# Immediate Implant Placement in Non-Infected Sockets versus Infected Sockets: a Systematic Review and Meta-Analysis

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**ABSTRACT**

**Objectives:** The aim of this systematic review is to compare immediate implant placement in infected extraction sockets with non-infected extraction sockets in terms of implant survival and function.
**Material and Methods:** An electronic search was conducted in PubMed, ScienceDirect, ISI Web of Knowledge and Google Scholar between January 2010 and February 2020. Studies evaluating implant survival rate and main clinical parameters were included for a qualitative and quantitative analysis.
**Results:** In total, nine studies were included and a pool of 2281 sockets were analysed. Compared with the non-infected group, the infected group showed no significant differences in implant survival rates (risk ratio [RR] = 0.99; 95% confidence interval [CI] = 0.98 to 1; P = 0.08). No significant statistical differences were found in marginal bone level (mean difference [MD] = -0.03; 95% CI = -0.1 to 0.04; P = 0.41), marginal gingival level (MD = -0.07; 95% CI = -0.17 to 0.04; P = 0.23), probing depth (MD = 0.06; 95% CI = -0.24 to 0.36; P = 0.7), modified bleeding index (MD = -0.00162196; 95% CI = -0.09 to 0.09; P = 0.97) and slight but significant changes were seen in width of keratinized gingiva (MD = 0.25; 95% CI = -0.3 to 0.8; P = 0.38) between the groups at the latest follow-up.
**Conclusions:** There were no significant difference in implant survival rates, marginal bone level, marginal gingival level, modified bleeding index and probing depth between infected sockets and non-infected sockets. However, slight but significant changes were seen in width of keratinized gingiva favouring the non-infected group.

**Keywords:** dental implantation; dental implants; infection; periapical granuloma; tooth socket.

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## INTRODUCTION

Currently, the treatment of choice to replace missing teeth has been implant supported dental rehabilitation due to its success rate and good long-term prognosis [1]. The first endosteal titanium implant was placed successfully in 1965 by Brånemark [2]. During the 1980s Brånemark introduced the original protocol for implant therapy and the recommendation included post extraction healing time of 5 - 6 months before the implant was placed into the alveolar ridge [1,2]. The conventional protocol was established on the belief that only complete hard and soft tissue healing would guarantee a favourable osseointegration [3]. The immediate implant placement in fresh-socket was firstly introduced in 1976 and in the year 1989 the first immediate implant was placed [2]. Due to the modern implantology and its findings of new designs and surfaces, it is now possible to modify the classical protocol that was introduced decades ago [5]. As of current, there are four different methods regarding the placement of implants into edentulous sites [6]:

- Immediate implant placement, when the implant is placed directly after the extraction;
- Early implant placement, the implant is placed 1 - 2 months after the extraction;
- Delayed implant placement, the implant is placed 3 - 4 months after the extraction;
- Late implant placement, when the implant is placed more than 4 months after the tooth extraction.

Immediate implant placement in fresh-socket is a protocol that has received a lot of attention and is now considered a common treatment step with predictable and successful results [2,7,8]. Immediate post extraction implant placement offers advantages such as:

- Reduced number of surgical interventions and shortening of the treatment procedure, ultimately leading to an increased patient satisfaction [2-6, 8-11];
- Optimal soft tissue aesthetics due to the preservation of soft tissue envelope [2,4,6].

However, immediate implant placement does not always provide optimal clinical outcomes. Preclinical and human studies documented suggest that this surgical protocol may not preserve the buccal bone crest. To prevent the dimensional changes of the alveolar bone and the soft tissue during immediate implant placement, numerous surgical techniques have been suggested [1,12]:

- Flapless technique;
- Use of bone grafts;
- Use of connective tissue grafts;
- Provisional restorations;
- Highlighting the importance of buccal bone plate thickness;
- Importance of alveolar bone thickness.

A recent clinical trial shows that using a bone replacement graft between the implant and the buccal bone plate notably improves the preservation of the bone after immediate implant placement [12].

A non-infected extraction socket has great benefit to the survival rate of immediate implant placement. However, in practice, teeth extractions are largely due to presence of chronic pathology that later leads to endodontic or periodontal apical lesions [13,14]. Thus, the aim of this systematic review was to evaluate if immediate implant placement in infected extraction sockets can be considered as successful in comparison to non-infected sockets.

## MATERIAL AND METHODS

### Protocol

The reporting of this systematic review was conducted by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15].

### Focus question

The following focus question was framed according to the problem, intervention, comparison and outcome (PICO) process (Table 1):

What is the outcome of immediate implant placement in patients with infected sockets versus non-infected sockets with the evaluation of survival rate, probing depth, marginal bone level, marginal gingival level, modified bleeding index and width of keratinized gingiva?

**Table 1.** PICO framework of the framed clinical question

| Definition | Description |
|---|---|
| **Patient (P)** | Patients with infected sockets |
| **Intervention (I)** | Immediate implant placement |
| **Comparison (C)** | A control group with non-infected sockets |
| **Outcome (O)** | Implant success by evaluating: survival rate, marginal bone level, marginal gingival level, width of keratinized gingiva, modified bleeding index and probing depth. |
| **Focus question** | What is the outcome of immediate implant placement in patients with infected sockets versus non-infected sockets with the evaluation of survival rate, marginal bone level, marginal gingival level, width of keratinized gingiva, modified bleeding index and probing depth? |

**Information sources**

An electronic search for articles in English language was performed using PubMed, ISI Web of Science, ScienceDirect and Google Scholar from January 2010 to February 2020.

**Search strategy**

The literature search strategy was done by following the PRISMA guidelines using PubMed, ISI Web of Science, ScienceDirect electronic databases and Google Scholar. The search was conducted using a combination of different search terms (Table 2).

**Types of publications**

The systematic review included only English clinical studies done on humans. Publications that were lacking full text, *in vitro* studies and studies done on animals were excluded.

**Types of studies**

The systematic review included all human retrospective and prospective observational studies published from January 2010 to February 2020.

**Types of participants/population**

Subjects, whose extraction sockets were classified as having infection and that were treated with immediate implant placement, were included in this systematic review.

**Outcome variables**

The primary outcome variable was the implant survival rates. The secondary outcome variables were the mean changes in marginal bone level (MBL), marginal gingival level (MGL), width of keratinized gingiva (WKG), modified bleeding index (mBI) and probing depth (PD).

**Inclusion criteria**

Studies were included if they followed the applied criteria:

- Studies with a sample size of > 5 patients in each group;
- Minimum follow-up of 6 months;
- Evaluated with one of the outcomes;
- If the sockets were classified as having an infection.

**Exclusion criteria**

Studies were excluded if they met any of the following applied criteria:

- Clinical studies with no control group;
- Animal studies;
- Non-English articles;
- Studies that did not mention the socket morphology;
- No clear methodology description;
- Secondary sources.

**Data extraction**

The following data was extracted from the articles included in this review:

- First author and publication year;
- Study design;
- Total number of patients;
- Total number of sockets and type of socket pathology;
- Follow-up period;
- Implant system;
- Site of implant placement;
- Number of smoking patients;
- Treatment methodology including flap technique, granulation tissue removal, bone graft, loading time, mouth rinse and antibiotic prophylaxis;
- Implant failure and implant survival outcomes;
- Secondary outcome measures namely MBL, MGL, WKG, mBI and PD.

**Table 2.** Keywords used to conduct the literature search

| Concept | Keywords |
|---|---|
| **First keyword terms** | ”Infected socket*” OR ”Periapical lesion*” OR ”Endodontic lesion*” OR ”Periodontal lesion*” OR ”Radicular lesion*” OR ”Periradicular lesion*” OR ”Apical lesion*” OR ”Apical pathology” OR ”Periradicular pathology” OR ”Radicular pathology” OR ”Endodontic pathology” OR ”Periapical pathology” OR ”Apical pathological feature*” OR ”Apical periodontitis” |
| **Second keyword terms** | ”Immediate implant*” OR ”Fresh-socket* ” OR ”Fresh extraction*” OR ‘’Post-extraction” |

First keyword terms and second keyword terms were combined with AND.
*truncation symbol.

### Statistical analysis

The meta-analysis was conducted in Review Manager Software version 5.3 (The Cochrane Collaboration, Oxford, UK). The Higgins index ($I^2$) statistic test was used to measure the heterogeneity across the studies. Cochrane Handbook guidelines were adopted to interpret the heterogeneity with 0 to 40% representing low, 30 to 60% may represent moderate heterogeneity, and 50 to 60% may represent substantial heterogeneity and 75 to 100% representing considerable heterogeneity [16]. The level of P-value was set at $< 0.05$.

