99m}Tc, and free ^{99m}Tc-HMPAO, from labeled WBCs. The resultant supernatant plasma after centrifugation was then discarded. The final product was then diluted with 1-2 ml of CFP. Soon afterwards, typically in almost all patients within 15 min of preparation, the prepared labeled leucocytes were injected intravenously. The administered activity range was 296-510 MBq (8-10 mCi).

All the fore-mentioned steps were performed in our cell labeling laboratory in a well sterilized environment using the manipulation cell laminar flow equipped with a lead shield, specially designed for handling radioactive materials and under complete aseptic conditions.

Imaging technique

Imaging was performed on a dual-head gamma camera (Siemens). ^{99m}Tc-labeled WBCs whole body scans in both anterior and positioner projections, as well as static spot views on the region of interest were acquired at 3 different time points after injection: 30 min (early images), 4 h, and 24 h (late images). The static images were acquired using an imaging time of 7 min in the early and 4-h images, while acquisition time was 15 min for the late images. Matrix size was 256 × 256; a low energy general purpose collimator was used.

^{99m}Tc-tin colloid bone marrow imaging

For all who were suspected to have positive labeled WBCs scans for osteomyelitis, bone marrow scans were acquired in a following day after performing the labeled WBCs study. Whole body scans in both anterior and posterior projections, as well as static spot views on the region of interest were obtained using the same gamma camera with a matric size of 256 × 256; a low energy general purpose collimator was used. Co-registration technique between the WBCs and marrow scans was also used.

Image interpretation

Evaluation criteria for combined WBCs/marrow scans were as follows: The scans were considered to be positive when abnormal localized activity in the region of interest increased in intensity or in extension in comparison with the contralateral region or with the ipsilateral adjacent bone segment, and no corresponding bone marrow activity could be detected on the acquired tin-colloid bone marrow scans. A scan was considered to be negative when there was no abnormal activity detected in the region of interest or when the local activity was identical to that present on the bone marrow images.

Triple phase bone scan

It was performed for all patients 2 days before performing the labeled WBC study; the average activity used was 740-925 MBq (20-25 mCi) of ^{99m}Tc-MDP. Early dynamic and blood pool images were obtained on the region of interest soon after intravenous tracer injection. 2-3 h later, late osseous scans (whole body survey and static spot views on the region of interest) were obtained, the usual matric used for the static spot views was 256 × 256, and a low energy general purpose collimator was used.

All scans were assessed and reported independently before performing the WBCs study. Cases were considered positive for infection when increased perfusion, metabolic blood pool activity and late osseous uptake in the region investigated were found.

Statistical analysis

In all patients, we calculated the Sn, Sp and accuracy for the main clinical symptoms and the laboratory data and we used the student *t*-test for unpaired data to compare the mean values of the WBCs count, percentage of neutrophils, and ESR. The evaluation of the results of the ^{99m}Tc-HMPAO labeled leukocyte scintigraphy in comparison with the clinical or instrumental follow (final diagnosis) was performed by traditional methods based on Sn, Sp, and accuracy. Furthermore, the bone scan and X-ray results were evaluated using the same methods.

Chi-square test was also used for assessment of the results of the three different imaging modalities (^{99m}Tc-HMPAO labeled leukocyte scintigraphy, the bone scan and X-ray), in comparison to the final diagnosis by tissue culture and follow-up.

RESULTS

Demographic data

We studied 75 patients (24 females, 51 males; mean age ± SD, 44.8 ± 15.54 years; age range: 18-75 years). Of these patients, 16 had more than one site of complaint; thus, a total of 91 sites were included, in the analysis.

The distribution of sites involved is displayed in Table 1 with the commonly affected sites in order are hips, knees and femori respectively.

The 91 sites investigated, were then divided in to two groups, first group included, those with current prosthesis (49 sites) and the second one included, those with no prosthesis (42 sites). However, 35 Sites of the latter group had history of previous surgical intervention and bone violation at the sites investigated.

How we diagnose true positive and negative cases

In 43 of the 91 sites assessed (47.25%), the clinical or microbiologic investigations confirmed the presence of infection (considered as true positive (TP)), whereas, no infection was found in 48 sites (52.75%) (considered as true negative (TN)).

