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Effect of nasoalveolar molding on nasal symmetry in cleft lip and palate patients: A systematic review

Running title: Effect of nasoalveolar molding ...

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Abstract

Context: One of the main types of nasal deformity is unilateral cleft lip/palate, which affects the process of breathing and smelling. It is supposed that nasoalveolar molding (NAM) has a positive effect on the reduction of the tension in lips and helps to simplify or even eliminate the subsequent orthodontic treatment.

Objective: This systematic review of papers focused on the effectiveness of NAM in patients with unilateral cleft lip/palate.

Data Sources: The web search of Google Scholar, PubMed, Web of Science, and Medline databases

Study Selection: The identification of 1282 articles published up to 2018. The selected papers were screened based on the eligibility criteria after the thorough investigation of the titles and abstract. In the next step, article inconsistent with our objectives were removed from the current study. Afterward, the papers were thoroughly studied and data related to our study goals were extracted and recorded in predetermined extraction forms. After the full-text evaluation of the articles, results in the selection of 22 articles.

Data Extraction: The search process was performed by the following keywords in combination with nasoalveolar molding or pre-surgical nasoalveolar molding or pre-surgical orthopaedic appliances: unilateral cleft lip/palate, UCL/P, Cleft lip, Cleft palate.

Results: Based on the literature review, various studies have supported the effectiveness of nasoalveolar molding appliance therapy on nasal symmetry in unilateral clefts of the lip and/or palate treatment.

Conclusions: The NAM therapy is effective in decreasing the severity of the initial cleft deformity, as well as repositioning of deformed nasal cartilage and alveolar process. It has many beneficial results in surgical outcomes. However, the long-term effect of this approach has remained unclear.

Keywords: Alveolar Bone Grafting; Cleft Lip; Cleft palate; Nasal Cartilages

1. Context

The nasal deformity is an abnormality in the structure and appearance of the nose, which involves the displacement of lower lateral nasal cartilage, oblique and short columella, depressed dome, overhanging nostril apex, and deviated septum. Difficulties in breathing and smelling are the main problems of this deformity. One of the main types of nasal deformity is unilateral cleft lip/palate (UCL/P). The reconstruction of the facial soft tissue is the most challenging issue for these patients (1).

The worldwide estimation of the UCLP prevalence indicated 0.5–3 number of cases per 1000 births (2). Genetic and local factors are the etiology of this problem (2). Moreover, the frequency of this deformity differs among people in terms of gender, population, and maternal features. The female/male ratio in children with UCLP is 1:2, and it is more common in the Caucasian population (2). The cleft of lip/palate is the fourth most common craniofacial abnormalities in Iranian children with a rate of 2.14 patients per 1000 births (3).

Rhinoplasty for UCL/P patients is very complicated and should be performed with caution due to the complex nature of unilateral cleft nasal deformity. There are several surgical approaches to correct the cleft lip tissue; however, wide and bilateral clefts had remained still a remarkable challenge (4). For this reason, pre-surgical infant orthopedics were introduced to manage the floating premaxilla and align the alveolar bone of maxilla (5). Firstly, Grayson et al. introduced pre-surgical nasoalveolar molding (PNAM) in 1999 in which the alveolar segments and deformed lower lateral cartilages is repositioned via active molding prior to the primary cheiloplasty. The main goals of PNAM therapy are the correction of the alveolar segments as a normal arc and decrease the cleft gap.

The PNAM helps to gradually shift nasal tissues to their normal positions (5). It is supposed that NAM has a positive effect on the decrease of the tension on the lip and helps to simplify or even eliminates the subsequent orthodontic treatment (4, 6). This approach was considered as the early intervention for UCL/P children in the 1960s and 1970s (7, 8).

The use of nasoalveolar molding has increased over the past two decades. So far, several attempts have been made to assess the efficacy of PNAM for nasal deformity (9-12). Although the use of NAM is increased to improve UCL/P patients, the effect of nasoalveolar molding is still challenging. The reason for this is that there is a small number addressing long-term randomized double-blind controlled trial, which drew a comparison between the patients with NAM therapy and those without NAM or the comparison of the effectiveness of this approach with other pre-surgical neonatal orthopedics. Moreover, there is insufficient scientific evidence on the long-term effect of NAM.

2. Objective

This study aimed to evaluate the literature regarding the effectiveness of NAM in patients with UCL/P, compared to those who did not undergo NAM therapy. The main issues in the assessment of the articles were the objectives, instruments, and short- and long-term effects of this technique on UCL/P patients. This study also addressed the prospect of this approach. We were focused to answer the following questions:

1. Does NAM therapy prior to primary repair surgeries have positive outcomes in UCLP patients, compared to those with no experience of this approach?
2. Does NAM therapy have better outcomes in UCLP patients, compared to other instruments?