The Mantel-Haenszel method was used for implant survival rates and implant failure rates (dichotomous outcome variables) together with fixed-effects model. The effect size between the control group and the test group was expressed as risk ratios (RR) and 95% confidence intervals (CIs). If significant heterogeneity (> 75%) was seen, the random-effects model was chosen.

The same process was followed for the continuous outcome variables (MBL, MGL, WKG, mBI and PD). However, they were based on inverse variance (IV) with effect size expressed as mean difference (MD) in millimetres and 95% CIs. A funnel plot was made with software (Review Manager Version 5.3; The Cochrane Collaboration, Oxford, UK) for the primary outcome, to investigate the possibility of publication bias.

### Risk of bias assessment

The risk of bias assessment was performed using the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies [17]. Questions that were evaluated can be found in Table 3.

## RESULTS

### Study selection

A total of 316 publications were screened, from which 294 articles were excluded based on the titles. In the next step the abstracts of all the 22 remaining studies were assessed for eligibility based on inclusion criteria. If an abstract provided insufficient amount of information to decide whether or not to include the article, the full version of the article was downloaded for further detailed evaluation. Subsequently, the full-text of the articles that were potentially relevant was obtained for assessment of the eligibility. A total of 12 full-articles were reviewed for inclusion and exclusion criteria in order to make the final decision.

After a detailed review, nine records met all the required criteria and were included in this review [18-26]. Figure 1 shows the PRISMA flow diagram which demonstrates the number of publications identified, screened, assessed for eligibility and included in this review.

### Study exclusion

Three studies were excluded after a full-text review due to: lack of control group [27], publication of the same patient records [28] and lack of control and test group details [29].

### Quality assessment of the included studies

The quality assessment of all the cohort studies revealed moderate or good qualities; the scoring of each study is summarized in Table 4.

**Table 3.** Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies

| Question number | Defined question |
|---|---|
| Q1 | Were the two groups similar and recruited from the same population? |
| Q2 | Were the exposures measured similarly to assign people to both exposed and unexposed groups? |
| Q3 | Was the exposure measured in a valid and reliable way? |
| Q4 | Were confounding factors identified? |
| Q5 | Were strategies to deal with confounding factors stated? |
| Q6 | Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? |
| Q7 | Were the outcomes measured in a valid and reliable way? |
| Q8 | Was the follow-up time reported and sufficient to be long enough for outcomes to occur? |
| Q9 | Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored? |
| Q10 | Were strategies to address incomplete follow up utilized? |
| Q11 | Was appropriate statistical analysis used? |

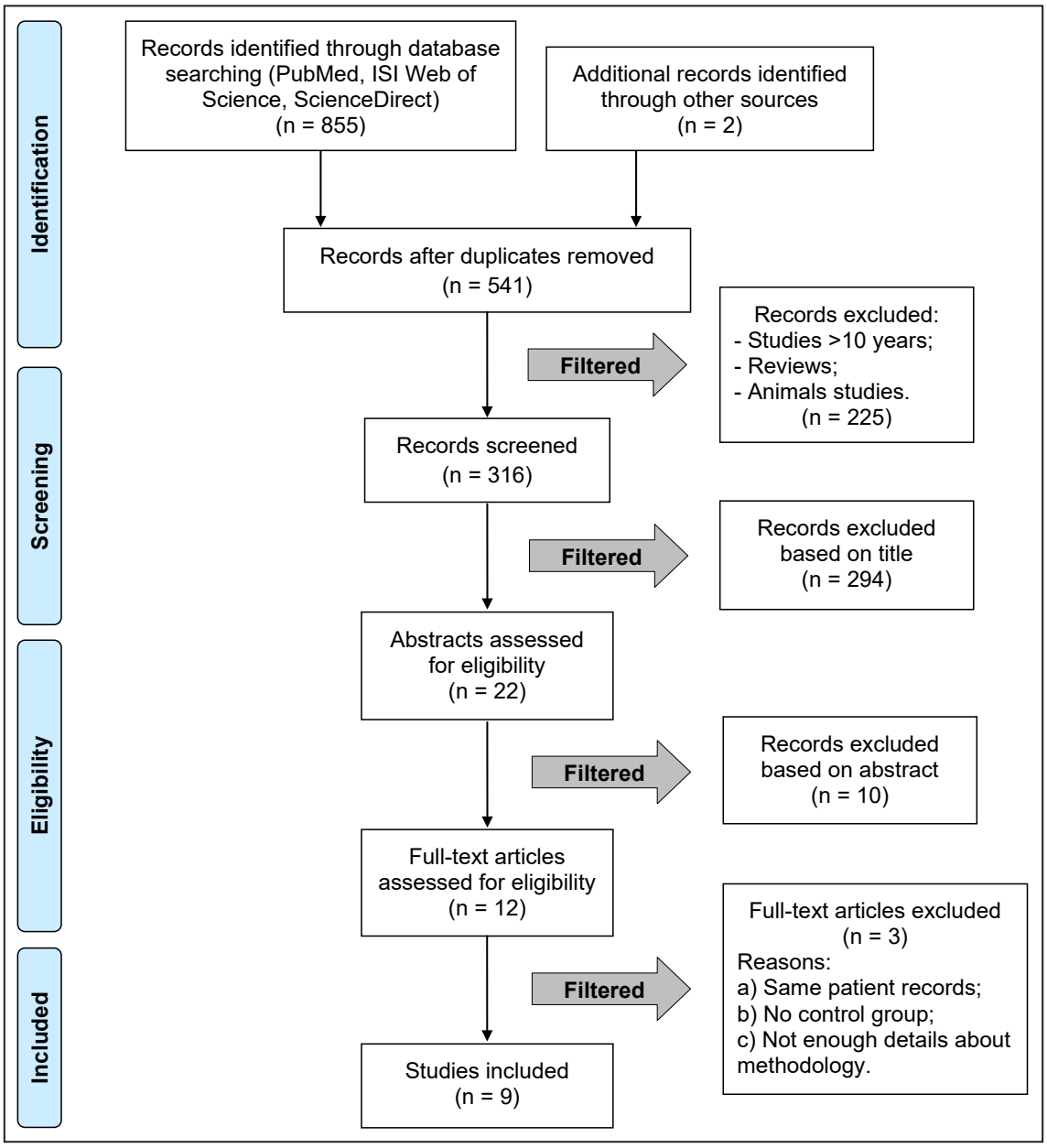


**Figure 1.** PRISMA flow diagram demonstrating the study selection.

**Table 4.** Quality assessment of all the included cohort studies using the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies

| Study | Year of publication | Study design | Checklist | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 |
| **Montoya-Salazar et al. [18]** | 2014 | Prospective | ? | + | + | - | - | + | + | + | + | N/A | + |
| **Jung et al. [19]** | 2012 | Prospective | + | + | + | + | N/A | + | + | + | + | N/A | + |
| **Crespi et al. [20]** | 2010 | Prospective | + | + | + | N/A | N/A | + | + | + | + | N/A | + |
| **Crespi et al. [21]** | 2010 | Prospective | + | + | + | N/A | N/A | + | + | + | + | N/A | + |
| **Hita-Iglesias et al. [22]** | 2016 | Prospective | + | + | + | N/A | N/A | + | + | + | + | N/A | + |
| **Blus et al. [23]** | 2015 | Prospective | ? | + | + | - | - | + | + | + | + | N/A | + |
| **Bell et al. [24]** | 2011 | Retrospective | + | + | + | + | + | + | + | + | + | N/A | + |
| **Fugazzotto [25]** | 2012 | Retrospective | + | + | + | N/A | N/A | + | + | + | + | N/A | + |
| **Zuffetti et al. [26]** | 2017 | Retrospective | ? | + | + | + | - | + | + | + | + | N/A | + |

N/A = not applicable; ? = unclear; + = yes; - = no.

**Study characteristics**

The characteristics and details of the treatment procedures of the included studies are presented in Table 5 and 6. Three of the included clinical trials were of retrospective design [24-26] and the other remaining six were of prospective design [18-23]. In total, a pool of 1346 patients and 2281 sockets were used in this present systematic review. A total of 933 immediate implants were placed in infected sites and 1348 in non-infected sites. Seven of the studies included smoking patients [18-21,24-26]. Only two of them specified the total number of smokers [19,24]. One of the studies did not mention if smoking patients were included or excluded [23]. Three of the articles mentioned the exclusion of heavy smokers (> 10 cigarettes a day) [20,21,25].