Table 1: Distribution of sites involved in studied groups

Joint	Fixed prostheses group I		No. prothesis group II		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Knee	22	44.9	6	14.3	28	30.8
Hip	20	40.8	11	26.2	31	34.1
Femur	6	12.2	11	26.2	17	18.7
Tibia	1	2	3	7.1	4	4.4
Ankle	0	0	4	9.5	4	4.4
Foot	0	0	3	7.1	3	3.3
Wrist	0	0	2	4.8	2	2.2
Upper limb	0	0	2	4.8	2	2.2
Total	49	53.8	42	46.2	91	100

On a total of the 43 positive cases for infection, 37 sites were deemed infected by tissue cultures, infecting organisms included, 20 cases of *staphylococcus aureus*, 11 cases of *Staphylococcus epidermidis*, 3 cases of *Escherichia coli*, 2 cases of *Pseudomonas auregonisa* and 1 case of *Streptococcus mitis*. As for the remaining 6 sites assessed, they were deemed infected clinically and by follow-up.

Sensitivities and specificities for clinical and laboratory variables were given in [Table 2]. Pain was seen in all patients, both infected and non-infected, and is entirely non-specific. Conversely, local erythema or swelling, local warmth, and fever are significant observations when identified, but their relative infrequency limits their role in the diagnosis of osteomyelitis. Sinus tracks are also uncommon findings but were always associated with infection in our study. Similar evaluation of laboratory tests shows that leukocytosis, and a differential shift to the left is quite helpful when present but are insensitive markers for infection. An elevated sedimentation rate is neither sensitive nor specific laboratory finding. The three laboratory parameters in the infected and uninfected groups, showed no significant difference (total and subgroups).

Table 2: Performance of clinical and laboratory indicators in diagnosis of bone infection

Indicator	Sensitivity (%)	Specificity (%)	Accuracy (%)
Clinical			
Pain	100	0	50
Fever	2	100	50
Warmth	12	96	53
Erythema or swelling	24	90	56
Sinus track	14	100	56
Laboratory			
WBCs count (>11000/uL)	15	98	55
Polymorphnuclear leucocytes (>77%)	25	98	58
ESR (>22 in males, and >29 in females)	55	25	41

WBCs: White blood cells, ESR: Erythrocyte sedimentation rate

Accuracy of diagnosis of plain radiograph, ^{99m}Tc-mdp bone scan and ^{99m}Tc-hmpao labeled WBCs

Results for the group with prosthesis

The frequency of sites affected in this group are displayed in Table 1, it included, 22 knee, and 20 hip joints' prostheses, 6 femoral fixation prostheses, and only one tibial fixation prosthesis. In this group, 20 sites were deemed infected on clinical and microbiological assessment, whereas, 29 sites were negative for infection [Table 3].

For ^{99m}Tc-HMPAO labeled WBCs/bone marrow studies, ^{99m}Tc-MDP triple phase bone studies and the plain X-ray modality they revealed 19, 18, and 8 TP cases respectively, 27, 18 and 12 TN cases respectively, 2, 11, and 17 false positive cases respectively, and 1, 2 and 12 false negative cases respectively [Table 3].

Accordingly, the accuracy for all three different imaging modalities in evaluation of bone infection is presented in Table 4, this includes, Sn, Sp, negative predictive values (NPV), positive predictive value (PPV), accuracy, false negative rate (FN rate), false positive rate (FP rate), likelihood ratio for positive test (LR +ve), as well as likelihood ratio for negative test (LR −ve). Furthermore results for comparing the results of the three imaging modalities with the tissue culture and clinical diagnosis via the Chi-square test are represented [Table 4].

With our criteria, plain radiographs were neither sensitive nor specific for diagnosis of bone infection. Bone scans were better indicators of infection, with Sn of 90%, but it was relatively non-specific (62%). The Sn, Sp, NPV, PPV and overall

Table 3: Results of bone affection (infected, i.e., true positive, and uninfected, i.e., true negative) by different modality

