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Network Meta-Analysis of Oral and Maxillofacial Regeneration Procedures

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Abbreviations

NMA: Network Meta-analysis

BG: Bone grafts

BA: Bioactive

Auto or AB: Autogenous bone graft

AG: Allografts

AP: Alloplast

XG: Xenografts

Bio: Biologics

PC: Platelet concentrates

CGF: Concentrate growth factors

GTR: Guided tissue regeneration

GBR: Guided bone regeneration

CTG: Connective tissue graft

CAF: Coronally advanced flap

BNMA: Bayesian hierarchical network meta-analysis

SUCRA: Surface under the cumulative ranking curve

ARP: Alveolar ridge preservation

RCT: Randomised control clinical trials

KGW: keratinised gingival width

CAL: Clinical attachment level

RW: Recession width

RH: Recession height

PD: Pocket depth

RBH: Residual bone height

Rhpdgf: recombinant human platelet-derived growth factor

PDGF: Platelet derived growth factor

rhFGF: Recombinant human fibroblast growth factor

IGF: Insulin Growth Factor

VEGF: Vascular endothelial growth factor

GDF: recombinant human growth/differentiation factor

rhBMP2: recombinant human bone morphogenetic protein

MSA: Maxillary Sinus Augmentation

KMT: Keratinised mucosa thickness

ADM: Acellular dermal matrix

PRP: Platelet rich plasma

PRF: Platelet rich fibrin

PPD: Periodontal pocket depth

CT: Connective tissue

RG: Residual Graft

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PICO: Population/participant, Intervention, Comparator and Outcome

List of publications

Specific Objective 1**:** Canullo L, Del Fabbro M, Khijmatgar S, Panda S, Ravidà A, Tommasato G, Sculean A, Pesce P. Dimensional and histomorphometric evaluation of biomaterials used for alveolar ridge preservation: a systematic review and network meta-analysis. Clin Oral Investig. 2022 Jan;26(1):141-158. doi: 10.1007/s00784-021-04248-1. Epub 2021 Nov 26. PMID: 34826029.

Specific Objective 2**:** Del Fabbro M, Tommasato G, Pesce P, Ravidà A, Khijmatgar S, Sculean A, Galli M, Antonacci D, Canullo L. Sealing materials for post-extraction site: a systematic review and network meta-analysis. Clin Oral Investig. 2022 Feb;26(2):1137-1154. doi: 10.1007/s00784-021-04262-3. Epub 2021 Nov 25. PMID: 34825280; PMCID: PMC8816783.

Specific Objective 3**:** Canullo L, Pesce P, Antonacci D, Ravidà A, Galli M, Khijmatgar S, Tommasato G, Sculean A, Del Fabbro M. Soft tissue dimensional changes after alveolar ridge preservation using different sealing materials: a systematic review and network meta-analysis. Clin Oral Investig. 2022 Jan;26(1):13-39. doi: 10.1007/s00784-021-04192-0. Epub 2021 Oct 20. PMID: 34669038; PMCID: PMC8791918.

Specific Objective 4**:** Panda S, Khijmatgar S, Arbildo-Vega H, Das AC, Kumar M, Das M, Mancini L, Del Fabbro M. Stability of biomaterials used in adjunct to coronally advanced flap: A systematic review and network meta-analysis. Clin Exp Dent Res. 2022 Feb;8(1):421-438. doi: 10.1002/cre2.461. Epub 2021 Nov 29. PMID: 34845864; PMCID: PMC8874057.

Specific objective 6**:** Khijmatgar S, Panda S, Das M, Arbildo-Vega H, Del Fabbro M. Recombinant factors for periodontal intrabony defects: A systematic review and network meta-analysis of preclinical studies. J Tissue Eng Regen Med. 2021 Dec;15(12):1069-1081. doi: 10.1002/term.3250. Epub 2021 Oct 8. PMID: 34585856.

Specific Objective 7**:** Panda S, Khijmatgar S, Das M, Arbildo-Vega H, Del Fabbro M. Recombinant Human Derived Growth and Differentiating Factors in treatment of periodontal intrabony defects: Systematic review and network meta-analysis. J Tissue Eng Regen Med. 2021 Nov;15(11):900-914. doi: 10.1002/term.3236. Epub 2021 Aug 17. PMID: 34370897.

Specific objective 9: Khijmatgar, S.; Del Fabbro, M.; Tumedei, M.; Testori, T.; Cenzato, N.; Tartaglia, G.M. Residual Bone Height and New Bone Formation after Maxillary Sinus Augmentation Procedure Using Biomaterials: A Network Meta-Analysis of Clinical Trials. *Materials* **2023**, *16*, 1376.

Title

Network Meta-Analysis of Oral and Maxillofacial Regeneration Procedures

Abstract

Background

Regenerative dentistry is a novel speciality in dentistry that aims to regenerate the loss tissue. It involves deep understanding of cell and molecular biology to design dental therapies that aim to restore, repair, rejuvenate, and regenerate dental tissues. Its application in oral and maxillofacial regeneration procedures namely; alveolar ridge preservation, periodontal regeneration, maxillary sinus augmentation, soft tissue augmentation, root coverage procedures to name a few is wide and has become common through the use of wide range of stem cells, biomaterials and biologics. The question remains unanswered because of few clinical trials available for each procedure to regenerate loss tissue. There is a strong need of evidence for such therapies for specific clinical indications in oral and maxillofacial regeneration. Since traditional meta-analysis compares only two types of intervention, network meta-analysis has been used as most common method to compare multiple interventions from different clinical trials. Therefore, using this methodology our main aim was to determine the best performing biomaterials and biologics for oral and maxillofacial regeneration procedures. The specific objectives were; **1.** to determine the most effective grafting/sealing biomaterial in maintaining horizontal and vertical dimensions after alveolar ridge preservation; **2**. to determine the most effective grafting/sealing biomaterial for new bone formation after alveolar ridge preservation; **3.** to determine the most effective biomaterial for soft tissue regeneration after tooth extraction; **4.** to determine the most effective biomaterial for gingival recession treatment in adjunct to coronally advanced flap; **5.** to determine the most effective dental implant abutment material; **6.** to rank the different combinations of recombinant human-derived growth and differentiation factors with/without scaffold biomaterial in the treatment of periodontal intrabony defects, through network meta-analysis of pre-clinical studies; **7.** to determine the best rank recombinant growth factor formulations agents through network meta-analysis of clinical studies; **8.** to determine the effectiveness of biomaterials used in soft tissue augmentation procedures; **9.** to determine the most effective biomaterial in increasing residual bone height after maxillary sinus lift procedures

Methods

The study protocols were recorded in the PROSPERO database, and a standard approach to searching for articles in various scientific databases was adopted. A patient/population, intervention, comparison and outcomes (PICO) format was used to form a research question for each specific objective in oral and maxillofacial regeneration procedures. A custom search strategy was developed for each set of objectives and specific outcomes that accurately represented the successful results of specific oral and maxillofacial regeneration procedures were chosen. The mean, standard deviation, type of interventions used in each treatment group, number of participants and blinding status were extracted. The risk of bias was evaluated for the studies included in the network meta-analysis. The analysis was conducted using STATA software and the methods recommended by Chaimani A and Salanti G. The findings were presented in the form of network plots, inconsistency plots, predictive intervals, SUCRA rankings, and multi-dimensional scale rankings based on feasibility. The ranking of biomaterials and biologics was calculated for each considered outcome, and a Bayesian method was used in the methodology. A Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist was followed to report the results of NMA.

Results

Specific objective 1: In this study, 88 randomized controlled trials were analyzed, including a total of 2805 patients and 3073 sockets. The biomaterials/biologics used were self-healing materials, xenografts, allografts, alloplasts, platelet concentrates, and combinations of these biomaterials. Xenografts and allografts, either alone or combined with bioactive agents, were found to be the most effective in preserving horizontal and vertical ridge dimensions. Platelet concentrates were shown to be the best in increasing the percentage of new bone formation. However, a previous network meta-analysis review that included six studies found that freeze-dried bone graft plus membrane was the most likely to be effective in reducing bone height remodeling. Meanwhile, autologous bone marrow was determined to be the most likely effective in terms of width remodeling.

Specific objective 2: A total of 12 trials underwent both qualitative and quantitative analysis, which involved evaluating 312 sites. The results indicated that the use of autologous soft tissue grafts resulted in improved horizontal changes compared to resorbable membranes. Furthermore, when comparing crosslinked and non-crosslinked membranes, non-crosslinked membranes were found to

be statistically superior, as confirmed by histomorphometric network meta-analysis. This study has no previous reviews to compare its specific objective 2.

Specific objective 3: In the network meta-analysis (NMA), 11 studies were analyzed. The included studies had moderate levels of bias. The highest-ranking treatment for vertical buccal height was crosslinked collagen membranes with a SUCRA score of 81.8%. Autogenous soft tissue grafts ranked highest in horizontal width change with a SUCRA score of 89.1%, while the control group had the highest ranking in keratinized mucosa thickness with a SUCRA score of 85.8%.

Specific objective 4: The best performers in enhancing KGW were CAF + connective tissue graft (CTG), CAF + platelet concentrate matrix (PCM), and acellular dermal matrix (ADM). In terms of improving the percentage of root coverage in gingival recession, the highest-ranking materials were CAF + collagen matrix (CM) + gingival fibroblasts (GF), CAF + ADM + platelet rich plasma (PRP), and CAF + ADM. These materials outperformed CAF alone.

Specific objective 5: Of the 1437 studies identified, 18 relevant studies were included in the analysis. The total number of patients treated was 612, and 848 abutments were inserted. The network meta-analysis (NMA) found that zirconia abutments had a 83.3% probability of being ranked first in terms of plaque index (PI), 87.0% in bleeding on probing (BOP), and 65.0% in probing depth (PD) outcomes. These results indicate that zirconia abutments generally performed better than titanium and alumina abutments.

Specific objective 6: 24 studies were included for qualitative analysis and 21 studies for quantitative analysis, published up until 2020. The combined total number of animals in the control and test groups was 162 and 339, respectively. The study duration ranged from 3 to 102 weeks. In the SUCRA rankings, rhBMP-2 was associated with the best performance for bone volume density. rhGDF-5/TCP had the best ranking in bone area (mm2), rhPDGF-BB/Equine in bone height (mm), rhBMP-2 in the percentage of new bone fill, rhBMP-2/ACS in new cementum formation, and rhGDF-5/b- TCP/PLGA in connective tissue attachment and junctional epithelium.

Specific objective 7: This study considered 12 clinical studies for qualitative and quantitative analysis. The network meta-analysis found that the combination of rhFGF and hyaluronic acid had the highest ranking in terms of probing pocket depth (PPD) and clinical attachment level (CAL) outcomes. The combination of rhPDGF-BB and β-tricalcium phosphate was ranked highest in terms of percentage of bone filling. Furthermore, all bioactive agents showed better performance compared to control groups without rhGFs.

Specific objective 8: In the majority of outcomes, connective tissue graft (CTG) performed the best. When it comes to increasing keratinized mucosa, free gingival graft (FGG) was found to be the best option. Both FGG and crosslinked collagen membranes (XCM) performed better in augmenting keratinized mucosa. As for increasing soft tissue in the buccal aspects, the best results were seen with vascularized connective tissue matrix (VCMX) compared to other matrices.

Specific objective 9: 67 studies were eligible for a network meta-analysis (NMA). The study included 1955 patients who underwent 2405 sinus augmentation procedures. The biomaterials used were grouped into: autogenous bone (Auto), xenografts (XG), allografts (AG), alloplasts (AP), bioactive agents (Bio), hyaluronic acid (HA), and combinations of these. A statistically significant inconsistency factor (IF) was found in the entire loop of XG, AP, and Bio+AP. The highest ranked biomaterials for the residual bone height (RBH) of less than 4 mm were XG+AG, XG+AP, and Auto. Similarly, the biomaterials with the highest surface under the cumulative ranking curve (SUCRA) for RBH of 4 mm or more were Auto, Bio+XG, and XG+Auto.

Conclusions

The rankings of biomaterials can differ depending on the specific clinical outcomes being evaluated. Therefore, it is important to consider all confounding factors and utilize more robust NMA methods to achieve more reliable rankings. The availability of predictive intervals for the majority of research questions enables clinicians to select the most effective biomaterials for future clinical studies, which promotes informed decision-making and reduces costs for patients. However, new evidence continues to emerge through clinical trials and non-randomized studies. As a result, diverse methods

such as multidimensional scale ranking, cluster plots for different outcomes, and predictive intervals should be employed when reporting the results of network meta-analyses.

Aim

To determine the effectiveness of different biomaterials, therapies, techniques in oral and maxillofacial Regeneration Procedures through an evidence-based approach based on systematic reviews and network meta-analysis.

Specific Objectives

1. To determine the most effective grafting/sealing biomaterial in maintaining horizontal and vertical dimensions after alveolar ridge preservation
2. To determine the most effective grafting/sealing biomaterial for new bone formation after alveolar ridge preservation
3. To determine the most effective biomaterial for soft tissue regeneration after tooth extraction
4. To determine the most effective biomaterial for gingival recession treatment in adjunct to coronally advanced flap
5. To determine the most effective dental implant abutment material
6. To rank the different combinations of recombinant human-derived growth and differentiation factors with/without scaffold biomaterial in the treatment of periodontal intrabony defects, through network meta-analysis of pre-clinical studies
7. To determine the best rank recombinant growth factor formulations agents through network meta-analysis of clinical studies
8. To determine the effectiveness of biomaterials used in soft tissue augmentation procedures
9. To determine the most effective biomaterial in increasing residual bone height after maxillary sinus lift procedures

1. Introduction

Regenerative dentistry has made significant advancements from its early stages and has reached a new level in the twenty-first century. We now have the opportunity to utilize effective biomaterials for the regeneration of both hard and soft tissues, which can lead to improved treatment success and make oral rehabilitation therapies more accessible to a wider range of patients.

William Haseltine first used the phrase "regenerative medicine" during a symposium at Lake Como in 1999. It was discovered historically in a study by Leland Kaiser (1). The labels "bioactive" (BA) and "regenerative" are most frequently described. The term "bioactive" refers to a technique that elicits a response from living tissue, while "regeneration" describes the process of restoring the form and function of tissues that were lost due to disease or injury by recreating the same tissues. This is distinct from repair, which involves partial or full restoration of function through the formation of a tissue that is different from the original, such as scar tissue. Although the term "bioactive" was first used by Hench in 1969, it may not be the appropriate term for the goal of tissue regeneration. Currently, cell-based therapies and biological or synthetic materials are used to regenerate both hard and soft tissues (2).

The most widely used methods for dental or cranial and maxillofacial bone regeneration include bioengineering tooth buds, dental pulp, and craniomaxillofacial bone and tooth constructs. These methods have inspired new approaches for regenerating various situations, such as sinus grafting, augmenting hard and soft tissue sites, restoring large and small bony deformities, preserving extraction sockets or alveolar ridges, and others. However, selecting the appropriate biomaterials to meet clinical demands remains a challenge (3). An ideal regenerative material must meet several criteria, including total biocompatibility, degradation kinetics that match the healing rate of the target tissue, a pH that promotes bone or dentin regeneration, non-irritating to tissues, antibacterial, tolerance to moisture, release of ions that form hydroxyapatite, ability to function in the presence of saliva without solubility, and others (4).

Possessing these properties gives a competitive advantage as a regenerative material. The future of regenerative medicine encompasses a range of developments, including coordinated bone and tooth regeneration, cell-free approaches to regenerate cranio-maxillofacial tissue using exosomes derived

from dental cells, harnessing the plasticity of dental cells for regenerative dentistry, and the use of epigenetic regulators for dental cell differentiation (5,6).

1.1 Biomaterials

A wide range of supporting materials have been effectively utilized in oral and maxillofacial bone regeneration procedures, classified based on their origin as:

Autografts from the same individual.

Allografts and allogenic materials from the same species.

Xenogeneic materials from a different species.

Synthetically fabricated alloplastic materials.

The use of natural and recombinant growth factors, such as TGF-beta, PDGF, FGF and bone morphogenetic protein, either alone or in combination with factor-based bone transplant.