Most of the studies indicated that implants has been placed in the incisor, canine or premolar area [18-23], while two of the clinical trials included the molar area as well [24,26]. Only one study exclusively reported on the incisor replacement [25]. Six of the studies used flapless approach [20-25], while two of them proceeded with a flap technique [18,19] and only one used both flap and flapless approach [26]. No grafting material was used in three of the studies reviewed [20-22]. Four of the included studies used xenograft materials [18,19,23,26], one used both autograft or xenograft together with platelet rich plasma [24], whiles the remaining one clinical trial included autograft, allograft or xenograft [25].

A delayed loading protocol was followed for all implants in six of the studies [18,19,21,22,24,25]. Only one study used an immediate loading protocol [20], whiles the two remaining used different types of loading protocols [23,26]. The patients received a preoperative antibiotic prophylaxis in seven of the studies [18,20-24,26] and five of the studies reported about prescription of postoperative antibiotics for the patients [18-22,25-26]. A postoperative instruction on chlorhexidine rinse was made in five of the clinical trials [18-21,26], while only one study followed a preoperative mouth rinse protocol [26].

All of the included studies reported the number of failed implants [18-26] while four of them reported about MBL changes [18-21]. Changes in mBI were reported by three clinical trials [18,20,21], MGL and PD by two [18,21] and WKG changes by three [18,19,21]. The minimum follow-up period of the secondary outcome variables (MBL, MGL, PD, mBI and WKG) was one year and the maximum follow-up period was five years. Table 7 shows detailed information about the extracted data from the different follow-up periods regarding MBL, MGL, PD, mBI and WKG.

**Quantitative synthesis**

***Implant survival rates and failures (primary outcome variables)***

In total 933 immediate implants were placed in infected sockets and 1348 in non-infected sockets [18-26]. The number of failed implants was 22 for the infected socket group and 19 for the non-infected socket group resulting in overall implant survival rates of 97.64% (911/933) for the infected group and 98.57% (1329/1348) for the non-infected group (Figure 2). Both of the groups showed similar results (RR = 0.99; 95% CI = 0.98 to 1; P = 0.08). Additionally, there was no significant difference in the implant failure rates between the infected and non-infected groups (RR = 1.8; 95% CI = 0.98 to 3.31; P = 0.06) as seen in Figure 3.

***Marginal bone level changes***

Four of the included clinical trials analyzed the MBL measurements [18-21]. In total 242 implants in the infected sockets and 126 implants in non-infected sockets were included in this analysis (Figure 4A - C). One of the studies reported three follow-up periods of 1, 2 and 3 years [18]. Another study reported three follow-up periods but of 1, 2 and 4 years [20]. The last two studies reported 1 and 2 years [21] and 5 years [19] respectively. No significant difference was found between the different groups at follow-up times, at 1 year the MD was -0.05 (95% CI = -0.15 to 0.04; P = 0.25) at year 2 the MD was 0.12 (95% CI = -0.14 to 0.38; P = 0.36) and at year 3 or more the MD was -0.03 (95% CI = -0.1 to 0.04; P = 0.41).

***Marginal gingival level changes***

Two of the included clinical trials analyzed the MGL changes [18,21]. The total number of implants included was 33 in the infected group and 33 in the non-infected group (Figure 5A and 5B). Meta-analysis showed no significant difference between the two groups. At 1 year follow-up the MD was -0.06 (95% CI = -0.15 to 0.03; P = 0.17) and at 2 year follow-up the MD was -0.07 (95% CI = -0.17 to 0.04; P = 0.23).

***Probing depth changes***

Two of the included clinical trials analyzed the peri-implant PD measurements [18,21]. In total, 33 implants were included in both infected and non-infected groups (Figure 6A and 6B).

**Table 5.** Characteristics of the included studies

| Study | Patients (n) | Sockets (n) | Smoking patients | IS pathology | Age (years) | Site | Follow-up (months) | Implant system |
|---|---|---|---|---|---|---|---|---|
| **Montoya-Salazar et al. [18]** | 18 | 36 (IS:18, NIS:18 | Included | Chronic periapical lesion | 18 - 50 | Incisors, canines and premolars | 36 | MIS C1 implants (MIS Implants Technologies Ltd.; Tel Aviv, Israel) |
| **Jung et al. [19]** | 27 | 27 (IS:12, NIS:15) | Included | Periapical pathologies | 31 - 87 (IS) 28 - 82 (NIS) | Incisors, canines and premolars | 60 | Straumann® Standard Plus or Tapered Effect (Straumann AG; Basal, Switzerland) |
| **Crespi et al. [20]** | 37 | 275 (IS:197, NIS:78) | Heavy smokers excluded (> 10 cigarettes/day) | Chronic periodontal lesions | 32 - 71 | Incisors, canines and premolars | 48 | Sweden and Martina SPA, Due Carrare, Padova, Italy |
| **Crespi et al. [21]** | 30 | 30 (IS:15, NIS:15) | Heavy smokers excluded (> 10 cigarettes/day) | Periapical lesions and radiolucencies | 34 - 71 | Incisors, canines and premolars | 24 | Seven (Sweden and Martina SPA, Due Carrare, Padova, Italy) |
| **Hita-Iglesias et al. [22]** | 60 | 168 (IS:66, NIS:102) | Non-smokers only | Chronic periapical lesions | 18 - 72 | Incisors, canines and premolars | 12 | Zimmer dental, USA |
| **Blus et al. [23]** | 86 | 168 (IS:83, NIS:85) | No data | Acute and chronic infection | 26 - 77 | Incisors, canines and premolars | 12 | Leader Implants; Milan, Italy or and Bioner Sistemas Implantológicos, Barcelona, Spain |
| **Bell et al. [24]** | 655 | 922 (IS:285, NIS:637) | Included | Chronic periapical lesion | Mean: 58.4 IS; 60.1 NIS | Incisors, canines, premolars and molars | 3 - 93 | Straumann® Tissue Level or Bone Level SLA (Straumann AG; Basal, Switzerland) |
| **Fugazzotto [25]** | 64 | 128 (IS:64, NIS:64) | Heavy smokers excluded (> 10 cigarettes/day) | Periapical pathologies | 21 - 71 | Incisors | 24 - 117 | No data |
| **Zuffetti et al. [26]** | 369 | 527 (IS:193, NIS:334) | Heavy smokers included (> 10 cigarettes/day) | Chronic infection | 22.8 - 81.9 | Incisors, canines, premolars and molars | Mean 52.1 | BIOMET 3i® (BIOMET 3i LLC; Palm Beach Gardens, Florida, USA).<br>Biohorizons® (BioHorizons Inc; Birmingham, Alabama, USA).<br>Nobel Biocare AG; Zürich, Switzerland.<br>Astra Tech Implant System™ (Dentsply Sirona; Göteborg/Mölndal, Sweden).<br>MegaGen Implant Co. Limited; Gyeong-buk, South Korea.<br>Neoss AB; Göteborg, Sweden. |

n = numbers; IS = infected socket; NIS = non-infected socket; ASA = The American Society of Anaesthesiologists physical status classification system.

**Table 6.** Details of the treatment procedures of the included studies

| Study | Flap technique | Granulation tissue | Bone graft | Loading time | Preoperative antibiotic prophylaxis | Preoperative chlorhexidine rinse | Postoperative antibiotic prophylaxis | Postoperative chlorhexidine rinse |
|---|---|---|---|---|---|---|---|---|
| **Montoya-Salazar et al. [18]** | Flap | Removed | Xenograft | Delayed | Yes | No | Yes | Yes |
| **Jung et al. [19]** | Flap | Removed | Xenograft | Delayed | No | No | Yes | Yes |
| **Crespi et al. [20]** | Flapless | Removed | None | Immediate | Yes | No | Yes | Yes |
| **Crespi et al. [21]** | Flapless | Removed | None | Delayed | Yes | No | Yes | Yes |
| **Hita-Iglesias et al. [22]** | Flapless | Removed | None | Delayed | Yes | No | Yes | No |
| **Blus et al. [23]** | Flapless | Removed | Xenograft | Immediate, early and delayed | Yes | No | No | No |
| **Bell et al. [24]** | Flapless | Removed | Autograft and/or xenograft together with platelet rich plasma | Delayed | Yes | Yes | No | No |
| **Fugazzotto [25]** | Flapless | Removed | Autograft or allograft or xenograft | Delayed | No | No | Yes | No |
| **Zuffetti et al. [26]** | Flapless or flap | Removed | Xenograft | Immediate, early and delayed | Yes | No | Yes | Yes |

