Is sonication superior to dithiothreitol in diagnosis of periprosthetic joint infections? A meta-analysis

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Abstract

Purpose Even though effective techniques in diagnosis of periprosthetic joint infections (PJIs) have been developed, the optimal modality has yet to be determined. The present meta-analysis aimed to compare the diagnostic accuracy of dithiothreitol (DTT) and sonication against the Musculoskeletal Infection Society criteria in patients undergoing revision joint surgery.

Methods We searched the PubMed, Scopus, and Central Cochrane register of controlled trials as well as gray literature until the 9th of November, 2021. We included articles considering the comparative diagnostic accuracy of sonication and DTT in adult patients having revision hip and knee arthroplasty for septic or aseptic reasons. We calculated pooled sensitivity, specificity, and diagnostic accuracy of the above diagnostic techniques against the Musculoskeletal Infection Society (MSIS) criteria and created receiver operating characteristics (ROC) curves to enable comparisons between each other. The quality of included papers was evaluated utilizing QUADAS-2 and QUADAS-C tools.

Results Data from five comparative studies totaling 726 implants were pooled together. The diagnostic accuracy of DTT and sonication were 86.7% (95% CI 82.7 to 90.1) and 83.9% (95% CI 79.7 to 87.5), respectively. Pooled sensitivity and specificity showed no statistically significant differences between DTT and sonication (0.7 [95% CI 0.62 to 0.77] vs 0.72 [95% CI 0.65 to 0.78], \(p = 0.14\); and 0.99 [95% CI 0.97 to 1] vs 0.97 [95% CI 0.93 to 0.99], \(p = 5.5\), respectively).

Conclusions This meta-analysis did not identify any clinically meaningful difference between the diagnostic potential of sonication and the chemical-based biofilm dislodgment methods. This finding remained robust after adjusting for the administration of antibiotics prophylaxis, implementation of the polymerase chain reaction of sonicated fluid, and study quality.

Keywords Sonication · Dithiothreitol · DTT · Sensitivity · Specificity · Diagnostic accuracy · Meta-analysis

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Introduction

Periprosthetic joint infection (PJI) is one of the most feared complications of arthroplasty, predominantly because of antibiotic resistance issues [1]. With an estimated revision burden of 1–2% for infected primary hip replacements and up to 40% in the case of revision procedures, the socioeconomic impact is considerable [2, 3]. It is an undeniable fact that establishing the diagnosis of a PJI is not always a straightforward task [4, 5] with significant numbers of occult infections being inadequately investigated and misclassified as aseptic failures [6]. Given the increasing volume of joint replacement surgery worldwide, a growing trend in the projected number of new PJIs is more likely to be observed in the foreseeable future. Thus, properly understanding and diagnosing this condition promptly is of the essence.

Cultures have long been considered the golden standard [7] with *Staphylococcus aureus* and *S. epidermidis* [8, 9] being the most commonly isolated microorganisms. In addition, gram-negative rods such as Enterobacteriaceae, *Pseudomonas aeruginosa*, as well as slow-growing anaerobic bacteria such as *Cutibacterium acnes* can be involved to a lesser extent, whereas some patients can present with polymicrobial infections [7]. Taking into account that retrieving false-negative culture results can occur in as high as 16% of all PJI cases [8] and the fact that in the setting of prolonged antibiotic use, the sensitivity of microbial culture can also be compromised [10, 11], the need to implement more effective diagnostic techniques is of great importance.

