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ABSTRACT

Objectives: To evaluate the timing, duration and incidence of bacteremia following invasive dental procedures (IDPs) or activities of daily living (ADL).

Methods: Eight databases were searched for randomized (RCTs) and non-randomized controlled trials (nRCTs) evaluating bacteremia before and after IDPs or ADL in healthy individuals. The risk of bias was assessed by RoB 2.0 and ROBINS-I. For the meta-analysis, the primary outcomes were the timing and duration of bacteremia. The secondary outcome was the incidence of bacteremia, measuring the proportion of patients with bacteremia within 5 minutes after the end of the procedure compared to baseline.

Results: We included 64 nRCTs and 25 RCTs. Peak bacteremia occurred within 5 minutes after the procedure and then decreased over time. Dental extractions showed the highest incidence of bacteremia (62%-66%), followed by scaling and root planing(SRP) (44%-36%) and oral health procedures (OHP) (e.g., dental prophylaxis and dental probing without SRP) (27%-28%). Other ADL (flossing and chewing) (16%) and toothbrushing (8%-26%) resulted in bacteremia as well. The majority of studies had some concerns (RCTs) or moderate risk of bias (nRCTs).

Conclusion: Dental extractions, SRP and OHP, are associated with the highest frequency of bacteremia. Toothbrushing, flossing and chewing also caused bacteremia in lower frequency.

List of Abbreviations

ADL = Activities of daily living

AP = Antibiotic prophylaxis

IDPs = Invasive dental procedures

IE = Infective endocarditis

nRCT = Non-randomized controlled trial

OHP = Oral hygiene procedures

PCR = Polymerase chain reaction

PJI = Prosthetic joint infection

RCT = Randomized controlled trial

SRP = Scaling and/or root planing

VGS = Viridans group streptococci

INTRODUCTION

It was first suggested over 100 years ago that bacteremia from the oral cavity could cause infective endocarditis (IE) (Horder, 1909). Reports later reinforced that viridans group streptococci (VGS) related to poor oral hygiene and dental extractions caused IE (Thayer, 1926, Okell & Elliott, 1935). Microorganisms that enter the circulation constitute a bacteremia, and in the case of IE, they have the potential to colonize damaged endocardium, usually a heart valve, and cause IE (Cahill & Prendergast, 2015). With the advent of antibiotics, the American Heart Association, in 1955, first recommended that individuals at increased risk of IE should be given antibiotic prophylaxis (AP) before invasive dental procedures (IDPs) (Jones et al., 1955). Subsequently, orthopedic surgeons recommended that patients with prosthetic joints should receive AP when undergoing IDPs (Lattimer et al., 1979), despite evidence that, compared to IE, only a very small proportion of prosthetic joint infections (PJI) are caused by bacteria from the mouth (Thornhill et al., 2022). AP has been formally or informally recommended at different times to prevent other types of distant site infection. However, with the possible exception of IE, there is little evidence to link them to IDP-related bacteremia (Lockhart et al., 2013).

Despite these recommendations, there has never been a randomized controlled trial (RCT) to establish AP efficacy in preventing IE or PJI (Thornhill et al., 2015). Therefore, these recommendations are largely predicated on the evidence of numerous studies that have demonstrated AP efficacy in reducing the incidence or duration of bacteremia following IDPs, where bacteremia was used as a surrogate marker for IE risk. A recent systematic review reviewed these studies and demonstrated a significant effect of AP in reducing the incidence of post-IDP bacteremia (Cahill et al., 2017).

The lack of RCT evidence of AP efficacy, concerns about the risk of adverse reactions to AP antibiotics, and pressure to reduce the unnecessary use of antibiotics have led to a re-evaluation of AP guidelines and a reduction in the situations where AP is recommended (Habib et al., 2009, Habib et al., 2015, NICE, 2008, Wilson et al., 2007, Wilson et al., 2021). There has also been a growing recognition that oral activities of daily living (ADL), e.g., toothbrushing, particularly in individuals with poor oral hygiene, may result in bacteremia with oral bacterial species that could pose a greater threat to that caused by IDPs (Lockhart et al., 2008, Lockhart et al., 2009).

