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Changes in Airway Dimensions After Face-Mask Therapy in Cleft Lip and Palate and Non-cleft Patients: Systematic Review and Meta-Analysis

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Abstract

Context: Maxillary deficiency can lead to the reduction of airway space and increase the chances of development of obstructive airway disorders. Facemask therapy is one of the main treatment protocols in developing maxillary deficient patients.
Objectives: The purpose of this systematic review and meta-analysis was to assess the changes in the airway dimensions after face-mask therapy in both cleft lip and palate and non-cleft patients.
Methods: A systematic search in different electronic databases (EMBASE, Pubmed, Cochrance Central register of controlled trials), IADR proceedings and a hand search by October 2020 were conducted and a meta-analysis and systematic review was performed.
Results: In patients without cleft lip and palate, upper pharyngeal width was significantly increased by mean of 2.05 mm (CI = 95%, 0.61 - 3.50) following facemask therapy in comparison to patients who did not receive the treatment. Other upper pharyngeal (nasopharyngeal) measurements also showed a statistically significant improvement after therapy: S-PNS by 4.64 mm (CI = 95%, 3.34 - 5.94), AD1-PNS by 3.81 mm (CI = 95%, 2.40 - 5.21), AD2-PNS by 2.90 mm (CI = 95%, 0.13 - 5.67) and Pm'-SPL by 2.53 (CI = 95%, 0.54 - 4.51). Lower pharyngeal measurments did not show any significant changes after the treatment ($P > 0.05$). In the analysis of studies with 3D imaging modalities, upper pharyngeal volume was also significantly increased by 499.29 mm^3 (CI = 95%, 69.58-929.00) after the treatment. In addition, a review of articles that included cleft lip and palate patients also showed after the treatment, the upper pharyngeal measurements all showed a significant improvement ($P < 0.05$), whereas the oropharyngeal region was relatively stable.
Conclusions: In maxillary deficient patients with or without an orofacial cleft, facemask therapy can improve the nasopharyngeal area dimensions; however, this treatment protocol appears not to have an effect on the oropharyngeal area of the airway tract.

Keywords: Airway, CBCT, Facemask

1. Context

The treatment of skeletal class III malocclusion is relatively challenging. This condition may be caused by a protruded mandible, a retrognathic maxilla or both (1, 2). Different treatment methods exist depending on the jaw responsible for the malocclusion. In young patients, facemask is usually used for maxillary protraction and chincup is utilized to prohibit and redirect abnormal mandibular growth (3).

In more than 40 percent of cases, a retrognathic maxilla is the sole reason for the class III discrepancy and in most cases, a deficient maxilla contributes to a class III malocclusion (4). Cleft lip and palate patients also commonly suffer from a deficient maxilla resulted from former surgical interventions. Maxillary deficiency in cleft lip and palate patients develops from a hindered maxillary growth and usually involves all three sagittal, vertical and transverse dimensions (5, 6).

A deficient maxilla can also lead to the reduction of airway space and cause dyspnea (7). Most airway disorders happen during sleep and commonly manifest as snoring or apnea (8). Sleep breathing disorders have a negative impact on the mental and physical health of patients and are related to cardiovascular diseases, diabetes, mental illnesses and impaired cognition (9-13). Face-mask therapy in addition to rapid palatal expansion(RPE) might be used to stimulate bone growth and protract the maxilla. Maxillary protraction can in turn increase the pharyngeal airway spaces but evidence claims that there is a great variability in results in class III patients after face-mask therapy (14-16).

2. Objectives

Therefore, the aim of this study was to assess the variations in airway dimensions after face-mask therapy in cleft lip and palate and non-cleft patients.

3. Methods

We conducted this systematic review and meta-analysis based on the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) and MOOSE Guidelines for Meta-Analyses .and Systematic Reviews of Observational Studies (17, 18).

3.1. Types of Studies

We considered all randomised controlled trials (RCTs) in English that evaluated the effects of face-mask therapy on the airway dimensions in cleft lip and palate and non-cleft patients.

3.2. Types of Participants

We included patients of any age, gender or race with or without cleft lip and palate who had been diagnosed to need face mask therapy. Our criteria for diagnosis and administration of this treatment were as follows: a retrognathic maxilla diagnosed by clinical observation and/or radiographic findings.

3.3. Types of Interventions

We assessed the effect of Face-mask and RPE treatment protocols on the stimulation of bone growth and protraction of the maxilla in the selected cases. We considered these techniques in two groups of the patients; those with cleft lip and palate and patients without cleft.

3.4. Types of Outcome Measures

The outcome measures of our study were the dimensions of the airway space and relevant landmarks in cephalometric and 3D images.

3.5. Search Methods for Identification of Studies

Two different electronic searches for studies patients with and without oral cleft were performed by E.B. The studies were then inspected utilizing the PICO format considering the exclusion and inclusion criteria.

3.6. Electronic Searches

Medline, EMBASE, Cochrane Central Register of Controlled Trials and IADR electronic databases were searched from beginning until October 26th of 2020 using the search strategies related to each database (Table 1). References of the retrieved articles were also hand searched for relevant studies. In addition, the international clinical trials registery platform of WHO and clinicaltrials.gov were searched for ongoing trials.

3.7. Selection of Studies

First, duplicate records were excluded and then the titles and abstracts of the retrieved studies were screened by two reviewers (H.S. and E.B.). Full text of the eligible studies were also assessed as required. Studies in languages other than English were first translated, then evaluated. In case of disagreement between the reviewers, consensus was reached by a third reviewer (M.D.).

