T. C.
YEDITEPE UNIVERSITY
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THREE-DIMENSIONAL EVALUATION OF THE NASOLABIAL EFFECTS OF NASOALVEOLAR MOLDING IN UNILATERAL CLEFT LIP AND PALATE PATIENTS

DOCTOR OF PHILOSOPHY THESIS

Dt. ALP DORUK BİRLİ

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SUPERVISOR
Prof. Dr. Derya Çakan

Istanbul, 2019

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ONAY

Bu tez Yeditepe Üniversitesi Lisansüstü Eğitim-Öğretim ve Sınav Yönetmeliğinin ilgili maddeleri uyarınca yukarıdaki jüri tarafından uygun görülmüş ve Enstitü Yönetim Kurulu'nun 28./06./2019. tarih ve 2019/11-33.........sayılı kararı ile onaylanmıştır.

Prof. Dr. Bayram YILMAZ

Sağlık Bilimleri Enstitüsü Müdürü

BEYAN

Bu tezin kendi çalışmam olduğunu, planlanmasından yazımına kadar hiçbir aşamasında etik dışı davranışımın olmadığını, tezdeki bütün bilgileri akademik ve etik kurallar içinde elde ettiğimi, tez çalışmasıyla elde edilmeyen bütün bilgi ve yorumlara kaynak gösterdiğimi ve bu kaynakları kaynaklar listesine aldığımı, tez çalışması ve yazımı sırasında patent ve telif haklarını ihlal edici bir davranışımın olmadığını beyan ederim.

Alp Doruk Birli

DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for the award of any other degree except where due acknowledgment has been made in the text.

Alp Doruk Birli

DEDICATION

This thesis is dedicated to my little daughter Arya and my beautiful wife Sabiha, who showed extraordinary patience and helpfulness during my research. I could not manage to accomplish such achievement without your unlimited support.

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LIST OF SYMBOLS AND ABBREVIATIONS

DDY	: dudak damak yarıklı
NAŞ	: nazoalveolar şekillendirme
CUCLP	: complete unilateral cleft lip and palate
3d	: three-dimensional
CLP	: cleft lip and palate
PIO	: presurgical infant orthopedics
NAM	: nasoalveolar molding
PNAM	: presurgical nasoalveolar molding
CL	: cleft lip
CL/P	: cleft lip and/or palate
TGF	: transforming growth factor
TGFα	: transforming growth factor alpha
TGFβ3	: transforming growth factor β3
MSX1	: maxilla X1
CREB	: cAMP response element binding protein
HLA-F13A	: Human leukocyte antigen F13A
MTHFR	: methylenetetrahydrofolate reductase
HFIAS	: household food insecurity access scale
SLOB	: same lingual opposite buccal
SFS	: shape from shading
n	: nasion
cph	: christaphiltri
en	: endocanthion
prn	: pronasale
ls	: labiale superior
sn	: subnasale
ch	: chelion
al	: alare
nbl	: nostril base lateral
ex	: exocanthion
nt	: nostril top

UCLP	: unilateral cleft lip and palate
C	: cleft
NC	: non-cleft

SUMMARY

Birli, AD (2019). Three-Dimensional Evaluation of the Nasolabial Effects of Nasoalveolar Molding in Unilateral Cleft Lip and Palate Patients. Yeditepe University Institute of Health Sciences, Department of Orthodontics, PhD Thesis, İstanbul.

The aim of this prospective study was to evaluate three-dimensional nasolabial changes in infants with complete unilateral cleft lip and palate (CUCLP) treated by nasoalveolar molding (NAM) and compare to non-cleft controls. Thirty-nine CUCLP patients treated with NAM (mean age of 23.1±6.5 days) composed the study group. The control group comprised 10 healthy infants with a mean age of 23.7±6 days. Stereophotogrammetric records of the subjects in the study group were taken at pre-NAM (T0) and post-NAM (T1) whereas the control subjects' records were taken at a matching interval. Linear, angular and proportional measurements were carried on 3d stereophotogrammetric images using a software program. At T0, the cleft patients had significantly greater nostril and nasal widths, smaller nostril and columella heights, shorter philtrum on the cleft side, deviated columella and decreased nasal projection ($p<0.001$). Following NAM, on the cleft side, lip gap, nostril base width and diameter decreased ($p<0.001$), nostril height increased ($p<0.001$). Initially increased nostril height ratio significantly decreased with treatment ($p<0.001$). Inclination angle of the columella was steepened ($p<0.001$). Nasal projection angle significantly increased ($p<0.01$). Proportional measurements improved significantly in NAM group whereas in control group they remained the same. At T1, comparison of the study and control groups revealed that alar width, nasal base width and nostril diameter were greater ($p<0.01$, $p<0.001$ and $p<0.001$ respectively). Columella height was shorter on the cleft side compared to the controls ($p<0.01$). Nostril height and nasal projection angle did not differ between groups ($p>0.05$). The initial nasolabial cleft deformity of the CUCLP patients were significantly improved with NAM treatment. This improvement was mainly correlated with the severity of the initial deformity. Nasal projection and nostril height reached the normal values, whereas the transversal measurements were found to be larger despite the significant reduction. On the other hand, asymmetry of most of the nasolabial structures was improved following treatment.

Key words: Complete unilateral cleft lip and palate, nasoalveolar molding, nasolabial changes, stereophotogrammetry, non-cleft control

ÖZET

Birli, AD (2019). Tek Taraflı Dudak Damak Yarığında Nazoalveolar Şekillendirmenin Nazolabial Etkilerinin Üç Boyutlu Değerlendirilmesi. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü, Ortodonti Anabilim Dalı, PhD (Doktora) Tezi, İstanbul.

Bu prospektif çalışmanın amacı, tam tek taraflı dudak damak yarıklı (DDY) bebeklerde nazoalveolar şekillendirme (NAŞ) tedavisi sonucunda oluşan nazolabial değişikliklerin üç boyutlu olarak incelenmesi ve sağlıklı kontrol grubu ile karşılaştırılmasıdır. Çalışma grubu, ortalama yaşı 23.1±6.5 gün olan otuz dokuz tam tek taraflı dudak damak yarıklı bebekten oluşmuştur. Kontrol grubu ise benzer şekilde ortalama yaşı 23.7±6 olan on sağlıklı bebekten oluşmuştur. Çalışma grubunun üç boyutlu stereofotogrametrik görüntüleri NAŞ öncesi (T0) ve sonrasında (T1), kontrol grubu kayıtları da benzer zaman aralığında alınmıştır. Doğrusal, açısal ve oransal ölçümler arayüz program ile yapılmıştır. T0 döneminde kontrol grubuyla karşılaştırıldığında, DDY'li bebeklerin yarık tarafında nostril ve nazal genişliklerin artmış, nostril, kolumella ve filtrum yüksekliğinin ve nazal projeksiyonun azalmış ve kolumellanın deviye olduğu gözlenmiştir ($p<0.001$). NAŞ sonrasında, çalışma grubunda yarık tarafta, dudak yarık mesafesi, nostril taban genişliği ve çapı azalmış ($p<0.001$), nostril yüksekliği artmıştır ($p<0.001$). Başlangıçta artmış olan nostril yükseklik oranı tedavi ile birlikte anlamlı şekilde azalmıştır ($p<0.001$). Kolumellar deviasyon açışı dikleşmiş ($p<0.001$) ve nazal projeksiyon açısı anlamlı şekilde artış göstermiştir ($p<0.01$). Oransal ölçümler çalışma grubunda anlamlı şekilde iyileşirken kontrol grubunda değişmemiştir. T1 döneminde çalışma ve kontrol gruplarının karşılaştırılması, çalışma grubunda alar, nazal genişlik ve yarık tarafı nostril çapının daha fazla olduğunu (sırasıyla, $p<0.01$, $p<0.001$, $p<0.001$) ve kolumella uzunluğunun daha kısa olduğunu ($p<0.01$) göstermiştir. Nostril yüksekliği ve nazal projeksiyon açısı ise gruplar arasında anlamlı fark göstermemiştir ($p>0.05$). Tam tek taraflı DDY'li bebeklerin nazolabial deformiteleri NAŞ tedavisi ile iyileşme göstermiştir. Bu gelişmenin temelde başlangıç deformitesinin şiddetiyle ilişkili olduğu bulunmuştur. Burun projeksiyonu ve nostril yüksekliği normal değerlere ulaşırken, transversal ölçümler belirgin şekilde azalmakla beraber yine de daha yüksek bulunmuştur. Diğer yandan, çoğu nazolabial yapının asimetrisi söz konusu tedavi ile iyileşme göstermiştir.

Anahtar sözcükler: Complete unilateral cleft lip and palate, nasoalveolar molding, nasolabial changes, stereophotogrammetry, non-cleft control

1. INTRODUCTION AND PURPOSE

Cleft lip and palate (CLP) is one of the most common congenital craniofacial deformities. In Turkey, the frequency of CLP was found to be 1/800 (1). That accounts for more than half of congenital disorders (2). Orofacial clefts are classified according to the affected tissues and the location of the cleft. It has been reported that unilateral clefts are more common than the other type of clefts and may present considerable variation in severity (3,4).

Complete unilateral CLP is characterized by disruption of the alveolus, the nostril sill and the lips. Thus, in cases with complete unilateral CLP, the facial appearance is also affected besides the alveolar region and more extensive clefts are associated with more significant nasolabial deformity. This deformity includes dysmorphology of the columella, nasal tip and alar cartilage. Therefore, unilateral cleft lip nasolabial deformity is characterized by separated lip segments, wider and retrodisplaced nostril, inward buckling nostril margin, horizontally positioned nostril aperture, posterolaterally displaced alar base, depressed and concave lower lateral nasal cartilage, shifted nasal base, deviated columella, depressed nasal dome, increased angle between short medial and long lateral crus and the appearance of an increased alar rim on the cleft side (4–6). This asymmetrical deformity should be corrected to obtain an acceptable facial appearance. However, as the severity of the cleft deformity increases, primary nasolabial repair becomes more difficult and optimal results cannot be achieved due to the extensive tension and distortion of the soft tissues. Thus, a technique of presurgical infant orthopedics (PIO) called nasoalveolar molding (NAM) was introduced by Grayson and Cutting in the early 1990's to reduce the severity of the alveolar and nasal (7). NAM differs from other forms of PIO because the rationale behind it lies in the cartilage reshaping ability in neonates (8). So, the goal of presurgical NAM in an infant with unilateral cleft deformity is not only to align and approximate the alveolar segments, but also to correct the malposition of the nasal cartilages and the alar base on the affected side, as well as to idealize the position of the philtrum and columella and create a good nose projection. It is suggested that these positive changes help the patient and surgeon by decreasing tension on the incision line and subsequent scar, and facilitating creation of a natural curvature to the alar rim. At the end, this procedure enables the surgeon to achieve a better, more symmetrical and predictable nasolabial outcome with less scar tissue formation in short term (4).

