WHITE CELL SCANS AND INFECTED JOINT REPLACEMENTS

FAILURE TO DETECT CHRONIC INFECTION

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We report the results of imaging with labelled white cells in 52 patients before the revision of 54 cemented joint prostheses at which the diagnosis of infection was made from biopsies. Twenty-five hips were imaged with ^{111}In-oxine-labelled cells; 20 hips and 11 knees were imaged with ^{99m}Tc-hexamethylpropylene-amineoxime-labelled cells. Of these, 13 hips and five knees proved to be infected.

The scans taken together had an accuracy of 82%, a sensitivity of 44% and a specificity of 100%. Indium scans gave 37% sensitivity, ^{99m}Tc labelling 50% sensitivity. Infected arthroplasties with positive scans had presented significantly earlier than those with negative scans, the time after the original insertion being 1.1 years for the true-positive scans and 6.1 years for the false-negative scans.

The value of labelled white-cell scans in the detection of infection in failed joint replacements is dependent on the activity of the infection. There is reduced sensitivity to the more insidious infections which affect arthroplasties and aspiration under controlled conditions remains an important investigation.

J Bone Joint Surg [Br] 1993; 75-B:371–4.
Received 13 August 1992; Accepted 16 December 1992

It is important to diagnose infected joint prostheses accurately since this influences the results of revision surgery. Low-grade infection may present as loosening and be missed if not actively sought (Hunter et al 1979; Whyte et al 1981). O'Neill and Harris (1984) recommended that all revision cases be aspirated to identify occult sepsis and the infecting organism, but this may fail in at least 13% of cases (Roberts, Walters and McMinn 1992). A reliable non-invasive investigation would help to identify those infected cases that require reaspiration.

The ESR and C-reactive protein levels are unreliable tests for infection, particularly in the presence of intercurrent disease (Carlsson 1978; Shih, Wu and Yang 1987; Sanzén and Carlsson 1989), and plain radiography cannot distinguish between early mechanical loosening and low-grade sepsis (Weissman 1983; O'Neill and Harris 1984).

Isotope bone scanning is sensitive for loosening, but scans may remain abnormal for over a year after a joint replacement (Utz, Lull and Galvin 1986; Hofmann et al 1990). Any distinction between septic and aseptic loosening depends on the demonstration of diffuse uptake with congruency between the initial and bone phases of three-phase imaging; not all infected prostheses show diagnostic features (Rushton et al 1982; Taylor et al 1989).

The use of labelled white-cell scans is established as a means of localising occult acute infections (Liewendahl 1987). Indium-labelled white-cell imaging has been used for failed joint replacements and it has been suggested (Pring et al 1986) that it can identify patients requiring aspiration to determine the bacteriology.

Recently, ^{99m}Tc-hexamethylpropylene-amineoxime (Tc-HMPAO) has become available as a white-cell label. It offers the potential for lower radiation exposure than ^{111}In-oxine with improved image resolution and single-day imaging (Peters et al 1986).

We present our experience of using both In-oxine- and Tc-HMPAO-labelled white-cell scans in the detection of infection in failed joint prostheses.

PATIENTS AND METHODS

Fifty-two patients undergoing 54 consecutive revision procedures had imaging with labelled white cells at least three weeks after stopping any antibiotic therapy. All 11 knee prostheses were imaged using Tc-HMPAO labelling. Either In-oxine or Tc-HMPAO labelling was used

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0301-620X/93/3591 $2.00

for the hips depending on isotope availability and administrative considerations.

Mixed autologous white cells were prepared from 50 ml of blood. In-oxine labelling was by a modification of the method of Thakur et al (1977), and 5 MBq were reinjected before imaging at 16 hours. Tc-HMPAO labelling was by the method of Solanki et al (1988), and 150 to 200 MBq were reinjected before imaging at four hours.

All joints were aspirated either one week before imaging or a few days after imaging. The methods of obtaining and processing the aspirate have previously been described (Roberts et al 1992). The ESR was measured at the time of imaging; 41 patients also had their C-reactive protein level measured.

At revision surgery, specimens of joint fluid and biopsies of the capsule and pseudomembrane were taken and processed as previously described. Prophylactic parenteral antibiotics were not given until the biopsy specimens had been taken.

The infective status of the joint was defined by the results of the culture of biopsies taken at revision operation. If none of the specimens was positive the joint was recorded as 'Not Infected'. If only one of the specimens was positive this was regarded as probable contamination and the joint recorded as 'Not Infected'. If all the specimens were positive or three out of four were positive, the joint was recorded as 'Infected' (Kamme and Lindberg 1981). The results were analysed statistically by Student's unpaired *t*-test.

