Technetium-99m-Nanocolloid Scintigraphy in Orthopedic Infections: A Comparison with Indium-111-Labeled Leukocytes

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Twenty-three patients with clinically suspected acute or chronic osteomyelitis and 21 patients with suspected joint prosthetic infection underwent scintigraphy using both ^{99m}Tc-nanocolloid and ^{111}In-labeled leukocytes. The scintigrams of the two tracers were blindly interpreted by three independent observers. Their evaluations showed high correspondence. Patients were classified as having no infection, probable infection or proven infection according to specific criteria which included results of bacteriological cultures and histopathological examinations. For proven and probable infection taken together, the sensitivity with ^{99m}Tc-nanocolloid was 94%, the specificity 84% and the accuracy 87%, compared with 75%, 90% and 85% with ^{111}In-labeled leukocytes. We conclude that ^{99m}Tc-nanocolloid scintigraphy is at least equivalent with ^{111}In-leucocyte scintigraphy, and its additional advantages are shorter examination time, less complexity and better radiation dosimetry.

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The diagnosis of muskuloskeletal infections may be difficult and great effort has been made to establish reliable diagnostic methods. An important diagnostic tool is bone scintigraphy, and the use of ^{111}In-labeled leukocytes has been shown to be a comparatively sensitive and specific technique (*1–3*).

Promising results have been published regarding a technique with bone marrow scintigraphy using a nanometer-sized, albumin-based colloid-labeled with ^{99m}Tc-Nanocoll® (*4–7*). This specific radiopharmaceutical was shown to be the most suitable for bone marrow scintigraphy in a recent study comparing four commercial ^{99m}Tc-labeled colloids (*8*).

In certain respects, ^{99m}Tc-nanocolloid scintigraphy (^{99m}Tc-NCS) offers important advantages over ^{111}In-leukocyte scintigraphy (^{111}In-LS). It requires considerably shorter investigation time and is easier to handle because it involves neither time-consuming preparation of leukocytes, or special facilities or technical expertise. Furthermore, ^{99m}Tc-NCS exposes the patient to a lower radiation dose, mainly due to use of ^{99m}Tc which has a more favorable radiation dosimetry than ^{111}In. Finally, ^{99m}Tc-NCS, also eliminates potential risks involved in handling blood.

The study's purpose was to obtain more information about the accuracy of ^{99m}Tc-NCS compared to ^{111}In-LS in skeletal infections.

PATIENTS, MATERIALS AND METHODS

Forty-four patients (21 males and 23 females) ranging in age from 16 to 82 yr (mean: 58 yr) underwent scintigraphic examination with both ^{111}In-LS and ^{99m}Tc-NCS for clinical suspicion of skeletal infection. A total of 45 examinations were performed which included a repeat examination of one patient after a 3-mo interval. Infected joint prostheses was suspected in 21 patients (Fig. 1) and acute or chronic osteomyelitis in 23 patients (Fig. 1; Table 1).

The radiopharmaceutical isotopes ^{111}In-oxine (Mallinckrodt CIL) and ^{99m}Tc-Nanocoll® (Solco Basle Ltd) were used according to manufacturer instructions.

The ^{99m}Tc-labeled nanocolloid was administered intravenously (250 MBq) and a scintigram was performed approximately 1 hr later. On average, after two days, 50 ml of venous blood was withdrawn in a syringe and mixed with 10 ml of Acid-Citrate-Dextrose (ACD) solution. Two milliliters of methylcellulose were added. One hour later the leukocyte-rich plasma was separated and the erythrocyte suspension discarded. The plasma was centrifugated at 1,600 rpm for 5 min and all the plasma subsequently removed. Two milliliters of phosphate buffer were added and the solution mixed until all leukocytes were suspended. These procedures were repeated once. Then 0.4 ml tris-buffer was mixed with the ^{111}In-solution (15–20 MBq ^{111}In-oxine), which subsequently was mixed with the leukocyte suspension. The mixture was incubated at room temperature for 15 min. A visual control was performed to exclude abnormal aggregation. The labeling efficiency—defined as activity in the leukocytes × 100/activity in leukocytes + activity in solution—was determined. The time from withdrawal of blood to reinjection did not exceed 3.5 hr. Imaging was performed the next day.