3. Materials and Methods

This study is a systematic review with comprehensive search strategies on the articles addressing the effectiveness of NAM therapy in UCL/P patients. We searched four databases, including Google Scholar, PubMed, Web of Science, and Medline for the published articles up to 2018. In this study, the researchers applied the recommendation stages of Cochrane Handbook (asking a question, determining the eligibility criteria, searching process, selecting papers and exclusion of inappropriate article, determining the features of article assessment, extracting data, as well as explaining and presentation) (13). We used PICO elements (population, intervention, comparison, and outcome) of PRISMA-P protocol (2015), which is suggested to create systematic reviews (14).

3.1. Eligibility criteria

This systematic review entailed all parallel randomized, quasi-randomized, prospective studies performed on human subjects focused on the effectiveness of NAM therapy in UCL/P patients. However, only the articles with a clear description of the treatment protocol and objective results measurements entered in this review. The exclusion criteria included the non-English papers, in vitro studies, and those with insufficient data, and animal samples. The use of other pre-surgical infant orthopaedics other than NAM, sample size smaller than 10 subjects, bilateral clefts of the lip and/or palate and articles with no control group was the other exclusion criteria. Moreover, retrospective studies, non-clinical studies, meta-analyses, expert opinions, editorial letters, case reports or case series, consensus statements, and qualitative studies were removed from this study.

3.2. Data Source

We conducted a systematic search in four electronic databases, including Google Scholar, PubMed, Web of Science, and Medline from December to October 2018. For the purpose of the study, two researchers were continuously in contact with each other to exchange the information and select the necessary papers. The search process was performed by the following keywords in combination with nasoalveolar molding or pre-surgical nasoalveolar molding or pre-surgical orthopaedic appliances: unilateral cleft lip/palate, UCL/P, Cleft lip, Cleft palate.

3.3. Study selection and data extraction

The selected papers were screened based on the eligibility criteria after the thorough investigation of the titles and abstract. In the next step, article inconsistent with our objectives were removed from the current study. Afterward, the papers were thoroughly studied and data related to our study goals were extracted and recorded in predetermined extraction forms. The selection process of the papers is shown in the PRISMA flow diagram (Figure 1).