As such, sonication [12], involving placement of the prosthesis in a sterile saline solution and sonicating for a particular amount of time, has been widely used [13, 14]. The sonicated fluid undergoes culture to ascertain the presence of a PJI [13]. While the literature on sonication has demonstrated satisfactory results especially in the setting of a non-suspected PJI and proven of superior diagnostic capacity over traditional cultures [15], the aforementioned modality does present drawbacks [7, 16, 17] including but not limited to increased cost of equipment and cross-contamination risks [17]. For that reason, chemically based biofilm dislodgement techniques (i.e., dithiothreitol [DTT]) featuring the use of a reducing agent denaturing proteins [18] have been introduced. More specifically, the above technique consists of prosthesis placement in 0.1% w/v of DTT solution followed by stirring for 15 minutes [7, 18] and fluid culture [7]. Given the controversial findings in studies assessing the diagnostic accuracy of sonication and DTT assay, we designed a meta-analysis to compare their efficacy in establishing the diagnosis of a PJI against the Musculoskeletal Infection Society (MSIS) criteria [19] in patients subjected to revision joint replacement surgery.

Methods

Eligibility criteria

Comparative articles assessing the diagnostic yield of sonication and DTT assays were considered in the systematic review. Studies considering adult patients undergoing revision hip or knee arthroplasty for septic and aseptic reasons were eligible for inclusion. Of note, animal research and in vitro laboratory studies were discarded. Additional exclusion criteria included the mechanical failure of the prosthesis and periprosthetic fracture.

Literature search and data selection process

The databases of PubMed, Scopus, and Cochrane Central Register for Clinical Trials as well as trial registries were considered with the aim to identify relevant papers published until November 9th, 2021. The search terms considered in our strategy were as follows: “periprosthetic joint infect*,” “implant infect*,” “fracture-related infect*,” “FRI,” “osteomyelitis,” “diagnosis,” “diagnostic method,” “sonication,” “DTT,” and “dithiothreitol” (Supplemental file 1).

Two authors performed the literature research independently, without language restrictions. The duplicates were removed, and the titles and abstracts were scanned for eligibility. Subsequently, the full texts were also screened. In the case of discrepancies, the study selection was resolved via discussion.

Data extraction

Two reviewers extracted information from the enrolled studies independently. Abstracted information included study design, number, and demographics of the included participants, the definition of PJI/inclusion criteria, countries where the investigations were performed, administration of antibiotics before sonication/DTT, and quality of the included studies.

Outcome assessment

Pooled sensitivity and specificity of the included tests were assessed against the Musculoskeletal Infection Society (MSIS) criteria [19], to identify which test is most accurate in diagnosis of PJIs. In addition, diagnostic accuracy, with the corresponding confidence intervals, was calculated for each diagnostic test.

Statistics

For a study of this systematic review to qualify for meta-analysis, MSIS criteria should have been followed. What is
more, sonication/DTT fluid culture was favored over fluid PCR because there is no proven diagnostic benefit when employing the latter technique [20]. To represent graphically the sensitivity and specificity of the source articles in a cumulative manner, Review Manager software (version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was utilized to generate summary receiver operating characteristics (ROC) curves. Subsequently, pooled sensitivity and specificity were calculated, and Pearson’s chi-square was executed to compare the results between the two diagnostic techniques [21]. It should be noted that a p value of < 0.5 indicated statistical significance.

Furthermore, sensitivity analyses according to pretreatment with antibiotic administration and PCR implementation following sonication and DTT were considered. In addition, the quality of the included articles and randomization were accounted for.

Quality appraisal and certainty assessment

The methodological quality of the included studies was evaluated using the revised Quality Assessment of Diagnostic Accuracy Studies checklist (QUADAS-2) [22] and the Quality Assessment of Diagnostic Accuracy Studies-Comparative checklist (QUADAS-C) [23]. The QUADAS-2 tool consists of four separate domains (i.e., patient selection, index test, reference standard, and flow and timing). Each domain is assessed for risk of bias, and the first three domains are also assessed for concerns regarding applicability. The QUADAS-C tool was developed as an extension of QUADAS-2 to assess the risk of bias in comparative diagnostic accuracy studies, consisting of additional questions to each QUADAS-2 domain. For the reference standard domain, studies were deemed to be at low risk of bias should they assessed diagnostic accuracy against MSIS criteria. In case a source study was published before MSIS guidelines, then no additional information should have been retrieved from papers at a low, unclear, or high risk of bias. Two authors independently populated both QUADAS-2 and QUADAS-C tables and resolved any disagreement through discussion.