Positive and negative for each investigation	Fixed prostheses group I		No. prothesis group II		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Number and percentage of true positive and negative cases as proved by clinical and microbiological examination						
True positive	20	40.8	23	54.8	43	47.8
True negative	29	59.2	19	45.2	48	42.2
	49	100	42	100	91	100
Accuracy of distribution of cases as detected by ^{99m}Tc-HMPAO labeled WBCs/marrow scans						
TP	19/20	95	18/23	78.3	37/43	86
TN	27/29	93.1	17/19	89.5	44/48	91.7
FP	2/29	6.9	2/19	10.5	4/48	8.3
FN	1/20	5	5/23	21.7	6/43	14
Accuracy of distribution of cases as detected by ^{99m}Tc-MDP bone scans						
TP	18/20	90	23/23	100	41/43	95.3
TN	18/29	62.1	4/19	21.1	22/48	45.8
FP	11/29	37.9	15/19	78.9	26/48	54.2
FN	2/20	10	0/23	0	2/43	4.7
Accuracy of distribution of cases as detected by plain X-rays						
TP	8/20	40	7/23	30.4	15/43	34.9
TN	12/29	41.4	11/19	57.9	23/48	47.9
FP	17/29	58.6	8/19	42.1	25/48	52.1
FN	12/20	60	16/23	69.6	28/43	65.1

WBCs: White blood cells, ^{99m}Tc-HMPAO: ^{99m}Tc-labeled hexamethylpropylene-amineoxime, TP: True positive, TN: True negative, FP: False positive, FN: False negative, ^{99m}Tc-MDP: Technetium-99m methylene diphosphonate

Table 4: Accuracy of different investigation to detect bone infection in studied groups

Accuracy parameter	WBCs			Bone scan			Plain X-rays		
	Group 1	Group 2	Total	Group 1	Group 2	Total	Group 1	Group 2	Total
Sensitivity	95	78.3*	86@	90	100	95.4@	40	30.4	34.9@
Specificity	93.1	89.5	91.7#	62	21.1**	45.8#	41.4	57.9	47.9#
NPV	96.4	77.3*	88	90	100	91.6	50	40.7	45
PPV	90.4	90	90.2	62	60.5	61.2	32	46.6	37.5
ACC	93.4	83.3	89	73.5	64.3	69.2	40.8	42.9	41.8
FPR	6.9	21.7*	14	38	0**	4.6	58.6	69.6	65.1
FNR	5	10.5*	8.3	10	78.9**	54.2	60	42.1	52.1
LPR	13.8	7.5*	10.3	2.37	1.27	1.8	0.68	0.7	0.67
LNR	5.4	0.24**	0.15	0.16	0*	0.1	1.45	1.2	1.36

*P<0.05,**P<0.01, @P<0.001 between plain X-ray and both WBCs and bone scan. #P<0.01 between WBCs and both plain X-rays and bone scan, WBCs: White blood cells, NPV: Negative predictive values, PPV: Positive predictive value, FPR: False positive rate, FNR: False negative rate, LPR: Likelihood positive ratio, LNR: Likelihood negative ratio, ACC: Accuracy

accuracy (95%, 93.1%, 96.4%, 90.4% and 93.9% respectively) of ^{99m}Tc-HMPAO labeled WBCs/bone marrow studies were much better than those of the other modalities.

The triple phase bone scan studies in this group diagnosed accurately 8 cases or loosening of hip prostheses, however, posterior in 2 of them associated infection was found on further microbiological assessment.

Group with no prothesis

The most commonly affected sites in this group are the hips (11 sites), femori (10 sites), and knees (6 sites) [Table 1].

Table 3 represents the number of proved positive (23 sites) and negative cases (19 sites) by culture and clinically. For ^{99m}Tc-HMPAO labeled WBCs/bone marrow studies, ^{99m}Tc-MDP triple phase bone scans and Plain X-ray in this group, there were 18, 23 and 7 TP cases respectively, 17, 4 and 11 TN cases respectively, 2, 15, and 8 false positive cases respectively, and 5, 0 and 16 false negative cases respectively.

In this group of patients, 4 ankles and 3 feet (7 sites) were included, ^{99m}Tc-HMPAO WBCs/Bone marrow studies differentiated uninfected from infected sites in all cases (3 infected and 4 uninfected). However, ^{99m}Tc-HMPAO labeled WBCs scanning missed three cases of septic arthritis. 2 of them were in the knees and the third was in the hip. All the three patients had history of previous surgical intervention in the joint affected. ^{99m}Tc-HMPAO labeled WBCs gave a false positive two cases in two cases, one patient with avascular necrosis of femoral head, and the other with fibrous dysplasia involving the right ulna.

