Immediate implant placement in periodontally infected sites- A systematic review and meta-analysis.

Jaspreet Kaur,[1] Gurparkash Singh Chahal,[1] Vishakha Grover,[1] Dipika Bansal[2] and Ashish Jain[1]

[1]Department of Periodontology, Dr.Harvansh Singh Jugde Institute of Dental Sciences and Hospital, Panjab University, Chandigarh, India; [2]Department of Pharmacy Practice, National Institute of Pharmaceutical Education and Research, Mohali, India.

Abstract

Aims: The purpose of this meta-analysis is to systematically evaluate published evidence literature pertaining to report the differences in the survival rate of immediate implant placement in infected sites and non-infected sites.

Methods: After application of the search strategy in PUBMED, SCOPUS and EMBASE research databases, a total of 1864 papers were found. Titles and abstracts were screened, yielding 77 full text papers. After overall assessment, 23 articles were recruited based on the inclusion criteria for analysis of data.

Results: Out of 23 studies, 14 studies were combined to assess risk ratio of survival rate of immediate implant placement between infected and non-infected sites, depicting no significant difference on the survival rate. Further pooled estimate of proportion of survival rates were 0.98 suggesting 98% survival rate of immediate implants placed in infected sockets when 9 retrospective and prospective studies (no control studies) were combined. These findings demonstrate that successful outcomes can be expected for immediate implants when placed into infected extraction sockets.

Conclusion: Within the limitations of this systematic review, equal predictability for successful osseointegration and long term functioning of immediate implants was found in infected as well as in healthy extraction sites, but astringent antiseptic environment is mandatory for wound healing of immediate implants.

Keywords: Dental immediate implants, infection, periodontal disease, extraction sockets.

Introduction

A new era in restorative clinical dentistry began in 1950 with the introduction of dental implants as a restorative option. Subsequently dental implants came to the forefront in dentistry and became a standard of care for oral rehabilitation (Branemark *et al.,*1969).

Branemark's original protocol advocated placement of an implant after the bone had completely healed after tooth extraction (several months to 1 year) (Adell *et al.,*1981). Although conventional dental implants have demonstrated long term success rates of around 88% after an observation time of 12.2 to 23.5 years, but this protocol of delaying the replacement of the missing tooth, associated function and aesthetics, resulted in severe compromise of hard and soft tissue architecture owing to rapid bone resorption after tooth loss (Wilson and Weber, 1993; Hammerle *et al.,* 2004; Chen *et al.,* 2004; Chen and Buser, 2008; Becker *et al.,* 2016).

Many protocols for implant placement have been proposed, to overcome this time gap and the associated loss of tissue. These protocols for implant placement include: immediate placement: immediate implant placement in an extraction socket; early placement: early implant placement after 4 to 8 weeks after tooth removal; delayed placement: early implant placement (delayed) after 12 to 16 weeks after tooth removal; and late placement: late implant placement more than 6 months after extraction (Wilson and Weber, 1993; Hammerle *et al.,* 2004).

Correspondence to: Ashish Jain, Department of Periodontology, Dr. Harvansh Singh Jugde Institute Of Dental Sciences and Hospital, Panjab University, Chandigarh. Email: ashish@justice.com

To provide rapid replacement of the tooth, prevent alveolar bone collapse during healing period, shorten treatment protocol, and reduce patient discomfort/ inconvenience, immediate implants were introduced as a protocol for implant placement. (Schulte and Heimke, 1976; Lazzara, 1989).

Initially, immediate implants were placed exclusively in healthy extraction sites. However, after attaining a reasonable treatment success rate in healthy sites, these procedures were tried in a variety of clinical situations such as esthetically demanding sites and periapical infected sites (Lazzara, 1989; Paolantonio *et al.,* 2001).

In general, teeth indicated for extraction are compromised and are often infected. The infectious process within the bony walls of infected sockets may affect the bone remodelling process. In such conditions, infected sockets are filled with fibrous tissue, ultimately affecting normal wound healing and osseous regeneration (Rosenquist and Grenthe, 1996; Quirynen *et al.,* 2003; Casap *et al.,* 2007). A variety of proposals have been put forward regarding immediate implant placement into infected sockets recognizing that the history of periodontal disease and periapical/periodontal infections are predictive markers for implant failure (Rosenquist and Grenthe, 1996; Polizzi *et al.,* 2000; Ayangco *et al.,* 2001; Quirynen *et al.,* 2003).

The success rates for early, immediate and for implants placed into healed extraction sockets have been reported to be 91.7%, 95.0% and 100% respectively (Annibali *et al.,* 2011). A systematic review has documented that sufficient evidence is not available to predict the possible advantages or disadvantages of immediate, immediate-delayed or delayed implants (Esposito *et al.,* 2010). Furthermore results from this systematic review suggested that immediate and immediate-delayed implants may be associated with higher risks of implant failure and complications than delayed implants but the aesthetic outcome might be better (Esposito *et al.,* 2010).

Immediate implant placement into infected sockets has resulted in variable success rates. Some studies have reported satisfactory results (Bell *et al.,* 2011; Fugazzotto, 2012b; Montoya-Salazar *et al.,* 2014; Blus *et al.,* 2015; Zuffetti *et al.,* 2017) whereas others have documented failures of implantswhen placed into infected sockets compared to noninfected sockets (Lindeboom *et al.,* 2006; Lang *et al.,* 2012; Marconcini *et al.,* 2013; Zhao *et al.,* 2016). Therefore, immediate implant placement into infected sockets raises a number of critical issues regarding the predictability of successful osseointegration.

To date results from published studies are inconclusive and unclear as to whether immediate implant placement into sites with periodontal or periapical infection increases the risk of implant failure or successful osseointegration. Therefore the purpose of this systematic review and meta-analysis was to evaluate published evidence related to immediate implant placement into sites with periodontal or periapical infection and report the differences in the survival rate of such implants.

Methods

Criteria for standardization and study type

The present analysis was performed according to the recommendations of the Cochrane Collaboration Guidelines for systematic reviews and meta-analyses (Higgins and Green, 2011). To ensure standardization of the data inclusion/exclusion criteria and analysis, Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria and recently issued systematic review models were followed (Moher *et al.,* 2009; Santiago *et al.,* 2018).

Protocol registration

The registration number for protocol is CRD42019133939 as per PROSPERO database

Eligibility criteria

The analysis was designed based on the PICO index as follows; (1) Population: patient who underwent immediate implant placement; (2) Intervention/Exposure: placement of an immediate implant into extraction site classified as having infection; (3) Comparison: group with immediate implant placement in periodontally infected sockets vs. group with immediate implant placement in healthy sockets; (4) Outcomes: survival rate of immediate implants placed in infected extraction sites.

Inclusion/ and exclusion criteria

Criteria for inclusion and exclusion are depicted in Table 1.

Search strategy

A search for articles published to January 2020 was conducted in the PUBMED (MEDLINE), SCOPUS and EMBASE data bases. The searches were made using key terms independently and by using Search strategies for the data bases illustrated in Tables 2 a, b & c.

Collection of data and information of extracted data

The literature research was carried out by two reviewers in an independent manner. Inter-reviewer reliability was determined by Cohen's k-test, with an assumed acceptable threshold value of 0.61 (Landis and Koch, 1977a; Landis and Koch, 1977b). After overall assessments, 23 articles were selected based on the inclusion criteria for analysis of data. Standardized information and a reporting form were used to obtain the following data from each publication : (1) name of author(s); (2) publication

Table 1. Criteria for inclusion and exclusion

Inclusion criteria
(1) Studies published in English;
(2) Human studies, randomized clinical trials, controlled clinical trials, prospective or retrospective studies with both case-control groups and cases group only;
(3) Periapical, periodontal and perioendodontically infected (having clinical and/or radiological signs of an infection, being periapical, perioendodontic (presence of acute inflammation of the periodontal ligament, pulpal necrosis, isolated deep pockets,andcircumradicular/ interradicular radiolucency, indicating an osseous defect along the periodontal ligament from apical to coronal), and/or periodontal (clinical signs include acute/ chronic inflammation of the gingiva, periodontal attachment structures, and alveolar bone, periodontal pockets, periodontal abscess may or may not be present, loss of both the attachment of the periodontal ligament and bony support, decreased vertical height of the bone surrounding the affected teeth) extraction sockets were considered for implant placement .
(4) Sockets not left for healing after extraction.
Exclusion Criteria
(1) Data from animal studies, invitro studies, clinical case reports, technical report review and incomplete data were excluded.