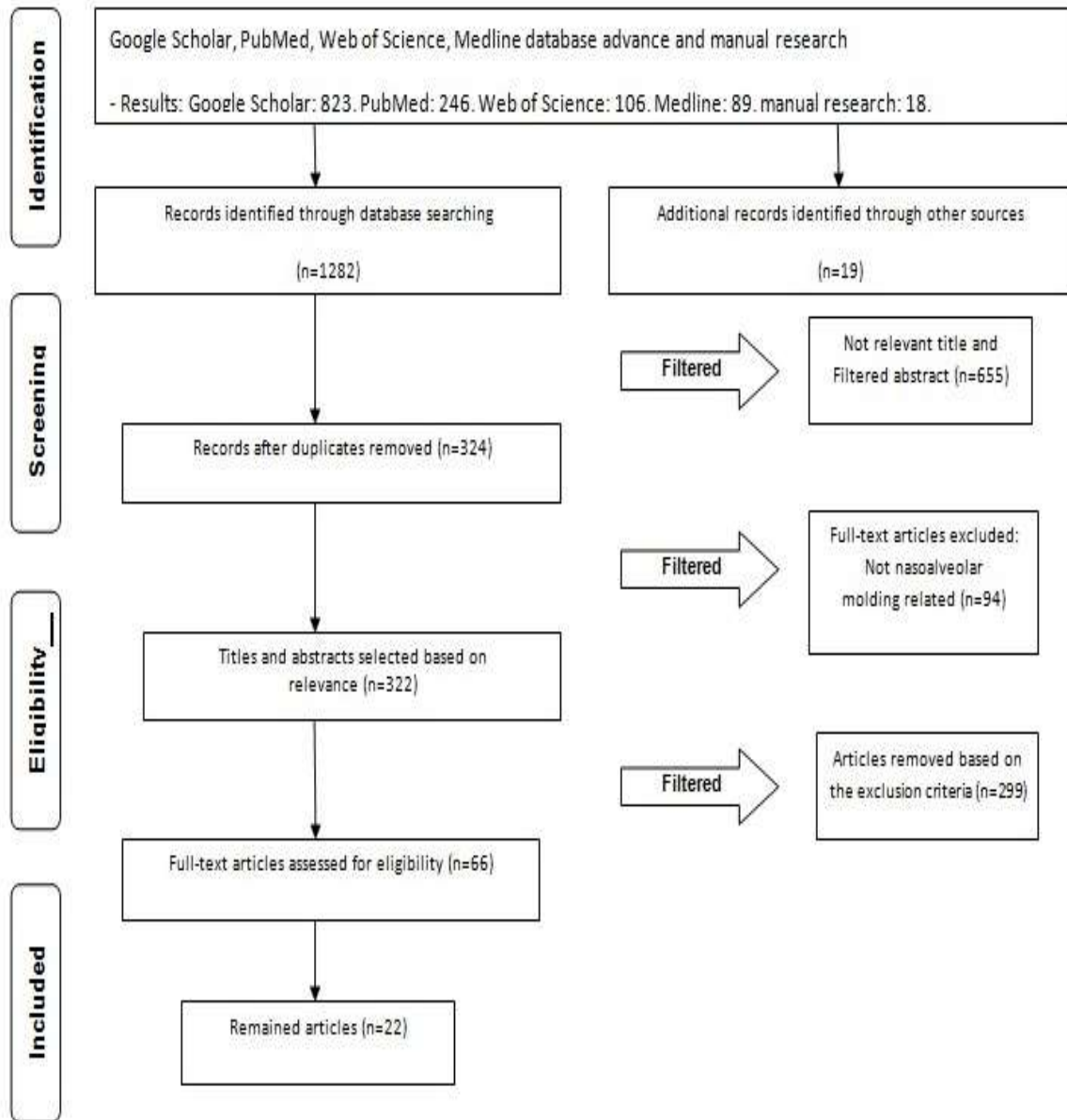


Fig1. Flow chart of study selection

3.4. Risk of bias in individual trials

We followed the Cochrane's risk of bias to assess the risk of bias in the included trials (15). This study focused solely on a randomized clinical trial. Figure 2 shows the quality assessment of the selected articles.

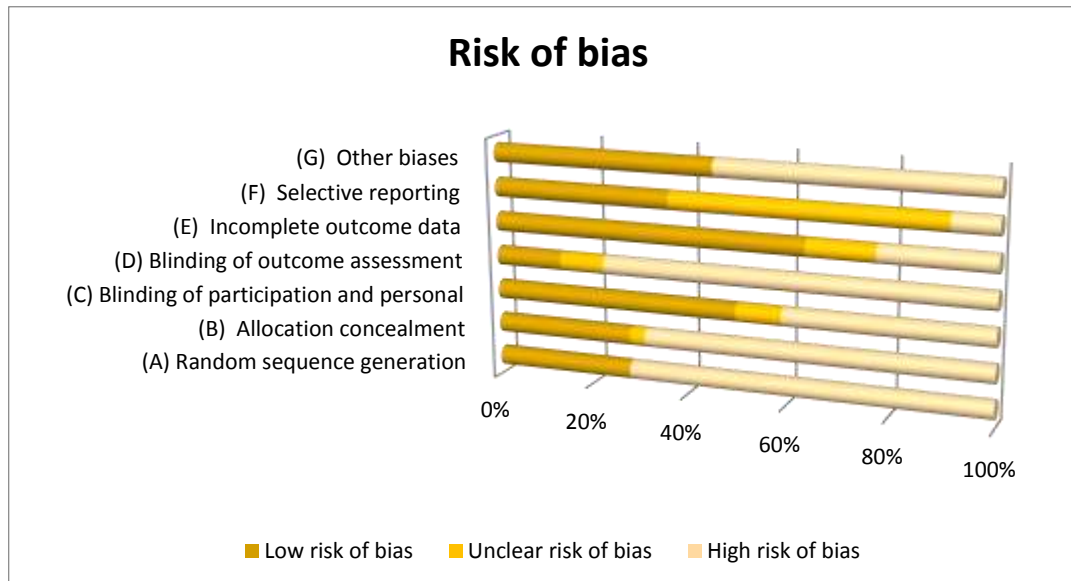


Figure2. Quality assessment of the articles included in the review process

3.5. Study design

Two researchers determined the number of citation for the articles in each database. They studied the titles and abstracts of all articles separately. In the first step, the paper titles were screened in order to remove the unrelated studies. In the first phase of the study, prospective comparative studies, in which NAM therapy was compared to other pre-surgical infant orthopedics with a minimum of 10 subjects in each group were entered in this study. Then, abstracts were screened to select the papers based on the inclusion criteria. Next, the eligible articles were selected for further evaluation and full-text study. Papers unrelated to our objectives or with insufficient data were excluded in this phase. The remaining papers were reviewed meticulously. Data were extracted using a standard electronic form. After the determination of final articles, the required data were extracted, including the research objective, time and place of the study, sample size, method assessment, follow-up, and outcomes. The last search was performed on October 1, 2018.

3.6. Quality assessment

To improve the quality of the study, the search process was performed by two researchers. They agreed on the inclusion and exclusion criteria and resolved their disagreement through discussion sessions. In order to decrease the risk of bias, they applied Cochrane recommendations (16).

4. Results

The search process leads to the identification of 1282 articles, from which 960 papers were removed after the initial evaluation due to duplications and relatedness. Accordingly, 322 papers were selected to further the evaluation; however, 299 eligible articles were screened based on the

inclusion and exclusion criteria. After a detailed evaluation of the full texts of the articles, 22 articles were selected for the final analysis (Figure 1).

