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Review Article

What Is the Role of Diagnostic and Therapeutic Sonication in Periprosthetic Joint Infections?

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ABSTRACT

Background: Periprosthetic joint infection (PJI) is one of the most dreaded complications in joint replacement surgery. Diagnosis and treatment can be difficult and biofilms are of major concern due to their low susceptibility toward antibiotics.
Methods: This review focuses on the use of sonication as an evolving diagnostic and adjunct treatment modality in the context of PJI. Therapeutic application of sonication is discussed separately for its (i) direct action on bacteria, (ii) synergistic effects with antibiotics, and (iii) effects on release of antibiotics from bone cement.
Results: Used as a diagnostic tool, sonication shows promising results with respect to sensitivity and specificity when compared to conventional methods, notably after previous administration of antibiotics. As an adjunct treatment modality, the chemical, physical, and mechanical effects of sonication are primarily driven by cavitation and recognized as the main cause for bactericidal effects but the exact underlying mechanisms have not been identified yet. Sonication alone does not have the ability to completely eradicate biofilms but synergistic effects when used in conjunction with antibiotics have been reported. There is also evidence for enhanced antibiotic release from bone cement.
Conclusion: Sonication is as an evolving modality in the context of PJIs. As a diagnostic tool, it has not been introduced in routine clinical practice and sonication as a treatment modality in PJIs is still in an experimental stage. Factors such as frequency, pressure, chemical activity, intensity, and exposure time need to be evaluated for optimal application of sonication and may also improve study comparison.
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Infection Is a Dreaded Complication in Total Joint Arthroplasty

Periprosthetic joint infection (PJI) (Table 1) is one of the most dreaded complications in joint replacement surgery. Currently, the overall risk for implant-associated infection in orthopedic surgery is below 1%-2% [3]. A complication-based analysis using worldwide registry data has demonstrated that in total hip arthroplasty, total knee arthroplasty, and total ankle arthroplasty, septic revision accounts for 7.5%, 14.8%, and 9.8% of all revision surgeries, respectively [4]. With increasing numbers of patients undergoing joint replacement surgery, the absolute number of implant-associated infections has increased [3], representing a trend that is counter-intuitive to the expected decrease in infection rates over time.

Biofilms are fundamental with respect to the pathogenesis and persistence of PJIs. Biofilms are defined as "a microbially derived sessile community, characterized by cells that are irreversibly attached to a substratum or interface or to each other, embedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription" [5]. As a result, biofilm bacteria, compared to free-floating bacteria (planktonic bacteria), display characteristics

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Table 1
Modified MSIS Criteria by the MSIS defining PJI as endorsed by the International Consensus Meeting on PJI[a] [1,2].

- Two positive periprosthetic cultures with phenotypically identical organisms OR
- Sinus tract communicating with the joint OR
- Three of the following minor criteria:

1 Elevated serum C-reactive protein and erythrocyte sedimentation rate
2 Elevated synovial fluid white blood cell count or ++ change on leukocyte esterase test strip
3 Elevated synovial fluid polymorphonuclear neutrophil percentage
4 Single positive culture
5 Positive histological analysis of periprosthetic tissue

[a] PJI may be present without meeting these criteria, specifically in the case of less virulent organisms [1].

that affect the identification of the causative organisms and antimicrobial therapy [6]. Biofilms may be formed by virulent bacteria or other opportunistic microorganisms, thus increasing the chance of biofilm formation on dead tissues and medical devices. This is clinically important as various studies have shown that treatment of biofilm bacteria is much more challenging compared to planktonic bacteria [7,8]: 100-1000 times the standard concentration of cell wall active antibiotics, for example, is required when treating biofilm bacteria [9]. The presence of extracellular matrix, heterogeneity of bacteria, expression of antibiotic resistance genes, and the communication system in biofilms, also known as “quorum sensing”, are some of the factors contributing to the lower susceptibility of biofilm bacteria toward antibiotics. These bacterial features are reviewed in detail elsewhere [5,8,10–13].

Sonication as a therapeutic approach in treating biofilms is well studied in dental literature and has also been reported in the context of soft tissue infections and wound healing [14–18]. The concept of sonication has been adopted by orthopedic surgery in clinical practice with regards to diagnosis of PJIs [19]. Experimental studies have further investigated the potential use of sonication in treating biofilms early after implantation of biomaterials [20–22]. This review focuses on sonication as an evolving diagnostic and adjunct treatment modality in the context of PJI.

