Clinical effectiveness of *Lactobacillus reuteri* in the treatment of peri-implant diseases: a systematic review and meta-analysis

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In the last decades, the presence of peri-implant diseases (PD) has increased. One of the therapies currently used is probiotics with Lactobacillus reuteri (LR). The aim of this article is to determinate, through a systematic review and meta-analysis, the clinical effectiveness of LR in the treatment of PD. We searched the literature until January 2021, in the biomedical databases: Pubmed, Embase, Scielo, Science Direct, Scopus, SIGLE, LILACS, Google Scholar and Cochrane Central Registry of Clinical Trials. The selection criteria of the studies were: randomized controlled clinical trials, without language and time restriction, reporting the clinical effects (depth to probing, plaque index and bleeding index) of the LR in the PD treatment. The risk of study bias was analyzed through the Cochrane tool for randomized studies using Review Manager software. The search strategy resulted in 6 articles of which four investigated peri-implantitis and three peri-implant mucositis. All studies reported that there was a difference in the depth of the probing in the treatment of PD, in favor of the group using LR, though not always achieving significance. The use of LR can be clinically effective in terms of pocket depth reduction in the treatment of PD.

In the past two decades, dental implants have become a widely accepted therapeutic method for replacing missing teeth and supporting fixed and partially removable dentures (1). The literature reports high long-term survival rates of dental implants for both systemically healthy patients (cumulative survival rate of 83.8% after 25 years and 96.1% after 10 years) (1–3) and medically compromised patients (e.g., patients with oral cancer in which cumulative implant survival rate after 20 years is 90.8%) (1, 4).

Despite these high survival rates and periodontal and prosthetic maintenance over time, implant failure can occur. In the last decades, the presence of peri-implant inflammations has increased substantially, affecting both soft and hard tissues, leading to failure

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or loss of the implant. These pathologies, called peri-implant diseases (PD), are seen as biological complications related to inflammatory conditions of the soft and hard peri-implant tissues, which are induced by bacterial biofilms and are classified into two types: peri-implant mucositis and peri-implantitis (1, 5–8).

Peri-implantitis was first described in 1987 by Mombelli et al (9). as an infectious disease with many characteristics common to periodontitis. Taking into account the multiple etiological factors and clinical characteristics, many definitions emerged, and, from the clinical perspective, no consensus was reached for a clear definition of peri-implantitis. Thus, peri-implantitis was defined as an inflammatory response of the peri-implant mucosa with marginal bone loss, while peri-implant mucositis was defined as inflammation of the soft tissues (1, 5).

Discrepancies in case definitions and lack of clear clinical parameters led to controversies and the reporting of a wide range in prevalence and incidence in various studies on PD, thus making it difficult to estimate the true incidence of these pathologies (1, 5, 10-12). However, in November 2017 at the World Workshop on Periodontology (TMP), the European Federation of Periodontology (FEP) and the American Academy of Periodontology (AAP) reached consensus and established a new definition with clear clinical cut points for PD, both for daily clinical practice (1, 13-14) and for epidemiological studies (15, 16).

The conventional therapy for management of PD includes local debridement, implant surface decontamination using abrasives, chemicals and laser, anti-infective therapies and various surgical regenerative approaches for management of advanced lesions. The anti-infective therapy has proved beneficial and more conservative strategy among all. However, it depends on identification of putative micros-organisms and composition of the subgingival microbial component is important for the choice of the drug. Moreover, oral distribution patterns of potential pathogens are also important in deciding whether an antimicrobial agent should be administered locally or systemically (17).

Today, there is a continuous search for improved therapies for PD, due to its high prevalence, and among the new therapies there are probiotics (18). Probiotics are living microorganisms that, when administered in adequate amounts, confer a health benefit on the host. These products are known to alter pre-existing flora and introduce benefits to host microbial communities, resulting in the improvement or prevention of inflammation and other systemic diseases. Probiotics influence oral health through different mechanisms, such as immune modulation, the competitive exclusion of certain pathogens and the inhibition of the adherence of pathogenic bacteria to the oral mucosa (19).