Cell-based bone grafts that employ cells to form new tissue on their own or with support from a matrix, such as mesenchymal stem cells.

Ceramic-based alternatives such as calcium phosphate, calcium sulphate, and bio-glass, which can be used alone or in combination.

Degradable and non-degradable polymers used alone or in combination with other materials in polymer-based bone grafts, like open porosity polylactic acid polymer.

The effectiveness of a biomaterial is evaluated by its ability to produce favourable results for a specific clinical application. This evaluation is influenced by various factors, including the material surface, bone proteins and other large molecules, cellular behaviour at the interface, the interface between the tissue and material, mechanical properties, and characteristics of different types of biomaterials (7).

1.2 Literature

Before starting my proposal in 2019, there were approximately 34 network meta-analyses published in the literature, covering a variety of topics in dentistry. My aim was to evaluate the best-performing biomaterials for various oral and maxillofacial regeneration indications. Relevant publications included works by Tu YK (2010 & 2012), Buti J (2013), Papageorgiou SN (2016), Cairo F et al (2016), Iocca O (2017), John MT (2017), and Caricasulo R (2018) (8-15). These studies aimed to determine the most effective biomaterials for various oral and maxillofacial regenerative procedures for different clinical conditions. They used different outcomes, even though they had similar clinical indications, but different review questions and methods of conducting network meta-analyses. The goal of my own network meta-analysis was similar, to determine the best-performing biomaterials for various clinical indications in oral and maxillofacial regeneration but with the inclusion of more updated scientific papers and also novel objectives for different clinical indication.

1.3 Challenges

The field of biomaterials science and bioengineering has seen tremendous growth, resulting in a vast amount of research data and studies. To effectively analyse and translate this information into scientific evidence, a specific method is needed. Meta-analysis is a common tool used to summarize and illustrate the existing evidence for a specific research question within a systematic review. This method has seen a significant increase in use in the past 20 years, and it allows for a more precise estimation of the effect of a treatment. However, meta-analysis has limitations, such as only being able to compare two groups at a time (16).

To address this limitation, a new tool called network meta-analysis (NMA) has been developed. NMA allows for the comparison of three or more treatments, diagnostics, or biomaterials in a single analysis, even if they were only compared two by two in the original studies. It provides a ranking based on the probability of a given treatment achieving the best performance compared to other options. In conclusion, NMA is a valuable tool in the field of biomaterials research, allowing for a more comprehensive and accurate analysis of data (17-19).

Meta-analysis has been widely used to determine the effectiveness of various biomaterials and biologics for oral and maxillofacial regeneration. However, due to its limitations, it can be challenging

to make decisions, particularly in the current boom in the dental material industry for oral and maxillofacial regeneration. Clinicians face a difficult task when choosing the best regenerative treatment for specific cases among various biomaterials.

In addition to the uncertainty in the effectiveness of different materials and combination biomaterials, there is also a need for justification for a standard recommended care when regeneration is an option compared to traditional approaches. For dental organizations to change guidelines and clinical recommendations for clinical practice, there is a need for sound scientific evidence derived from a thorough analysis of the scientific literature.

Unfortunately, only about half of patients globally receive recommended care, and up to 20% receive non-recommended or "low-value" care. Despite the development of evidence-based guidelines aimed at improving clinician's practice patterns, they are frequently ignored. Healthcare officials have long questioned the best strategy to modify clinician behaviour and increase care quality and efficiency (20-21).

It is crucial for evidence to be translated into clinical practice and for generating evidence to help in decision-making. This would impact how clinicians approach the concept of regeneration and related biomaterials. Evidence-based decision making is essential to improve the quality of care and efficiency in the field of oral and maxillofacial regeneration.

In order to improve the quality of patient care and translate scientific evidence into clinical practice, various strategies have been introduced by healthcare policy makers. One such strategy is Pay-for-Performance (P4P), where healthcare practitioners are rewarded for following clinical criteria and achieving better outcomes. However, research suggests that these centralized incentive programs have limitations in improving patient outcomes (22-23). Another strategy includes decision making through behavioural economics, where clinicians are encouraged to justify their clinical decisions. This has led to a decrease, although not significant, in the direct extraction or drilling of teeth by clinicians (24).

The focus on organizational culture has also been considered to influence the decision making of clinicians and patient outcomes. A supportive organizational culture, where employees are encouraged to solve problems and improve processes, and where senior leadership supports them, has been found to drive good changes in patient care and quality. This would encourage practitioners

to employ newer treatment strategies and later try to explore the evidence available for such treatment strategies.

Therefore, the research question arises: "What is the available evidence for biomaterials used in oral and maxillofacial regeneration?" and "With the growing number of publications, how can we utilize research data in various biomaterials literatures and turn it into scientific evidence to aid in solving specific scientific questions?"

1.4 Meta-analysis

Meta-analysis is a statistical method which was first performed by Karl Pearson (25). Meta-analysis is a statistical method that critically examines and statistically combines the findings of previous studies in an attempt to summarize the overall data pertaining to a specific medical problem. Clinicians and scientists have traditionally relied largely on "informed" editorials or narrative reviews when seeking evidence and agreement in difficult or innovative areas. There is now compelling evidence that these traditional methodologies are biased and inaccurate. In disputed areas, such as assessments of the usage of novel techniques and procedures, the evidence may be related with the reviewer's specialization rather than the findings of the trials. Because most modern clinical assessments do not utilize research methods to evaluate and dissipate the data, different reviewers frequently reach contradictory findings based on the same data. For these reasons, a formal statistical review process (meta-analysis) should take the place of the informal method. When reports, editorials, or reviews disagree, meta-analysis can be used to resolve doubt.

Traditionally, randomised controlled trials are suggested to find the treatment effects. But recently, non-randomised and observational studies can also be included for conducting meta-analysis. The advantages include; 1. Increase precision: Many studies are too small to provide strong data about the impact of interventions on their own. Estimation is frequently enhanced when new information is supplied. 2. To provide answers to questions that the individual research did not address: Primary studies generally use a specific set of individuals and interventions. A sample of studies with these differences can be utilized to assess effect consistency across a broader variety of populations and interventions. It may also allow for the analysis of the reasons behind differences in effect estimates, if appropriate. 3. To settle disagreements caused by seemingly contradicting studies or to offer new hypotheses: The statistical synthesis of findings enables for the degree of dispute to be explicitly measured, as well as the study and quantification of the causes of differing results.

1.4.1 Principles of Meta-analysis

1. In the first stage, a summary statistic is calculated for each experiment in order to describe the claimed intervention effect consistently across studies. For example, if the data is dichotomous, the summary statistic could be a risk ratio, or a difference between means if the data is continuous.
2. The second stage involves the calculation of a summary (combined) intervention effect estimate as a weighted average of the intervention effects estimated in the individual studies.

A prospective meta-analysis is a meta-analysis of studies (usually randomized trials) that were identified or designed as a group to be eligible for the meta-analysis before the research results were known (26). They are frequently carried out by a collaborative group that includes the authors of the included studies, and they collect and analyze individual participant data. Meta-analysis is typically represented by a forest plot, which displays effect estimates and confidence intervals for both individual studies and meta-analyses (27).

1.4.2 Gaps in Meta-analysis

Some of the common reasons why a meta-analysis may not be possible due to legitimate causes that include a lack of evidence, incompletely reported outcome/effect estimates, or differing effect measures used across research, and bias. Other widely mentioned reasons for not to proceed with meta-analysis include a lack of clinical or methodological diversity, as well as statistical heterogeneity. However, under these instances, meta-analysis approaches should be examined because they can yield crucial insights if carried out and interpreted correctly (28,29).

Table 1: Limitations of Meta-analysis and solution to the problems (from the Cochrane review handbook. Authors Joanne E McKenzie, Sue E Brennan. Chapter 12: Synthesizing and presenting findings using other methods)

Scenario	Description	Examples of possible solutions*
There is insufficient evidence to make a predetermined comparison.	When there are no or only one study, meta-analysis is impossible. This could be due to the fact that research in a certain area is still in its early stages, or because the PICO for the synthesis is focused on a single question.	In the analysis plan, include provisions for grouping one or more of the PICO elements at a higher level.
Estimate of result or effect that has not been fully disclosed	The intervention effects may not be well recorded within a study (e.g. effect estimate with no measure of precision; direction of effect with P value or statement of statistical significance; only the direction of effect).	If possible, use the current statistics to compute the effect estimate and precision measure. Fill up the blanks with missing statistics whenever possible (such as standard deviations). Use additional synthesis method(s), as well as methods to graphically display and communicate available effects.
Various effect measurements	The same result may be evaluated or analysed differently in different studies (for example, a time-to-event outcome may be dichotomized in particular studies). Both conditions may result in distinct effect measures (e.g. hazard ratios and odds ratios).	Calculate the impact estimate and precision measure for the same effect measure, if possible, using the statistics provided. Measure transform effect whenever possible (e.g., convert standardized mean difference to odds ratio). Use additional synthesis method(s), as well as methods to graphically display and communicate available effects.
Evidence for bias	Concerns about missing studies, missing data within studies, or bias in studies are all legitimate reasons to avoid performing a meta-analysis. These problems also apply to other synthesis processes. Incompletely stated outcomes/effects may skew meta-analyses, but not other methods of synthesis.	When there are substantial concerns about bias in the evidence, consider systematic reporting of the available implications using tables and visual presentations. Consider alternate synthesis methods in addition to meta-analysis for outcomes/effects that have not been completely stated.
Varieties in clinical and methodological practice	Concerns concerning population variety, interventions, outcomes, and study designs are frequently stated as grounds for avoiding utilizing meta-analysis (Ioannidis et al 2008). Arguments against utilizing meta-analysis due to excessive diversity also apply to alternative synthesis methods. (Valentine et al 2010).	Planned comparisons should be modified, providing rationale for ad hoc alterations.
Heterogeneity in statistics	The failure to report the meta-analysis outcome is commonly attributed to statistical heterogeneity (Ioannidis et al 2008). In this scenario, reporting an average combined effect can be deceptive, especially if the anticipated effects across the research are both negative and positive.	Make an effort to eliminate heterogeneity (e.g. checking the data, correcting an inappropriate choice of effect measure) Make an attempt to explain heterogeneity (e.g. using subgroup analysis)

		Consider offering (if possible) a prediction interval, which provides a forecasted range for the genuine intervention impact in a specific study (Riley et al 2011), highlighting intervention effect uncertainty.

1.5 Principles of Network Meta-analysis

Research in dentistry frequently has several outcomes and scientists now have a significant challenge when attempting to integrate data from various studies, especially in light of the expansion in the volume and complexity of the information that is currently available (30-34).

It is challenging to summarize research results to guide clinical decision-making since it frequently also involves contrasts between different outcomes and multiple treatment comparisons. Typically, one would focus on a primary outcome in a meta-analysis and add a number of additional outcomes to the combination. Those analyses are normally carried out independently. Using a multi-outcome meta-analysis, we may investigate several associated outcomes at once. In a random effects model context, it is possible to model correlation structures considering both outcomes and treatments; however, the estimations will become more difficult to accommodate a wide range of outcomes.

Numerous NMA methods have been proposed, the most common of which is the bayesian hierarchical network meta-analysis (BNMA) model. The rank probability of each treatment can be estimated using this model. A recent study proposed a bayesian hierarchical model to account for between-study heterogeneity in a network meta-analysis of various treatments and numerous outcomes (35).

Network meta-analysis is used to examine three or more treatments for the same disease (Figure 1). It is ideally done using the p-value which works without resampling. This is known as frequentist NMA (36,37). In a *Bayesian framework type*, the posterior distributions of all treatments can be used to calculate the likelihood that each treatment will be the best or, more generally, the probability that it will have a specific rank. The *"posterior distribution"* is a way to describe how likely it is that a certain answer is correct, based on all the information available. It combines what was known before (the "prior information") with what was learned from new data. By summarizing all this information into a "probability distribution," we get a better understanding of how confident we can be in our answer.

In simpler terms, the posterior distribution is like a bar graph that shows how likely each answer is, considering all the information we have. The surface under the cumulative ranking curve (SUCRA) can then be used to order the ranking of the treatments.

When performing frequentist NMA, it should be reported along with the SUCRA rankings to have more validated and comparable results that enable decision making because frequentist and Bayesian framework have their own limitations.

The validity of network meta-analysis is based on the underlying assumption that there is no imbalance in the distribution of effect modifiers across different types of direct treatment comparisons, independent of the structure of the evidence network.

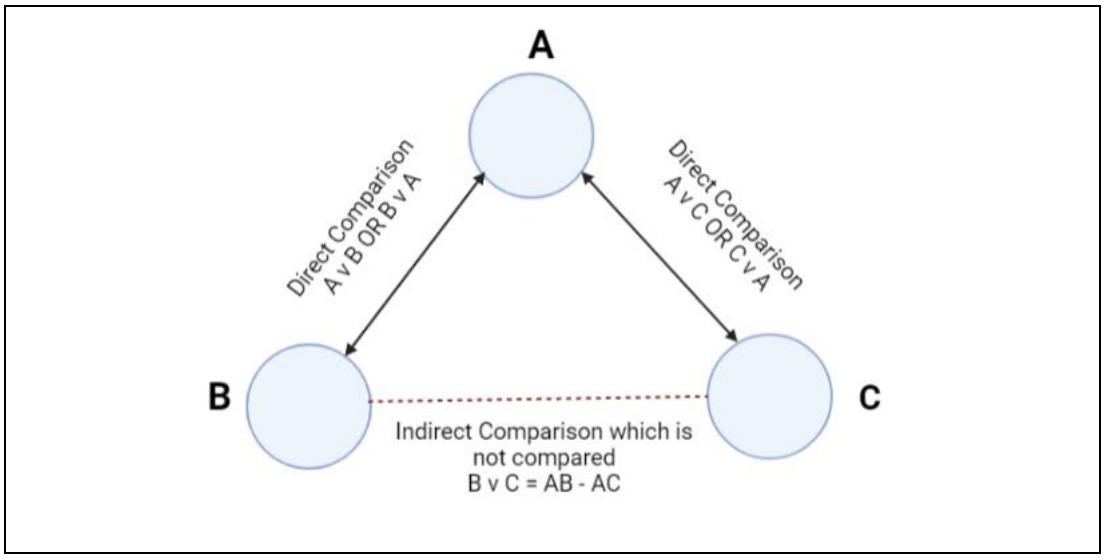

Figure 1: Treatment comparisons illustrating direct, indirect and mixed evidence

2. Hypothesis and Rationale

2.1 Specific Objectives

1. **To determine the most effective grafting/sealing biomaterial in maintaining horizontal and vertical dimensions after alveolar ridge preservation**

Several systematic reviews and meta-analysis of randomized clinical trials [59-61,38] assessed various preservation procedures as well as tooth extraction followed by spontaneous healing. However, only two network meta-analyses (NMA) on alveolar ridge preservation have been reported to the best of our knowledge (13). In contrast to traditional pairwise meta-analysis, NMA uses indirect data to reach conclusions about the effects of treatments that have not been directly compared. Iocca et al. (13) included only six RCTs published up to January 1, 2016 to measure bone height (only on the buccal side) and breadth reduction; hence, many materials that were more recently reported were missing. Canellas et al. (38) concentrated solely on histomorphometric results. The authors of the latter study did not attempt aggregation of similar materials (they estimated the likelihood of a given material being ranked first among 34 different grafting materials and sealing techniques), resulting in high fragmentation of the results and, as a result, low strength of the findings. To date, no NMA has explored the dimensional clinical changes as well as the proportion of newly produced bone following ridge preservation using various grafting materials. As a result, the purpose of this revised systematic review and network meta-analysis was to assess and compare the efficacy of various grafting materials for alveolar ridge preservation following tooth extraction.

2. **To determine the most effective grafting/sealing biomaterial for new bone formation after alveolar ridge preservation**

The effect of different biomaterials utilized to seal the socket on ultimate ridge dimensions or histologic results following ARP is not fully understood at this time (39). As a result, the current systematic review and meta-analysis sought to assess and compare the efficacy of various ARP covering materials (autologous palatal gingival grafts, resorbable membranes, and non-resorbable membranes).