**Table 7.** Data of the primary and secondary outcomes of the included studies

| Study | Number of implants (n) | | | Failed implants (n) | | | Implant survival rate (%) | | MBL (mm) Mean (SD) | | MGL (mm) Mean (SD) | | PD (mm) Mean (SD) | | mBI (mm) Mean (SD) | | WKG (mm) Mean (SD) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IS | NIS | Total | IS | NIS | Total | IS | NIS | IS | NIS | IS | NIS | IS | NIS | IS | NIS | IS | NIS |
| **Montoya-Salazar et al. [18]** | 18 | 18 | 36 | 1 | 0 | 1 | 94.4 | 100 | 1 years: 0.73 (0.22); 2 years: 0.84 (0.15); 3 years: 0.53 (0.13) | 1 years: 0.73 (0.29); 2 years: 0.54 (0.15); 3 years: 0.60 (0.16) | 1 years: 0.88 (0.75); 2 years: 0.83 (0.85); 3 years: 1 (0.59) | 1 years: 1.13 (0.23); 2 years: 1.11 (0.21); 3 years: 1.16 (0.24) | 1 years: 2.53 (0.44); 2 years: 2.76 (0.8); 3 years: 2.51 (0.44) | 1 years: 2.44 (0.28); 2 years: 2.6 (0.37); 3 years: 2.53 (0.44) | 1 years: 0.88 (0.75); 2 years: 0.83 (0.85); 3 years: 0.94 (0.63) | 1 years: 1.38 (0.84); 2 years: 1.05 (0.99); 3 years: 1 (1.02) | 1 years: 3.33 (1.08); 2 years: 3.33 (1.08); 3 years: 3.38 (0.6) | 1 years: 2.74 (0.73); 2 years: 2.61 (1.14); 3 years: 2.88 (1.27) |
| **Jung et al. [19]** | 12 | 15 | 27 | 0 | 0 | 0 | 100 | 100 | 5 years: 1.5 (0.8) mesial; 1.7 (0.7) distal | 5 years: 1.4 (0.5) mesial; 1.5 (0.6) distal | N/D | | N/D | | N/D | | 5 years: 3.3 (1.5) | 5 years: 3.7 (1.2) |
| **Crespi et al. [20]** | 197 | 78 | 275 | 2 | 0 | 2 | 98.9 | 100 | 1 years: 0.77 (0.39); 2 years: 0.82 (0.52); 4 years: 0.79 (0.38) | 1 years: 0.86 (0.47); 2 years: 0.84 (0.46); 4 years: 0.78 (0.38) | N/D | | N/D | | 4 years: 0.78 (0.23) | 4 years: 0.75 (0.39) | N/D | |
| **Crespi et al. [21]** | 15 | 15 | 30 | 0 | 0 | 0 | 100 | 100 | 1 years: 0.83 (0.51); 2 years: 0.86 (0.54) | 1 years: 0.80 (0.47); 2 years: 0.82 (0.52) | 1 years: 0.16 (0.13); 2 years: 0.2 (0.13) | 1 years: 0.21 (0.13); 2 years: 0.25 (0.18) | 1 years: 1.8 (0.64); 2 years: 1.99 (0.57) | 1 years: 1.85 (0.68); 2 years: 2.05 (0.66) | 1 years: 0.69 (0.3); 2 years: 0.72(0.36) | 1 years: 0.68 (0.34); 2 years: 0.77 (0.33) | 1 years: 3.64 (0.68); 2 years: 3.62 (0.65) | 1 years: 3.68 (0.72); 2 years: 3.67 (0.61) |
| **Hita-Iglesias et al. [22]** | 66 | 102 | 168 | 6 | 2 | 8 | 90.8 | 98.1 | N/D | | N/D | | N/D | | N/D | | N/D | |
| **Blus et al. [23]** | 83 | 85 | 168 | 2 | 1 | 3 | 97.6 | 98.8 | N/D | | N/D | | N/D | | N/D | | N/D | |
| **Bell et al. [24]** | 285 | 637 | 922 | 7 | 8 | 15 | 97.5 | 98.7 | N/D | | N/D | | N/D | | N/D | | N/D | |
| **Fugazzotto [25]** | 64 | 64 | 128 | 1 | 1 | 2 | 98.1 | 98.2 | N/D | | N/D | | N/D | | N/D | | N/D | |
| **Zuffetti et al. [26]** | 193 | 334 | 527 | 3 | 7 | 10 | 98.4 (0.9) | 97.9 (0.8) | N/D | | N/D | | N/D | | N/D | | N/D | |

MBL = marginal bone level; MGL = marginal gingival level changes; PD = probing depth; WKG = width of keratinized gingiva; mBI = modified bleeding index; IS = infected socket; NIS = non-infected socket; N/D = no data; SD = standard deviation; n = numbers.