The excluded articles were selected in the following process: studies focused on the other pre-surgical infant orthopedics (n=53), studies addressing the NAM therapy of bilateral cleft patients (n=10), studies focused on the animal (n=1), papers providing techniques other than NAM (n=30), non-comparative articles (n=27), experimental studies (n=2), descriptive and cross sectional studies (n=10), inaccessibility of the full-text version (n=4), and insufficient data (n=5). Moreover, retrospective studies (n=42), editorial letters (n=11), survey of previous experiences (n=3), books (n=2), case reports (n=30), case series (n=19), qualitative and narrative articles (n=26), systematic reviews (n=14), and papers published in non-English languages (n=10).

In this study involved the assessment of the manuscripts adopting randomized control trials or comparative prospective studies. These studies were performed in 11 different countries. Five were in North America, three in South America, and five in the Far East. Furthermore, seven, two, and one were performed in India, Germany, and Taiwan, respectively. Moreover, one study was conducted in Iran. Approximately, these studies were performed on 1099 subject (see Table 1). Table 2 illustrates the risk of bias assessment for the included trials.

Table 1. Variables evaluated in the reviewed studies							
Authors (Years) References	Country	Sample size	Type of study	Technique	Method assessment	Follow-up	Outcomes
Singh et al. (2007) (17)	USA	N=25 NAM=15 No cleft: 10	Prospective study	Three-dimensional analysis (CAD)	Digital stereophotogrammetry used to capture three-dimensional facial image	37 weeks after CAD 4 weeks after surgery	The three-dimensional facial morphology virtually was indistinguishable from the non-cleft.
Nakamura et al. (2009) (18)	Japan	N=30 NAM:15 Hotz:15	Prospective comparative	Nasal stent impact on nasal and alveolar molding	Two-dimensional photographs casts	1-5 years	The nostril height and width ratio and the height of the top of the alar groove in the correction group were better in NAM, compared to controls.
Bennun et al. (2009) (19)	Argentina	N=93 NAM:46 No-NAM:48	Prospective comparative	Aesthetic and functional impacts	--	6 years	The nasal morphology differences were less in NAM group than non-pre-surgically treated cases.
Mishra et al. (2010) (20)	India	N=34 NAM:17 No-NAM:17	Prospective comparative	Nasal stent impact on nasal and alveolar molding	Two-dimensional photographs	1 year	Nasoalveolar molding is a useful approach for the treatment of cleft lip nasal deformity.
Clark et al. (2011) (21)	USA	N=25 NAM:20 No-NAM:5	Prospective study	Nasal and alveolar molding	Three-dimensional scanner	5 years	There was more improvement in nasal and lip anatomy in the PNAM group.
Isogawa et al. (2010) (22)	Japan	N=10 NAM:5 Hotz::5	Prospective study	Nasal stent impact on nasal and alveolar molding	Casts	4 months	The method was effective in nasal molding and alveolar molding in PNAM group.
Sasaki et al. (2012) (23)	Japan	N=28 NAM:13 Hotz:15	Prospective study	Nasal stent impact on nasal and alveolar molding	Two-dimensional photographs casts	--	Naris morphology was improved and the cleft gap was smaller in the NAM group.
Yu et al. (2013) (24)	China	N=30 NAM:15 CAD/CAM:15	Randomized control study	Three-dimensional analysis (CAD) and printing (CAM)	Measurement on scanned cast	--	There was a difference before and after CAD-NAM therapy in terms of arch length, cleft gap, labial frenum deviation, anteroposterior relation of the

							cleft to non-cleft segment, and alveolus height.
Liang et al. (2015) (25)	Taiwan	N=84 NAM:42 No-NAM:42	two-group, parallel, retrospective, randomized clinical trial	Nasal stent impact on nasal and alveolar molding	Two-dimensional photographs casts	--	The improvement of the nasal and alveolar of PNAM group was observed before primary cheiloplasty, which facilitated less invasive surgical repair. However, to maintain long-term nostril symmetry there was no significant difference between the two groups.
Shetty et al (2012) (26)	India	N=45 NAM:30 No-NAM:15	Prospective study	Nasal and alveolar molding improvement with NAM	Two-dimensional photographs, dentofacial impression	18 months before surgery	There was an improvement in nasal measurements in NAM group.
Monasterio et al. (2010) (27)	Chile	N=40 Grayson: 20 nasal elevator: 20	Prospective study	Nasal stent impact on nasal and alveolar molding	Two-dimensional photographs casts	3 months before surgery	Nasal asymmetry and reduction of the cleft width were improved by two approaches
Chang et al. (2014) (28)	Taiwan	N=15 Grayson:15 Figuroa:15	Randomized prospective, single blind trial	Evolution of the NAM procedure	Two-dimensional photographs	6 months after surgery	Similar results were found in NAM approaches in term of the nasal outcome.
Rubin et al. (2015) (29)	USA	N:20 NAM: 10 No-NAM: 10	Quasi-experimental study	Impact on primary repair surgeries	Two-dimensional photographs	Before the surgery	The necessity of secondary nasal revision surgery was 3% and 21% in the NAM group and in the non-NAM group, respectively.
Shetty et al (2016) (30)	India	150 1 month: 50 1 - 6 months:50 6 months to 1 year: 50	prospective study	Nasal and alveolar molding improvement with NAM	Cast landmark	1 year	There was a decrease in the nasal height, nasal dome height, columella height, and intersegment distance after NAM therapy.