Over the past decade, NAM has become very popular and been used increasingly to treat patients with clefts, thereby improving nasal symmetry and lip closure. Meanwhile, the effectiveness of NAM has been questioned and its short-term nasolabial effects has been evaluated by various investigators (9–13). These studies revealed an improvement in nasal shape and symmetry following NAM in UCLP patients. On the other hand, a recent study claimed that facial growth is largely responsible for the improvement on the nasal symmetry, criticising the short-term benefit of NAM (14). These controversial findings show the importance of carrying out studies including control subjects. Therefore, it is necessary to study the effects of nasoalveolar molding treatment on nasolabial structures and make comparison with the same aged infants without cleft as a control group in order to eliminate the effects of growth and to assess the true correction of the nasal deformity.

When evaluating the facial changes in cleft infants, direct or indirect anthropometric measurements are made. Indirect anthropometry requires facial modeling. For this purpose, numerous methods have been used such as two- dimensional facial photography, facial impression taking, laser scanning or three-dimensional (3d) photography. Because it is essential to take reliable 3d records free of distortion in order to evaluate these facial changes, stereophotogrammetry has become as the gold standard for record taking. This precise and reliable method is advantageous in terms of noninvasiveness, accuracy and easiness in use while working on infants (15,16,25–29,17–24).

Therefore, the purpose of this study is to evaluate the nasolabial region before and after NAM using stereophotogrammetry and compare the nasolabial changes with that of the control group.

2. GENERAL INFORMATION

2.1. Embryology

In embryologic life, facial development begins at the 4th week and continues until the 12th week of intrauterine period. The facial appearance is becoming clear in the 8th-10th week. According to the studies, the cleft lip (CL) and / or palate (CLP), appears within the first 8 to 12 weeks of embryological development (30–32). The medial nasal process, lateral nasal process, and maxillary process combine to form the normal nose, upper palate and lip anatomy. The separation of the oral and nasal cavities is caused by the merging of the maxillary processes and the medial nasal processes (33). Cleft lip formation occurs in the intrauterine period at the 11th and 12th weeks due to fusion failures in the medial line of maxillary bones (34).

The maxillary palatal processes move from the vertical position to the horizontal position approximately in the seventh week and rise over the tongue to merge the midline. If this fusion does not happen, cleft palate occurs. Palatal clefts are in the group of secondary palate defects and this anomaly occurs between the 7th and 12th weeks of gestation (35). Cleft palate can involve soft palate and/or hard palate.

The primary palate is composed of prolabium, anterior nasal septum and premaxilla. In other words, the structures between the upper lip and the incisive foramen are called primary palate, and it develops between 4th and 7th week. During the prenatal development period the upper lip forms when the mesoderm of all the aforementioned prominences grow and contact each other. If any of these groups show incomplete development, thinning in the epithelium of that part and then tearing occur, which leads to cleft lip (35). These are the clefts extending to the incisive foramen. If non-fusion occurs on one side between the medial nasal process and the maxillary process, it is defined as unilateral cleft lip, if it occurs on both sides then it is defined as bilateral cleft lip.

Maxillary processes begin to fuse from anterior to posterior by forming hard palate, soft palate and uvula similar to a zipper. Therefore, if any fusing failure develops, it means there would be a cleft related to that area (31).

2.2. Epidemiology

Orofacial clefts are the most common defects in craniofacial birth defects; cleft lip and palate takes 65% of all the congenital disorders are taken into account (2). Cleft lip and palate is one of the most common congenital disorders and seen around 800-1000 births worldwide (36–38). Likewise in Turkey, this ratio is 1/800 (1). These patients are happened to be, 0,95/1000 CLP and 0,77/1000 isolated cleft patients (39,40). The prevalence of CLP depends on various factors such as geography, ethnicity and gender. For example, Asian population has the highest prevalence while black population has the lowest. Vanderas (41) stated, CL/P was found to be between 0,91 and 2,69 in 1000 in white and 0,18 to 1,67 in 1000 in black population. In addition, the European region showed prevalence 1,30 and 1,94 in 1000 whereas, in Canada, CL/P incidence was reported between 1,06 and 1,97 in 1000. Similar to these, Australia had the frequency of CL/P between 1,21 and 1,73 at 1000. In the United States, this ratio is recorded as 0,95 to 2,69 in 1000.

Chinese population presented the highest cleft prevalence (1,45 to 4,04 in 1000) whereas, Japanese population has been assessed and the occurrence was found to be ranging from 0,85 to 2,68 in 1000. When live births are compared to stillbirths and abortions, the incidence of cleft lip and / or palate in live births is three times lower than that of stillbirths (41).

Other than these, unilateral clefts are found to be affecting left side rather than right and this situation unrelated with race, severity or gender (42–46). Moreoever, Jagomagi et al.(47) found similar results about left side laterity of unilateral clefts are more than twice of right side. Also, in studies it is shown that Caucasian patients with CLP is two times more frequent in male gender (41,47). Apart from epidemiological studies, also in other studies conducted with patients with CLP, study group’s demographic datas show similarity (48–51).

The percentage of patients with bilateral cleft lip and palate is much lower compared to the percentage of unilateral cleft lip patients and they are less than 10% of the total amount of deformities seen in the entire lip or palate or both (52).

2.3. Etiology

The etiology of cleft lip and palate is multifactorial. Cleft lip and palate anomalies occur from genetic or environmental factors or a combination of both factors (36–38).

Current researches focus on the complex molecular embryology of development. Molecular order and certain defects in the networks may play a role in the etiology of the clefts. The incidence and etiology of orofacial clefts may have some clues about the causes of these clefts (55).

2.3.1. Genetics

Developmental anomalies are not observed in non-syndromic individuals with cleft. It has been reported that approximately 70% of the total of cleft lip palate cases is present in the non-syndromic patients with clefts (56). Upon the existence of the effect of genetic mechanism in the aetiology of orofacial clefts was firstly showed in human studies by Fogh-Andersen in 1942 (46). In many studies, patients with CLP and their families have been evaluated for the effects of hereditary characteristics, family history, and risk of affection. While genetic studies are continuing, there are strong evidences that genetic effect has a role in the formation of the cleft lip palate (57). First-degree relatives of the individuals with cleft lip palate were found to have a 40-fold greater risk of cleft lip palate (58).

Cleft lip or cleft lip and palate increases with consanguineous marriage and familial story (59–61). In consanguineous marriages; the similarity of the gene structure increases the encounter possibility of recessive genes that carries the disease (62). Marazita et al. (63) mentioned that for these kind of studies it is important to have a large sample size, eventhough, with a relatively small study, they found positive linkage between consanguineous marriages and CLP.

On the other hand, a study done in the Brazilian population shows that, marriage of relatives and the story of familial cleft were not related with CLP (64).

Ardinger et al. (65) firstly reported that transforming growth factor (TGF) contributes to the formation of orofacial clefts. The genes that are considered to be responsible for head and face development are, transforming growth factor alpha (TGFα), transforming growth factor β3 (TGFβ3) and Msh Homeobox 1 (MSX1) (66,67). In addition, growth factors (Jagged 1, cAMP response element binding protein (CREB), fibrillin and aggrecan) play a major role in head and face development (68,69). When there is any change in the structure of these genes, facial clefts may occur.

In recent studies, chromosomal regions 2,4,6,17,19 have been found to contain regions related to clefts (70). Especially MSX1 and human leukocyte antigen-F13A (HLA-F13A) chromosomal studies are preliminary (71). It has been shown that the region of the orofacial clefts is in the long arm of the 6th chromosome (72). In another study, it was stated that the region which is important in the development of orofacial clefts was localized in the p13 band of the short arm of chromosome 2 (53). Similarly, Aşlar et al. (73) showed that, in Turkish population methylenetetrahydrofolate reductase (MTHFR) gene's polymorphism plays an important role in occurrence of nonsyndromic CLP. Other than that, another study conducted by Derelli et al. (67) concluded on, there is a significant relation between TGFa/HinfI polymorphisms and nonsyndromic CLP. Eventhough, these findings are crucial to understand the genetic background of CLP it is recommended to study on different ethnicities with larger samples sizes on both study and control groups (67).

Further studies are needed because genes that have an effect on cleft lip palate etiology are still controversial. In order for the etiology to be understood more clearly, genetic factors should be considered together with environmental factors.

2.3.2. Environmental Factors

In the etiology of clefts, besides genetic factor, environmental factors such as malnutritions, medicine intakes, gestational age and smoking were also found effective (74).

2.3.2.1. Nutritional deficiencies

Food reliability is found to be associated with the risk of cleft lip and / or palate (75). Household food insecurity access scale (HFIAS) is a scale that assesses not only hunger but also uncertainty, anxiety, nutritional quality and social acceptability in food consumption (76). Studies using HFIAS have shown that low nutritional quality increases the risk of oral clefts (75,77,78). It has been studied that the use of multivitamins in the periconceptional period reduces the risk of oral clefts (79–84). On the other hand, it is not yet known which foods reduce the risk of clefts. Some studies indicate that low zinc concentration increases the risk of oral cleft, but this relationship varies with location (85–87). In a recent study conducted in Thailand, a decrease in liver consumption was associated with an increased risk of oral clefts (88). On the other hand, another study examining liver consumption was made in Denmark and no association between liver consumption and oral clefts was observed. However, in that study, it was reported that the risk of cleft lip and / or palate decreased in those with the highest vitamin A levels, which were thought to be derived from liver consumption, and usage of nutritional supplements (89).

2.3.2.2. Medicine Intake

Some studies have shown that steroid treatment can be responsible for cleft palate and lip (53). Some studies reported that the usage of aspirin in the first 3 months of pregnancy may cause cleft lip and palate, although there is no definitive evidence in animal and human trials (71).

2.3.2.3. Gestational Age

Maternal and paternal ages at gestation have been investigated as risk factors in cleft lip palate formation (84,90–93). Herkrath et al. (94) examined whether paternal age is a risk factor on the cleft lip palate and concluded to become a father at 40 years and older and a mother of 35-39 years increases the occurrence of having a baby with cleft palate. The 40-year-old and older mothers are in a higher risk group of having babies with cleft lip and palate, cleft lip or just cleft palate. There is no evidence has been found for the possibility of a high-risk group in terms of likelihood of having babies with cleft in younger parents (84,90,91,94,95). In another study, it was stated that maternal and paternal age had no effect on the cleft lip and palate, cleft lip or cleft palate formation (96).

Jia et al. (84) and Campos Neves et al. (96) found that the individuals with cleft were mostly second or subsequent gestations and occurrence of cleft has a positive correlation with the number of gestation. Similar to these studies Messer et al. (90) found that most of the cleft cases were seen in people who had had 3 or more gestations before.

