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Review Article

Application of the orthopedic implant sonication method to diagnosis of periprosthetic joint infections

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Abstract

Arthroplasty is one of the most common surgical procedures in Orthopaedic Surgery. Periprosthetic joint infection (PJI) constitutes a rare complication of arthroplasties, but with severe social and economic impact, if the large and growing daily number of arthroplasties is taken into account. PJI diagnosis presents, even today, serious difficulties. Correlation of the specific infection pathogenesis to the microorganism ability to grow in biofilms has opened a new field of research. The method of implant sonication is a relatively recent development, applied to facilitate removal of microbes from the attached biofilm and subsequent cultivation and isolation of them. During the years following the first application of the method, multiple different protocols have been applied with different results, in comparison to the reference method, which is the conventional implant culture. Most studies yield encouraging results, implying superiority of the sonication technique in comparison with classic cultivation methods. In view of these results, the sonication method appears to be a reliable as well as easy to apply, fast and low cost examination technique, offering effective contribution to timely diagnosis of PJI.

Keywords: Orthopedic implant, PJI, Sonication method

Introduction

A large increase in the number of arthroplasties performed worldwide during the last decade has resulted in improvement in the quality of life for thousands of patients. However, a small percentage of these patients are bound to exhibit some complication and be subjected to revision. One of the most dangerous complications is periprosthetic joint infection (PJI), involving the implant joint and periprosthetic tissues. Though the PJI cases' percentage is small, their absolute number is significant and tends to further increase. PJI prolongs hospitalization, increases mortality rate and greatly degrades the patients' quality of life, resulting in huge social and economic costs. For many years, timely diagnosis has been of great interest to clinical and laboratory doctors, in order to establish a common approach for immediate diagnosis and treatment, to the great patients' benefit.

Arthroplasty and PJI

Arthroplasty is the surgical replacement of a joint with durable and human body compatible implants. This method has been characterized as one of the greatest achievements of orthopedics. Notably, it has been referred to as the operation of the century[1]. The multiple benefits of arthroplasty, consisting mainly in reduced pain and improved functionality of the joint, and hence patient's quality of life, have resulted in rapid increase in the number of such operations in recent years[2,3]. According to the 2017 yearly report from American Joint Replacement Registry[4], arthroplasty procedures increased from 45,517 in 2012 to 281,746 in 2016. Similarly, according to the 2018 yearly report from National Joint Registry for England, Wales and Northern Ireland[5], a total of 252,251 arthroplasty procedures were performed up to 2017, with an increase of 9,632 over 2016. Notwithstanding the impressive clinical results, some complication cases may and do arise, but accumulation of study and experience over the years is highly beneficial to mitigation efforts. Most frequent complications

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of arthroplasty, mainly of hip and knee that constitute about 85% of all arthroplasty surgeries, include: thromboembolic disease, periprosthetic fracture, implant fracture, implant loosening, bleeding, neural deficit, heterotopic ossification, instability, vascular injury, and of course periprosthetic joint infections which are the subject of the present work[6,7].

Periprosthetic joint infection is defined as infection involving the joint prosthesis as well as adjacent tissues. Since thorough reporting of PJI incidences is difficult, the corresponding epidemiological data is unclear. Most centers report percentages of incidence between 0.5-1% for hip, 0.5-2% for knee and shoulder and <9% for elbow arthroplasties, with regard to primary surgeries[8-13]. A great advance in PJI diagnosis was achieved via relating its pathogenesis to formation of biofilm, which is defined as a complex community of microorganisms embedded in an extracellular matrix. The biofilm is composed by the cells themselves and attached on the surface of the prosthesis in a non-reversible way (i.e. cannot be removed by mild washing)[14].

