Is There a Role for Tissue Biopsy in the Diagnosis of Periprosthetic Infection?

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Received: 31 March 2009 / Accepted: 15 January 2010 / Published online: 4 February 2010
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Abstract

Background Successful treatment of an infected joint arthroplasty depends on correctly identifying the responsible pathogens. The value of a preoperative biopsy remains controversial.

Questions/purposes We (1) compared the sensitivity and specificity of both tests separately and in combination, and (2) asked whether the combination of tissue biopsy and aspiration would improve our diagnostic yield in the evaluation of periprosthetic joint infections.

Patients and Methods We prospectively followed 120 patients with suspected infection of a total joint arthroplasty: 64 with THAs and 56 with TKAs. All patients had aspiration with culture and biopsy.

Results The sensitivity was 83% for aspiration, 79% for biopsy, and 90% for the combination of both techniques. The specificity was 100% for aspiration and biopsy and the combination. The overall accuracy was 84%, 81%, and 90%, respectively.

Conclusions Our data suggest tissue biopsy alone offers no clear advantage over joint aspiration. However, the combination of both techniques provides improved sensitivity and accuracy. We recommend the use of tissue biopsy as an adjunct to joint aspiration in the diagnosis of total joint infection.

Level of Evidence Level II, diagnostic study. See the Guidelines for Authors for a complete description of levels of evidence.

Introduction

Various prophylactic measures including improved patient selection (eg, elimination of remote infections), routine use of prophylactic antibiotics, use of laminar airflow, use of body exhaust suits, minimized activity in the operating room, and use of antibiotic impregnated bone cement have helped reduce the deep infection rate after primary THA from the historical 11% to less than 1% [12, 13, 53, 54, 56]. Currently reported deep infection rates after primary TKA are approximately 1% to 2% [14, 48].

However, as a result of the increasing number of primary THAs and TKAs performed, the number of infections after a total joint arthroplasty is a common and challenging problem. The goals of treatment are eradication of the infection, alleviation of pain, and restoration of function [27]. The treatment options include antibiotic suppression, open débridement, resection arthroplasty, arthrodesis, reimplantation of another prosthesis, and amputation [27]. The decision is made based on the type of infection and microorganism, quality of the bone stock and soft tissues, status of the prosthesis, and age and general health of the patient [26, 30]. Because many aspects of treatment are influenced by accurate identification of the causative

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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microorganism(s), a rapid and correct microbiologic diagnosis is essential to the successful outcome of an infected joint arthroplasty [27].

The diagnosis of an infection can be made using the results of clinical examination and hematologic, radiographic, and nuclear medicine scanning tests. These tests have a definite role in the workup of an infected joint arthroplasty, but some lack accuracy and none identify the

causative pathogen and its antibiotic sensitivity pattern [1, 5, 11, 17, 33, 36, 40, 46, 55, 57, 59, 67]. Therefore, aspiration and/or tissue biopsy are used to obtain specimens for additional microbiologic investigation. However, the sensitivity of these tests reportedly varies from 12% to 100% (Table 1). Two studies reported a superiority of tissue biopsy over aspiration for diagnosis of periprosthetic infections in TKA [20, 22]. However, one comparative

Table 1. Value of joint aspiration and biopsy in the diagnosis of the infected joint replacement

