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Review Analysis and Evaluation // Diagnosis/Treatment/Prognosis

DECLARATIVE TITLE:

Amoxicillin is the most effective oral antibiotic prophylaxis regimen for reducing post-invasive dental procedure bacteremia

REVIEWER: Martin Thornhill

PURPOSE/QUESTION:

Which antibiotic prophylaxis regimens are most effective at reducing post-invasive dental procedure bacteremia?

ARTICLE TITLE AND BIBLIOGRAPHIC INFORMATION:

Zeng BS, Lin SY, Tu YK, Wu YC, Stubbs B, Liang CS, Yeh TC, Chen TY, Carvalho AF, Lin PY, Lei WT, Hsu CW, Chen YW, Tseng PT, Chen CH. Prevention of Postdental Procedure Bacteremia: A Network Meta-analysis. J Dent Res. 2019 Oct;98(11):1204-1210. doi: 10.1177/0022034519870466. Epub 2019 Aug 30. PubMed PMID: 31469596.

Strength of Recommendation Taxonomy (SORT) Grading

STRENGTH OF RECOMMENDATION GRADE:

Grade C Consensus, disease-oriented evidence, usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention, or screening.

LEVEL OF EVIDENCE:

Level 2 Limited-quality, patient-oriented evidence

SOURCE OF FUNDING:

There were no sources of funding associated with the work.

TYPE OF STUDY/DESIGN:

Systematic review with meta-analysis of data

KEY WORDS

Prophylaxis, dental procedure, antibiotics, antimicrobial, intervention, endocarditis, meta-analysis

Summary

Subjects or Study Selection:

This systematic review compared the efficacy of different antibiotic prophylaxis (AP) regimens for reducing the incidence of post-invasive dental procedure bacteremia. The key words “prevention”, “bacteremia” and “dental procedure” were used to search ClinicalKey, Cochrane CENTRAL, Embase, ProQuest, PubMed, ScienceDirect, Web of Science and ClinialTrials.gov from inception to December 4, 2018, and identified 217 citations. After exclusions, 24 studies, covering 2,147 participants, were identified that met the inclusion criteria of reporting randomized controlled trials (RCT) of placebo- or active-controlled design (comparison of different prophylactic interventions) and included adult or pediatric participants. To make these comparisons, a network meta-analysis (NMA) also known as a multiple treatment comparison meta-analysis was performed. This is a meta-analysis in which multiple treatments, that is, three or more, are compared using both direct comparisons of interventions within RCT and indirect comparisons across trials based on a common comparator.[1]

Key Study Factor:

The main purpose of AP before invasive dental procedures is to prevent infective endocarditis (IE) in those at high-risk of the condition. It may also be used to prevent other distant site infections e.g. prosthetic joint infections, in those at risk. Ideally, the efficacy of AP would be tested in RCT that compared any reduction in the incidence of IE following invasive dental procedures performed with and without AP cover. Since the incidence of IE is low, and studies would need to be performed on individuals at high-risk of IE, ethical concerns and the size and cost of such studies have precluded any to date. As a surrogate for such studies, RCT measuring the effect of AP on the incidence of bacteremia following invasive dental procedures have been used instead, and these are the type of study evaluated in this systematic review. The data, therefore, while important, highly clinically relevant and among the best currently available, may not directly translate to efficacy in preventing IE.

Main Outcome Measure:

The main outcome evaluated was the reduction in incidence of post-invasive dental procedure bacteremia that occurred with different AP regimens.

Main Results:

The study found that the oral AP regimen that was most effective in reducing overall post-procedural bacteremia was 3g of amoxicillin (Odds ratio [OR] 0.1; 95% confidence interval [CI], 0.02-0.44). An OR <1 indicates that there is less incidence of post-procedural bacteremia than with placebo/control. The smaller the OR, the more effective that regimen is in reducing post-procedural bacteremia, and the reduction is likely to be significant if the CI does not include 1. The next most effective regimen was 2g of amoxicillin (OR, 0.16, 95% CI, 0.05-0.54). For intravenous regimens, 1,000/200 mg of amoxicillin/clavulanate provided the least

incidence of post-procedural bacteremia (OR, 0.03, 95% CI, 0.00-0.63). Some other intravenous regimens were also effective.