3. **To determine the most effective biomaterial for soft tissue regeneration after tooth extraction**

   Although ARP does not prevent post-extraction ridge atrophy, it may restrict the extent to which it occurs (40). Interestingly, some studies have found a decrease in keratinized soft tissue following tooth extraction (41,42), highlighting the possible necessity for further soft tissue augmentation operations for implant site growth (43). In their literature review, Chappuis et al. discovered no significant differences between the biomaterials and techniques utilized for ARP; however, the types of treatments and biomaterials have not been separated for bone filling and socket sealing, therefore more research is needed to clarify these elements (44). Although osseous post-extraction modifications are very well recognized, soft tissue dimensional changes utilizing various biomaterials are less so. As a result, the current systematic review sought to assess and compare the impact of various ARP procedures on soft tissue dimensions after extraction. Furthermore, a network meta-analysis (NMA) was carried out to determine which sealant material utilized in ARP procedures produced the greatest results.

4. **To determine the most effective biomaterial for gingival recession treatment in adjunct to coronally advanced flap**

   Previous network systematic reviews attempted to collect data evaluating the clinical advantages of each connective tissue graft (CTG) substitute, but they were limited by several factors, including a 6-month follow-up period, the inclusion of randomized clinical trials (RCTs) with a high risk of bias influencing results, and the inclusion of RCTs with smoker patients or RCTs where the absence or presence of smoker patients was not reported (45,46). Thus, the objective of this systematic review and NMA was to compare the clinical effects of CTG substitutes versus controls or coronally advanced flap (CAF) alone or in combination for long-term regeneration of keratinised gingival width (KGW), clinical attachment level (CAL), recession width (RW), recession height (RH), and pocket depth (PD) outcomes.

5. **To determine the most effective dental implant abutment material**

   Zirconia abutments have increased in favour in recent years due to their white tint, which appears to combine outstanding mechanical strength and biocompatibility with significant cosmetic features. In addition, in vitro and in vivo studies demonstrated that titanium abutments exhibited comparable biological features in terms of microbial adherence and soft tissue integration. Given the variety of implant abutments available today, the purpose of this systematic review was to shed light on the clinical outcomes of abutments made of different materials. The study sought to determine the effect of abutment material on peri-implant hard and soft tissue health and stability.

6. **To rank the different combinations of recombinant human-derived growth and differentiation factors with/without scaffold biomaterial in the treatment of periodontal infrabony defects, through network meta-analysis of pre-clinical studies**

   Standard pairwise meta-analysis can disclose the efficacy/effectiveness of each given bioactive factors versus control in the absence of direct comparison, but no hierarchy of such recombinant growth factors can be constructed. Network meta-analyses (NMA) would provide guidance for future pre-clinical investigations by providing researchers with up-to-date information and minimizing clinical study expenditures. There were no published NMAs on rh factors in combination with scaffolding biomaterial and bioactive agents to show which combination was the most successful for periodontal regeneration. Therefore, the research question was which is the most effective recombinant growth factor in infra-bony bone defects?

7. **To determine the best rank recombinant growth factor formulations agents through network meta-analysis of clinical studies**

   Similar to the previous objective of utilising pre-clinical studies to conduct NMA in order to determine the most effective recombinant growth factors in periodontal regeneration (infrabony bone defects). In this specific objective clinical trials are used.

8. **To determine the effectiveness of biomaterials used in soft tissue augmentation procedures**

   Many researches evaluated and compared the efficacy of autogenous and non-autogenous grafts in terms of gingival thickness, gingival volume, and keratinized width growth. However, there is still no clear general evidence on the topic, and effective volume gain and stability over time have yet to be demonstrated.

   The goal of this systematic review and network meta-analysis is to compare the efficacy of different collagen matrices to autologous soft tissue grafts in terms of both volumetric and dimensional changes in soft tissue thickness and keratinized mucosa width following peri-implant soft tissue augmentation.

9. **To determine the most effective biomaterial in increasing residual bone height after maxillary sinus lift procedures**

   The impact of residual bone height (RBH) on new bone formation has been investigated through clinical studies and meta-analyses (47-51). However, no comprehensive review evaluated a possible combined effect of RBH and the grafting material in promoting formation of new bone. The objective of the present study was to investigate through a network meta-analysis the effect of RBH on new bone formation after lateral sinus augmentation using different biomaterials. The null hypothesis is that new bone formation is independent of RBH and of the grafting material used. The alternative hypothesis is that, in order to achieve the highest NBF, the choice of the grafting material may depend upon RBH.

3. Methods

3.1 Protocol and Registration

The protocol for conducting systematic review and NMA was drafted before conducting originally planned systematic review and NMA. The registration of the protocol was done on PROSPERO and all the protocols registered would be assessed through the following link https://www.crd.york.ac.uk/prospero/#searchadvanced.

3.2 Eligibility Criteria

Population/patients, intervention, comparison/comparator and outcome (PICO) questions were pre-determined and framed for specific objectives set. The studies published in English were considered due to proficiency of authors in English and lack of understanding of language published in other languages. All studies that are published and indexed in the databases are considered for inclusion. All studies were included that used interventions that compared with control/placebo and test group which might contain one control/placebo biomaterial and one or more than one biomaterial included in the test group. The eligibility criteria for specific objectives set for each oral regenerative techniques and procedures was illustrated in our published articles.

3.3 Information sources

A literature search was carried out using electronic databases (MEDLINE (PubMed), Web of science, Scopus, EMBASE, Cochrane Central Register of Controlled Trials, using an ad hoc search string that was adapted to each database. A specific search strategy for specific objectives set for each oral regenerative techniques and procedures was illustrated in our published articles. A hand search was carried out into the hard copies of the journals.

3.4 Search strategy

The specific search strategy for objectives set were;

1. **To determine the most effective grafting/sealing biomaterial in maintaining horizontal and vertical dimensions after alveolar ridge preservation**

   (((((((“tooth extraction”) OR “socket”) OR “alveolus”) OR “dental extraction”)) AND ((((((((((“bone grafts”) OR “biomaterials”) OR “autografts”) OR “collagen”) OR “cell therapy”) OR “platelet concentrates”) OR “alloplasts”) OR “allografts”) OR “xenograft”) OR “bioceramic scaffolds”))) AND (((((“alveolar ridge preservation”) OR “socket preservation”) OR “socket grafting”) OR “socket filling”) OR “ridge maintenance”). The last search was done on March 2021.

2. **To determine the most effective grafting/sealing biomaterial for new bone formation after alveolar ridge preservation**

   (((((((“tooth extraction”) OR “socket”) OR “alveolus”) OR “dental extraction”)) AND ((((((((((“bone grafts”) OR “biomaterials”) OR “autografts”) OR “collagen”) OR “cell therapy”) OR “platelet concentrates”) OR “alloplasts”) OR “allografts”) OR “xenograft”) OR “bioceramic scaffolds”))) AND (((((“alveolar ridge preservation”) OR “socket preservation”) OR “socket grafting”) OR “socket filling”) OR “ridge maintenance”). *The electronic search was conducted up to 4th April, 2021.*

3. **To determine the most effective biomaterial for soft tissue regeneration after tooth extraction**

   (((((((“tooth extraction”) OR “socket”) OR “alveolus”) OR “dental extraction”)) AND ((((((((((“bone grafts”) OR “biomaterials”) OR “autografts”) OR “collagen”) OR “cell therapy”) OR “platelet concentrates”) OR “alloplasts”) OR “allografts”) OR “xenograft”) OR “bioceramic scaffolds”))) AND (((((“alveolar ridge preservation”) OR “socket preservation”) OR “socket grafting”) OR “socket filling”) OR “ridge maintenance”) AND ((“soft tissue OR “mucosa”) AND ((“horizontal width” OR (“vertical” OR “buccal” OR “vestibular “ OR “lingual” OR “palatal” OR “volume”) AND “change”). The last search was done on* 06 April 2021.

4. **To determine the most effective biomaterial for gingival recession treatment in adjunct to coronally advanced flap**

   "((((Coronally advanced flap) OR (CAF)) OR (modified coronally advanced flap)) OR (coronally displaced flap)) AND ((((((((((Enamel matrix derivative) OR (Connective tissue graft)) OR (Guided tissue regeneration)) OR (Collagen matrix)) OR (Acellular dermal matrix)) OR (platelet rich fibrin)) OR (platelet rich plasma)) OR (PRF)) OR (PRP)) OR (barrier membrane)) OR (amniotic membrane)) OR (hyaluronic acid)) OR (Emdogain)) OR (CTG))." The last search was done till year 2020.

5. **To determine the most effective dental implant abutment material**

   dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields] OR ("dental"[All Fields] AND "implant"[All Fields]) OR "dental implant"[All Fields]) AND ("abutment"[All Fields] OR "abutment s"[All Fields] OR "abutments"[All Fields]) AND ("titanium"[MeSH Terms] OR "titanium"[All Fields] OR "titaniums"[All Fields]) AND ("zirconia"[All Fields] OR "zirconias"[All Fields] OR "zirconium oxide"[Supplementary Concept] OR "zirconium oxide"[All Fields] OR "zirconia"[All Fields] OR "gol d"[All Fields] OR "PEEK"[All Fields]). The last search was done on Feb 2022.

6. **To rank the different combinations of recombinant human-derived growth and differentiation factors with/without scaffold biomaterial in the treatment of periodontal intrabony defects, through network meta-analysis of pre-clinical studies**

   ((((((intra-bony defect) OR (intrabony defect)) OR (intrabony defects)) OR (periodontal defect)) OR (intraosseous defects)) AND ((((((((((((recombinant human platelet-derived growth factor) OR (rhpdgf)) OR (PDGF)) OR (rhPDGF)) OR (recombinant human fibroblast growth factor)) OR (rhFGF)) OR (insulin growth factor)) OR (IGF)) OR (Vascular endothelial growth factor)). OR (VEGF)) OR (recombinant human growth/differentiation factor)) OR (GDF)) OR (Recombinant human bone))) AND ((((((((((Cats) OR (cats)) OR (feline cats)) OR

(feline)) OR (((((Dogs) OR (dog)) OR (dogs)) OR (canine)) OR (canines))) OR (((Guinea Pigs) OR (guinea pig)) OR (guinea pigs))) OR (((((((Mice) OR (mice)) OR (mice model)) OR (mouse)) OR (mouse model)) OR (mus)) OR (murine))) OR (((Primates) OR (non-human primate)) OR (non-human primates))) OR (((((((((Rabbits) OR (rabbit)) OR (rabbits)) OR (lagomorpha)) OR (Rats)) OR (rat)) OR (rats)) OR (rodent)) OR (rodents))) OR ((((Sheep) OR (sheep)) OR (ovis)) OR (ovine))) OR (((((Swine) OR (swine)) OR (pig)) OR (pigs)) OR (porcine))). The search was done until November 2020

7. **To determine the best rank recombinant growth factor formulations agents through network meta-analysis of clinical studies**

   (Intra-bony defects OR Intraosseous defects OR Intrabony defects OR Periodontal defects) AND (recombinant human-derived growth factors OR recombinant human platelet-derived growth factor OR rhPDGF OR rhPDGF-BB OR recombinant human fibroblast growth factor OR rhFGF OR recombinant human insulin derived growth factors OR recombinant human vascular endothelial growth factors OR recombinant human growth or differentiating factors OR recombinant human bone morphogenetic protein OR rhBMP2). The search was done until November 2020

8. **To determine the effectiveness of biomaterials used in soft tissue augmentation procedures**

   (("soft tissue" AND "augmentation" AND "tooth implant") OR "peri implant") AND ("collagen matrix"). The search strategy was done until 7th April 2021.

9. **To determine the most effective biomaterial in increasing residual bone height after maxillary sinus lift procedures**

   ((((((maxillary sinus) OR (sinus lift)) OR (maxillary sinus lift)) OR (maxillary sinus lift technique)) OR (maxillary sinus lift lateral)) OR (maxillary sinus augmentation)) OR (sinus lift)) OR (sinus lift procedure)) AND (((histomorphometric) OR (histomorphometric analysis)) OR (bone histomorphometry)). The search strategy was done until January 2023.

3.5 Study selection

To avoid bias, two team members independently analysed all of the studies. Initially to find the relevant articles, two team members vote only on the basis of the titles and abstracts to include or remove each study which was based on PICO criteria. After both team members have examined the articles, the selection was compared, and if differences found that was resolved by discussion and consultation with the third reviewer. Following this step, members use the full-text articles to evaluate the remaining studies. The two team members keep track of the reasons for excluding articles based on the predetermined inclusion/exclusion criteria. Following the evaluation of the articles by both team members, the selection was compared and disagreements are resolved by discussion and consultation with the third reviewer. The selection of articles was based on following basic criteria i.e. the articles published in English, human studies, articles related to the specific research question and PICO criteria, randomised patients to each treatment groups, studies involved more than 5 patients.

3.6 Data collection

The following information was used to extract data: study characteristics (author, year, title, location), participant characteristics (age, gender, diseases), methodology (study type, patient recruitment/selection/allocation, blinding, performance bias, reporting bias, outcome bias, selection bias, other biases), intervention (control group, test group biomaterials), outcomes (unit and method of measurement, length of follow-up, number of patients), intervention (control group, test group biomaterials), outcomes (unit and method of measurement, length of follow (included). The mean, sd, number of samples in each intervention was recorded to enable quantitative analysis. The data extracted will be used for drafting characteristics tables of included studies and for further qualitative analysis. Primary outcome mean values and standard deviations were extracted or estimated when possible. When an article did not offer the mean values and standard deviations, or when data was missing, the relevant author was contacted to provide the missing information. The study was discarded if there was no or an inadequate response.

3.7 Data Analysis

3.7.1 Risk of Bias Assessment

As part of the data extraction process, two reviewers independently and in duplicate evaluated the methodological quality of the included studies. Randomization method, concealed allocation of treatment, blinding of outcome assessors, completeness of outcome assessment reporting, completeness of information on reasons for withdrawal by trial group, other biases (sample size calculation, definition of inclusion/exclusion criteria, and comparability of control and test groups at entry) were used to assess the risk of bias in the included trials. All of these criteria were rated adequate/inadequate/unclear. Because neither the surgeon nor the patient can be efficiently masked to the bone graft material utilized in socket preservation, especially if it is autogenous bone, blinding of participants and personnel (performance bias) was not considered. The authors of the highlighted studies were contacted by the reviewers for clarification or to provide missing information.

Studies were classified as low risk of bias (plausible bias unlikely to seriously alter results) if all criteria were judged adequate; moderate risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were considered unclear; or high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were judged inadequate. The criteria for measuring the risk of bias in RCTs were derived from the instrument described in the Cochrane Handbook for Systematic Reviews of Interventions. Disagreements between the two reviewers were resolved by conversation or consultation with a third reviewer. The funnel plot was used to examine publication bias in the key comparisons.

3.7.2 Heterogeneity

Estimates for primary outcomes were obtained using both pairwise and network meta-analysis. The effect of an intervention was estimated using mean differences (MDs) and 95% confidence intervals (CIs). Cochran's test for heterogeneity was used to examine heterogeneity among included studies, with a significance level of $p<0.05$. I^2 statistics were used to measure the heterogeneity, which indicates the total percentage of variation across studies that is due to heterogeneity rather than chance. When I^2 was greater than 50%, significant heterogeneity was considered. For pairwise meta-analysis computations, the program RevMan (Review Manager Version 5.4, 2020; The Nordic

Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) was utilized. Data from split-mouth and parallel group trials were integrated in RevMan and STATA 17.0 version using the general inverse variance approach.

3.8 Undertaking Network Meta-analysis

The idea of an indirect comparison is crucial to network meta-analysis. When studies do not directly compare two treatments, indirect comparisons are necessary to determine their relative effectiveness. Through indirect comparisons, we can estimate the relative effects of two drugs that have not been directly tested in a trial. The methods discussed here follow the steps outlined in Chaimani A. (2019) (52,53).

3.8.1 Transitivity

For a NMA to be valid, all competing therapies must be randomly assigned together. This can be achieved by conducting a single, multi-arm randomized study in which all therapies are evaluated at the same time. Another way to view this is to consider the "missing" interventions as not being present in a specific trial due to reasons unrelated to their effectiveness. (Caldwell et al 2005 (54), Salanti 2012 (53).