Results

Study selection and characteristics

The literature search yielded a total of 1484 records. Following deduplication, abstract, and full-text screening, 6 articles were eligible for inclusion in the systematic review with a total of 897 patients undergoing revision hip and knee replacements (Table 1). Of these articles, four were conducted in Europe [7, 24–26] and the other two in Asia [27, 28]. The MSIS criteria were followed in all but one study [29]. Ultimately, five articles were considered in the quantitative synthesis (that is meta-analysis) [7, 25–28] (Fig. 1).

Results of individual studies

Comparable diagnostic accuracy was demonstrated on the ROC curve (Fig. 2). In addition, the sensitivity of sonication in the individual studies varied between 0.57 and 0.93, and specificity ranged from 0.89 to 1 (Fig. 3). Likewise, for DTT, sensitivity was reported to be between 0.4 and 0.9, with specificity fluctuating around 1 (Fig. 3).

Meta-analysis results

The diagnostic accuracy of sonication and DTT against MSIS criteria was found to be 83.9% (95% CI 79.7 to 87.5%) and 86.7% (95% CI 82.7 to 90.1%), respectively. Pooled sensitivity and specificity showed no statistically significant differences between sonication and DTT (0.72 [95% CI 0.65 to 0.78] vs 0.7 [95% CI 0.62 to 0.77], p = 0.14; and 0.97 [95% CI 0.93 to 0.99] vs 0.99 [95% CI 0.97 to 1], p = 5.5, respectively). Regarding the results of our sensitivity analyses, we detected no significant differences compared to the findings of our primary analysis.

Risk of bias and level of certainty assessment

We applied the QUADAS-2 checklist and the QUADAS-C extension to assess the quality of the included studies. Overall, the quality of the studies as well as the certainty of evidence was deemed satisfactory (Table 2). More specifically, in the patient selection domain, all studies had a low risk of bias in the QUADAS-2 tool, whereas two studies had a high risk of bias [25, 26] and one had unclear risk bias [27] in the QUADAS-C tool. The limitation was that the studies either did not utilize a fully paired or randomized design or they failed to report it, respectively. For the index test domain, most of the studies were considered to have a low risk of bias, except for two studies that did not report sufficient microbiological details to enable a reliable evaluation of the implemented techniques [25, 26]. For the reference standard domain, no study was found to be at a high risk of bias. Regarding the flow and timing domain, all studies were found to have a low risk of bias. Overall, all the domains were judged to be at low risk of bias (Fig. 4).
It is undeniable that PJI represents a major cause of morbidity, leading to longer hospitalizations, implant failures, and revision joint replacement surgery [30, 31]. With the clinical presentation of PJI being variable, a high level of suspicion should be maintained by clinicians and, as such, all patients with a painful total joint arthroplasty should be considered infected unless proven otherwise [32]. To overcome the drawbacks of sonication, DTT has been introduced with satisfactory results. However, no clear evidence exists as to which of those tests yields superior diagnostic accuracy. Therefore, in the current paper, we sought to compare the diagnostic potential of sonication relative to DTT by using a meta-analysis study design. We demonstrated no statistically significant difference between the above techniques based upon pooled evidence from six papers comprising 726 implants from revision hip and knee replacements. It is worth mentioning that this finding remained unchanged when we controlled for the administration of antibiotic prophylaxis for PJI and randomization of included articles. The level of certainty provided in the present systematic review was deemed to be of moderate strength given the fact that non-randomized evidence was considered in addition to randomized data. Nevertheless, the included non-randomized papers were judged to be of high quality, thus allowing for safe conclusions to be drawn.