In the last decade, many scientific groups have published definitions for the diagnosis of PJI. An infection is defined as confirmed when identical microorganisms isolated from 2 or more cultures or sinus tract communicating with the prosthesis, according to the International Consensus Meeting (ICM) for definition of PJI of 2018[15]. Secondary criteria are: elevated serum CRP or D-Dimer values (score 2), elevated serum erythrocyte sedimentation rate (ESR) value (score 1), elevated synovial fluid leukocyte or their esterase count (score 3), positive synovial fluid alpha-defensin (score 3), elevated synovial fluid PMN % value (score 2) and elevated synovial fluid C-reactive protein (CRP) value (score 1). Infection definition requires score ≥6, probable infection with score 2-5, while with score 0-1 infection is considered improbable[15]. For patients without confirmed pre-operation score, besides the previous criteria, the following additional ones may also be applied: positive histological examination of periprosthetic tissue (score 3), purulence surrounding the prosthesis (score 3) and single positive culture (score 2). Infection definition requires score >=6, probable infection with score 4-5, and lack of infection with score ≤3[15].

Method of prosthesis sonication

Orthopedic prostheses have always posed a special challenge to microbiologists, since their large size obstructed culture and made rolling onto solid culture media impractical. Relating of the PJI pathogenesis to formation of biofilm opened a new field of research, as planktonic bacteria forms, in contrast to biofilm attached forms, were considered easier to isolate by conventional culture techniques. Seeking ways to dislodge biofilm and the associated bacteria from the surface of the implant, various techniques were proposed, including mechanic (sonication, vortexing), biochemical (enzyme treatment) and electrical ones[16]. Among them, sonication is the one most intensely studied. The method uses low-frequency ultrasound waves which pass through liquid surrounding the prosthesis, creating areas of high and low pressure. During the high-pressure stage, microscopic bubbles are formed, which subsequently collapse during the low-pressure stage, releasing energy on the surface of the implant. This movement may dislodge or decompose the biofilm, causing liberation of bacteria from the surface[17,18]. After sonication, the fluid surrounding the implant can be cultivated or analyzed by other methods for definition of bacteria.

The sonication technique protocol

The first published and widely known study of application of sonication to orthopedic prosthesis was carried out by Tunney et al[19] in 1998. In this study, femoral and acetabular implants were aseptically placed into sterile bags filled with Ringer's lactate solution. The bags were placed into the sonication device and exposed for 5 min to ultrasound waves at frequency of 50 kHz. The sonicate fluid was then plated onto blood agar and incubated under aerobic and anaerobic conditions[19]. In 2007, Trampuz et al[20] modified Tunney's protocol by substitution of bags with rigid polypropylene containers, after a previous study of the same investigators[21] had demonstrated possible contamination as a shortcoming of the use of bags. A second modification proposed in the same study was vortexing of the containers for 30 sec, in order to enhance removal of bacteria from the surface of the prosthesis[20]. In a 2011 study, Vergidis et al proposed an additional step of centrifugation of the sonicate fluid[22], in an effort to increase the density of bacteria removed from the prosthesis. Based on these advantages, this protocol is usually recommended for sonication of orthopedic prostheses.

Sonication method and conventional tissue culture

For many years, culture of periprosthetic tissue has been the reference method (gold standard) for PJI diagnosis. Upon introduction of the new sonication method, comparison with the conventional reference method was of immediate interest.

The first large study of the sonication technique was carried out by Trampuz et al[20], with promising results. The object of the study were specimens of prostheses and periprosthetic tissue from 331 patients with total knee (207 patients) or hip (124 patients) arthroplasty. Among patients, 252 suffered from aseptic failure and 79 from PJI. The sensitivity of tissue culture and sonicate fluid was found to be 60,8% and 78,5%, respectively, with corresponding specificities of 99,2% and 98,8%. In 14 PJI cases, a microorganism was detected by sonicate fluid culture, while the corresponding tissue culture was negative. Further on, the sonicate fluid method exhibited a much greater sensitivity of 75%, in comparison with 45% for tissue culture, for patients receiving antimicrobial therapy in less than 14 days prior to surgery[23].

These results were confirmed by a 2014 study by Scorzolini et al[24], who studied PJI patients subjected to knee or hip revision, compared the two approaches and reported sensitivities of 75% and 56,5% for sonicate fluid culture and tissue culture, respectively, for patients not receiving antimicrobial therapy for more than 15 days prior to surgery. The difference was more impressive for cases where the antimicrobial therapy stopped less than 15 days prior to surgery, with corresponding sensitivities of 80% and 16,6%, respectively. Another important finding of the same study concerns multiple bacterial infections which were accurately detected only with the sonication technique, while in corresponding cases only one microorganism was detected by the conventional method.

