Systematic Review Article

Do adjunctive interventions in patients undergoing rapid maxillary expansion increase the treatment effectiveness? *A systematic review*

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ABSTRACT

Objectives: To evaluate the clinical effectiveness of adjunctive interventions in individuals undergoing rapid maxillary expansion (RME).

Materials and Methods: MEDLINE, Web of Science, Cochrane, Scopus, LILACS, and Google Scholar were searched without restrictions up to June 2020. Trials involving participants undergoing orthopedic or surgical RME, along with adjunctive interventions, were included. Risk-of-bias assessments were performed using the Cochrane tool for randomized trials-2. The certainty level of evidence was assessed through the Grading of Recommendations Assessment, Development and Evaluation tool.

Results: Six randomized clinical trials, with low to high risk of bias, were included. Low certainty of the evidence suggested that low-level laser facilitated opening of the midpalatal suture during the active phase of RME. Likewise, moderate certainty demonstrated that low-level laser accelerated the healing process of the suture during the retention phase. The clinical impact of this outcome, that is, stability and retention time, was not evaluated. Very low evidence indicated that osteoperforations along the midpalatal suture increased maxillary transverse skeletal gains in young adults undergoing RME. Low evidence suggested that platelet-rich plasma therapy did not minimize the vertical and thickness bone loss after RME in the short term.

Conclusions: Based on currently available information, the use of low-level laser associated with maxillary expansion seems to provide a more efficient suture opening and bone healing. Limited evidence suggests that osteoperforations improve the skeletal effects of RME in non-growing individuals**.** There are no adjunctive interventions capable of reducing the periodontal side effects of RME. (*Angle Orthod.* 2021;91:119–128.)

KEY WORDS: Systematic review; Rapid maxillary expansion; Palatal expansion technique

INTRODUCTION

Rapid maxillary expansion (RME) is a common therapy for patients with maxillary constriction and transverse deficiencies, promoting opening of the midpalatal suture. However, the relapse tendency of RME is high.[1,2] This can be attributed in part to the rate of bone deposition in the suture area, which seems to reach sufficient levels to minimize relapse only after 6 months of retention.[3]

Therefore, a method that accelerates bone healing in the suture area can be useful in preventing relapse and reducing retention time. Several trials reported adjunctive interventions in patients undergoing RME focused on enhancing tissue response by inducing stem cell activity and biological substrate, including laser therapy, photobiomodulation, injection of growth factors, hormones, and proteins.[4–9] In addition to healing capacity, these interventions could increase others parameters of clinical success of RME, such as improving skeletal changes and reducing periodontal side effects.[7,9] This makes it an interesting topic for

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clinical practice, mainly due to the potential benefits it can bring to patients. Nevertheless, there is still controversy regarding the effects of these interventions, and the methodological heterogeneity and the inconclusive results of these studies could bias the evidence and mislead practitioners. Therefore, a critical systematic review addressing this topic would be beneficial to clinicians.

For these reasons, the aim of this systematic review was to provide a synthesis of the available evidence to answer the following main focused question: Do adjunctive interventions (I) in patients undergoing RME (P) increase the effectiveness of treatment (O) compared to conventional RME protocol (C)?

MATERIALS AND METHODS

Protocol and Registration

The study protocol was registered on PROSPERO (CRD42020168673). The report of this systematic review followed the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[10]

Eligibility Criteria

A PICOS (population, intervention, comparison, outcomes, study design) question was established as an inclusion criterion:

Population (P): subjects of any gender without restriction of ethnicity or age, undergoing RME (orthopedic or surgical).

Intervention (I): use of adjunctive interventions that included: laser irradiation, osteoperforation, pulsed electromagnetic waves, intermittent resonance vibration, pharmacological methods, or novel materials described by authors.

Comparison (C): control group of subjects without the use of adjunctive interventions.

Outcomes (O): the effectiveness of interventions was assessed using the following parameters: primary: stimulation of bone regeneration/healing; secondary: improvement in skeletal/dentoalveolar measurements, enhancement of the midpalatal sutural opening, decreased periodontal side effects (such as buccal alveolar bone thickness, bone loss, gingival recession), and greater stability.