Table 2a. Depicting Search Strategy for PUBMED

((((((((((((((((((Diseases, Periapical[MeSH Terms]) OR Periapical Abscesses[MeSH Terms]) OR Suppurative Periapical Periodontitides[MeSH Terms]) OR Dental Granuloma[MeSH Terms]) OR Periodontitis, Apical, Chronic Nonsuppurative[MeSH Terms]) OR Periapical Periodontitis, Chronic Nonsuppurative[MeSH Terms]) OR Periapical Granuloma[MeSH Terms]) OR Apical Alveolar Abscesses[MeSH Terms]) OR Apical Alveolar Abscess[MeSH Terms]) OR Dentoalveolar Abscess, Apical[MeSH Terms]) OR Acute Nonsuppurative Periodontitis[MeSH Terms]) OR Acute Nonsuppurative Periodontitides[MeSH Terms]) OR Periodontitides,Periapical[MeSH Terms]) OR Periapical Periodontitides[MeSH Terms])) OR ((((((((((((((Diseases, Periapical[Title/Abstract]) OR Periapical Abscesses[Title/Abstract]) OR Suppurative Periapical Periodontitides[Title/Abstract]) OR Dental Granuloma[Title/Abstract]) OR Periodontitis, Apical, Chronic Nonsuppurative[Title/Abstract]) OR Periapical Periodontitis, Chronic Nonsuppurative[Title/Abstract]) OR Periapical Granuloma[Title/Abstract]) OR Apical Alveolar Abscesses[Title/Abstract]) OR Apical Alveolar Abscess[Title/Abstract]) OR Dentoalveolar Abscess, Apical[Title/Abstract]) OR Acute Nonsuppurative Periodontitis[Title/Abstract]) OR Acute Nonsuppurative Periodontitides[Title/Abstract]) OR Periodontitides,Periapical[Title/Abstract]) OR Periapical Periodontitides[Title/Abstract])) OR ((((((((((((((Diseases, Periapical) OR Periapical Abscesses) OR Suppurative Periapical Periodontitides) OR Dental Granuloma) OR Periodontitis, Apical, Chronic Nonsuppurative) OR Periapical Periodontitis, Chronic Nonsuppurative) OR Periapical Granuloma) OR Apical Alveolar Abscesses) OR Apical Alveolar Abscess) OR Dentoalveolar Abscess, Apical) OR Acute Nonsuppurative Periodontitis) OR Acute Nonsuppurative Periodontitides) OR Periodontitides,Periapical) OR Periapical Periodontitides))) AND ((((((((((((((Early Dental Implant Loading[MeSH Terms]) OR Dental Implant Loading, Immediate[MeSH Terms]) OR Single-Tooth Implants[MeSH Terms]) OR Implant-Supported Denture[MeSH Terms]) OR Implant-Supported Dental Prostheses[MeSH Terms]) OR Dental Implant Platform Switching[MeSH Terms]) OR Morse Taper Dental Implant-Abutment Interface[MeSH Terms]) OR Dental Implant-Abutment Connection[MeSH Terms]) OR Dental Implant-Abutment Interface[MeSH Terms]) OR Dental Implant Abutment Design[MeSH Terms]) OR Surgical Dental Prostheses[MeSH Terms]) OR Dental Implant[MeSH Terms])) OR ((((((((((((Early Dental Implant Loading[Title/Abstract]) OR Dental Implant Loading, Immediate[Title/Abstract]) OR Single-Tooth Implants[Title/Abstract]) OR Implant-Supported Denture[Title/Abstract]) OR Implant-Supported Dental Prostheses[Title/Abstract]) OR Dental Implant Platform Switching[Title/Abstract]) OR Morse Taper Dental Implant-Abutment Interface[Title/Abstract]) OR Dental Implant-Abutment Connection[Title/Abstract]) OR Dental Implant-Abutment Interface[Title/Abstract]) OR Dental Implant Abutment Design[Title/Abstract]) OR Surgical Dental Prostheses[Title/Abstract]) OR Dental Implant[Title/Abstract])) OR ((((((((((((Early Dental Implant Loading) OR Dental Implant Loading, Immediate) OR Single-Tooth Implants) OR Implant-Supported Denture) OR Implant-Supported Dental Prostheses) OR Dental Implant Platform Switching) OR Morse Taper Dental Implant-Abutment Interface) OR Dental Implant-Abutment Connection) OR Dental Implant-Abutment Interface) OR Dental Implant Abutment Design) OR Surgical Dental Prostheses) OR Dental Implant))

year; (3) study design; (4) number of implants installed; (5) mean age of the patients; (6) follow-up time; (7) type of pathology; (8) implant survival rates; (9) implant healing time; (10) marginal bone levels; (11) clinical attachment levels; (12) width of keratinized mucosa around implants; (13) treatment rendered.

Table 2b. Depicting Search Strategy for SCOPUS

(((KEY («Periapical Abscesses»)) OR (KEY («Suppurative Periapical «)) OR (KEY («Dental Granuloma»))) OR ((KEY («Chronic Nonsuppurative")) OR (KEY ("Periodontitis Apical")) OR (KEY ("Periapical Granuloma")))) OR (((TITLE-ABS-KEY (" Periapical Abscesses")) OR (TITLE-ABS-KEY ("Dental Granuloma")) OR ((TITLE-ABS-KEY ("Chronic Nonsuppurative") AND TITLE-ABS-KEY (periodontitis AND apical)))) OR ((TITLE-ABS-KEY ("Periodontitis Apical ")) OR (TITLE-ABS-KEY ("Periapical Granuloma")) OR ((TITLE-ABS-KEY ("Apical") AND TITLE-ABS-KEY ("Alveolar Abscesses"))) OR (TITLE-ABS-KEY ("Dentoalveolar Abscess "))) OR ((TITLE-ABS-KEY (diseases, AND periapical)) OR (TITLE-ABS-KEY ("Diseases, Periapical")) OR (TITLE-ABS-KEY ("Periapical Abscesses"))))) AND (((KEY ("Early Dental Implant Loading")) OR (KEY ("Dental Implant Loading, Immediate")) OR (KEY ("Dental Implant Loading")) OR (KEY ("Dental Implant Loading, Immediate")) OR (KEY ("Implant-Supported Denture")) OR (KEY ("Implant-Supported Dental Prostheses")) OR (KEY ("Dental Implant Platform Switching")) OR (KEY ("Morse Taper Dental Implant-Abutment Interface")) OR (KEY ("Dental Implant-Abutment Connection")) OR (KEY ("Dental Implant-Abutment Interface")) OR (KEY ("Dental Implant Abutment Design")) OR (KEY ("Surgical Dental Prostheses")) OR (KEY ("Dental Implant"))) OR (KEY ("Dental Implant")))

Table 2c. Depicting Search Strategy for EMBASE

('tooth periapical disease'/exp OR ('subdural empyema'/exp AND periapical) OR ('subdural empyema'/exp AND apical) OR ('tooth socket'/exp AND apical) OR ('chronic periodontitis'/exp AND apical) OR 'dentoalveolar surgery'/exp OR 'dental granuloma' OR ('chronic nonsuppurative' AND periapical) OR 'dentoalveolar abscess,') AND ('tooth implantation'/exp OR 'early dental implant loading' OR 'dental implant loading,' OR 'morse taper dental implant-abutment interface' OR ('dental abutment'/exp AND 'morse taper') OR ('dental abutment'/exp AND ('alveolar bone loss'/dm OR 'tooth disease'/dm) AND ('dental abutment'/dv OR 'single tooth implant'/dv OR 'tooth implant'/dv)) OR 'abutment connection' OR 'dental implant-abutment connection' OR ('abutment connection' AND 'tooth implant'/dv) OR ('abutment design' AND ('dental abutment'/dv OR 'tooth implant'/dv)) OR ('tooth prosthesis'/exp AND surgical) OR 'implant-supported denture'/exp OR 'implant-supported dental prostheses' OR 'dental implant platform switching' OR ('platform switching' AND 'tooth implant'/dv) OR 'single-tooth implants' OR ('implant-supported denture' AND ('implant-supported denture'/dv OR 'tooth prosthesis'/dv)))

Evaluation of the study quality and risk of bias

The National Health and Medical Research Council (NHMRC) bias scale was utilized for assessment of the study quality of the selected studies. This bias scale depicts evidence levels of different categorical studies, thus stratifying studies at various levels (Higgins and Thompson, 2002).

Measurements and statistical analysis

The R-programmer software was used for the analysis of risk ratio (RR) (overall effect) with a fixed effect model and corresponding 95% confidence interval (CI). Subgroup analyses stratified by different follow-up periods were performed. For all analyses, values were considered significant if $p < 0.05$.

Anticipated outcomes

Primary Outcome

1. The primary outcome was the immediate implant survival rate.

Secondary Outcomes

1. The secondary outcomes were marginal bone levels, keratinized mucosa width, clinical attachment level around installed immediate implants.

Risk of bias of quantitative data

If no significant differences were found in the data, a fixed effect model was used. On the other hand, if heterogeneity was found in the data, a random effect model was conducted. Heterogeneity was considered significant at $p < 0.1$ and was evaluated using the Q (x^2) test and I^2 value.

Results

After application of the search strategy in the PUBMED, SCOPUS and EMBASE research data bases, a total of 1864 papers were found. Titles and abstracts were screened, yielding 77 full text papers. After overall assessment, 23 articles were selected based on inclusion criteria for analysis of data (Figure 1).

Of the 23 analyzed articles, 6 studies were retrospective, 16 studies were prospective and 1 study was a split-mouth nonrandomized experimental clinical study (Hita-Iglesias *et al.,* 2015). All the studies provided information regarding patient's age, number of patients participated in the study, number of implants placed, follow–up period, treatment provided, survival rate, clinical parameters assessed and type of pathology except 9 studies, in which there was no information mentioned regarding marginal bone levels (Pecora *et al.,* 1996; Casap *et al.,* 2007; Bell *et al.,* 2011; Jofre *et al.,*