When doing a systematic review, it's normal for studies to have differences in the way they were done and in the results. Before making indirect comparisons, researchers need to see if these differences are big enough to affect the results. In theory, you can check this by looking at how things that might change the results are spread out among the different comparisons. However, for the comparisons to be valid and the results to be reliable, these things should be even across all comparisons. To make sure, researchers have to identify and measure these things. There are also different statistical methods that can be used to see if the results are still connected even with these differences (Salanti 2012 (53), Cipriani et al 2013 (55), Jansen and Naci 2013) (56).

3.8.2 The Validity of Network Meta-Analysis and Indirect Comparisons

3.8.2.1 Combining direct and indirect evidence

The ability to compare interventions indirectly using one or more common comparators is frequently possible as well as having direct evidence for a specific comparison of interventions. Direct and indirect estimates ought to be considered together if the crucial transitivity assumption is thought to be plausible. For a specific comparison, when both the direct and indirect intervention effects are available, they can be combined to produce a single impact estimate. The intervention effect estimate is frequently referred to as a combined or mixed estimate.

The transitivity principle is utilized because combined estimates take indirect comparisons into consideration. The accuracy of indirect and mixed estimations is threatened by transitivity violations. Naturally, biased direct intervention effects for any of the comparisons raise questions about the reliability of a combined effect (Madan et al 2011) (57).

3.8.2.2 Coherence (or Consistency)

The core principle of transitivity is that there could be clinical and methodological heterogeneity between the many comparisons. Data from various sources of evidence may differ in their estimates, which could reflect these disparities. Constantly referred to as coherence or consistency, transitivity's statistical form is both. Using the former, we will set the idea apart from heterogeneity (or inconsistency) in typical meta-analyses. It is implied by coherence that the various forms of evidence, both direct and indirect, go along each other.

3.8.2.3 Validity of Network Meta-analysis

The fulfilment of underlying assumptions is necessary for network meta-analysis to be valid. Every indirect comparison that could be made should be transitive, and every loop of evidence in the network should be coherent (see Section 11.4.4 cochrane handbook). Each direct comparison in the network should consider heterogeneity according to the current guidelines for traditional pair-wise meta-analysis. Generally, the validity of network meta-analysis is predicated on the underlying

assumption that, regardless of the shape of the evidence network, there is no imbalance in the distribution of effect modifiers across different types of direct treatment comparisons.

3.8.2.4 Expertise required for conducting Network Meta-analysis

It's very important to have a team with different expertise when doing a network meta-analysis. This team should include a statistician who knows how to do this type of analysis. The statistician and the expert in the subject being studied need to work closely together to make sure that the studies they choose are similar in every way except for the treatments being tested. Doing a network meta-analysis is more complicated than doing a simple meta-analysis, so the statistician can't use easy-to-use tools like RevMan. Instead, the statistician needs to use special statistical software programs like Stata, R, WinBUGS, or OpenBUGS.

3.8.2.5 Importance of well-defined research questions and objectives in Network Meta-analysis

The following recommendations should be followed when developing a study subject for a systematic review aimed at comparing various therapies. Because network meta-analysis can be used to assess the relative ranking of the included interventions, studies that want to rank the competing interventions should specify this in their objectives (Salanti et al. 2011, Chaimani et al. 2013). Chaimani and colleagues, 2017 (62-64) To complement the relative impacts, review authors could consider estimate relative ranking.

3.8.2.6 Choosing populations and Interventions

Because of the possibility of resistance, it is frequently necessary to examine populations and interventions simultaneously (see Section 11.2.2 of Cochrane handbook). One guiding concept is that each eligible participant should be able to be assigned to any of the listed interventions at random (Salanti 2012 (53) and Jansen and Naci 2013) (56). The reviewers kept this in mind as the review authors chose their target audience. According to Chaimani and colleagues, more consideration must be made when determining the eligible interventions (Chaimani et al 2017). (60). Consider a systematic review in which four chemotherapy regimens for a given disease are compared. However, both stage I and stage II patients, not just stage II patients, should utilize regimen (D) (A). Only patients at stage I should use the following two regimens (B and C). Assume A, B, and C were

compared in stage I patients, whereas A, D, and A were compared in stage II patients (see Figure 2). The fact that regimen D is not provided to the same patient group as regimens B and C makes it unlikely that the network's four treatments will meet the transitivity criteria. As a result, doing a four-arm, randomized trial that compares all medicines (A, B, C, and D) at the same time is not a feasible study.

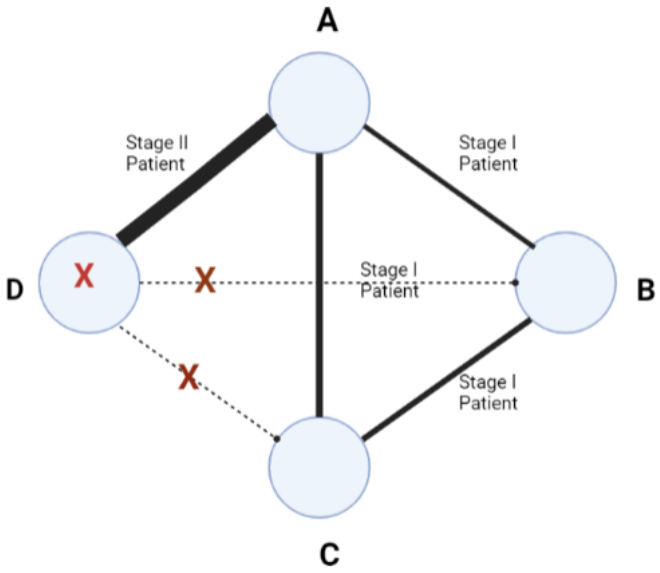

Figure 2: Example of a network comparing four chemotherapy regimens, where transitivity is violated due to incomparability between the interventions (Chaimani A (2019).

4. Summary of the results

1. To determine the most effective grafting/sealing biomaterial in maintaining horizontal and vertical dimensions after alveolar ridge preservation

There were a total of 2805 patients and 3073 sockets across 88 RCTs. 1740 sockets in total underwent alveolar ridge preservation using various materials (1432 were covered by a membrane). The characteristic table for the included studies was illustrated in supplementary file of following published paper Canullo L et.al (2022) (91). A pairwise meta-analysis revealed that all materials statistically significantly reduced both horizontal and vertical shrinkage when compared to spontaneous healing. Xenografts (XG) and allografts (AG), either alone or in combination with bioactive agents (Bio + AG), were found to be the most predictable materials for maintaining the horizontal and vertical dimensions of ridges, while platelet concentrates outperformed them in terms of the percentage of new bone formation. The summary of risk of bias was illustrated in the published paper Canullo L et.al (2022) (91).

2. To determine the most effective grafting/sealing biomaterial for new bone formation after alveolar ridge preservation

The quantitative and qualitative study covered 12 trials, evaluating 312 sites. Comparing autologous soft tissue grafts to resorbable membranes, better horizontal alterations were seen. The characteristic table for the included studies was illustrated in supplementary file of following published paper Del Fabbro M et al.2022 (94). When resorbable membranes were compared to no membrane, a statistically significant difference was detected, although there was no statistically significant heterogeneity. A study of histomorphometric NMA data revealed a statistically significant difference in favour of the non-crosslinked membranes when comparing crosslinked and non-crosslinked membranes. The results of the NMA need to be evaluated carefully given the relatively high variation found in terms of treatment procedures, materials, and outcome evaluation. The summary of risk of bias was illustrated in the published paper Del Fabbro M et al.2022 (94).

3. **To determine the most effective biomaterial for soft tissue regeneration after tooth extraction**

   For NMA, a total of 11 studies were included. Overall, there was a modest amount of bias in the included research. The characteristic table for the included studies was illustrated in supplementary file of following published paper Canullo L et al.2022 (95). Crosslinked collagen membranes (SUCRA rank 81.8%), autogenous soft tissue grafts (SUCRA rank 89.1%) and controls (SUCRA rank 85.8%) all performed best in terms of vertical buccal height (VBH), horizontal width change (HWch), and keratinized mucosa thickness (KMT). The summary of risk of bias was illustrated in the published paper Canullo L et al.2022 (95).

4. **To determine the most effective biomaterial for gingival recession treatment in adjunct to coronally advanced flap**

   The characteristic table for the included studies was illustrated in supplementary file of following published paper Canullo L et al.2022 (96). The best performing combinations for enhancing KGW were CAF + connective tissue graft (CTG), CAF + platelet concentrate matrix (PCM), and acellular dermal matrix (ADM). In terms of materials, CAF + collagen matrix (CM) + gingival fibroblasts (GF), CAF + ADM + platelet rich plasma (PRP), and CAF + ADM outperformed CAF alone in terms of increasing the percentage of root coverage in gingival recession. The summary of risk of bias was illustrated in the published paper Canullo L et al.2022 (96).

5. **To determine the most effective dental implant abutment material**

   Eighteen relevant studies, from 1331 identified, were included. Overall, 612 patients were treated, and 848 abutments inserted. Five studies presented a low risk of bias. The characteristic table and risk of bias for the included studies was illustrated in the appendix publications section titled “Effect of the abutment materials on tissue health and stability – A Systematic Review and Network Meta-analysis”. Pairwise meta-analysis showed that, as compared to titanium, zirconia abutment presented a significantly reduced MBL (0.20 mm (95%CI [0.14 to 0.26], $p<0.00001$). No significant differences were found for the other outcomes. In NMA, zirconia abutments demonstrated 83.3% probability to achieve the highest rank in PI, 87.0% in BOP and 65.0% in PD

outcome, suggesting that zirconia abutments generally performed better than titanium and alumina abutments.

6. **To rank the different combinations of recombinant human-derived growth and differentiation factors with/without scaffold biomaterial in the treatment of periodontal intrabony defects, through network meta-analysis of pre-clinical studies**

   There were N = 24 studies for the qualitative analysis and N = 21 studies for the quantitative analysis that were published up until 2020. N = 162 and N = 339, respectively, were the cumulative total number of animals used in the control and test groups. The trial lasted between three and 102 weeks. The characteristics of included studies and risk of bias was illustrated in the published paper *page 1074* of Khijmatgar et al.2021 (92). In SUCRA, rhBMP-2 was scored higher as the substance that produced the highest results for bone volume density. The best results were achieved by rhGDF-5/TCP in terms of bone area (mm2), rhPDGF-BB/Equine in terms of bone height (mm), rhBMP-2 in terms of the percentage of new bone fill, rhBMP-2/ACS in terms of the formation of new cement, and rhGDF-5/b- TCP/PLGA in terms of junctional epithelium and connective tissue attachment. No adverse effects that might have impacted the various results for regeneration in intra-bony defects were found in the literature. The regeneration of the periodontium's soft and hard tissue supporting structures can be effectively aided by a number of recombinant factors. Diverse agents, whether or not they were connected to biomaterials, rated better when different outcomes were considered.

7. **To determine the best rank recombinant growth factor formulations agents through network meta-analysis of clinical studies**

   Twelve clinical investigations were taken into consideration for qualitative and quantitative analysis. The characteristics table and risk of bias of included studies was illustrated in the published paper *page 904* of Panda et al.2021 (93). According to network meta-analysis, the combination of rhFGF and hyaluronic acid had the best results for PPD and CAL. The combination of rhPDGF-BB and -tricalcium phosphate had the highest percentage of bone filling. Additionally, all bioactive drugs outperformed control groups devoid of rhGFs.

8. **To determine the effectiveness of biomaterials used in soft tissue augmentation procedures**

   The characteristic table and risk of bias for the included studies was illustrated in the appendix publications section titled “Soft tissue augmentation: autogenous graft vs collagen matrix. A systematic review and network meta-analysis”. CTG performed best in all of the majority outcomes and FGG seems to be the best in terms of keratinized mucosa increase. FGG and XCM perform better if used to augment the keratinized mucosa. VCMX performs better in increasing soft tissue in the buccal aspects compared to all the other matrices.

9. **To determine the most effective biomaterial in increasing residual bone height after maxillary sinus lift procedures**

   The characteristic table and summary of risk of bias for included studies was illustrated in appendix publication section titled “Residual Bone Height and New Bone Formation using Biomaterials in Maxillary Sinus Augmentation Procedure: A Network Meta-Analysis” (96). For the purpose of qualitative analysis, 84 studies in total were chosen for data extraction. N=67 were qualified for quantitative analysis and network meta-analysis. The biomaterials used were grouped into: autogenous bone (Auto), xenografts (XG), allografts (AG), alloplasts (AP), Bioactive agents (Bio), hyaluronic acid (HA) and combinations of them. Inconsistency factor (IF) was seen in entire loop of the XG, AP and Bio+AP and found to be statistically significant. The highest ranked biomaterials for the <4mm RBH outcome were XG+AG, XG+AP and Auto. Similarly, the surface under the cumulative ranking curve (SUCRA) of biomaterials for ≥4mm RBH were Auto, Bio+XG, and XG+Auto.

5 Discussion

5.1 Overview

In network meta-analysis, the concept of an indirect comparison is crucial. When two therapies are not directly tested in a trial, indirect comparisons must be done to determine the relative effectiveness of the two interventions. Using indirect comparisons, we can estimate the relative effects of two therapies that have not been directly studied. This was accomplished through the use of strategies such as establishing transitivity, coherence and consistency, setting meaningful research questions, selecting a well-defined population and intervention. The most common examples of oral and maxillofacial regeneration procedures are ridge preservation, soft tissue augmentation, periodontal regeneration, and sinus augmentation operations. NMA method was feasible for our objectives established within these regenerative processes since they all matched the criteria for conducting the NMA.

5.2 Discussion of results related to Objectives

The specific objectives included the assessment of ridge preservation, socket sealing, soft tissue augmentation and regeneration, residual bone height in sinus lift procedures, various abutment materials, the most effective biomaterial for treating gingival recession, and combinations of recombinant human-derived growth factors. Previous studies have shown that xenografts are the best biomaterial for maintaining the dimensions of the extraction socket, a finding supported by our research question 1. Our results showed that a combination of allograft and biologics would provide the best performance in preserving socket dimensions and offer additional benefits compared to a single biomaterial. Histomorphometry analysis revealed that platelet concentrates were associated with better new bone formation than other biomaterials. However, it is important to consider factors such as duration of follow-up, number of trials, and sample size when interpreting the results for each specific intervention. This holds true for the other specific objectives studied as well.

The impact of socket sealing on clinical outcomes was evaluated as part of the second specific objective. The goal was to identify the type of sealing material that would provide the best results. Our findings showed that non-crosslinked membranes performed better than crosslinked membranes.

However, it is important to consider the diverse number of trials, treatment protocols, materials, and outcome evaluations when interpreting the results of the network meta-analysis (NMA).

In the third specific objective, 11 eligible studies were found to determine the most effective biomaterial for soft tissue regeneration after tooth extraction. The results showed that crosslinked collagen membranes (SUCRA rank 81.8%), autogenous soft tissue grafts (SUCRA rank 89.1%), and controls (SUCRA rank 85.8%) performed best in terms of vertical buccal height (VBH), horizontal width change (HWch), and keratinized mucosa thickness (KMT).

Gingival recession is a widespread condition around the world, and numerous techniques, biomaterials, and procedures have been developed with promising therapeutic effects. However, the long-term effectiveness (follow-up ≥12 months) of biomaterials in gingival recession treatment as an adjuvant to coronally advanced flap was unknown (Specific objective 4). Our NMA review revealed that CAF + connective tissue graft (CTG), CAF + platelet concentrate matrix (PCM), and acellular dermal matrix were the highest performing combinations for improving KGW (ADM). In terms of materials, CAF + CM + GF, CAF + ADM + PRP, and CAF + ADM beat CAF alone in terms of increasing the percentage of root coverage in gingival recession.