Broder et al. (2016) (31)	USA	N=100 NAM:62 No-NAM:48	Non-randomized, prospective multicenter study	Impact on primary repair surgeries	Two-dimensional photographs	13 months	The better post-surgery outcome was reported in NAM group compared to the non-NAM group, especially in relation to the appearance of the nose.
Ritschl et al. (2016) (32)	Germany	N:12 CAD NAM: 6 traditional NAM: 6	Comparative Prospective	Compare traditional NAM with CAD technology	--	--	There were similar outcomes in two groups.
Cerón et al. (2016) (33)	Colombia	N=32 NAM:16 Hotz:16	Comparative Prospective	Evolution of the NAM procedure	Three-dimensional laser scanning	Yes	Cleft depth was highly improved in NAM group at the larger segment. The deeper cleft was observed in children treated with Hotzs in compare to PNAM.
<u>Rachwalski</u> et al. (2017) (34)	India	N=80 NAM:40 No-NAM:40	comparative Prospective	Evolution of the NAM procedure	Digital three-dimensional laser scanning	Yes	There was an increase in nasal height, nasal width. Moreover, columellar length was closer to a natural columellar angle in patients underwent PNAM therapy, compared to those without PNAM.
Shetty et al (2017) (35)	India	N=120 NAM:60 No-NAM:60	Comparative Prospective analysis	Evolution of the NAM procedure	Digital three-dimensional laser scanning	long-term	Reduced intersegment distance following PNAM improves arch symmetry and stability and prevents an arch collapse in the long-term.
Astani et al. (2018) (36)	Iran	N=40 NAM:26 No-NAM:14	comparative Prospective analysis	Evolution of the NAM procedure	Two-dimensional photographs	--	There was a difference in nasopharyngeal volume of NAM group. There was no significant difference in oropharyngeal and total pharyngeal airway.
Singh et al. (2018) (37)	India	N=22 Grayson:11 Figueroa:11	Prospective analysis	Evolution of the NAM procedure	Digital three-dimensional laser scanning	--	There were similar results on the increase of nostril height and nostril width in the NAM groups. The reduction of the alveolar gap and increase of the arch width was better in Figueroa's approach.

Grill et al. (2018) (38)	Germany	N=14 CAD/CAM:170 RapidNAM:7	Prospective analysis	Evolution of the NAM procedure	Digital dimensional scanning	three- laser	--	There was an increase in the cleft-side nasal height and better nose symmetry towards symmetry after the application of the two approaches.
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NAM: nasoalveolar molding

CAD: computer-aided design

CAM: computer-aided manufacturing

PNAM: pre-surgical nasoalveolar molding

Table 2. Quality assessment of the inserted article in this study							
Publication	Adequate sequence generation?	Allocation concealment?	Blinding of participants/?	Blinding of outcome assessors?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other biases?
Singh et al. (2007)	No	No	No	No	No	No	Unclear
Nakamura et al. (2009)	No	No	Unclear	No	No	Unclear	Unclear
Bennun et al. (2009)	No	Unclear	No	No	Unclear	No	Unclear
Mishra et al. (2010)	Yes	Yes	No	No	Yes	Yes	Unclear
Clark et al. (2011)	No	No	Yes	No	No	Unclear	Yes
Isogawa et al. (2017)	No	No	No	No	Unclear	Unclear	Unclear
Sasaki et al. (2012)	No	No	Unclear	Unclear	Yes	Unclear	Unclear
Yu et al. (2013)	No	No	No	No	Yes	Unclear	Unclear

Liang et al. (2015)	Yes	Yes	Yes	No	No	Unclear	Yes
Shetty et al (2012)	Yes	Yes	Yes	No	Yes	Unclear	Yes
Monasterio et al. (2010)	No	No	No	No	Yes	Unclear	Unclear
Chang et al. (2014)	Yes	Yes	Yes	No	No	Unclear	Yes
Rubin et al. (2015)	No	No	No	No	Unclear	Yes	Unclear
Shetty et al (2016)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Broder et al. (2016)	No	No	Yes	No	Yes	Yes	Yes
Ritschl et al. (2016)	Yes	Yes	No	No	Yes	Yes	Unclear
Cerón et al. (2016)	No	No	Yes	No	Yes	Unclear	Yes
<u>Rachwalski</u> et al. (2017)	No	No	Yes	No	Yes	Unclear	Yes
Shetty et al (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Astani et al. (2018)	Yes	Yes	Yes	No	Yes	Yes	Yes
Singh et al. (2018)	Yes	Yes	Yes	No	Yes	Yes	Yes
Grill et al. (2018)	No	No	No	No	Unclear	Yes	Unclear