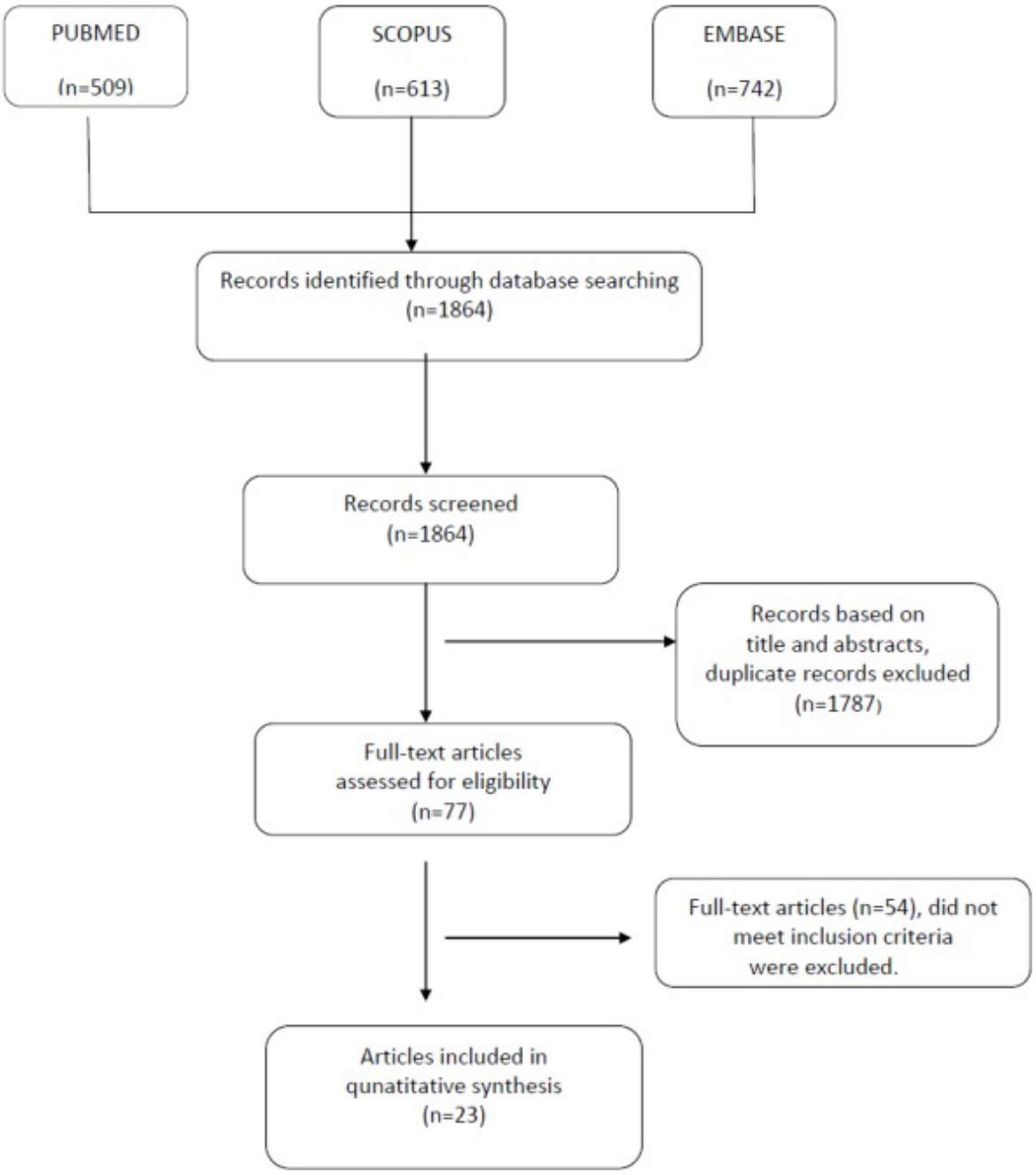

Figure 1: Study screening process.

2012; Fugazzotto, 2012a; Fugazzotto, 2012b; Blus *et al.,* 2015; Hita-Iglesias *et al.,* 2016; Zuffetti *et al.,* 2017). In addition, 6 studies examined additional parameters including: clinical attachment levels and width of keratinized mucosa around implants (Siegenthaler *et al.,* 2007; Crespi *et al.,* 2010a; Truninger *et al.,* 2011; Jung *et al.,* 2012; Marconcini *et al.,* 2013; Montoya-Salazar *et al.,* 2014). 4 studies assessed aesthetic parameters also (Lindeboom *et al.,* 2006; Jung *et al.,* 2012; Anitua *et al.,* 2016; Medikeri *et al.,* 2018).

Out of 23 studies, 9 studies reported case groups only (i.e. immediate implants placed into infected sites) without including control groups (Pecora *et al.,* 1996; Del Fabbro *et al.,* 2009; Casap *et al.,* 2007; Fugazzotto, 2012a; Jofre *et al.,* 2012; Marconcini *et al.,* 2013; Anitua *et al.,* 2016; Velasco-Ortega *et al.,* 2018; Medikeri *et al.,* 2018).

Patient characteristics

A total of 1164 implants were placed into infected sites and 1621 implants into healthy sites in studies including both case and control groups. In studies without control groups, a total of 738 implants were placed into infected sites (Pecora *et al.,* 1996; Del Fabbro *et al.,* 2003; Casap *et al.,* 2007; Fugazzotto, 2012a; Jofre *et al.,* 2012; Marconcini *et al.,* 2013; Anitua *et al.,* 2016; Velasco-Ortega *et al.,* 2018; Medikeri *et al.,* 2018). Five studies included smoker

patients (Pecora *et al.,* 1996; Del Fabbro *et al.,* 2003; Bell *et al.,* 2011; Jung *et al.,* 2012; Zuffetti *et al.,* 2017).

In almost all studies, antibiotics were prescribed before the surgical procedures were carried out (Table 3). Implants were immediately placed into infected extraction sites after socket degranulation. Two studies performed socket degranulation with laser irradiation and ultrasonic bone surgery device in addition to degranulation with curettes and physiologic saline (Montoya–Salazar *et al.,* 2014, Blus *et al.,* 2015).

Five studies did not mention the type (manufacturer) of implants used (Casap *et al.,* 2007; Fugazzotto, 2012b; Jofre *et al.,* 2012; Marconcini *et al.,* 2013; Blus *et al.,* 2015). Table 3 lists the 16 studies that used grafting and guided bone regeneration (GBR) procedures during implant placement (Pecora *et al.,* 1996; Siegenthaler *et al.,* 2003; Del Fabbro *et al.,* 2003; Lindeboom *et al.,* 2006; Casap *et al.,* 2007; Bell *et al.,* 2011; Truninger *et al.,* 2011; Fugazzotto, 2012a; Fugazzotto, 2012b; Jung *et al.,* 2012; Marconcini *et al.,* 2013; Crespi *et al.,* 2016; Anitua *et al.,* 2016; Crespi *et al.,* 2017; Zuffetti *et al.,* 2017; Medikeri *et al.,* 2018). Follow up period varied >5 years among these studies (Table 3).

One study also performed microbiologic analysis of granulation tissue to assess microbial flora at infected sites (Lindeboom *et al.,* 2006).

Meta-analysis outcome/results

All the studies mentioning comparable outcomes of immediate implant placement in infected sites and non infected sites were combined to determine the difference in survival rates between cases and controls (Figure 2).

Results of meta-analysis revealed that placement of immediate implants into infected and healthy sites showed similar survival rates as the RR was 0.99 (0.98;1.00) with no evidence of heterogeneity. The confidence intervals of pooled RR crossed the line of equality indicating that the infection at extraction sites does not increase implant failure risk. The overall effect was not significant between both groups.

For different follow-up periods a subgroup analysis was carried out which showed that the pooled RRs were 0.98 (95% CI: 0.96; 1.00) and 0.99 (95% CI: 0.98, 1.01) at <36 months and > 36 months follow-up time points for implants placed in infected and non-infected sites respectively, depicting similar survival rates (Figure 3).The overall effect was not significant among the different follow up periods.

Funnel plot visual examinations indicated no evidence of publication bias (p = 0.7169) (Figure 4).

All the studies with case groups were combined for assessing the proportion of survival rate among implants introduced in infected sites. Results revealed that if implants were inserted into infected sites, pooled estimate of studies using random effect modeling for the proportion of successful implants placed into infected sites was 0.98 (0.97; 0.99) (Figure 5). There was no significant heterogeneity found since the Q value was found to be 5.68, with degree of freedom 6 and p value came out to be 0.49.

Five studies (Siegenthaler *et al.,* 2003, Crespi *et al.,* 2010a, Jung *et al.,* 2012, Truninger *et al.,* 2011, Montoya-Salazar *et al.,* 2014) were used to evaluate the width of keratinized mucosa from baseline to the latest follow-up; two groups depicted no statistically significant difference (p=0.24) (Figure7a). The width of keratinized mucosa in the infected versus healthy sites came out to be 0.19mm (95% CI: -0.13 to 0.51; I^2=0%; $P_{heterogeneity}$ = 0.66). Five studies (Crespi *et al.,* 2010a, Crespi *et al.,* 2010b, Montoya-Salazar *et al.,* 2014, Crespi *et al.,* 2016, Crespi *et al.,* 2017) depicted the change in marginal bone levels from baseline to the latest follow-up, with no statistically significant differences found between the two groups (0.9) with I^2= 96% (Figure 7b). The difference in marginal bone levels in infected versus healthy sites was 0.01mm (95% CI: -0.26 to 0.28; I^2=96%; $P_{heterogeneity}$ <0.01). 4 studies (Siegenthaler *et al.,* 2003, Lindeboom *et al.,* 2006, Truninger *et al.,* 2011, Jung *et al.,* 2012) were used for assessing marginal bone levels (MBL) at mesial and distal sites, but there were no statistically significant differences at both sites between infected and non-infected groups (Fig 7c, d). The pooled MD (mesial) for MBL was -0.03mm (95% CI: -0.10; 0.06; I^2 = 0%,) and pooled MD for MBL (distal) was -0.02 mm (95% CI: -0.06, 0.09; I^2 = 0%).

Three studies (Siegenthaler *et al.,* 2003, Jung *et al.,* 2012, Truninger *et al.,* 2011) were used to assess the clinical attachment level (CAL) at mesial and distal aspects of the adjacent teeth facing the implant, but there were no statistically significant differences at these sites between infected and non-infected groups (Figure 8a,b). The pooled MD (mesial) was -0.34mm (95% CI: -1.02; 0.35; I^2 = 55 %,) and pooled MD for CAL (distal) was -0.49 mm (95% CI: -0.95, -0.02; I^2 = 17 %,).

Discussion

Today, placement of immediate implants is a very well accepted clinical procedure, but placement into an infected socket is considered a relative contradiction. The literature suggests that infected sockets provide a bacterial environment for implant contamination thereby affecting osseointegration (Chrcanovic *et al.,* 2015). Therefore most clinicians avoid immediate placement of implants into infected sockets. Support for this approach has been reported indicating that immediate placement of dental implants into infected sites is associated with a statistically significant higher risk of failure than for those placed into non-infected sites (Zhao *et al.,* 2016, de Oliveira-Neto O *et al.,* 2019).

Table 3. Characteristics of studies included

Author Name	Year	Design of study	Implant no. (Patient no.)	Age (mean, years)	Follow Up (months)	Treatment	Implant failed	Survival rate (%)	MBL (Mean ± SD) mm	Type of infection	GBR/GTR	CAL / MGL (Mean ± SD) mm	Width of keratinized mucosa, buccally (Mean ± SD) mm
Pecora *et al.*	1996	Retrospective	7 (31) 9-moderate-heavy smokers	22–61 (41)y	16.3m	Socket degranulation, placement with or without nonresorbable polytetrafluoroethylene (PTFE) membranes(GBR), postsurgical antibiotics for 7 days, postsurgical chlorhexidine for 8 weeks.	1 (1)-heavy smoker	85.7 (96.9)	NM Radiographs compared with baseline, gingival tissues showed no signs of inflammation	Combined endodontic-periodontal involvement	E-PTFE (Goretex periodontal membrane)	-	-
Lindeboom *et al.*	2006	Prospective RCT	50 -25(IP) 25(DP)	19-69 y	12m	600 mg clindamycin 1 hour before surgery, socket degranulation, GBR, postsurgical chlorhexidine for 7 days.	2/25 (IP),0/25 (DP)	92 (IP),100 (DP)	Mesial 0.49 ±0.11 (IP) 0.52 ±0.16 (DP) Distal 0.53 ±0.12 (IP) 0.52 ±0.14 (DP)	Chronic periapical periodontitis	Autogeneous bone graft+Bio Gide	-	-
Casap *et al.*	2007	PS-NCG	30 (20)	26–67 (43)y	12–72m	Antibiotics from 4 days before surgery up to10 days after surgery, socket debridement,peripheral intrasocket ostectomy, GBR, primary closure.	1/30	96.7	NM	Subacute periodontal, chronic periapical, chronic perioendodontic, chronic periodontal lesions, periapical cyst	Bio-oss+ Gore-tex	-	-

Table 3 continued overleaf...