Zirconia abutments have grown in popularity in recent years because they appear to combine great mechanical strength and biocompatibility with strong cosmetic features due to their white color. Furthermore, in vitro and in vivo investigations revealed that titanium abutments had similar biological properties in terms of microbial adherence and soft tissue integration. Given the wide range of implant abutments accessible today, the goal of this systematic review was to shed light on the clinical outcomes of abutments composed of various materials. The goal was to analyse the influence of the abutment material on peri-implant hard and soft tissue health and stability (specific objective 5). Zirconia abutments revealed 83.3% chance of achieving the highest rank in PI (plaque index), 87.0% in BOP (bleeding on probing), and 65.0% in PD (probing depth) result, indicating that zirconia abutments performed better than titanium and alumina abutments. This was first of its kind results, as there were no such NMA reviews in the literature before 2019. Again, only 11 studies found to be eligible for NMA and hence needed further clinical studies and research.

In the absence of direct comparison, standard pairwise meta-analysis can reveal the efficacy/effectiveness of each given bioactive agent versus control, but no hierarchy of such agents

can be formed. Network meta-analyses (NMA) would provide direction for future pre-clinical investigations by aiding researchers with up-to-date information and lowering the costs involved with clinical studies. There were no published NMAs on rh factors in combination with scaffolding biomaterial and bioactive substances to demonstrate the most successful combination for periodontal regeneration procedures (Specific objective 6 and 7). The outcomes accessible in the literature from two types of investigations, pre-clinical and clinical, were varied, making it difficult to compare the results acquired from both studies. Pre-clinical study outcomes were bone area (mm2), bone height (mm), percentage of new bone development (%), cementum production, junctional epithelium, and connective tissue attachment. Because these outcomes could be included in pre-clinical research, we will not be able to examine them in clinical investigations. The clinical study outcomes comprised periodontal pocket depth (PPD), clinical attachment loss (CAL), and percentage of bone fill (%). The proportion of bone fill (%) was the same for both. In pre-clinical studies, rhBMP-2 and a combination of rhPDGF-BB and -tricalcium phosphate performed best in terms of percentage of new bone filling and there was no such confirmation from any previous reviews. Definitely, different recombinant factors were considered in different studies and could have influenced the ranking. This gives an overview on the factors that investigators should consider while designing pre-clinical and clinical studies.

In soft tissue augmentation procedure (Specific objective 8), the focused question was, if In case of soft tissues deficiencies around dental implants is there a specific type of matrix which provides greater results in terms of 1. peri-implant buccal soft tissue thickness and 2. keratinized mucosa width compared to autogenous soft tissue graft?. NMA results found that, CTG/SCTG performed best in all of the majority outcomes. FGG seems to be the best in terms of keratinized mucosa increase. There was not enough data for secondary outcomes like patient reported outcome measures (PROMs), periodontal measurements such as Pocket Depth (PD), Bleeding on Probing (BOP), Marginal Bone Loss (MBL), surgical time, and volumetric changes. In order to have evidence to such clinical question, it was recommended from our review that further split-mouth design and patient level analysis is required, a minimum number of sample size of 20 patients (adequate statistical power) is needed, method for soft tissue evaluation by using CBCT, an optical scanner with the superimposition of the images and determining the gold standard. Further recommendations include, RCT with a longer follow-up (at least 360 days), regarding timing: RCTs comparing soft tissue augmentation

before and after implant placement are extremely recommended in future studies at different time (before or after implant placement).

Influence of residual bone height (RBH) on new bone formation after lateral sinus augmentation utilizing different biomaterials, through a network meta-analysis was rare (Specific objective 9). The biomaterials utilized were classified as autogenous bone (Auto), xenografts (XG), allografts (AG), alloplasts (AP), bioactive agents (Bio), hyaluronic acid (HA), and combinations of these. Inconsistency factor (IF) was discovered to be statistically significant throughout the complete loop of the XG, AP, and Bio+AP. The top three biomaterials for the <4mm RBH result were XG+AG, XG+AP, and Auto. Similarly, the surfaces under the cumulative ranking curve (SUCRA) of bio-materials for >4mm RBH were Auto, Bio+XG, and XG+Auto. Stacchi et al. has revealed that a percentage of mineralised tissue formation occurs at various rates in distinct anatomical sites inside the same maxillary sinus and that there is a negative link between sinus width and new bone production.

Seeing all the specific objectives, each clinical question met with uncertainty in terms of conducting NMA. Each objective had its own limitations, mainly due to the characteristics of studies, outcomes, samples and number of studies.

5.3 Previous reviews

In the year 2020, NMA work by Al Moraissi E A (2020) (58) aimed to determine the most effective biomaterials producing higher new bone formation (NBF) and lower residual graft (RG) and connective tissue (CT) following maxillary sinus augmentation (MSA). The time duration for which articles were considered were March 2018. Outcome variables were new bone formation (NBF%), residual graft (RG%), and connective tissue (CT%). Healing time was considered. A frequentist network meta-analysis method using Stata software was employed. Fifty-two RCTs (1483 biopsies) were included. At a healing time <6months, autogenous bone graft (AB) was ranked higher than the alloplast (AP) and xenograft (XG) in NBF% outcome and also for healing time >6months. AB was ranked higher in CT outcome. RB was lower in AB than in AP and XG. Different outcomes have ranked different materials as best, which strongly indicates that ranking of materials should be taken careful consideration, as it varies with type of studies, number of samples and outcomes compared (58). This NMA revealed that AB alone is most likely the best option for achieving higher NBF following MSA in the first 6 months after surgery. Furthermore, the findings of this network meta-

analysis support the concept that osteoconductive bone substitute materials should be paired with osteogenic or osteoinductive grafts for superior histomorphometric outcomes in MSA.

To establish the nonsurgical therapy of chronic periodontitis, John MT (2017) gathered the most complete library of clinical trials on scaling and root planing (SRP) with and without adjuncts. The author compared these supplements using the NMA method. NMA was generated based on 36 indirect comparisons of clinical attachment-level (CAL) increases among nine adjuncts in 74 studies from the Clinical Practice Guideline. All pairwise differences exhibited wide confidence intervals, and none of the adjuncts outperformed the others statistically significantly. Local doxycycline hyclate and photodynamic treatment with a diode laser were the favourites to win first and second place, respectively. There was a noticeable publication bias, with fewer studies with small effects published than expected (14).

Locca Oreste (2017) attempted to use Bayesian NMA to synthesize data from randomized controlled trials on various socket grafting materials and incorporate the resulting indirect evidence in order to derive conclusions about treatments that were not expressly compared. This evaluation reflected our specific objective. 1. Bone height and width remodelling were chosen as the outcomes. The six included studies yielded seven comparisons. For both height and width remodelling, traditional meta-analysis demonstrated statistically significant findings in favour of grafting the socket versus no-graft. According to a bayesian NMA, the most likely best material for bone height remodelling treatment was freeze-dried bone graft plus membrane. When it came to width remodelling, autologous bone marrow proved to be the most effective (13). Our specific objective 1 found different results. This may be due to increased number samples and interventions. Also, included a greater number of clinical studies.

Papageorgiou SN (2016) sought to compare the histomorphometric efficacy of bone grafts using evidence-based methods. The primary outcome was new bone development as determined by histomorphometric analysis. There were 12 trials in total (5 parallel; 7 cluster) with a total of 231 patients (302 grafted sites). In pairwise analyses of any two bone grafts, no statistically significant changes in the percentage of new bone were identified. AUT is for autograft, ALL stands for allograft, SYN stands for synthetic bone graft, and XEN stands for xenograft. According to the treatment NMA rating, autografts had the highest percentage of new bone, followed by synthetic grafts, xenografts, and allografts. There were no changes based on patient age, gender, healing period, membrane

used, or type of surgical graft used (12). Due to study limitations, the graft ranking was modest. The authors concluded that there were no significant variations in the percentage of new bone between the two grafts. Individual biomaterials as well as various combinations were considered in our review objective 1. Buti J (2013) used randomized controlled trials (RCTs) and the bayesian network meta-analysis (NM) method to rank the efficacy and best strategy for coronally advanced flap (CAF)-based root coverage operations. This was comparable to our specific objective number four. Recession reduction (RecRed), clinical attachment gain (CALgain), keratinized tissue gains (KTgain), and total root covering were the outcomes (CRC). Twenty-nine studies were included, with 20 rated as having a high risk of bias. CAF+connective tissue graft (CTG) was the most effective for recession reduction (Pr = 40%) and clinical attachment level gain (Pr = 33%); CAF+enamel matrix derivative (EMD) was slightly better for complete root coverage (CRC); and CAF+Collagen Matrix (CM) appeared effective for Keratinized tissue gain (Pr = 69%) (10).

Tu Y-K (2012) employed NMA in clinical studies to compare Guided tissue regeneration (GTR) and enamel matrix derivatives (EMD), and their combination therapies to determine the best effective therapy. Changes in probing pocket depth (PPD), clinical attachment level (CAL), and infra-bony defect depth were among the treatment outcomes. One group was treated: barrier membranes and various types of bone grafts. This evaluation comprised 53 papers, and discovered statistically and clinically insignificant differences across regenerative treatments. PPD decrease was larger with GTR and GTR-related combination medications than with EMD and EMD-related combination therapies. Combination therapy increased CAL growth slightly more than EMD or GTR alone. GTR with bone grafts had the highest defect fill rate. The authors concluded that while combination medicines outperformed single therapy, the additional benefits were marginal (9). Our specific objective 1 also confirmed a combination of biomaterials have better performance in terms of hard tissue regeneration.

Similarly, Tu Y-K (2010) (8) aimed to see if EMD in combination with other regenerating materials performed better than EMD alone in the treatment of infra-bony defects larger than 3mm. Changes in probing pocket depth (PPD), clinical attachment level (CAL), and infra-bony defect depth were among the outcomes examined. Different types of bone grafts (or barrier membranes) were treated together at first, then individually. The review includes 28 studies in total. EMD + bone grafts and EMD plus membranes reduced PPD by 0.24 mm [95% HPD intervals: 0.38, 0.65] and 0.07 mm (95% HPD

intervals: 1.26, 1.04) more than EMD alone. For CAL increase, EMD plus bone grafts achieved 0.46 mm (95% HPD intervals: 0.17, 0.83) and EMD plus membranes achieved 0.15 mm (95% HPD intervals: 1.37, 0.30), respectively. When different types of bone grafts and barrier membranes were treated separately, EMD with bovine bone grafts produced the best results. The authors concluded that there was little data to back up the increased benefits of EMD when combined with other regeneration materials (8).

5.4 Interpretation of Network Meta-analysis

5.4.1 Network Plots

The network plot command uses nodes and edges to depict a network of interventions (Figure 3). Edges indicate the available direct comparisons between treatment pairings, whereas nodes represent the competing treatments. Network plot offers weighting and coloring choices for both nodes and edges based on predefined properties (Chaimani et al.2013) (63). Important variations in the traits of treatments or comparisons can be revealed through the use of weighting and color schemes. The assumption underlying network meta-analysis may occasionally be violated as seen by discrepancies in comparisons (Salanti 2012; Jansen and Naci 2013) (53,56). The disconnection in case of only one unique comparison is demonstrated in Figure 4.

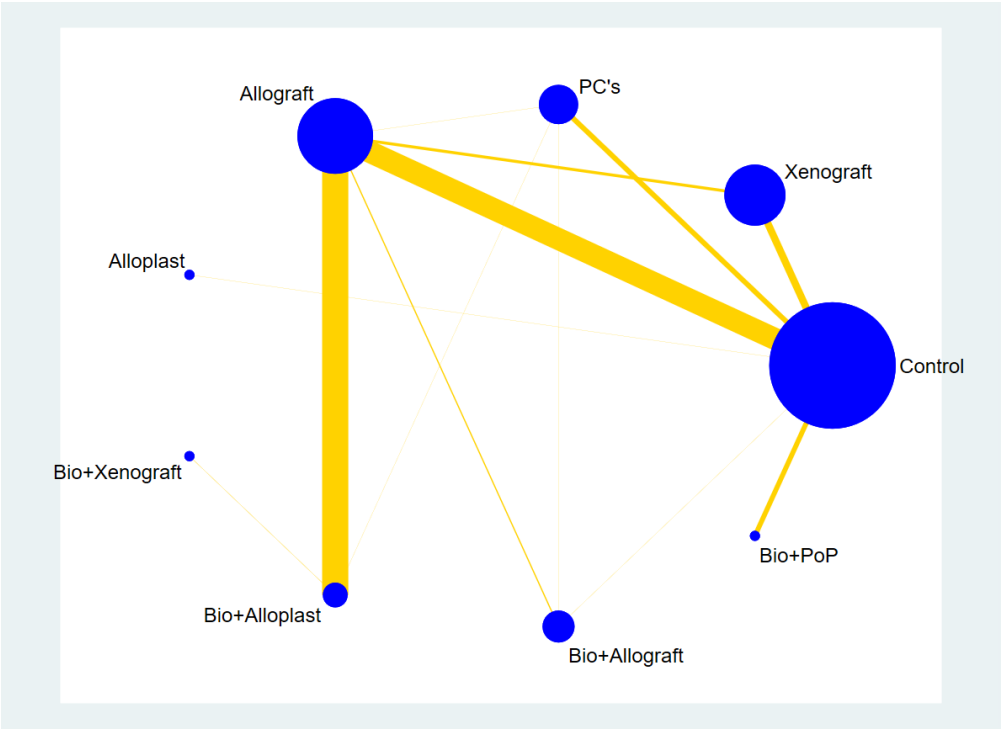

Figure 3: Network Plot illustrating different interventions for alveolar ridge preservation. The blue nodes represent the number of samples in each group of intervention from pooled clinical studies. The lines represent the number of comparisons between two biomaterials in the selected clinical studies. The width of the line represents the number of comparisons i.e. thicker the line, more the number of comparisons and vice versa. The risk of bias is also reported in the network, where yellow colour indicates the moderate risk of bias, green low risk of bias and red indicates high risk of bias.

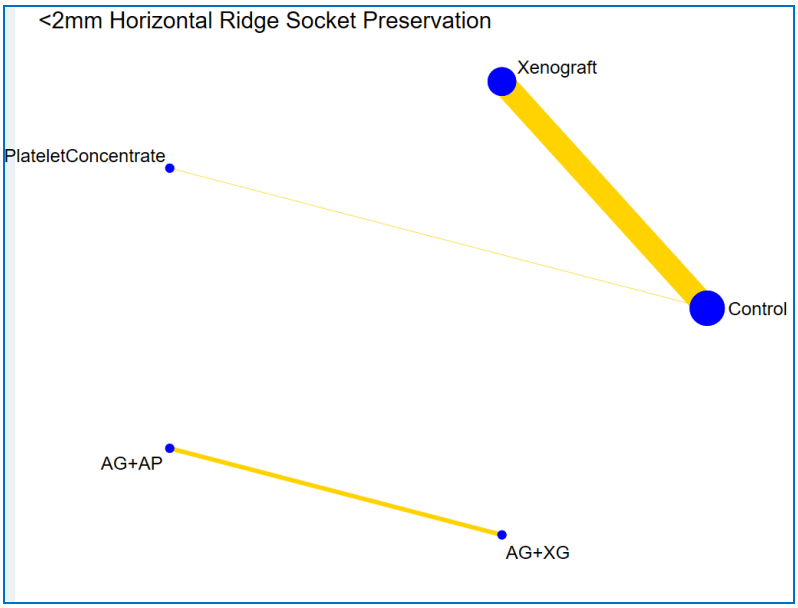

Figure 4: Network plot illustrating the disconnection. AG+AP v AG+XG materials is the only single study available for comparison and has been disconnected with the network as there are no control, XG or PC's for direct comparison for buccal, lingual side with AG and AP and vice versa.

5.4.2 Contribution plots

Each direct comparison used in a network meta-analysis adds a distinct weight to the assessment of each summary effect ((65-66). Finding comparisons with significant or little contributions is quite interesting and improves comprehension of the evidence flow. The value of the evidence from network meta-analysis has also been assessed using the contributions of the many pieces of evidence inside a network (Salanti et al. 2014) (67). These contributions are derived as complex functions of the variances of each pairwise direct summary effect and the network topology.

The net-weight command constructs the design matrix, computes the direct pairwise summary effect sizes with their variances, and calculates the percentage contribution of each direct comparison to the network summary estimates. The contribution plot is then constructed by depicting the various contributions using weighted squares. In addition, the command can combine the estimated contributions with a specific trial-level characteristic (such as the risk of bias in the studies) and generate a bar graph illustrating the proportion of each network estimate's information that corresponds to the various levels of the characteristic.