2.3.2.4. Alcohol Intake

A positive relationship was found between alcohol intake during pregnancy and cleft occurrence in some studies (60,95–98), whereas other studies mentioned no relationship (84,92). The reason of this controversy is the quantity of alcohol intake in pregnancy. Alcohol consumption in higher amounts during pregnancy is required to be evaluated as an anomaly effect, however it is rarely encountered (97).

2.3.2.5. Folic Asid and Vitamin Intake

Mothers who use folic acid and vitamins are less likely to have babies with cleft lip palate (73,79,84,99). But the conclusions about this factor are not very consistent (79,82). In addition, the mechanism of the protective effect of these substances is still not understood (82).

2.3.2.6. Smoking

Maternal smoking and the increase of oral clefts was found to be fairly related (60,92,93,100–103). Paternal smoking was also directly related to the cleft palate lip incidence (84,93,96). In recent studies, it has been observed that exposure to passive smoking increases the risk of oral cleft by 1.5 times (75,104). Indeed, maternal smoking seems to be the most negative environmental factor in terms of risk of oral clefts (75).

2.4. Classification

Cleft lip and palate have different types depending on the time of affection and anatomical region that has been affected. Cleft lips are one of the most recognizable and most common defects in the facial region. Yet, different professionals such as pediatricians, geneticists, surgeons, speech therapists etc. usally uses the term of "cleft lip" differently (105). Multidisciplinary treatment approach with inter-professional communication is important in these anomalies for accurate identification of the severity and type of these anomalies, proper diagnosis and treatment planning. CLP classification should be as simple and understandable as possible, however, involving the severity of malformation, premaxillary protrusion, collapse of alveolar arcs, deviation of nasal structures and severity of deformity and velopharyngeal function (106).

Beginning from the twentieth century, there has been a wide range of classification methods which have been used. Among these methods, Davies and Richie (107) went further by suggesting the termination of the term of *harelip* and they made their classification method regarding to the deformations' affection with the alveolar crest and named them as prealevolar, alveolar and postalveolar for the first time in 1922. Nine years after Davies and Richie (107), Veau (108) defined a new classification based on anatomical structures dividing clefts into four groups as: isolated soft palate, soft palate and hard palate, complete unilateral and bilateral cleft extending to soft palate from the alveolar crest. Later, in 1942 Fogh-Andersen (46) has proposed an alternative classification based on embryological perspective. As well as Fogh-Andersen, in 1958 Kernahan and Stark (109) defined another classification according to the developmental theory of embryological formation and provided support to Fogh-Andersen. In their classification, incisive foramen has counted as a reference point to the alveolar crest, and the anterior part of the incisive foramen is called primary palate (upper lip, philtrum, premaxilla, and 4 incisor teeth) and the posterior part is called secondary palate (hard and soft palate). Meanwhile, these classifications lead to confusions because of miscommunication between the cleft palate teams, since those teams were getting more complicated day by day, there were not only surgeons and dentists also there were speech therapists, geneticians and biologists in the multi-disciplinary teams. American Cleft Palate-Craniofacial Association has made a refinement (110) in 1962 to overcome these problems and used Greek and Latin terminology only. The committee concluded on two main anatomical divisions and six subdivisions according to affected tissues. On the other hand, Pfeifer (111) made the first symbolic classification by using lines and dots to indicate complete and incomplete clefts in 1966. One year later, International Confederation for Plastic and Reconstructive Surgery has assigned a subcommittee in order to make a classification similar to Fogh-Andersen's. Broadbent was the chaired, and the committee made the classification in 1969 with two-tiers and described clefts in three main divisions -anterior, anterior and posterior and posterior clefts- and several subdivisions of affected tissues (112). Nevertheless, in 1973, Victor Spina (113) had an argument on the terms of main divisions called anterior/posterior and he suggested to make a minor revision by using the terms of preforaminal, transforaminal and postforaminal. In 1971, Kernahan (114) made a new symbolic classification, which he called 'the striped Y', based on the classification he had previously described. In this classification, the arms of Y represent the primary palate, while the base represents the secondary palate and the circle in the conjuction of the two is the foramen incisivum. The primary palate is divided into right and left. The segments that have cleft are indicated by the plots. The presence of the submucous cleft or Simonart band is indicated by horizontal lines and median cleft is shown by drawing a vertical straight line between the arms of Y. Elsahy (115) created the modified striped Y classification with the reason of the clefts' severity on the lip could not be clearly specified, premaxillary protrusion and alveolar arc's collapse could not be identified, the function could not be coded and velopharyngeal failure could not be specified in the traditional striped Y classification. In 1977, Millard (116) modified the striped Y scheme a bit further and included the nose by adding two inverted triangles to the top of Y with the purpose of defining the nose wings. Friedman et al. (117) formed a new Y-scheme in 1991, combining the schematics of Elsahy (115) and Millard (116). They did the coding with numbers and letters instead of plotting, crossing and drawing lines. They aimed to facilitate a standardized classification for clinical and epidemiological investigations by establishing medical data and transferring the standardized data. Smith et al. (118), inspired by the striped Y-diagram, has created a new classification in which the deformity is defined more simply and the digital coding is done. In this classification, premaxilla and velopharyngeal functions are not considered. In this scheme, the secondary palate is divided into right and left.

In symbolic classifications; the presence of the cleft, the extention of it on tissues were defined, but not enough objective information on the severity of the deformity were transferred. However, it is important to clearly define the severity of deformation for selecting preoperative orthopedic treatment or surgical treatment approaches (111). Therefore, Ortiz et al. (119) have identified a new classification that also shows the severity of deformation and the amount of tissues that has been affected. However, this classification has a large and complicated structure with more than one scheme. In order to create a simpler and clearer classification, Rossel (120) has created a new classification called 'The Clock Diagram' based on the degree of distortion. This classification method is based on the surgical results of 1043 patients who were selected by Rossel according to their classification protocol and includes 4 basic structures (nose, lip, primary palate, secondary palate). Rossel (120) compared his classification with the Kernahan diagram in a study. In the case of two patients with the same tissues but with different cleft severity, the Kernahan diagram indicated that both patients were coded the same way, but the clock diagram could be coded differently by defining the cleft's severity.

Coşkuner (121) defined a newer classification through numerical models for CLP infants in her thesis study in 2012. In this classification, coding is done with 3-digit numbers. In the code, digit of hundreds indicates the cleft type, digit of tens indicates the size of the cleft, and digit of units indicates the degree of dislocation (soft-hard palate cleft's length). Lastly, Elsherbiny and Mazeed (122) suggested a more reliable, user friendly and understandable classification method in 2017. This classification uses the Kernahan's striped Y method as basis, but has integrated with severity degrees for each part of the cleft. This provides clinician to understand the severity and extention of the cleft much easily.

2.5. Intraoral and Extraoral Characteristics of Complete Unilateral Cleft Lip and Palate

The unilateral cleft deformity is characterized by distruption of the alveolus, lips and nostril sill. The alveolar segments are separated with anterolateral displacement of the greater segment in general. The lesser segment may show medial or lateral rotation (123–125). Facial features of patients with unilateral clefts consist of extraordinarily positioned orcibularis oris muscles on both sides of the cleft which associated with different grades of nasal deformity because of the collapse on the cartilages of nasal housing. This ends up with depressed and concave lower lateral cartilage on the affected side which is parted from the other side which causes the nasal dome to get depressed and displaced. Moreover, this issue is related to the drooping of the affected side's nostril apex. Other than these, both columella and nasal septum are leaned over the gap of parted segments and base is shifted to the non-cleft side (126). If there is a cleft of the palate, the nasal septum will deviate to the noncleft side with an associated shift of the nasal base. Above mentioned unilateral cleft deformities is challenging for the surgeon in obtaining symmetry of the nasolabial unit as well.

2.6. Presurgical Orthopedic Approaches

Presurgical orthopedic treatment was advocated to reduce the severity of the initial cleft deformity, to restore the normal anatomy, to stimulate palatal growth or to guide growth and development of the maxillary alveolar segments. Therefore, a number of orthopedic techniques has been developed over the years to overcome the problems that may occur in patients with unilateral and bilateral clefts of lip and palate (127). Presurgical orthopedic approaches were firstly arisen in the 16th century when the surgeons wanted to achieve better surgical outcomes by retracting the protruded premaxilla (128). Until today, several techniques were used such as extraoral devices, active and passive plates, NAM, lip tapes and lip adhesion (7,125,129–135).

Before the 20th century there were several techniques that had been suggested, however those were primitive and unsufficient. As an initial, Franco in 1561 mentioned some suture methods to close the gap of lips, later than that Hoffmann used a head cap in 1686 for the same purpose. Louis, Chaussier and Desault in the 18th century, took the advantage of bandages to compress premaxilla. In the 19th century, treatment modalities have changed and improved after medical adhesive tapes were imroved. Hullihen, Von Bardeleben, Thiesch, Von Esmarch and Kowalzig used different tape, rubber band and head cap or bonnet devices to proximate the cleft segments before the surgical intervention (126).

McNeil (130) was the first who described modern presurgical orthopedic treatments in 1950. According to his treatment modality, he used a series of orthopedic plates in order to approximate the alveolar segments. McNeil believed that molding the palatal segments into the anatomical correct position would produce a normal maxilla while reducing the palatal and alveolar cleft at the sime time. He also suggested that the gentle pressure created by the plates on the palatal mucosa a short distance away from the margins of the palatal cleft would stimulate the growth of the underlying bone (130).

Another preoperative neonatal maxillary orthopedic treatment is Millard-Latham method (136). This active maxillary plate is fixed to the palate by pins. Activation is achieved by turning a screw and using elastic chains applied to alveolar segments to approximate them. The appliance produces anteriorly directed forces to the lesser segment and posteriorly and medially directed forces to the greater segment in unilateral cases whereas expansive forces to the posterior segments and retractive forces to the premaxilla are created in bilateral cases. Since this technique is fixed, there is limited need of cooperation of the parents or caregivers. Another advantage of the technique is the reduced number of control appointments. However, this method requires general anesthesia for fixing the appliance so it is an invasive method.

Hotz and Gnoinski (133) introduced a passive plate system in 1976, which does not apply active forces to the alveolar segments. According to them, the primary aim of neonatal orthopedics was not to facilitate the surgery or to stimulate the growth as postulated by McNeil, but to take advantage of intrinsic developmental potentials. These maxillary plates were made out of hard acrylic on the outer layer and soft in the inner layer, they work by sequential grindings from the hard layer and adding soft acrylic to inner layer so that the alveolar segments move to the designated positions with natural growth. This method, described as Zurich approach, do not use extraoral elastic tapes because of a possible interference on maxilla's sagital growth (134,137). The benefits of the method were listed as helping feeding, maintaining the width of the maxilla, enabling the palate to increase spontaneously in all three dimensions without impeding its growth potential, and permitting the soft palate to grow to its maximum length prior to surgery (138).