Lactobacillus reuteri (LR) is found to have anti-inflammatory properties and shows reduction in expression of interleukin 8 and human beta-defensins when assessed for its invitro-effects on infected epithelial cells (20). Recent in-vivo studies have reported the use of probiotics in the inhibition of gingival inflammation (19, 21, 22). Additionally, probiotic therapy, using *Lactobacillus reuteri* (LR), has been reported to decrease plaque and gingival index among people with periodontal disease (23). However, currently, there is no systematic review of studies examining the clinical benefits of LR probiotics evaluating both peri-implant mucositis and peri-implantitis. Therefore, the objective of this study was to determine the clinical effectiveness of LR in the treatment of PD.

MATERIALS AND METHODS

This review was carried out in accordance with a previously prepared research protocol following the guidelines of the PRISMA standards (24). The search strategy was developed and performed by two independent reviewers (HAV and SP).

Data Search

A comprehensive search strategy was carried out in biomedical databases Pubmed, Embase, Scielo, Science Direct, Scopus, SIGLE (System of Information on Grey Literature in Europe), LILACS, Google Scholar and in the Cochrane Central Register of Clinical Trials and a manual search was also added in the periodontology journals with the greatest impact as Periodontology 2000, Journal

of Clinical Periodontology y Journal of Periodontology until January 31, 2021; using a combination of thematic headings using the following keywords and Boolean connectors: (lactobacillus reuteri) AND ((((dental implant) OR periimplant) OR mucositis) OR peri implantitis).

Selection criteria

Inclusion Criteria:

• Articles published on indexed journals, that report the use of LR.

• Articles that report clinical effects of LR (depth to probing, plaque index and bleeding index) in the treatment of PD.

• No publication time and language restrictions.

• A follow-up time greater than or equal to 3 months.

Exclusion Criteria:

• Articles from non-indexed journals, websites, or any other non-official source.

Data selection and extraction process

The titles and abstracts of each of the studies obtained with the inclusion and exclusion criteria previously described were reviewed; and the full texts of the studies that met these parameters were obtained to determine their risk of bias. To evaluate the studies, a checklist was made in duplicate, in order to extract the information of interest and switch the data. Two reviewers (AR and FC) independently carried out the evaluation of the articles regarding name, author, year of publication, type of study, number of patients (proportion between men and women), number of implants examined, mean age and age range of patients, follow-up time, country where the study was conducted, study groups, number of patients per study group, LR strains used, form of presentation of the LR, type of administration of the LR , LR dosage, inclusion and exclusion criteria, reduction in probing depth, change in plaque index and change in bleeding index, and risk of bias for each study. In order to resolve any discrepancies between the reviewers, they met and discussed together with a third reviewer (EI) in order to reach an agreement.

Analysis of results

The data from each study was placed and analyzed in the RevMan 5.3 program (Cochrane Group, UK). For the assessment of risk of bias, each study was analyzed according to the specific tool for randomized studies, described in the Cochrane Handbook of Systematic Reviews of Interventions (25).

RESULTS

Selection of studies

The initial search in the biomedical databases determined a total of 274 titles, available until January 2021, of which 23 were duplicates, leaving only 251 studies. The titles were read and 203 were excluded, leaving 48 eligible. Their summaries were read, discarding those who did not meet the inclusion criteria. Finally, 6 articles were selected for an exhaustive review of their content, their methodology and subsequent meta-analysis (Fig. 1).

Characteristic and results of the studies

In the included studies (26–31) the number of patients ranged from 19 to 80 with a follow-up time of between 3 months and 6 months. The mean age of the patients in the included studies ranged between 35.8 and 67.34 years. Overall, there were 119 men and 153 women. All studies (26–31) included patients of 18 years of age or older. The countries where the studies were carried out were Belgium (26), Saudi Arabia (27), Spain (28, 29), Japan (30) and Sweden (31) (Table I).