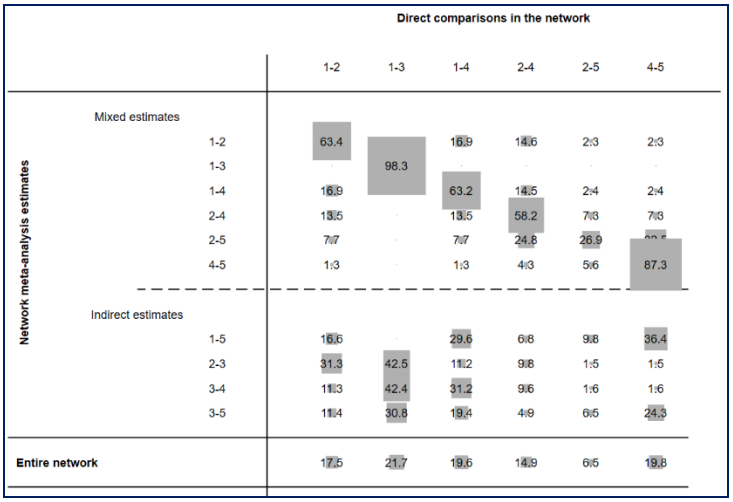

Figure 5: Contribution plot illustrating the different biomaterials coded as numbers and percentage of evidence contributed by each comparative biomaterials. It gives the percentage of evidence contributed by direct, indirect and mixed comparisons.

5.4.3 Inconsistency Factor plots

A crucial presumption for network meta-analysis is consistency, which states that direct and indirect estimates should not significantly deviate in a closed loop made up of three or more treatments. The results of network meta-analysis are at risk if there are significant inconsistencies in one or more loops of a network of interventions (Caldwell, Ades, and Higgins 2005; Salanti 2012). (53,68)

The "loop-specific technique" (Bucher et al. 1997) is used to examine inconsistency in each closed loop of a network of treatments independently (69). The inconsistency factor inside each loop l (l=1,..., L) in a network with L total loops is calculated as the difference between the direct and indirect estimates for one of the comparisons in this specific loop.

Loops with statistically significant inconsistency are those in which the lower confidence interval limit of the inconsistency factor does not meet the zero line. The absence of a statistically significant difference, however, does not rule out the possibility of an inconsistency due to the numerous and correlated tests performed, as well as the approach's limited power (Veroniki et al. 2014) (70).

There are a few methods for managing inconsistency once it has been discovered. Reviewers must first ensure that the data extraction process was error-free. The potential effect modifiers of research within inconsistent loops need to be looked at more carefully after that. The potential impact of effect modifiers on the outcomes could be examined by fitting network meta-regression models. It may also be useful to check the robustness of results by omitting studies that could be causes of discrepancy. NMA may not be the best strategy for syncing the data if there is significant inconsistency and the so sources cannot be determined (Figure 6 and 7).

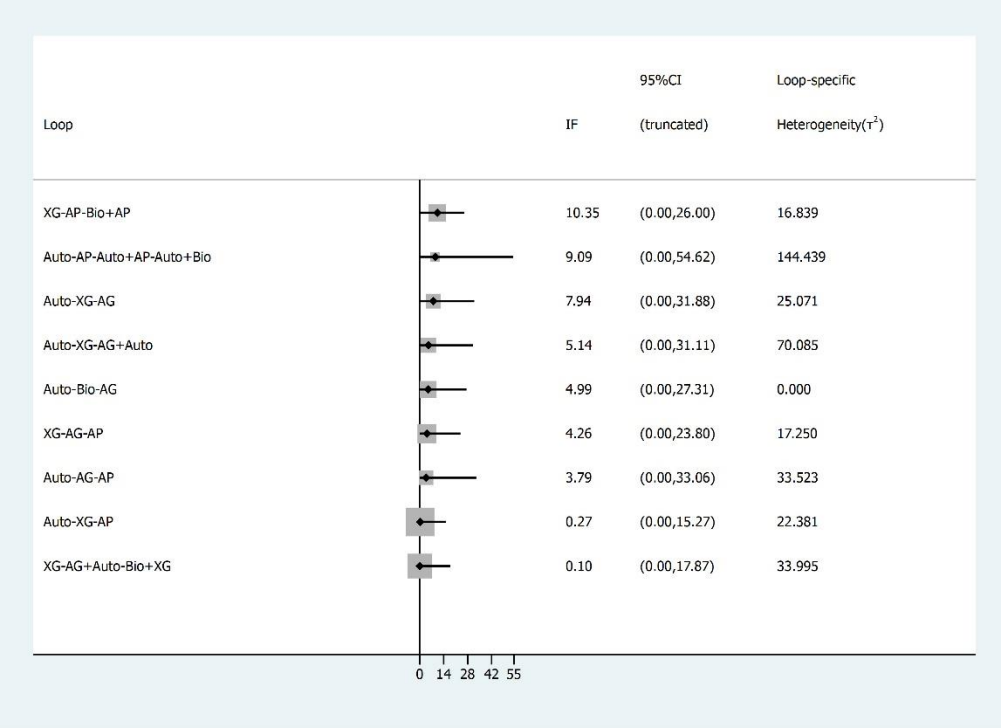

Figure 6: Inconsistency plot illustrating the inconsistencies existing for each comparison of biomaterials in closed loop of network.

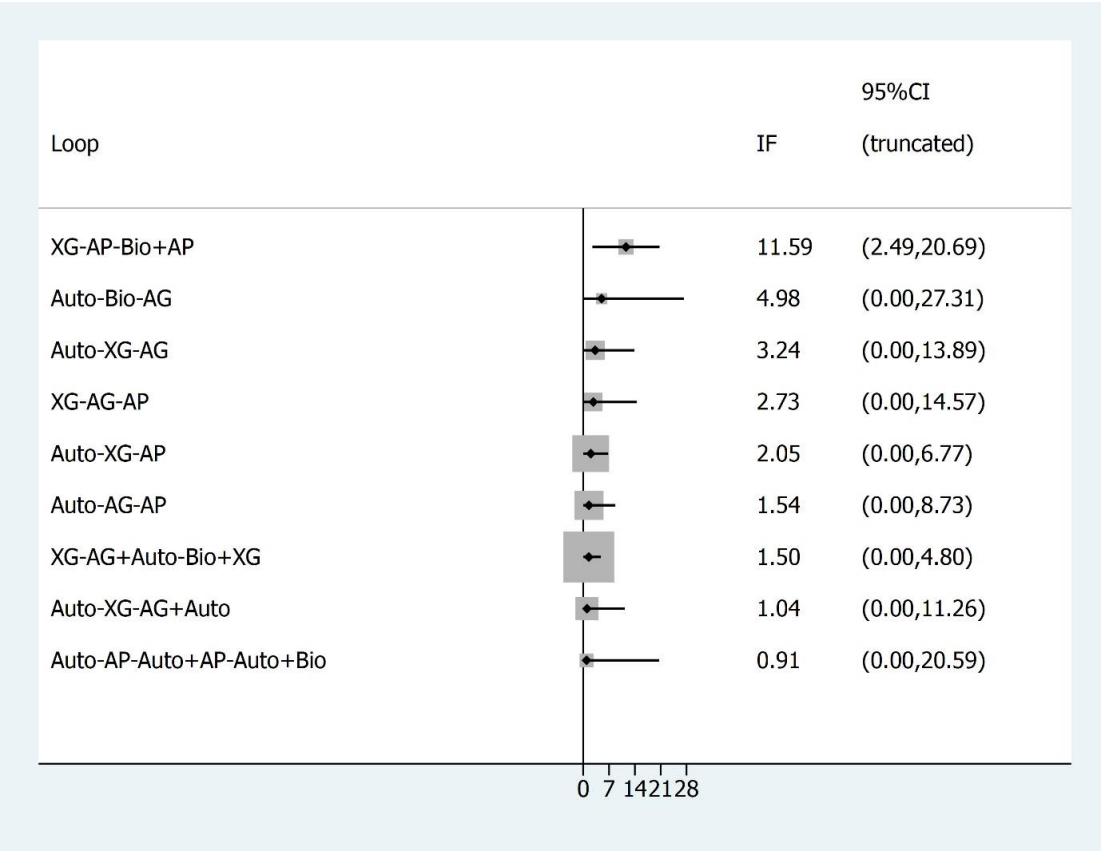

Figure 7: Inconsistency plot illustrating comparison of inconsistencies between biomaterials in entire network

5.4.4 Net-funnel Plots

In paired meta-analysis, funnel plots are frequently employed to assess the presence of small-study effects (important differences in treatment-effect estimates between small and large studies). For each trial, a funnel plot is a scatterplot of a precision measure (such as standard error or variance) vs the estimated treatment effect. The funnel plot indicates no evidence of small-study effects if the study estimates are symmetrically distributed around the line representing the meta-analysis summary effect.

Differences in the relative effects of small and large trials in a network of interventions frequently bring the interpretation of pairwise aggregate effects into doubt and demand additional research. Different treatment comparisons must be considered when extending the funnel plot from pairwise to network meta-analysis: each comparison has its own overall effect. As a result, none of the network investigations share a symmetry reference line. In the comparison-adjusted funnel plot, the horizontal axis indicates the difference between each i-estimate study's and the direct summary effect for the corresponding comparison, while the vertical axis represents dispersion. All studies are predicted to cluster symmetrically around the comparison-adjusted funnel's zero line in the absence of small-study effects.

The net-funnel command provides a comparison-adjusted funnel plot for assessing small-study effects within a network of interventions (Figure 8).

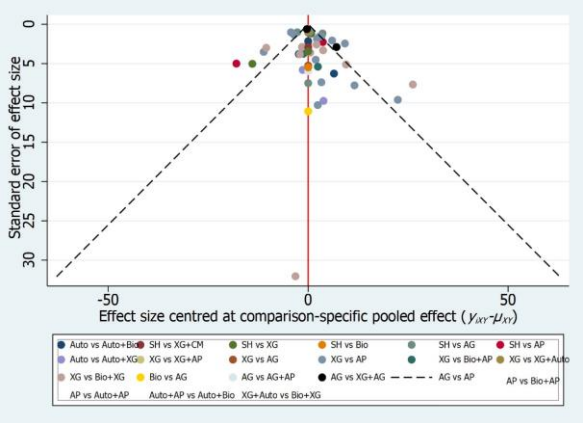

Figure 8: Net-funnel plot for sinus lift augmentation illustrating small study effects (important differences in treatment-effect estimates between small and large studies) of biomaterials. The horizontal axis depicts the difference between each i-estimate study's and the direct summary effect for the associated comparison, while the vertical axis depicts y iXY dispersion.

5.4.5 Predictive interval plots

The prediction intervals that consider the degree of heterogeneity reflect the level of uncertainty in the predicted treatment effects in meta-analysis in addition to the confidence intervals. The interval that a future study's projected relative treatment impact would fall inside is known as the prediction interval. For all pairwise comparisons in a network meta-analysis, a common heterogeneity estimate is often made. Its influence on the various comparisons, however, might vary (that is, it can affect only the precision of the estimates or also the direction).

For all pairwise comparisons in a network meta-analysis, the interval-plot command depicts the predicted effect sizes and associated uncertainty. To be more precise, interval-plot creates a forest plot with the horizontal lines that indicate the confidence intervals extended to also display the predicted intervals. Utilizing Stata's mvmeta (or network) program (White 2011; White et al. 2012; White 2015) (71-73) or alternative software, the treatment effects and associated uncertainty can be calculated.

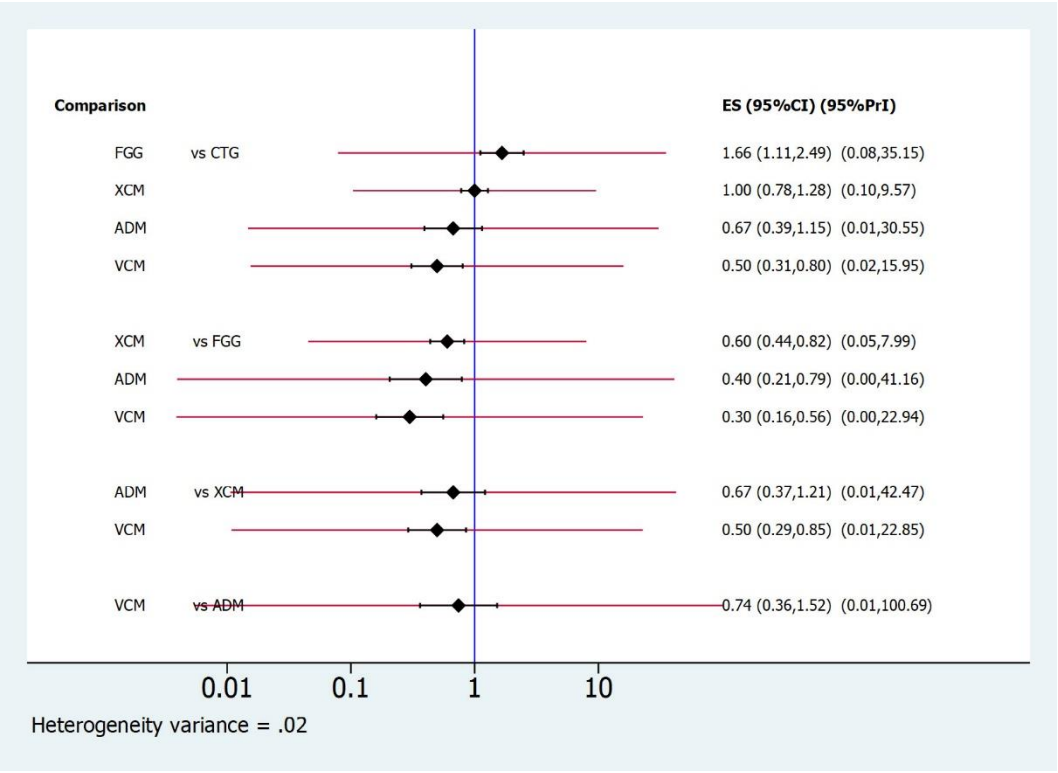

Figure 9: Predictive interval plots

5.4.6 Net leagues

The net-league command provides a "league table" that illustrates the relative treatment effects for all conceivable pairwise comparisons derived using a network meta-analysis in off-diagonal cells (Cipriani et al. 2009). (74) The names of competing therapies are contained in the network's diagonal cells, which can be arranged in any order.