Study design (S): randomized clinical trial (RCT), quasirandomized clinical trial, or non-randomized clinical trial. The exclusion criteria were: case reports, animal and in vitro studies, descriptions of clinical technique, studies with orthodontic/orthopedic approaches performed concomitant with RME, studies that evaluated distraction osteogenesis, and studies evaluating individuals with craniofacial deformities, syndromes, or cleft lip/palates.

Information Sources and Search Strategy

Electronic searches in MEDLINE (via PubMed), Web of Science, Cochrane Library, Scopus and LILACS were conducted up to June 2020. Google Scholar was investigated to partially access the gray literature. The Controlled Trials Database of clinical trials (http://www.controlled-trials.com) and the Clinical Trials: U.S. National Institutes of Health (http://www.clinicaltrials.gov) were consulted to check for possible ongoing studies. Finally, manual searches in the reference list of the included articles were also carried out. There was no restriction of language, year, or status of publication for inclusion.

Detailed search strategies were developed for each database based on the search strategy developed for MEDLINE, and subsequently adapted for the other databases (Appendix).

Study Selection

In the first phase, two reviewers (LGS, LSM) independently and in duplicate screened the titles/abstracts of the references. Those that met the eligibility criteria were included. References with insufficient information in the title/abstract for a decision on inclusion or exclusion were retrieved for full-text evaluation. In the second phase, the full-texts were accessed and those studies that met the eligibility criteria were included. Agreement between reviewers was measured using the kappa index. In both phases, differences were resolved by consensus.

Data Extraction and Items Extracted

A standardized table was used to extract the following data: authors, year of publication, study design, characteristics of participants, description of groups and interventions, details of evaluations, and main findings. Data were compared for accuracy, and any discrepancy was resolved through reexamination of the original study.

Assessment of Bias Risk Within Studies

The risk of bias in RCT was assessed using the revised Cochrane risk-of-bias tool for randomized trials-2,[11] which includes the following domains: randomization processes; deviations from intended interventions; missing outcome data; measurement of outcome; and selective outcome reporting. After answering the signaling questions for each domain following the recommendations of the Cochrane

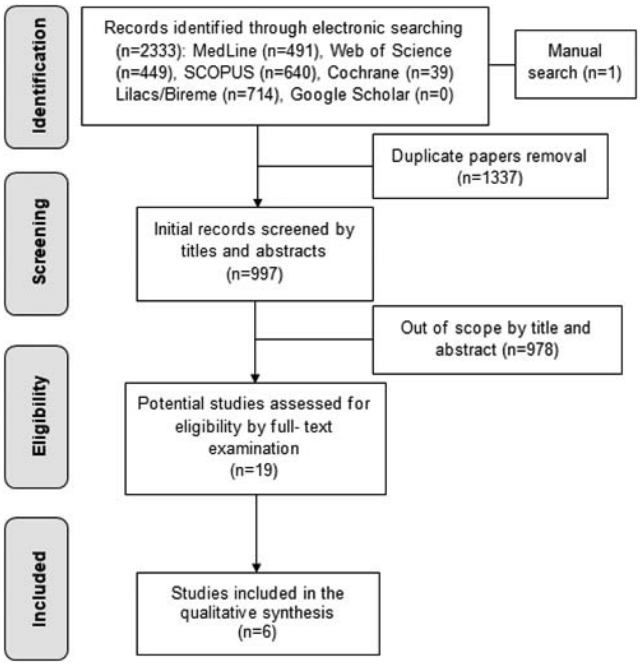

Figure 1. PRISMA flowchart of article retrieval.

Handbook for Systematic Reviews of Interventions 6.0 (https://training.cochrane.org/handbook), each source of bias was graded as: "low" risk, "some concerns," or "high" risk of bias.

Evaluation of the Level Evidence (Risk of Bias Across Studies)

The level of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation Pro software (GRADEpro Guideline Development Tool, available online at gradepro.org).[12] For each outcome examined, the GRADE assesses the number of studies included, the study designs, risk of bias, inconsistency, indirectness, imprecision, and other considerations (such as publication bias). Based on this assessment, the certainty of the evaluation of the outcome could be very low, low, moderate, or high quality.

Summary Measurements

Measurements were based on continuous data (millimeters or degrees) and nominal/ordinal data from clinical indices, dental casts, radiographs, or cone-beam computed tomography (CBCT).