The total number of patients treated and implants examined was 272. However, on analysis one study (31) recorded a loss of follow-up for 3 implants at the end of 3 months, amounting to a total of implants examined to be 269. In all studies (26–31) a control group was used. Four studies (27, 28, 30, 31) considered smoking patients and a study (29) considered patients with a history of mild or moderate chronic periodontitis. Within the treated PDs, it was observed that three studies (26, 29, 30) treated peri-implantitis and four studies (27–29, 31) treated peri-implant mucositis (Table I).

Within the evaluated clinical parameters, it was observed that all the studies (26–31) reported reduction of depth to sounding; in 5 studies (26–30) changes in plaque index were reported; and in 5 studies (26–30) changes in bleeding rate were reported (Table I).

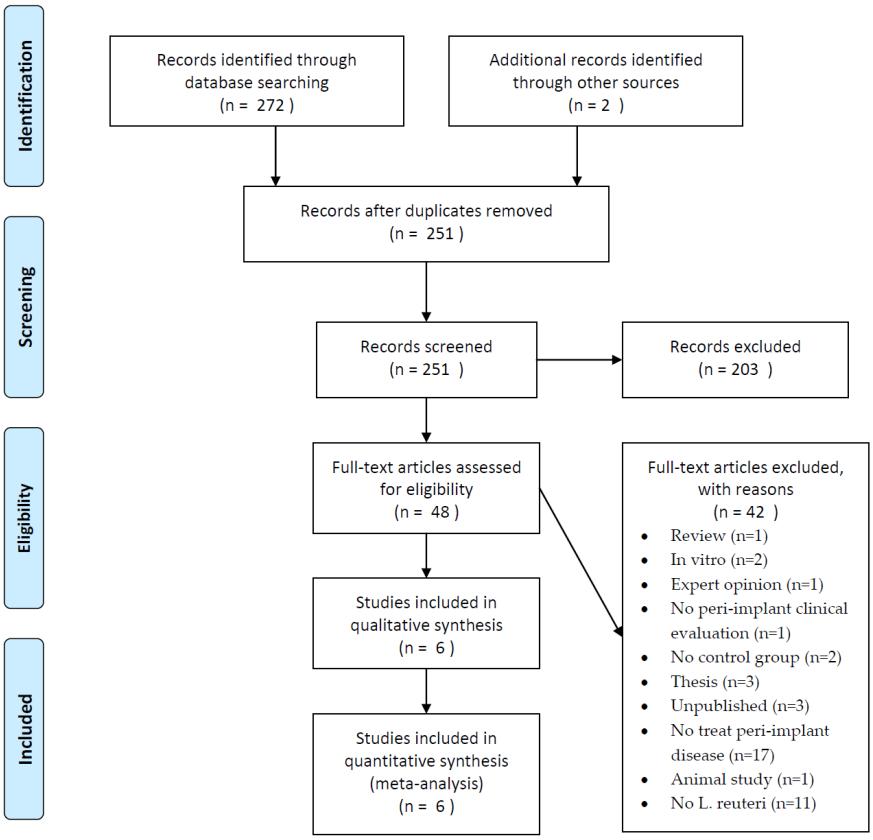
All studies (26–31) reported that the LR strains