Although many studies have demonstrated bacteremia following different IDPs and ADL, there has never been a systematic review to compare the timing, duration and incidence of the bacteremia from these procedures. This information is important to allow clinicians and guideline committees to draw conclusions about the likelihood of different IDPs or ADL causing bacteremia and rank the invasiveness and potential risk from different procedures.

This study aimed to conduct a systematic review and meta-analysis to evaluate and compare the timing, duration and incidence of the bacteremia in healthy individuals from different types of IDP and ADL.

MATERIALS AND METHODS

Information sources

This review was conducted according to the PRISMA Statement 2020 (Page et al., 2021). The review question was CoCoPop for prevalence/ incidence reviews (Munn et al., 2018):

Context (Co): any IDP (e.g., dental extraction, scaling and root planing (SRP), oral surgery, polishing and other procedures involving manipulation of dental or mucosal tissues around the teeth); or ADL (e.g., toothbrushing, flossing, chewing and others) – measured before, during and after the procedure.

Condition (Co): bacteremia (number of individuals with positive blood samples for bacteremia)

Population (Pop): healthy individuals of any age and sex;

Design (D): RCTs and nRCTs.

Eligibility criteria

Inclusion criteria were: patients who underwent any IDP and/or ADL and studies reporting the number of individuals with bacteremia. The indication for a dental procedure is a clinical decision rather than a randomization process, so we included nRCTs as supplementary evidence when RCTs were unethical, unfeasible or unavailable (Cuello-Garcia et al., 2021). We also included RCTs because they have the highest level of evidence (Cuello-Garcia et al., 2021). When an RCT compared an intervention (e.g., antibiotics/antimicrobials vs. placebo), we included only the control or placebo group.

Exclusion criteria were: patients taking medication that could influence bacteremia (e.g. antibiotics); patients receiving oral antimicrobial agents (e.g. chlorhexidine mouthwash, povidone-iodine); patients with medical conditions requiring medication (e.g. heart disease, diabetes, cancer, under the risk of IE); studies reporting the number of bacterial cultures rather than number of individuals with bacteremia, and studies with no control/baseline blood sample. There were no restrictions regarding the date of publication and language.

Search strategy

The following databases were searched from inception to October 12, 2022, with no restrictions on language or date of publication: Medline (Ovid), Embase (Ovid), Cochrane Database of Systematic Reviews, CENTRAL, and Web of Science. Ongoing studies were searched on World Health Organization International Clinical Trials Registry Platform (ICTRP), Clinical Trials, and ISRCTN Controlled Trials. Grey literature was searched on Proquest Dissertation & Theses. A manual search was conducted on the reference list of included studies and relevant systematic reviews.

A search strategy was created for each database by an expert in systematic reviews (CCM) and validated by a librarian expert in systematic reviews. The search strategies are shown in Appendix Table 1. Studies were organized in Endnote X9 (Clarivate, USA).

Selection process

The references were transferred to Rayyan software for screening (https://rayyan.ai/cite). Titles, abstracts, and then full texts were independently screened by two reviewers from a pool of reviewers (CCM, MT, RTF, TC, MD, CK), all trained by the principal investigator (CCM) using a 5% sample of the studies. When reviewers' opinions differed, a consensus decision was made. If disagreement persisted, the principal investigator made the final decision.

Data collection process

Paired independent reviewers (CCM, PL, MT, RTF, CK, IGPOA) extracted data into an Excel spreadsheet (Microsoft Corporation, USA). Before data extraction, reviewers were trained with a set of two studies. In the case of disagreement, the reviewers came to a consensus. The principal investigator had the casting vote if a consensus could not be achieved.