Synthesis of Results

Data collected were synthetized in a descriptive table. A meta-analysis was planned if there was relative homogeneity among included studies.

Table 1. List of Studies Excluded With Reasons After Full Text Evaluation

Reference	Reason for Exclusion
Abreu et al., 2010	Case report
Altan et al., 2013	Animal study
Arat et al., 2003	Study not related with the research objective
Bulut et al., 2020	Animal study
da Silva et al., 2012	Animal study
Duarte et al., 2017	Animal study
Giuliani et al., 2018	Study not related with the research objective
Hirose et al., 1988	Animal study
Hong et al., 2017	Animal study
Provatidis et al., 2007	In vitro study
Robiony et al., 2014	Description of clinical technique
Santagata et al., 2019	Description of clinical technique
Tang et al., 2011	Animal study

RESULTS

Study Selection

The search strategy yielded a total of 2334 studies (Figure 1). After the removal of duplicates and application of the eligibility criteria, 19 studies were considered for full-text evaluation. Among them, 13 were excluded, and the reasons are provided in Table 1. Good agreement between the reviewers was found (Kappa index, 0.75). At the end of the eligibility phase, only six studies were included in this systematic review.

Study Characteristics

Table 2 provides the descriptive characteristics of the included studies. All studies were RCT, and one[9] used a non-parallel design (split-mouth). Concerning population items, a total of 63 individuals participated in the intervention group and 54 individuals were controls in studies with parallel design. A total of 18 individuals were enrolled in the split-mouth study.[9] The mean age of participants at baseline ranged from 8[8] to 17[13] years. In one study,[14] only the age range of the individuals included was reported. Four studies[9,13–15] reported the diagnosis of transverse maxillary deficiency as an inclusion criterion, while two[8,16] studies only cited the need for RME.

Regarding the adjunctive interventions evaluated by the included studies, one study[13] performed osteoperforations produced by the erbium-doped yttrium aluminium garnet (Erbium-YAG) laser along the region of the midpalatal suture. Three studies[8,15,16] carried out the application of low-level laser therapy (LLLT) around the midpalatal suture adjunctive to the orthopedic RME, and one study[14] applied the laser after surgically assisted RME. Finally, one study[9] used platelet-rich plasma (PRP) injected in the buccal alveolar mucosa along the roots of the anchoring teeth (first molars and first premolars).

Table 2. Summary of Study Characteristics and Results of the Included Studies[a]

Study	Study Design	Type of Appliance/ Technique	Patients Characteristics, Mean or Range Age	Interventions Protocol and Control Group (N)
Angeletti et al., 2010	RCT	Hyrax appliance after SARME	Patients with diagnosis of maxillary transverse deficiency (>7.0 mm) 8 to 33 y	IG: patients underwent expansion period of 7 d after SARME with irradiation of LLLT (GaAlAs diode laser diode, emitting a laser with a wavelength of 830 nm, power of 100 mW, and 0.06 cm^2 tip diameter) in anterior MPS with 48 h interval (n = 7) CG: patients underwent expansion after SARME without irradiation (n = 6)
Cepera et al., 2012	RCT	Hyrax appliance/1 full turn initially and a half turn daily until overcorrection)	Patients with any kinds of RME treatment need 10.2 y	IG: Application of LLLT (780 nm wavelength, 40 mW power, and 10 J/cm^2 density) at 10 points located around the MPS. The application stages were 1 (days 1–5 of activation), 2 (at screw locking, on 3 consecutive d), 3, 4, and 5 (7, 14, and 21 d after stage 2, respectively) (n = 14) CG: RME only (n = 13)
Ferreira et al., 2016	RCT	Hyrax expander (twice daily activation) for 14 d approximately	Diagnosis of unilateral or bilateral posterior crossbite, maxillary atresia and/or lack of space in the maxilla for eruption of the permanent teeth 11 y	IG: RME was followed by 12 LLLT sessions (GaAlAs, wavelength = 780 nm, power = 70 mW, diameter = 0.04 cm^2) contact with the mucosa (incisal papilla, right and left of MPS) twice a week for the first month, once in the the second month (n = 10) CG: RME only (n = 4)
Garcia et al., 2016	RCT	Hyrax expander with an acrylic splint adhered to molars (twice daily activation until transversal overcorrection	Cl I or Cl II malocclusion subjects had to be a stage prior to the pubertal growth peak 8.4 y	IG: Application of LLLT diode (wavelength = 660 nm, power = 100 mW, diameter = 0.26 cm^2, and energy density = 332 mW/cm^2) 60 s to four points along MPS, and 30 s to a point each side of the suture. A total of seven applications were made on days 1, 7, 14, 28, 42, 56, and 70 of the retention phase RME (n = 20) CG: RME followed by the application of the placebo laser mode in the same periods as the IG (n = 19)
Moawad et al., 2016	RCT	Hyrax expander (two activations per day for the first week and then one activation every other day until overcorrection)	Patients with permanent dentition and presenting transverse maxillary deficiency 17.6 y (IG) 17.2 y (CG)	IG: RME assisted with the application of Erbium-YAG laser interventions or three months in order to make osteoperforations along the MPS (n = 12) CG: RME only (n = 12)
Alomari et al., 2019	RCT (split-mouth)	Hyrax expander (activated twice a day until overcorrection)	clinical maxillary transverse deficiency, complete emergence of first molars premolars 14.0 y	IG: PRP was injected into the mucosa along the roots of the buccal aspect of supporting teeth (first molar and first premolar) before and after the end of activation (n = 18 halves) CG: RME only (n = 18 halves)