Table I. *General characteristics of all included studies.*

Author	Study Design	N° of patients (men / women)	N° of implants	Mean Age (range)	Follow-up	Country	LR strains	Form of Delivery	Dose	Study Groups	N° of patients per group	RPD (mm)	CPI (%)	CBI (%)
Laleman et al. 2019 (26)	RCT parallel double-blind	19 (9 / 10)	19	66.5	6 months	Belgium	LR DSM 17938 and LR ATCC PTA 5289 (10^8 CFU of each strain / 5 drops or pill) (BioGaia AB, Lund, Sweden)	Drops and pills	NR	LR	9	1.02 ± 0.69	13 ± 14	27 ± 23
										Placebo	10	4.04 ± 0.84	2 ± 16	33 ± 27
Alqahtani et al. 2019 (27)	RCT parallel double-blind	80 (40 / 40)	80	35.8	6 months	Saudi Arabia	LR DSM 17938 and LRATCC PTA 5289 (10^8 CFU of each strain / pill) (PerioBalance Rubber, Sunstar Etoy, Switzerland)	Pills	One pill every 12 hours for 3 weeks, after brushing their teeth	NS + LR	20	0.9 ± 0.36	21 ± 8.03	26.3 ± 8.05
										NS + MD	20	0.2 ± 0.54	18.1 ± 7.72	17.3 ± 8.05
										S + LR	20	0.6 ± 0.42	4 ± 15.9	5.3 ± 3.98
										S + MD	20	0.8 ± 0.58	4.2 ± 11.73	4.1 ± 4.18
Peña et al. 2019 (28)	RCT parallel triple-blind	50 (21 / 29)	50	58.6	4.5 months	Spain	LR DSM 17938 and LR ATCC PTA 5289 (10^8 CFU of each strain / tablet) (Periobalance®, Sunstar S.A., Switzerland)	Pills	One pill after brushing their teeth at night for 1 month.	LR	25	0.21 ± 0.48	0.07 ± 0.09	0.07 ± 0.1
										Placebo	25	0.34 ± 0.5	0.07 ± 0.09	0.05 ± 0.07
Galofré et al. 2018 (29)	RCT parallel triple-blind	44 (23 / 21)	44	60	3 months	Spain	LR DSM 17938 and LR ATCC PTA 5289 (10^8 CFU of each strain / tablet) (Periobalance®, Sunstar S.A., Switzerland)	Pills	One pill for 10 minutes, once a day, just after tooth brushing.	PM + LR	11	0.48 ± 0.5	0.16 ± 0.17	0.32 ± 0.24
										PM + Placebo	11	0.15 ± 0.36	0.09 ± 0.04	0.07 ± 0.24
										P + LR	11	0.55 ± 0.37	0.16 ± 0.09	0.2 ± 0.22
										P + Placebo	11	0.2 ± 0.35	0.1 ± 0.11	0.1 ± 0.18
Tada et al. 2018 (30)	RCT parallel double-blind	30 (8 / 22)	30	67.34	6 months	Japan	LR DSM 17938 and LR ATCC PTA 5289 (10^8 CFU of each strain / tablet) (Periobalance®, Sunstar S.A., Switzerland)	Pills	One pill per day for 6 months	LR	15	0.69 ± 1.03	0.54 ± 1.03	1.67 ± 1.89
										Placebo	15	0.57 ± 1.48	0.27 ± 1	1.34 ± 2.52
Hallström et al. 2016 (31)	RCT parallel double-blind	49 (18 / 31)	46	58.5 (24 – 85)	3 months	Sweden	LR DSM 17938 and LR ATCC PTA 5289 (10^8 CFU of each strain / tablet) (Periobalance®, Sunstar S.A., Switzerland)	Drops and pills	One pill every 12 hours	LR	24	0.6 ± 1.7	NR	NR
										Placebo	22	0.5 ± 2.05	NR	NR

LR: *Lactobacillus reuteri;* ***CFU:*** *Colony forming unit;* ***NR:*** *Not reported;* ***RCT:*** *Randomized clinical trial;* ***RPD:*** *reduction in probing depth;* ***CPI:*** *changes in the plaque index; C****BI:*** *changes in the bleeding index;* ***NS:*** *No smoker;* ***S:*** *Smoker;* ***PM:*** *Peri-implant mucositis;* ***P:*** *Periimplantitis.*

used were DSM 17938 and ATCC PTA 5289. Two studies (26, 31) reported that the form of presentation of the LR used was in drops and pills, while in four studies (27–30) the presentation of the LR used was only in tablets. Two studies (26, 31) reported that the LR administration method used was local and systemic, while in four studies (27–30) the form of administration of the LR used was only systemic. Five studies (27–31) reported that the systemic or local dosage of the LR was different (Table I). Three studies showed high risk of bias (26, 30, 31) and the other three studies (27–29) showed low risk of bias (Fig. 2).



Note: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses (24).