Table I. Results of white-cell scans of 56 joint replacements

		Infected		Non-infected	
		Scan		Scan	
Type of scan	Arthroplasty	+ve	−ve	+ve	−ve
In-oxine	Hip	3	5	0	17
Tc-HMPAO	Hip	0	5	0	15
	Knee	5	0	0	6
	Hip and knee	5	5	0	21
Both	Hip	3	10	0	32
All		8	10	0	38

RESULTS

Two patients had imaging with both In-oxine- and Tc-HMPAO-labelled cells, while two patients had bilateral revisions, so that 56 scans were available for study. Imaging was at an average of 7.3 years after their index arthroplasty; revision surgery was at an average of 3.9 months after the scan. A total of 25 hips were imaged with In-oxine-labelled cells; 20 hips and 11 knees were imaged with Tc-HMPAO-labelled cells.

Eighteen joints were infected, 13 hips and five knees. Of the infected hips eight had been imaged using In-oxine; three were predicted. The other five infected hips had been imaged with Tc-HMPAO; none was predicted. All five infected knees had been predicted by Tc-HMPAO. There were no predictions of infection in joints proven to be non-infected (Table I).

The accuracy of the scans (true-positive and true-negative scans divided by the total number of scans) was 82%. The sensitivity (true-positive scans divided by the number of infected cases) was 44%. The specificity (true-negative scans divided by the number of non-infected cases) was 100%.

For imaging of the hip, In-oxine scans had an accuracy of 80%, with a sensitivity of 38%, but Tc-HMPAO scans failed to detect any of the infections, giving a sensitivity of 0%. By contrast, Tc-HMPAO detected all infected knees with a sensitivity of 100%. For hip and knee results combined Tc-HMPAO gave an accuracy of 84% and a sensitivity of 50%.

The interval between the index procedure and scan was 3.84 years on average for prostheses proven at revision to be infected and 8.95 years for those proven not to be infected (Table II).

For the positive scans, the average time from the

Table II. Interval from arthroplasty to scan (mean, range) in months

		Infected			
		Scan			
Type of scan	Arthroplasty	True +ve	False −ve	All	Non-infected
In-oxine	Hip	17.7 (7 to 38)	61.2 (10 to 120)	44.9 (7 to 120)	116.9 (24 to 244)
Tc-HMPAO	Hip	-	84.2 (29 to 133)	84.2 (29 to 133)	120.7 (24 to 249)
	Knee	10.0 (3 to 19)	-	10.0 (3 to 19)	46.8 (10 to 90)
	Hip and knee	10.0* (3 to 19)	84.2* (29 to 133)	47.1 (3 to 133)	101.0 (10 to 249)
Both	Hip	17.7* (7 to 38)	72.7* (10 to 133)	60.0 (7 to 133)	118.7 (24 to 249)
All		12.9† (3 to 38)	72.7† (10 to 133)	46.1 (3 to 133)	107.3 (10 to 249)

* difference, $p < 0.01$
† difference, $p < 0.001$

index procedure to imaging was 1.07 years, significantly earlier than the average interval for scans that missed a proven infection (6.06 years; $p < 0.001$). For prostheses imaged with Tc-HMPAO the time from index procedure to imaging was also significantly different between true-positive scans and false-negative scans (0.83 v 7.02 years; $p < 0.01$). For hips imaged with In-oxine only early infections were identified, although the difference was not significant (1.47 v 5.10 years; $p > 0.05$). For hips imaged by either label, the difference was significant (1.47 v 6.06 years; $p < 0.01$). Infected joints tended to fail earlier than the non-infected joints (3.84 v 8.95 years; $p < 0.001$), but those with false-negative scans did not fail significantly sooner (6.06 years v 8.95 years).

Joint aspiration had an accuracy of 95%, a sensitivity of 89% and a specificity of 97%: in the whole series two infections were not detected and there was one false-positive aspiration. Neither of the false-negative aspirations was in patients with positive scans; although ten patients had repeat aspirations these were for 'dry taps' and not in response to positive scans.

Infection was correctly predicted in 13 of the 18 infections by a raised ESR or raised C-reactive protein level or both, but these tests gave nine false-positive results, five in patients with rheumatoid arthritis. Thus the accuracy for serology was 77%, the sensitivity 83% and the specificity 74%.

