

Three phase bone scintigraphy with ^{99m}Tc -MDP and serological indices in detecting infection after internal fixation in malunion or nonunion traumatic fractures

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Abstract

Objective: To evaluate the diagnostic efficacy of technetium-99m-methylene diphosphonate (^{99m}Tc -MDP) three phase bone scintigraphy in detecting infection in malunion or nonunion traumatic fractures after internal fixation. **Subjects and Methods:** One hundred and eighty four patients with malunion or nonunion fractures after internal fixation (130 men and 54 women; age range, 16-79 years) underwent ^{99m}Tc -MDP three phase bone scintigraphy (3PBS). They were divided into the infection group (n=96) and the control group without infection (n=88) based on the final diagnosis after operation. The sensitivity, specificity, accuracy, positive prediction value (PPV) and negative prediction value (NPV) were calculated and compared. All patients carried out other laboratory tests related to infection such as complete serum blood cells count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). **Results:** The ^{99m}Tc -MDP 3PBS for the blood flow phase showed sensitivity, specificity, accuracy, positive predictive value and negative predictive value, 91.7% (88/96), 72.7% (64/88), 82.6% (152/184), 78.6% (88/112) and 88.9% (64/72), respectively and for the blood pool phase, 93.8% (90/96), 61.4% (54/88), 78.3% (144/184), 72.6% (90/124) and 90.0% (54/60) respectively. The semiquantitative indices of the ratio between the abnormal and the normal region of interest (ROI), called by us the A/N ratio, for both blood flow and blood pool phases as estimated between the infection group and the control group were statistically different. **Conclusion:** It is the opinion of the authors that ^{99m}Tc -MDP 3PBS provided high predictive values in diagnosing infection in patients with malunion or nonunion traumatic fractures after internal fixation. The diagnostic value of blood flow and blood pool phases of the 3PBS was better than the laboratory indices: white blood cell counts, CRP, and ESR.

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Introduction

Infections are the main cause of poor healing of traumatic fractures. Bone scintigraphy with technetium-99m-methylene diphosphonate (^{99m}Tc -MDP) has been used to detect bone infection [1, 2]. Negative bone scintigraphy results can exclude osteomyelitis [3]. In non-traumatic osteomyelitis, three phase bone scintigraphy (3PBS) was reported to have high sensitivity and specificity, typically showing in the blood flow, the blood pool and the delayed phases, increased tracer uptake. However, there are some difficulties in diagnosing traumatic fractures after surgery [4] due to changes in blood supply and bone metabolism. Surgical treatment of traumatic fractures, especially when internal fixation is applied [5] is usually assessed radiologically [6] and/or by computed tomography (CT) [7]. However, the quality of CT images is poor due to high photon absorption from the examined surgically treated area [8]. Bone scintigraphy with ^{99m}Tc -MDP can image infection in malunion or nonunion bones after traumatic fractures and internal fixation quite better than scintigraphy with gallium-67 citrate, labeled white blood cells or immunoglobulin antibodies [4, 9]. In our country, China, the use of white blood cells labeled with ^{99m}Tc or indium-111 and ^{99m}Tc human immunoglobulin, has not been approved for imaging inflammation by the Chinese FDA. Therefore, the aim of the present study was to investigate the value of the 3PBS using ^{99m}Tc -MDP in the diagnosis of infection in malunion or nonunion bones after traumatic fractures and internal fixation.

Subjects and Methods

Clinical data

Between April 2010 to May 2014 in Beijing Jishuitan hospital, we retrospectively studied 184 malunion or nonunion cases 130 males, 54 females, aged 16~79 years old, median age of 39 years, after internal fixation for treatment of traumatic fractures were included in the present study.

The inclusion criteria were: a) patients who received internal fixation surgery after traumatic fracture; b) patients who had the clinical manifestation of fracture malunion, nonunion or delayed union after internal fixation, had no further healing tendency within 3 months, had a clearly visible fracture line, or excessive anterior or posterior tilt combined with shortening of the long bone, or bone end hardening or signs of bone end atrophy by X-rays or fake joint shown in X-rays. All patients met the diagnostic standards of fracture malunion or nonunion [10-13].

The exclusion criteria were: a) patients who underwent joint replacement after traumatic fracture; b) patients who received debridement or antibiotic therapy before the diagnosis of bone infection; c) if the "bolus injection" failed and blood flow phase was unavailable.