The following data were extracted for each study: author, publication year, participants (sample, country of the sample, age, sex), setting, type of procedure, test used for bacteremia (culture versus molecular), use and type of anesthesia, use of skin disinfection, number of patients with bacteremia before and following the dental procedures, funding, and conflict of interest statements.

Data Items

For simplicity, procedures were grouped into eight major groups of similar procedure type:

1) ADL-toothbrushing with a manual or powered toothbrush. We kept toothbrushing apart from other ADL because it is the main form of daily oral hygiene;

2) Other ADL, including interdental cleaning procedures (dental flossing or use of stimudents, toothpicks, oral irrigation devices) and chewing;
3) Dental extractions, to include single, multiple or third molar extractions
4) Oral surgery, including cleft palate, piezoelectric surgery, periodontal surgery, implant surgery or osteosynthesis plate removal;
5) Scaling and/or root planing (SRP), either manual or ultrasonic;
6) Orthodontic procedures, including banding or debanding orthodontic fixed or removable appliances; archwire adjustment, orthodontic mini-implant removal, or orthodontic separator placement;
7) Oral hygiene procedures (OHP), including dental prophylaxis using a rubber cup and hand piece (without scaling) or periodontal probing (without SRP);
8) Other procedures, including dental restorative procedures, use of slow and fast drill for dentine removal performed before restorations, procedures with a risk of gingival bleeding such as placement of a rubber dam clamp or matrix band wedge between teeth, impression taking, suture removal, anesthetic injection, or endodontic treatment;

Studies reported different time points for blood sample collection. They were grouped as follows: baseline (immediately before the procedure), within 5 minutes after the end of the procedure, from 6 to 20 minutes after the end of the procedure, from 30 to 60 minutes after the end of the procedure, and more than 2 hours after the end of the procedure.

Study risk of bias assessment

Three reviewers assessed the risk of bias (CCM, RTF, IGPOA) using the Cochrane "revised tool to assess the risk of bias of randomized studies" (RoB 2.0) (Sterne et al., 2019) and the "assessing risk of bias in a non-randomized study" tool (ROBINS-I) (Sterne et al., 2016). Reviewers were first trained by the principal investigator with a set of studies of each design. Disagreements were solved by discussion until a consensus was reached. The reviewers underwent two more training rounds with other studies until they could complete the assessment reproducibly. After that, each reviewer assessed the risk of bias of a set of studies that were cross-checked by another reviewer.

Effect measures

The primary outcomes were the timing and duration of bacteremia. For each procedure studied, we extracted data on the number of individuals with positive blood samples for bacteremia at each time point (timing). At each time point, the proportion of positive blood samples (duration) was plotted using Excel (Microsoft).

The secondary outcome was the overall incidence of bacteremia, calculated from baseline and within 5 minutes after the end of the procedure. This decision was made after analyzing the timing and duration of bacteremia and observing that the peak of bacteremia occurred within 5 minutes after the end of the procedure. For the overall incidence of bacteremia, we calculated the difference in the proportion of patients with bacteremia within 5 minutes after the end of the procedure compared to the proportion at baseline. We calculated the 95% confidence intervals (CI) for all estimates.

Synthesis of methods

Data were separately analyzed for RCTs and nRCTs and entered in STATA software (version 12, StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). A meta-analysis of proportion was performed for both the timing and duration of bacteremia and the overall incidence of bacteremia. For studies reporting interventions with the same oral procedure, we merged the number of incidences and sample size. The metapro STATA command was used with Freeman-Tukey double arcsine transformation. This permits the inclusion of studies with zero prevalence/incidence (Doi & Xu, 2021). In all cases, heterogeneity was calculated through Cochran's Q-test, and the proportion of the total variation caused by heterogeneity was quantified using I^2 (Deeks et al., 2022).