All studies with inclusion criterias were considered for data extraction . This stage was also conducted by two authors.

3.8. Data Extraction and Management

The required data were extracted from studies using custom extraction forms by two authors (H.S. and M.D.). Two different data forms were created for 2D and 3D studies using the available data from the articles. For the 3D studies, airway volume measurments were extracted and for 2D studies, cephalometric parameters related to the airway were extracted (Table 2).

3.9. Assessment of the Risk of Bias in Included Studies

The risk of bias was assessed using the Newcastle-Ottawa scale. The biases were divided into three main categories: selection bias, confounding bias and measurement bias. Selection bias was further subdivided into representative sample size, selection of a comparison group, ascertainment of exposure by secure record and outcome not present at beginning of study. The measurement bias was also divided into assessment of outcome, length of the follow up period and percentage of patient follow up. If a study met the requirements, it was given a single point for each subcategory and two for confounding bias. A study with a score of 9 was considered low risk; the scores of 7 and 8 were viewed as medium risk and scores of 6 and under were considered high risk.

3.10. Measures of Treatment Effect

Due to the differneces in the intervention and measurement methods, and the differences for the study population of investigations regarding age and sex, we applied random-effects models for the meta-analysis.

Table 2. Traits of the Final Included Studies

Study (Author, Year)	Methods		Participants			Intervention	Outcomes	
	Study Design	Duration (Mo)	Number of Participants (Age ± SD)	Sex Of Participants	Cleft Condition		Imaging Modality	Landmarks Measured
Kilinc, 2008 (19)	R		C: 17 (10.9 ± 0.82), E: 18 (10.5 ± 0.93)	C(M:8, F:9), E(M:7, F:11)	NC	C: Untreated, E: FM+RPE	2D	ad1-PNS, ad2-PNS
Kaygisis, 2009 (20)	R	48	E: 25 (11.32 ± 1.08)	E(M:14, F:11)	NC	E: FM+RPE	2D	S-PNS, ad1-PNS, ad2-PNS, AA'-Pm', Pm'-SPL, NA Alan, AA-PNS, ve-Pve, MPS, SPS, IPS, eb-Peb, OA Alan
Akin, 2015 (16)	R	6	C: 17 (10.1 ± 1.3), E1:25 (10.3 ± 1.5), E2:17 (9.8 ± 1.6)	C(M:8, F:9), E1(M:10, F:15), E2(M:9, F:16)	NC	C: Untreated, E1: FM+RPE, E2:CC	2D	Pharyngeal width measurements (upper & lower), Nasopharyngeal area measurements (aerial & adenoidal & total), HRGN, H-MP, C3H, H-C3Me
Baccetti, 2010 (14)	P	42	C: 14 (9.8 ± 1.9), E: 22 (10.5 ± 1.3)	C(M:8, F:6), E(M:10, F:12)	NC	C: Untreated, E: FM+RPE	2D	Pharyngeal width measurements (upper & lower), ad1-PNS, ad2-PNS
Seo, 2017 (15)	P	6	E1: 28 (10.3 ± 1.4), E2: 24 (11.2 ± 1.1)	E1(M:8, F:20), E2(M:12, F:12)	NC	E1: FM+RPE, E2: SKFM	2D	Pharyngeal width measurements (upper & lower),
Balos Tuncer, 2015 (21)	R	12	C: 11 (9.1 ± 1.1), E1: 17 (11.3 ± 0.98), E2: 17 (11.5 ± 1.1)	C(M:8, F:3), E1(M:9, F:8), E2(M:10, F:7)	NC	C: Untreated, E1: NFFM+RPE, E2: LFFM+RPE	2D	H-MP, C3H, S-PNS, ad1-PNS, ad2-PNS, AA'-Pm', Pm'-SPL, NA Alan, AA-PNS, ve-Pve, MPS, SPS, IPS, eb-Peb, OA Alan
Yagci, 2015 (22)	P	6	C: 15 (9.8 ± 1.6), E1: 15 (9.6 ± 1.3), E2: 15 (9.5 ± 1.5)	C(M:8, F:7), E1(M:7, F:8), E2 M:8, F:7)	NC	C: Untreated, E1: FM+RPE, E2: MFM+RPE	2D	Pharyngeal width measurements (upper & lower), Nasopharyngeal area measurements (aerial & adenoidal & total)
Chen, 2015 (23)	R	10	C: 30 (10.41 ± 0.42), E: 30 (9.56 ± 0.22)	C(M:16, F:14), E(M:16, F:14)	NC	C: Untreated, E: FM+RPE	3D, 2D	Upper pharynx volume, Velopharynx volume, Glossopharynx volume, Hypopharynx volume, C3-H
Pamporakis, 2014 (24)	R	8	E1: 12 (10.1 ± 0.2), E2: 10 (10.1 ± 0.2)	M:8, F:14	NC	E1:FM (400gr)+RPE, E2:FM (800gr)+RPE	3D	Upper Pharynx volume, Lower Pharynx volume, Total Pharynx volume
Kecik, 2016 (25)	R	17	C: 26 (8.1 ± 2.5), E: 23 (8.3 ± 2.4)	C (M:12, F:14), E(M:11, F:12)	CL/P, NC	C: NC FM+RPE, E:CL/P FM+RPE	2D	ad1-PNS, ad2-PNS, Nasopharyngeal area measurements
Fu, 2016 (26)	P	18	C: 14 (9.62 ± 1.74), E: 18 (10.37 ± 1.31)	C (M:9, F:5), E (M:13, F:5)	CL/P	C: Untreated, E: FM + RPE	3D	Upper, middle and lower pharyngeal airway area and sagittal and transverse diameter