Triple phase bone scan revealed the presence of avascular necrosis of femoral head in two cases.

In this group of 42 sites, plain radiographs had the least Sn, Sp and accuracy (30.4%, 57.9%, and 42.9% respectively). Whereas, triple phase bone scan was the most sensitive modality in detecting infection (100%) and it also had the highest negative predictive value (100%), but it showed poor Sp (21.1%) [Table 4].

^{99m}Tc-HMPAO labeled WBCs/bone marrow study was the most specific (89.5%), and it also was the most accurate modality (accuracy was 83.3%) and had the highest (PPV = 90%) [Table 4].

Total results

The final results for the 91 sites included in the study ^{99m}Tc-HMPAO labeled WBCs/bone marrow studies were the most accurate modality in differentiating uninfected from infected sites, as shown in Table 4.The total results for the three modalities are shown in Table 4, with the highest Sn bone scan 95.4%, but still insignificant with that of HMPAO-WBCs (86%) ($P > 0.05$), but both statistically are higher than plain X-ray (34.9%, with $P < 0.001$). The highest Sp is found at HMPAO-WBCs study (91.7%), which is statistically higher than that of bone scan (45.8%, with $P < 0.01$) and plain X-rays (47.9%, with $P < 0.01$). Similarly, accuracy was found to be highest in HMPAO-WBCs (89%), which are statistically higher than bone scan (69.2%, with $P < 0.05$) and plain X-ray (41.8%, with $P < 0.001$).

The total results for ^{99m}Tc-HMPAO labeled WBCs/bone marrow studies were 37 TP foci out of 43 foci deemed infected on final diagnosis, and they excluded infection in 44 sites out 48 uninfected sites [Table 5] with strong degree of matching with the golden standard (Clinical, laboratory and microbiological diagnosis) of 89% ($P < 0.001$). For ^{99m}Tc-MDP triple phase bone scan, it showed 41 TP sites out of 43 sites and 22 TN sites out of 48 sites with modest degree of matching (69.2%, with $P < 0.05$). Plain radiographs had the highest incidence of false negative results (28 sites out of-5 and they also detected only 15 sites of the TP sites (15 out of 43) with poor degree of matching (41.8%) ($P > 0.05$) [Table 5].

DISCUSSION

The current study revealed that ^{99m}Tc-HMPAO labeled WBCs combined with ^{99m}Tc-sulfur colloid marrow imaging is one of the most accurate modalities and that it is superior to plain radiographs and triple phase bone scan in assessment of bone infection in prosthetic group.

Skeletal infection continues to be a common difficult condition in clinical practice and early accurate diagnosis is more challenging.[9,10]

Table 5: Degree of matching between the golden standard (clinical, laboratory and microbiological) and other imaging modalities

Investigation used	Status	Combined clinical, laboratory and microbiological		Total
		Infected	Uninfected	
^{99m}Tc-HMPAO-labeled WBCs	Infected	37/43	6/43	43/43
	Uninfected	4/48	44/48	48/48
	Total	41/91	50/91	81/91
Degree of matching=89%, $P<0.001$				
^{99m}Tc-MDP Bone scan	Infected	41/43	2/43	43/43
	Uninfected	26/48	22/48	48/48
	Total	67/91	24/91	63/91
Degree of matching=69.2%, $P<0.05$				
Plain X-rays	Infected	15/43	28/43	43/43
	Uninfected	25/48	23/48	48/48
	Total	40/91	51/91	38/91
Degree of matching=41.8%, $P>0.05$				

WBCs: White blood cells, ^{99m}Tc-HMPAO: ^{99m}Tc-labeled hexamethylpropylene-amineoxime, ^{99m}Tc-MDP: Technetium-99m methylene diphosphonate

In addition, treatment of infection after arthroplasty or previous bone violation is costly because of the subsequent need for further surgery and the prolonged hospitalization often required eradicating the infection. Methods to prevent, diagnose, and treat infection must be perfected to reduce the social costs of arthroplasties. However, infection after arthroplasty is often a diagnostic challenge. The consequences of misdiagnosis are considerable. Reimplantation of a prosthesis into an infected tissue bed, without appropriate debridement, is likely to result in persistent infection.[6,10]