Lip adhesion is a surgical approach which is done before the main surgical operation (139,140). In this technique complete clefts are converted into incomplete ones in order to minimise the tissue tension which occurs in the main surgical correction. Also in this method, it is aimed to approximate the alveolar segments and decrease the cleft width by lip pressure (136,139,140).

2.6.1. Nasoalveolar Molding Technique

A paradigm shift occurred at the end of 20th century in presurgical infant orthopedics in terms of the extended objectives of this treatment approach. In 1993, Grayson et al. described nasoalveolar molding technique to correct the alveolus, lip, and nose in infants born with cleft lip and palate (129). This technique does not only aim to mold the alveolus but also the nasal complex. NAM method provides orthopedic treatment before surgery to reduce the cleft size in the alveolar bone, reshape the deformed structures and minimize the nasal deformity. Thus, decreasing the severity of anomalies enables the surgeon to repair a smaller cleft deformity under minimal tension of the soft tissues and to achieve a finer surgical scar, good nasal tip projection, and more symmetrical nasolabial complex (141,142).

Nasal molding by stents were first used in the past to treat post-operative, nasopharyngeal stenosis and clefts in order to preserve the shape of the alar cartilages after surgical correction (143–147). However, in NAM, the nasal stents are used to mold the nasal cartilages prior to the primary surgeries. Nasoalveolar molding is based on high plasticity caused by transient high estrogen and hyaluronic acid present in the cartilages of neonates in the early postnatal period. In 1984, Matsuo et al. (8) showed that auricular cartilage can be shaped during the first 6 weeks after birth and that the treatments performed during this period are permanent. In the perinatal period, the amount of estrogen that comes from the mother increases and this triggers the increase of hyaluronic acid. Hyaluronic acid reduces the elasticity of the tissue by destroying the intercellular matrix of cartilage, ligament and connective tissue. This process is crucial for the fetus to pass safely through the birth tract. After approximately 6 weeks, the level of estrogen falls rapidly and the plasticity of cartilage decreases. Matsuo et al. (148,149) later applied these findings to the nasal deformities of patients with cleft lip. However, there was a restrictive feature of their nasal stent design, which was the necessity of a nostril base that was in contact with each other. This resulted in the inability to use stents in infants without Simonart band, and in severe cases who were more commonly in need for the use of nasal stents in general. Since there was no nasal base in contact in these cases, Matsuo sometimes planned a primary lip connection and then the actual lip-nose repair with the use of a stent.

Based on Matsuo's work, Grayson et al. (130,150) added a nasal stent to the appliance that they used to approximate and reshape the alveolar segments prior to surgery. A nostril base with integrity was not needed because the nasal stent was supported by an intraoral appliance. Thanks to the reliable base which the plate was providing, the desired placement, orientation and force control could be transmitted precisely to the deformed nasal tissue through the nasal stent. The pre-surgical NAM application would reduce the amount of incisions in cartilages which would also reduce risk of scar tissue formation and relapse of the treatment.

Another advantage of NAM was that the lips were approaching each other through elastic tapes without surgery. The use of tapes provided less scarring by reducing the tissue tension that would occur after surgical repair.

NAM is a very technique sensitive approach. In order to optimize functional and aesthetic outcome in the NAM of cleft lip and palate deformity, the treatment steps must be performed at most appropriate timing (8–10). For NAM, an intraoral impression is taken from the infant. Acrylic plate is made by clear resin according to the cast. It is aimed to orient and approximate the alveolar segments with gradual addition of soft liner and removal of hard acrylic from the plate at the same time, in other words “negative sculpting”. Weekly adjustments are made to mold the alveolus. In conjunction with the plate, elastic tapes are applied to the retention arm reaching out of the mouth through the cleft site. These elastic tapes allow the acrylic plate to be held in the mouth and they improve the efficacy of the appliance (128). In addition to these elastic tapes, a horizontal lip tape is used to approximate the lip segments and to upright the inclined columella along the midsagittal plane, providing some of the benefits of surgical lip adhesion. After the width of the cleft gap is reduced to less than 5 mm, kidney-shaped nasal stent is added to the appliance and the nose can be shaped with this stent (142) (Figure 2.6.1.). The upper lobe of the nasal stent enters the nose and gently lifts the dome, whereas the lower lobe lifts the nostril apex and defines the top of the columella. The nasal stent is activated by adding soft liner throughout the weekly appointments. The caregivers are instructed about how to use the plate and the tapes. The retention tapes are changed daily.

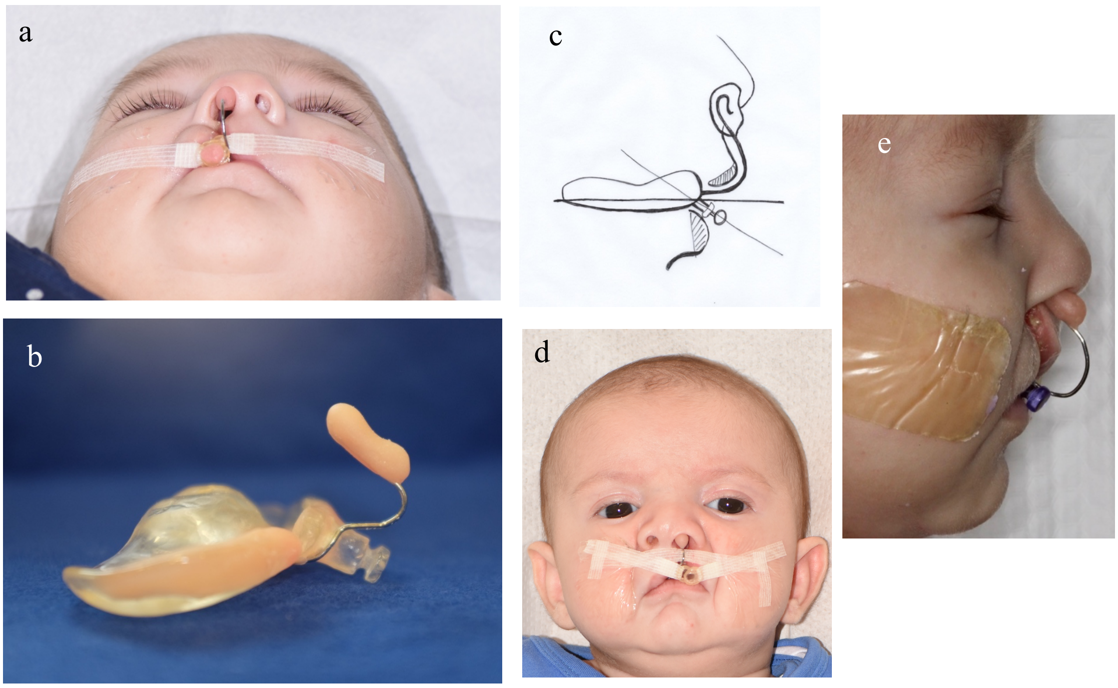

Figure 2.6.1. (a) View of a unilateral cleft patient with lip tapes and nasal stent. (b) NAM appliance with nasal stent. (c) Position of retention arm and kidney shaped nasal stent. (d) Frontal view of an infant with NAM appliance with nasal stent (e) Profile view of a patient with NAM appliance and nasal stent

NAM therapy generally takes 3-5 months in infants with unilateral cleft lip and palate. Then the patient is ready for the primary lip and nose repair.

Short and Long-term Effects of Nasoalveolar Molding

The principle objective of NAM is reducing the severity of the initial cleft deformity (4). The reported outcomes of the treatment method in unilateral cleft lip and palate are approximation of the alveolar and lip segments, decrease in anterolateral protrusion of the greater segment, reduction of the cleft size, achieving convexity and symmetry of the lower lateral nasal cartilage, uprighting of the columella, expansion of the columellar tissues and increasing the projection of the nose. As the alveolar gap width is decreased, the alignment of the base of the nose and the lip segments is improved. Because the nasal base width reduces, the initially overstretched alar rim shows some laxity, enabling the elevation of the nose into a more symmetrical and convex form by molding of the nasal cartilages. In the short term, the proper alignment of the tissues enables the surgeon to achieve a better, more symmetrical and predictable outcome with less scar tissue formation. The effectiveness of NAM is supported by robust evidence in the treatment of nasoalveolar deformities of patients with cleft (7,10,125,151–154).

A prospective, longitudinal study evaluated 3d nasal morphology changes in 10 UCLP infants treated with NAM (13). The analysis of stereomorphometric images taken before and after treatment revealed that nostril width and alar concavity were decreased, nasal projection was increased whereas the columellar and alar lengths were maintained following NAM. Columellar deviation was reduced and the columella moved toward the midline. The overall changes indicated improvement in the symmetry of the nose.

In a study by Pai et al. (155) published in 2005, photographic records of 57 infants with UCLP who had undergone NAM were assessed in four time periods, before NAM, after NAM and before primary lip repair, 1 month after surgery, and 1 year of age. Angle of columella and nostril height and width were measured on the slides and alveolar gap width was measured intraorally. In order to minimize the photographic errors, they used the ratio nostril height and width of affected side to nonaffected side. The ratio of nostril heights was 0.5 at the beginning of NAM and 0.8 after NAM. The ratio of nostril widths was 1.7 and reached 1.2 following treatment. As the ratios approached to 1, the symmetry of the nostrils was improved with NAM. The columella was uprighted from 53° to 70°

and the gap was significantly reduced after 3 months of treatment. They concluded that nasoalveolar molding is an effective treatment modality to improve the nasal symmetry regarding the nostril height, width and columellar angulation. Although the nostril shape was even more symmetrical 1 month after the surgery, they reported relapse rates of 10%, 20% and 5% in height, width and angulation of the columella, respectively, at 1 year of age.

Keçik and Enacar (10) evaluated the short-term effects of NAM on nasal and alveolar morphology in 22 patients with UCLP. Pre and post-treatment maxillary and facial models obtained after intraoral and extraoral impression taking were scanned and measurements were made on 2d images. They showed that cleft width, arch length, affected alar width and total alar base width decreased significantly whereas columellar deviation angle and nostril area increased. They concluded that the arch form was improved, the columella was uprighted and nostril shape of the cleft side was almost symmetrical to the noncleft side. However, they stated that the absence of a control group because of the ethical impossibility of obtaining facial impressions from newborn infants was the weakness of their study, leading to inability to compare their findings with the control subjects to achieve more specific and reliable results.

Fuchigami et al. (156) investigated the effects of NAM on both the alveolar structures and the nose using maxillary dental casts and conventional photographs. They found that alveolar cleft width decreased due to posteromedial movement of the anterolateraly displaced greater segment. This movement was correlated with the improvement in columella deviation. The authors hypothesized that the lip taping leading to the rotation of alveolus with the movement of the columella base toward the cleft side and nasal stent elevating the nasal tip helped to correct the columella deformation.