Table 2: Illustrating the network league table for biomaterials in the sinus lift augmentation in new bone formation

SH	AG+AP	XG+AG	Auto+Bio	XG+AP	XG+CM	Bio+XG	AG+Auto	Auto+AP	Bio+AP	AP	AG	Bio_	XG
SH	-0.47 (-17.13, 16.19)	8.98 (-3.61,21.57)	-8.82 (-17.99, 0.36)	1.94 (-9.60,13.48)	-5.80 (-16.28, 4.68)	-1.61 (-7.97,4.74)	-2.81 (-9.96,4.35)	-7.31 (-19.80, 5.17)	-2.63 (-11.64, 6.39)	-8.24 (-13.43,-3.06)	-4.28 (-10.21, 1.66)	-4.80 (-15.20, 5.61)	-4.82 (-9.96,0.33)
0.47 (-16.19, 17.13)	_AG+AP	9.45 (-9.68,28.58)	-8.35 (-27.30, 10.60)	2.41 (-17.40, 22.23)	-5.33 (-25.01, 14.35)	-1.14 (-18.50, 16.22)	-2.33 (-20.09, 15.42)	-6.84 (-27.37, 13.68)	-2.16 (-20.62, 16.30)	-7.77 (-24.67, 9.13)	-3.81 (-19.38, 11.77)	-4.33 (-23.63, 14.97)	-4.35 (-21.26, 12.57)
-8.98 (-21.57, 3.61)	-9.45 (-28.58, 9.68)	_XG+AG	-17.80 (-33.29,-2.31)	-7.04 (-23.58, 9.50)	-14.78 (-31.16, 1.60)	-10.59 (-24.09, 2.91)	-11.78 (-25.78, 2.21)	-16.29 (-33.67, 1.09)	-11.61 (-26.49, 3.28)	-17.22 (-30.12,-4.32)	-13.26 (-24.36,-2.15)	-13.78 (-29.70, 2.14)	-13.80 (-26.71,-0.88)
8.82 (-0.36,17.99)	8.35 (-10.60, 27.30)	17.80 (2.31, 33.29)	Auto+Bio	10.76 (-3.77,25.28)	3.02 (-10.91, 16.94)	7.20 (-3.67,18.08)	6.01 (-5.40,17.43)	1.50 (-11.41, 14.42)	6.19 (-6.40,18.77)	0.57 (-9.57,10.72)	4.54 (-6.26,15.34)	4.02 (-9.84,17.88)	4.00 (-6.21,14.21)
-1.94 (-13.48, 9.60)	-2.41 (-22.23, 17.40)	7.04 (-9.50,23.58)	-10.76 (-25.28, 3.77)	XG+AP	-7.74 (-23.32, 7.84)	-3.55 (-14.71, 7.61)	-4.75 (-16.75, 7.26)	-9.25 (-25.40, 6.89)	-4.57 (-17.43, 8.29)	-10.18 (-20.96, 0.60)	-6.22 (-18.48, 6.04)	-6.74 (-22.15, 8.67)	-6.76 (-17.09, 3.57)
5.80 (-4.68,16.28)	5.33 (-14.35, 25.01)	14.78 (-1.60,31.16)	-3.02 (-16.94, 10.91)	7.74 (-7.84,23.32)	XG+CM	4.19 (-8.07,16.44)	2.99 (-9.69,15.68)	-1.51 (-17.81, 14.78)	3.17 (-10.65, 16.99)	-2.44 (-14.13, 9.25)	1.52 (-10.52, 13.57)	1.00 (-13.76, 15.77)	0.98 (-10.69, 12.66)
1.61 (-4.74,7.97)	1.14 (-16.22, 18.50)	10.59 (-2.91,24.09)	-7.20 (-18.08, 3.67)	3.55 (-7.61,14.71)	-4.19 (-16.44, 8.07)	Bio+XG	-1.19 (-7.19,4.80)	-5.70 (-18.72, 7.32)	-1.02 (-9.72,7.69)	-6.63 (-11.77,-1.49)	-2.66 (-10.34, 5.02)	-3.19 (-15.25, 8.88)	-3.20 (-7.43,1.02)
2.81 (-4.35,9.96)	2.33 (-15.42, 20.09)	11.78 (-2.21,25.78)	-6.01 (-17.43, 5.40)	4.75 (-7.26,16.75)	-2.99 (-15.68, 9.69)	1.19 (-4.80,7.19)	AG+Auto	-4.51 (-18.12, 9.10)	0.18 (-9.56,9.92)	-5.44 (-12.11, 1.24)	-1.47 (-10.00, 7.06)	-1.99 (-14.51, 10.53)	-2.01 (-8.12,4.10)
7.31 (-5.17,19.80)	6.84 (-13.68, 27.37)	16.29 (-1.09,33.67)	-1.50 (-14.42, 11.41)	9.25 (-6.89,25.40)	1.51 (-14.78, 17.81)	5.70 (-7.32,18.72)	4.51 (-9.10,18.12)	Auto+AP	4.69 (-9.68,19.05)	-0.93 (-13.08, 11.23)	3.04 (-10.34, 16.41)	2.52 (-13.66, 18.70)	2.50 (-9.91,14.91)
2.63 (-6.39,11.64)	2.16 (-16.30, 20.62)	11.61 (-3.28,26.49)	-6.19 (-18.77, 6.40)	4.57 (-8.29,17.43)	-3.17 (-16.99, 10.65)	1.02 (-7.69,9.72)	-0.18 (-9.92,9.56)	-4.69 (-19.05, 9.68)	Bio+AP	-5.61 (-13.41, 2.18)	-1.65 (-11.56, 8.27)	-2.17 (-15.80, 11.47)	-2.19 (-9.85,5.47)
8.24 (3.06, 13.43)	7.77 (-9.13,24.67)	17.22 (4.32, 30.12)	-0.57 (-10.72, 9.57)	10.18 (-0.60,20.96)	2.44 (-9.25,14.13)	6.63 (1.49, 11.77)	5.44 (-1.24,12.11)	0.93 (-11.23, 13.08)	5.61 (-2.18,13.41)	AP	3.97 (-2.61,10.54)	3.44 (-8.02,14.90)	3.43 (0.35,6.50)
4.28 (-	3.81 (-11.77,	13.26 (2.15,	-4.54 (-	6.22 (-	-1.52 (-	2.66 (-5.02,1	1.47 (-7.06,1	-3.04 (-	1.65 (-8.27,1	-3.97 (-	AG	-0.52 (-	-0.54 (-

1.66,10.21)	19.38)	24.36)	15.34, 6.26)	6.04,18.48)	13.57, 10.52)	0.34)	0.00)	16.41, 10.34)	1.56)	10.54, 2.61)		11.93, 10.89)	7.14,6.06)
4.80 (-5.61,15.20)	4.33 (-14.97, 23.63)	13.78 (-2.14,29.70)	-4.02 (-17.88, 9.84)	6.74 (-8.67,22.15)	-1.00 (-15.77, 13.76)	3.19 (-8.88,15.25)	1.99 (-10.53, 14.51)	-2.52 (-18.70, 13.66)	2.17 (-11.47, 15.80)	-3.44 (-14.90, 8.02)	0.52 (-10.89, 11.93)	Bio	-0.02 (-11.46, 11.42)
4.82 (-0.33,9.96)	4.35 (-12.57, 21.26)	13.80 (0.88, 26.71)	-4.00 (-14.21, 6.21)	6.76 (-3.57,17.09)	-0.98 (-12.66, 10.69)	3.20 (-1.02,7.43)	2.01 (-4.10,8.12)	-2.50 (-14.91, 9.91)	2.19 (-5.47,9.85)	-3.43 (-6.50,-0.35)	0.54 (-6.06,7.14)	0.02 (-11.42, 11.46)	XG

5.4.7 SUCRA Ranking

It is usual practice to calculate the ranking probabilities p tr for each treatment being in order while conducting a network meta-analysis. Then, using the cumulative odds that therapy t is rated among the top r positions, the competing treatments can be categorized. The following are two relative ranking measures that take the uncertainty in treatment sequence into account:

1. Without a doubt, the surface under the cumulative ranking curves (SUCRA), which reflects the proportion of efficacy or safety that each treatment has in comparison to a "ideal" treatment, always came in top (Salanti, Ades, and Ioannidis 2011) (62).

2. The mean rank, which is the average of the ranking probabilities' distribution.

The sucra command outputs rankograms (line plots of the probabilities versus ranks) and cumulative ranking plots (line plots of the cumulative probabilities vs ranks) for all treatments in a network of interventions in addition to providing the SUCRA percentages and mean rankings.Multidimensional ranking.

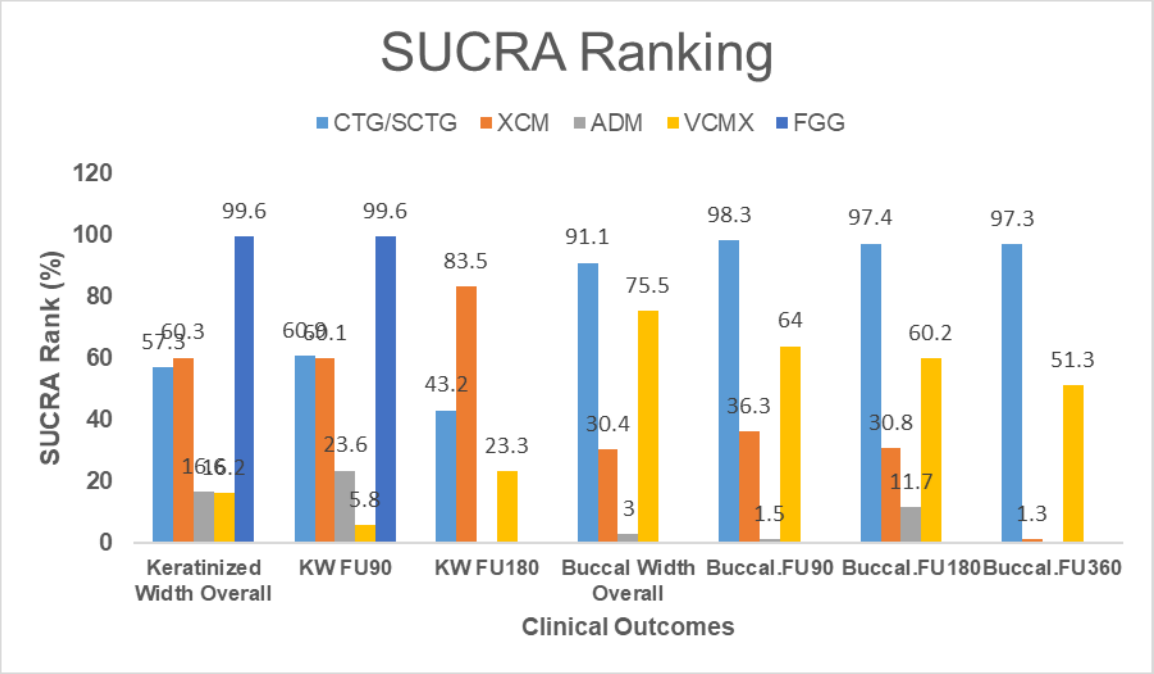

Figure 10: SUCRA ranking for soft tissue augmentation

5.4.8 Quality of Evidence in NMA

For a single outcome, a network meta-analysis delivers two types of findings: the relative treatment effect for all pairwise comparisons and a treatment ranking. It is critical to assess the degree of certainty with which these two sorts of outcomes can help physicians, policymakers, and patients make informed decisions. A method for calculating confidence in the results of a network meta-analysis is through Grading of Recommendations Assessment, Development and Evaluation (GRADE) (75).

The GRADE working group was formed in the year 2000 as an informal collaboration of people interested in addressing the flaws of grading systems in health care. The working group has created a standardized, reasonable, and transparent method for assessing the quality (or certainty) of evidence and the strength of recommendations. Many worldwide organizations contributed to the development of the GRADE approach, which is today regarded as the gold standard in guideline development.

5.4.8.1 Why Grading should be done?

Decisions about evidence and recommendations in healthcare are difficult. For example, those making recommendations on whether to recommend a new generation of biomaterials for patients undergoing various regenerative procedures must agree on which outcomes to consider, which evidence to include for each outcome, how to assess the quality of that evidence, and how to determine whether biomaterials do better than harm. Because resources are continually limited, and money spent on regeneration operations may be spent on other beneficial efforts, they may have to weigh if any incremental health spending has benefits that outweigh the extra costs.

Systematic studies of the outcomes of healthcare provide necessary but insufficient knowledge to make effective decisions. Reviewers and those who use reviews make implicit or explicit judgments regarding the quality of the evidence. These decisions are guided by such judgments. Therapeutic actions, for example, are likely to change depending on whether the evidence demonstrating that biomaterials truly achieve regeneration that is capable of meeting clinical demand is strong (high quality) or unconvincing (low quality).

Similarly, persons who use practice guidelines make unconscious or explicit judgments regarding the strength of recommendations. Using the same example, a guideline advocating therapy for individuals with inadequate bone or post-extraction alveolar socket may suggest that all patients should be treated, or that patients should probably be treated, indicating that treatment is not always required. A systematic and explicit approach for making such judgments can aid in error prevention, critical appraisal of these judgments, and information dissemination.

5.4.8.2 Criteria for Grading

1. Adhere to the GRADE Working Group's definitions of evidence certainty.

2. Carefully evaluate each of the GRADE domains when determining the certainty of the evidence (even if different terminology is used).

3. Assess the overall confidence in the evidence for each important outcome using either four or three categories (such as high, moderate, low, and/or extremely low) with definitions that align with the GRADE Working Group's criteria. The evidence summaries and evidence-to-decision criteria should serve as the basis for determining the evidence certainty and strength of recommendations.

4. Utilize evidence profiles, ideally based on systematic reviews, to assess the evidence certainty. Proper documentation of the evidence evaluated and the methods used to locate and assess the evidence is necessary. Each of the GRADE criteria should be considered when making recommendations or judgments, including the direction and intensity. The GRADE evidence-to-decision frameworks should be used to provide transparent disclosure of the researched evidence, additional considerations, and judgments.

5. Assess the strength of recommendations using two categories (either for or against an option) with definitions such as strong and weak/conditional that follow the GRADE Working Group standards (although different terminology may be used) (76-78) (Figure 11).

	Direct Evidence		Indirect Evidence		Network Evidence	
Biomaterials	Co-Effie (95% CI)	Certainty of Evidence	Co-Effie (95% CI)	Certainty of Evidence	Co-Effie (95% CI)	Certainty of Evidence
< 4mm RBH Trials: 49 Subjects: 1071						
Auto V XG	6.65 (-15.38,2.07)	Low	3.91 (-10.47,2.65)	Low	2.74 (-13.61,8.12)	Low
Auto V Biologics	3.76 (-15.35,7.83)	Low	9.75 (-34.5,15.0)	Low	5.99 (-21.41,33.40)	Low
Auto V AG	3.18 (-10.8, 4.43)	Low	6.30 (-16.36, 3.75)	Low	3.11 (-9.50, 15.73)	Low
Auto V AP	10.26(-19.36, -1.17)	Low	7.26(-13.84,-0.68)	Low	3.00(-14.24,8.22)	Low
Auto V XG+Auto	1.25(-13.88, 11.37)	Low	3.63(-12.55,5.27)	Low	2.38(-13.08,17.85)	Low
Auto V Auto+Bio	8.09(-18.14,1.95)	Low	12.99(-37.05,11.06)	Low	4.90(-21.18,30.98)	Low
XG V AG	4.70(-19.37,9.97)	Low	1.94(-5.59,9.49)	Low	6.64(-23.15,9.85)	Low
XG V AP	3.71 (-7.09,-0.33)	Low	1.60(-9.76,6.54)	Low	2.10(-10.93,6.73)	Low

Figure 11: Illustrating the Grading of Evidence for different comparisons of biomaterials in formation of new bone when there is <4mm residual bone height for sinus lift procedures (76-78)

5.5 Factors contributing for Implementation of NMA results in clinical settings

The requirements for doing an NMA can be roughly classified as follows: assessments and analyses to test the assumptions required in NMA, presentation and reporting of outcomes, and justification for modelling decisions. Assumptions of NMA is the most important criteria that has impact on the NMA results and conclusions and more especially, when there is high heterogeneity between studies. The key assumptions include; similarity (direct comparison), transitivity (indirect comparison) and consistency/inconsistency (mixed comparisons= direct and indirect comparisons) (79). This criterion

may be not effective when testing the sensitivity. This sensitivity checking can be time-consuming, especially when models join and fit well after sufficient number of studies are included.

Some criterion or requirements required to conduct NMA unlikely to affect in conducting NMA and hence may not be important. For example, a graphically illustrating the ranking probabilities. However, because the ranking probabilities can be easily obtained using software such as WinBUGs (which is frequently used for Bayesian NMAs), skipping this step is unlikely to result in efficiency. Furthermore, consistency testing is typically performed at the end of the NMA process. Many published NMAs do not include the findings of such assessments. Inconsistencies in NMA results are typically explained by heterogeneity observed (80-81).

Another important factor that could affect NMA results are the effect modifiers like patient characteristics, types of study associated with the treatment effects (82). These effect modifiers differ not only among studies (creating heterogeneity), but also between comparisons (causing inconsistency). If the distribution of effect modifiers between different types of direct comparisons is skewed, the relevant indirect comparisons will be skewed as well. If it is agreed that this is not the case, network meta-analysis is just as valid as pairwise meta-analysis.

Reporting of NMA results is another factor that could influence the interpretation. In order to have a cohesive reporting, PRISMA extension statement for network meta-analysis has the checklist for reporting NMA (83).