BBCL indicates buccal bone crest level; BBPT, buccal bone plate thickness; CBCT, cone beam computed tomography; CG, control group; d, days; IG, intervention group; LLLT, low-level laser therapy; MPS, midpalatal suture; OD, optical density; mo, months; PRP, platelet rich-plasma; RCT, randomized clinical trial; RME, rapid maxillary expansion; SARME, surgically assisted rapid maxillary expansion; y, years.

All studies used the hyrax expander, with different activation protocols as described in Table 2. The mean time of posttreatment evaluation varied substantially and ranged from 75[8] to 210[14] days.

Risk of Bias Within Studies

The methodological appraisal of the included studies is reported in Figure 2. Overall, one study[9] was judged to be "low" risk of bias for all domains. Three studies[8,14,16] were graded as having "some concerns" regarding bias arising from the randomization processes domain due to not reporting any information about allocation concealment. In addition, one study[16] did not provide information regarding the blinding of the evaluator. Two studies were graded as overall "high" risk of bias. The first study[15] carried out the random-

Table 2. Extended

Evaluation Period	Outcomes Evaluated	Survey Methods	Author's Conclusions
preoperatively, and postoperative d 30, 60, 90, 120, and 210.	Stimulation of bone healing at MPS	OD by digital periapical radiographs	IG had higher bone regeneration rates than the CG ($P < .001$) at all postoperative times. However, the OD measurements after 7 mo were lower in comparison with the preoperative
Pretreatment (T1), day of locking (T2), 3–5 d after T2 (T3), 30 d after T3 (T4), and 60 d after T4 (T5)	Stimulation of suture opening and bone healing at MPS	OD by digitized occlusal radiographs	The results showed that the laser application improved the opening of the MPS and accelerated the regeneration process of suture ($P < .05$).
At the end of disjunction and after 4 mo	Stimulation of bone healing at MPS	OD by CBCT	Difference between T0 and T1 of OD values was observed in the IG ($P < .001$), but this difference was not significant in the control group ($P = .20$). Intergroup comparison of OD values at T1 revealed higher OD in the laser-treated group ($P = .05$)
Pretreatment, and 75 days later	Stimulation of bone healing at MPS	Intrasuture distance by CBCT	The MPS presents different levels of reorganization depending on the analyzed area. The irradiated patients presented a greater percentage of approximate zones in the anterior ($P = .008$) and posterior ($P = .001$) superior suture, and less approximation in the posterior superior suture ($P = .040$) than the CG
Pretreatment (T1), at the end of expansion (T2) and after three months at the end of retention (T3)	Skeletal and dentoalveolar parameters	Posteroanterior cephalogram and dental casts	The IG achieved more skeletal changes in latero-nasal width (+2.19 mm, $P < .001$), maxilla-mandibular width (+3.94 mm, $P < .001$) and maxillary width (+2.98 mm, $P < .001$) compared with CG at T2. There were no differences in dentoalveolar measurements, and stability at T3 ($P > .05$).
Pretreatment (T0) and after 3 mo of retention (T1)	BBPT, BBCL, and incidence of dehiscence and fenestrations	CBCT	There was no difference in BBPT and BBCL between the two groups after RME ($P > .05$). A higher prevalence of dehiscence (3.5%) was found in the IG.

ization of the participants after the RME procedure, generating bias in randomization, in addition to dropping out of half of the participants in one of the groups, generating attrition bias. The second study[13] failed to provide information about the randomization process and blinding outcome evaluators.

