AUDIT

Role of frozen section histology in diagnosis of infection during revision arthroplasty

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The accurate diagnosis of deep infection in total joint arthroplasty is difficult. No single test on its own is entirely reliable. Frozen section histology has been used for the last two decades as an adjunct to diagnose infection with variable results. In this retrospective analysis, experience of the use of frozen section histology as a diagnostic tool in 45 cases of suspected infected total joint arthroplasty is reported.

Taking intraoperative cultures as the "gold standard", the results showed 50% sensitivity, 95% specificity, positive predictive value of 60%, negative predictive value of 92%, and an accuracy of 89%, which is similar to other existing reports in the literature. Based on these findings, the use of frozen section histology in diagnostic work-up of all suspected cases of total joint infection is recommended.

Diagnosis of deep infection in patients with symptomatic total joint arthroplasty remains a challenge. Reliable evidence on presence or absence of infection is ideal for planning either one or two stage reconstruction of failed arthroplasty. Preoperative and intraoperative identification of infection in loose, painful total joint replacements is often difficult.

The number of total joint arthroplasties and revision joint arthroplasties performed worldwide is increasing every year, so is the incidence of infection. The infection rate of revision joint arthroplasty is at least four times higher than primary surgery.^{1,2}

The cost of revision arthroplasty can be up to four times more than that of primary arthroplasty.³ In the United States the annual cost to treat the 3500 to 4000 infections that develop after total joint arthroplasty each year is between 150 and 200 million dollars.⁴ With an ageing population that will need an increasing number of arthroplasties, rational methods to prevent, diagnose, and treat this complication must be found in order to reduce both the cost of total joint arthroplasty to society and the substantial impact of an unrecognised infection, which may lead to a decreased quality of life for patients.⁵

When evaluating a patient with a painful prosthetic joint, it is critical to differentiate mechanical from septic loosening. It is important for the choice of further surgical management and for the prediction of final outcome. Unfortunately, to date, there is no preoperative test that is 100% sensitive and specific for infection.

A careful history can provide some hints about occult and indolent infection. Delayed wound healing, prolonged drainage, rest pain, or lack of a pain-free interval after surgery should raise suspicion. On the other hand, when cellulitis, induration, or active drainage is present, the diagnosis is not difficult.

Serum laboratory tests are an important part in the evaluation of any patient suspected of infection. A raised white cell count and an erythrocyte sedimentation rate (ESR) of more than 30 mm/hour are usually present in infected total hips.⁶ However, as an acute phase reactant, the ESR may be raised in an assortment of disease processes, and has always been criticised for its lack of specificity. Furthermore, it may remain raised for as long as six months after an arthroplasty, even in patients who do not have infection.⁷

C-reactive protein may be a more sensitive indicator as it is consistently high in septic cases and has the ability to return to normal levels three weeks after surgery in patients who are not infected.⁸

Plain radiographs may also be useful to predict occult sepsis when showing areas of osteolysis, scalloping, and periosteal elevation; although not diagnostic, these findings could all be suggestive of infection.

Hip aspiration is another common preoperative tool in detecting infected joints; however it is recommended only in patients who have some clinical or radiographic evidence of infection.⁹

Bone scans have also been used to differentiate aseptic from septic loosening. Technetium-gallium scans seemed to have improved the sensitivity of scanning, although there are studies that show no correlation between combined scans and operative culture.¹ Sequential technetium and indium scanning have proved recently to have a high sensitivity and specificity in detecting occult prosthetic infection.¹⁰

The surgeon's impression during the operation is sometimes a determinant to whether there is an infection or not, and suspected infection might influence surgical planning.

Intraoperative frozen section histology has also been used in detecting occult infection. Many authors have suggested that the presence of acute inflammation correlates well with positive intraoperative cultures, and they recommend delayed reimplantation until the infection is controlled in these situations.^{11–14} Mirra *et al* were first to report on the efficacy of frozen section histology as a tool to diagnose deep infection.^{12,13} In their study, the presence of ≥ 5 polymorphonuclear leucocytes (PML) per high power field (seen on haematoxylin and eosin stain of periprosthetic tissue) strongly correlated with deep infection. As many authors have stated, samples should be sent as soon as possible, multiple small samples may be more effective in detecting focal areas of inflammation, and samples should include tissue from the membrane of the loose component, joint pseudocapsule, and any other uncharacteristic tissue in the periarticular area.¹⁵

Abbreviations: ESR, erythrocyte sedimentation rate, PML, polymorphonuclear leucocytes

Frozen section histology has been available at our institution since November 2000 and has been used for all cases of revisions with suspicion of infection and at all second stage reimplantation.