In 2017, Fernandez-Sampedro et al[25], in a five year study, compared sonication with the conventional culture technique, in knee and hip PJI, distinguishing the results according to the time of infection (early, delayed and late). In early infections, sensitivity and specificity are 83,3% and 100%, respectively, identical for the two methods. The sonication method appears to be better for delayed infections with a sensitivity of 94,3% versus 65,7% of the tissue culture, as well as for late ones with a sensitivity of 80,5% versus 55,8%, respectively. By combination of histological evaluation and tissue culture, diagnosis was achieved for all early infection cases, 97% of delayed infection and 94,8% of late infection cases. On the other hand, combination of sonication and histological evaluation findings achieved 100% sensitivity for all infection cases.

Janz et al extended the comparison to specimens under histological evaluation[26]. Sensitivities of 91%, 75% and 87% were found for sonication, tissue culture and histological evaluation, respectively. Out of three cases of confirmed PJI with a negative histological evaluation result, P. Acnes was detected by sonicate fluid culture in two and S. epidermidis by tissue culture in the third one.

In 2017, Rothenberg et al[27], comparing the two methods for patients with knee or hip arthroplasty, include in their study a large number of aseptic failure cases. For a subcategory of cases with all three culture techniques of sonicate fluid, tissue and synovial fluid applied, sensitivities of 97%, 70% and 57%, and specificities of 90%, 97% and 100%, respectively, were found. Of particular interest in this study was the detection of different pathogens in PJI and aseptic cases using the sonication technique. While in both cases coagulase-negative Staphylococcus was the first pathogen, additional microorganisms, including P. Acnes, Diphetheroids, Micrococcus and Peptostreptococcus, were detected only in aseptic cases[27].

In a recent study, Tani et al[28], in contrast to Fernandez-Sampedro et al results, showed an advantage of sonication method over conventional tissue culture not only for delayed and late infections but also for early ones. According to this study, the sonication technique appears to be more sensitive for hip than knee infections, since for the latter ones it does not exhibit statistically greater sensitivity than tissue culture.

Though the majority of current studies concerns PJI of knee and hip arthroplasties, comparative studies exist covering other kinds of arthroplasties as well. Piper et al in 2009[29] studied 136 patients with shoulder arthroplasties. Sensitivities of sonication method and tissue culture were 66,7% and 54,05% and specificities were 98% and 95,1%, respectively. The study was focused on P. acnes, a pathogen appearing in large percentages of shoulder PJI, which was detected in 40% of positive cultures by sonication method and 38,9% by tissue culture. In 2011, Vergidis et al[30] studied patients with revision of elbow arthroplasty and found 89% sensitivity for sonication method, as compared with 55% for tissue culture, and 100% and 93% specificity, respectively.

According to the majority of studies, the sonication method appears more sensitive than tissue culture, nevertheless there are also studies with opposite results. As an example, Dudareva et al in a recent study[31] report sensitivities of 57% and 69% for sonication and tissue culture, respectively, regarding the latter as the reference method (gold standard).

Inoculation of sonicate fluid into blood culture bottle

Aiming to improve diagnosis of PJI, various approaches have been tested. Previous studies showed that inoculation of synovial fluid or tissue suspension into blood culture bottle may increase sensitivity of the method[32,33-35].

In 2015, Shen et al[36] inoculated synovial fluid as well as sonicate fluid from patients with hip and knee arthroplasty revision into blood culture bottles. Aerobic and anaerobic bottles (BD Bactec Plus) were used and cultured for up to 5 days. The sonication method sensitivity was 88% against 64% for synovial fluid method. In cases of antimicrobial treatment within 14 days before surgery, the sensitivity was 81% for sonication method and 52% for synovial fluid method, while for more than 14 days the sensitivity was 93% and 72%, respectively. Moreover, using the sonication method, significantly more pathogens were detected than using the synovial fluid method (44 against 32 cases). Two cases of polymicrobial infection were detected only by the sonication method.