A sub-group analysis was performed for risk of bias, method of bacteremia detection (culture or molecular) and presence/absence of baseline bacteremia samples (studies that reported some patients with baseline bacteremia or studies that reported no baseline bacteremia for all patients). The difference in effect estimates between subgroups and the overall incidence was tested by a bivariate test with significance set at p-value <0.05

RESULTS

Study selection

Eighty-nine studies were included in the systematic review: 64 nRCTs and 25 RCTs (Appendix Figure 1). Included studies are shown in Appendix References 1 and excluded studies (along with the reason) in Appendix Table 2.

Study characteristics

Appendix Table 3 details the study characteristics according to study type (nRCTs, RCTs and all studies). Most were published after 2000 (29.2% between 2000-2009 and 30.3% after 2010). Most were conducted with populations from Europe (33.7%), North America (23.6%) or the Middle East (12.4%). Most were published in English (97.8%) and had no conflicts of interest statement (74.2%) or source of funding (57.3%). The most common setting was a dental school/hospital (66.3%), and 68.5% of studies reported disinfecting the skin before venipuncture. Although age groups varied, 53.9% of studies included only adults. The total sample size comprised 4,406 participants. Intervention arms were evenly distributed between nRCTs and RCTs and included studies with one (68.5%), two (18.0%), three (7.9%), or four (5.6%) intervention arms. In total, 137 oral procedures were studied (Appendix Table 4).

Risk of bias

For nRCTs, confounding represented the main risk of bias, and only one study reported having a research protocol before conducting the study. Thus, almost all studies had a problem due to bias in the selection of the reported outcome (Appendix Figures 2 and 3). For RCTs, the main source of bias was the randomization process, deviations from the intended intervention and measurement of outcomes. Only two RCTs reported having a protocol before starting the study (Appendix Figures 4 and 5).

Results synthesis

All procedures studied had the potential to cause bacteremia. Not all studies reported all time points (Figures 1a,b). The timing and duration of bacteremia are best illustrated by the nRCTs because of the larger number of nRCTs. The majority of studies had baseline bacteremia equal to zero. Some procedures had some degree of contamination at baseline, most prominent for the orthodontic procedure and other procedures (RCTs) (please, see details in Appendix Table 5). For both RCTs and nRCTs, peak bacteremia was within 5 minutes after the end of the procedure. Bacteremia incidence then decreased slowly for up to 2 hours. For both nRCTs and RCTs, dental extractions exhibited the highest incidence of bacteremia. Appendix Table 5 and Appendix Forest plots 1P-64P detail the meta-analysis for timing and duration of bacteremia following each procedure type.

Table 1 shows the overall incidence of bacteremia for each procedure. In the nRCTs, this was highest for dental extractions (66%; 95%CI: 57-74; I^2: 90.8%), followed by SRP (44%; 95%CI: 31-58, I^2: 86.5%), oral surgery (27%; 95%CI: 13-43, I^2: 79.9%) and OHP (27%, 95%CI: 19-36, I^2: 0%). Other ADL (16%; 95%CI: 7-29, I^2: 88.0%), orthodontic procedures (14%; 95%CI: 6-24, I^2: 76.9%), ADL-toothbrushing (8%; 95%CI: 1-19, I^2: 87.2%) and other procedures (4%; 95%CI: 0-17, I^2: 62.6%) had a lower bacteremia incidence.

There were fewer RCTs available for analysis, and some procedure types (other ADL and oral surgery) were not covered (Table 1). Nonetheless, the incidence of bacteremia following extractions was also the highest and with a similar frequency to that found in the nRCTs (62%; 95%CI: 44-78, I^2: 87.3%). This was followed by SRP (36%; 95%CI: 27-46, I^2:

0%) and OHP (28%; 95%CI: 21-36, I^2: 0%). However, the incidence of bacteremia identified in the RCTs following ADL-toothbrushing (26%; 95%CI: 13-41, I^2: 80.3%), orthodontic procedures (26%; 95%CI: 20-33, I^2: not estimated) and other procedures (25%; 95%CI: 12-41, I^2: 83.2%) was higher than in the nRCTs. Overall, however, there were similar results between the RCTs and nRCTs regarding the procedures most likely to induce bacteremia.