Conclusions:

This NMA suggests that 3g oral amoxicillin and 1,000/200 mg intravenous amoxicillin/clavulanate are likely the best antibiotic prophylaxis interventions for preventing post invasive dental procedure bacteremia.

Commentary and Analysis

Infective endocarditis (IE) is an infection of heart valves. Affected individuals are acutely ill and often require intensive care. Treatment is with intravenous antibiotics but ~50% also require surgical replacement of one or more heart valves. First year mortality is ~30% and survivors suffer serious lifelong complications and increased risk of further IE.[2]

Oral bacteria account for 35-45% of IE cases.[3] However, there is controversy about the contribution made by invasive dental procedures and daily activities, e.g. toothbrushing, flossing and mastication, to the development of oral bacterial IE.[4] Currently, apart from maintaining good oral hygiene, the only active IE prevention measure recommended by most guideline committees around the world is the use of antibiotic prophylaxis (AP) before invasive dental procedures for those at highest-risk, even though there are no randomized controlled trial (RCT) data to support its use.[3, 4] This is because ethical concerns and the size and cost of RCT has prevented their use to test AP efficacy to date. As a consequence, researchers have had to resort to less compelling observational studies and RCT using surrogate markers for IE, such as post-procedural bacteremia, to evaluate AP efficacy.

Bacteremia studies are not without their problems. Ideally, one would like to know how much the number of oral bacteria with the capacity to cause IE that are released into the circulation following a dental procedure is reduced by AP compared to no or placebo prophylaxis. However, techniques that can quantify the bacterial load and identify those species that cause IE have only become available comparatively recently. Hence, most bacteremia studies report not the size but the frequency with which a bacteremia was detected, i.e. how often a bacteremia exceeded the lower detection limits of the method used. Different methods have different lower detection limits, and most studies have not focused on those oral bacteria capable of causing IE. Therefore, there are significant methodological difference between studies.

A recent systematic review and meta-analysis of 21 AP clinical trials found AP to be effective in reducing overall post-procedural bacteremia (risk ratio 0.53, 95% CI 0.49-0.57), but noted that methodological issues mean that post-procedural bacteremia may not always be a good surrogate endpoint for IE.[5] Nonetheless, this and the current study[6] both conclude that AP is likely to be effective in reducing post-procedural bacteremia. The current study goes a step further though, by performing a NMA to compare the efficacy of different AP regimens in reducing post-procedural

bacteremia.[6] Although the results should be treated with some caution, they will be of considerable interest to clinicians and guideline committees world-wide.

The finding that amoxicillin is the most effective oral AP preparation will reassure many. The finding that amoxicillin 3g may provide better protection than 2g, however, should cause guideline committees that recommend the lower dose to revaluate their dosage recommendations, particularly as the higher dose is arguably less likely to generate antibiotic resistance and has been shown to be associated with a very low risk of adverse-reactions.[7]

Data from this study is less reassuring about the efficacy of AP alternatives for those allergic to amoxicillin. Neither clindamycin 600mg (OR 0.61, 95% CI 0.21-1.78) nor azithromycin 500mg (OR 0.35, 95% CI 0.07-1.68) showed significant overall efficacy. This reinforces the importance of labelling only those with true penicillin allergy as penicillin allergic, particularly given the worse adverse-reaction profile of amoxicillin alternatives, specifically clindamycin.[7, 8]

For intravenous use, 1,000/200mg amoxicillin/clavulanate (OR 0.03, 95% CI 0.00-0.63) had greatest overall efficacy, although other IV regimens were also effective.

NMA is a complex methodology that allows multi-directional comparisons to be made between treatment based on studies that will largely have comparisons only made between one treatment and placebo, or one treatment and another.[1] This can be incredibly helpful for clinicians who have to choose between multiple treatment options, many of which will not have been formally tested in a study. However, NMA methodology assumes homogeneity of methodology between studies and this may not be the case when different dental procedures, methods of anaesthesia/analgesia and patient populations have been studied, and different bacteremia detection methods used. The 95%CI will also be larger for AP regimens where few studies exist. A degree of caution should be exercised, therefore, when interpreting the results. Nonetheless, the data on overall AP efficacy is compelling and particularly strong for oral amoxicillin efficacy.

In conclusion, this study provides important new evidence that oral amoxicillin and IV amoxicillin/clavulanate are likely the most effective prophylactic interventions for reducing post-invasive dental procedure bacteremia.

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