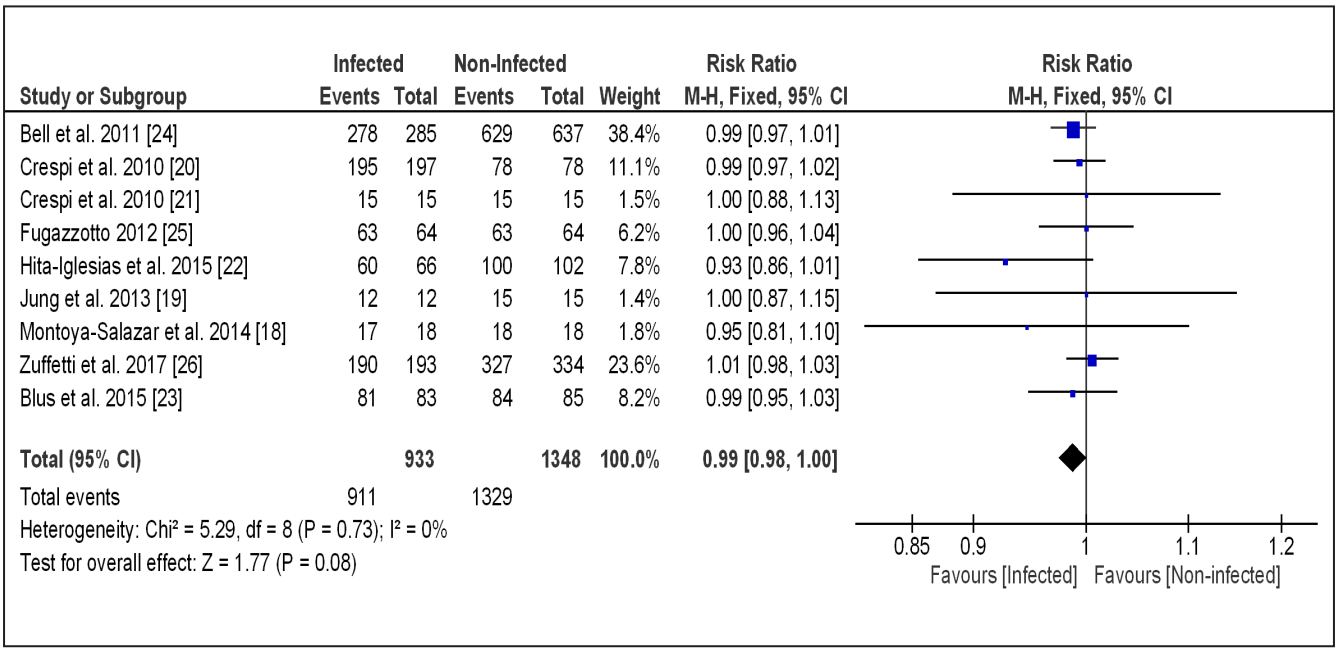


**Figure 2.** Implant survival rates of the included studies.

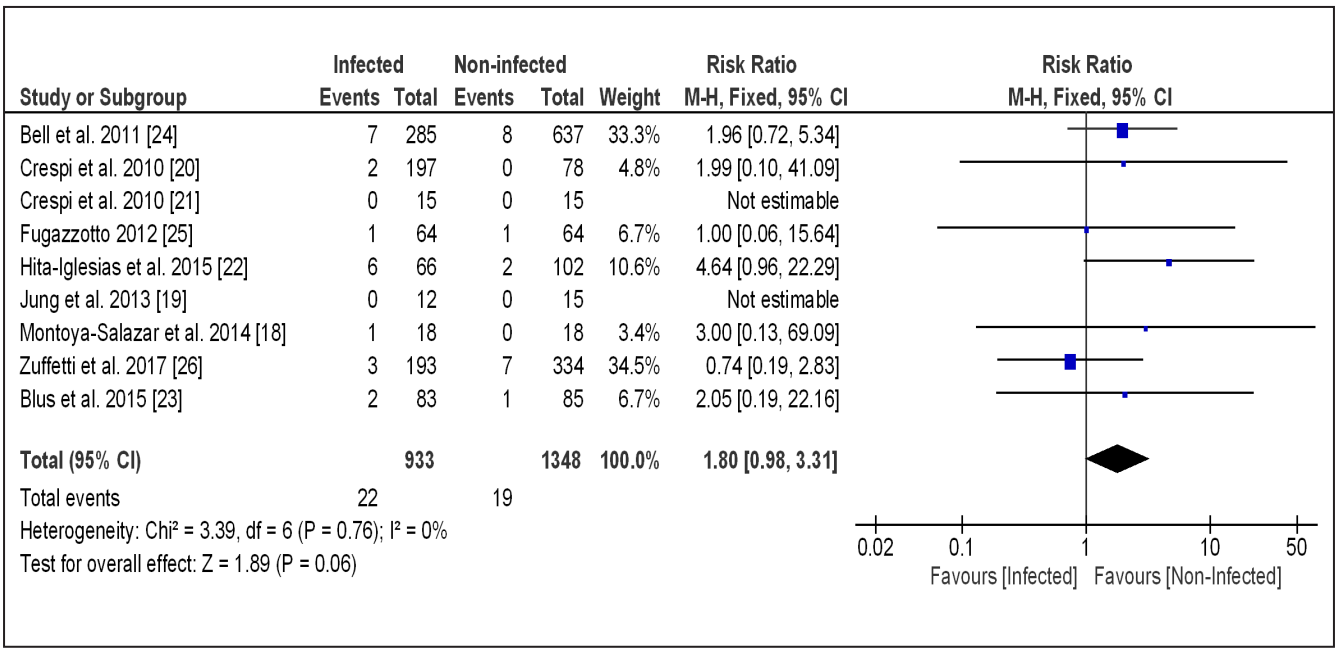


**Figure 3.** Implant failure rates of the included studies.

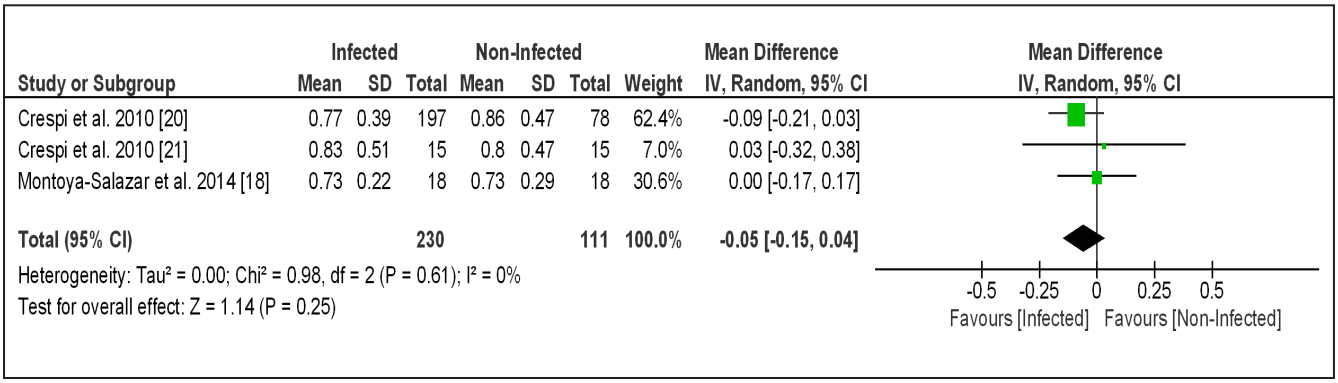


**Figure 4A.** Marginal bone level changes at the follow-up period of 1 year.

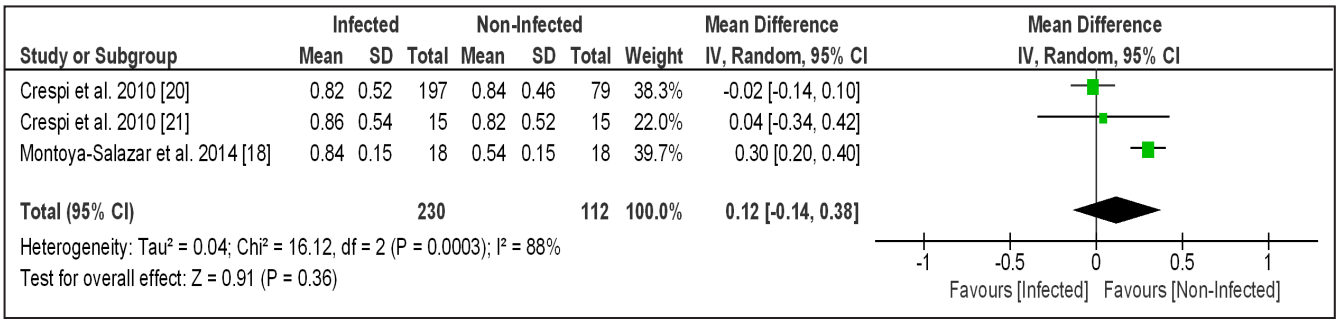


**Figure 4B.** Marginal bone level changes at the follow-up period of 2 years.

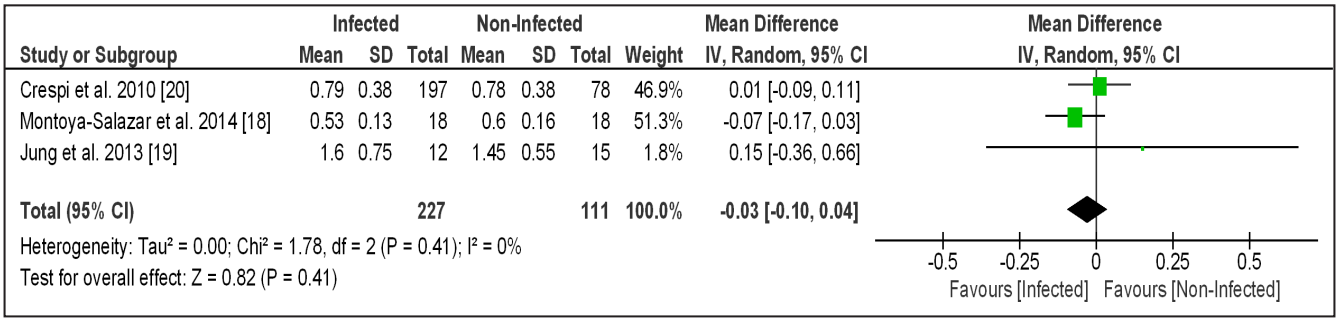


**Figure 4C.** Marginal bone level changes at the follow-up period of > 3 years.

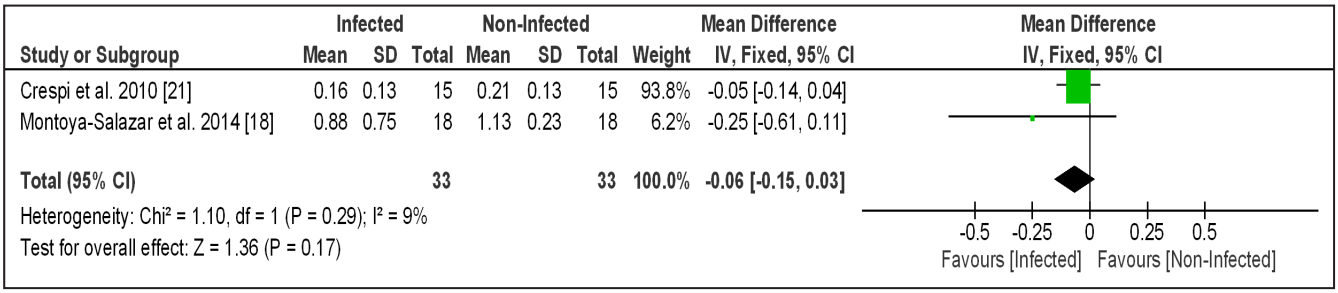


**Figure 5A.** Marginal gingival level changes at the follow-up period of 1 year.

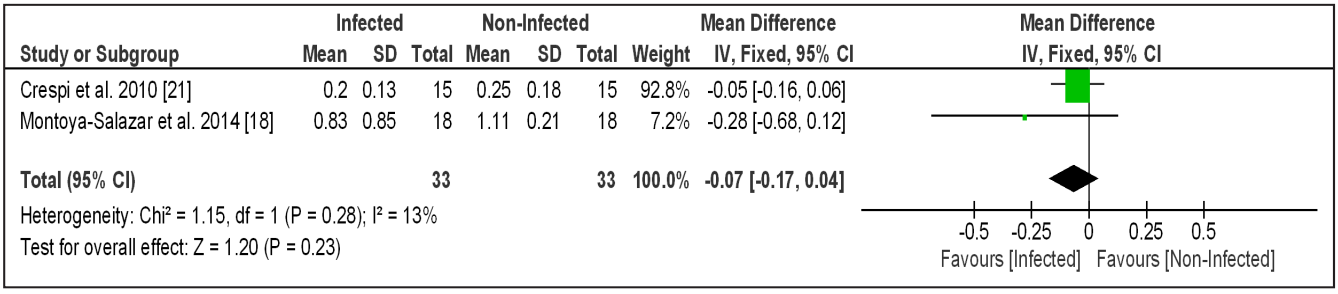


**Figure 5B.** Marginal gingival level changes at the follow-up period of 2 years.

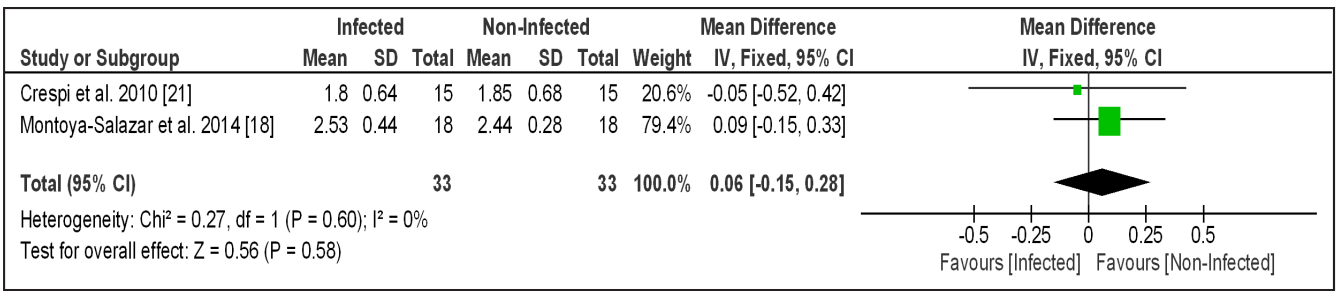


**Figure 6A.** Probing depth changes of the included studies at the follow-up period of 1 year.

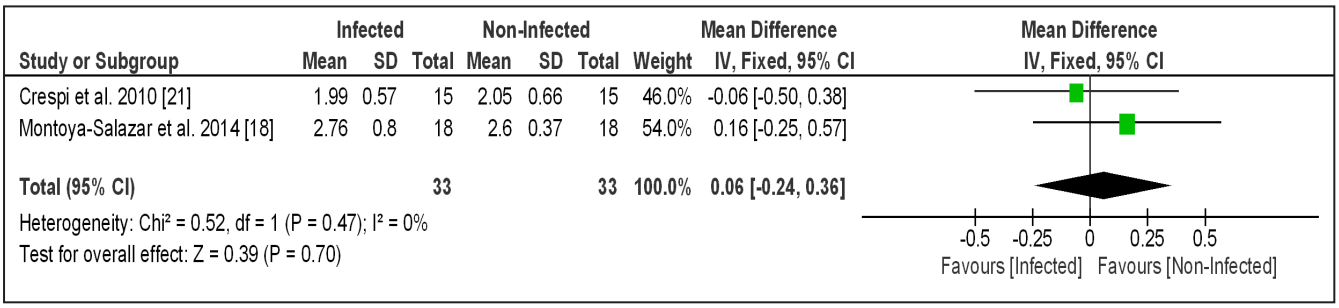


**Figure 6B.** Probing depth changes of the included studies at the follow-up-period of 2 years.

No significant difference was found between the groups at follow-up, at year 1 the MD was 0.06 (95% CI = -0.15 to 0.28; P = 0.58) and at year 2 the MD was 0.06 (95% CI = -0.24 to 0.36; P = 0.7).