Abbreviations: R: randomized clinical trial; P: prospective clinical trial; C: control group; E1: intervention group; M: male; F: female; NC: non-claft patients; CL/P: clef lip and/or palate; FM: face-mask; RPE: rapid palatal expansion; PNS: posterior nasal spine; H: upperior superior portion of hyoid bone; MP: mandibular plane; C3: superior anterior portion of third cervical vertebrae; MPS: middle pharyngeal space; SPS: superior pharyngeal space; IPS: inferior pharyngeal space; SPL: sphenoid line tangent to lower border of sphenoid; ad1: posterior pharyngeal wall along the line from PNS to basion; ad2: adenoid tissue along the line from PNS to hormion

3.11. Assessment of Heterogeneity

We assessed heterogeneity using Higgins I^2. In case of substantial heterogeneity (I^2 greater than 60%), we didn't perform meta-analysis and only a systematic review was conducted.

3.12. Data Synthesis

Data synthesis was conducted using Review Manager (version 5.3, Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2014).

4. Results

4.1. Non-cleft Studies

After performing the electronic database search, 521 records were found initially. In addition, 17 records were found from hand searching of the relative studies. After removing the duplicates, 312 records remained. Full texts of 13 articles were retrieved for further evaluation and four of the studies were excluded (27-30). Finally, after evaluating the rest of the records based on the inclusion and exclusion criteria, 9 articles were included in this review consisting of 7 articles from electronic search and 2 articles from hand search. Among these 9 articles, three were prospective studies (14, 21, 22) and the rest were retrospective (15, 16, 19, 20, 23, 24). Three studies were not controlled due to ethical issues (15, 20, 24). Five of the studies had different comparison groups (skeletal anchorage face-mask (15), chin-cup (16), face-mask in patients with long face (21) and face-mask with 800g force (24) and modified face-mask (22) which were not included in the final analysis. The traits of the finally included studies are shown in Table 2. The mean age of the subjects of the included studies was 10 - 11 years at the beginning of the treatment except for one study (14), in which the mean age of patients at the beginning of the study was 8.9 years.

According to the Newcastle-Ottawa quality assessment, one study (14) was classified as low risk regarding biases, six studies presented medium risk of bias (15, 16, 19-23) and only one study (24) had high risk for biases (Table 3).

4.2. Cleft Studies

Our electronic search resulted in 364 records after correcting for duplication, of which 241 were original studies. No new articles were found after performing a hand search. After screening the title and abstract of the studies, only two articles were compliant with our inclusion and exclusion criterias and full texts of both studies were retrieved and both publications met the inclusion criteria after screening the full text of the selected publications (see Figure 1 for details of the PRISMA).

Finaly, two articles were included in the final review in this group. One investigation was a retrospective study (25) and the other (26) was a prospective study. The age range for the Fu et al.'s (26) study was between 9.5 and 10.5 years at the start of the treatment and the mean age of patients in the Kecik (25) study was around 8.5 years. The included studies' traits can be found in Table 2.

Fu et al. used 3D imaging to assess the effects of face-mask treatment on patients. However, Kecik (25) used 2D imaging to determine the changes that occur in intervention and control groups. Different measurements were used in the articles. Therefore, a meta-analysis could not be performed. Both studies had a medium risk of bias according to the Newcastle-Ottawa quality assessment (Table 3).

4.3. 2D Studies Results

After performing the meta-analysis on the effects of face-mask therapy with RPE, comparing before and after results of the intervention group (one-arm analysis), the effect of face-mask therapy combined with RPE on lower pharyngeal width was 0.20 mm (-0.56 – 0.96) which is negligible (Figure 2A). This result was obtained by analyzing four studies with a total of 90 patients. Because of the high amount of hetrogenity between studies (I^2 = 77%), a meta-analysis for the before and after treatment measurements of upper pharyngeal width could not be performed. But three of the base studies which measured the Mcnamara's upper airway width (MD for Akin = 3.83, Seo = 1.32 and Yagci = 2.15, $P < 0.01$) concluded that the upper airway width improvement was statically significant after treatment with face-mask.

Nevertheless, in one study (Baccetti), no statistically significant improvement was observed. The one-arm analysis demonstrated a mean difference of - 0.42 mm (-1.54 – 0.69) (Figure 2B) for distance of hyoid bone from mandible (H-MP) and a - 0.17 mm (-1.15 – 0.80) (Figure 2C) mean difference for distance of hyoid from C3 vertebra. Most of other nasopharynx landmarks also showed significant increases (4.64 mm [3.34, 5.94] for S-PNS (Figure 2D), 3.81 mm [2.40, 5.21] for ad1-PNS (Figure 2E), 1.29 mm [- 0.23, 2.82] for AA'-Pm' (Figure 2F) and 2.53 mm [0.54, 4.51] from Pm' to SPL (Figure 2G)). Because of the high hetrogenity between the studies that measured ad2-PNS before and after treatment (I^2 = 84%), no conclusion from the meta-analysis could be made; hence the meta-analysis was not performed. Oropharynx and hypopharynx landmarks did not show as much of an increase (under 1.5 mm); including AA-PNS (1.20 [- 0.17, 2.57]) (Figure 2H), MPS (1.09 [0.01, 2.16]) (Figure 2I), SPS (1.46 [0.58, 2.35]) (Figure 2J), IPS (-0.21 [-1.24, 0.83]) (Figure 2K) and eb-Peb (1.12 [-0.22, 2.46]) (Figure 2L). The results of the oropharyngeal and hypopharyngeal