Table 3 Continued...

Siegenthaler *et al.*	2007	Prospective RCT	29 -16 (C),13 (T)	23-77y (C) 23-82y (T)	12m	Antibiotics 1 hour before surgery, chlorhexidine rinse, socket debridement, GBR, antibiotics for 5 days postsurgery, postsurgical chlorhexidine for 2 weeks.	0/16 (C),0/13 (T)	100 (C,T)	Mesial 1.8 ±1.1 (C) 1.9 ±1.4 (T) Distal 1.6 ± 1.1 (C) 1.7± 1.4 (T)	Periapical radioluency	Bio-oss+Bio-guide	Buccal- 3 ±1.3 (C) 3.3 ±0.6(T) Lingual- 3.1 ±1.1(C), 3 ±0.7 (T)	3±1.9 (C) 3.2 ±1.6 (T)
Del Fabbro *et al.*	2009	PS-NCG	61(30)	31–75 (55.8)y	18.5 (10–24)m	Socket degranulation, plasma rich in growth factors coating of implant, surgical reentry procedure was performed after 3 to 4 months of healing.	1/61	98.4	0.41 1 0.22 (1 year)	Chronic periapical lesion of endodontic or endoperiodontal origin	PRGF	-	-
Crespi *et al.*	2010a	Prospective RCT	30 -15(C),15 (T)	34-71y	24m	Amoxicillin 1 hour before surgery up to 7 days after surgery, debridement, saline rinse, postsurgical chlorhexidine for 15 days.	0/15 (C),0/15 (T)	100(C,T)	0.82±0.52(C) 0.86±0.54(T)	Chronic periapical lesion	-	0.25 ±0.18 (C) 0.20 ±0.13 (T) MGL	3.67±0.61 (C) 3.62±0.65 (T)
Crespi *et al.*	2010b	Prospective CCT	275 (37)-197 (T) 78 (C)	32–71(52.5) y	48m	Amoxicillin from 1 hour before surgery up to 7 days after surgery, debridement, saline rinse, postsurgical chlorhexidine for 15 days.	0 /78 (C), 2/197 (T)	100 (C), 98.9(T)	0.78 ±0.38 (C) 0.79 ±0.38 (T)	Endodontic periodontal lesions, root fracture.	-	-	-
Bell *et al.*	2011	RA	637 (C) (477),285 (T) (256)	60.1y (C) 58.4y(T)	3–93 (19.75)m	Preoperative chlorhexidine rinse, intravenous antibiotics, socket debridement, saline rinse, platelet-rich plasma + bone graft.	8/637 (C),7/285 (T)	98.7(C) 97.5(T)	NM	Chronic periapical pathology	PRP+ Bone graft+ Collatape	-	-

Table 3 continued overleaf...

Table 3 Continued...

Truninger *et al.*	2011	Prospective RCT	29 -16 (C),13 (T)	58y (C) 48y (T)	36m	Antibiotics 1 hour before surgery, chlorhexidine rinse, socket debridement,GBR, antibiotics for 5 days postsurgery, postsurgical chlorhexidine for 2 weeks.	0/16 (C),0/13 (T)	100	Mesial 1.57 ±0.57 (C) 1.54 ±0.88 (T) Distal 1.59 ±0.8 (C) 1.69 ±0.92 (T)	Periapical pathology with pain, radiolucency ≥1 mm, fistula, suppuration, or a combination of these findings	Bio-oss+Bio-guide	Mesial -3.4 ±1.3 (C) 2.7 ±1 (T), Distal -3.6 ±1.3 (C) 2.7 ±0.9 (T)	3±1.3 (C) 3.5±1.7 (T)
Jofre *et al.*	2012	PS NCG	31	19–84 (48)y	6–297(15)m	3 days before surgery: dental prophylaxis, drainage of abscess and irrigation with chlorhexidine 0.12%, and antibiotics + chlorhexidine 0.12% rinse twice a day. At the surgery: curettage/ degranulation of sockets, irrigation with chlorhexidine 0.12%. Postoperative: Antibiotics and chlorhexidine for 7 days.	0/31	100.0	NM	Acute or chronic endodontic or periodontal disease, chronic apical lesions	-	-	-
Fugazzotto	2012a	RA	418 (432)	18–73y	24–204 (67.3)m	Amoxicillin 500 mg 3×/day for 10 days. Etodolac 400 mg 3×/day for 5 days. Curettage of periapical lesions, debridement of soft tissues, placement of autologous bone of particulate materials and covering membranes when needed.	5/418	98.8	NM	Periapical pathology	Autologous bone+ DFDBA+ DBBM+e-PTFE membrane	-	-

Table 3 continued overleaf...

Table 3 Continued...

Fugazzotto	2012b	RA	148(64)-64(C), 64(T)	21–71(46)y	≤117 (64) m	Amoxicillin 500 mg 3times/day for 10 days. Etodolac 400 mg 3times/day for 5 days. Curettage of periapical lesions, debridement of soft tissues, placement of autologous bone of particulate materials and covering membranes when needed.	1/64 (C) 3 /64 (T)	98.2(C) 98.1(T)	NM	Periapical pathology	Autologous bone+ DFDBA+ DBBM+e-PTFE membrane		-
Jung *et al.*	2012	Prospective RCT	27- 15(C) ,12(T)	60y (28-82)C , 53y(31-87)T	60m	Antibiotics 1 hour before surgery, chlorhexidine rinse, socket debridement, GBR, antibiotics for 5 days postsurgery, postsurgical chlorhexidine for 2 weeks.	0/15 (C), 0/12 (T)	100 (T,C)	Mesial-1.4±0.5 (C), 1.5 ±0.8 (T) Distal-1.5 ±0.6 (C), 1.7 ±0.7 (T)	Periapical pathology with pain, radiolucency≥1 mm, fistula, suppuration, or a combination of these findings	Bio-oss+gore-tex	Mesial-3.5 ±1.2 (C) 2.8 ±1.0 (T) Distal-3.3 ±1.1 (C) 2.7 ±0.9 (T)	3.3±1.5 (C) 3.7±1.2 (T)
Marconcini *et al.*	2013	PS-NCG	20(13)	24–65y	12m	Amoxicillin 2 g 1 hour before surgery, thereafter, 1 g twice daily for 5 days,socket curettage, postsurgical chlorhexidine.	0/20	100	0.5	Tooth fracture and presence of an acute infection, acute endodontic failure, or chronic endodontic failure	Corticocan-cellous por-cine bone + Bio Gide membrane	0.9	3.3 ± 0.5

Table 3 continued overleaf...

Table 3 Continued...

Montoya-Salazar V *et al.*	2014	Prospective RCT	36 -18 (C),18 (T)	18-50y	36m	The teeth of the CG, which were periodontally compromised, were treated one month before surgery with scaling and root planning. All patients underwent antibiotic treatment with Azithromycin in a single dose of 250 mg/ day for 5 days after an initial loading dose of 500 mg to stop any active periodontal infection. One month later, patients were prescribed 1.5 g of amoxicillin (or 0.9 g of clindamycin in penicillin-sensitive patients).Total daily dosage of antibiotic was administered in 3 equal doses every 8 h. The antibiotic treatment started 4 days before surgery and was kept for a total of 10 days. Implants (test group (TG), n = 18) were immediately placed in infected sites after being debrided, curetted, cleaned with 90% hydrogen peroxide, and irradiated with yttrium–scandium–gallium– garnet (Er,Cr:YSGG) laser.	0/18 (C), 1/18 (T)	100 (C) , 94.44 (T)	0.06 ±0.16 (CG) 0.53 ±0.13(TG)	Periapical lesion	Bio-oss+gore-tex	1.16±0.24 (C) 1.00±0.59 (T) MGL	2.88±1.27 (C) 3.38±0.60 (T)

Table 3 continued overleaf...

Table 3 Continued...

Hita-Iglesias C *et al.*	2015	Nonrandomized experimental clinic study with split-mouth design	168 (60) -102(C),66 (T)	18-72 y	12m	On the day before the surgery, all patients were required to take amoxicillin/ clavulanic acid every 8 hours (875/125 mg tablets) or, if allergic to penicillin, clindamycin every 8 hours (300 mg tablets). After the surgical procedures, patients were asked to continue with the amoxicillin/ clavulanic acid (875/125 mg TID) or clindamycin (300 mg TID) regimen for 4 days. Patients were also provided with anti-inflammatory medication (600 mg Ibuprofen tablets) for at least 4 days.	2/102 (C), 6/66 (T)	98.1(C), 90.8 (T)	NM	Chronic periapical lesion	-	-	-
Blus *et al.*	2015	Prospective	168- 85C 36(Ta); 47, (Tc)	26–77y	12m	Amoxicillin with Clavulanic acid, 2 × 1 g/day for 5 days, starting 6–12 h before extraction. Infected sites were carefully curetted to remove the granulation tissue and were ultrasonicated during 30 seconds at 72 W.	1/85 (C), 2/36 (Ta), 0/47 (Tc)	98.8 (C), 94.4 (Ta) 100(TC)	NM	Acute, chronic periapical lesion	-	-	-
Crespi *et al.*	2016	Prospective RCT	60 -30(RG),30 (LG)	32-67 y	12m	Amoxicillin from 1 hour before surgery up to 7 days after surgery, debridement, saline rinse, postsurgical chlorhexidine for 15 days.	0/30 (RG),0/30 (LG)	100 (RG,LG)	6.45 ±1.00(LG) 7.22 ±1.01(RG)	Asymptomatic periodontitis 4-7mm in diameter	Collagen sheet in molar region	-	-

Table 3 continued overleaf...