### *Modified bleeding index changes*

Three of the included clinical trials analyzed the mBI (Figure 7A - C) [18,20,21]. One of the studies reported three follow-up periods of 1 year, 2 years and 3 years [20]. Another one reported two follow-up periods of 1and 2 years [21] and the remaining study included only a 4 year follow-up [20]. Both of the 1 year and 2 year analysis included 33 implants in both infected and non-infected groups. The 3 year or more follow-up included 215 implants in the infected sockets and 96 implants in the non-infected sockets. No statistical significant difference was seen between the groups at different follow-up times, at year 1 the MD was -0.07 (95% CI = -0.28 to 0.14; P = 0.5), at year 2 the MD was -0.07 (95% CI = -0.3 to 0.15; P = 0.52) and at year 3 or more the MD was -0.00162196 (95% CI = -0.09 to 0.09; P = 0.97).

### *Width of keratinized gingival changes*

Three clinical trials [18,20,21] analyzed changes of WKG. One of the studies reported three follow-up periods of 1 year, 2 years and 3 years [18]. Another one reported two follow-up periods of 1 year and 2 years [21] and the remaining study included one follow-up period of 5 year [19] (Figure 8A - C). Both of the 1 year and 2 year analysis included 33 implants in both infected and non-infected groups. The 3 year or more follow-up period included 30 implants in the infected group and 33 implants in the non-infected group. There was a slight, but significant decrease of WKG which favoured the non-infected group (1 year, MD = 0.22; 95% CI = -0.17 to 0.6; P = 0.27; at year 2, MD = 0.16; 95% CI = -0.22 to 0.55; P = 0.4; and at 3 years or more, MD = 0.25; 95% CI = -0.3 to 0.8; P = 0.38).