Table 3. Risk of Bias Assessment Using the Newcastle-Ottawa Scale

First Author, Year	Sources of Bias								Total Score
	Selection Bias				Confounding Bias*	Measurement Bias			
	Representative Sample Size	Selection of A Comparison Group	Ascertainment of Exposure by Secure Record	Outcome Not Present at Beginning of Study		Assessment of Outcome	Follow Up Length	Follow-Up Rate ≥ 90%	
Akin, 2015 (16)	1	1	1	0	2	1	0	0	6
Baccetti, 2010 (14)	1	1	1	0	2	1	1	1	8
Chen, 2015 (23)	1	1	1	0	2	1	0	0	6
Kaygısız, 2009 (20)	1	0	1	0	2	1	1	1	7
Pamporakis, 2014 (24)	1	0	1	0	2	1	0	0	5
Seo, 2017 (cct) (15)	1	0	1	1	2	1	0	0	7
Balos Tuncer, 2015 (21)	1	1	1	0	2	1	0	0	6
Kilinc, 2008 (19)	1	1	1	0	2	1	0	0	6
Yagci, 2011 (22)	1	1	1	1	2	1	0	0	7
Kecik, 2016 (Cleft) (25)	1	1	1	0	2	1	0	0	6
Fu, 2016 (Cleft) (26)	1	1	1	1	2	1	0	0	7

landmarks were based on two studies and 42 patients. We were unable to perform a meta-analysis for ve-Pve since the I^2 was around 61%. In one study (Tuncer), ve-Pve showed significant improvement after treatment ($P = 0.003$) but in the other study (Kaygisiz), the improvement was not significant ($P > 0.05$).

We also were able to perform a two-arm analysis by comparing the weighted mean difference between intervention and control groups. Based on three studies and 108 participants, the mean difference in the upper pharyngeal width was 2.05 mm [0.61, 3.50] (Figure 2M) and the lower pharyngeal width showed a MD of - 0.10 mm [- 1.15, 0.95] (Figure 2N). Mean differences for H-MP and C3-H was 0.15 [- 1.04, 1.34] and -0.89 [- 2.65, 0.86] (Figure 2O and P, respectively). Based on three studies with 99 patients, Ad1-PNS had a mean difference of 2.55 [1.26, 3.84] (Figure 2Q). A meta-analysis for Ad2-PNS could not be performed because of the high hetrogenity ($I^2 = 90\%$); but a review of the studies which measured the differences between the control and treatment groups revealed that in two studies (Kilinc and Tuncer), there was a significant difference between the groups ($P < 0.05$). Nonetheless, in the study performed by Baccetti, no significant difference between the control and treatment groups could be found ($P > 0.05$).

4.4. 3D Studies Results

Because of the differences in the measured 3D landmarks between studies that used CBCT imaging for assessment of changes, only one variable (upper pharynx volume) could be included in the final analysis. following the one-arm analysis that included 2 studies and 42 participants, the mean difference was 499.29 mm^3 (CI = 95%, 69.58 - 929.00) (Figure 2R).

4.5. Cleft Studies Results

The different landmarks and measurements used by two studies investigating the effects of facemask therapy on patients with cleft lip and palate prevent us from performing a meta-analysis. In the study conducted by Kecik (25), nasopharyngeal area (34.67 ± 8.76), ad1-PNS (2.32 ± 1.67) and ad2-PNS (2.76 ± 2.18) all showed significant increases after face-mask therapy ($P < 0.001$); however, regarding the oropharyngeal area, there was a statically significant decrease after the treatment (-57.39 ± 12.45, $P < 0.001$), which the author attributed to the clockwise rotation of the mandible. There was no statistically significant difference in any measurements between the treatment and control group ($P > 0.1$). In the Fu et al.'s study, the total pharyngeal volume (3001.9 ± 4128.0 mm^3, $P < 0.01$), upper pharyngeal area (63.30 ± 87.33 mm^2, $P < 0.01$), upper pharyngeal sagittal (2.32 ± 4.46 mm, $P < 0.05$) and transverse diameter (1.31 ± 2.18 mm, $P < 0.05$), and lower pharyngeal area(50.88 ± 61.44 mm^2, $P < 0.01$), sagittal (1.63 ± 0.86 mm, $P < 0.01$)and transverse diameter (3.16 ± 3.12 mm, $P < 0.001$) all showed significant changes after the treatment; but the changes in the middle pharyngeal area (22.97 ± 85.87 mm^2, $P > 0.05$), middle sagittal (0.07 ± 2.89 mm, $P > 0.05$) and transverse diameter (1.41 ± 4.53 mm, $P > 0.05$) were not significant. There was also a significant difference between the treatment and control group in total volume,

