Decreased Sensitivity of Early Imaging with In-111 Oxine-Labeled Leukocytes in Detection of Occult Infection: Concise Communication


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Imaging with leukocytes labeled with indium-111 oxine is a sensitive technique for detecting sites of occult infection. Traditionally, imaging is performed 24 hr after injection. We undertook a prospective study of 35 patients (40 studies) with possible occult infection to see whether a 24-hr delay in imaging is really necessary. Patients were imaged at 1–4 hr and again at 24 hr after injection. The early images had a sensitivity of only 33%, compared with 95% for the 24-hr images. Of the seven studies that were positive on both early and delayed images, 71% had more intense uptake at 24 hr. There were no false-positive early images. We conclude that imaging 1–4 hr after injection with indium-111 oxine-labeled leukocytes has a low sensitivity for detecting occult infection. However, a positive early image is specific for a site of infection.


Imaging with leukocytes labeled with In-111 oxine has been shown to be a sensitive technique for detecting sites of occult infection (/–7). In these studies, imaging was performed 24 hr after injection. Recently there have been two reports indicating that abdominal abscesses and other inflammatory sites could be detected as early as half an hour after injection. One of these studies used In-111 oxine-labeled donor cells, while the other used In-111 tropolonate-labeled cells (4,5). If labeled leukocytes could make a more rapid diagnosis of occult infection, this would overcome one of its main disadvantages in comparison to TCT and ultrasound. We therefore undertook a prospective study to determine whether the usual 24-hr delay in imaging In-111 oxine-labeled leukocytes is really necessary for diagnosing abdominal abscesses and other types of occult infection.

MATERIALS AND METHODS

Patient selection. Thirty-five consecutive patients (24 M, 11 F; age range 20–77, mean 52) suspected of having sites of occult infection were prospectively studied after obtaining informed consent. During their hospitalization, some patients underwent several examinations, making a total of 40 examinations performed.

Labeling technique. The patient’s white cells were labeled with indium-111 oxine using a modification of the method first described by Thakur et al. (6,7). Specifically, the labeling was performed as follows:

1. Thirty to 50 cc of venous blood was obtained in a syringe containing 1–2 ml of heparin. The cells were allowed to sediment for 60 min in the inverted syringe.

2. The leukocyte-rich supernatant was then removed from the syringe using a butterfly catheter, and placed in a centrifuge tube.

3. To obtain a white-cell button, the supernate was centrifuged at 300–350 g for 5 min.

4. Leukocyte-poor plasma supernate was removed and stored in an identical sterile centrifuge tube.

5. The white-cell button was resuspended in 5 cc of sterile saline.

6. One millicurie of In-111 oxine was added to the concentrated cell suspension and incubated for 30–40 min. During the incubation, the suspension was gently agitated every 10 min.

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5. Five to eight cc of leukocyte-poor plasma were added to the suspension of leukocytes, and the mixture was again centrifuged for 5 min at 450 g. This removed any unbound indium.

6. The supernatant was removed and saved for evaluation of labeling efficiency. Five to eight milliliters of the previously obtained leukocyte-poor plasma were gently added to the labeled white-cell button and agitated to resuspend the labeled cells. These cells were assayed in a dose calibrator.

7. The In-111-labeled leukocytes were then drawn into a syringe and reinjected into the patient. The activity in the final product was limited to a maximum of 500 μCi (range 397–500). The maximum time from blood drawing to reinjection was approximately 2 hr.

Imaging technique. The patients were imaged 1–4 hr after injection, with a repeat study performed at 24 hr. Images were obtained on a large-field scintillation camera with medium-energy collimator, using 20% windows set on the 173- and 247-keV photopeaks of In-111. An initial image was performed over the liver for an information density of 500 ct/cm². The time needed to obtain that image was recorded and the remainder of the images were performed for that length of time.

The patient’s chest, abdomen, and pelvis were routinely imaged. The extremities or the patient’s head were imaged if clinically indicated.

Review of images and confirmation of diagnosis. All images were read by two experienced observers who were unaware of the clinical history and the results of other imaging studies. The images were interpreted as showing or excluding a site of infection, and whether showing increased diffuse lung activity or no abnormal activity. There were no disagreements between the observers. The clinicians were informed of the results of the early images, but in all cases they elected to wait until a definitive answer was given at 24 hr. The final clinical diagnosis was confirmed by a combination of the clinical course and supplemental radiographs, TCT, ultrasound, surgery, needle biopsy, or necropsy.

Statistical analysis was performed using the Fisher exact test.

RESULTS

Fifty-three percent (21/40) of either early or late patient studies were positive for infection. The early images had a sensitivity of only 33% (7/21) compared with 95% (20/21) for 24-hr imaging. The falsely negative early images included: four abdominal abscesses, three infected grafts, two pneumonias, one abdominal wall abscess, one dental abscess, one case of pyelonephritis, and one case of osteomyelitis. The one false-negative delayed study (also falsely negative on the early images) was from a patient with multiple small pneumocystic abscesses in the kidney, liver, spleen, and psoas muscles. There were no false-positive scintigrams with either early or delayed imaging. The diagnoses were confirmed by surgery, biopsy, or autopsy in 25 cases, and by clinical course, laboratory data, and supplemental radiographs in 15.