Table 3 Continued...

Anitua *et al.*	2016	Retrospective Clinical Study	43(30)	44 - 82	72M	1g of amoxicillin (600 mg of clindamycin for allergic patients) 60 minutes before surgery and 1 g of acetaminophen 30 minutes preoperatively.7-day antibiotic therapy with amoxicillin 500 mg three times a day and acetaminophen.	0/43	93%	1.42	Endodontic, periodontal lesions	The socket was carefully curetted to remove any granulation tissue before immediate implant placement. Activated fraction of plasma rich in growth factors was injected into the socket. The gap, if available, between the dental implant and the alveolus margin was filled with Endoret (PRGF) only (gap size < 0.5 mm) or with autologous bone + Endoret (PRGF) (gap size ≥ 0.5 mm).	-	-

Table 3 continued overleaf...

Table 3 Continued...

Crespi *et al.*	2017	Prospective RCT	372 (60) -186 (RG),186 (LG)	35-72y	36m	Amoxicillin from 1 hour before surgery up to 7 days after surgery, debridement, saline rinse, postsurgical chlorhexidine for 15 days.	2/186 (RG), 3/186 (LG)	98.2 (RG), 98.39 (LG)	0.93 ±0.33 (RG), 0.88 ±0.23(LG)	Asymptomatic periodontitis	Collagen sheet in molar region	-	-
Zuffetti *et al.*	2017	Retrospective Clinical Study	527(369)-193(T), 334(C)	22.8-81.9y	52.1m	1 g amoxicillin with clavulanic acid thrice (or 300 mg clarithromycin twice) (for 6 days); 500 mg naproxen sodium; 0.2% chlorhexidine rinse BID for 2 weeks. Thorough curettage to remove granulation tissue, first by using manual instruments and then using piezosurgery inserts, and finally irrigated with sterile saline solution.	3/193 (T),7/334 (C)	98.4% (T), 97.9%(C)	NM	Chronic periodontal disease , chronic endodontic disease .	Bovine deproteinized bone (Bio- Oss) used to fill gap between socket wall and implant, when necessary. Collagen membrane (Bio-Gide) used to cover graft.	-	-
Medikeri *et al.*	2018	PS-NCG	12(8)	23-44y	12m	Amoxicillin 500 mg thrice 24hrs before surgery thereafter, thrice daily for 5 days, socket curettage, analgesic was prescribed 1 day before procedure and continued for 5 days. Prerinse of 10 ml of 0.2% chlorhexidine rinses twice daily for 2-3 weeks.	1/12	91.67%	Buccal 0.97±1.06 Lingual 0.9±0.86 Mesial 0.66±0.68 Distal 0.56±0.78	Periapical lesion	Freshly prepared PRF and DFDBA (300-500 µm) to fill gap between socket wall and implant		

Table 3 continued overleaf...

Table 3 Continued...

Velasco-Ortega E *et al.*	2018	Prospective RCT	116 (56)	33-63y	48m	One hour prior to surgery, the patients received prophylactic antibiotic therapy (500 mg amoxicillin and 125 mg clavulanic acid 1 hour before surgery); they also continued the treatment after the procedure, taking 3 capsules daily for 7 days. After surgery, a chlorhexidine mouthwash was prescribed for twice-daily use for 30 days. Ibuprofen (600 mg, 4 times daily) was prescribed for 7 days.	3/116	97.4	0.67±0.4	Periodontitis	-	-	-

T, test (infected) group; C, control group; IP, immediately placed implants; DP, delayed placed implants; RG, granulomatous tissue removal group; LG, granulomatous tissue left group; NM, not mentioned; CAL,Clinical attachment level (interproximal clinical attachment level at the tooth-sides of the adjacent teeth facing the site of the implantation); MBL, marginal bone levels; MGL, marginal gingival levels; CCT,controlled clinical trial; GTR, guided tissue regeneration; GBR, guided bone regeneration;DFDBA,decalcified freeze- dried bone allograft; DBBM, Deproteinized bovine bone mineral; PTFE,polytetrafluoroethylene membrane,PRF, platelet rich fibrin; PRP, platelet rich plasma; PRGF, platelet rich in growth factors; PS-NCG, prospective study with no control group; RA, retrospective analysis; RCT, randomized controlled trial.

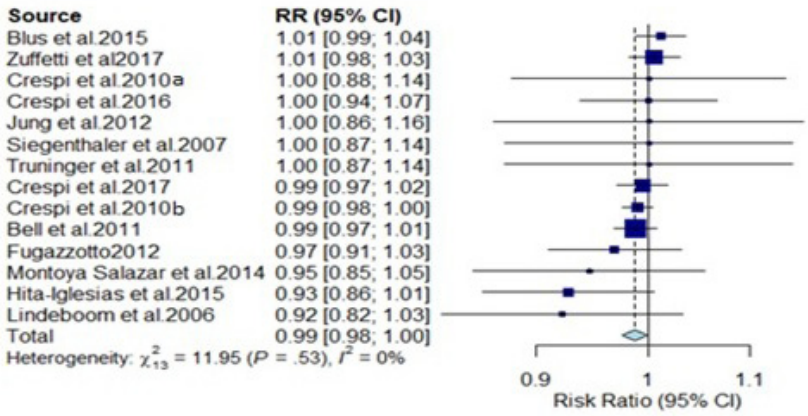

Figure 2: Forest Plot to present risk ratio of success/survival of immediate implants among infected and non-infected groups.

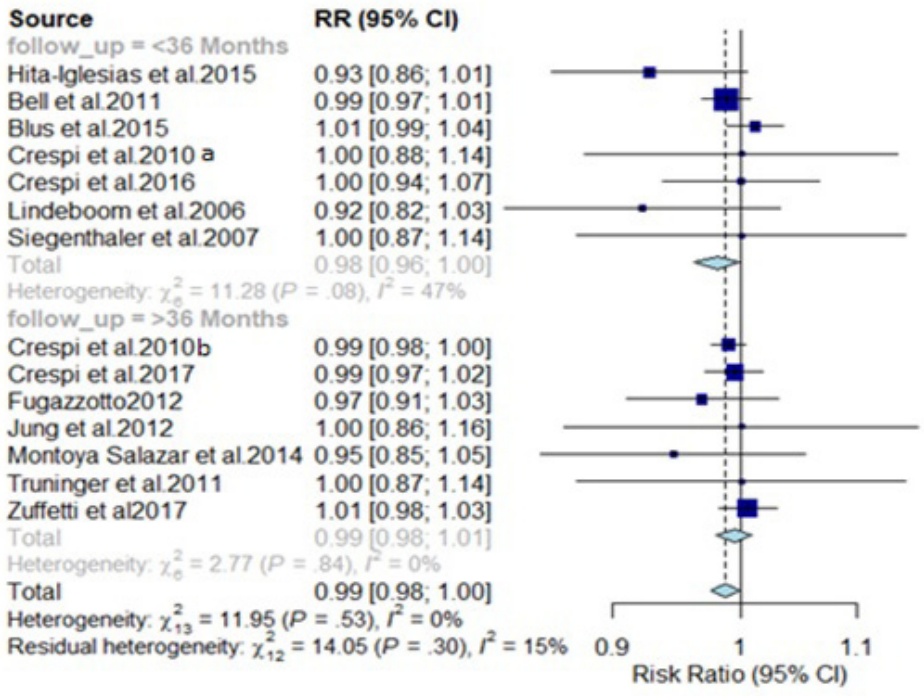

Figure 3: Subgroup analysis of survival rate of immediate implants for different follow up times in various studies.

The goal of this systematic review and meta-analysis was to critically analyze and review the published literature regarding the association between immediate placement of an implant into an infected socket and the implant survival rate. A total of 23 studies were analyzed as per the stated inclusion criteria. Out of these 23 studies, 14 studies were combined to assess risk ratio of survival rate of implant between infected and non-infected sites. There was no significant difference on the survival rate of implants between infected and healthy extraction sites. These findings are supported by other systematic reviews and meta analyses (Lee *et al.,* 2018, Chen *et al.,* 2018). The findings from the current meta-analysis also demonstrated that immediate implant placement into infected sockets may not affect the survival rate of implants.

The clinical studies conducted so far, and included in this meta-analysis, have reported that immediate implant placement into extraction sockets can be a predictable and successful clinical procedure. Pecora *et al.,* 1996**,** performed the first case series analysis on 32 titanium implants placed immediately into infected extraction sockets. The results reported failure of one implant placed into a socket associated with an endodontic-periodontic infection. In a subsequent study, Casap *et al.,* 2007 reported that only 1 implant showed osseointegration failure out of 30 immediate placed implants into debrided infected sockets. In another study, no differences in survival rates of implants placed in infected and healthy sites were reported (Fugazzotto, 2012b). Furthermore, Bell *et al.* (2011) also reported similar findings of no differences in success /survival rate

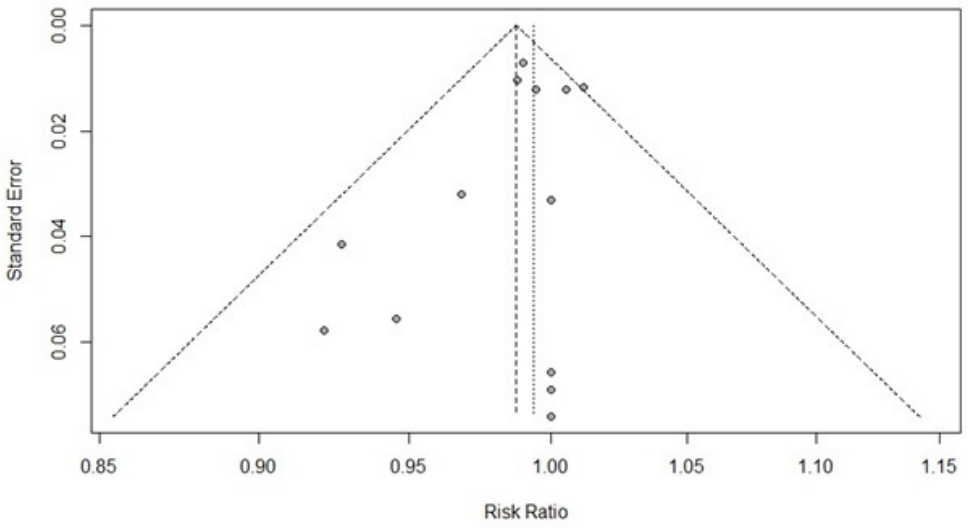

Figure 4: Funnel Plot for immediate implant survival among infected and non infected groups.