Nur-Yılmaz and Germeç-Çakan (9) conducted a study in 2018 with facial plaster casts of 42 infants with CUCLP in two stages (pre- and post-NAM). Researchers have used stereophotogrammetry indirectly, first they obtained models through impressions and then captured 3d images of the models. The results showed that, most of the horizontal measurements were decreasing, while vertical ones were increasing and authors emphasized that, symmetry of the nasolabial structures have improved with NAM. Other than that, they have evaluated both surface and linear measurements and concluded that except nasal width, there were no difference between those measurements.

A retrospective study assessed the stereophotometric images of 20 infants with UCLP taken at pre-NAM, post-NAM and after primary lip and nose surgery and compared the postsurgical morphology of the patients to that of a historical, age-matched, healthy control group to quantify the 3d nasolabial morphology (12). The study group comprised patients from different ethnic groups and with both complete and incomplete clefts. A progressive improvement in all the measurements was noticed. Nasal base width decreased with 4 mm, nasal tip projection was increased approximately 2 mm and columellar deviation and cleft-noncleft asymmetry was mostly corrected by NAM. After primary lip and nose repair, nose symmetry was achieved and nasal tip was found to be overcorrected compared to the controls.

In 2012, Gomez et al. (11) published a study evaluating 2 dimensional changes of the nasal morphology following a modified NAM technique. This modified method, proposed by Figueroa and Polley (157) did not use extraoral taping particularly for mild to moderate cases, restricting its use only for severe cases. The authors showed a reduction in columella deviation, increase in columella length, alar cartilage convexity, nostril height and area on the cleft side as well as a more pronounced nasal tip. On the other hand, the measurements of the noncleft area remained almost the same after the treatment. They concluded that it was possible to achieve greater nostril height with this modified technique, however the increment in alar base width was a short-coming which could be eliminated by lip taping.

In a study by Yu-Fang Liao et al. in 2012, both Grayson and Figueroa techniques showed positive effects on the improvement of nasal deformity and narrowing of the alveolar cleft area in patients with complete unilateral cleft lip and palate, similar to previous studies (6,107–112,115–118). The improvement in nasal symmetry was more vertical. Although vertical symmetry improvement was observed in both groups, the Grayson technique provided a significant reduction in nostril width. This can be attributed to Grayson's technique in which nasal stents are inserted after the cleft area is narrowed as 5mm. Initiation of overhanging nasal contouring of 5 mm as in Figueroa technique can cause an increase in the horizontal direction especially around the lateral alar wall, which is an undesirable result. This is a major concern for surgeons and is called 'mega nostril' (7). Also, Jaeger et al. (141) mentioned in their study about overexpanded nostril alar rim, so called mega-nostril, could become a potential problem caused by NAM.

Although Figueroa's technique has some advantages, it also has disadvantages that may limit treatment for patients and caregivers living away from the hospital (159,160). For example, if a relative who is undergoing through this treatment applies lip bands every day for an average of 3 months, it should be checked once a week. In addition, patients' relatives suffer from anxiety of harming the infant by, nasoalveolar misshaping, facial irritation or overactivation that can be caused by lip bands, the presence of uneven bulges on the mucosal contact surface of palatal acrylic or mucosal ulceration complications and it worsens the cooperation (161). In order to reduce such disadvantages, Yun-Fang Chen et al. (162) developed a slightly improved technique of Figueroa in 2010, and instead of the four bands used in the classical method, a completely passive appliance design (complete block-out of alveolar and palatal cleft sites) with the use of a single long band to reduce irritation. As a result, it has improved better in terms of less adjustments needed compared to conventional (periodic acrylic addition and removal is not required) and reduction of medical costs (162).

The 3d long-term effects of NAM in UCLP patients were first shown by Maull et al. (151) . They compared the nasal shape of 10 patients who had presurgical orthopedic treatment with a nasal stent with that of a control group (10 patients) who had only alveolar molding. They found that the nasal symmetry was better in NAM group and maintained in long-term. The depressed dome, wide alar width, deficient columella, and the deviation of the nasal septum were improved after NAM whereas these characteristics of UCLP were still obvious in the control group. However, they stated that the control group with a mean age of 9 years was not age matched with the study group with a mean age of 4.5 years.

In 2004, Liou et al. (158) have evaluated, 25 infants' 2d images in five different stages. They analyzed nasal asymmetry and concluded on that, with NAM asymmetry significantly improves before and following the primary surgery. However, there was a significant relaps in the first year postoperatively and then remained stable. The authors blamed, different nasal growing patterns on each side and the relapse of the columellar length on the cleft side for these results.

In a study conducted by Ezzat et al.(152) in 2007, twelve patients who had NAM therapy were evaluated. Firstly, researchers obtained impressions from the infants, then captured images of casts. Eventhough, relatively small number of patients were included in their study, the authors found that, NAM therapy, improved nasal symmetry and vertical deficiency, as well as, intraoral intersegment cleft distance. In addition to that study, Ruiz-Escolano et al. (163) conducted a similar study with twenty patients and concluded on similar results with Ezzat et al., moreover, they mentioned about the ease in the primary surgery by improving symmetry and reducing the tissue tension.

Barillas et al. (153) evaluated 25 children, 15 treated with NAM and surgery and rest of them treated with surgery alone, with CUCLP in 2009. All surgical procedures were same for all of those patients and done by the same surgeon. Researchers obtained nasal impressions from those patients when they are 7 to 11 years old (mean age was 9) and created stone casts for measurements. They evaluated four distances and two angular relationships. Five of these measurements showed statistically significant difference yet one was not significant. However, with those results authors concluded that, infants who had undergone NAM therapy had more symmetrical nasal structures in the long-term.

According to one study, it was determined that nasoalveolar shaping is a method effective in cleft width, nasal shape correction, and in making unilateral and bilateral patients more symmetrical. Although there are different ideas about the long-term effect, the short-term effect of treatment is very helpful to lip and palate surgery (127).

Clark et al. (164) conducted a long-term study in 2011 with twenty-five patients whose mean age is 5.1 years. While twenty of them received NAM, others did not go through such therapy. The researchers found that, eventhough the results did not show any significant difference between groups, authors concluded on a trend towards to clinical improvement in nasal and lip anatomy of patients treated with NAM. They also found that, while a lip scar was seen in 60% of the NAM group patients, the ratio is 100% in the non-NAM group.

In another study, it has been reported that nasoalveolar molding has many advantages in treating patients with CLP. Proper alignment of the alveols, lips and nose are very important for the surgeon who will perform the lip operation to obtain a more successful surgical result. As a result of pre-surgical NAM treatment, the cleft sites are narrowing and the approach of the alveolar processes, allows the lip segments to be closed as primer in the operation and also helps the surgeon to operate a successful gingivoperioplasty (165).

Long-term studies have shown the improvement in nasal deformity is stable, which is the result of nasoalveolar molding, results in a lesser scar tissue with a better lip and nasal form (151). As a result, it is observed that the amount of surgical revisions that may be required due to overdevelopment of scar tissue, oronasal fistula, nasal and lip deformities decreases (166). It has been reported that the alveolar segments that reach a better position with nasoalveolar molding and the bony bridges in the cleft region are able to permanent teeth to erupt in better positions with adequate periodontal support (167).

In a study conducted by Koya et al. in 2016 (168), significant improvement in nasal symmetry, columella, and bi-alar width and length was observed in infants who underwent nasoalveolar shaping therapy with the Figueroa technique. Extension of columella in superior and medial directions increased the height of nostril and improved nasal form. Measurements made on plaster models of all patients showed that the anterior alveolar cleft line was reduced. There was a significant increase in the length of the large and small segments and in the maxillary arch width. This expansion was accompanied by bi-alar enlargement. This has shown that treatment does not prevent the nasal and maxillary growth in the transverse direction and that nasoalveolar molding therapy generally directs alveolar segments. The mega nostril formation, a complication of early initiation of nasal stenting, was not observed in any patient, but three patients could be followed for 3 years postoperatively.

In 2018 Liang et al. (51) made a research with relatively large sample size, 84 patients with CLP, 42 of them underwent NAM therapy and the rest did not receive any presurgical infant orthopedics. They evaluated photographs of these patients at 4- to 5-years old and concluded that, there is no difference between groups. However, there were two problems according to the authors. Firstly, the initial severity of the patients in groups was not known and secondly, the nose development at 5 years of age is still immature and do no express secondary characteristics.

Again in 2018, Alhayyan et al. (50) conducted a long-term follow up study with 39 subjects and found no significant difference between NAM and non-NAM groups in terms of midfacial symmetry. At the same time, they mentioned about high standart deviation in the mean distances of landmarks from the midline, which might be a result of poor parental compliance during treatment and differentiation of initial severity of the deformity.

According to the studies performed, 60% of the patients who underwent nasoalveolar molding and gingivoperiosteplasty did not need secondary bone grafts (169). The remaining 40% of the patients in need of bone grafting were found to have a higher amount of bone than those in the grafting area without gingivoperiosteoplasty (167). Fewer surgeries reduce the financial burden of patients' families (170).

Another discussed long-term complication is limitation of maxillary growth which studied by Lee et al. (171) and according to this study midfacial growth as a result of nasoalveolar molding and gingivoperiosteoplasty is not affected in the sagittal and vertical directions.

Significant changes have been observed in the results obtained from the primary surgical operation of cleft, since the nasoalveolar molding took place for preoperative treatment. Nasoalveolar molding, that has been administered with good training and clinical abilities of a professional, is beneficial to the treatment of cleft lip and palate, while at the same time facilitates the surgeon who is operating the primary surgery (142).

2.7. Record Taking and Imaging

Record collection is the milestone in every medical approach to compose the most proper treatment plan. Other than medical and dental examination, the essentials of patient records include various two- and three-dimensional records such as photographs, radiographs and patient models (172). In addition, patient records also are important for follow up the changes due to therapy or physiological growth, evaluation of treatment outcomes and to communicate with other specialists (173). In patients with cleft lip and palate and craniofacial anomalies, record collection has to be made more carefully due to the variation of anatomical structures. In those patients with cleft lip and palate and craniofacial deformity the lower third of the face including the nose and mouth region, is distorted and reliable measurements are needed to determine the severity of deformity (174). Moreover, in daily life facial appearance is quite important while communicating with others, so that one of the main objectives of these patients' treatment is enhancing the esthetic appearance. Therefore in recent studies, there is a shift from hard to soft tissue analysis to evaluate treatment outcomes (175). For this reason, records should include, not only skeletal structures but also, facial soft tissues.

Anthropometry (direct clinical examinations) on patients have been used by clinicians for many years (176). While some researchers have attempted to compare direct nasolabial linear measurements and proportional measurements of patients with clefts and individuals without cleft (177), especially in newborns, children, or patients with mental retardation this method overstrains the clinicians. Apart from this, when patients are evaluated with their colleagues, only the clinical examination can be discussed and the patient needs to be present.

