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Review

A *meta*-analysis of randomized trials assessing the effects of probiotic preparations on oral candidiasis in the elderly

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ABSTRACT

Objective: Oral candidiasis is the most common fungal infection and can be attributed in part to dysbiosis, an imbalance in the resident oral microflora. Therefore, probiotics, which counter pathogenic microorganisms through competitive, antagonistic, and immunological effects, have been used by some clinicians. To date, the effect of probiotics in preventing oral candidiasis in the elderly is controversial. A systematic review that summarizes and critically appraises the available clinical trials is therefore necessary.

Design: Electronic searches were performed using the Pubmed, Embase, and Cochrane databases. Only randomized controlled trials were included. The Mantel–Haenszel test was used to appraise the odds ratio for single studies and an overall combined odds ratio for all studies combined.

Results: Three studies matched the inclusion criteria and were homogeneous. The data from one study that estimated candida growth from plaque and saliva were subdivided, thus a total of four studies with 595 people were included. The overall combined odds ratio was 0.54 (95% CI: 0.38–0.77). Three studies provided that active treatment reduced the risk of oral candidiasis more than placebo: Hatakka et al. (OR 0.51, 95% CI 0.26 to 0.97; 192 participants, plaque); Kraft-Bodi et al. (OR 0.46, 95% CI 0.24 to 0.86; 174 participants, palatal); Kraft-Bodi et al. (OR 0.50, 95% CI 0.26 to 0.98; 174 participants, plaque), while one study provided reverse result: Ishikawa et al. (OR 1.24, 95% CI 0.48 to 3.58; 55 participants, saliva).

Conclusion: Probiotics have a preventative effect on oral candidiasis in the elderly.

1. Introduction

The incidence of oral candidiasis, caused by a commensal and opportunistic pathogenic fungus, called candida, has escalated markedly in recent years, especially in the elderly population (Williams & Lewis, 2011). Oral candidiasis, which is attributed in part to dysbiosis, accounts for a major proportion of fungal infections found in the oral cavity (Coronado-Castellote & Jimenez-Soriano, 2013). A review of different techniques for diagnosis of oral candidiasis reported a dysbiosis prevalence in at least 87% of oral candidiasis cases (Coronado-Castellote & Jimenez-Soriano, 2013). Oral dysbiosis mostly results from the use of medicine, such as broad-spectrum antibiotics and immunosuppressive agents, while systemic disease, such as diabetes and malignancies, age (children or the elderly), and AIDS are other systemic factors (Lalla, Patton, & Dongari-Bagtzoglou, 2013; Patil, Rao, Majumdar, & Anil, 2015). Overgrowth of candida in the oral cavity can lead to local discomfort, such as burning pain and altered taste sensation. More seriously, if the infection spreads through the bloodstream or upper gastrointestinal tract in immune-compromised patients, infection can lead to significant morbidity and mortality (Akpan & Morgan, 2002).

To date, systemic and local antifungal agents have proven to be successful in preventing mucosal and invasive fungal infections. However, antifungal drugs have marked side effects, such as hepatic and renal toxicity, nausea, vomiting, and diarrhea (Oliver, Dhaliwal, Theaker, & Pemberton, 2004). The unpleasant taste of nystatin is also a drawback. Furthermore, the increased number of resistant strains and antifungal prophylaxis remains problematic (Sardi, Almeida, & Mendes Giannini, 2011; Sardi, Scorzoni, Bernardi, Fusco-Almeida, & Mendes Giannini, 2013). As elderly individuals are usually weak and wear dentures, oral candidiasis frequently recurs or is chronic. Thus, agents with low toxicity or no side effects, and effective against candida are needed (Pfaller, 2012).

Probiotics, the vast numbers of microorganisms dwelling in the

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mucous membrane of the host, are safe and beneficial to the host (Cremonini et al., 2002). The definition of probiotics in this study was somewhat vague, since it comprises different species with different characteristics. The most commonly used probiotic material is yogurt (Fisberg & Machado, 2015), which is generally used in daily life (Sanders, 2008). *Lactobacilli (L. rhamnosus HS 111, L. acidophilus HS101)* and bifidobacteria, termed "bifidus", are the species most commonly used as probiotics (Saarela, Mogensen, Fonden, Matto, & Mattila-Sandholm, 2000). To a lesser extent, *Enterococci*, *Streptococci, Propionibacterium, Lactococcus* and *Saccharomyces* spp. have also been used (Saarela et al., 2000). Previous studies have reported the positive effects of probiotics in systemic diseases, such as candida vaginitis (De Seta et al., 2014), dermatophytosis (Kumar, Mahajan, & Kamra, 2014), gastrointestinal infection (Hayama et al., 2014), and colon carcinoma (Wang, Zhang, & Shan, 2015; Zitvogel et al., 2015). Additionally, probiotics may assist the regulation of blood pressure (Khalesi, Sun, Buys, & Jayasinghe, 2014) and cholesterol levels (Jones, Tomaro-Duchesneau, Martoni, & Prakash, 2013). In dentistry, probiotics were first used for caries prevention, gingivitis, and periodontal conditions (Twetman, 2012). However, to date, the effect of probiotic agents on preventing oral candidiasis in the elderly population is conflicting (Hatakka et al., 2007; Ishikawa et al., 2015; Kraft-Bodi, Jorgensen, Keller, Kragelund, & Twetman, 2015). Probiotics may be effective in preventing candida-associated stomatitis in the elderly population according to Hatakka et al. and Kraft-Bodi et al., but adverse effects are also reported by Ishikawa et al. It is therefore essential to conduct a systematic review to summarize and critically appraise the available trials.