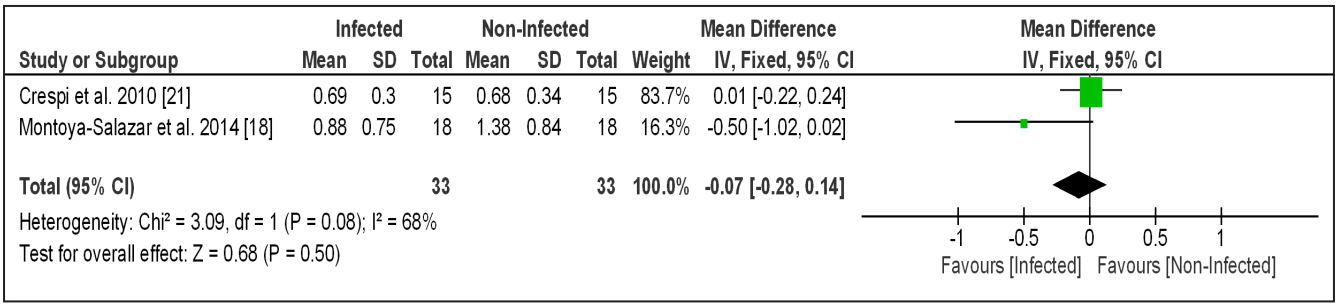


**Figure 7A.** Modified bleeding index changes of the included studies at the follow-up period of 1 year.

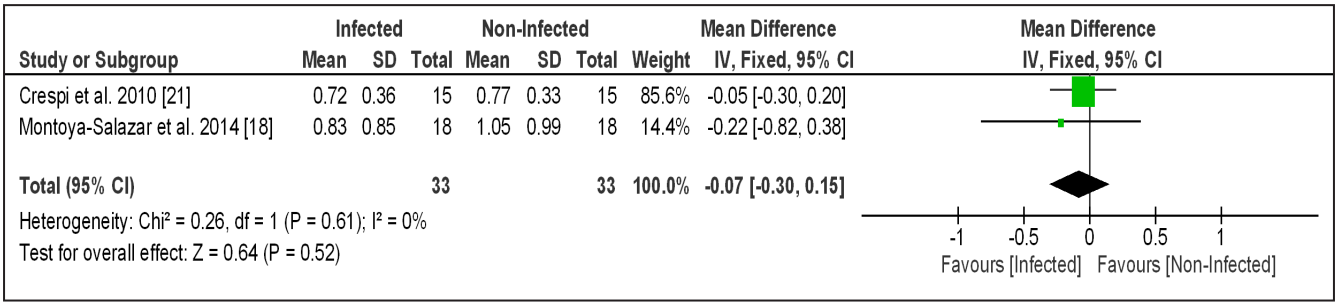


**Figure 7B.** Modified bleeding index changes of the included studies at the follow-up period of 2 years.

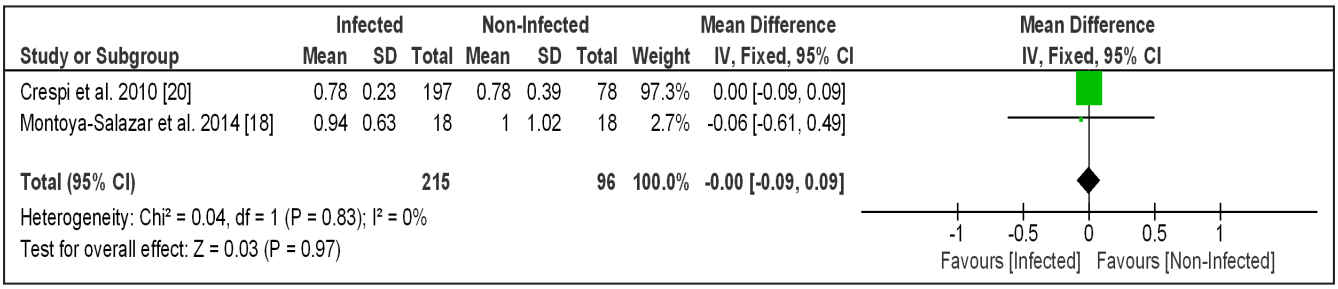


**Figure 7C.** Modified bleeding index changes of the included studies at the follow-up period of > 3 years.

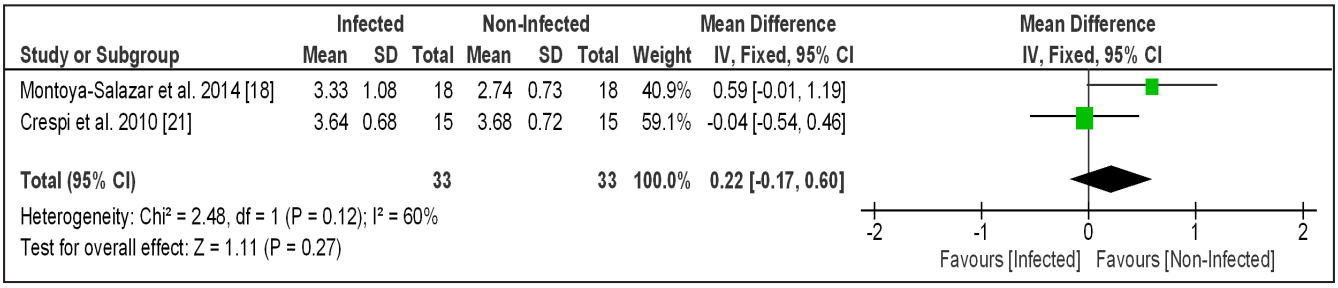


**Figure 8A.** Width of keratinized gingiva of the included studies at the follow-up period of 1 year.

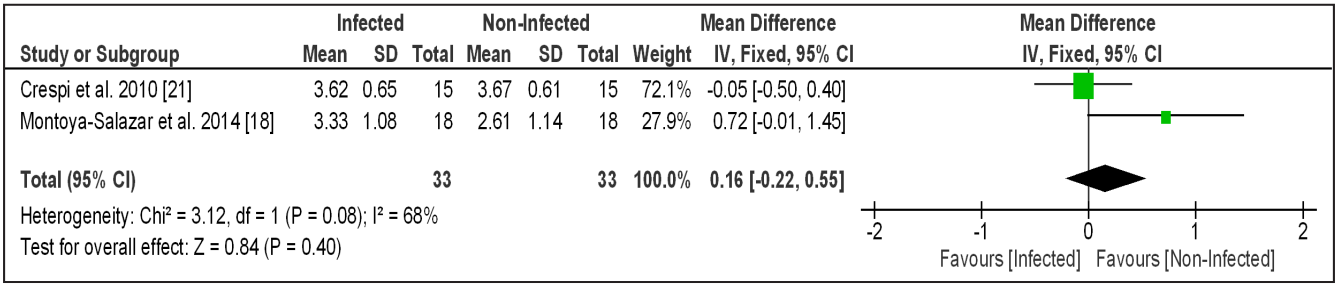


**Figure 8B.** Width of keratinized gingiva of the included studies at the follow-up period of 2 years.

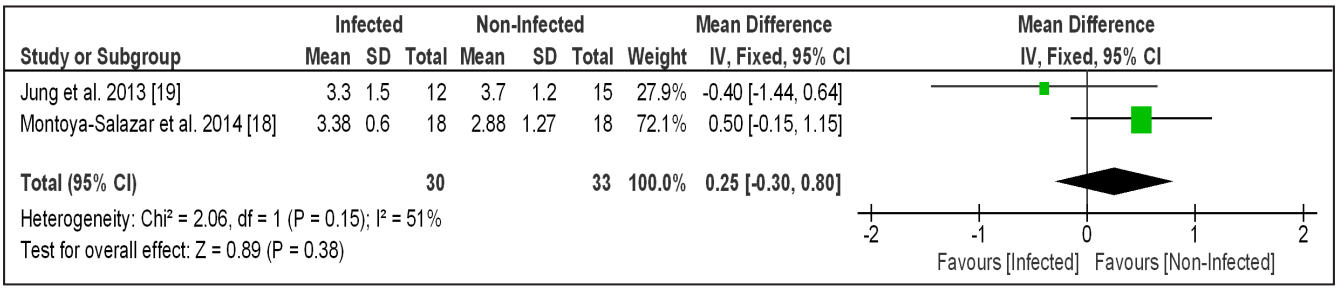


**Figure 8C.** Width of keratinized gingiva of the included studies at the follow-up period of > 3 years.

## Publication bias

No obvious visual publication bias was observed in the funnel plot analysing the implant survival rate (primary outcome variable) seen in Figure 9.

## DISCUSSION

### Principal findings

The results of this meta-analysis suggest that there is no statistical significant difference in implant survival rates (RR = 0.99; 95% CI = 0.98 to 1; P = 0.08) between immediate implant placement in infected sockets and non-infected sockets. Furthermore, all of the secondary outcome variables (MBL, MGL, mBI and PD) showed equal favourable results except for WKG that showed a slight but significant decrease in the infected group.

Implant survival depends on the MBL changes and is one of the factors to determine the success of the implant survival [30,31]. In this present review no significant difference was found between the two groups (1 year, MD = -0.05; 95% CI = -0.15 to 0.04;

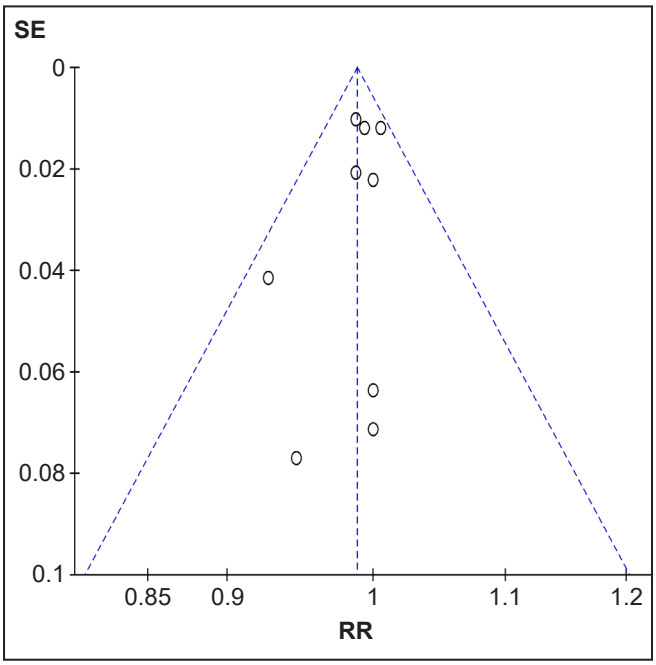


**Figure 9.** Funnel plot demonstrating publication bias.
SE = standard error; RR = risk ratio.

P = 0.25; year 2, MD = 0.12; 95% CI = -0.14 to 0.38; P = 0.36; > 3 years, MD = -0.03; 95% CI = -0.1 to 0.04; P = 0.41). Albrektsson and Isidor [32] suggested that implant success is valid if less than 1.5 mm of bone loss is seen during the first year after functional loading and thereafter a loss of < 0.2 mm annually. Thus, meaning that marginal bone loss is inevitable. Early MBL changes are a type of adaptive non-infective process that is influenced by surgical factors (surgical trauma, bone overheating, excessive implant tightening and crestal width) and prosthetic trauma (occlusial overload, type of implant design, microgap, abutment height and foreign body reaction to cement residue) [30,34,35]. A study done by Galindo-Moreno et al. [34] found that early high MBL changes of 0.44 mm at six months (after loading) were strongly associated with a subsequent increase of MBL changes of > 2 mm at 18 months. Hence, this six month period may be used as an indicator for long term bone loss prognosis.