Sonication

The application of sound energy is known as sonication. The chemical, physical, and mechanical effects of sonication are primarily driven by cavitation. Cavitation describes the growth, oscillation, and collapse of microbubbles in a medium that can produce high-energy phenomena [23,24]. The initiation of cavitation, also known as cavitation threshold, is determined by various factors including hydrostatic pressure, dissolved gas tensile strength, the temperature of the liquid medium, and the volume of gas in the bubble [25]. According to Joyce et al [26] antimicrobial mechanisms include (i) cell fatigue secondary to forces from surface resonance of the bacterial cells, (ii) shear forces induced by microstreaming, and (iii) chemical effects of radicals in aqueous medium including the formation of hydrogen peroxide by sonochemical degradation. These authors pointed out that higher intensities result in superior cavitational effects. Typically, frequencies between 20 and 200 kHz are considered as low-frequency, whereas high-frequency ultrasound uses frequencies of more than 1 MHz [27]. Ultrasound can be applied continuously or in a pulsed manner.

Sonication as an Adjunct Diagnostic Option

An early and accurate diagnosis of PJI is crucial for patient management as a direct correlation between failure in prompt diagnosis and outcome has been shown [28,29]. The Musculoskeletal Infection Society has proposed criteria (MSIS criteria) based on which a PJI can be diagnosed. These criteria, endorsed and slightly modified by the Philadelphia Consensus group on PJI, are outlined in Table 1 [1,2]. Conventional diagnostic methods include clinical presentation, joint fluid cell count, imaging studies, histopathology, inflammatory markers, and microbiological assessment. Various new diagnostic options have been recently proposed including molecular techniques, nuclear imaging modalities, and other techniques such as microcalorimetry, the alpha-defensin immunoassay, and the leukocyte esterase colorimetric strip test [30–32]. Further innovative techniques that are in development include microarrays, electrical methods, and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry [30]. Among them, sonication is recognized as a promising entity.

Diagnostic sonication is based on the disruption of the biofilm from the retrieved prosthetic components with the aim to increase the yield of cultures and/or histopathology. Although different protocols for sonication of retrieved prosthetic components have been described, most studies follow the recommendations by Trampuz et al [28]. A representative diagnostic sonication process is illustrated in Figure 1.

To date, different types of implants including modular megaprostheses [33] and cement spacers at the time of second-stage revision surgery [34,35] have been subjected to sonication. Sonication of spacers might be particularly useful in determining the presence of (subclinical) infection at the time of second-stage revision surgery. Prospective studies have shown that sonication results of antibiotic-loaded cement spacers can predict failure during two-stage revision [36] and that high bacterial counts from the sonicate are associated with inferior clinical outcomes [37]. Despite the fact that culture results of the sonicate are only known postoperatively and, thus, may not guide intraoperative decision making, these results may be essential for future management and overall prognosis of the patient [36].

Numerous studies have focused on the diagnostic effect of sonication by culture of the sonicate fluid alone or in combination with molecular techniques [28,36,38–48]. The improved sensitivity of sonication as compared to conventional tissue culture has been particularly shown in patients who received antibiotic treatment prior to revision surgery [28,39–42]. Table 2 provides an overview of studies comparing the effect of previous antibiotic treatment on the sensitivity of sonication as a diagnostic adjunct in PJIs.

Two meta-analyses comprising 12 and 16 clinical trials showed a pooled sensitivity of 0.80 (95% confidence interval [CI] 0.74-0.84) and 0.79 (95% CI 0.76-0.81) and a pooled specificity of 0.95 (95% CI 0.90-0.98) and 0.95 (95% CI 0.94-0.96), respectively [19,49]. Limitations of these analyses include the incorporation of heterogeneous patient cohorts and studies that have used PJI definitions which deviate from the MSIS consensus criteria. A recent diagnostic level III study has strictly used the MSIS consensus criteria for definition of PJI and investigated sonicate cultures from patients with revision total hip arthroplasties and total knee arthroplasties preoperatively and intraoperatively at each stage. These authors concluded that sonicate cultures in revision surgeries improved the diagnostic accuracy of joint infection cultures for both, clinical and occult infections [50].

Sonication has further been combined with other diagnostic methods such as molecular techniques. Literature suggests that these combinations are of similar sensitivity and specificity compared to sonicate fluid culture but superior in detecting PJIs compared to conventional tissue culture [38,40,51–55].

Limitations and Controversies

Defining the optimal cut-off for the bacterial count from the sonicate is an inherent problem in any method that is based on

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