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Review article

Comparative effectiveness of natural and synthetic bone grafts in oral and maxillofacial surgery prior to insertion of dental implants: Systematic review and network meta-analysis of parallel and cluster randomized controlled trials

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ABSTRACT

Objectives: Bone grafts are often used to enhance bone volume/quality prior to implantation insertion. This systematic review compares the histomorphometric effectiveness of bone grafts in an evidence-based manner.
Data: Randomized clinical trials comparing histomorphometrically the % of newly-formed bone between two grafts were included. Risk of bias within and across studies was assessed with the Cochrane tool and the GRADE approach, respectively. Random-effects pairwise meta-analyses were conducted, followed by network meta-analysis, network meta-regression and sensitivity analyses.
Sources: Four electronic databases were searched from inception to June 2015 without limitations.
Study selection: A total of 12 trials (5 parallel; 7 cluster) with a total of 231 patients (302 grafted sites) were included. No statistically significant differences were found in the % of new bone from pairwise comparisons between any two bone grafts. Treatment ranking based on the evidence network indicated that autografts presented the highest percentage of new bone, followed by synthetic grafts, xenografts, and allografts. No differences according to patient age, sex, healing time, membrane used or kind of surgical graft use were identified. Our confidence on pairwise comparisons was moderate to very low due to study limitations, inconsistency, and imprecision; our confidence on graft ranking was moderate due to study limitations.
Conclusions: No significant differences were found in the percentage of new bone between any two grafts.
Clinical significance: Synthetic bone substitutes or xenologous bone grafts can be used as an alternative to autologous graft in order to overcome problems of additional surgeries or limited graft availability.

1. Introduction

1.1. Background

Resorption of the edentulous or partially edentulous alveolar ridge frequently compromises dental implant placement in a prosthetically ideal position. Therefore, augmentation of an insufficient bone volume is often indicated prior to or in conjunction with implant placement to attain predictable long-term functioning and an esthetic treatment outcome. Autogenous bone grafts (AUTs) are considered the gold standard in bone regeneration procedures [1]. However, donor site morbidity, transmission of living viruses, unpredictable resorption, limited available quantities, and the need to include additional surgical sites are amongst the autografts-related drawbacks that have intensified the search for suitable alternatives [2].

Bone-substitute materials have increased in popularity as adjuncts to or replacements for AUTs in bone augmentation procedures to overcome many of their limitations [3]. Bone-substitute materials can be categorized in three groups: (1) allogenic grafts (ALLs), from another individual within the same

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species; (2) xenogenic grafts (XENs), from another species; or (3) alloplastic, synthetically produced grafts (SYNs). According to contemporary trends, the ideal characteristics of a bone-substitute material include space maintenance, pre-specification of the desired anatomical form, support to the periosteum, acceleration of bone remodeling, osteoconductive guidance, carrier function for antibiotics, growth factors or gene therapy approaches or scaffolds for tissue engineering [2,4–6]. It may be too optimistic to expect that a single grafting material fulfills all these functions and will be suitable for all indications.

A large number of systematic reviews with meta-analyses has been published in the last five years [7–15], but most were of suboptimal conduct or reporting and/or had methodological limitations [16], while none performed network meta-analysis to compare directly all existing bone graft alternatives.

1.2. Objective

We conducted a systematic review of parallel and cluster randomized trials (RCTs) including network meta-analysis in order to investigate the comparative effectiveness of bone grafts used in oral and maxillofacial surgery prior to implant placement in humans and to compare all grafts with the current gold standard (AUT).

2. Materials and methods

2.1. Protocol and registration

The protocol for this review was made *a priori* based on the PRISMA-P statement [17], registered in PROSPERO (CRD42015023467), and all *post hoc* changes were noted. This systematic review was conducted according to Cochrane Handbook [18] and reported according to the newly-published PRISMA Extension for network meta-analyses [19].