Hence, we here performed a *meta*-analysis and systematic review of the literature to assess the efficacy of probiotics in preventing candida-associated stomatitis in the elderly population.

2. Methods

2.1. Search strategy

This *meta*-analysis was conducted according to Reporting Items for Systematic Reviews and Meta-analyses recommendations (David Moher, Jennifer, Douglas, & the PRISMA Group, 2009), and was registered through the international prospective systematic review register system (registration number: CRD42016035863). A computer-based search of PubMed/Medline, EMBASE, and the Cochrane Library database was performed to obtain titles and abstracts of studies using the following search strategy: ((((((((((((Thrush[Title/Abstract]) OR Candidiases, Oral[Title/Abstract]) OR Oral Candidiases[Title/Abstract]) OR Oral Candidiasis[Title/Abstract]) OR Moniliasis, Oral[Title/Abstract]) OR Moniliases, Oral[Title/Abstract]) OR Oral Moniliases[Title/Abstract]) OR Oral Moniliasis[Title/Abstract])) OR "Candidiasis, Oral"[Mesh])) AND ((elderly[Title/Abstract]) OR "Aged"[Mesh])) AND ((probiotic[Title/Abstract]) OR "Probiotics"[Mesh])) AND ((randomized controlled trial[publication type] OR controlled clinical trial [publication type] OR randomized[title/abstract] OR placebo[title/abstract] OR randomly[title/abstract] OR trail[title/abstract] OR groups[title/abstract])) (PubMed), ('candidiasis'/exp OR 'candidas' OR 'monilia' OR 'monilias' OR 'torulopsis utilis' OR 'candida utilis') AND ('probiotic agent'/exp OR 'probiotic' OR 'probiotics') AND ('aged'/exp OR 'elderly')AND ('randomized controlled trial'/exp)(EMBASE), and ([candida] OR candidiasis: ti,ab,kw OR Candidiases: ti,ab,kw OR Thrush: ti,ab,kw OR Moniliasis: ti,ab,kw OR Moniliases: ti,ab,kw) AND ([probiotics] OR probiotics: ti,ab,kw) AND ([Aged]OR elderly: ti,ab,kw). (Cochrane Library). We also conducted manual searches of the reference lists of the identified papers as an adjunctive search. The search was limited to papers published in English from January 2004 to January 2017.

2.2. Study selection criteria

The inclusion criteria were as follows. (1) Randomized controlled trials that compared probiotics (at any dosage and in any form) with a placebo. (2) Subjects who were independent "healthy" elderly, aged 60–102 years, without restriction on patients' sex or race. (3) Studies with a substantive interventional aim of preventing oral candida infection by using probiotics, and reported on candidiasis that was assessed using the reference standard (i.e., by evaluating the viable counts of candida). (4) Studies that allowed the construction of at least one 2×2 table of test performance by extracting data from the study. (5) Studies that included more than 30 patients. Studies were excluded if the subjects included patients who infected with human immunodeficiency virus, had recently undergone organ transplants, or had heart disease.

2.3. Data extraction

Initially, two investigators independently selected and evaluated the abstracts that were found to meet the inclusion and exclusion criteria approximately. Once an investigator regarded the reference as eligible, the full-text article was obtained for a complete assessment. Secondly, two investigators independently evaluated the eligibility and quality of the full-text articles according to the inclusion and exclusion criteria. Another reviewer resolved discrepancies between these two reviewers based on the screening procedures. After excluding studies with serious design flaws, three articles encompassing four parameters were collected for the initial analysis (Fig. 1).

2.4. Risk of bias of the included studies

Two reviewers evaluated the risk of bias of the individual studies independently. The approach we used for assessing risk of bias in included studies was recommended by Cochrane reviews. According to Cochrane handbook a bias is a systematic error in results or inferences, which means that multiple replication of the same study would reach the wrong answer on average(Higgins, Deeks, Altman, & on behalf of the Cochrane Statistical Methods Group, 2011). The biases that were considered were as follows: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias) (Fig. 2).

2.5. Data synthesis and analysis

Review manager 5.2 (Cochrane IMS, Oxford, UK) was used to analyze reports and the odds ratios (ORs) were determined.

2.6. Statistical analysis

The data in each trial were extracted, and 2×2 tables (e.g., probiotics/comparison vs. high/low counts of candida) were constructed to calculate the relation between the viable counts of candida and the use of probiotics. We estimated the beneficial effect of using probiotics on oral candidiasis by means of OR and their respective 95% confidence intervals (CIs). Then, these estimates were combined using the Mantel–Haenszel method. Heterogeneity across trials was quantified with the I^2 metric. Since less than 10 studies were included, a funnel scatterplot was not used to estimate possible publication bias (Ioannidis, 2008).