Study	Journal	Year	Number of patients	Joint	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Johnson et al. [31]	J Nucl Med	1988	28	Hip and knee	12	81	25	65	58
Levitsky et al. [35]	J Arthroplasty	1991	72	Hip and knee	67	96	75	94	91
Roberts et al. [51]	J Bone Joint Surg Br	1992	78	Hip	87	95	81	97	94
Barrack et al. [5]	J Bone Joint Surg Am	1993	291	Hip	60	88	15	98	87
Glithero et al. [24]	J Bone Joint Surg Br	1993	54	Hip and knee	89	97	94	95	94
Kraemer et al. [33]	J Arthroplasty	1993	72	Hip	57	97	89	83	84
Tigges et al. [63]	Radiology	1993	147	Hip	93	92	54	99	92
Steinbrink et al. [60]	Orthopade	1995	2158	Hip	82	96	87	94	92
Taylor et al. [61]	Clin Radiol	1995	90	Hip	93	96	82	99	96
Duff et al. [18]	Clin Orthop Relat Res	1996	43	Knee	100	100	100	100	100
Fehring et al. [19]	J Arthroplasty	1996	171	Hip	50	88	21	98	87
Lachiewicz et al. [34]	J Bone Joint Surg Am	1996	156	Hip	85	97	85	97	95
Mulcahy et al. [43]	J Arthroplasty	1996	71	Hip	69	91	69	91	86
Barrack et al. [6]	Clin Orthop Relat Res	1997	69	Knee	75	96	88	90	90
Cheung et al. [15]	AJR Am J Roentgenol	1997	34	Hip	83	100	100	97	97
Spanghel et al. [59]	J Bone Joint Surg Am	1999	180	Hip	86	94	67	98	93
Teller et al. [62]	Clin Orthop Relat Res	2000	166	Hip and knee	28	99	83	90	90
Itasaka et al. [29]	J Orthop Sci	2001	48	Hip	40	92	42	91	83
Virolainen et al. [65]	Scand J Surg	2002	68	Hip and knee	75	100	—	—	—
Somme et al. [58]	Joint Bone Spine	2003	109	Hip	83	100	100	86	92
Bernard et al. [8]	Scand J Infect Dis	2004	127	Hip and knee	82	94	99	43	83
Kordelle et al. [32]	Z Orthop Ihre Grenzgeb	2004	39	Knee	50	100	100	50	67
Malohttra et al. [39]*	J Arthroplasty	2004	41	Hip	80	100	100	97	97
Williams et al. [66]	J Arthroplasty	2004	273	Hip	80	94	81	93	90
Williams et al. [66]*	J Arthroplasty	2004	273	Hip	83	90	74	94	88
Fuerst et al. [22]	Z Orthop Ihre Grenzgeb	2005	86	Knee	69	97	85	92	91
Fuerst et al. [22]*	Z Orthop Ihre Grenzgeb	2005	86	Knee	100	95	87	100	96
Panousis et al. [47]	Acta Orthop	2005	92	Hip and knee	70	95	78	92	90
Sadiq et al. [52]*	J Arthroplasty	2005	159	Hip and knee	88	91	47	90	89
Ali et al. [2]	J Arthroplasty	2006	73	Hip	82	91	74	94	89
Van den Bekerom et al. [64]	Acta Orthop Belg	2006	68	Knee	71	74	84	57	72
Fink et al. [20]	J Bone Joint Surg Br	2008	145	Knee	73	95	85	90	89
Fink et al. [20]*	J Bone Joint Surg Br	2008	145	Knee	100	98	95	100	99
Muller et al. [44]	J Orthop Surg	2008	50	Hip	57	50	78	29	54
Current study	Clin Orthop Relat Res	2010	120	Hip and knee	83	100	100	35	84
Current study*	Clin Orthop Relat Res	2010	120	Hip and knee	79	100	100	30	81
Current study†	Clin Orthop Relat Res	2010	120	Hip and knee	90	100	100	48	91

* biopsy; † combination of aspiration and biopsy; PPV = positive predictive value; NPV = negative predictive value.

study suggests tissue biopsy in THA offers no advantage over aspiration and should be avoided because it is a more invasive procedure [66].

We therefore (1) compared the sensitivity and specificity of both tests separately and in combination, and (2) asked whether the combination of tissue biopsy and aspiration would improve our diagnostic yield in the evaluation of periprosthetic joint infections.

Patients and Methods

We prospectively followed all 120 patients (120 joints) treated in our department with revision arthroplasty for an established infection between 2000 and 2006; all patients treated during this time had biopsy and aspiration preoperatively. Of these, 64 had a THA and 56 had a TKA. The study was approved by the hospital Ethics Committee and all patients provided informed consent to participate in the study.

Before microbiologic examination of the aspirate and tissue specimen were obtained, the tentative diagnosis of an infection was made by means of history (delayed wound healing, postoperative superficial infection, persisting wound drainage, and/or pain), C-reactive protein (CRP) (greater than 10 mg/L), erythrocyte sedimentation rate (greater than 30 mm/hour), radiographs (periostitis, osteopenia, endosteal reaction, and/or rapid progressive loosening or osteolysis), and/or bone scan. When at least two of these parameters were observed, a joint aspiration and biopsy were performed. All antibiotic therapy was stopped 4 weeks before aspiration and biopsy to minimize the risk of false-negative results [10, 38, 42].