Most of the included studies used guided bone regeneration (GBR) as a type of treatment method. The buccal bone plate can undergo more than 50% of horizontal reduction following the placement of immediate implants; this can lead to gingival recession, impairing the aesthetics. Additionally, a mean of 1 mm vertical bone loss can be seen in the presence of a thin buccal bone [35,36]. In this study no significant changes of MGL were seen between the groups (year 1, MD = -0.06; 95% CI = -0.15 to 0.03; P = 0.17; year 2, MD = -0.07; 95% CI = -0.17 to 0.04; P = 0.23).

The structural characteristics of the gingiva have been considered important for the integrity of the periodontium. A movable gingival margin facilitates the introduction of biofilm into the gingival crevice, resulting in sub-gingival plaque that triggers the activation of lymphocytes and neutrophils. This biofilm penetration induces a chronic inflammatory response [37]. However, as there are anatomical and structural differences between natural dentition and implants, the same consensus might not be applicable. The significance of the keratinized mucosa on peri-implant health has been widely discussed [38]. A study done by Pranskunas et al. [39] concluded that implants with narrow WKG (< 2 mm) had significantly more plaque, signs of inflammation, decreased stability of peri-implant site and increased mucosal recession than those with wider WKG (> 2 mm). These finding are supported by other studies [37,38,40]. However, when adequate plaque control is followed, data suggests no correlation between WKG and peri-implant conditions [37-40]. On the other hand, Monje and Blasi [37] found a correlation between narrow keratinized mucosa and a decrease in vestibular depth – which may impair patients' ability to implement correct oral hygiene measures. Additionally, WKG of < 2 mm is associated with increased brushing discomfort and as well as inadequate aesthetical outcome [39-41]. The present review and meta-analysis showed that a slight but significant amount of WKG (1 year, MD = 0.22; 95% CI = -0.17 to 0.6; P = 0.27; at year 2, MD = 0.16; 95% CI = -0.22 to 0.55; P = 0.4; and at 3 years or more, MD = 0.25; 95% CI = -0.3 to 0.8; P = 0.38) is lost during the immediate implant placement in infected sites. This suggests that WKG should be of concern in clinical situations were optimum plaque control is not feasible or when there is a high aesthetic demand.

Additionally, PD and mBI clinical parameters were collected and compared to determine if there were any soft tissue changes indicating inflammation. The two groups showed no significant statistical differences in both of the analyses; PD (year 1, MD = 0.06; 95% CI = -0.15 to 0.28; P = 0.58; and year 2, MD = 0.06; 95% CI = -0.24 to 0.36; P = 0.7) and mBI (year 1, MD = -0.07; 95% CI = -0.28 to 0.14; P = 0.5; year 2, MD = -0.07; 95% CI = -0.3 to 0.15; P = 0.52 and year 3 or more, MD = -0.00162196; 95% CI = -0.09 to 0.09; P = 0.97).

Immediate loading was used in some of the included studies. In the review conducted by Pigozzo et al. [42] showed that both immediate and early loading protocols in single implant crowns had high success rate. Another study done by Gallucci et al. [43] showed a survival rate of 98.4% and a success rate of

87% to 100% in immediate implant placement with immediate loading.

All of the included studies reported about removing of the granulation tissue before the implant placement. In general, most studies recommend curettage of the implant site before placement or suggest antibiotics to aid the success rate of immediate implant placement [44]. During the primary stability, the outer implant threads are in close proximity with the surrounding bone, providing mechanical interlocking between the bone and implant [45,46]. However, the inner surfaces of the threads are unable to have an implant-to-bone contact and the void formed will be occupied with blood, subsequently forming into a blood clot characterized by a fibrin coagulum with thrombocytes, neutrophils, erythrocytes and macrophages/monocytes [45]. The fibrin coagulum network will progressively form into granulation tissue when penetration of vascular units and fibroblast-like cells is initiated. This initial wound healing response will start the bone apposition between the implant and the surrounding bone, indicating the build-up of the secondary stability [45,46]. On the contrary, when in presence of infection, sites showing pathology may increase the risk of microbial interference with the initial wound healing [47,48]. Even after vigorous curettage and irrigation of the infected socket, some microbial pathogenic species are able to survive in a vegetative state at the site and once the implant is placed they might reactivate and colonize the implant surface initiating retrograde peri-implantitis and bone loss [48-50]. However, recent evidence suggests that granulation tissue collected from infected sites behave similarly to granulation tissue of healing wounds. The findings imply that the cell cultures taken from these granulation tissues contain pluripotent stem cells that might aid tissue healing if the infection is controlled [48]. The study done by Crespi et al. [48] compared two infected socket groups: for one group debridement was performed, and for the second group the granulation tissue was left. The results showed equal favourable outcomes for both of the groups after a period of one year. Although the study has showed favourable results, more long-term randomized clinical trials evaluating clinical and histological results are needed as the data is very limited.

All of the included clinical trials used either preoperative, postoperative or both antibiotic prophylaxes as a treatment protocol. The usage of antibiotics as a preventive measurement in healthy patients for suppressing the residual infection left during debridement, postoperative infections and oral implant failures is still disputed [51]. Questions about the type of antibiotics, the dosage and regimen to follow still remain. Romandini et al. [52] found in their review that all introduced protocols reduced early implant failures; however, postoperative prescription due to its prolonged course was associated with higher adverse events (resistance). Nonetheless, further research is needed for a definite protocol.

**Previous systematic reviews**

The findings of this present meta-analysis are similar to the two previous meta-analyses done on this subject [53,54]. Both of those studies indicated that the placement of immediate implants into infected sockets does not significantly affect the rate of implant survival. The quantitative analyses performed by Lee et al. [53] included only three of the studies presented in this review [18,19,21]. Clinical parameters such as MBL, MGL, PD, mBI and WKG were included in the meta-analysis. However, separate analyses for different follow-up periods to decrease the heterogeneity were not made; only the latest follow-up periods were compared. The meta-analysis done by Chen et al. [54] included all of the studies presented in this review but exclusion was made on all implants that were not placed in the aesthetic zone. Clinical parameters such as MBL and MGL were included; however, meta-analysis was not conducted on PD, mBI and WKG.

**Limitations and future scientific recommendations**

It is important to highlight that no randomized clinical trials were found concerning this subject. It may not be feasible to compare these protocols for the reason that it can be quite challenging to apply similar selection criteria as there are many cases that present with extraction site risk factors such as presence of thin or absent buccal bone, making them less preferable for one protocol. In addition, only English studies were included, a factor that can cause bias with paper selection due to exclusion of any possible primary studies in other languages.

Numerous scientific studies made on osseointegrated implants use the terms “implant survival” and “implant success” synonymously which can generate confusion. It is of importance to differentiate these two terms in order to facilitate the same quality and outcome data within all studies. “Implant survival” is defined as implant and fixed prosthesis present in the mouth regardless of biological and technical complications, while “implant success” involves both clinical (PD, mBI, and modified plaque index) and radiological aspects [55-57].

The survival rates of modern implantology are considered high and predictable. Hence, additional criteria such as the aesthetics of the peri-implant soft tissues have become one of the important factors to evaluate the implant success criteria [2,7,8]. Bone characteristics and soft tissue dimensions are critical factors in achieving a satisfactory aesthetic outcome [1,12]. Therefore, a classification of the fresh-sockets including both soft and hard tissues is necessary [58]. The authors Juodzbalys et al. [59] for example, have proposed a classification system and treatment recommendations incorporating both soft and hard tissues for immediate implant placement. The classifications assessing the fresh-socket morphology are helpful tools for the clinician to plan and judge future clinical situations. Only few of the included studies documented clinical and radiographic parameters such as presence of keratinized mucosa, PD, attachment level, plaque index, bleeding index, MBL, MGL and the peri-implant maintenance therapy. Furthermore, classification of the socket pathology origin was vague and varied among the studies. For future investigation, clinical trials should be conducted with proper documentation of the fresh-socket site morphology and origin of pathology as well as treatment and measurement procedures together with appropriately set inclusion criteria.

## CONCLUSIONS

The conducted meta-analysis suggests that there is no statistical significant difference in survival rates between infected sockets and non-infected sockets. All of the secondary outcome variables showed equal favourable results, except for width of keratinized gingiva, which slightly but significantly favoured the non-infected group. However, randomized controlled clinical trials with large samples should be made in order to draw a definite conclusion about the efficacy and safety of the treatment.

## ACKNOWLEDGEMENTS AND DISCLOSURE STATEMENTS

The authors confirm no conflicts of interest related to this systematic review.

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