Results of Individual Studies

Owing to a significant amount of population, clinical, methodological, and statistical heterogeneity, meta-analysis was not justifiable. Identified sources of heterogeneity were: distinct survey methods, different parameters to identify similar outcomes, studies with population undergoing orthopedic and surgical RME, and the different follow-up durations. Thus, a descriptive comparison was reported (Table 2).

As far as the pattern of changes in the midpalatal suture were concerned, three studies reported[8,15,16] that application of low-level laser in the suture region associated with orthopedic RME stimulated the suture

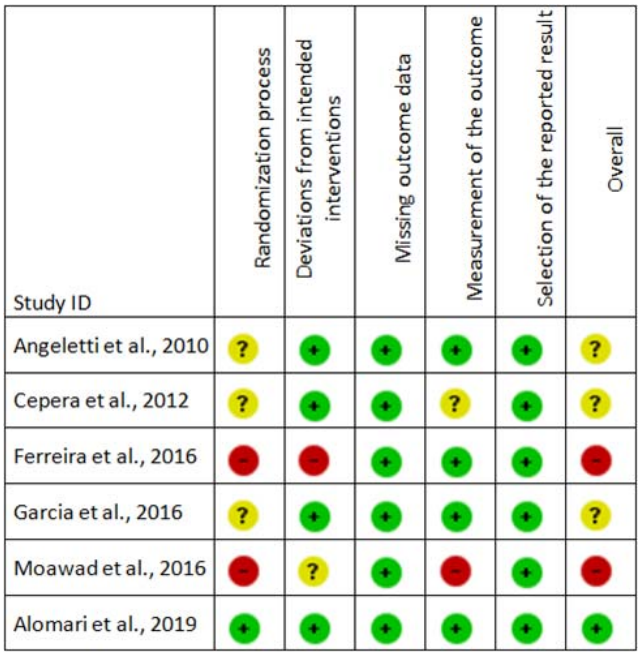

Figure 2. Summary of the risk of bias assessment according to the Cochrane tool for randomized trials-2.

opening or healing pattern. Improvement in the opening of the midpalatal suture was reported[16] during the screw activation phase, with a significant decrease of 2.3-fold ($P = .049$) in bone density compared to the control group. During the retention phase, three studies reported[8,15,16] significant rates of stimulation of bone healing. The highest rate was a 3.5-fold ($P = .017$) acceleration after approximately 3 months.[16] A study[15] that used CBCT scans found similar values of bone repair in the suture region in the irradiated group after 4 months of retention ($P < .005$). Regarding the areas of the suture that had accelerated healing with the use of LLLT, the anterior superior ($P = .008$) and posterior ($P = .001$) margins of the suture in the laser group seemed to be the most sensitive to respond to the laser stimulus.[8]

Similar to the orthopedic RME, the application of LLLT adjunctive to surgically assisted RME[14] in eight sessions at intervals of 48 hours after surgery led to a progressive increase in the rate of bone healing in the region of the midpalatal anterior suture compared to the control group, ranging from +10.6% in the first month to +26.3% after 7 months ($P < .001$). In addition, it was found that the mean rate of bone remineralization in patients in the control group after 7 months was similar to the average values found between the second and third months of patients who underwent laser application.

A high risk of bias study[13] evaluated the application of Erbium-YAG laser to create osteoperforations in the suture region in subjects with maxillary atresia undergoing orthopedic RME. The outcomes evaluated were skeletal and dentoalveolar measurements, and the intervention group achieved more skeletal increase in lateronasal width (+2.19 mm, $P < .001$), maxillomandibular width (+3.94 mm, $P < .001$), maxillary width (+2.98 mm, $P < .001$) compared with the control group at the end of the expansion phase. After 3 months of retention follow-up, relapse was similar between the groups.