Fig. 1. *Study flow diagram (PRISMA) showing the study selection process.*

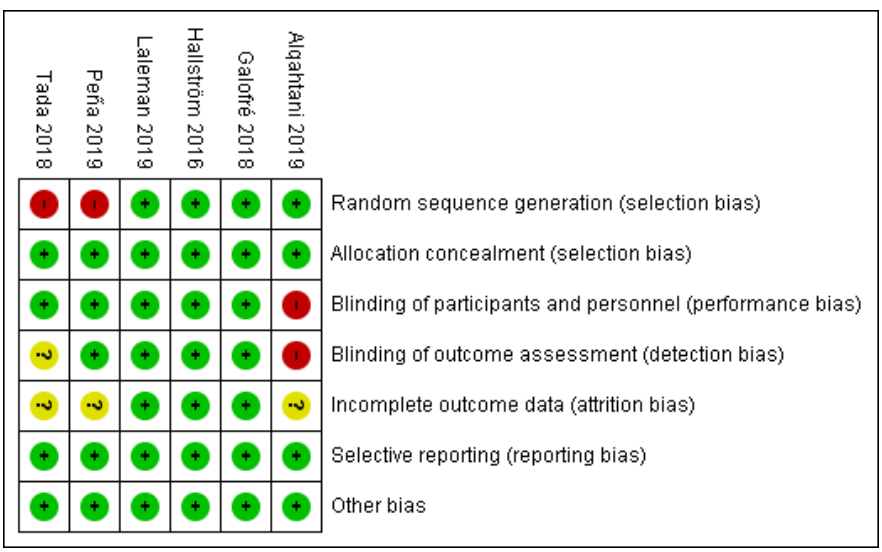


Fig. 2. Risk of Bias

Synthesis of results (Meta-analysis)

The clinical parameters evaluated, to determine the effectiveness of the LR in the treatment of peri-implant mucositis, were determined in 4 studies (27–29, 31) revealing that there was a significant overall difference (0.12, 95% CI (0.01,0.22), p=0.03), favoring the use of the LR in treatment of peri-implant mucositis (Fig. 3).

The clinical parameters evaluated, to determine the effectiveness of the LR in the treatment of peri-implantitis, were determined in 3 studies. (26, 29, 30) It was found that there was a significant overall difference (0.08, 95% CI (0.01,0.16), p=0.02), favoring the use of the LR in treatment of peri-implantitis (Fig. 4).

DISCUSSION

This systematic review analyzed six randomized clinical trials (26–31) which evaluated the effectiveness of using LR in treatment of PD. The meta-analysis comparing the use of LR with various controls showed significant improvement in probing depth reduction in treatment of both peri-implant mucositis and peri-implantitis. All the included studies (26–31) showed a low risk of bias.

These results may possibly be because the LR alters the pre-existing flora and introduces benefits for the microbial communities of the oral cavity, resulting in an improvement or prevention of peri-implant inflammation. The benefits conferred by the probiotic strains are mostly delivered by few possible mechanisms. These includes: (a) providing nutrients and cofactors, (b) competition with pathogens, (c) interaction with virulence factors of pathogens, and (d) stimulating the immune response of the host. The ability of the probiotics to carryout modifications in the pathogenicity of biofilm include the inhibition of proliferation and growth of micro-organisms and replacing them with beneficial ones (19).