In 19 cases the camera used was Toshiba GCA-901A/W2 with LEHR (RDC-901A) collimator or LEGP (RDC-900A) collimator for the technetium colloid and MEGP (RDC-930A) collimator for the indium. The computer for this camera is GMS-5500 using the operative system GMS. In 26 patients, the camera Technicare Sigma 438 was used with a high-resolution or GAP (general all purpose) collimator, both optimized for 140 keV energy for the

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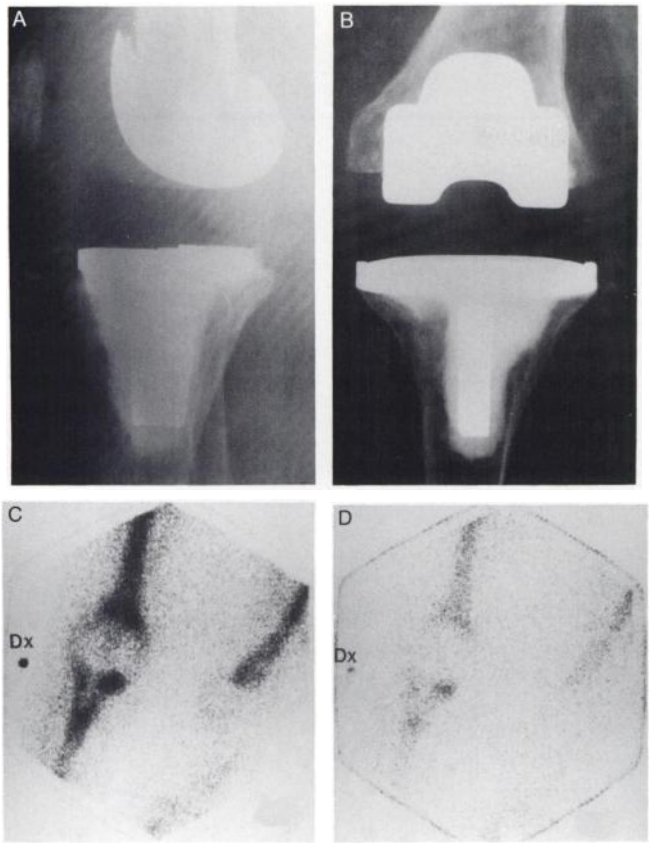

FIGURE 1. Case 16. Sixty-eight-year-old female with history of rheumatoid arthritis and a knee prosthesis for 1 yr. The patient experienced pain on weightbearing and at rest. (A) Radiographs show no signs of loosening. (B) Technetium-99-NCS shows increased uptake (++) corresponding to the distal femur and proximal medial tibia. (C) The uptake with ^{111}In-LS was classified as slightly increased (+). Bacterial cultures at operation were positive for *staphylococcus epidermidis*.

technetium nanocolloid studies and high-energy collimator (400 keV) for the indium studies with a Spectrum 550/560 computer. Both the technetium and the indium studies were obtained for time (5 min and 10 min respectively). For the indium studies, 20% windows were symmetrically centered on the 171 and 245 keV peaks; for the technetium studies, a 20% window was symmetrically centered on the 140 keV peak.

Images were blindly interpreted by three independent observers marking their visual findings on a five-grade scale (−, 0, +, ++, +++).

Patients were evaluated by clinical examination, radiography, ESR, WBC, bacteriological cultures and histopathological examination of infected tissue.

The diagnosis of *proven infection* was established according to one or more of the following criteria: fistulation; repeated positive cultures with the same bacteria at aspiration; positive blood culture with the same bacteria as in the infection focus; and more than two of five positive tissue-biopsy cultures.