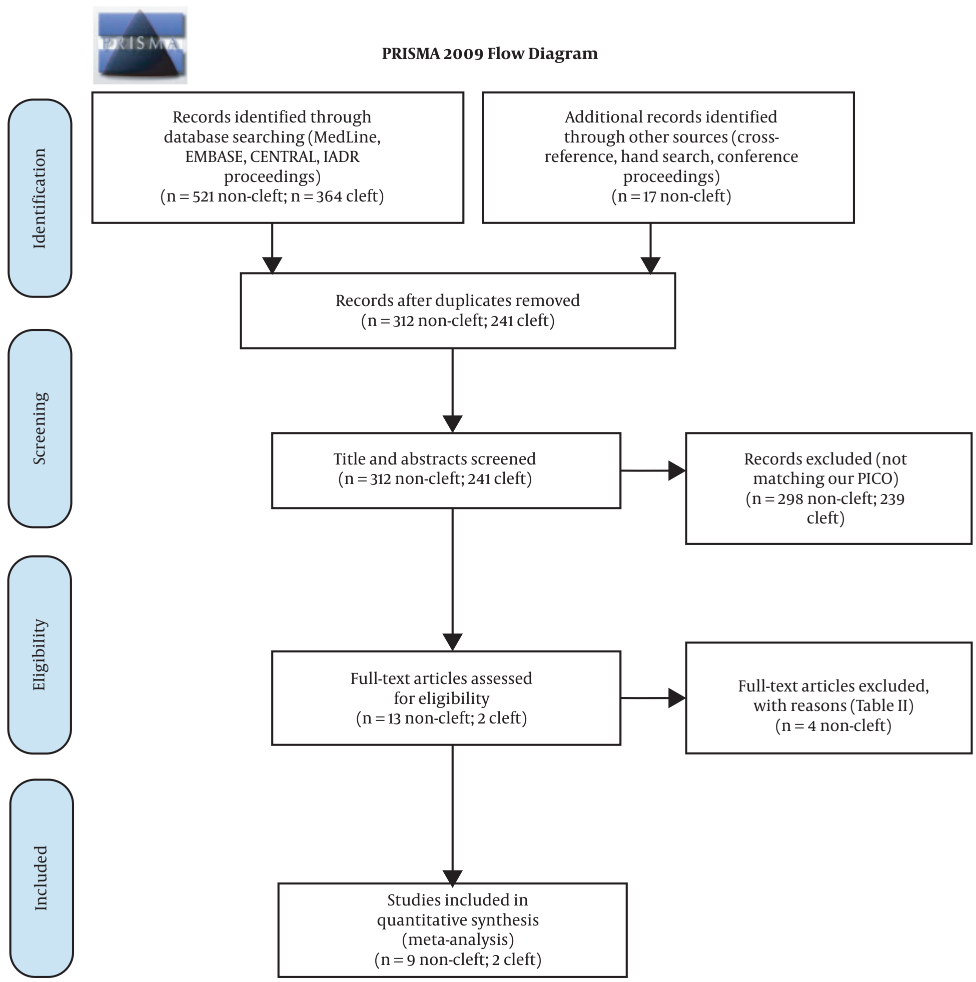

Figure 1. PRISMA flow diagram

upper pharyngeal and lower pharyngeal airway measurements ($P < 0.01$) except for lower pharyngeal transverse diameter ($P > 0.05$). There was no significant difference between the treatment and control group for middle pharyngeal measurements ($P > 0.05$).

5. Discussion

5.1. Pharyngeal Width

McNamara defined upper and lower pharyngeal width in his cephalometric analysis. He described upper pharyngeal width as the distance between upper soft palate and the closest point on the posterior pharyngeal wall and lower pharyngeal dimension as the interval between posterior pharyngeal wall and the point intersecting the posterior of tongue and mandibular bone (31). The one-arm analysis on the upper pharyngeal width could not be performed, but three of the base studies showed that the upper airway had a statistically and clinically significant change after face-mask therapy and RPE. Also, the meta-analysis showed that the lower pharyngeal width did not change significantly after treatment (0.20 mm). Some studies suggest that the clockwise rotation of mandible in facemask therapy can be the reason for the stability or even the decrease of lower pharyngeal dimensions (21). McNamara also points out that the upper pharynx dimension increases with age, whereas age does not impact lower pharyngeal width (31); therefore, the differences between pharyngeal widths before and after treatment might be a consequence of aging and not the treatment. The effect of aging could be much lower on the two-arm analysis because