Another traditional recording method is photography which delivers two-dimensional data (178). Photographic records are taken from different views such as frontal, lateral and oblique (179–181). However, it is difficult to standardize facial photographs, especially in patients with craniofacial deformities. Training is needed as the experience of the photographer, education and personal performance is directly influence the quality of the photograph (182). Another disadvantage is that there will be various distortions and data loss when three-dimensional anatomical structures are evaluated on two-dimensional data.

Facial impression taking allows three-dimensional reconstruction of the anatomical structures (5). However, in a study conducted by Germeç-Çakan et al. (172) it is mentioned that the weight of the impression material and tension could cause distortions. It has been observed that a difference of 1 to 3 mm can be observed between the actual anatomy and the cast model, when the impression is taken with alginate material. Furthermore, the infants are crying during facial impression taking, which may lead to changes in facial expression and stretch of the soft tissues. The areas where the distortions in the alginate impressions are most frequently observed are the lower face region; the nasal, the subnasal region and the cheeks. Apart from this, some errors can be observed in the forehead, glabella and nasal floor, although they are not excessive (183). Although these disadvantages can be reduced by using a lower weight impression material and by positioning the patient upright, they can not be completely eliminated. Another problem with the acquisition of facial impressions, is that the patient's respiratory tract has to be protected. For this, respiratory tubes can be inserted, but nasal or oral tubes disrupt the shape of soft tissues, making reliable measurements on the models impossible. Other than that, Nur -Yılmaz et al. (184) concluded that, even though respiratory tract is protected, oxygen saturation of the infants are dropping dramatically if there are not any oxygen support delivered to the infants especially when taking the extraoral impressions. In newborns, this technique can be quite dangerous and should be performed under the supervision of the anesthesiologist with an intubation kit for emergency use (185).

Facial plaster models are fragile and prone to breakeage and wearing, which may cause data loss. In addition, extra space is required for archiving. Storing plaster models as digital data by scanning can solve some of these disadvantages. Most parameters show that the average difference between digital and plaster models is less than 0.5mm, which means reliable measurements can be made (186).

In recent years, along with the development of computer technologies, various three-dimensional recording systems such as laser surface scanning, stereophotogrammetry and structural lighting have been developed. Non-contact 3d surface imaging systems are rapidly replacing the traditional anthropometry that is preferred to obtain quantitative information about facial soft tissues (18,22). These systems offer many different advantages, such as non-invasive, fast image capture time (usually below one second), and ease of archiving the images for later analysis (23,187). In addition, a series of independent studies show that various 3d surface analysis techniques have high precision and accuracy (17,184–195). The safety, data consistency and speed provided by these systems are beneficial in facial features to be digitally recorded and measured, especially when working with children (16,17). Other than these, developing softwares allow 3d measurements and analyzes to be performed more precisely and effectively (187).

The measurement of nasal morphology was traditionally provided by linear and angular values between points marked on two-dimensional photographs (193–196). Later on, computers were used to make complex measurements. Coghlan et al. in 1987 (197) and Laitung et al. 1993 (198) developed a software for the measurement of nasal symmetry with two-dimensional digital drawings of frontal and anteroposterior. In 1988, Cutting et al. (199) scanned the surfaces of objects with a laser scanner then they planned and assessed the surgical procedures. In 1996, Bush and Antonyshyn (200) transferred a human face model to digital image with a high resolution surface scanner. After Bush and Antonyshyn in 1999, Maull et al. (151) digitized nasal impressions of babies treated with NAM with a three-dimensional surface scanner. Then, they superimposed nose images with the mirroring technique and evaluated the symmetry. Later, various linear measurements between anthropometric landmarks done in a 3d environment.

2.7.1. Computed Laser Surface Scanning Methods

Computed surface scanning methods are being used to transfer an object or a scene to a digital media as 3d models. There are four basic methods for this application.

2.7.1.1. Stereo Analysis

Stereo analysis is one of the easiest methods to understand because it works like humans' vision system which is called stereopsis. In binocular vision, the two images are different from each other and this provides the perception of depth. The difference is due to the parallax phenomenon (201). Parallax is a displacement or difference in the apparent position of an object viewed along two different lines of sight (eye or camera), and is measured by the angle or semi-angle of inclination between those two lines. In dentistry, this concept is used to decide about buccolingual positions of impacted teeth with Clark's rule (202) also known as same lingual opposite buccal (SLOB) or similar techniques. In this method, periapical radiographs are taken from two different angles of the tooth are compared and the relations with the peripheral structures are examined. If the tooth is displaced in the same direction as the tube of the x-ray apparatus, it is thought that the tooth is lingually, and if it is displaced in the opposite direction, it is buccally positioned.

In the stereo analysis method, two cameras are used to capture the image of the object. The cameras are positioned at a certain distance from each other, so images taken at this point are different from each other due to parallax. In the simplest case, two cameras with the same focal length whose optical axes are parallel to each other are used. Two photographs of the scene are taken from two separate cameras. Any point on the scene is projected to the two corresponding points in both photographs. To find the distance between a point on the scene and the cameras, the difference between the corresponding image points is measured. Using known parameters of the set-up, such as the distance between the cameras and the focal length, it is possible to calculate the distance between the selected points and the camera, and therefore the shape of the objects (201).

Identifying the points on smoothly changing surfaces, such as skin or tooth surfaces are not easy and can cause serious problems, while objects with clear corners or edges that are geometrically well defined and drawable, such as blocks or bricks, are easier to visualize.

The depth resolution in the stereo analysis method varies depending on the distance between the two cameras and the distance of the object to the camera. The greater the distance between the cameras, better the resolution of the depth. The greater the distance between the object and the camera, the lower the resolution. However, increasing the distance between the cameras relative to the distance between the object and the cameras will result in two very different images in the two cameras. This may result in deterioration of the correspondence between the images as well as the narrowing of the displayed area of the scene, which may lead to a decrease in measurements that can be made from the images (201).

2.7.1.2. Shape from Shading

The human brain also uses a method called shape from shading (SFS) to understand 3d form. The intensity of the light reflected from the objects in the environment varies. This is due to three main factors:

- The intensity of global illumination (sun or artificial lighting)
- Albedo. The light reflection properties of the object
- The angle of the object surface with the eye and light source.

This latter factor can be used to understand the shape of the object. If we assume that the object has a dull surface (if there are no reflections such as flares or mirrors-like reflections), the brightness varies with the angle the object surface makes with the direction of light arrival (201). More specifically, Lambert's cosine law says that the radiant intensity or luminous intensity observed from an ideal diffusely reflecting surface or ideal diffuse radiator is directly proportional to the cosine of the angle between the direction of the incident light and the surface normal. If the direction of the light source is known, the positions of each part of the object's surface can be determined in three dimensions, and then the shape of object can be determined and can be modelled in 3d. Of course, in practice, things are not so easy, and the shape from shading technique generally gives unsuccessful results in terms of computers. One of the reasons for this is that the same brightness can be obtained from different parts of the object by positioning the same object differently. To reach the correct solution, it is necessary to make various restrictions and make simple assumptions. Methods have been proposed for this technique that involve various assumptions and constraints. Examples include the assumption that the objects are convex, smooth and continuous, that there are no sudden changes in surface orientation, and that the illumination is from a parallel light source. Another difficulty is that all surfaces of the objects are not homogeneous. Also, the glare and reflections on the surfaces increase the problems.

2.7.1.3. Photometric Stereo

Photometric stereo is an extension method of the shape from shading and also, almost the opposite of the stereo analysis method. In this technique, instead of using two cameras and a light source, a camera and two light sources are used. Two images of the object are recorded; The first image with the first light source, the other image with the other light source. As the position of the camera does not change, there is no compatibility problems between the two images as in the stereo analysis. More accurate images can be obtained because the light sources are distant from each other and each part of the object surface is displayed under the light from two different directions. The brightness of each image and the brightness differences between the images provide much more information than simple shape from shading methods.

2.7.1.4. Structured Lighting

In order to determine the shape of an object in the method of structural lighting, a known pattern of light beam is directed towards the object. In the simplest method, a bright spotlight, usually a laser, is directed at the subject. The camera is stationary and the laser scans the entire scene and object. The scene, camera and laser installation geometry allow the depth of the spots to be calculated with simple trigonometry, and all these data are combined with a computer to reveal the shape of the object. In another type of spotlight method, light is continuously directed to the scene in the form of a stripe. This light can be provided with a cylindrical lens or with a slit-tipped slide projector (a black slide with thin white strip can be used). The mathematical processing of the solution is still relatively simple. There are two options for modeling the object in three dimensions: either the object is held still and light strip moves around to scan all surfaces of the object, or the object is placed on a rotating table and rotated so that the light strip scans the whole object (201).

These two methods use a point or strip light source, so the object must be scanned in order to reveal the entire shape. These techniques are called serial techniques. However, there are also parallel techniques that use two-dimensional lighting schemes, which are planned to cover the whole scene. Frequently preferred schemes are a series of parallel light strips, point grid mesh-based arrangements or colored strips. Parallel methods can scan the entire object with a single shot and can transfer the model in real time (203). In the structured lighting method, resolution is directly related to the sensitivity of the light used.

There are a number of issues that need to be considered in order to choose the most appropriate method for a particular application. The following factors are more important in orthodontics, especially in the three-dimensional imaging of the face and teeth:

- Safety. The use of laser light causes some safety concerns. When scanning faces using structured lighting methods, eyes may need to be closed due to the use of laser light.
- Speed. Speed is a problem when scanning on individuals because the movement of the individual can cause artifacts in the data. In structured lighting methods using light strips, the individual may need to remain immobile for a few seconds or perhaps even more. Cyberware (Monterey, Calif., www.cyberware.com) reports that an average scan time of 17 seconds is required for a full head scan, which is a too long to ensure that facial expressions can be reliably recorded without artifacts. Other lighting methods can reduce the scan time.
- Accuracy. The desired accuracy depends on the application and use of the data. It has been observed that head and face scans made with a laser can record data with a sensitivity of about 0.5 mm, but this sensitivity has been reported to be insufficient for scanning dental models.

Another problem that is frequently encountered in three-dimensional scanning devices is the holes in the scanned surface. These holes may result in the laser beam reflecting too lightly in some dark areas, such as the hairy parts of the skin, hair etc., or in some areas of the surface contacting the camera or laser. The use of powder is recommended for more reliable data recording of surfaces such as hair. Areas that are not fully scanned due to camera or laser contact can be scanned again and then whole scanned images could be combined together as one, which would give a much more reliable data (201).

2.7.2. Stereophotogrammetry

The methods of evaluating facial form are becoming increasingly important in dysmorphology, genetics, orthodontics and surgical disciplines (204–211). These methods also have the potential to improve clinical practice, facilitate surgical planning, improve outcome evaluation, and help identify syndromes (207,212–215).

The most preferred three-dimensional surface imaging systems is digital stereophotogrammetric technology (Figure 2.7.1.) (216). These systems can accurately reproduce the facial surface geometry with realistic color and texture, combined together in the image data. The mathematical and optical engineering principles involved in the creation of 3d photogrammetric surface images have been described in detail in various sources (187,217–219). The combination of fast image acquisition and wide scene coverage (up to 360 degrees) offers significant advantages over older surface imaging methods such as laser scanning.