The diagnosis of *probable infection* was made on the basis of one or more of these criteria: positive tissue biopsy; one positive culture at aspiration; microscopy showing infection; and radiography showing osteomyelitis.

Sensitivity, specificity and diagnostic accuracy were calculated as: sensitivity: true-positive images/patients with infection; specificity: true-negative images/patients without infection; and accuracy: true-positive plus true-negative images/all patients.

RESULTS

The presence of infection was identified in 12 patients—five patients with osteomyelitis and seven with prostheses infections, two in hip prostheses and five in knee prostheses (Figs. 1, 2). Probable infection was identified in four patients—two patients with osteomyelitis and one each with infections of hip and knee prostheses. All patients met at least two of the criteria established for infection. Of the total number of patients in the study, 26 were classified with no infection. Infection could not be established in two patients.

In the cases of both proven and probable infections, the findings of the three observers yielded the mean values illustrated in Table 2. The corresponding values for proven infection alone are illustrated in Table 3.

The markings − and 0 were classified as negative values; +, ++ and +++ as positive. Calculating sensitivity and specificity using only ++ and +++ as positive, gave a sensitivity of 46% and a specificity of 100% for ^{111}In-LS, compared with 65% and 99% respectively for ^{99m}Tc-NCS.

Table 4 illustrates the mean values for osteomyelitis and infection of prostheses.

Observers' correspondence was estimated according to the Kendall Coefficient of Concordance, which varies between 0 and 1 where 1 signifies complete correspondence and 0 signifies no correspondence. For ^{111}In-LS, this quotient was 0.92 ($p < 0.001$) and for ^{99m}Tc-NCS it was 0.94 ($p < 0.001$).

All false-negative results occurred in patients with chronic osteomyelitis. With ^{111}In-LS, the three observers found five, four and three false-negative cases, respectively. Only one of these was deemed false-negative with

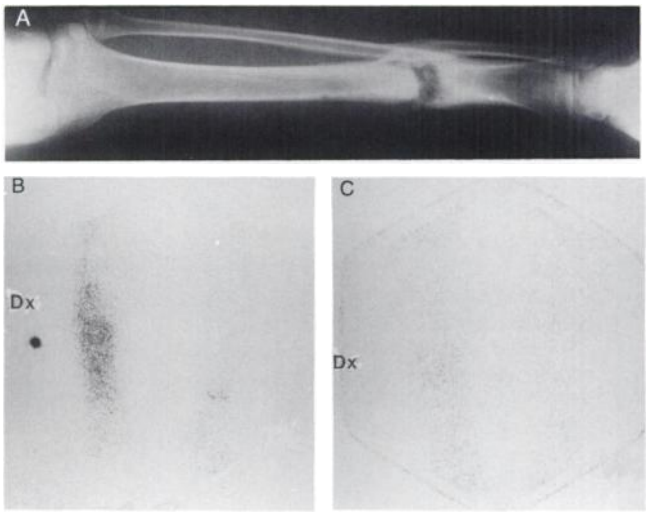

FIGURE 2. Case 37. (A) Sixteen-year-old male with post-traumatic chronic osteomyelitis 8 mo after fracture of his right lower leg. (B) Technetium-99-NCS showed increased uptake (++). (C) Indium-111-LS showed only slightly increased uptake (+). Bacteriological culturing were positive for *straphylococcus epidermidis*.