Regarding the methods to minimize the periodontal side effects of RME, a low risk of bias study[9] evaluating the effectiveness of injection of PRP on the periodontal tissue found no significant differences ($P > .05$) in vertical bone loss (mean difference ranged from -0.08 mm to 0.2 mm) and buccal bone thickness (mean difference ranged from -0.15 to 0.85 mm) in anchorage teeth in patients after conventional RME when compared to patients in the group with injections with PRP. A higher prevalence of dehiscence (3.5%) was found in the intervention group for all supporting teeth.

Assessment of the Certainty of Evidence

The certainty of evidence was evaluated according to the GRADE approach (Table 3). Reasons for downgrading the evidence are detailed there. The level of certainty for the bone regeneration outcome was graded as moderate while, for the outcomes suture opening and reduction of periodontal side effects, levels of certainty were low. For the outcomes skeletal/dentoalveolar measurements, the certainty was graded as very low.

DISCUSSION

Summary of Evidence

This review systematically assessed the available evidence for the effectiveness and safety of adjunctive interventions in patients undergoing RME under the main aspect: bone healing in the suture region. In addition, the outcomes stimulation of suture opening, improvement of skeletal changes, and reduction of periodontal side effects were evaluated.

The results of this systematic review consistently suggested, with a moderate level of certainty, that interventions with LLLT were effective to increase bone mineralization in the midpalatal suture in children and adolescents after orthopedic RME. Likewise, the rate of bone remineralization in patients undergoing LLLT after surgical maxillary expansion seemed to be accelerated a few months compared to patients without laser intervention.[14] The hypothesis is that the laser acted at the molecular level, stimulating osteoblastic activity.[17,18] A possible useful clinical interpretation of this result may be the prevention of relapse and the

Table 3. GRADE Evidence Profile About Outcomes of Adjunctive Interventions With RME[a]

Certainty Assessment								
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Consideration	Impact	Overall Certainty of Evidence
Skeletal/dentoalveolar measurements								
1	RCT	Very serious[b]	Not serious	Not serious	Serious[c]	Serious[d]	Osteoperforation resulted in greater skeletal changes in maxillary width after RME	⊕ VERY LOW
Midpalatal suture opening								
1	RCT	Serious[b]	Not serious	Not serious	Serious[c]	None	Opening of the midpalatal suture was facilitated with the application of low-level laser.	⊕⊕ LOW
Bone Regeneration								
4	RCT	Serious[b]	Not serious	Not serious	Not serious	None	Low-level laser accelerates midpalatal suture regeneration after RME.	⊕⊕⊕ MODERATE
Reduction of periodontal side effects								
1	RCT	Not serious	Not serious	Not serious	Serious[c]	Serious[e]	Platelet-rich plasma does not minimize the adverse effects of RME on alveolar bone.	⊕⊕ LOW

[a] GRADE indicates Grading of Recommendations, Assessment, Development and Evaluation; RCT, randomized clinical trial; RME, rapid maxillary expansion.
[b] Based on the risk of bias assessment tool.
[c] Due to the estimate coming from only one study.
[d] There was insufficient information about the process of random sequence generation, concealment of allocation, and blinding of outcome assessors.
[e] The follow-up period is not adequate for the objectives of the study.

reduction of retention time by the local application of LLLT. Notwithstanding, at this time, it is not possible to draw conclusions about this with the current literature.

Current knowledge comparing different RME appliances indicated that no expander appeared to be superior when it came to opening the midpalatal suture, including bone-borne appliances.[19] An important finding reported by this review was the facilitated and improved opening of the suture with the application of LLLT. Despite the low level of evidence, this outcome may represent some clinical benefits, such as the increased orthopedic effects and the arch perimeter of the therapy,[3] a reduction in the loss in thickness and height of the buccal alveolar bone, and the frequency of dehiscence and fenestrations. Nevertheless, it is important to mention that the studies that used LLLT did not investigate the outcomes that are believed to have clinical importance.