There was no statistically significant difference in effect estimates between subgroups ($p>0.05$). Appendix Forest plots 1I-38I detail the meta-analysis for incidence.

DISCUSSION

Most procedures had the potential to cause bacteremia. Although there were significant differences in the incidence of bacteremia following different procedures, the timing of the bacteremia followed a similar pattern. Depending on the methodology used to identify bacteremia and the care taken to sample in a sterile manner, most studies found that baseline blood samples were negative for bacteria. In almost all cases, peak bacteremia frequency was detected within 5 minutes after the end of the procedure. The level of bacteremia then decreased significantly between 6 and 20 minutes and, with few exceptions, disappeared after 2 hours. These results suggest that the initial clearance of bacteria from the blood circulation is fast. This is consistent with the findings of research into the mechanisms of bacterial clearance from the circulation (Broadley et al., 2016 , Minasyan, 2016).

Analysis of the overall incidence of bacteremia revealed a hierarchy of procedures. There was an agreement between the nRCT and RCTs concerning procedures most likely to result in bacteremia (dental extractions, SRP and OHP). However, RCTs demonstrated a higher bacteremia incidence than nRCTs for toothbrushing, orthodontic and other procedures.

This information is helpful for clinicians and guideline committees as it indicates the relative risk of bacteremia following different types of procedures. Currently, most AP guidelines state that any procedure that involves the manipulation of the gingival or periapical tissues should be considered invasive and be covered by AP for those at high-risk (Habib et al., 2015, Wilson et al., 2007, Wilson et al., 2021). However, some procedures (particularly extractions, SRP, OHP and surgical procedures) are likely to pose a greater incidence of bacteremia than others.

The effect of risk of bias and the presence/absence of bacteria at baseline on study outcomes was investigated in the sub-group analyses. There was no statistically significant difference between effect estimates in each subgroup for nRCTs and RCTs, although many studies had a serious, critical or high risk of bias.

There were also differences in the techniques used for bacteremia identification. Some studies used molecular methods for identifying the presence of bacteria, while others used culture techniques. There are advantages and disadvantages to the different techniques available. Most studies used Bactec (Becton Dickinson) or lysis filtration culture methods. Molecular techniques were not available at the time of the older studies, were less widely available until recent years, and only three studies included in the meta-analysis used them (Ashare et al., 2009, Crasta et al., 2009, Perez-Chaparro et al., 2009). Molecular techniques have higher sensitivity and a lower limit of detection compared to culture methods; that is, they are more likely to identify the presence of bacteremia than culture methods (Reis et al., 2018). Furthermore, molecular methods do not distinguish between live and dead bacteria, while culture techniques only identify live bacteria. Molecular methods can, therefore, overestimate the presence and risks of bacteremia, although there is a lack of statistically significant difference between subgroups. This is a particular problem for studies on AP efficacy since molecular techniques will continue to register bacteria recently killed by antibiotics (Reis et al., 2018).

A problem with all methods used for detecting bacteremia is that none are reliably able to determine the bacterial magnitude or load in the circulation. Unfortunately, an accurate means of determining bacteremia magnitude is not readily available. It is important information to have in the determination of the invasiveness of a procedure, the potential risks to the patient, and the impact of AP given to reduce the bacteremia. It can be speculated that the duration and perhaps the incidence of a bacteremia may be influenced by the magnitude, but this has not been validated. Cell lysis filtration methods are commonly used to determine magnitude, but they suffer from high rates of bacterial contaminants (e.g., staphylococci) and are not good at detecting streptococcal species (important in oral bacteremia studies). Quantitative PCR methods have been used to determine bacteremia magnitude. However, the high sensitivity of PCR methods, ability to detect difficult to culture and previously uncultivatable bacteria, and inability to distinguish live from dead bacteria, can lead to false positive or inaccurate results, including the over-estimation of bacterial load. These problems make evaluating the results difficult, particularly when comparing with culture methods. However, one study that used quantitative PCR reported that the incidence and magnitude of bacteremia were larger following dental extractions than after supra-gingival scaling (Reis et al., 2018).