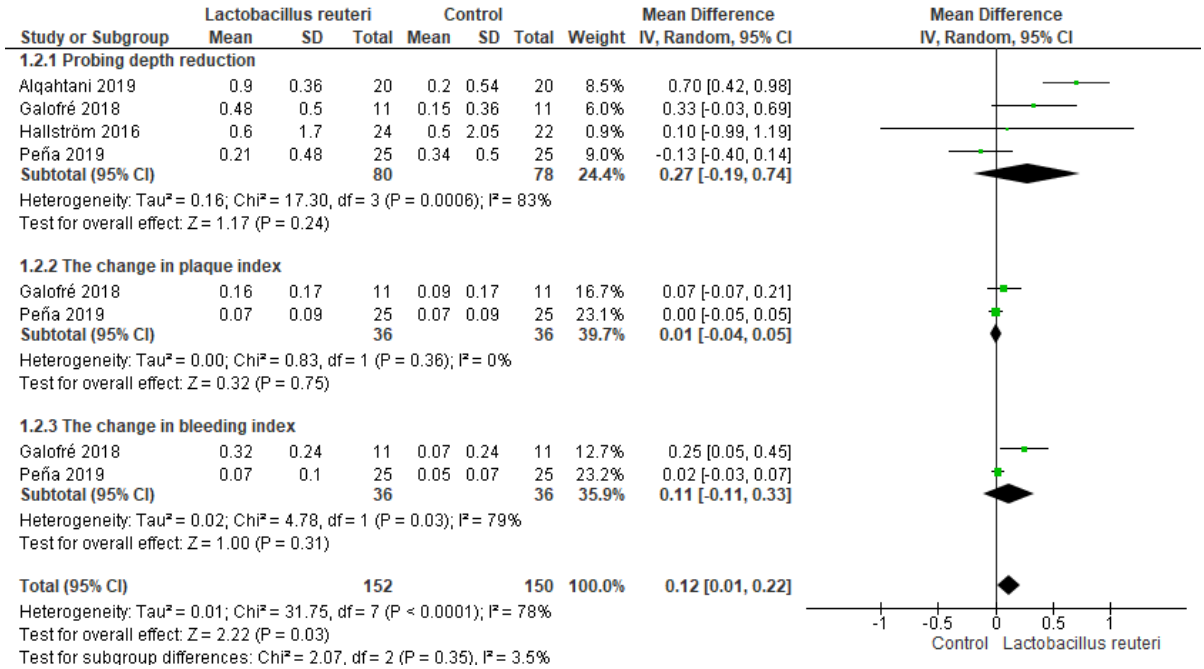
The review provides an insight and difference in management of peri-implant mucositis and peri-implantitis. The improvement could be attributed to adjunctive non-surgical therapy employed prior to administration of LR or placebo.

The beneficial role of LR owes to its immunomodulatory effect on the biofilm by suppressing human TNF production by lipopolysaccharide-activated monocytoid cells (32). The administration of Lactobacillus reuteri as a probiotic, shows low MMP-8 and high TIMP-1 levels, suggesting reduction of inflammation associated markers at the end of follow-up (33). The strains of LR synthesize an anti-microbial compound named *reuterin* (beta-hydroxypropionaldehyde), which has an ability to inhibit both gram negative and gram-positive bacteria, along with other fungi, protozoal infections (34). Reuterin prevents microbial colonization by interfering with pathogen's adhesion to host surface.

In this study, a random effects model was used for the meta-analysis in the treatment of peri-implant mucositis, due to the heterogeneity that existed between each of the studies. This heterogeneity is due to the difference in the follow-up periods, in the number of patients who participated and who culminated in the studies, and in the selection criteria of each study.

The strength of this systematic review lies in the selection of studies because an exhaustive search of the most important databases was used, strict inclusion criteria were used and all the included RCTs had a low risk of bias. A recent systematic review (35) showed the same results as the present study, despite the fact that these authors included one study (18) that used photodynamic therapy as additional therapy for plaque removal and also uses combination of two different strains of lactobacillus (brevis and plantarum), and another study (36) that used patients without peri-implant disease as a control group. The review also includes 2 studies with cross-over design. Our study aimed at including the studies using LR with similar strains (LR DSM 17938 and LRATCC PTA 5289) containing 10^8 CFU of each strain in form of drops or pills.