Portillo et al[37], also in 2015, compared sonicate fluid culture in blood culture bottles with simple sonicate fluid culture and conventional periprosthetic tissue culture. Inoculation into blood culture bottle appeared to improve sensitivity of the sonication method from 87% to 100%, against 59% for simple tissue culture. In this study, the effect of antimicrobial treatment is also reported. More particularly, after use of preoperative antimicrobials, the sensitivity for simple tissue culture decreases from 65% to 55% and for sonicate fluid culture from 87% to 77%, while for inoculation method the sensitivity is not affected, remaining at 100%. Another important point of this study is investigation of the time to positivity for each one of the

three techniques. Thus, within the first 24 hours, 72% of the bottle culture specimens were positive, but only 28% and 18% of the simple sonicate fluid culture and tissue culture specimens, respectively.

Molecular diagnosis using sonicate fluid

Regardless of improvements in the conventional periprosthetic tissue culture technique and the new sonication technique with very encouraging results, aseptic periprosthetic infections still pose important clinical challenges. Introduction of molecular techniques changed the diagnostic approach to various clinical problems. Thus, widespread use of polymerase chain reaction (PCR) has been made for PJI diagnosis.

Achermann et al[38] in 2010 investigated a then new approach combining sonicate fluid culture and PCR of the same fluid. A previous approach to molecular detection was based on so-called "broad-range" PCR of periprosthetic tissue, resulting in a limited sensitivity of 50%[39-41]. The molecular technique employed by Achermann was real time multiplex PCR (RT-multiplex PCR), designed for detection and identification of the most common bacterial and fungal pathogens in blood. Comparing tissue culture, sonicate fluid culture and sonicate fluid PCR, sensitivities of 65%, 62% and 78%, respectively, were achieved. Seven out of eight false negative results of PCR concerned pathogen P.acnes, which was not included in the primers of the kit used for the study. An important finding of the study was the conclusion that, even though the DNA load decreased in case of antimicrobial treatment, detection was still possible up to 43 days after treatment. Thus, in the group of patients receiving antibiotics in less than 14 days before surgery, the sensitivity of PCR increased to 100% against 42% of sonicate method.

In 2012, Gomez et al[42], using 16S rRNA real-time PCR sequencing and, in contrast to Achermann et al, including in the panel additional PJI pathogens (such as Propionibacterium and Corynebacterium), did not find significant statistical difference between the three methods. More specifically, the sensitivity for tissue culture, sonicate fluid culture and sonicate fluid PCR, was 70.4%, 72.6% and 70.4%, respectively. The same basic group with Cazanave et al[43] a year later demonstrated an advantage of the molecular method over the other two ones, using this time a special closed-circuit, fast and real-time molecular technique (a genus-/group-specific RT PCR). Sensitivity for tissue culture, sonicate fluid culture and sonicate fluid PCR was 70.1%, 72.9% and 77.1%, respectively, and specificity was 97.9%, 98.3% και 97.9% respectively. In some cases, PCR gave a positive result even a month after antimicrobial treatment, demonstrating presence of bacterial DNA in specimens of bone and joint after antibiotic treatment[44,45]. The multiplex PCR used by Cazanave et al exhibited a better performance for multibacterial infections in comparison with other techniques, as well as the broad range PCR previously used by the same group in 2012.

In 2014, the same group[42,43] with Greenwood-Quaintance et al[46] tested with sonicate fluid another molecular technique, namely PCR-electrospray ionization mass spectrometry (PCR-ESI/MS), previously used for broad range detection of bacteria and fungi in blood culture bottles for infection diagnosis. This method detects and identifies 3,400 bacteria, four resistance genes (vanA, vanB, blaKPC, and mecA) and over 40 types of Candida. PCR-ESI/MS was more sensitive (77.6%) than sonicate culture (69.7%) but less specific (93.5% and 99.3%, respectively). As regards other molecular techniques tested by the same group in the past[42,43], PCR-ESI/MS was more sensitive than 16S rRNA PCR (77.6% and 70.4%, respectively) and similar to genus-/group- specific RT PCR (77.1%) but less specific (93.5% and 97.9%, respectively). The two last mentioned molecular techniques also exhibited similar sensitivity for the sub-population receiving antimicrobial treatment.