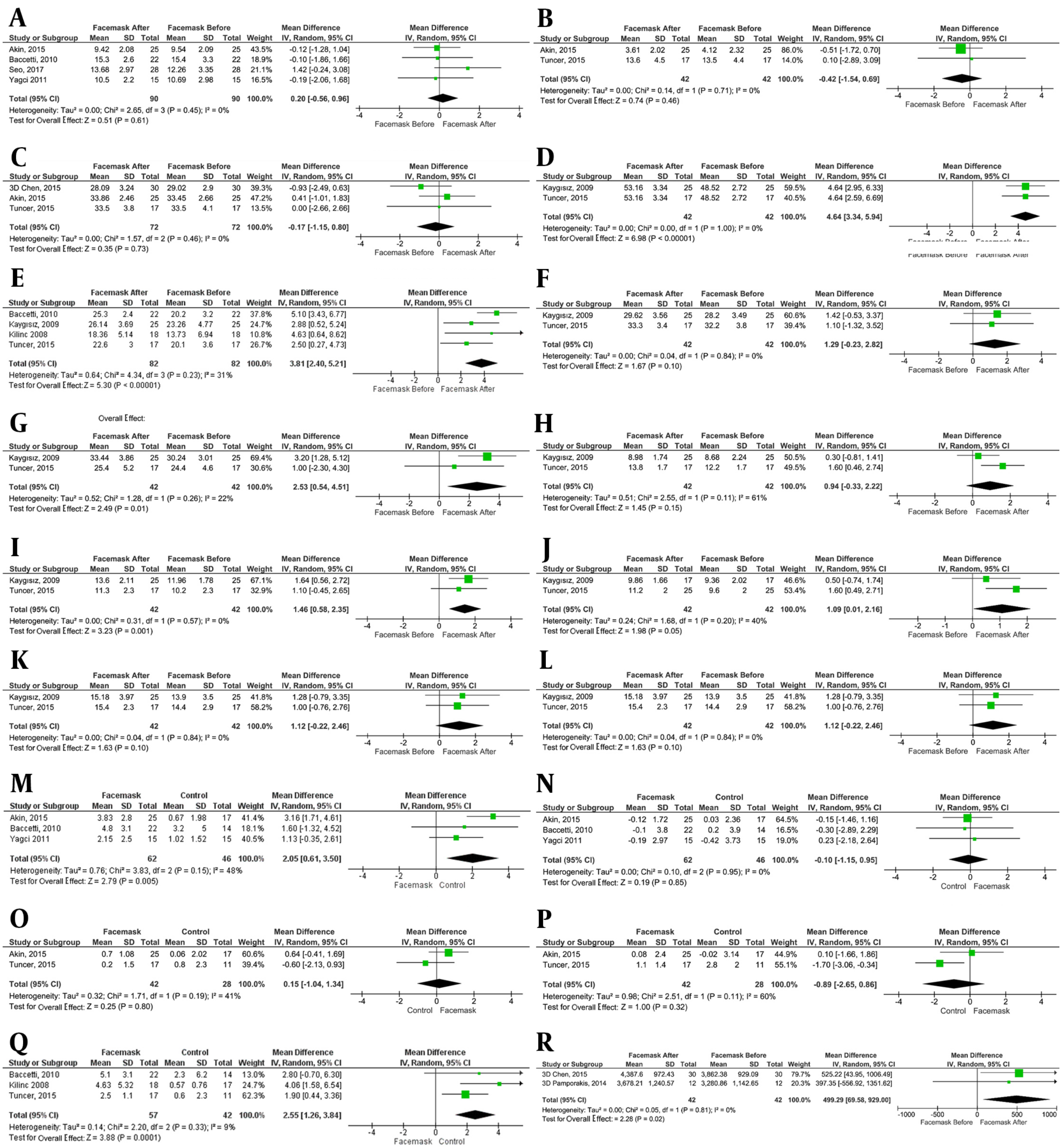

Figure 2. The mean differences of the cephalometric landmarks before and after face-mask therapy: A, lower pharyngeal width; B, hyoid bone and mandible (H-MP); C, hyoid bone and C3 vertebra (C3-H); D, distance of sella and posterior nasal spine (S-PNS); E, distance of posterior pharyngeal wall along the line from PNS to basion (ad1) and posterior nasal spine (ad1-PNS); F, distance of the pterygo-maxillary line along palatalline to soft palate and anterior of atlas (AA'-Pm'); G, distance of the pterygo-maxillary line along palatalline to sphenoid line tangent to lower border of sphenoid (Pm'-SPL); H, distance of the anterior of atlas and posterior nasal spine (AA'-PNS); I, middle pharyngeal space (MPS); J, supperior pharyngeal space (SPS); K, inferior pharyngeal space (IPS); L, distance from the vallecula epiglottis to the horizontal counterpart on the posterior pharyngeal wall along the parallel line to the Frankfurt horizontal plane (eb-Peb). The mean difference of cephalometric landmarks between face-mask and control group: M, lower pharyngeal width; N, lower pharyngeal width; O, H-MP distance; P, C3-H distance; Q, Ad1-PNS; R, The mean difference of upper pharyngeal volume before and after face-mask therapy.

the intervention and control groups both experience aging similarly.

The result of the two-arm analysis on pharyngeal dimension still demonstrates a positive effect on upper pharyngeal width after combine RPE and face-mask therapy (MD = 2.05 mm).

5.2. Hyoid Position

The hyoid bone does not have any direct connections to other bones and it is only attached to muscles in the pharyngeal region (32). Hyoid position can change by the way that pharyngeal muscles are positioned, for that reason it is a good indicator for airway function (33). The vertical positon of hyoid bone can be measured by the distance between the hyoid bone and the mandibular plane (H-MP) and the sagittal position of hyoid bone can be measured by the distance between hyoid and the C3 vertebra (C3-H) (34). Studies have indicated that the sagittal and specially the vertical position of the hyoid bone change as an adaptive measure after alterations in the airway condition. Patients with restricted airway spaces have higher H-MP distances and after treatment of problems regarding the airway, H-MP decreases (35-37). After performing a one-arm meta-analysis, H-MP and C3-H dimensions decreased insignificantly by -0.42 mm and -0.17 mm respectively. It is also important to consider that, like upper pharynx width, H-MP and C3-H distances also increase by age. Two-arm meta-analysis on H-MP (MD = 0.15 mm) and C3-H (MD = - 0.89) did not show any significant difference between treated and untreated groups.