The effectiveness of osteoperforations to improve skeletal changes in late adolescents and young adults undergoing RME was investigated using the Erbium-YAG laser. This method aimed to decrease sutural interdigitation to enable significant transverse skeletal changes in non-growing individuals through orthopedic maxillary expansion. The results indicated significant gains in the measures of maxillary width. However, it is important to note that in addition to the high risk of bias reported in the study[13] that evaluated this intervention, the method was invasive and repeated over 3 months. In view of the possible need to repeat the procedure, further studies are needed evaluating outcomes such as acceptance among patients, pain/discomfort, and possible postoperative complications to make this intervention clinically realistic as an alternative to surgically assisted RME.

PRP used as adjunct to RME failed to produce any healing effect in periodontal tissue. Nevertheless, the evaluation was limited to post-retention, without assessing long-term changes and possible subsequent healing. The potential effect of periodontal regeneration caused by growth factors seemed to be more apparent after a few months.[20] Therefore, long-term studies are recommended to indicate the effectiveness of this therapy.

Two previous reviews[21,22] were conducted evaluating the effects of LLLT associated with RME regarding bone regeneration. However, those reviews did not consider the effect on dentoalveolar/skeletal measures, suture opening and periodontal health, as well as other adjuvant interventions were not considered. In one of them,[22] the search was restricted to the English language, which probably limited the inclusion of potential studies, and the other review included results of animal studies.[21] Additionally, no analysis of level of certainty supporting the conclusions was considered, which decreased confidence of the recommendations.

Limitations

A quantitative analysis was not feasible given the heterogeneity among the included studies. Fundamental questions such as survey methods and units of measurement used, stage of growth at the beginning of treatment, post-treatment follow-up, and the protocols for the application of the interventions used varied substantially and were a source of heterogeneity.

A qualitative review presents significant drawbacks in comparison to mathematical synthesis, since it becomes quite challenging to weigh the data coming from individual studies. The use of the GRADE tool should have taken this into consideration. A possible selection bias was avoided by extensive searches across multiple electronic databases and accessing partial gray literature without language or publication status restrictions.

This review included individuals without restriction of age or degree of maxillary transverse deficiency. These items may influence the effects of RME. Generally, the opening of the midpalatal suture becomes progressively more difficult as patients grow older.[23] Finally, several adjunctive interventions were investigated and some methods had only one study to be analyzed. This impacted the level of evidence certainty of some outcomes.

Implications for Practice and Research

The use of the LLLT is effective as an adjunct tool to facilitate the opening of the suture during the activation of the screw, and accelerates bone healing after orthopedic and surgical RME. It is important to emphasize that the clinical impact of these results still needs to be better elucidated. Osteoperforation along the midpalatal suture appears to increase the transverse skeletal gains of the maxilla in late adolescents and young adults. Nevertheless, the use of this intervention must be done carefully in clinical practice due to limited evidence.

There was great variation in the survey method used by the included studies to assess changes in the midpalatal suture. For this outcome, three-dimensional assessment using low-dose computed tomography can be considered more favorable.[24]

Some RCTs failed to provide details on the sample size, sample randomization/allocation, blinding outcome assessor, and statistician. There is a need for well-designed and reported clinical trials following guidelines such as CONSORT (Consolidated Standards of Reporting Trials)[25] to increase the certainty of evidence about the proposed adjunctive methods to boost the benefits of RME. It is important that future studies assess the clinical significance of the improvement in opening of the suture (such as changes in the maxillary width and less periodontal side effects) and the stimulation of bone regeneration (such as the relapse rate and the possibility of reducing retention time). The clinical meaning of these variables is more relevant and may be a determining factor for RME therapy success.

CONCLUSIONS

Based on the level of certainty (GRADE assessment), the evidence suggests:

- Low to moderate certainty that the use of LLLT facilitates the opening (2.3-fold) and accelerates the bone healing process (up to 3.5-fold) of the midpalatal suture in patients undergoing RME. However, the available evidence is not adequate to assess whether these benefits effectively result in skeletal gains, greater stability, or shorter retention time.
- Very low certainty indicates that osteoperforations along the midpalatal suture associated with RME results in transverse skeletal increases in the maxilla ranging from 2 to 4 mm.
- Low level of certainty that PRP did not minimize alveolar side effects after RME in the short term.