Discussion

A large increase in arthroplasty operations during the last decade has resulted in an increase of PJI cases, making them an implant health issue, directly related to increase in morbidity and mortality rates, hospitalization duration and healthcare costs. Timely diagnosis of PJI is of great importance, enabling immediate (antimicrobial or surgical) treatment, possibly achieving even implant retention. Nearly 25 years ago, the National Institute of Health of U.S.A.[47] regarded PJI diagnosis as an outstanding challenge, insofar as then existing microbiological methods were considered imprecise. Since then, great advances in diagnosis have been made, by improvements in older techniques and introduction of new ones. Periprosthetic tissue culture, still today the reference method, has undergone various modifications, such as increase of the number of specimens and of the incubation time, resulting in improvement of sensitivity. However, in a large percentage (30%) of PJI cases, negative tissue culture is observed[48].

Relating of the PJI pathogenesis to formation of biofilm created the need for a method to dislodge the associated bacteria from it. Sonication of removed implants was proposed to cover this need. Multiple papers comparing conventional culture methods with sonication ones have been published. The sensitivities of these methods vary between laboratories, deviating by up to ~30% for sonication method (62-94%), as well as tissue culture (54-88%)[14,19-21,49,50]. These deviations are due to multiple causes, the main ones being related to the application of different protocols by each laboratory. Implant transportation, use of vortexing and/or centrifugation of the sonicate fluid, time of culture incubation as well as the threshold number of colonies for assessment of positive culture, are important factors affecting the final outcome. Besides these laboratory-related factors, use of different criteria for determination of

PJI, and hence selection of patients included in each study, is a source of problems in comparative analysis of studies and corresponding conclusions.

Notwithstanding these considerations, valid for all methods, the majority of published studies have shown a definite superiority of the sonication method[19-21,46,47,49,51]. In the first study in 2007 by Trampuz et al[20], the most important finding was the improved sensitivity of the sonication method for patients receiving antimicrobial therapy in a short preoperative interval (less than 14 days). This finding was confirmed in subsequent studies and appears to be related to the development of biofilm on the surface of the implant, since the free (planktonic) forms of microbes found in periprosthetic tissues are much more susceptible to antimicrobial factors than those attached to implants via biofilm. Thus, the increase of viability of microbes in the sonicate fluid due to biofilm results also in facilitating diagnosis of PJI by the sonication method.

Various researchers, e.g. Rothenberg et al[27] in 2017, pointed out the usefulness of the sonication method for isolation of pathogens in aseptic revision arthroplasties. Also, the sonication method can help in showing the important pathogenic role of some normal skin flora microbes, such as P.acnes. This is a relatively low-virulence, slowly growing microbe, residing in the biofilm with a low metabolic activity, which due to these factors is very difficult to isolate in conventional cultures. Other researchers pointed out the improved sensitivity of the sonication method in delayed and late PJI cases in comparison with early ones[25]. A possible explanation may be related to the fact that in an acute infection the organism has not yet been organized inside the biofilm, or that in a chronic infection the biofilm consists of several layers and is more firmly attached to the prosthesis[43]. Thus, tissue culture exhibits a similar sensitivity to that of the sonication method for acute infections, but a lower one for chronic infections. These conclusions appear quite consistent, taking into account that delayed and late infections are caused by low-virulence microorganisms. Late PJIs, in particular, where the main contaminants are frequently skin microbes, are often presumed to be cases of aseptic failure.

The sonication method appears also highly appropriate for diagnosis of polymicrobial infections, as several studies have shown greater sensitivity of this method than tissue culture[18,25,52]. The advantage of the sonication method seems to be larger for hip and shoulder PJI and smaller for knee PJI[22,28]. A possible explanation may be based upon wide use of antibiotic-loaded cement in total knee arthroplasty, affecting the structure of the biofilm and decreasing the sensitivity of the sonication method. As regards shoulder PJI, P.acnes being one of the main pathogens in such infections also supports the above conclusions.