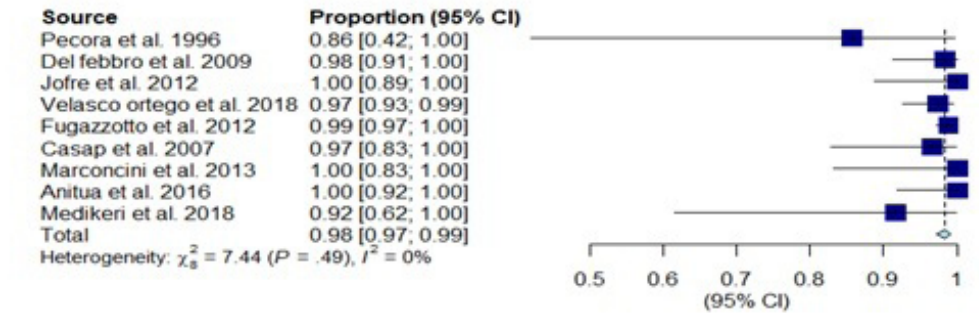

Figure 5: Forest Plot to present proportion of survival rate in immediate implants among infected group.

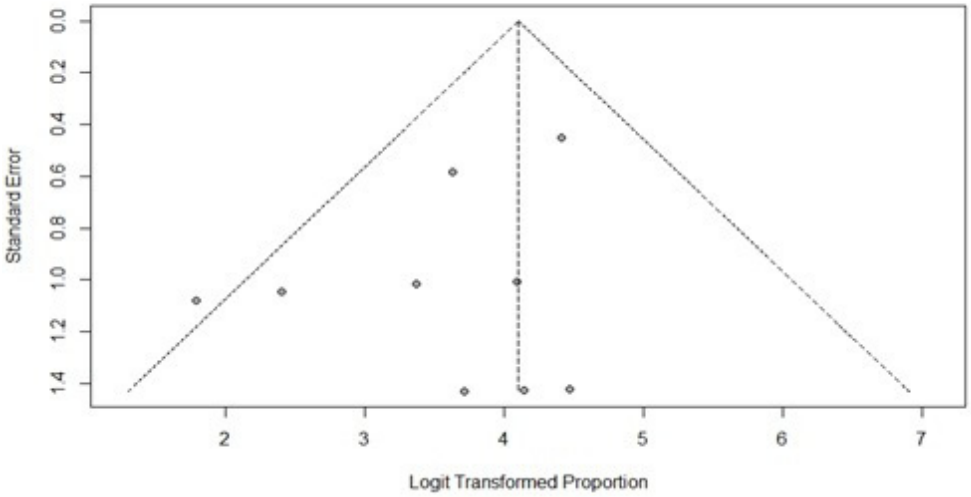

Figure 6: Funnel plot for immediate implant survival among infected group.

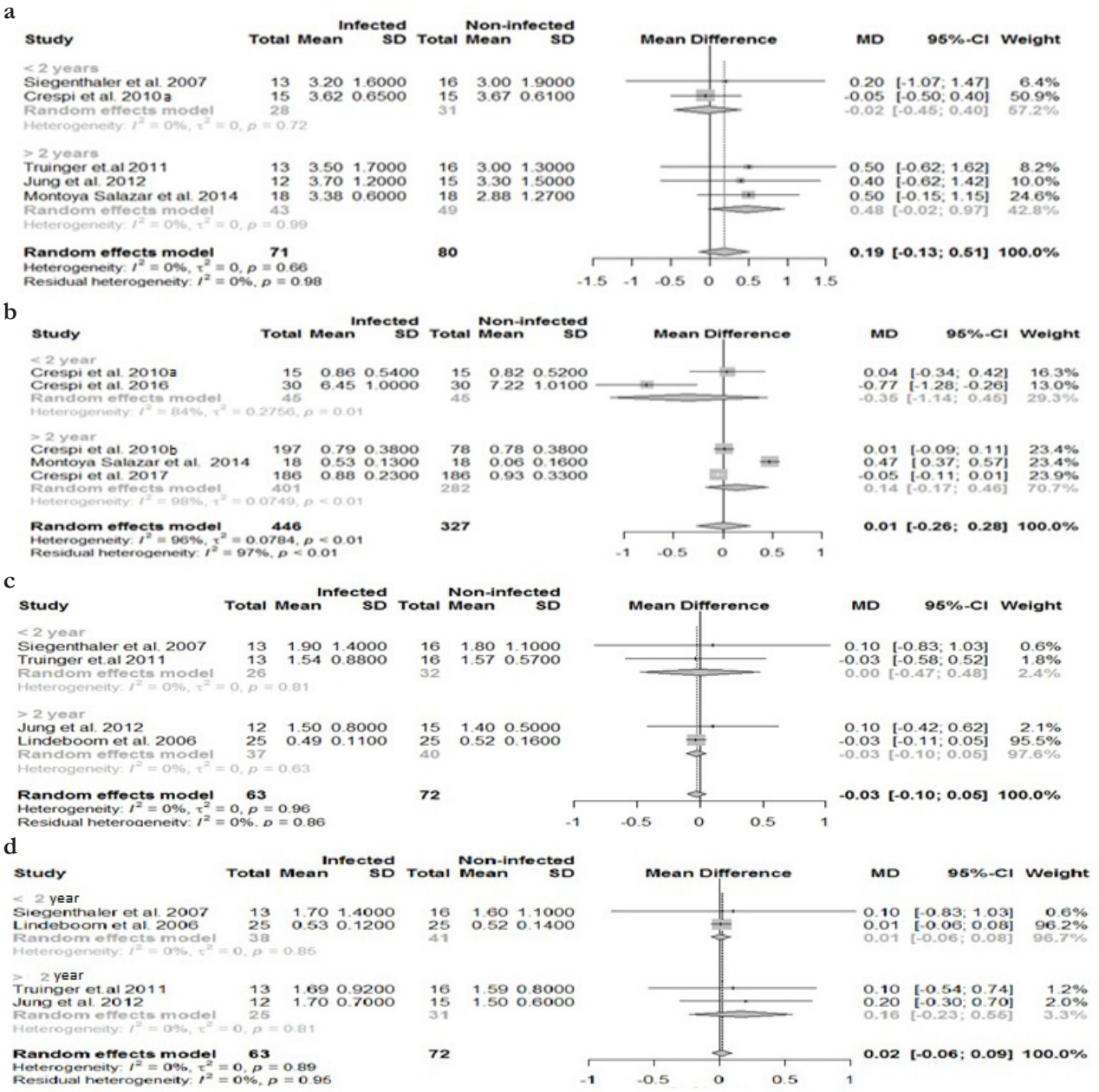

Fig 7: Mean difference (MD) and forest plot for the (a) width of keratinized mucosa (b) mean marginal bone levels (c) (d) marginal bone levels (MBL, mesial, distal) in the infected and non-infected group over follow up period of less than and more than 2 years in immediate implants

of implants placed in infected and healthy sockets. A study by Anitua *et al.,* 2016 has also reported that infected sockets are not a risk factor for immediate implant placement as no implant failure was found after 6 years of follow-up. Meanwhile, Zuffetti *et al.,* 2017 reported failure of 3 immediate implants placed into periodontally/endodontically infected sites as compared to a non-infected group in which 7 implants failed within 1 year of implant placement.

In all of the reported studies, it is noted that considerable stress is placed on strict antiseptic protocols for the extraction of the involved teeth with lesion degranulation and an appropriate level of antibiotic prophylaxis. Such protocols could lead to the eradication of microorganisms, which may result in a decreased inflammatory response and bone-resorption at the infected site. The results of this metanalysis found that granulation tissue and other infectious elements should be thoroughly curetted from infected sockets, thereby reducing any inflammatory load.

A variety of antiseptic protocols were followed in the studies which apart from systemic antibiotics, also included local antisepsis. Chlorhexidine (CHX) has been documented as a good oral antiseptic which could efficiently decrease the bacterial contamination in infected sockets. A study by Barbour *et al.,* 2009 reported that dental implants should be exposed to 0.1 g/L CHX for 60 seconds, which significantly would reduce invasion of *Streptococcus gordanii* on the implant surface.

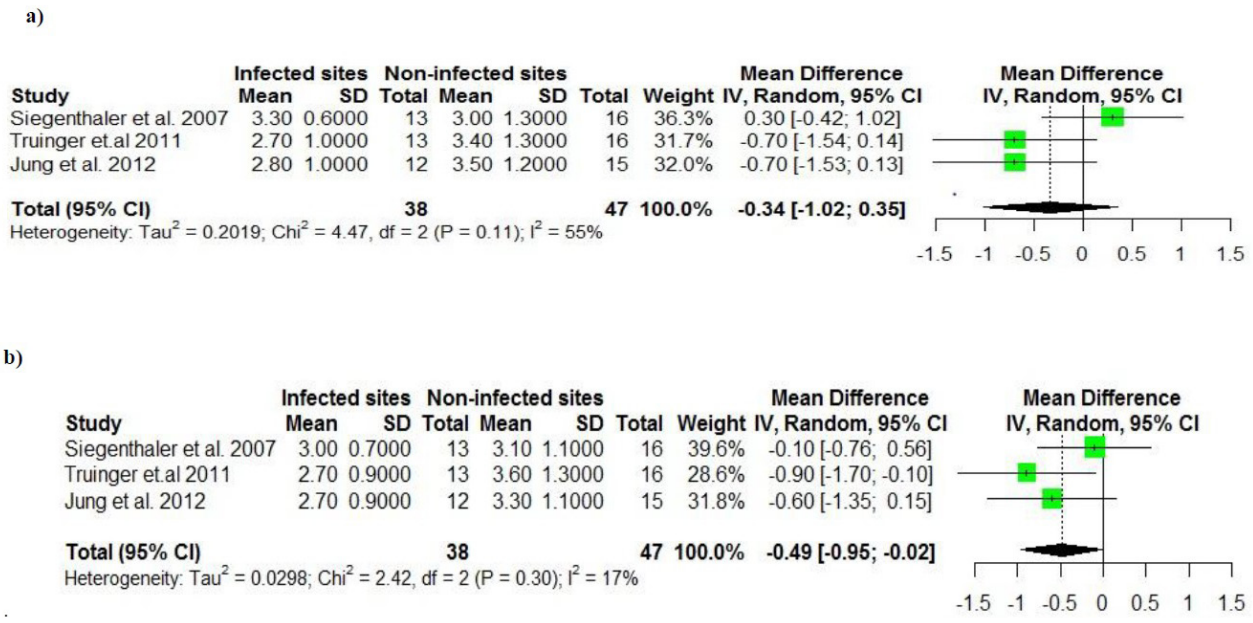

Figure 8: Mean difference (MD) and forest plot for the (a) clinical attachment level, mesial (CAL) (b) clinical attachment level, distal (CAL), (interproximal clinical attachment level at the tooth-sides of the adjacent teeth facing the site of the implantation) in immediate implants.