Plain X-ray films are likely the first radiological step in the assessment of osteomyelitis. However, low to moderate Sn (43-75%) and with moderate Sp (75-83%) had been reported due to its dependence on bone destruction and periosteal reactions, which occurred very late.[11] with much more reduction in the diagnostic accuracy in the violated bone to be (30-50%).[12] This confirms the low results of the current study (34.9% overall Sn and 47.9% Sp) with the note that the current study included 49 sites with current prostheses and 35 sites with history of previous bone violation in contrary to the studied previous reports, which included only 7 sites with previous surgical intervention or bone violation. Eventually, plain X-ray is still considered the first imaging modality to be used in assessing suspected bone infection, as it may provide clues for other pathologic conditions, it provides anatomical landmarks for other imaging modalities, and it may suggest the correct diagnosis in absence of bone violation.[11,12]

Scintigraphic procedures using different radiopharmaceuticals are becoming a very essential part in the diagnostic work up for osteomyelitis. The most commonly used bone radiopharmaceutical in clinical practice is the ^{99m}Tc-MDP with three phase bone scan, which revealed the classic appearance of focal hyperperfusion, focal hyperemia, and focally increased bone uptake. This classic pattern, is highly sensitive for osteomyelitis (Sn 73-100%).[13,14] This is concordant with our results where total Sn of triple phase bone scan was 95.4%. However, our observed low Sp (45.8%), could be explained by the number of previously violated sites (84 sites), which might cause a positive bone scan such as trauma, surgery, orthopaedic devices, and possible bone tumors; very similar to those who reported low Sp 38%.[5,15]

Moreover, the positivity of bone scan in patients with prostheses could persist for as long as 1 year after an uncomplicated hip replacement and for 2 years after insertion of prosthesis without cement. Accordingly, these scans cannot be used to differentiate between infection and aseptic loosening.[15] Very similar to our study where we could not, by bone scan, differentiate infected from non-infected in the group of endoprostheses (90% Sn, and 62% Sp), in comparison to our higher results with ^{99m}Tc-HMPAO labeled WBCs study (95%, and 93.1% respectively). An example for Bone scan situation, it could diagnose 2 cases of avascular necrosis of femoral heads and 6 cases of aseptic loosening of hip prostheses accurately in our study, which helped a lot in final diagnosis and further management of these patients. However, there were two other sites diagnosed falsely by bone scan as loosening, but positive for infection by both microbiological assessment and the labeled WBCs/marrow colloid imaging.

^{99m}Tc-HMPAO-leukocyte scintigraphy has been evaluated alone and in combination with other radiotracers. However, due to relatively low Sn (50-100%) and Sp (45-100%), of using ^{99m}Tc-HMPAO-leukocyte scintigraphy alone,[13,16,17] it has been reported to be better used in combination of ^{99m}Tc-labeled sulfur colloid bone marrow imaging to improve its diagnostic accuracy in bone infection.[18,19] The reported results of labeled leukocytes plus sulfur colloid bone marrow imaging are superior to imaging with labeled leukocytes alone or in combination with routine bone scintigraphy.[20] Accordingly, the current study adopted this procedure, where we performed complementary marrow imaging in all patients deemed infected on labeled WBCs scans. The overall result in our study for this combined technique was 86% Sn, 91.7% Sp and 89% accuracy.

Group (A) with suspected infected joint prosthesis

Differentiation of an infected from an uninfected prosthesis (such as loosening) is essential for optimal and cost-effective management of patients with arthroplasties. Accurate confirmation or exclusion of infection before revision surgery can substantially simplify plans in these circumstances. In addition, the outcome can be significantly influenced by an accurate initial diagnosis.[6,10]

Plain radiography has a limited role for the diagnosis of infection associated with prostheses because findings are common to both septic and aseptic failure, which is concordant to our results. Also, infection and loosening commonly show no finding. Therefore, aspiration biopsy of the joint is perhaps the most useful investigative tool for preoperative confirmation of infection,

with Sn and Sp ranging from 50% to 93% and from 82% to 97%, respectively.[21] However, the Sn of even preoperative joint aspiration is not high enough to exclude infection with an acceptable certainty. Moreover, the administration of antibiotics before aspiration biopsy can further reduce the Sn of this approach.[22] Furthermore, cross-sectional imaging modalities are hampered by artefacts produced by the prosthetic device themselves. On the contrary radionuclide imaging is not affected by the presence of metallic hardware and therefore useful for evaluating painful prosthesis.[6,10]