This study examines our experience of the reliability of frozen section histology for identifying periprosthetic infection, by determining its sensitivity, specificity, and accuracy and comparing the results found in the literature.

PATIENTS AND METHODS

In this retrospective analysis, case notes and all investigations of 45 patients, who had intraoperative frozen section histology between November 2000 and March 2002, were reviewed. The mean age of our patients was 69 years (range 48–86 years). There were 32 men and 23 women. In our study, 26 patients had total hip replacements and 19 had knee replacements. The indication for their index joint replacement was osteoarthritis in 39 patients, rheumatoid arthritis in four patients, and avascular necrosis in two patients.

Thirty two patients had frozen section examination during first stage revision, where either haematological markers or three phase bone scan or preoperative aspiration/biopsy had suggested infection. Thirteen patients had frozen section histology during second stage reimplantation, after initial debridement and insertion of antibiotic loaded cement spacer and administration of systemic antibiotics for six weeks.

The samples submitted for frozen sections were taken from the joint pseudocapsule, from the membrane of loose components, and from any area that appeared suspicious for possible infection. Suspicious areas included synovial proliferation, unusually pigmented tissue, or areas of bone erosion. All our frozen section samples were analysed by one experienced musculoskeletal pathologist. The same pathologist also performed a complete histological analysis on permanent sections prepared from the tissue submitted for frozen section.

As described by Feldman *et al*, the sections were analysed according to several criteria to minimise sampling error⁷: (1) granulation tissue was preferentially analysed; (2) at least two samples of tissue were used; (3) the five most cellular fields (determined on the basis of the number of PML) were analysed; (4) PML counts were performed under high power ($\times 40$) magnification in these five fields; and (5) only PML, identified with well defined cytoplasmic borders, were included in the count.

A frozen section was considered positive if there was evidence of acute inflammation characterized by the presence of ≥ 5 PML per high power field in at least five separate microscopic fields.^{7 11 12 15 16}

We determined the sensitivity and specificity of frozen sections as a diagnostic intraoperative tool in detecting occult periprosthetic infection during revision arthroplasty. The

relationship between frozen section, intraoperative cultures, and the permanent histology was evaluated in a comparative fashion.

RESULTS

Of the 45 frozen section investigated, there were five cases positive for infection. Frozen sections were reported to be positive for infection in four cases of first stage revision, and one case was reported positive for infection at planned second stage reimplantation. Two of our positive results were for revision hip arthroplasty whereas the other three were positive for knee arthroplasty. Details of positive patients are shown in table 1.

Using intraoperative cultures as the “gold standard”, sensitivity, specificity, predictive values, and accuracy were determined. We found two cases of false positive results and three cases of false negative results.

Comparison of the results of frozen section with analysis of permanent histology showed 100% correlation. Therefore, the result of frozen section analysis was found to be a reliable indicator of the final histological diagnosis.

Our results showed that the frozen section examination was only 50% sensitive. However, the specificity of frozen section was found to be 95%. The positive predictive value (ratio of true results to the total number confirmed as infected) was found to be 60%, the negative predictive value (ratio of true negative results to the number of cases found not to be infected) was 92.5%, and the accuracy (ratio of true results, true positive and true negative results divided by the total number of results) was 89%.

We found no correlation of frozen section with preoperative ESR and C-reactive protein.

DISCUSSION

With increasing number of joint replacements being performed every year, the number of infected arthroplasties is rising. The ability to accurately identify those patients who have underlying infection as a reason for loosening of a prosthetic joint has significant therapeutic implications. Two stage reimplantation has enjoyed a greater success rate than primary reimplantation.^{17–21} If patients with sepsis can be accurately identified preoperatively or intraoperatively, a better outcome might be achieved from revision surgery. Although a combination of preoperative investigations can point towards infection, no test has yet proved to be totally accurate.

The technique of using frozen section histology as an intraoperative tool was first mentioned by Charosky *et al*, who concluded that if at the time of reoperation frozen section tissues from the pseudocapsule showed acute inflammatory changes or severe chronic inflammation then that could be presumptive evidence of infection.¹¹

Table 1 Details of patients with positive frozen section histology

Patient No	Age	Radiograph	Three phase bone scan	ESR (mm/hour)	C-reactive protein	Primary diagnosis	Frozen section	Postoperative histology	Intraoperative culture	Organism isolated
1	65	Loose	? Aseptic loosening	20	<5	Osteoarthritis of hip	Infected	Positive	Negative	
2	70	Loose	? Aseptic loosening	64	14	Osteoarthritis of hip	Infected	Positive	Positive	Coagulase negative <i>Staphylococcus aureus</i>
3	69	Loose	? Low grade sepsis	6	<5	Osteoarthritis of knee	Infected	Negative	Negative	
4	80	Normal	Not done	20	<5	Osteoarthritis of knee	Infected	Positive	Positive	Enterococcus
5	65	Loose	Not done	45	<5	Osteoarthritis of knee	Infected	Positive	Positive	Enterococcus