5.3. Other Chephalometric Measurements

Different cephalometric points, planes and measurements were created to assess different parts of airway space from cephalometric radiographs. The measurements were categorized into nasopharyngeal, oropharyngeal and hypopharyngeal measurements. Nasopharyngeal measurements consist of S-PNS (the distance from sella turcica [S] to posterior nasal spine [PNS]), Ad1-PNS (the distance from PNS to the pharyngeal wall along the line from basion [ba] to PNS), Ad2-PNS (the distance from PNS to the adenoid tissue along the line from PNS to the midpoint of the line intersecting ba to sella turcica), AA'-Pm' (the distance between the perpendicular intersections of anterior atlas and pterygmaxillary line along the palatal line), Pm'-SPL (sphenoid line tangent to the lower border of sphenoid registered on basion). Oropharyngeal landmarks are AA-PNS (distance between anterior atlas and PNS), ve-Pve (the distance of velum palatinum to the horizontal counterpart on the posterior pharyngeal wall along the parallel line to Frankfurt horizontal), MPS (the distance of the tip of the soft palate to the horizontal counterpart on the posterior pharyngeal wall along the parallel line to Frankfurt horizontal), SPS (the distance of the midpoint of the line from PNS to the tip of the soft palate [P] to the horizontal counterpart on the posterior pharyngeal wall along the parallel line to Frankfurt horizontal), IPS (the distance of the intersection points on the anterior and posterior pharyngeal walls through anterior inferior point of second vertebrae [Cv2ai] along the parallel line to the Frankfurt horizontal). and eb-Peb (the distance from the vallecula epiglottis to the horizontal counterpart on the posterior pharyngeal wall along the parallel line to the Frankfurt horizontal plane) (14, 19, 20) is the only hypopharyngeal measurement in this analysis.

The differences after conducting a single-arm analysis were statically significant for most of the nasopharyngeal measurements (4.64 mm for S-PNS, 3.81 mm for ad1-PNS and 2.53 mm from Pm' to SPL). One of the oropharyngeal measurements (SPS (MD = 1.46) also showed a statistically significant increase which was not clinically as significant. Lower bound of the confidence interval for one of the nasopharyngeal measurements (AA'-Pm' with MD = 1.29 mm) and most of the oropharyngeal and hypopharyngeal measurements (AA-PNS with 1.20 mm), MPS (MD = 1.09 mm), SPS (MD = 1.46 mm), IPS (MD = -0.21 mm) and eb-Peb (MD = 1.12 mm)) were negative which suggest that the difference was not statistically significant. These results further confirm the changes that were observed by assessing the upper pharyngeal width.

Two-arm meta-analysis could only be performed on Ad1-PNS which resulted in a statistically significant mean difference of 2.55 mm (1.26 - 3.84, CI = 95%).

5.4. 3D Imaging Analysis

Compared to 2D imaging, 3D imaging modalities do not have the problems with head position, distortion, magnification and overlapping of nearby structures (38). CBCT is considered as the main 3D imaging modality in orthodontic cases (39). Some authors have suggested CBCT to be used as the standard imaging method for assessing airway in patients (40, 41).

From the included studies, two studies used CBCT for evaluating the treatment effects from face-mask therapy in conjunction with RPE. These studies used different nomenclature for classifying airway into different subsets. There is no consensus on the way that respiratory system should be anatomically divided. Different studies have used different classifications but the most notable would be Gray's classification; the airway tract is divided into nasopharynx (between nares and hard palate), oropharynx (from soft palate to upper part of epiglottis) and hypopharynx (from base of tongue to cricoid cartilage) (42). Pamporakis et al. (24) categorized the airway tract to upper airway and lower airway; these were divided using the hard plate plane. Chen et al. divided the respiratory tract into three subsects: nasopharynx, oropharynx and hypopharynx. Hard palate plane was used to separate the nasopharynx and oropharynx and upper hyoid also separated the oropharynx from hypopharynx. The point of uvula subdivided oropharynx into velopharynx and glossopharynx.

Pamporakis et al. (24) found that there was an insignificant increase (by 397.95 mm^3) in the volume of upper airway (from palate plane upwards), and an insignificant increase of 19.15 mm^3 in the volume of lower airway. Chen et al. discovered that the volume of nasopharynx, velopharynx and glossopharynx regions all increased significantly (525.22 mm^3; P = 0.006, 998.15 mm^3; P = 0.001 and 358.82 mm^3; P = 0.016 respectively). However, the hypopharynx showed no significant difference (-139.48 mm^3; P = 0.107). Because of the similarities between the definition of upper airway region by Pamporakis et al. (24) and nasopharynx by Chen et al., we performed a before and after meta-analysis between these studies. The nasopharyngeal airway volume after face-mask therapy and RPE were significantly increased by 499.29 mm^3.

5.5. Cleft Palate Patients

Studies attribute the maxillary deficiency in oral cleft patients to scars caused from previous surgeries on the maxilla. These scars prohibit sagittal, vertical and transverse maxillary growth and as a result cause maxillary deficiency in all three dimensions which in turn can decrease the available pharyngeal space in these patients (5, 6). Therefore, the use of facemask and RPE treatment protocol can be truly beneficial for oral cleft subjects. Both included studies in this review showed a significant increase in upper pharyngeal airway dimensions but failed to show any enhancement in lower (oropharyngeal) dimensions. Kecik (25) discovered that the oropharyngeal area significantly decreased after treatment with face-mask, which is in line with some other non-cleft studies. Fu et al. (26) demonstrated that the oropharyngeal dimension changes are insignificant, which is the same as the result that we deduced from conducting the meta-analysis in non-cleft patients. Fu describes nasopharynx as the upper pharyngeal airway and oropharynx as the middle pharyngeal airway.

6. Conclusions

After the treatment of non-cleft patients with maxillary retrognathia using face-mask and RPE, different nasopharyngeal region measurements (nasopharyngeal volume, upper pharyngeal width, S-PNS, Ad1-PNS, Ad2-PNS and Pm' to SPL) significantly increased and thus it can be said that the treatment improved the nasopharyngeal region. The treatment did not have a significant effect on the oropharyngeal and hypopharyngeal regions; from the measurements only superior pharengeal space had a statistically significant increase after face-mask therapy which was not clinically significant.