TABLE 1
Materials and Results

A	B	C	D	E	F	G	H	I	J	K	L	M
1	82	M	1	70	8	3	++	+	++	+	+	+
2	80	F	1	55		3	+++	++	+++	++	+	++
3	80	F	2	68	11	1	0	0	0	0	0	0
4	78	M	1	12		1	+	0	0	+	0	+
5	78	F	2	64	9	3	++	+	++	++	++	++
6	77	F	2			3	+++	++	+++	+++	++	++
7	77	F	1			1	0	0	0	0	0	0
8	76	F	1	150	12	2	++	+	+	++	+	+
9	74	M	2			3	+	+	+	++	++	++
10	74	F	2	32	8	1	0	0	0	+	+	+
11	73	M	4			3	−	−	−	−	−	−
12	73	F	2	70	9	2	+++	++	++	+++	++	++
13	72	F	1	60		1	0	0	0	0	0	0
14	71	F	3	40	6	1	−	−	−	−	−	−
15	70	M	1	6		1	0	0	0	0	0	0
16a	70	M	1	70	20	1	+	+	+	0	+	0
16b	70	M	1	85		1	0	+	0	0	+	0
17	70	F	5	30		1	0	0	0	0	0	0
18	68	F	2	68	6	3	++	+	+	+++	++	++
19	68	F	6	36	5	1	0	0	0	+	+	+
20	66	F	7	60	8	1	0	0	0	0	0	0
21	65	M	5	90	8	1	0	0	0	0	0	0
22	63	F	8			4	++	++	+	+	+	+
23	63	F	1	13		1	0	0	0	0	0	0
24	60	F	1	45		1	0	0	0	0	0	0
25	60	F	4	56		1	0	0	0	0	0	0
26	56	M	1			1	0	0	0	0	0	0
27	55	M	3		5	1	0	0	0	0	0	0
28	54	M	4	26	9	1	0	0	0	0	0	0
29	53	F	2			3	++	+++	++	++	++	++
30	52	F	5		12	1	0	0	0	0	0	0
31	51	M	1	22		1	0	0	0	0	0	0
32	50	F	8			4	+	+	0	+++	++	++
33	50	M	1	80	7	1	0	0	0	0	0	0
34	49	M	3		4	1	0	0	0	0	0	0
35	43	M	6		6	1	+	+	+	+	+	++
36	43	M	4	12	12	2	0	0	0	++	+	++
37	42	F	4	38	8	3	++	++	++	++	+	+
38	40	F	4			3	+	0	0	++	+	+
39	29	M	4	2		1	0	0	0	0	0	0
40	26	M	5	10	10	1	0	0	0	0	0	0
41	26	M	4	65	12	2	+	+	++	++	++	++
42	24	M	4	10		3	0	0	0	+	++	+
43	22	M	3	20		1	−	−	−	−	−	−
44	16	M	4	5	5	3	+	+	0	++	++	+

A: Patient number.
B: Age
C: Sex
D: Suspected diagnosis:
1 = hip prosthetic infection.
2 = knee prosthetic infection.
3 = acute osteomyelitis.
4 = chronic osteomyelitis.
5 = pelvic bone infection.
6 = foot infection.
7 = spondylitis.
8 = septic arthritis.
E: ESR.
F: WBC.

G: Infection
1. no infection.
2. probable infection.
3. proven infection.
4. no diagnosis established.
H, I, J: ^{111}In-LS findings by observers 1, 2, 3.
K, L, M: ^{99m}Tc-NCS findings by observers 1, 2, 3:
− Decreased activity.
0 No increase in activity.
+ Slightly increased activity.
++ Obviously increased activity.
+++ Highly increased activity.

TABLE 2
Sensitivity, Specificity and Accuracy for Proven and Probable Infection Taken Together

Radionuclide	Sensitivity	Specificity	Accuracy
^{111}In-LS	75%	90%	85%
^{99m}Tc-NCS	94%	84%	87%

^{99m}Tc-NCS. This occurred in a patient who had had chronic osteomyelitis for 60 yr and showed decreased activity on the scintigraphs (cold area). Decreased activity was also found in two true-negative cases, one with post-traumatic femoral head necrosis and the other with osteolytic tibial fracture.