In order to compensate for deficient bone in infected extraction sockets some researchers have performed guided tissue regeneration (GTR) and guided bone regeneration (GBR) procedures with or without plasma rich in growth factors (PRGF) with a high success rate, high patient satisfaction and hard and soft tissues preservation (Pecora *et al.,* 1996; Siegenthaler *et al.,* 2003; Del Fabbro *et al.,* 2003; Lindeboom *et al.,* 2006; Casap *et al.,* 2007; Bell *et al.,* 2011; Truninger *et al.,* 2011; Fugazzotto, 2012a; Fugazzotto, 2012b; Jung *et al.,* 2012; Marconcini *et al.,* 2013; Crespi *et al.,* 2016; Anitua *et al.,* 2016; Crespi *et al.,* 2017; Zuffetti *et al.,* 2017; Medikeri *et al.,* 2018; Del Fabbro *et al.,* 2003).

Analysis of secondary outcomes (width of keratinized mucosa, bone marginal levels, clinical attached levels around installed implants) depicted no significant differences between both groups. Width of keratinized mucosa around installed implants, showed no significant difference between both the groups at different follow up time period. Similar results were noted for comparison of marginal bone levels at the mesial and distal aspects of the implants. Clinical attachment levels at the mesial and aspects of the adjacent teeth facing the implant in both groups at variable follow up periods showed no significant differences. Results of these secondary outcome measures suggested that immediate implant placement in infected sites results in favorable hard and soft tissue integration.

Nine retrospective and prospective studies (no control studies) were combined for assessing the survival rates of implants placed into infected extraction sockets (Pecora *et al.,* 1996; Del Fabbro *et al.,* 2003; Casap *et al.,* 2007; Fugazzotto, 2012a; Jofre *et al.,* 2012; Marconcini *et al.,* 2013; Anitua *et al.,* 2016; Velasco-Ortega *et al.,* 2018; Medikeri *et al.,* 2018). Pooled estimate of the proportion of survival rate was 0.98 suggesting 98% survival rate of implants placed into infected extraction sockets. These findings further emphasized the successful outcomes of implants placed into infected sockets

The results from this meta-analysis indicated that immediate implant placement in infected sockets does not lead to any radiological, clinical and aesthetical differences around implants as compared to implants that were installed into healthy sites.

Limitations of this systematic review included the lack of homogeneity in data due to reporting of different clinical situations at the site of implant placement. There was variance between studies regarding the different tooth sites for implant placement, different implant systems and characteristics of the lesion under investigation. Moreover, studies analyzed presented with non-uniform reporting of clinical parameters such as bleeding and plaque indices, and amount of bone loss. Accordingly there were differences in the criteria used for assessing success or failure of implants in the studies and this could significantly lead to bias in clinical outcome parameters.

Though, all studies demonstrated that immediate implant placement into infected extraction sockets can be successful, provided that proper antiseptic protocols are followed. However, the literature also suggests that there are factors such as primary stability at the time of

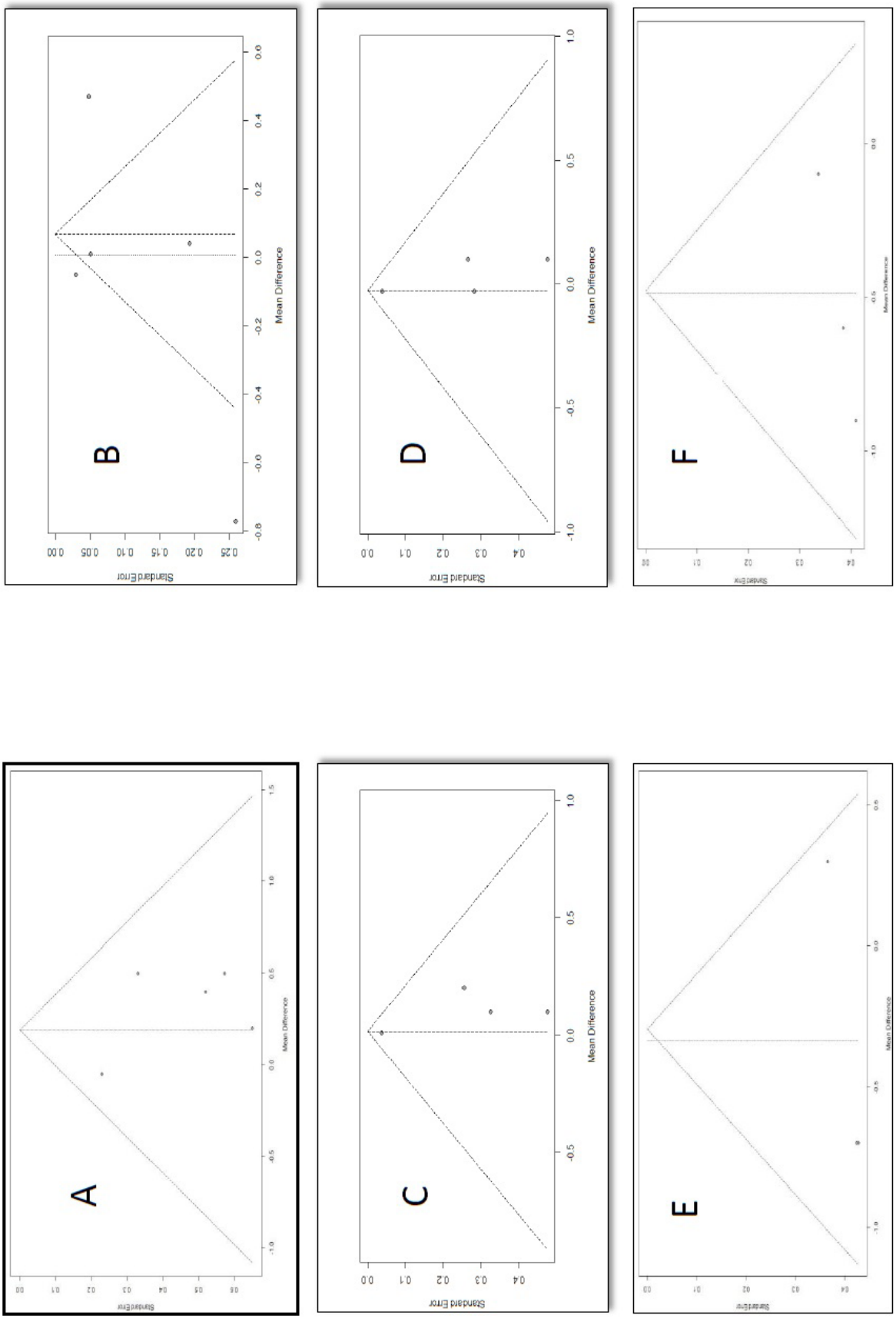

***Figure 9:** A funnel graph for the homogeneity representation of the meta-analysis. The data shows that the plotted homogeneity is acceptable for A) width of keratinized mucosa (B) mean marginal bone levels (MBL), heterogeneity (96%) (C) marginal bone level, mesial (D) marginal bone level, distal (E) clinical attachment level (CAL), mesial (F) clinical attachment level (CAL), distal, (interproximal clinical attachment level at the tooth-sides of the adjacent teeth facing the site of the implantation) in immediate implants.*

implant placement, implant positioning, socket anatomy, soft tissue morphology, tooth position, implant system used and administration of antiseptic protocols which could change the predictability of success of immediate placement of implants into infected extraction sockets.

Conclusions

Immediate implant placement is a viable option to help maintain good hard and soft tissue architecture. Within the limitations of this systematic review, the following conclusions can be made. First there is no difference in survival rate of immediate implants placed into infected and healthy extraction sites and this signifies equal potential /predictability for successful osseointegration and long term functioning of immediate implants. Secondly, antiseptic protocols such as systemic and local use of antibiotics, oral rinses used before and after surgery and thorough curettage of granulation tissue from the extraction socket to provide an adequate environment for healing wound are mandatory for optimal healing / chances of osseointegration in infected extraction sockets.

Acknowledgements

We duly acknowledge Mr. Mir Asrar for his kind support and assistance regarding analysis of data.

Conflict of Interest

The authors claim no conflict of interest in this study.

REFERENCES

Adell R, Lekholm U, Rockler B, *et al.* A 15-year study of osseointegrated implants in the treatment of the edentulous jaw. *International Journal of Oral Surgery* 1981; **10**:387-416.

Anibali S, Bignozzi I, Iaccovazzi L, La Monaca G and Cristalli MP. Immediate, early and late implant placement in first molar sites: a retrospective case series. *International Journal of Oral Maxillofacial Implants* 2011; **26**:1108-1122.

Anitua E, Pinas L and Alkhraisat MH. Long-Term Outcomes of Immediate Implant Placement Into Infected Sockets in Association With Immediate Loading: A Retrospective Cohort Study. *Journal of Periodontology* 2016; **87**:1135-1140.

Ayangco L and Sheridan PJ. Development and treatment of retrograde peri-implantitis involving a site with a history of failed endodontic and apicoectomy procedures: a series of reports. *International Journal of Oral Maxillofacial Implants* 2001; **16**:412-417.

Barbour ME, Gandhi N, El-Turki A, O'Sullivan DJ and Jagger DC. Differential adhesion of Streptococcus gordonii to anatase and rutile titanium dioxide surfaces with and without functionalization with chlorhexidine. *Journal of Biomedical Material Research* 2009; **90:**993-998.