Establishing a PJI diagnosis

In this article, we utilized the Musculoskeletal Infection Society (MSIS) [4] criteria which represent the most widely accepted tool in this field nowadays. As per this diagnostic instrument, either one major criterion or 6 minor criteria should be fulfilled for this condition to be confirmed. In particular, either the presence of a sinus tract or at least two positive cultures of the same pathogen are necessary to establish a PJI. Due to the emergence of new diagnostic tests, an updated set of the criteria was then published by Parvizi et al. in 2018 [4], which resulted in improved sensitivity and specificity reaching 98% and 99.5%, respectively. To be more exact, elements of the revised criteria include elevated levels of serum ESR, CRP, or D-dimer, and synovial changes such as elevated CRP, A-defensin,
and leukocytosis [4]. Furthermore, inter-test interaction has been accounted for in this new set of criteria which are not merely based on intra-operative findings [33]. Despite this, the revised tool may still be inaccurate in particular subgroups including inflammatory and/or crystalline deposition arthropathy patients as well as cases secondary to adverse tissue reactions [4].

**Confound factors in PJI laboratory analyses**

We wish to underline that many microbiological parameters should be taken into account when comparing the diagnostic accuracy of two techniques including but not limited to the grade of infection, microbiological processing of the sonicated/chemical fluid as well as the biomaterial undergoing sonication/chemical processing. In addition, caution should be exercised when it comes to investigating spacers as the diagnostic potential of sonication in the presence of spacers appears to decrease [29, 34]. We would also like to draw readers’ attention to the fact that transportation, storage delay of samples, and/or inappropriate storage temperature do impact the detection of pathogens in PJIs [35].

**Transition to clinical practice**

Although this study showed no clinically meaningful difference between DTT and sonication, several parameters should be considered before making a balanced decision on which diagnostic technique should be adopted in everyday clinical practice. First of all, it is widely known that sonication is a long-lasting process requiring sophisticated equipment, not to mention the substantial risk of contamination of specimens during manual handling. Second, the cost of the devices used to mechanically dislodge bacteria from orthopaedic implants is considerable. On top of that, evidence has suggested that sonication exhibits a significant antibacterial effect in a time-dependent manner [36] which may influence the microbiological evaluation of the sonicated fluid. On the flip side, DTT is cheaper, bears a lower risk of cross-contamination, and exhibits a degree of satisfactory reproducibility [24]. More importantly, DTT is useful for biofilm dislodgement and pretreatment of biopsies due to involving chemical processing [37] of specimens. On the contrary, sonication is inherently not applicable to biopsies or liquids.

Furthermore, we underline that there is no need to omit pre-operative antibiotics when sonication has been planned, as there has been no scientific evidence to support the discontinuation of chemoprophylaxis before surgery [38]. This notion was confirmed by the present meta-analysis as we identified no significant difference when antibiotic pretreatment was accounted for in a sensitivity analysis.

What is more, avoiding common diagnostic and surgical errors such as incomplete evaluation of joint aspirate, suboptimal microbiological procedures including an insufficient number of periprosthetic samples, underdebridement, and overdebridement is crucial [39]. In tackling those technical
**Fig. 2** Receiver operating characteristics curve demonstrating comparable sensitivity and specificity between sonication and dithiothreitol. DTT, dithiothreitol

**Fig. 3** The sensitivity and specificity of individual studies are demonstrated. CI, confidence interval; DTT, dithiothreitol; FP, false positive; FN, false negative; TP, true positive; TN, true negative
problems, multidisciplinary (MDT) work coordinated by clinical microbiologists, orthopaedic surgeons, and infectious disease specialists is more likely to result in a successful outcome.

**Emerging techniques**

While the validity of diagnostic criteria for PJI has been well-documented, a diagnostic gold standard to determine the persistence of infection at reimplantation is still lacking. For that reason, there has been extensive ongoing research over the last years looking for more advantageous diagnostic techniques. To elaborate further, it has been accepted that molecular methods can lead to increased sensitivity as they require smaller microbial loads than traditional culture methods [40, 41]. This is especially true in the case of low virulence organisms [33]. However, despite the initial promising reports supporting the use of polymerase chain reaction (PCR), recent data have shown that the sensitivity of PCR might be lower compared to that of traditional cultures of sonicated fluid [20].