5. Discussion

The decrease in the severity of the initial cleft deformity is the main purpose of NAM (39). Moreover, this approach paves the way for the repositioning of deformed nasal cartilage and alveolar process. Moreover, this approach aimed to place lip segments in their proper side without any lip adhesion and scar, as well as decreasing the need for secondary alveolar bone grafts and surgical procedures (39, 40). In the present review, we focused on the answer two main questions: Does NAM therapy prior to primary repair surgeries have positive outcomes in UCLP patients, compared to those with no experience of this approach? Does NAM therapy have better outcomes in UCLP patients, compared to other instruments?

5.1. Effectiveness of NAM therapy on nasal symmetry and maxillary arch

The efficacy of NAM on initial surgeries is confirmed by several articles. Pre-surgical orthopedics, such as NAM in patients with UCL/P, is used to improve facial symmetry before the surgery (11). Following a 12-month or longer observation, Matsuo et al., showed that the use of NAM during the first week of life (for three months) leads to superior nasal shape symmetry in comparison with traditional surgeries (41). A study conducted by Clark et al. was indicative of the improvement in the long-term nasal symmetry in patients who had NAM in combination with alveolar molding, compared to those without NAM. Moreover, they showed long-term clinical improvement in nasal and lip anatomy but not in dental arch configuration and occlusion of patients who underwent NAM, compared to those without NAM. A remarkable improvement in nasal symmetry and normalization of the dental arch is demonstrated in a short-time study conducted by Ezzat et al. (42).

Based on a study performed by Jaeger et al., NAM therapy may lead to nostril overexpansion (43). Therefore, orthodontic force should be kept low enough that prevents the extension of soft tissues constituting the nasal cavity during longitudinal correction. Sasaki et al showed a remarkable decrease in the alveolar cleft after NAM therapy. The improvement in the naris morphology is a result of the modify of the position of maxillary bone and the elevation of cartilage by stent insertion (23).

Deficient columella, overhanging nasal apex, and depressed dome remain as the main problems after cheiloplasty (44, 45). Based on one study, a reduction in deficient columella, depressed dome, wide alar width, and deviated nasal septum were reported after using PNAM (46). A comparative study conducted by Liang et al. on the long-term effect of nasal contour between patients underwent NAM and those without NAM revealed that NAM leads to improved nasal symmetry after cheiloplasty (25). A normal anatomical position in the columella, philtral column, apex of the nose, and nasal ala were reported three months after using PNAM. The main advantages of PNAM include lengthening of the deficient columella, repositioning of the deformed nasal cartilage, and decreasing the intra-alveolar gapless, limitation of invasive surgery, and reducing recovery time. Nasoalveolar molding leads to the decrease -in cleft width, premaxillary protrusion, and deviation, as well as the increase in the arch circumference, columellar length, and width. Moreover, it can improve maxillary midline and nasal symmetry (10, 24, 42, 47-50)

The slight overcorrection of the alar dome on the cleft direction is suggested by Singh et al. (48), which is the short-term positive effect of nasoalveolar molding reported in many studies (10, 24,

42, 47-50). However, the long-term effect of this approach is still challenging. According to one study, an increase in nose symmetry would remain until early childhood (48), while other studies indicated a relapse of columella length in some cases after three years of follow-up (47) and relapse of nostril shape (10).

According to a study conducted by Baek and Son, NAM leads to positive effects in the anterior and posterior alveolar segments in cases with UCL/P (50). Based on another study, alveolar height decreased in UCL/P neonates who were treated with computer-aided design-as alveolar molding (CAD-NAM). This result was indicative of the inhibitory impact of the traction force of the appliance on the vertical development of the alveolar bone (24).

In NAM approach, anterior alveolus in the non-cleft position is moved inward and both sides of alveolar segments shape the normal arc form. Due to the vertical component forces of the retention tapes, the alveolar height and canine segments decrease after NAM therapy. This means that this process prevents the vertical growth of alveoli. However, pre-surgical orthopedics by intraoral devices are still challenging due to an unclear effect of NAM therapy on the alveolar growth inhibition and upper alveolar growth.

Growth process may have an effect on the nasal structure and even the shape of the nose after the operation. There is no available parameter for digitizing the results of the surgery. Therefore, the investigation of the relationship between the cleft jaw and the shape of the nasal cavity is challenging. There are various measures to evaluate the nasal morphology (47, 48); however, when the deformities are complex, the results of surgery cannot be assessed by simple estimation of the ratio of height to width of the alar groove or angles. Hausdorff distance is a parameter determining the geometrical resemblance between two objects that provides an accurate value even for complicated graphics. A high correlation between Hausdorff distance and the human visual assessment of symmetry is reported by Sasaki et al., which is very important in analyzing the aesthetics of the nose (23).