Of the seven studies positive on both early and delayed imaging, 71% (5/7) had more intense uptake at 24 hr. In no case was the early image more intense than the delayed. None of the studies that were positive early became negative on late imaging.

Twenty-seven of 40 studies imaged early showed diffuse lung uptake. This pattern was seen on only one 24-hr image. Eighty-six percent (12/14) of the falsely negative early studies showed diffuse lung uptake, whereas 42% (3/7) of the true positives had this pattern. The difference between these two groups was not statistically significant (p > 0.05).

Representative cases are illustrated in Figs. 1–4.
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24 Hours . 1/S Scan

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FIG. 2. Posterior 4- and 24-hr leukocyte images of 61-yr-old male, operated on to repair perforated duodenal ulcer, who developed fever postoperatively. Four-hour image is normal. Twenty-four hour study shows focus of uptake that proved to be abscess at surgery.

tensively to diagnose intraabdominal abscesses. The sensitivity of In-111 leukocytes is very high, comparing favorably with that of TCT and ultrasound (2). An advantage of indium-labeled leukocyte imaging over radiographic procedures is that the entire body can be imaged without any increase in radiation exposure. This is especially useful in patients with fever of unknown origin who have no localizing signs to direct a radiographic search.

Traditionally, In-111 leukocyte scintigraphs have been performed 24 hr after injection (3). There are few animal data to support this delay (8). Krieves and McDougall have recommended caution in using negative early images to exclude an abscess. They described a case in which early imaging failed to detect an abscess that was obvious on the delayed images (9).

Other investigators have obtained good results with early imaging. Dutcher et al. reported great success with In-111 oxine-labeled leukocytes in granulocytopenic patients (4). When 14 patients with known sites of infection, were given ABO matched donor cells, 13 showed increased activity after approximately 30 min. Subsequent images at both 4 and 24 hr were positive at the same site, with the later scintigrams showing more intense uptake. These authors used computer enhancement to improve the quality of their images.

A recent study using In-111 tropolonate for labeling leukocytes was also successful using early imaging (5). Of 36 positive studies, 27 were detected 40 min after injection, and an additional nine were imaged successfully at 3 hr. Of their other 15 studies, 11 were studied for the first time at 3 hr, at which time they were all

FIG. 3. 60-yr-old male who had infected aortofemoral grafts removed and became febrile. TCT scan was normal. Four-hour leukocyte image does not show any uptake in right pelvis; 24-hr image demonstrates uptake that was confirmed to be small abscess at surgery.

FIG. 4. 60-yr-old male with fever, chills, and right upper quadrant pain. Top: Anterior leukocyte scintigram over liver and spleen; 4-hr study is normal. Image at 24 hr shows uptake in left lobe of liver, just lateral to spinal activity. Center: Anterior liver-spleen study demonstrates defects in left lobe, corresponding to increased uptake of leukocytes. Bottom: Small abscess in left lobe is shown on TCT, confirmed surgically.
positive. These authors felt their success was related to enhanced viability of leukocytes with tropolonate labeling. They noted that removal of cells from plasma, as is required when oxine is used as the chelating agent, may significantly decrease the viability of leukocytes. The early lung uptake seen with indium oxine may be due to damage sustained by the cells in the labeling process (10). In fact, when leukocytes are heat-damaged, more lung uptake is seen (11).

Our results differed from the two studies just quoted. We would have expected results at least equal to those of Dutcher (4), since our cells were autologously labeled. Activity that Dutcher imaged at 30 min may represent blood pool, as has been suggested by Doherty and Goodwin (12). Differences in the design of the study should also be considered. Dutcher knew in advance that each patient had a clinical infection and where it was located. Our study, on the other hand, reflected the usual clinical situation, in which the reader has little or no advance information. Finally, it is possible that the computer manipulation of the images improved their sensitivity. We did not formally study this.

The differences between our oxine studies and Peters' tropolonate studies (5) also are not clear. It is possible that tropolonate does improve the viability of labeled cells. However, other authors have actually found decreased viability with tropolonate at concentrations required for optimal labeling (13). In our study we did not find a statistically significant correlation between early diffuse lung uptake (which may be a sign of decreased leukocyte viability) and the decrease in sensitivity of leukocytes for diagnosing infections at an early time. Moreover, this would not account for our differences with Dutcher et al., who used oxine for cell labeling. Another factor to consider is the differences in the patient population. We studied patients with suspected occult infections; Peters imaged patients with a variety of causes of inflammation in addition to infection. In fact, half of his patients had inflammatory bowel disease. His sensitivity for abdominal abscesses was actually the lowest of all the disease types he looked at. Out of 37 cases of suspected infection, there were two false negatives, giving a sensitivity of 90% compared with 96% for all causes of inflammation.

Further studies are needed to determine whether tropolonate is a superior agent, and whether the labeling technique accounts for the differences between our findings and those of Peters.

REFERENCES

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