Vertical adjustment may be required to ensure that the entire face of the individual is within the viewing area. This can be done with an adjustable seat and / or adjustable tripod (s) (220). Subnasal and submental regions are prone to data loss and artifact formation. Proper head positioning allows these areas to appear on the image sensors. Raising an individual's head a few degrees up is usually sufficient to catch these regions (199,200,221). If the subnasal region needs to be assessed in detail (e.g. shape / asymmetry assessment of the nostril), the operator may ask the individual to stretch the head for additional images and tilt the head backward (222).

Figure 2.7.1. Stereophotogrammetry device with two camera pods and flashes.

Working with young children can cause unique challenges (192,223–225). Also, for infants with rapid movements, stereophotogrammetry might be the best option because image capturing takes approximately 1.5 milliseconds according to the manufacturer. The child's anxiety about equipment can often be eliminated by allowing the parent to be with the child, so adults should be able to move without disturbing the equipment (192,225).

There are several studies done in order to evaluate if stereophotogrammetry is a reliable method for record taking. In 2006 Krimmel et al. (29) and 2012 Sforza et al. (226) evaluated stereophotogrammetry on measuring models and they concluded that, this method is sufficiently accurate and reliable also it has several advantages over other techniques such as speed and easiness. Also, Schwenzer-Zimmerer (223) mentioned, digital images are much better than direct measurements because it is possible to evaluate the patient when the patient is not there and provides datas for multi-centered studies. Other than these, Germeç-Çakan et al. (172) described this technique as promising and might be better than laser scanning method due to the color identification in datas for selecting the correct anatomical reference points between different tissues such as lip region. Moreover, they concluded that this method is better for deeper tissues such as nostrils which is suitable for evaluating CLP patients' facial properties. Some researchers used stereophotogrammetry in order to evaluate the treatment outcomes of infants with CLP and found this technique is fast, non-invasive and lack of parallax errors which is much better than direct anthropometric measurements or laser scanning (9,227,228).

3. SUBJECTS AND METHODS

Our study has been approved by Yeditepe University Medical Faculty Clinical Research Evaluation and Ethics Committee (Decision no: 600, Date: 21/04/2016). All of the families of individuals who were willing to be involved, received information about the study and signed the informed consent form.

3.1. Subjects

This prospective clinical study was carried out on CUCLP caucasian infants who were treated by NAM therapy and healthy infants without CLP.

NAM Group

The following criteria were used in the selection of infants with cleft lip and/or palate included in the NAM group:

- Nonsyndromic patients with complete unilateral cleft and palate
- Patients who were referred to the clinic between 0-30 days postpartum

From fourty-nine complete unilateral cleft lip and palate (CUCLP) caucasian infants, who were referred to recieve NAM therapy between the years 2016-2018 in the Department of Orthodontics of Yeditepe University, Faculty of Dentistry, 10 subjects were excluded because of late referral, poor cooperation during treatment or discontinuation of the therapy. After the exclusion, 39 infants meeting the inclusion criterias composed the NAM group (Figure 3.1.1.). The mean age of the 39 infants with CUCLP (20 females, 19 males) at the beginning and at the end of the treatment is given in Table 3.1.1. In addition, for the NAM group only, cleft side ratio was assessed as well (Table 3.1.2.).

Figure 3.1.1. 3d image of an infant from NAM group at T0 and T1

Table 3.1.1. Demographic characteristics of NAM group

		NAM Group (n:39)		
		Mean±SD	**Min**	**Max**
T0 (Day)		23.1±6.5	12	30
T1 (Day)		99.3±32.7	68	135
T1-T0 (Day)		76.2±27.9	46	105
Gender	**Male**	20	51.28%	
	Female	19	48.72%	

Table 3.1.2. Cleft sides ratio of NAM group

Cleft Side	NAM group	
Right	18	46.15%
Left	21	53.85%

Nasoalveolar molding therapy of all these individuals were performed according to the technique of Grayson et al. (7,125,142) . Firstly, an intraoral silicone impression (Zetaplus, Zhermack, Italy) was taken from the infant in the operation room while monitoring the baby under oxygen supply (184,229). After the impression was taken, a cast model was obtained and all the undercuts were blocked out with wax. Afterwards, NAM appliance was fabricated with cold acrylic. To stabilize the appliance, a retention button with 45° downward angulation was applied on the anterior part of the plate (Figure 3.1.2.).

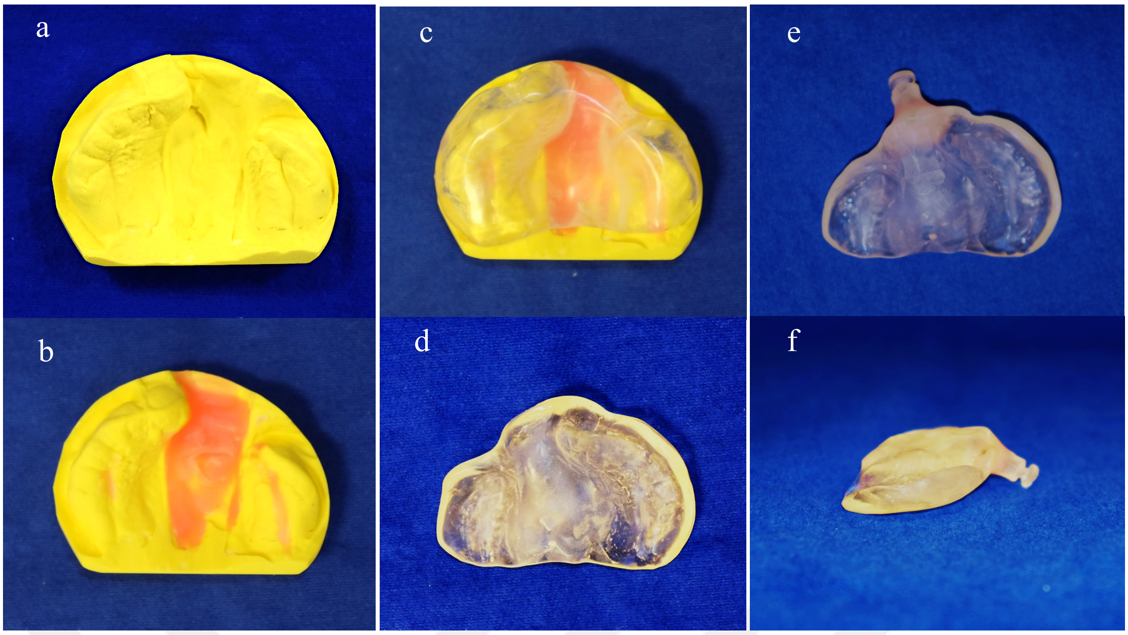

Figure 3.1.2. Fabrication of NAM appliance. (a) Cast model (b) Wax block-out (c) Acrylic appliance on the model (d) NAM appliance base (e, f) Position of the retention button

In terms of alveolar molding; soft liner was added to the inner surface of the greater segments' buccal side and hard acrylic was removed from the opposite sides' medial and inner surfaces. Removal of hard acrylic was also done from the buccal and medial surface of the plate corresponding to the lesser alveolar segment to ease its growth toward the greater segment and expansion when necessary (Figure 3.1.3.). Each session, adjustments of removing hard acrylic or adding soft liner were made without exceeding 1-1.5mm. In addition, during each activation session, grinding of posterior region was performed to prevent contact of the appliance with the pharyngeal tissues. When the alveolar segments became close enough, the acrylic between alveolar segments was completely removed. During this procedure, retention tapes and horizontal lip tapes attached to orthodontic elastics (1/4 4.5 oz. medium) were used to keep the appliance in its place and to approximate the lip segments, respectively (Figure 3.1.4.).

Nasal molding was initiated when the alveolar cleft width decreased to 5 mm or less in order to avoid creating meganostril (7). The nasal stent was bent in the shape of a swan neck from 0.8 mm of diameter stainless-steel wire. The intranasal part of the wire was bent in the shape of a kidney and then covered with hard acrylic to increase durability. Then, hard acrylic is covered with soft liner to prevent tissue irritation (Figure 3.1.5.).

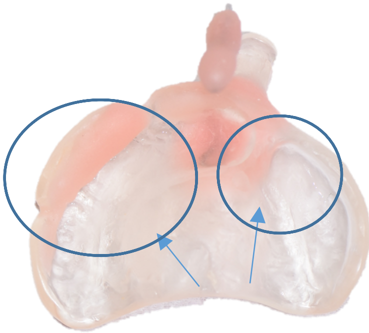

Figure 3.1.3. Activation of NAM appliance by removal of hard acrylic from the plate and addition of soft liner

Figure 3.1.4. The use of NAM plate with retention and horizontal tapes

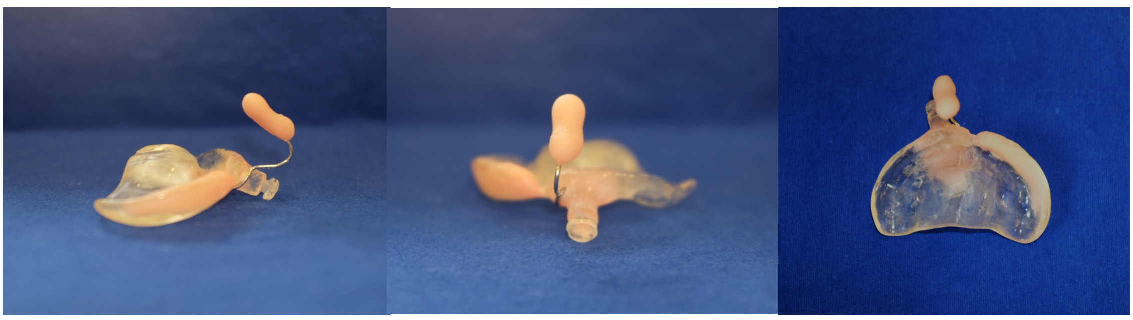

Figure 3.1.5. NAM appliance with nasal stent

During the nasal molding, activations were made either by adding soft liner to intranasal part or bending the wire (Figure 3.1.6.). Patient was followed up with weekly controls and when the desired nasoalveolar changes were obtained, treatment was terminated and the patient was referred to the surgeon for primary surgery (Figure 3.1.7.).