As for joint arthroplasty, radionuclide imaging has been extensively used for the diagnosis of infection after joint replacement. One of the earlier radiotracers used in assessment of osteomyelitis and joint prosthesis infection is ^{67}Gallium but with inherent limitation even after combination with MDP bone scan (70-80% 9 overall accuracy).[19,21]

In our study, we used the ^{99m}Tc HMPAO labeled WBCs method with "Sn, Sp and accuracy" were "95%, 93.1%, 93.9%" respectively for assessment of joint arthroplasty. These results are: (a) Similar to some reports such as Palestro, *et al*.,[16] in spite of using ^{111}Indium-labeled leukocyte/^{99m}Tc-sulfur colloid imaging in suspected peri-prosthetic infection; or (b) even better than other reports such as Sonmezoglu, *et al*.,[23] where they reported a Sn of 63% and accuracy of 77%, while their reported Sp was a bit higher than ours (96% vs. 93.1%).

In this group of patients with current prosthesis (49 sites), the reported two false positive scans of ^{99m}Tc-HMPAO labeled WBCs were ascribed to clinically evident active rheumatoid arthritis in one patient, similar to Magnuson, *et al*.,[24] report. The other false positive scan in our study was uninfected knee prosthesis subjected to multiple surgical interventions in that joint including debridement surgeries and total arthroplasty more than once.

With no current prosthesis

Due to the high number of false negative results (5 cases), labeled WBCs scans showed modest Sn (78.3%). This is probably attributed to the initial diagnosis of a negative labeled WBCs scan, and subsequently no complementary marrow imaging was ordered "assuming that the bone marrow configuration in these sites is normal." In these 5 reported false negative cases, there was history of previous intervention in the sites investigated; suggesting the presence of abnormal marrow configuration, and thus, the complementary marrow scans would have been so helpful in differentiating marrow uptake from foci of active infection. Similar results were also reported by Joseph, *et al*.[25]

In one of the 5 false negative cases on labeled WBCs scans, the final diagnosis by clinical follow-up and by regional MRI was mainly a soft tissue abscess related to the greater trochanter of the femur and implicating on it. In another one of the false negative cases, the final diagnosis was low grade infection by *S. aureus*. There were also two false positive results, one of them was finally diagnosed as healing phase of avascular necrosis of the femoral head, and the other one was fibrous dysplasia in the right ulna of a female patient. Sonmezoglu, *et al*.,[23] in his study comparing ^{99m}Tc-ciprofloxacin (infecton) scan with ^{99m}Tc-HMPAO leukocyte in assessment of bone infection, they also reported a false positive result in a patient with avascular necrosis of head of femur.

In our study, we also assessed 7 sites with suspected active infection in the feet (3 sites), and ankles (4 sites), in these sites the combined ^{99m}Tc-HMPAO labeled leukocyte/^{99m}Tc-labeled bone marrow imaging accurately differentiated infected (3 sites) from uninfected (5 sites) accurately. The number of sites investigated isquite low, however, the results obtained matches and even better than many studies reported on the role of labeled WBCs in assessment of pedal infection as those reported by Tehrenzada, *et al*.,[12] and Poirier, *et al*.[26]

CONCLUSION

The labeled WBCs study was the most accurate modality in detecting osteomyelitis in all groups investigated "the accuracy of labeled WBCs in patients with current prosthesis was 93.87%, in patients with no prosthesis was 83.3%, and total accuracy was 89%" and hence, it aided much in the final management of the patients and in avoiding unnecessary management steps. It can also limit the number of non-contributing (invasive) tests required and the time to diagnosis and thus, facilitates adequate antibiotic or local (surgical) therapy. This is the most appreciated in patients with joint prosthesis, where differentiation of an infected from an uninfected prosthesis (such as loosening) is essential for optimal and cost-effective management of these patients. Accurate confirmation or exclusion of infection before revision surgery can substantially simplify plans in these circumstances. In addition, the outcome can be significantly influenced by an accurate initial diagnosis. With plain radiographs and bone scan, they did not provide a combined Sn and Sp adequate for accomplishing these goals. Whereas, the ^{99m}Tc-HMPAO labeled white blood cell scanning, combined with ^{99m}Tc-colloid bone marrow imaging, provided superior Sn and Sp for detecting infection in this setting.

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