Cerón-Zapata et al. showed a reduction in the interior dimension of the cleft in all UCL/P patients underwent NAM in comparison to patients who had no experience of NAM (33). This finding was in line with a study conducted by Mishima et al. (51). A reduction in the width of the cleft in the anterior segment after treatment with active plates was observed in the other study (52). In a study performed by Cerón-Zapata et al., anterior width was largely decreased using PNAM approach compared to Hotz's appliance, which may be due to the lip adhesion with the use of the tape. The decrease in the width of the alveolar cleft could be considered as a positive predictor of the surgical outcome. However, there was no significant difference between PNAM and Hotz's appliance regarding the changes in intercanine width. The decrease in width at the canine area distance was larger using Hotz's plate than PNAM, which can be due to the soft material of the plate (33). However, the study by Mishima et al. showed contradictory results (51). Moreover, both PNAM and Hotz increased the length and depth of the cleft, which indicated the potential of maxillary segments in the neonatal period (33).

Stable reduction in the width of the mid-part of the larger and smaller segments due to the treatment with the plate was reported by another study (50). Age is another main predictor to the success of the treatment. The main goal of pre-surgical orthopedics in UCL/P neonates is the alignment of maxilla segments and premaxilla into a normal form. The efficacy of NAM in the repositioning of maxillary segments and facilitating the surgical repair of nasal deformities is

reported in many studies (53-55). The NAM therapy helps to create a better outcome by reforming the lower lateral cartilages, decreasing gap, and aligning the gingiva. The correction of the gap may prevent a step deformity, and the lip repair is performed under less tension with the possibility of acquiring enough closure to allow a more straightforward repair (21).

According to Shetty et al., alveolar clefts were narrowed using PNAM before cheiloplasty. Moreover, PNAM can facilitate the surgery procedure to primary cleft lip closure (56, 57). Quan et al. indicated that CAD-NAM therapy can decrease the alveolar cleft gap and arch length as well as correcting upper denture midline deviation. Moreover, there was a decrease in the outward rotation of the maxillary arch in the non-cleft side and improvement in the contour of the alveolus (24). The decreased width of the alveolar cleft and the sagittal arch length of the anterior arch after NAM therapy are also reported in other studies (21, 58).

The CAD-NAM approach is designed for alveolar growth in each modality and maintenance of the maxilla width. Quan et al. showed a slight growth in arch width after CAD-NAM therapy. Moreover, there was a report of the decrease in the anteroposterior relation of the cleft to non-cleft segment and anteroposterior maxillary alveolar length of the non-cleft side after CAD-NAM therapy for the sagittal dimension, which showed that CAD-NAM could improve the protrusion of the anterior upper alveolus (24).

Moreover, Astani et al. evaluated the morphometrics of pharyngeal airway in patients with a cleft lip and palate, which showed nasopharyngeal volume was different between patients undergoing NAM group compared to the control group. However, there was no confirmation of volumetric differences in oropharyngeal and total pharyngeal airway. Therefore, NAM can enlarge the nasopharyngeal airway size in patients with a cleft lip and palate (36).

5.2. Three-dimensional technology

Three-dimensional technology (CAD-CAM) is one of the developed techniques for medical imaging in which laser surface scanning is applied for obtaining three-dimensional images and providing high-accuracy measurements from the defined sites. This study was an evaluation of the pre-surgical cleft treatment using a CAM system (36). We found two prospective-comparative studies confirming CAD systems as reliable techniques for the evaluation and quantification of the nasal and alveolar improvement following NAM therapy (17, 24).

Yu et al. assessed the efficiency of computer-aided design–nasolabial molding (CAD-NAM) on maxillary alveolar morphology. Rapidform XOR3 software was used to analyze the maxillary morphology and all pre- and post-CAD-NAM variables. They indicated a trend toward morphological improvement in maxillary alveoli. In other words, these findings revealed the obstructive effects of traction force of CAD-NAM appliance on the vertical growth of the alveolar bone (24).

Another study was performed by Singh et al. to assess three-dimensional (3D) facial morphology in UCLP patients following NAM. They showed 3D facial morphology in UCLP patients was indistinguishable from the control group (17). Yilmaz et al. performed a study to evaluate the effects of NAM therapy on three-dimensional nasolabial morphology in UCLP neonates. They showed an increase in all measurements before and after NAM therapy except for lip gap, nostril floor width, and nostril diameter, which showed improvement in the nasal and lip symmetry. Three-dimensional technology helps to the diagnosis and measurement of the UCLP upper alveolar morphology using laser scanning. With regard to this approach, treatment procedure

could also be visible on the computer and the final treatment goals could be simulated. However, this technology is recently developed and there are not enough prospective-comparative studies in this regard; therefore, it is recommended to conduct future studies with larger sample size and longer follow-ups.