The average time between the 3PBS and the fracture was about 14 months (between 3 months to 15 years). The fracture location is shown in Table 1. Qualitative analysis of 3PBS and other indices are shown in Table 2. Based on the follow-up results and clinical data, the 184 patients were divided into the infection group (including 96 patients) and the control group without infection (including 88 patients). The final clinical diagnosis of the 88 patients did not include infection. Forty nine of 88 patients had aseptic inflammation, while 39 of 88 patients were negative for inflammation. Patients were followed up for more than 6 months to eliminate potential infection in the control group. All patients had: peripheral blood cells count, erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) tests. This study

was approved by the Institutional Review Board of our Hospital, Capital Medical University.

^{99m}Tc-MDP three phase bone scintigraphy

Patients were injected intravenously with 740MBq (range, 718-763MBq) of ^{99m}Tc-MDP. The image acquisitions were performed on a dual head gamma camera equipped with a low-energy high resolution collimator (Infinia VC, GE, USA). An initial dynamic imaging of the blood flow phase (phase 1), 60 frames of 2s each, in 64×64 matrix, started after visualization of the tracer activity in suspected locations after radiotracer injection. Following the blood flow phase, static blood pool imaging was acquired for 5min in 256×256 matrix (phase 2) at 5min post injection. A delayed static image was taken at 3-4h after injection for 10min in 256×256 matrix (phase 3).

The interpretation of the ^{99m}Tc-MDP 3PBS and quantitative and semiquantitative analysis

Results were read by two experienced nuclear medicine physicians. All cases were visually assessed for any asymmetry of tracer uptake in the suspected location. Diffused or locally increased uptake in the affected sites shown in any of the 3PBS phases as compared with the same of the contralateral side was considered as a positive sign, while symmetrical uptake as a negative sign. A rectangular region of interest (ROI) was drawn around every positive region. With mirror shadow technology, same size and shape ROI were also drawn in the contralateral normal area.

A semiquantitative analysis was also obtained by calculating the counts of the increased uptake region (A) and those of the contralateral normal area (N) as shown in the 3PBS. The A/N ratio in blood flow and blood pool phases was calculated in both groups of patients. The background activity was not measured in the affected or the contralateral

Table 1. The fracture location of all 184 patients

Fracture location	Humerus	Ulna and radius	Pelvis	Femoral neck	Trochanter	Femoral shaft	Femoral condyles	Patella	Tibia and fibula	Ankle and foot
Cases number	12	4	8	22	6	72	8	2	44	6

Table 2. Qualitative analysis of three phase bone scintigraphy and other indices

Groups	Blood flow		Blood pool		ESR		CRP		White blood cells	
	+	-	+	-	+	-	+	-	+	-
Infection group (96)	88	8	90	6	46	50	66	16	36	14
Control group (88)	24	64	34	54	16	72	30	72	52	54

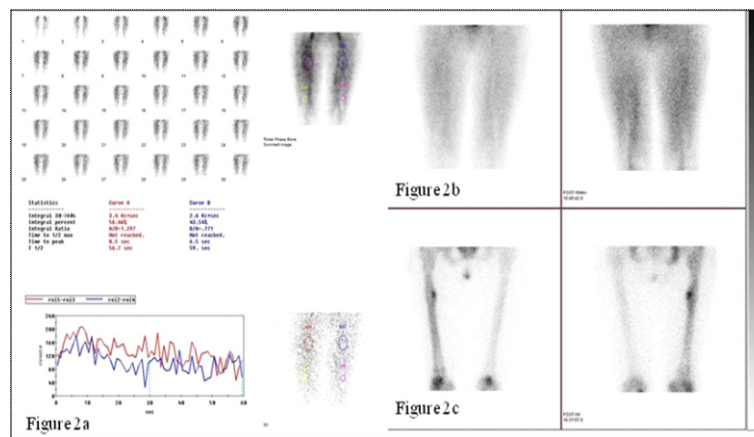


Figure 1. A 43 years old male patient was operated after left femoral trochanteric fracture 1 year before. The 3PBS showed increased tracer uptake in the fracture site in the blood flow (1a), the blood pool phase (1b) and the delayed phase (1c). Based on these images, the diagnosis of an active infection was made.