Table 2 Comparison of various studies on frozen section histology

Investigators	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)	PMN/high power field	Correlation against
Fehring <i>et al</i> (1994) ¹⁵	18.2	89.5				≥ 5	Permanent histology and cultures
Feldman <i>et al</i> (1995) ⁷	100	100			100	≥ 5	Permanent histology and cultures
Athanasou <i>et al</i> (1995) ¹⁴	90	96	88	98	95	≥ 5	Cultures
Lonner <i>et al</i> (1996) ¹⁶	84	96	70	98		≥ 5	Permanent histology and cultures
	84	99	89	98		≥ 10	
Spanghel <i>et al</i> (1999) ⁵	80	94	74	96		≥ 5	Permanent histology
Banit <i>et al</i> (2002) ^{3*}							
All	67	93	67	93		≥ 10	Cultures
Hip	45	92	55	88		≥ 10	
Knee	100	96	82	100		≥ 10	
Musso <i>et al</i> (2002)	50	94.9	60	92.5	89	≥ 5	Cultures

PMN, polymorphonuclear neutrophils.

*≥ 10 PMN is selected for its better positive predictive value.

Mirra *et al* reported a strong correlation between finding 5 PML per high powered field and infection,¹² and delayed reimplantation was recommended if ≥ 5 PML were found on frozen section. In a later study, the same authors reiterated their earlier opinion that acute inflammation correlated well with bacteriology, and two stage revision surgery was recommended.¹³

Lonner *et al* concluded that the presence of at least 10 PML per high power field on analysis of intraoperative frozen section was highly suggestive of active infection.¹⁶ Also, contrary to previous reports, they found the presence of 5–9 PML per high power field not necessarily to be consistent with infection.

In a recent study, Banit *et al* found that intraoperative frozen section analysis with ≥ 10 PML per high power field being an indication of infection was not sensitive enough for revision total hip arthroplasty, but had an acceptable sensitivity and positive predictive value in total knee arthroplasty.³

The usefulness of a diagnostic tool for a particular disease is generally determined by its sensitivity, which is the ability to correctly identify those with the disease (true positive results divided by the sum of true positive and false negative results). Upon close review of previous reports, a frozen section's sensitivity ranges between 18%¹⁵ and 100%.⁷ This wide range in sensitivity of a frozen section depicts the power of each study, the criteria used to diagnosed infection, and the experience of the histopathologist.

The ability of a diagnostic tool to determine correctly the absence of a disease process is defined by its specificity (true negative results divided by the sum of true negative and false positive results). Frozen sections can be considered to be fairly specific, as reported in previous studies, with a range of 89.5%¹⁵ to 100%,⁷ but because of the sampling errors with this technique, a negative frozen section should not be viewed as an absolute indicator of the absence of infection.

A false positive frozen section with a negative intraoperative culture might occur as a result of the presence of fastidious organisms, which fail to grow in vitro. It can also occur if the exact area sampled by frozen section was not cultured, or an underlying active inflammatory arthritis or fracture was not previously documented. The presence of polymorphonuclear neutrophils unrelated to sepsis can occur

if the sample is taken late in the case when leucocyte margination and perivascular migration of neutrophils might have already started from the surgical insult. Sampling from deep within the femoral canal can also cause confusion by introducing marrow elements, and also thermal artefact can induce changes in the histiocytes that can result in convolution of their nuclei and closely mimic neutrophils. The primary reason for a false negative (negative frozen section with positive culture) is most probably due to sampling errors, which emphasises the importance of wide sampling.

The results of intraoperative frozen section histology were found to be highly specific in our study but had a low sensitivity. These results are very similar to previous reports cited in the literature (table 2).

CONCLUSION

In conclusion, due to its high specificity, negative frozen section histology indicates absence of infection; hence one stage revision arthroplasty could be carried out. On the other hand, a positive frozen section does not necessarily confirm infection because of its low sensitivity. However it will be safer to proceed with two staged revision surgery in the presence of a positive result.

Frozen section histology is a rapid and relatively inexpensive means of distinguishing between aseptic and septic loosening. Its routine use is dependent upon the availability of an experienced musculoskeletal pathologist.

Our results matches previously reported studies and we recommend frozen section histology as part of every protocol in diagnosis of infection in total joint arthroplasty.

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