The aspiration and tissue biopsy were performed in the operating room under strict aseptic conditions and with

the patient sedated. The patient was placed supine on a radiolucent table. The skin was prepared using iodine and draped. A small skin incision was made to prevent contamination with skin flora. A 14-gauge spinal needle was used to aspirate fluid. For a THA, injection of 2 mL contrast medium and fluoroscopy were used to confirm correct positioning of the needle and ascertain that specimens were obtained from the periprosthetic space. Using the same trajectory, and after correct placement of a 6-inch long, 14-gauge Tru-Cut needle (Tru-Cut; Cardinal Health, Galway, UK), the biopsy was performed by holding the inner needle of the Tru-Cut needle in one hand while the cutting needle was advanced with the other hand. At least three tissue specimens were obtained. All cultures were inoculated in aerobic and anaerobic culture media.

At the time of the revision procedure, a minimum of five tissue samples from the joint were obtained, including fluid, capsule, and pseudocapsule [4]. Intraoperative antibiotics were withheld until all the tissue samples were retrieved. They were subjected to microbiologic investigation. We compared the prerevision culture results of the aspiration and tissue biopsy with those obtained at the time of the revision. The intraoperative culture was used as the definitive diagnostic test [4, 59].

In the laboratory, all preoperative and intraoperative specimens were inoculated directly onto two blood agar plates, one incubated aerobically with CO₂ and the other anaerobically for 48 hours. They also were inoculated in brain heart infusion broth and fastidious anaerobe broth, which were incubated for 7 days, examined daily for turbidity, and subcultured on blood agar plates as described previously, if there was any suspicion of growth, and then terminally subcultured at 7 days. If the same organism grew on two or more specimens, this was regarded as a

Table 2. Calculations of features of a diagnostic test as compared with gold standard

Measure	Question addressed	Formula
Sensitivity	How good is the test at detecting people who have the condition?	$\text{True-positives}/(\text{true-positives} + \text{false-negatives})$
Specificity	How good is the test at correctly excluding people without the condition?	$\text{True-negatives}/(\text{false-positives} + \text{true-negatives})$
Positive predictive value	If patient's test is positive, what is the probability that he or she has the condition?	$\text{True-positives}/(\text{true-positives} + \text{false-positives})$
Negative predictive value	If patient's test is negative, what is the probability that he or she does not have the condition?	$\text{True-negatives}/(\text{false-negatives} + \text{true-negatives})$
Accuracy	What proportion of all tests has given the correct result?	$(\text{true-positives} + \text{true-negatives})/\text{total number}$
Likelihood of a positive test	How much more likely is a positive test to be found in a patient with the condition than in a patient without it?	$\text{sensitivity}/(1-\text{specificity})$
Likelihood of a negative test	How much more likely is a negative test to be found in a patient without the condition than in a patient with it?	$(1-\text{sensitivity})/\text{specificity}$

positive culture. Growth from one specimen only usually was regarded as a contaminant, but only after discussion with a consultant microbiologist who specialized in bone and joint infection. Histologic analysis of the specimens was not performed.

Results were recorded in a two-by-two contingency table for each test and for the combination of both tests. Sensitivity, specificity, accuracy, positive predictive value, negative predictive value, and likelihood ratios of aspiration biopsy and the combination of both techniques were calculated (Table 2). McNemar's test with the continuity correction was performed using GraphPad Prism Version 5.00 (GraphPad Software, San Diego, CA) to compare the results of the different tests.

Results

Of the 120 joint arthroplasties with suspected infections, 110 were infected as confirmed by the specimens taken at the time of the revision surgery (Table 3). Of these 110, 91 of the aspiration specimens and 87 of the tissue biopsy specimens were positive (Table 4). There were 19 negative aspiration and 23 negative tissue biopsy samples. No positive aspiration or tissue biopsy results were obtained when samples taken at the time of the revision surgery remained sterile (Table 5). In three patients, only one of four samples taken with aspiration and tissue biopsy was positive. Repeat aspiration and biopsy were performed 3 weeks later in one of the three patients, confirming the diagnosis of infection. In the other two patients, we considered the finding a contaminant; in both cases, samples taken at the time of the revision surgery were sterile. In two other patients, repeat aspiration and tissue biopsy

were performed to confirm the growth of an unusual organism.

If the two techniques were combined, 99 of 110 specimens were positive on either aspiration or tissue biopsy. This means there was an improvement of the accuracy from 81% in tissue biopsy alone and 84% in aspiration alone to 91% for the combination of both techniques. In two patients, extra organisms were identified with tissue biopsy that were not detected by aspiration alone (Table 5). We observed a difference in the number of discordant pairs between aspiration and the combination of both techniques ($p = 0.021$) and between biopsy and the combination of both techniques ($p = 0.0015$). No difference ($p = 0.50$) was found between aspiration and biopsy alone. There were no technical complications during the study period.