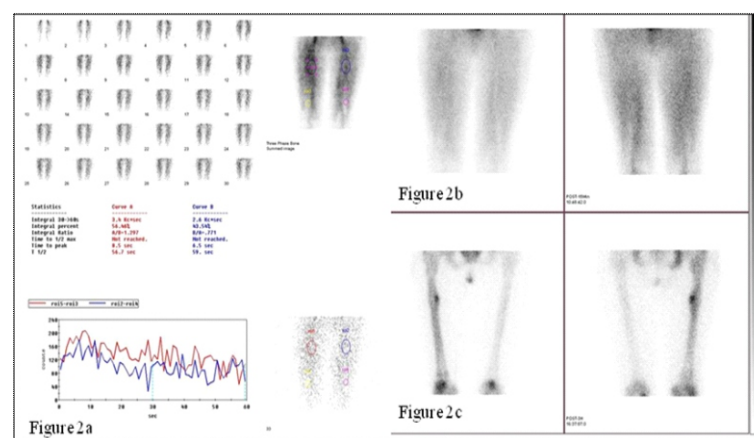


Figure 2. A fifty years old female patient with the diagnosis of nonunion of the right femur shaft. The ESR of the patient was 30mm, CRP was 13.9mg/L. The blood flow (2a) and the blood pool phase (2b) of 3PBS did not show increased ^{99m}Tc -MDP distribution in the right femur. Based on these findings, infection of the right femur shaft was excluded.

side, in order to avoid potential sources of error related to nonspecific inflammation arthritis. The two nuclear medicine physicians who evaluated the above findings were not aware of the patients' laboratory tests or their clinical diagnosis.

Based on visual analysis, the qualitative analysis index was acquired in both the infection and the control group.

Based on this delineation method, the A/N ratio of blood flow and blood pool was studied and compared in both groups. To the above ratios, the diagnostic value of ESR, CRP and white blood cell counts was compared.

Due to increased uptake of the tracer in the fractured malunion or nonunion areas, the semiquantitative index of the delayed phase of the 3PBS was not included in the present study.

Statistical analysis

All statistical tests were performed by using SPSS 20.0 software (SPSS, Inc., Chicago, IL, USA) and MedCalc Statistical software (Turkey). All semiquantitative data were presented as mean \pm standard deviation ($M \pm SD$). The sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of different indices were calculated. We used the receiver operating characteristic

(ROC) curve and the area under the ROC curve (AUC) as statistical criterion. Large AUC indicated high accuracy in differentiating diagnosis of infection in malunion or nonunion traumatic fractures. A two-tailed P value of 0.05 was considered as statistically significant.

Results

From the qualitative analysis and other indices

The qualitative results are shown in Table 2. Based on the data of the present study, the sensitivity, specificity, accuracy, PPV and NPV of blood flow phase were 91.7%, [88 cases (88/96) with true positive results and 8 cases (8/96) with false negative results], 72.7% [64 cases (64/88) with true negative results and 24 cases (24/88) with false positive results] and in total (96+88=184), 82.6% (152/184), 78.6% (88/112), and 88.9% (64/72), respectively. The sensitivity, specificity, accuracy, PPV and NPV of the blood pool phase were 93.8% (90/96), 61.4% (54/88), 78.3% (144/184), 72.6% (90/124), and 90.0% (54/60), respectively. Typical images are shown in Figures 1 and 2.

The semiquantitative analysis and other indices

The semiquantitative indices of A/N for blood flow and for A/N blood pool of the infection group and the control group were analyzed. Due to the abnormal distributions of the index of A/N blood flow and A/N blood pool, the median and quartile spacing were used to describe the concentration and dispersion of these data. Results are shown in Table 3. Data of the infection group and the control group were compared using the rank sum test, which showed that the P values were less than 0.01. These data suggested that the differences of A/N blood flow and A/N blood pool of the infection group and the control group were statistically significant.

Table 3. Results of semiquantitative analysis of the 3PBS

Group (n)	A/N blood flow		A/N blood pool	
	Median	Inter-quartile range	Median	Inter-quartile range
	M	Q	M	Q
Infection group (96)	2.72	1.91	2.63	1.07
Control group (88)	1.18	0.86	1.59	0.082
Z	-6.234		-5.382	
P	<0.001		<0.001	

Q: the interquartile range (IQR), in descriptive statistics, the IQR also called the midspread fifty, being equal to the difference between the upper and lower quartiles, $IQR = Q3 - Q1$. M: The median equals the midhinge, the average of the first and third quartiles.

Comparison of the 3PBS and other indices in the diagnosis of infection

The ESR, CRP and white blood cell count of all subjects were studied. The sensitivity of these tests for the diagnosis of infection in malunion or nonunion traumatic fractures with internal fixation was 47.9%, 68.8%, and 37.5% respectively. Their specificity was 81.8%, 81.8%, and 84.1% and accuracy was 64.1%, 75.0%, and 59.8%. The ROC curve was used to detect the difference of diagnostic values of these indices. For A/N blood flow we used the cut-off value of 2.26 and for A/N blood pool we used the cut-off value of 2.03 in order to differentiate the infection group from the control group. The area under the ROC of A/N blood flow, A/N blood pool, ESR, CRP and the serum blood cells count was 0.878, 0.826, 0.690, 0.772 and 0.667 respectively. The diagnostic efficiency of A/N blood flow and A/N blood pool was significantly higher

($P < 0.05$) when compared to the three laboratory tests.