Limitations

A wide variety of different IDPs and ADL were investigated, and only one study existed for some procedures. Therefore, we grouped procedures into eight categories, and we may have lost detail for some individual procedures. E.g., for 42 extraction procedures, 10% were single extraction, and 21% were third molar extraction (partially or fully impacted, or fully erupted). Also, 39% of extractions did not detail the operative procedure, and many other studies reported the extraction of single or multiple teeth. Thus, it was impossible to subgroup dental extractions, despite the differences in complexity. Moreover, we decided to create the oral surgery group, excluding dental extractions. Although the degree of invasiveness, the oral surgery group intended to group less contaminated operative procedures than dental extractions. Finally, we tried to group some procedures according to specialties, such as orthodontic procedures and other procedures that included all restorative procedures. However, the diversity of procedures included in some categories (e.g., other procedures) indicates that more studies are needed to determine outcomes for these.

The studies differed widely in methodology. Sterility and aseptic technique are essential to avoid contamination, particularly the introduction of skin bacteria into the culture media. Some studies had a thorough explanation of the methods used to ensure aseptic blood sampling. Unfortunately, we could not subgroup the analysis between studies reporting aseptic methods or not, as many studies made no mention of this. Due to the efficiency with which bacteria are removed from the circulation, baseline blood samples are expected to be negative. The presence of baseline bacteremia in some studies raises questions about sterile technique, especially when common skin commensals were among the organisms identified.

Very few studies took account of the effect that oral hygiene status might have on bacteremia following the different procedures. Nonetheless, there is some evidence that individuals with poor oral hygiene are more likely to develop bacteremia with organisms that could lead to IE following both dental procedures (e.g., extractions) and ADL (e.g., toothbrushing) (Lockhart et al., 2009).

Implications for practice and future studies

These studies suggest bacteremia can occur following ADL, including toothbrushing. However, IDPs, particularly extractions, SRP, OHP and other oral surgery procedures, are more likely to result in a post-procedure bacteremia. Given that daily activities occur with far higher frequency than IDPs, there is a developing consensus that improvement in oral hygiene may be as, if not more, important in preventing IE than providing AP for people at risk of IE undergoing IDPs. To understand this better, we need to know more about the magnitude of bacteremia produced by IDPs, toothbrushing and other ADL. Individual factors, particularly standards of oral hygiene, are likely to play an important role in increasing or decreasing both the incidence and magnitude (and hence risk of IE) associated with IDPs and ADL. Although the studies in this systematic review did not analyze oral hygiene, maintenance of good oral hygiene is likely to be important in minimizing the risk of bacteremia following both ADL and IDP and should be encouraged.

CONCLUSION

There is a rapid onset of bacteremia caused by different IDPs and ADL. Independent of procedure type, bacteremia peaks within 5 minutes after completing the procedure before decreasing over time. The overall incidence of bacteremia was highest following dental extractions, oral surgery procedures, SRP and OHP. The meta-analysis also demonstrated a significant, albeit lower, incidence of bacteremia following toothbrushing and other oral ADL.

REGISTRATION AND PROTOCOL

This systematic review was registered *a priori* at PROSPERO database under the record #CRD42020172632. The protocol planned a set of pairwise meta-analyses comparing pairs of different oral procedures using the Review Manager. In addition, the protocol planned to assess the certainty of the evidence using the GRADE approach. (Zhang et al., 2018) Due to the lack of studies comparing the same oral procedures, these analyses were not feasible. Instead, we descriptively analyzed the timing and duration of bacteremia using a meta-analysis of proportion through STATA software.

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CONFLICT OF INTERESTS

The authors have no conflict of interests.

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FIGURE LEGENDS

Figure 1. a. Timing and duration of bacteremia among nRCTs. **b.** Timing and duration of bacteremia among RCTs.