DISCUSSION

Initial results of the use of indium-labelled white-cell scans for the detection of infected prostheses were reported to be promising, with a high sensitivity, but often a poor specificity (Mulamba et al 1983; Merkel et al 1985; Pring et al 1986; Wukich et al 1987; Magnuson et al 1988; Palestro et al 1990; Rand and Brown 1990). Unlike our series, not all of these studies used a definitive diagnosis by biopsy at the time of revision surgery, as suggested by Kamme and Lindberg (1981). Several of these authors found that indium-labelled white-cell scans were superior to either technetium phosphate scans or sequential scans with gallium. McKillop et al (1984) reported disappointing results with labelled white cells, which he believed to be due to the chronicity of the low-grade infections that he was studying.

The introduction of Tc-HMPAO offered the possibility of improved image resolution, reduced exposure and imaging in a single day (Peters et al 1986), but its use in orthopaedic practice has not yet been fully evaluated. Costa, Lui and Ell (1988) compared imaging with In-oxine- and Tc-HMPAO-labelled white cells in a variety of infective and inflammatory conditions and found that Tc-HMPAO was better because of improved image quality. Rüther et al (1990) reported a sensitivity of 94.1% and specificity of 57.1% for Tc-HMPAO-labelled white-cell imaging of non-vertebral orthopaedic infections. Only seven joint replacements were included in their study; all had positive scans even although three of them were not infected. Moragas et al (1991) imaged 35 joint prostheses with a sensitivity of 100% and specificity of 91.3%.

In view of the potential benefits we started to use Tc-HMPAO labelling for imaging all knee prostheses. Tc-HMPAO-labelled white cells show greater physiological bowel activity than In-oxine-labelled cells, which may impair imaging around the pelvis. We continued to use In-oxine labelling to image hips in addition to Tc-HMPAO, the choice of marker being based on isotope availability at the time of imaging. In practice, bowel activity from Tc-HMPAO did not seem to be a problem.

Indium-labelled white-cell scintigraphy is useful in localising occult infections especially in the abdomen, but false-negative findings are frequent in chronic infections, especially in chronic osteomyelitis (Sfakianakis et al 1982; Liewendahl 1987; Syrjälä et al 1987). The preparation of the white cells aims to mark granulocytes, but a proportion of lymphocytes is labelled as well. The labelling of 'pure granulocytes' has been found to improve sensitivity, as labelled lymphocytes are associated with higher background activity (Pring et al 1986). Tc-HMPAO produces less stable labelling of lymphocytes than does In-oxine (Peters et al 1986) and should also show reduced background activity.

The failure of the Tc-HMPAO-labelled white-cell scans to detect hip infections appears to reflect the greater chronicity of the infection in that group when compared with either those imaged with In-oxine or those at the knee. The average interval since the index procedure was 3.7 years at the hip in the indium group, 0.83 years at the knee, and 7.02 years at the hip in the technetium group.

Labelled white-cell scans are most effective when the cellular response is granulocytic. Infection of arthroplasties may lead to early failure, but when the infection is low-grade, the inflammatory changes are predominantly lymphocytic (Hughes et al 1979; Walter and Israel 1987). The presence of the prosthesis itself and the possible isolation of the infecting organism within the 'glycocalyx' (Gristina and Costerton 1985) may also be associated with a suppressed cellular response which will reduce the sensitivity of white-cell scintigraphy. Mixed white cells labelled with indium are more sensitive to chronic infection than pure granulocyte preparations (Schauwecker et al 1988), so that Tc-HMPAO, which produces a purer granulocyte marker than In-oxine, may show a further reduction in sensitivity to chronic infections (Vorne et al 1989).

Previous authors have usually discussed the pureness of the labelled granulocytes used, but have rarely reported details of the intervals since the index procedure. The average in several series is under two years. Wukich et al (1987), using In-labelled cells, missed no infections although specificity was only 45%, with an average interval of five years for both infected and non-infected joints. Moragas et al (1991) felt that the purer granulocyte

label using Tc-HMPAO did not reduce the sensitivity to chronic prosthetic infection, but the average interval from index procedure to scan was 1.5 years, much less than in our study.

Conclusions. White-cell scans have a limited role in the detection of infected joint replacement. They may be helpful soon after arthroplasty, before the characteristic radiological changes of infection have developed and while the bone scan is still abnormal. For late failures, white-cell scans have insufficient sensitivity for use in screening for infection.

Aspiration is still the most reliable preoperative investigation of the failed joint. Inaccuracy occurs with a dry tap (Roberts et al 1992), where a positive white-cell scan may be an indication to proceed to biopsy, but the converse is not true. A negative scan, especially in late failure, cannot exclude the need to aspirate the joint before revision.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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