Looking at more modern modalities, metagenomic next-generation sequencing (mNGS) is a potentially revolutionary technique allowing for deoxyribonucleic acids sequencing from synovial fluid [42]. This innovative technique could be particularly useful not only in the setting of a culture-negative PJI but also in antimicrobial resistance characterization [42]. Early results have also indicated that mNGS yields superior results to traditional cultures of sonicated fluid [43]. However, bearing in mind the current increased cost of NGS, which can be as high as $500, its feasibility for routine use might be limited in the future.

**Study limitations**

We recognize that the present systematic review has a few limitations. First of all, we underline that this meta-analysis was conducted by synthesizing evidence not only from randomized but also from non-randomized research. Accordingly, the strength of recommendations provided by the present systematic review was deemed to be moderate, thus reflecting on the fact that complex data pooling does not compensate for the inclusion of level B evidence.

On top of that, clinical heterogeneity was detected given the methodological differences across the included papers. In particular, there was lack of standardization in the microbiological techniques of sonication and DTT which might have influenced the accuracy of meta-analysis results. To elaborate further, not only ultrasound parameters such as frequency [44], but also the number of cultures and growth
duration [45] varied across the source studies. With the aim to decrease the impact of clinical diversity on the results of our meta-analysis, we only pooled data from studies implementing the MSIS criteria. However, we wish to highlight that more reliable and widely accepted tools such as the WAISOT [46] and Infectious Diseases Society of America (IDSA) [47] exist. Moreover, all cases in the present retrospective paper referred to revision hip and knee joint surgery which demonstrates that evidence on fracture-related infection research is scarce and insufficient. Therefore, safe conclusions as to what the diagnostic accuracy of sonication and DTT is in the setting of fracture surgery cannot be made for the time being. Likewise, infection research on spacers appears to be limited to inform clinical decision-making.

Implications for future research

We recommend further research focused on diagnostic methods of fracture-related infection be conducted. What is more, we advocate future authors take into account the grade of infection when investigating the potential of various diagnostic techniques as there has been no sufficient literature looking at the influence of this confounding factor as of yet. Furthermore, the diagnostic outcomes in shoulder joint PJs should be further investigated as the particular clinical features and prevalence of *Cutibacterium acnes*-induced infections might exert a different influence [48].

Conclusions

It is widely accepted that both sonication and DTT are not as broadly used in the clinical practice as they should have been, despite their satisfactory diagnostic accuracy demonstrated in the present meta-analysis. The current study showed comparable diagnostic accuracy between sonication and DTT, and this conclusion was based on the certainty of moderate strength. Health policymakers should consider the ease of use, risk of contamination during manipulation, and cost, prior to determining which technique should be favored over the other by clinicians. Further optimization of the available diagnostic techniques is encouraged, given the clinical importance of correct identification of microorganisms implicated in PJs and fracture-related infections.

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Author contribution Mr. Tsikopoulos conceptualized the idea before conducting this study, handled the statistical software, and drafted the original manuscript. Mr. Christofilos and Mr. Gravalidis contributed to the data extraction and drafting of this meta-analysis. Mr. Sidiropoulos contributed to the literature search and quality assessment. Mr. Kitridis assessed the methodological quality of the papers and contributed to the literature search. Mr. Stoikos contributed to the data extraction and editing of the article. Professor Givissis and Professor Papioanannidou supervised and reviewed the paper. All authors have read and agreed to the current version of the manuscript. Mr Christofilos participated in this study while he was an intern at Professor Maniatis’s group at the University College London.

Data Availability  Not applicable.

Declarations

Ethics approval  We declare that ethical approval was not required for this study.

Consent to participate  Patients’ consent to participate was not applicable.

Consent for publication  Patients’ consent to publish was not applicable.

Competing interests  The authors declare no competing interests.

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Prospective registration: We have registered this study to PROSPERO (CRD42021290099), and PRISMA 2020 guidelines have been followed [49].

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