Table 3. Number of organisms cultured intraoperatively

Organism	Number	Percent
Coagulase-negative staphylococci	29	24.17
Staphylococcus aureus		
Methicillin-sensitive	20	16.67
Methicillin-resistant	8	6.67
Corynebacterium species	11	9.17
Pseudomonas aeruginosa	8	6.67
Bacteroides fragilis	7	5.83
Enterobacter species	5	4.17
Escherichia coli	4	3.33
Propionibacterium species	4	3.33
Acinetobacter species	2	1.67
Polymicrobial	12	10.00
No growth	10	8.33

Table 4. Number of organisms identified preoperatively

Organism	Aspiration	Biopsy	Combination
Coagulase-negative staphylococci	20	22	23
Staphylococcus aureus			
Methicillin-sensitive	18	14	20
Methicillin-resistant	8	8	8
Corynebacterium species	11	8	11
Pseudomonas aeruginosa	8	8	8
Bacteroides fragilis	5	5	6
Enterobacter species	3	3	3
Escherichia coli	4	3	4
Propionibacterium species	2	2	2
Acinetobacter species	2	2	2
Polymicrobial	10	12	12
No growth	29	33	21

Table 5. Results of the different tests

Measure	Aspiration	Biopsy	Combination
True-positive	91	87	99
True-negative	10	10	10
False-positive	0	0	0
False-negative	19	23	11
Sensitivity	82.7%	79.1%	90.0%
Specificity	100.0%	100.0%	100.0%
PPV	100.0%	100.0%	100.0%
NPV	34.5%	30.3%	47.6%
Accuracy	84.1%	80.8%	90.8%
LR+	∞	∞	∞
LR−	0.173	0.209	0.1

PPV = positive predictive value; NPV = negative predictive value; LH+ = likelihood ratio of a positive test; LH− = likelihood ratio of a negative test.

Discussion

When a patient presents with a painful or loose joint replacement, infection must be ruled out because the treatment of an infected joint replacement is fundamentally different from the treatment of a noninfected joint replacement. Several tests are used in the diagnosis of a periprosthetic infection. The serum level of CRP is regarded as an important diagnostic parameter and has a high sensitivity [59]. However, the specificity is generally lower, especially when patients with rheumatoid arthritis are included [20, 25, 65], and it does not identify the microorganism in question. Aspiration and biopsy offer the only chance of identifying the infective microorganism preoperatively [9, 23, 49, 50]. Identifying the causative pathogen and its sensitivity can alter antibiotics given at the time of a revision arthroplasty. If a two-stage revision is performed with the use of a cement spacer, antibiotics used in the spacer can be adjusted according to the sensitivity of the pathogen. When considering single-stage exchange procedures, success depends considerably on correct identification of the bacterial species responsible and an accurate antibiogram of antibiotic sensitivity. The goal of our study was to compare the results of aspiration and biopsy and to determine whether there was an additional benefit from doing tissue biopsies in combination with aspiration.

The major limitations of our study are: (1) the use of contrast medium to confirm correct placement of the aspiration and biopsy needle in THA; (2) obtaining an appropriate tissue sample with tissue biopsy; (3) the inclusion criteria for aspiration and tissue biopsy; (4) only growth of two specimens was considered as a positive finding; (5) unrecognized iatrogenic damage; and (6) the use of intraoperative cultures as a gold standard to determine the presence of periprosthetic infection at the time of revision surgery. Percutaneous aspiration and biopsy of the knee can be performed easily without fluoroscopy, but because of the anatomy of the hip, fluoroscopy is used in combination with contrast medium. Because the injection of contrast medium could lead to dilution, it might cause a lower bacterial load and greater likelihood of false-negative results. The contrast medium could affect the results of the culture, but there are no studies that have examined the effect of contrast medium on the microbiologic culture. The contrast medium was injected only in patients with a THA, but we did not find a difference in sensitivity or specificity when compared with patients with a TKA.

The highest bacterial concentrations in case of a periprosthetic infection occur on the surface of the prosthesis and the synovial villi. Beaulé et al. reported a high success rate for obtaining synovial membrane with a surgical technique similar to the one we used [7]. Some surgeons use aspiration as a routine test in all revision cases. As a

result of the low incidence of infection and the low detection rate for true infection, it should be used only when an infection is suspected. Samples taken regardless of the level of suspicion lead to the inclusion of a large number of noninfected joint arthroplasties. In this case, there is a risk of having more false-positive findings as suggested by Barrack and Harris [5], which decreases the specificity and positive predictive value of a test. The predictive value of a positive result of a culture of joint fluid is greater if the study is not used as a screening test for infection, but is used instead as a confirmatory test for patients in whom clinical findings (or prior laboratory test results) already have raised the suspicion of infection. We use aspiration and tissue biopsy to confirm clinical suspicion of infection and to identify the microorganism causing the infection. We performed aspiration and tissue biopsy in the operating room under strict aseptic conditions to reduce the number of contaminants and false-positive results.