Out of the 11 patients with internal fixation after femur neck fractures, 7 showed low radioactivity distribution and a typical "doughnut" sign in the delayed phase. Based on these findings, we made the diagnosis of femoral head necrosis and excluded the possibility of postoperative infection. After these findings physicians changed therapy strategy.

Accordingly, we noticed that the sensitivity of our findings for diagnosing infection was more than 90%, specificity 61.4%~72.7% (relatively low) and the NPV quite high.

In the control group, 54 of 88 patients showed true negative results in the blood pool phase. 34 of 88 patients showed false positive results in the blood pool phase. Out of these 34 cases, 4 had a second fracture 1 month before the 3PBS, 4 showed severe shifting in the fracture site and 4 demonstrated ectopic ossification on CT images. Based on the final clinical diagnosis of other 22 cases, no infections were reported. While, aseptic inflammation was reported in all the 22 cases.

Discussion

Internal fixation of fractures induces local irritation and damage. Infection increases local blood perfusion. In patients with nonunion fractures, it is important to diagnose infection in order to decide for further treatment. Patients with infection would perform debridement, antibiotic chain bead implantation and after control of local infection could have a second operation. Patients without infection on the other hand could have a second operation or bone grafting.

In clinically highly suspected infection cases, several diagnostic imaging methods have been used, including computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography and fluorine-18-fluorodeoxy-glucose positron emission tomography (^{18}F -FDG PET) [14]. However, the value of magnetic resonance imaging and CT is limited [14, 15] due to the artifact of internal fixation implantation. There are some simple screening methods, such as serum blood cells routine examination, CRP, and ESR. However, elevated white blood cell count, ESR, and CRP cannot differentiate accurately infectious from non-infectious inflammation. Moreover, the white blood cell count of some patients may not be elevated [15]. Isolation of pathogenic microorganisms from bone tissue is considered the gold standard [16], but this method is invasive, time-consuming and could spread infection through the overlying soft tissues to the bone.

The value of $^{99\text{m}}\text{Tc}$ -MDP 3PBS for the diagnosis of infected nonunion fracture

Bone scintigraphy is very sensitive to alterations in bone tissue turnover. Other papers have shown increased blood flow and blood pool in cases of osteomyelitis [17]. The 3PBS is highly sensitive in the diagnosis of bone diseases, can perform a whole body bone examination, has no absolute contraindications, gives relatively low absorbed radiation dose and is economical. The main advantage of the 3PBS is

its high negative predictive value. Traumatized bone, post-surgery bone or diabetic foot infection, may hamper the scintigraphic diagnosis of infection and have a relatively low specificity for the 3PBS in the diagnosis of infection [18]. In order to decrease the false positive rate of 3PBS, the average time between the 3PBS and the fracture was about 14 months (more than 3 months). The A/N ratio in blood flow and the pool phase both had statistical differences between the infection group and the control group. However, the A/N ratio in the delayed phase did not differ statistically between the infection group and the control group. At the present study, there were 24 cases with false positive results in the blood flow phase and 34 cases with false positive results in the blood pool phase. The specificity of the present study was similar with a previous study [15]. The false positive results in the blood flow and the blood pool phases are due to a second fracture before the 3PBS, severe shifting of the fracture site and ectopic ossification. Combining the laboratory findings and the 3PBS findings especially evaluated semiquantitatively, may increase the accuracy for diagnosing infected nonunion fracture. However, the causes of false positives should be noticed. Using ^{99m}Tc -MDP and single photon emission tomography (SPET/CT) or other modalities may decrease false positive results.

Limitations of the present study

We recognize several limitations of this study. First, it was a retrospective study with a small number of patients. Second, we used SPET, not SPET/CT, which provides less specific information of malunion or nonunion and allows for less accurate localization of the tracer [18-24]. Third, the diagnosis of malunion or nonunion traumatic fractures was based on clinical signs and X-rays examination. Multicenter prospective studies with a larger number of patients and a cost effective study are warranted to confirm the results of this study.

In conclusion, it is the opinion of the authors of the present study that ^{99m}Tc -MDP 3PBS was a rather accurate diagnostic modality for bone infection and provided a highly negative predictive value in malunion or nonunion traumatic fractures after fixation using blood flow and blood pool findings.

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