The need for further improvement of PJI diagnosis led into consideration of various combinations of existing methods. Thus, inoculation of sonicate fluid into blood culture bottle appears to improve diagnosis in comparison with inoculation of synovial fluid or tissue suspension, even for polymicrobial infections, and to increase the number of isolated pathogens. Inoculation of sonicate fluid exhibits better sensitivity even than culture of the same fluid[36,37]. Of special importance, with regard to all these methods, is the impact of antimicrobial treatment, the method of inoculation of the sonicate fluid into bottle being the one affected much less, if at all[36]. Another important factor is the time required to get positive results (Time To Positivity, TTP). In the study of Portillo et al[37] the sonicate fluid bottle technique exhibits a clear advantage over other methods (TTP in the first 24 hours: 72%, in comparison with 28% for the tissue bottle technique and 18% for the synovial fluid bottle technique). These results may obviously be explained by the presence of antibiotic binding factors inside the blood culture bottle, allowing microbe growth right after inoculation. The method of sonicate fluid inoculation into blood culture bottle has multiple advantages, achieving isolation of microbes in specimens with negative culture (either a conventional sonicate fluid one or tissue one), which had also been detected in the sonicate fluid by broad range or multiple PCR[38,53]. It is still unclear if the negative culture result in such cases is due to low microbial viability or low microbial load, below the detection threshold of the conventional sonicate fluid culture.

Introduction of molecular techniques into laboratory practice led to application of such techniques for PJI diagnosis improvement, since for an important portion of these infections no pathogen was identified. Various versions were applied, including RT-Multiplex PCR, broad range PCR (such as 16S rRNA Real time PCR Sequencing), genus/group specific RT PCR και PCR ESI/MS, to detect microbes in the sonicate fluid. The molecular method with most significant shortcomings appears to be the broad range PCR. Some of the 16S rRNA PCR starters cross-react with human DNA when clinical specimens are directly examined. Thus, many false positive results are observed, decreasing the specificity of the method. An additional disadvantage of the broad range PCR is lack of discrimination between multi- and single-bacterial infections. However, detection of a broad range of microorganisms is considered the main advantage of the method. Most studies have demonstrated increased sensitivity of molecular techniques for sonicate fluid, in comparison with conventional tissue culture, as well as sonicate fluid culture. Molecular techniques may detect challenging microbes, difficult to culture with conventional methods. Their results also seem to be less influenced by use of antimicrobial treatment. Another important advantage of molecular methods is also fast delivery of the results. In contrast with conventional methods, where the result may be available in multiple days (especially in cases of slowly growing microbes), the result of molecular methods is typically available in 4-24 hours (depending on the specific method), with important impact on the clinical treatment of

PJI. A disadvantage of molecular methods is that there is no sensitivity test beyond pathogen detection. However, they are regarded as helpful to detection of genes of resistance to various categories of antibiotics, like quinolones, methicillin, rifampicin etc[38,43], contributing to PJI therapy.

Adoption of the sonication method for routine laboratory use is still an unsettled issue, as relevant opinions diverge. In 2018, the International Consensus Meeting on PJI (ICM) did not encourage routine use of the method, suggesting it only in cases of possible PJI with a failure to isolate pathogen, as well as cases of preoperative antimicrobial treatment within less than 14 days[54]. Puig-Verdie et al, in the same year, propose use of the method only for delayed and late PJI cases. Conversely, various other researchers consider the method quite reliable and recommend routine use[26,28,55-58].

Conclusion

Any painful arthroplasty should be considered as presumed PJI until definite contrary evidence is obtained. Timely diagnosis is the key to successful treatment of these infections. Multiple studies have shown high sensitivity and specificity of the sonication technique. This method appears advantageous over conventional methods and may contribute to timely diagnosis of PJI, especially combined with application of molecular techniques to the sonicate fluid. Moreover, sonication of removed prostheses is a simple, low cost technique, applicable in any laboratory, since it does not require specially trained personnel. It is up to each laboratory, according to its needs and specific features, to decide upon inserting it in its routine. Further research on diagnostic methods in the near future is expected to better clarify cases currently designated as "negative culture PJI", contributing to timely diagnosis and treatment of these infections.

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