Varying sensitivity and specificity were reported in different studies (Table 1). This is mainly the result of the different techniques and the different criteria used for positive findings. We do not consider growth of one specimen to be a positive finding unless clinical, serologic, and microbiologic investigations dictate otherwise. In that case, the results are discussed with consultant microbiologists with a special interest in periprosthetic joint infection and, if necessary, repeat aspiration and tissue biopsy should be performed. Another reason for the variation of sensitivity and specificity could be the unrecognized or unreported use of antibiotics. Therefore, antibiotics should be stopped for a minimum of 2 weeks and preferably 4 weeks before the aspiration and biopsy are performed to obtain optimal results [10, 38, 42]. Correct handling of the samples, immediate inoculation, and immediate transfer to the laboratory are mandatory to prevent contamination of the samples. Because bacteria that lead to a periprosthetic infection sometimes exist in low numbers and grow slowly [10, 16, 45], an adequate length of incubation is important. We chose to incubate our specimens for 14 days [21, 25, 28, 60].

A potential concern is that tissue biopsy of the knee is performed in a blinded fashion, which could lead to damage to the surface of the components. However, Fink et al. [20] examined the knee arthroscopically after biopsies were obtained and did not observe any damage. We observed no complications or technical problems with the use of the Tru-Cut needle.

We used the intraoperative tissue cultures as the criterion reference for an infected joint arthroplasty. This generally is accepted as the highest standard using a minimum of two positive samples but these cultures are not always positive even in patients who have positive results by all the other criteria for infection [4, 59]. Some authors advocate the use

of intraoperative frozen section and histology for the diagnosis of a total joint infection [3, 37, 41]. Different criteria have been used as a cutoff, but the variable nature of this test limits its role. To minimize sampling errors, obtaining an appropriate sample of tissue without necrosis is important. A dedicated and interested pathologist is necessary to interpret the results. We therefore do not routinely use it in our practice for diagnosis of infection of a joint arthroplasty.

Our data show the combination of aspiration and tissue biopsy leads to a major improvement in correct identification of the microorganism causing a periprosthetic infection (accuracy 90.8% versus 80.8% and 84.1% for biopsy and aspiration, respectively). Tissue biopsy offers the advantage that more samples can be obtained, which might increase the chance of diagnosing infection. The procedure can be performed at the same time as the aspiration. It also offers the advantage of combining bacteriologic and histologic examinations.

In a study of 145 TKAs planned for revision surgery attributable to component loosening, Fink et al. [20] showed that preoperative synovial biopsy, obtained using an arthroscopic biopsy forceps, was superior to joint aspiration for diagnosis of periprosthetic infection. Aspiration had a sensitivity of 72.5% and specificity of 95.2%. Synovial biopsy had a sensitivity of 100% and a specificity of 98.1%. Williams et al. did not observe a benefit of tissue biopsy and did not advocate its use as a result of the more invasive nature of the procedure [66]. In that study, a tissue biopsy was obtained with a trochar in 338 consecutive THAs regardless of the clinical suspicion of infection. Their data suggest more true-positive results (59 versus 57) and less false-negative results (12 versus 14) with biopsy. As a result of the high number of false-positive results in the group of biopsy specimens (21 versus 13), this leads to a lower specificity and positive predictive value.

Our data suggest aspiration and biopsy are valuable tools in diagnosing an infected joint arthroplasty. These are the only tests that can determine the microorganism, which is important for additional treatment. We recommend these procedures especially in patients with a high index of suspicion for an infected total joint arthroplasty. Because of the substantial improvement, we recommend the use of tissue biopsy as an adjunct to aspiration in the diagnosis of a periprosthetic infection, especially when correct identification of the microorganism is crucial to successful treatment. It also offers the possibility to perform a histologic examination, which can be used as a preoperative diagnostic method to confirm or rule out the presence of late periprosthetic infection.

Acknowledgments We acknowledge the microbiologic support provided by Geoff Ridgeway, Geoff Scott, Vanya Gant, John Holton, and Bruce Macrae.

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