Becker ST, Beck-Broichsitter BE, Rossmann CM, Behrens E, Jochens A and Wiltfang J. Long-term survival of Straumann dental implants with TPS surfaces: a retrospective study with a follow-up of 12 to 23 years.*Clinical Implant Dentistry and Related Research* 2016; **18**:480-488.

Bell CL, Diehl D, Bell BM and Bell RE. The immediate placement of dental implants into extraction sites with periapical lesions: a retrospective chart review. *Journal of Oral Maxillofacial Surgery* 2011; **69**:1623-1627.

Blus C, Szmukler-Moncler S, Khoury P, *et al.* Immediate implants placed in infected and noninfected sites after atraumatic tooth extraction and placement with ultrasonic bone surgery. *Clinical Implant Dentistry and Related Research* 2015; **17(Suppl 1)**: e287-e297.

Branemark PI, Adell R, Breine U, Hansson BO, Lindstrom J and Ohlsson A. Intra-osseous anchorage of dental prostheses I. Experimental studies. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery* 1969; **3**:81-100.

Casap N, Zeltser C, Wexler A, Tarazi E and Zeltser R. Immediate placement of dental implants into debrided infected dentoalveolar sockets. *Journal of Oral Maxillofacial Surgery* 2007; **65**:384-392.

Chen ST, Wilson Jr TG and Hammerle CH. Immediate or early placement of implants following tooth extraction: review of biologic basis, clinical procedures, and outcomes. *International Journal of Oral Maxillofacial Implants* 2004; **19(Suppl.)**:12-25.

Chen S and Buser D. Implants in post-extraction sites. A literature update. In Buser D, Belser U and Wismeijer D: *ITI Treatment Guide, vol. 3*. Berlin: *Quintessence*; 2008; 9-14.

Chen H, Zhang G, Weig IP and Gu X. Immediate placement of dental implants into infected versus noninfected sites in the esthetic zone: A systematic review and meta-analysis. *The Journal of Prosthetic Dentistry* 2018; **76**:338-345.

Chrcanovic BR, Martins MD and Wennerberg. A. Immediate placement of implants into infected sites: a systematic review. *Clinical of Implant Dentistry and Related Research* 2015:**17 (Suppl. 1)**: e1-e16.

Crespi R, Capparè P and Gherlone E. Fresh-socket implants in periapical infected sites in humans. *Journal of Periodontology* 2010a; **81**:378-383.

Crespi R, Capparè P and Gherlone E. Immediate loading of dental implants placed in periodontally infected and noninfected sites: a 4-year follow-up clinical study. *Journal of Periodontology* 2010b; **81**:1140-1146.

Crespi R, Capparé P, Crespi G, Lo Giudice G, Gastaldi G and Gherlone E. Dental Implants Placed in Periodontally Infected Sites in Humans. *Clinical Implant Dentistry and Related Research* 2016; **19**:131-139.

Crespi R, Capparè P, Crespi G, Lo GG, Gastaldi G and Gherlone E. Immediate implant placement in sockets with asymptomatic apical periodontitis.*Clinical Implant Dentistry and Related Research* 2017; 19:20-27.

de Oliveira-Neto OB, Lemos CA, Barbosa FT, de Sousa-Rodrigues CF and Camello de Lima FJ. Immediate dental implants placed into infected sites present a higher risk of failure than immediate dental implants placed into non-infected sites: Systematic review and meta analysis. *Medicina Oral Patologia Oral y Cirugia Bucal* 2019; **24:**e518-528.

Del Fabbro M, Boggian C and Taschieri S. Immediate implant placement into fresh extraction sites with chronic periapical pathologic features combined with plasma rich in growth factors: preliminary results of single-cohort study. *Journal of Oral Maxillofacial Surgery* 2009; **67**:2476-2484.

Esposito M, Grusovin MG, Polyzos IP, Felice P and Worthington HV. Interventions for replacing missing teeth: dental implants in fresh extraction socket (immediate, immediate-delayed and delayed implants). *Cochrane Database of Systematic Reviews* 2010; **9**:CD005968.

Fugazzotto P. A retrospective analysis of immediately placed implants in 418 sites exhibiting periapical pathology: results and clinical considerations. *International Journal of Oral Maxillofacial Implants* 2012a; **27**:194-202.

Fugazzotto PA: A retrospective analysis of implants immediately placed in sites with and without periapical pathology in sixty-four patients. *Journal of Periodontology* 2012b; **83**:182-186.

Hammerle CH, Chen ST and Wilson TG Jr. Consensus statements and recommended clinical procedures regarding the placement of implants in extraction sockets. *International Journal of Oral Maxillofacial Implants* 2004; **19(Suppl)**:272-278.

Higgins JP and Thompson SG.Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002; **21**:1539–1558

Higgins J and Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*.The Cochrane Collaboration: London, UK, 2011; Available online: www.cochrane-handbook.org

Hita-Iglesias C, Sanchez-Sanchez FJ, Montero J, *et al.* Immediate implants placed in fresh sockets associated with periapical pathology: a split-mouth design and survival evaluation after 1-year follow-up. *Clinical Implant Dentistry and Related Research* 2016; **18**:1075-1083.

Jofre J, Valenzuela D, Quintana P and Asenjo-Lobos C. Protocol for immediate implant replacement of infected teeth. *Implant Dentistry* 2012; **21**:287-294.

Jung RE, Zaugg B, Philipp AO, Truninger TC, Siegenthaler DW and Hammerle CH.A prospective, controlled clinical trial evaluating the clinical radiological and aesthetic outcome after 5 years of immediately placed implants in sockets exhibiting periapical pathology. *Clinical Oral Implants Research* 2012; **24**:839-846.

Lazzara RJ. Immediate implant placement into extraction sites: Surgical and restorative advantages. *International Journal of Periodontics Restorative Dentistry* 1989; **9**:332-343.

Landis JR and Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. *Biometrics* 1977a; **33**: 363-374.

Landis JR and Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977b; **33**:159-174.

Lang NP, Pun L, Lau KY, Li KY and Wong MC. A systematic review on survival and success rates of implants placed immediately into fresh extraction sockets after at least 1 year. *Clinical Oral Implants Research* 2012; **23**:39-66.

Lee J, Park D, Koo KT, SeoYJ and Lee YM. Comparison of immediate implant placement in infected and non-infected extraction sockets: a systematic review and meta-analysis. *Acta Odontologica Scandinavica* 2018; **76**:338-345.

Lindeboom JA, Tjiook Y and Kroon FH. Immediate placement of implants in periapical infected sites: a prospective randomized study in 50 patients. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontology* 2006; **101**:705-710.

Marconcini S, Barone A, Gelpi F, Briguglio F and Covani U. Immediate implant placement in infected sites: a case series. *Journal of Periodontology* 2013; **84**:196–202.

Medikeri RS, Meharwade V, M Wate P and V Lele S. Effect of PRF and Allograft Use on Immediate Implants at Extraction Sockets with Periapical Infection -Clinical and Cone Beam CT Findings. *The Bulletin Tokyo Dental College* 2018; **59**:97-109

Moher D, Liberati A, Tetzlaff J and Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*. 2009; **6**:e1000097.

Montoya-Salazar V, Castillo-Oyague R, Torres-Sanchez C, *et al.* Outcome of single immediate implants placed in post-extraction infected and non-infected sites, restored with cemented crowns: a 3-year prospective study. *Journal of Dentistry* 2014; **42:**645-652

NHMRC: National Health and Medical Research Council. How to Use the Evidence: Assessment and Application of Scientific Evidence. https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-risk-bias

Paolantonio M, Dolci M , Scarano A, *et al.* Immediate implantation in fresh extraction sockets. A controlled clinical and histological study in man. *Journal of Periodontol*ogy 2001; **72**:1560-1571.

Pecora G, Andreana S, Covani U, De Leonardis D and Schifferle RE. New directions in surgical endodontics; immediate implantation into an extraction site. *Journal of Endodontics1996*; **22**:135-139.

Polizzi G, Grunder U, Goené R, *et al.* Immediate and delayed implant placement into extraction sockets: a 5-year report. *Clinical Implant Dentistry and Related Research* 2000; **2**:93-99.

Quirynen M, Gijbels F and Jacobs R. An infected jaw-bone site compromising successful osseointegration. *Periodontology 2000* 2003; **33**:129-144.

Rosenquist B and Grenthe B. Immediate placement of implants into extraction sockets: implant survival. *International Journal of Oral Maxillofacial Implants* 1996; **11**:205-209.

Santiago Jr JF, Biguetti CC, Matsumoto MA, *et al*. Can Genetic Factors Compromise the Success of Dental Implants? A Systematic Review and Meta-Analysis. *Genes (Basel)*. 2018; **9**:444.

Schulte W and Heimke G: The Tubingen immediate implant. *Quintessenz* 1976; **27**:17–23.

Siegenthaler DW, Jung RE, Holderegger C, Roos M and Hammerle CH. Replacement of teeth exhibiting periapical pathology by immediate implants: a prospective, controlled clinical trial. *Clinical Oral Implants Research* 2007; **18**:727-737.

Truninger TC, Philipp AO, Siegenthaler DW, Roos M, Hämmerle CH and Jung RE.A prospective, controlled clinical trial evaluating the clinical and radiological outcome after 3 years of immediately placed implants in sockets exhibiting periapical pathology. *Clinical Oral Implants Research* 2011; **22**:20-27.

Velasco-Ortega E, Wojtovicz E, Espana-Lopez A, *et al*. Survival rates and bone loss after immediate loading of implants in fresh extraction sockets (single gaps). A clinical prospective study with 4 year follow-up Medicina *Oral* Patologia *Oral* y Cirugia *Bucal* 2018; **23:** e230-236.

Wilson TG and Weber HP. Classification of and therapy for areas of deficient bony housing prior to dental implant placement. *International Journal of Periodontics and Restorative Dentistry* 1993; **13:**451-459.

Zuffetti F, Capelli M, Galli F, Del Fabbro M and Testori T. Post-extraction implant placement into infected versus non-infected sites: A multicenter retrospective clinical study. *Clinical Implant Dentistry and Related Research* 2017; **19**:833-840.

Zhao D, Wu Y, Xu C and Zhang F. Immediate dental implant placement into infected vs. non-infected sockets: a meta-analysis. *Clinical Oral Implants Research* 2016; **27**:1290-1296.