2.2. Eligibility criteria and literature search

RCTs on human patients comparing any two natural or synthetic bone grafts were included. No lumping of interventions was performed during the study selection phase. Non-RCTs were excluded due to bias [20–23]. Both parallel (one graft per patient) and clustered trials (>one graft per patient) were included and assessed appropriately together, by calculating for the latter clustering-adjusted estimates through random-effects regression. The pre-specified eligibiligy criteria can be found in Appendix 1.

Four electronic databases were searched systematically by one author (SNP) without any limitations from inception up to June 15th, 2015 and re-checked in October 2015 for manual additions (Appendix 1). Four additional sources (Scopus, Google Scholar, ClinicalTrials.gov, and ISRCTN registry) were manually searched for additions. Authors contacted for missing data were asked about additional missed trials. No search limitations concerning language, publication year or status were applied, except for studies on humans, where available. The reference/citation lists of the included trials and relevant systematic reviews were manually searched as well.

2.3. Study selection

Titles identified were screened by one author (SNP) with a subsequent duplicate independent checking of their abstracts/full-texts against the eligibility criteria by two authors (SNP, PNP), while conflicts were resolved by a third author (JD).

2.4. Data collection

Characteristics of included trials and numerical data were extracted in triplicate by three authors (SNP, PNP, JD) using *a priori* constructed and piloted extraction forms. Lumping of identified grafts was performed into four categories: AUT, ALL, SYN, and XEN. In case of combinations of grafts, the graft was categorized according to the graft with over 70% contribution (Appendix 1). Piloting of the forms was performed during the protocol stage until over 90% agreement was reached. Missing or unclear information was requested per e-mail by the trials' authors.

2.5. Risk of bias in individual trials

The risk of bias of the included trials was assessed using Cochrane's risk of bias tool [18] after initial calibration by three review authors (SNP, PNP, JD) and any disagreements were discussed with a fourth author (WG). The risk of bias assessment for each trial was based on the primary outcome (% new bone) or, if this was not included in the trial, on the trial's primary outcome. The risk of bias was incorporated in data synthesis using the framework of Salanti et al. [24].

2.6. Data synthesis

As the outcome of bone augmentation could be influenced by the bone graft, the technique, the patient's individual biological response, and post-operative management, a random-effects model according to DerSimonian and Laird was deemed appropriate to encompass this variability [25]. Both pairwise and network meta-analyses were conducted to obtain estimates for primary and secondary outcomes, and presented as Mean Differences (MDs) or Relative Risks (RRs) with 95% Confidence Intervals (CIs). Heterogeneity was conventionally assessed with tau^2 and I^2 (Appendix 2) and 95% Prediction Intervals (PrIs) were calculated to predict effects in a future clinical setting by incorporating heterogeneity. For clustered trials, the raw data were requested from the trial's authors and clustering-adjusted estimates were calculated with univariable and multivariable regression.

The results of all direct and mixed comparisons were presented in league tables and forest plots. The latter were augmented with contours of effect magnitude based on multiples of the mean standard deviation of the included outcome (10%): 0–10%—clinically-irrelevant effect, 10–20%—moderate effect, 20–30%—large effect, and >30%—very large effect. In order to rank treatments for an outcome, the Surface Under the Cumulative RAnking (SUCRA) probabilities were used, which express as a percentage the effectiveness of every intervention relative to an imaginary intervention that is always the best without uncertainty [26,27]. Thus, large SUCRA scores indicate a more effective intervention. All analyses were done with Stata version 13 (StataCorp, College Station, TX) by one author (SNP), with the commands xtgee, metan, mvmeta, network and the routines from Chaimani et al. [28]. A two-tailed P-value of 0.05 was considered significant for hypothesis-testing.

The following pre-specified effect modifiers were checked as possible sources of inconsistency/heterogeneity at patient or study level with conventional methods (Appendix 2): (a) characteristics of patients (age, gender), (b) type of graft, (c) surgical procedure conducted, (d) use of membrane, (e) membrane type, and (f) healing time.

2.7. Risk of bias across studies

The overall quality of clinical recommendations (confidence in effect estimates) for each of the main outcomes and for the