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APPENDIX 1. Search Strategy for Each Database

Electronic Database	Search Strategy Used	Items Found
MEDLINE Searched via PubMed on June 7, 2020	#1 (((((((palatal expansion technic[MeSH Terms]) OR expansion technics, palatal[MeSH Terms]) OR expansion technique, palatal[MeSH Terms]) OR expansion technic, palatal[MeSH Terms]) OR palatal expansion techniques[MeSH Terms]) OR maxillary expansion[MeSH Terms]) OR expansion, maxillary[MeSH Terms]) OR rapid maxillary expansion #2 ((((((bone regeneration[MeSH Terms]) OR bone regenerations[MeSH Terms]) OR bone remodeling[MeSH Terms]) OR wound healing[MeSH Terms]) OR bone density) OR midpalatal suture) OR palatal suture #1 AND #2	**491**
Scopus Searched on June 7, 2020	#1 (TITLE-ABS-KEY (palatal AND expansion AND technic) OR TITLE-ABS-KEY (expansion AND technics, AND palatal) OR TITLE-ABS-KEY (expansion AND technique, AND palatal) OR TITLE-ABS-KEY (expansion AND technic, AND palatal) OR TITLE-ABS-KEY (palatal AND expansion AND techniques) OR TITLE-ABS-KEY (maxillary AND expansion) OR TITLE-ABS-KEY (expansion, AND maxillary) OR TITLE-ABS-KEY (rapid AND maxillary AND expansion) OR TITLE-ABS-KEY (rapid AND midpalatal AND suture AND disjunction) OR TITLE-ABS-KEY (maxillary AND orthopedic AND expansion)) #2 (TITLE-ABS-KEY (bone AND regeneration) OR TITLE-ABS-KEY (bone AND regenerations) OR TITLE-ABS-KEY (bone AND remodeling) OR TITLE-ABS-KEY (wound AND healing) OR TITLE-ABS-KEY (bone AND density) OR TITLE-ABS-KEY (palatal AND suture) OR TITLE-ABS-KEY (midpalatal AND suture)) #1 AND #2	**640**
Cochrane Central Register of Controlled Trials Searched on June 7, 2020	(palatal expansion technic$ OR expansion technics, palatal OR expansion technique, palatal OR palatal expansion technique$ OR maxillary expansion OR expansion, maxillary OR rapid maxillary expansion OR maxillary orthopedic$ expansion OR sutural disjuct*):ti,ab,kw AND (bone regeneration$ OR bone remodel* OR wound healing OR bone densit* OR palatal suture OR midpalatal suture):ti,ab,kw	**39**
Web of Science Searched on June 7, 2020	#1 TÓPICO: (palatal expansion technic$) OR TÓPICO: (expansion technics, palatal) OR TÓPICO: (expansion technique, palatal) OR TÓPICO: (palatal expansion technique$) OR TÓPICO: (maxillary expansion) OR TÓPICO: (expansion, maxillary) OR TÓPICO: (rapid maxillary expansion) OR TÓPICO: (maxillary orthopedic$ expansion) OR TÓPICO: (sutural disjuct*) #2 TÓPICO: (bone regeneration$) OR TÓPICO: (bone remodel*) OR TÓPICO: (wound healing) OR TÓPICO: (bone densit*) OR TÓPICO: (palatal suture) OR TÓPICO: (midpalatal suture) #1 AND #2	**449**
LILACS database Searched on June 7, 2020	#1 tw:((tw:(palatal expansion technic)) OR (tw:(expansion technics, palatal)) OR (tw:(expansion technique, palatal)) OR (tw:(expansion technic, palatal)) OR (tw:(palatal expansion techniques)) OR (tw:(maxillary expansion)) OR (tw:(expansion, maxillary)) OR (tw:(rapid maxillary expansion)) OR (tw:(maxillary orthopedic expansion)) OR (tw:(midpalatal suture disjunction))) #2 tw:((tw:(bone regeneration)) OR (tw:(bone regenerations)) OR (tw:(bone remodeling)) OR (tw:(wound healing)) OR (tw:(bone density)) OR (tw:(midpalatal suture)) OR (tw:(palatal suture))) #1 AND #2	**714**
Google Scholar Searched on June 7, 2020	"rapid maxillary expansion" + "interventions"	**0**
Manual Search		**1**
Sum		**2334**