Network meta-analysis (NMA) is a statistical technique that combines the results from multiple clinical trials to compare different treatments simultaneously, using both direct and indirect evidence. Statistical heterogeneity refers to the different aspects of intervention effects studied in various NMA research. One approach to managing statistical heterogeneity is to employ a random effects NMA, which includes the variance between studies in the statistical model. A commonly accepted assumption in the random effects NMA is that the between-study variance is consistent across all interventions. However, in some NMA scenarios, this single between-study assumption may not be accurate, and the model should incorporate multiple sources of between-study variance (84,85).

NMA incorporates only randomised trials either parallel or split-wise but there is scarcity of non-randomised trials that are used for evidence synthesis. This would be useful when there is scarcity of trials in the literature and could use non-randomised studies for evidence synthesis and also when

there is disconnection of network treatments. Complex NMA methods like contrast-based (CB) and arm-based (AB) parametrisations are necessary when merging diverse sources of data to solve concerns such as participant selection bias, incorporating single-arm trials (SATs), and synthesizing a blend of individual participant data (IPD) and aggregate data (AD) (85,86)

Dental clinical research ideally includes multiple treatment comparisons with multiple outcomes. When summarizing information to inform an economic evaluation, it is critical that the analysis appropriately reflects the association between the variables within the data, because correlations between outcomes may have implications for assessing the net benefit of treatment. A multivariate NMA is a solution and it provides a framework for evaluating numerous treatments across different outcome measures while accounting for outcome association structure (87-90).

6. Conclusions

1. **To determine the most effective grafting/sealing biomaterial in maintaining horizontal and vertical dimensions after alveolar ridge preservation**

   When compared to sockets that have not been treated, alveolar ridge preservation effectively reduces both horizontal and vertical shrinkage. The consistency of XG for ridge dimension preservation was validated by NMA, but other materials and combinations, such as AG, Bio + AG, and AG + alloplasts, outperformed XG in clinical evaluations. The value of such alternatives to XG for alveolar ridge preservation requires more proof. In retaining ridge dimension and concentrating platelet activity throughout the development of new bone, Bio + AG outperformed the other materials. However, in the bulk of the clinical comparisons, alloplasts, xenografts, and AG + AP consistently displayed good performance.

2. **To determine the most effective grafting/sealing biomaterial for new bone formation after alveolar ridge preservation**

   It has been demonstrated that the use of autologous soft tissue grafts and membranes covering graft materials in post-extraction sites allows for less hard tissue shrinkage than does the lack of such material. Comparing crosslinked and non-crosslinked membranes using histomorphometric techniques, it may be seen that the latter facilitate better hard tissue regeneration.

3. **To determine the most effective biomaterial for soft tissue regeneration after tooth extraction**

   When covered with crosslinked collagen membranes, grafting materials showed statistically considerably higher performances in terms of soft tissue thickness and vertical buccal height alterations. The performance of soft tissue grafts was superior in horizontal width alterations. Non-crosslinked membranes and other substances or mixtures produced results that were marginally worse.

4. **To determine the most effective biomaterial for gingival recession treatment in adjunct to coronally advanced flap**

   When used in conjunction with CAF, CTG, ADM, platelet concentrates, and CM + GFs demonstrated enhanced stability over 12 months of follow-up, a higher percentage of root coverage, and increased keratinized gingival width.

5. **To determine the most effective dental implant abutment material**

   Zirconia abutments appear to be a practical alternative to the usage of traditional titanium abutments within the limitations of the current investigation. To get results that are more reliable, further clinical investigations are required.

6. **To rank the different combinations of recombinant human-derived growth and differentiation factors with/without scaffold biomaterial in the treatment of periodontal intrabony defects, through network meta-analysis of pre-clinical studies**

   The periodontium's supporting soft and hard tissues can regenerate with the help of a variety of recombinant factors. The results of animal research are particularly beneficial in understanding the efficacy and mechanisms of action of the medications that might be used to treat human illnesses, even though there is still some transferability to the clinical setting. The current NMA showed that when comparing various periodontal regeneration outcomes, specific criteria performed better, whether or not they were linked to biomaterials. The ideal combination and formulation of bioactive agents and scaffolds for periodontal regeneration can therefore be determined, based on the objectives and goals of the therapeutic situation.

7. **To determine the best rank recombinant growth factor formulations agents through network meta-analysis of clinical studies**

   According to the findings of our network meta-analysis, periodontal regeneration works best when recombinant growth factors are used in conjunction with alloplastic scaffolds. In order to make the best treatment choice, practitioners may use NMA, but numerous factors, such as patient preferences, treatment costs, and defect characteristics, need also be /lconsidered.

8. **To determine the effectiveness of biomaterials used in soft tissue augmentation procedures**

   According to the results of the network meta-analysis, CTG performed best in all of the majority outcomes and FGG seems to be the best in terms of keratinized mucosa increase. FGG and XCM would perform better in future clinical studies if used to augment the keratinized mucosa. VCMX would perform better in future clinical studies in increasing soft tissue in the buccal aspects. RCTs studying this topic with larger sample sizes are needed in order to better elucidate the effects of different matrices on soft tissue augmentation.

9. **To determine the most effective biomaterial in increasing residual bone height after maxillary sinus lift procedures**

   Different biomaterials performed differently according to RBH after sinus augmentation. The combination of xenograft and autograft ranked best in performance for 4mm RBH, while the combination between xenograft and autogenous bone ranked best when RBH is 4mm. These biomaterials are also most likely to perform best in future clinical studies. In order to achieve the greater amount of new bone formation, the amount of residual bone may be critical for the choice of the material.

7. Future line of research in NMA

In the future, conducting network meta-analyses (NMA) is expected to see improvements in various aspects of the review process. Firstly, the characteristics of the review, such as the research question, eligibility criteria, and methods for searching and selecting studies, assessing the risk of bias and quality of evidence, interpreting results, and reporting findings, may impact the way NMA is performed. As a result, changes are likely to be made in these areas in future reviews, such as incorporating studies from previous systematic reviews as the baseline for selecting primary articles and developing the search strategy. Secondly, future methodological research may explore the usefulness and robustness of different statistical methods and identify situations in which certain methods or models are more appropriate and efficient than others. For example, using real-world evidence data to conduct NMA may be evaluated (85,91).

The results of network meta-analyses can be influenced by a variety of factors such as the total number of trials in the network, trials with multiple comparison groups, and factors like heterogeneity, inconsistency, and bias. Heterogeneity, inconsistency, and bias can have a ripple effect throughout the network and impact effect estimates differently in various parts of the network. To address these challenges, various methods have been proposed for detecting, assessing, and managing heterogeneity, inconsistency, and bias. However, before these techniques can be widely adopted, it is important to evaluate their effectiveness through simulations and practical studies (85).

It is necessary to develop new software that blends user-friendliness with statistical sophistication and incorporates built-in methodological assistance. Furthermore, new software should be capable of handling many types of outcomes (e.g., continuous outcomes, binary outcomes), numerous outcomes, outcomes at different follow-up times, as well as pair-wise and network meta-analysis at the same time.

With the emergence of new, user-friendly tools, there is worry that network meta-analysis will be attempted and implemented incorrectly. Thus, systematic reviewers should be trained to identify possible research problems where network meta-analysis may be acceptable and where it is not, especially when evidence is scarce.

8. Future line of research for Oral and Maxillofacial Regeneration

Oral and maxillofacial regeneration is a fast-emerging discipline that aims to restore normal structure and function to areas of the head, neck, face, and jaw that have been damaged by accident, congenital defects, or disease. Future research in this area will most likely concentrate on establishing new and improved approaches for tissue engineering, gene therapy, and regenerative medicine.

Tissue engineering will very certainly play a role in the future of oral and maxillofacial regeneration. Using natural or synthetic biomaterials in combination with cells, growth factors, and other bioactive chemicals, this discipline strives to build functioning and anatomically accurate tissues. Researchers are developing new scaffolds, materials, and procedures for cultivating and differentiating stem cells into functional tissues that can replace damaged or diseased tissues. Also, some nano-based biomaterials and smart cells play wider role in regenerating hard and soft tissues. The role of immunomodulation in enhancing regeneration has wider role and is the area that has significant research questions.

Another promising path for oral and maxillofacial regeneration is gene therapy. This method entails inserting therapeutic genes into cells in the oral and maxillofacial region using viral or non-viral vectors. These genes can then be exploited to boost cell proliferation and differentiation, improve blood vessel creation, and induce the expression of growth factors and other signaling molecules. Gene therapy has already showed significant promise in the treatment of craniofacial abnormalities and other oral and maxillofacial disorders, with more progress expected in the future years.

Regenerative medicine methods such as stem cell therapy, in addition to tissue engineering and gene therapy, are likely to play a key role in the future of oral and maxillofacial regeneration. Because stem cells have the unique ability to develop into numerous cell types and build new tissues, they have shown considerable promise in the treatment of craniofacial abnormalities and other oral and maxillofacial disorders. Researchers are attempting to improve the isolation, growth, and differentiation of stem cells for use in oral and maxillofacial regeneration, as well as the delivery of these cells to the damaged tissues. One such area is the use of stem cells specific to the type of tissue for example; skeletal stem cells might provide better clinical outcomes and need rather using dental pulp or gingival stem cells for regenerating bone.

The use of growth factors and other signaling molecules in oral and maxillofacial regeneration is another potential field of investigation. These medicines have the potential to enhance tissue growth and regeneration as well as improve the outcomes of other regenerative medicine techniques. Researchers are striving to better understand the molecular mechanisms driving oral and maxillofacial regeneration, as well as to create new strategies for delivering growth factors and other signaling molecules to damaged tissues.

Finally, developments in imaging and computer-aided design and manufacturing technology will almost certainly play a significant role in the future of oral and maxillofacial regeneration. These technologies can be used to construct custom-designed implants and scaffolds, guide the delivery of regenerative medicine medicines, and evaluate tissue regeneration progress.

9. Resources for conducting NMA

1. **https://methods.cochrane.org/cmi/network-meta-analysis-toolkit**
2. **https://training.cochrane.org/handbook/current/chapter-11**
3. **https://methods.cochrane.org/cmi/comparing-multiple-interventions-cochrane-reviews**

Conflict of Interest

None to declare

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96. Khijmatgar, S.; Del Fabbro, M.; Tumedei, M.; Testori, T.; Cenzato, N.; Tartaglia, G.M. Residual Bone Height and New Bone Formation after Maxillary Sinus Augmentation Procedure Using Biomaterials: A Network Meta-Analysis of Clinical Trials. *Materials* **2023**, *16*, 1376.

Conferences

1. Europerio10 Copenhagen 2022 European Federation of Periodontology
2. Same Problems New Directions, Annual Scientific Meeting Faculty of Dentistry Royal College of Surgeons, Ireland 28th-29th October 2022
3. **Annual Scientific Meeting Faculty of Dentistry, Royal College of Surgeons, Ireland 30th October 2021**
4. IAOMS Virtual Conference 2021 Earned 2.00 for the course "2021 IAOMS Virtual Conference"
5. IAOMS Virtual Conference – in collaboration with Osteo Science Foundation Session: Biologisation of Bone Substitute Materials and Collagen Membranes to Enhance Regeneration Processes in Oral and CranioMaxillofacial Surgery July 2 2020
6. Imaging and Applied Optics Congress 22 - 26 June 2020 & Optical Sensors and Sensing Congress

Training

1. SAS certification Data Literacy
2. AI in Healthcare Stanford Medical School

Figures

Figure 1: Treatment comparisons illustrating direct, indirect and mixed evidence

Figure 2: Example of a network comparing four chemotherapy regimens, where transitivity is violated due to incomparability between the interventions (Chaimani A (2019).

Figure 3: Network Plot illustrating different interventions for alveolar ridge preservation. The blue nodes represent the number of samples in each group of intervention from pooled clinical studies. The lines represent the number of comparisons between two biomaterials in the selected clinical studies. The width of the line represents the number of comparisons i.e. thicker the line, more the number of comparisons and vice versa. The risk of bias is also reported in the network, where yellow colour indicates the moderate risk of bias, green low risk of bias and red indicates high risk of bias.

Figure 4: Network plot illustrating the disconnection. AG+AP v AG+XG materials is the only single study available for comparison and has been disconnected with the network as there are no control, XG or PC's for direct comparison for buccal, lingual side with AG and AP and vice versa.

Figure 5: Contribution plot illustrating the different biomaterials coded as numbers and percentage of evidence contributed by each comparative biomaterial. It gives the percentage of evidence contributed by direct, indirect and mixed comparisons.

Figure 6: Inconsistency plot illustrating the inconsistencies existing for each comparison of biomaterials in closed loop of network.

Figure 7: Inconsistency plot illustrating comparison of inconsistencies between biomaterials in entire network

Figure 8: Net-funnel plot for sinus lift augmentation illustrating small study effects (important differences in treatment-effect estimates between small and large studies) of biomaterials. The horizontal axis depicts the difference between each i-estimate study's and the direct summary effect for the associated comparison, while the vertical axis depicts y iXY dispersion.

Figure 9: Predictive interval plots

Figure 10: SUCRA ranking for soft tissue augmentation

Figure 11: Illustrating the Grading of Evidence for different comparisons of biomaterials in formation of new bone when there is <4mm residual bone height for sinus lift procedures (76-78)

Appendix I

Published Papers

Specific Objective 1**:** Canullo L, Del Fabbro M, Khijmatgar S, Panda S, Ravidà A, Tommasato G, Sculean A, Pesce P. Dimensional and histomorphometric evaluation of biomaterials used for alveolar ridge preservation: a systematic review and network meta-analysis. Clin Oral Investig. 2022 Jan;26(1):141-158. doi: 10.1007/s00784-021-04248-1. Epub 2021 Nov 26. PMID: 34826029.

Specific Objective 2**:** Del Fabbro M, Tommasato G, Pesce P, Ravidà A, Khijmatgar S, Sculean A, Galli M, Antonacci D, Canullo L. Sealing materials for post-extraction site: a systematic review and network meta-analysis. Clin Oral Investig. 2022 Feb;26(2):1137-1154. doi: 10.1007/s00784-021-04262-3. Epub 2021 Nov 25. PMID: 34825280; PMCID: PMC8816783.

Specific Objective 3**:** Canullo L, Pesce P, Antonacci D, Ravidà A, Galli M, Khijmatgar S, Tommasato G, Sculean A, Del Fabbro M. Soft tissue dimensional changes after alveolar ridge preservation using different sealing materials: a systematic review and network meta-analysis. Clin Oral Investig. 2022 Jan;26(1):13-39. doi: 10.1007/s00784-021-04192-0. Epub 2021 Oct 20. PMID: 34669038; PMCID: PMC8791918.

Specific Objective 4**:** Panda S, Khijmatgar S, Arbildo-Vega H, Das AC, Kumar M, Das M, Mancini L, Del Fabbro M. Stability of biomaterials used in adjunct to coronally advanced flap: A systematic review and network meta-analysis. Clin Exp Dent Res. 2022 Feb;8(1):421-438. doi: 10.1002/cre2.461. Epub 2021 Nov 29. PMID: 34845864; PMCID: PMC8874057.

Specific objective 6**:** Khijmatgar S, Panda S, Das M, Arbildo-Vega H, Del Fabbro M. Recombinant factors for periodontal intrabony defects: A systematic review and network meta-analysis of preclinical studies. J Tissue Eng Regen Med. 2021 Dec;15(12):1069-1081. doi: 10.1002/term.3250. Epub 2021 Oct 8. PMID: 34585856.

Specific Objective 7**:** Panda S, Khijmatgar S, Das M, Arbildo-Vega H, Del Fabbro M. Recombinant Human Derived Growth and Differentiating Factors in treatment of periodontal intrabony defects: Systematic review and network meta-analysis. J Tissue Eng Regen Med. 2021 Nov;15(11):900-914. doi: 10.1002/term.3236. Epub 2021 Aug 17. PMID: 34370897.

Specific objective 9: Khijmatgar, S.; Del Fabbro, M.; Tumedei, M.; Testori, T.; Cenzato, N.; Tartaglia, G.M. Residual Bone Height and New Bone Formation after Maxillary Sinus Augmentation Procedure Using Biomaterials: A Network Meta-Analysis of Clinical Trials. *Materials* **2023**, *16*, 1376.