5.3. Comparison of nasoalveolar molding therapies

The researchers found four prospective studies comparing the different approaches toward NAM. In a study conducted by Singh et al., the effectiveness of Grayson's technique and Figueroa's modified pre-surgical nasoalveolar technique were compared in the treatment of UCLP patients. Based on the obtained results, there was an increase in nostril height of the cleft side. Moreover, nostril width on the cleft side was decreased; while there was no difference between the efficacy of Grayson's and Figueroa's approaches. The reduction of the alveolar gap and increase of the arch width were better in Figueroa technique compared to Grayson technique (37), which was confirmed by another similar study (27). Moreover, the effectiveness of Grayson approach on the alveolar cleft using adhesive tape tractions across the cleft lip was confirmed by other studies (53, 59). There was a probability that the decreased cleft width resulted in the combined impact of redirecting the growth of the alveolar segments by molding plate and active molding (37).

Ritschl et al. compared CAD-NAM with traditional NAM in a study. The findings revealed similar outcomes in the two approaches (32). Another study conducted by Grill et al. aimed to compare two methods of CAD/CAM-NAM and RapidNAM approaches. The results showed an increase in the cleft-side nasal height and better nose symmetry after applying the two approaches (38). In another study conducted by Chang et al., the modified Figueroa and the modified Grayson techniques were compared. The obtained results revealed no significant difference between these two techniques regarding total costs, nostril height, or nostril area ratio(28). Therefore, future studies are recommended in this regard.

5.4. Application of nasoalveolar molding appliances

The modern concept of pre-surgical maxillary orthopedics was described by McNeil in 1950. This approach is still preferred and applied in various types of neonatal maxillary orthopedic appliances. Active, semi-active, and passive devices are the main types of this approach. In active appliances, a force enters into alveolar segments and move them in a specified side by some appliances, such as spring or screw; while in semi-active appliances, the dental cast is divided into sections and the position of maxillary segments is changed to a more favorable place and forces the palatal segments in a predetermined position when the pre-made plate is placed in the oral cavity (60). In passive appliances, the certain region of the palate is exposed to grinding away acrylic material. The reason for this is to induce arch alignment during growth, which focused on the correct spontaneous development of the segments and prevented the collapse of cleft segments (60, 61). In nasoalveolar molding, the stent is inserted into the affected nostrils and helps to reform, expand, and reposition the external nasal structures. Accordingly, the palatal segments are repositioned by the intraoral plate. This act is performed when the baby is sleeping (61).

5.5. Complications

Due to the imposition of excessive force by the applied appliance of NAM, it is essential to assess and correct the adjustment of the appliance carefully. Irritation of the oral mucosa, gingival tissue, and nasal mucosa are the main complications of this approach (62). Moreover,

the lack of oral hygiene or fulltime wear of molding plate may lead to the fungal infection, which can be managed by local Nystatin or systemic Amphotericin (4).

5.6. Short- and long-term effects

The PNAM is applied widely in patients with cleft lip/palate. Although short time effectiveness of PNAM before cheiloplasty is supported, its long-term impacts are still challenging. In this regard, the experience of surgeons plays an important role in the efficacy of this surgery. Based on Shaw et al., the experience of surgeons should be considered as the main factor in the success of surgery and its outcome (63). The evaluation of the long-term effect of Hotz and Gnoinski1 revealed that concomitant surgical intervention should be performed with the same technique, at the same timing, and by the same surgeon (64). Therefore, it is recommended to conduct future studies on the long-term effects of nasoalveolar molding.

Since the pre-surgical orthopedic treatment occurs in the neonatal period, the evolution and estimation of its long-term effects are difficult. Sasaki et al. assessed the effect of NAM therapy in patients aged 3-18 years. The NAM therapy was commonly performed until the end of the primary cleft palate surgery in all reported cases by Sasaki et al. (23).

5.7. Research limitations

In this study, we followed the Cochrane's risk of bias to assess the risk of bias in the included trials and focused solely on a randomized clinical trial. However, data insufficiency and lack of homogeneity among studies was the main limitations of our research, which may lead to bias in our outcome. In addition, the use of different nasoalveolar molding techniques and lack of follow-up in some of the reviewed studies may have affected our findings.

6. Conclusion

Based on the literature review, the positive effect of NAM appliance therapy on nasal symmetry in unilateral clefts of the lip and/or palate treatment is supported in various studies. The NAM therapy is effective in decreasing the severity of the initial cleft deformity, as well as repositioning of deformed nasal cartilage and alveolar process, which has many beneficial results in the surgery outcome. However, the long-term effect of this approach remains unclear.

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Conflicts of interest

Authors declare no financial and personal relationships with other people or organizations.

Disclaimer

It should be noted that the present study was informational in nature; therefore, the described strategies might not be suitable for other conditions or purposes.

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