There was a slightly higher frequency of false-positive results with ^{99m}Tc-NCS than with ^{111}In-LS. All observers found one false-positive case with both methods in a patient with a suspected post-traumatic foot infection. False-positive results also occurred in two patients who had loosening of hip prostheses, one who had a soft-tissue infection of the foot and a third who had pain from a knee prosthesis inserted one year earlier. The latter two cases were found false-positive with ^{99m}Tc-NCS only.

DISCUSSION

A number of studies have evaluated the efficacy of ^{111}In-LS in detecting muskuloskeletal infections and have shown ^{111}In-LS to have a higher specificity and as good a sensitivity as ^{99m}Tc-MDP and ^{67}Ga scintigraphy used separately or sequentially. Sensitivity has ranged from 81% to 97% and specificity from 73% to 93% with diagnostic accuracies in the range of 83% to 92.5% (*1–3,9–11*).

A few studies have evaluated the more recent method with ^{99m}Tc-NCS (*5–7,12,13*), and results indicate values similar to those of ^{111}In-LS with sensitivity varying from 87% to 95% and specificity between 77% and 100%. Streule et al. (*5*) conducted a study similar to ours with crossover comparison between ^{111}In-LS and ^{99m}Tc-NCS that showed a specificity of 93% for both methods and sensitivity values of 81% for ^{111}In-LS and 87% for ^{99m}Tc-NCS. They conclude that the methods are equivalent.

Our study demonstrates a sensitivity of 75% with ^{111}In-LS and 94% with ^{99m}Tc-NCS and a specificity of 90% with ^{111}In-LS and 84% with ^{99m}Tc-NCS. Diagnostic accuracy was 85% and 87%, respectively. Sensitivity and specificity were also calculated and markings of "slightly increased activity, (+)", were regarded as a negative result of imaging. As could be expected, this resulted in an almost 100% specificity and a considerably lower sensitivity for both methods. A subclassification according to degree of positivity appears to add no further information.

TABLE 3
Sensitivity, Specificity and Accuracy for Proven Infection Alone

Radionuclide	Sensitivity	Specificity	Accuracy
^{111}In-LS	75%	82%	80%
^{99m}Tc-NCS	93%	73%	78%

TABLE 4
Sensitivity, Specificity and Accuracy for the Two Main Groups of Patients

Radionuclide	Sensitivity	Specificity	Accuracy
Osteomyelitis			
^{111}In-LS	43%	93%	76%
^{99m}Tc-NCS	86%	86%	86%
Prosthetic infection			
^{111}In-LS	100%	87%	92%
^{99m}Tc-NCS	100%	82%	89%

The difference between ^{111}In-LS and ^{99m}Tc-NCS in the cases of chronic osteomyelitis in which ^{99m}Tc-NCS correctly identified infection while ^{111}In-LS showed false-negative results, may be explained by the different distribution mechanism of the two tracers. The ^{111}In-labeled leukocytes are mainly attracted to places of acute inflammation because granulocytes are similarly labeled and are hardly involved in chronic osteomyelitis. On the other hand, nanometer-sized colloids continue to find their way into the extravascular space independent of the duration and etiology of the inflammatory process (*4,5*).

Gallium-67-citrate has been shown to be a useful agent in diagnosing chronic bone infections. In this respect, ^{67}Ga is probably superior to ^{111}In-LS, but the energy maximum of ^{67}Ga is less appropriate for the gamma-camera than ^{99m}Tc. That is, the resolution is poor, the radiation dose to the patient is high and the interval between administration and scintigraphy is long. Moreover, ^{67}Ga is expensive and it is not always available.

Our results appear to agree with earlier studies. A comparison between the two methods demonstrates that ^{99m}Tc-NCS is equivalent to ^{111}In-LS in regard to sensitivity, specificity and accuracy. When these facts are added to recognized advantages of ^{99m}Tc-NCS over ^{111}In-LS such as time, complexity and radiation dosimetry, it appears justified to recommend more extended use of ^{99m}Tc-NCS in diagnosing skeletal infections.

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