From all the above, we believe that these results cannot yet be generalized, since the RCTs present high heterogeneity. In fact, four studies (27, 28, 30, 31) included both smokers and non-smokers patients; in one study (29) patients had a history of mild or moderate chronic periodontitis. In addition, the RCTs



Note: CI = confidence interval; df = degrees of freedom; I^2 = Higgins I^2 test; Chi^2 = Chi square test

Fig. 3. *Forest plot of the event "Clinical effectiveness of the Lactobacillus Reuteri in the treatment of peri-implant mucositis".*

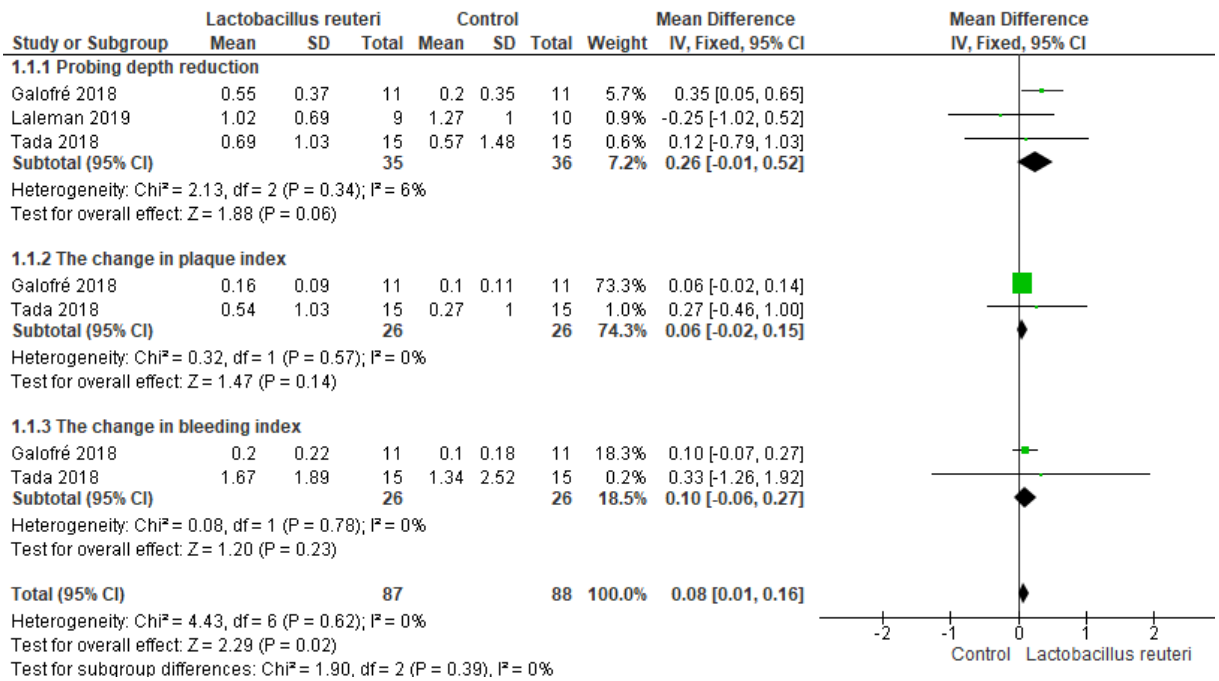


Fig. 4. *Forest plot of the event "Clinical effectiveness of the LR in the treatment of peri-implantitis". CI: confidence interval; df: degrees of freedom; I2: Higgins I2 test; Chi2: Chi square test.*

were performed in different countries in Europe and Asia and, therefore, these countries do not represent the whole world. This can provoke a dilemma since each continent and country has its own culture, ethnic group, and type of food; and we believe that these factors may influence the results. (37) For this reason, we recommend that well-designed RCTs be carried out, avoiding heterogeneity between each of the studies, and that they deal with this topic in other countries on the rest of the continents, to be able to compare the results and reach a clearer and general conclusion. The limitations of this review are inclusion of RCTs with small sample size, and not able to consider the difference between smokers and non-smokers. The review also did not take the presence of prior periodontal disease into account and most importantly, did not assess the microbiological benefits of using LR in treatment of PD.

In general, and based on the results obtained, the use of LR in the treatment of both peri-implant mucositis and peri-implantitis, is clinically effective. However, the evidence obtained in this review was based on a small number of studies and should be considered as a preliminary result. This would encourage further clinical trials with larger sample size with long term follow-up, to establish the profound effect of LR both clinically and microbiologically in treatment of PD.

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