Patients with cleft lip and palate also showed significant enhancement in their nasopharyngeal region after treatment with face-mask and RPE, but the oropharyngeal region did not increase or decreased after the treatment.

Footnotes

Authors' Contribution: Study concept and design: E. B., and H. S.; Analysis and interpretation of data: E. B., and M. M.; Drafting of the manuscript: B. M., and E.B; Critical revision of the manuscript for important intellectual content: H. S., and M. M.; Statistical analysis: E. B., B. M.

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Table 1. Databases Applied Search Strategy, and Numbers of Retrieved Studies

Database of Published Trials	Search Strategy Used	Numbers of Retrieved Studies	Hits
	Search Strategy of Non-cleft Studies		
MEDLINE searched via PubMed searched on October 26, 2020, via www.ncbi.nlm.nih.gov/sites			97
	#16 Search (#15 NOT #11)	97	
	#15 Search (#12 AND #13 AND #14)	120	
	#14 Search (#9 OR #10)	1760829	
	#13 Search (#6 OR #7 OR #8)	192413	
	#12 Search ((#1 OR #2 OR #3 OR #4 OR #5))	8380	
	#11 Search Ventilation	288242	
	#10 Search Imaging, Three dimensional[MeSH Terms]	65272	
	#9 Search imaging	1759313	
	#8 Search airway dimension	450	
	#7 Search airway	139655	
	#6 Search *pharyn*	58149	
	#5 Search maxilla* advanc*	3441	
	#4 Search maxilla* protraction	406	
	#3 Search maxilla* deficien*	1643	
	#2 Search headgear	1046	
	#1 Search face*mask	2325	
EMBASE searched via ScienceDirect on October 26, 2020, via www.embase.com	(face*mask OR headgear OR maxilla* deficien* OR maxilla* protraction OR maxilla* advanc*) AND airway AND imaging AND NOT ventilation AND NOT surgery		233
Cochrane Central Register of Controlled Trials searched via the Cochrane Library Searched on October 26, 2020, via www.thecochranelibrary.com			107
	#1 face*mask	364	
	#2 headgear	163	
	#3 maxilla* deficien*	118	
	#4maxilla* protraction	49	
	#5maxilla* advanc*	233	
	#6 *pharyn*	11755	
	#7 airway	16620	
	#8 airway dimension	56	
	#9 ventilation	17579	
	#10 (#1 or #2 or #3 or #4 or #5) and (#6 or #7 or #8)	201	
	#11 #10 not #9	107	
Databases of Dissertations and Conference Proceedings	Search Strategy Used	Numbers of Retrieved Studies	Hits
International Association of Dental Research was searched on October 26, 2020 via https://live.blueskybroadcast.com/bsb/client/_-new_default.asp	Facemask		84
Total			521
	Search Strategy for Cleft Studies		
Database of Published Trials	**Search Strategy Used**	**Numbers of Retrieved Studies**	**Hits**
MEDLINE searched via PubMed searched on October 26, 2020 via www.ncbi .nlm.nih.gov/sites			10
	#21 Search (#20 NOT #12)	10	

	#20 Search (#16 AND #17 AND #18 AND #19)	10	
	#19 Search (#13 OR #14 OR #15)	24180	
	#18 Search (#10 OR #11)	1784782	
	#17 Search (#7 OR #8 OR #9)	194452	
	#16 Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6)	9516	
	#15 Search Oral Cleft	10664	
	#14 Search Cleft Lip[MeSH Terms]	13544	
	#13 Search Cleft Palate[MeSH Terms]	18756	
	#12 Search Ventilation	290684	
	#11 Search Imaging, Three dimensional	95084	
	#10 Search imaging	1783250	
	#9 Search airway dimension	457	
	#8 Search airway	141357	
	#7 Search *pharyn*	58532	
	#6 Search maxilla* advanc*	3502	
	#5 Search maxilla* protraction	414	
	#4 Search maxilla* deficien*	1664	
	#3 Search Extraoral Traction Appliances[MeSH Terms]	1822	
	#2 Search headgear	1055	
	#1 Search face*mask	2349	
EMBASE searched via ScienceDirect on October 26, 2020, via www.embase.com	(face*mask OR headgear OR maxilla* deficien* OR maxilla* protraction OR maxilla* advanc*) AND (oral cleft OR cleft palate OR cleft lip) AND airway AND imaging AND NOT ventilation		346
Cochrane Central Register of Controlled Trials searched via the Cochrane Library Searched on October 26, 2020, via www.thecochranelibrary.com			5
	1 face*mask	368	
	#2 headgear	164	
	#3 MeSH descriptor: [Extraoral Traction Appliances] explode all trees	153	
	#4 maxilla* protraction	49	
	#5 maxilla* advanc*	234	
	#6 *pharyn*	11938	
	#7 airway	16724	
	#8 airway dimension	55	
	#9 MeSH descriptor: [Cleft Lip] explode all trees	194	
	#10 MeSH descriptor: [Cleft Palate] explode all trees	255	
	#11 (#1 or #2 or #3 or #4 or #5) and (#6 or #7 or #8) and (#9 or #10)	5	
Databases of Dissertations and Conference Proceedings	**Search Strategy Used**	**Numbers of Retrieved Studies**	**Hits**
International Association of Dental Research was searched on October 26, 2020 via https://live.blueskybroadcast.com/bsb/client/_-new_default.asp	Facemask, Cleft-LIP, Cleft-PALAT		3
Total			364