Figure 3.1.6. The use of NAM appliance with nasal stent

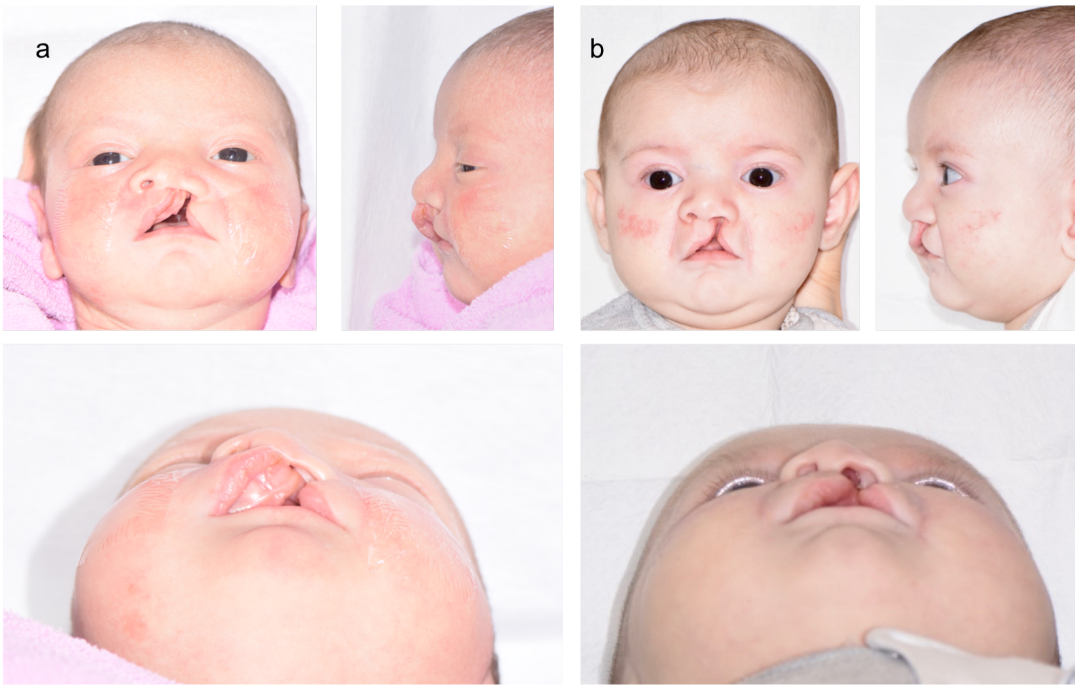

Figure 3.1.7. Pre- (a) and post- (b) treatment extra oral views of an infant with CUCLP

Control Group

Inclusion criteria for the control subjects were as follows:

- Healthy individuals without any congenital deformities, systemic and/or genetic disorders.
- Individuals whose age was corresponding to patients' age in the NAM group. (Table 3.1.3.)

The control group (10 infants; 5 females, 5 male) were composed from the healthy babies fulfilling the inclusion criteria (Figure 3.1.6.). For this purpose, the parents of the patients and the staff of Yeditepe University, Dental Hospital were informed about the aim of our study and the stereophotogrammetric record taking procedure which is a non-invasive method. The parents who were willing to participate to the study were asked to bring their babies at the matching periods of the NAM group for taking 3d records. The parents/guardians of infants signed a consent form and they voluntarily accepted to be a part of this study.

Table 3.1.3. Demographic characteristics of the control group

		Control Group (n:10)		
		Mean±SD	**Min**	**Max**
T0 (Day)		23.7±6	14	29
T1 (Day)		112.5±65.4	44	169
T1-T0 (Day)		97.8±59.1	39	158
Gender	**Male**	5	50.00%	
	Female	5	50.00%	

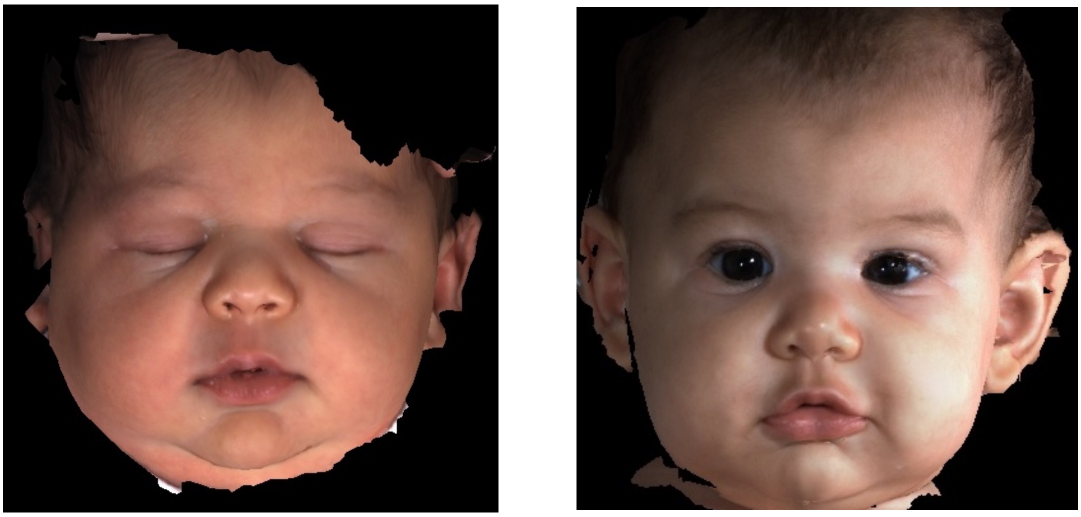

Figure 3.1.7. 3d image of an infant from control group at T0 and T1

3.2. Methods

3.2.1. Acquisition of the three-dimensional images

Three-dimensional images of the patients were taken before (T0) and after (T1) NAM treatment. 3dMDface system (3dMD LLC, Atlanta, USA) was used in order to capture 3d facial images. Same procedures of acquisition were applied to the infants in the control group at corresponding T0 and T1 periods.

The 3dMDface system has two modular units with six cameras and an industrial-grade synchronized flash system. Before starting to capture an image, stereophotogrammetry system was calibrated. Calibration required two image of a specially designed panel and the software guides the operator through the process. After calibration, the infant was summoned to the imaging room with the caregiver. Then, the caregiver sat to the designated seat which was approximately 1-meter distance to the stereophotogrammetry camera while holding the infant in an upright position, facing towards the imaging system. The orthodontist adjusted the seat's height and rotated it if needed according to the preview on the computer screen. Lastly, the orthodontist captured the image, which took approximately 1.5 millisecond through the computer and checked the image for major abnormalities, such as indistinctive areas and saved this image to patient's folder.

Figure 3.2.1. Acquisition of an image from an infant with CUCLP

3.2.2. Refinement of the Images

Three-dimensional images were imported into 3dMD Vultus software (3dMD LLC, Atlanta, USA) program. All images of the patients were stored as files (.tsb format) and refined in order to have a clearer view (Figure 3.2.2.). Initial phase of refinement was cleaning the extrafacial parts of the infant in the image, for example the parent or guardian's face or hands or the infant's body by using the paintbrush tool in the refinement section and deleting those parts (Figure 3.2.3.). Then, the residual segments were removed by dividing the image to islands (Figure 3.2.4.).

Figure 3.2.2. 3D image of an infant with CUCLP at the beginning of refinement process

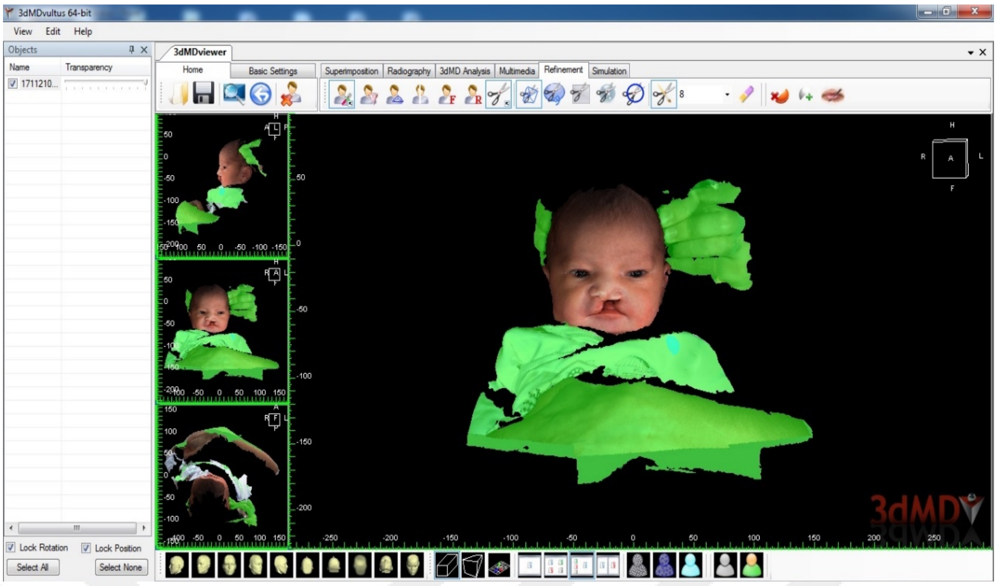

Figure 3.2.3. Use of paintbrush tool to select extra facial structures

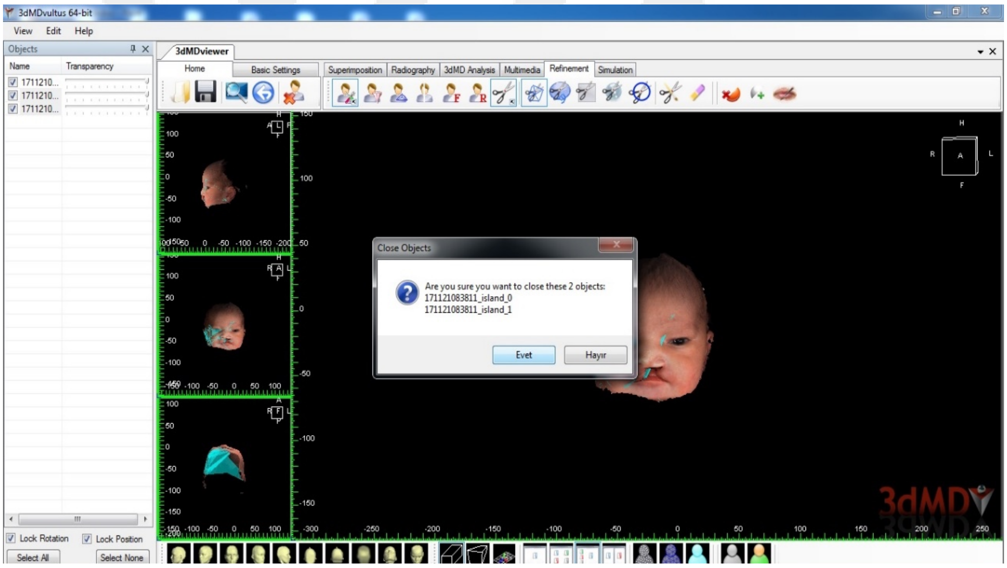

Figure 3.2.4. Dividing islands for refinement

Second phase of refinement was face orientation (Figure 3.2.5.). For each dimension (x, y, z coordinate system) it was done separately by unlocking the position and rotation options. Firstly, soft tissue nasion (n) set as (0,0,0) by using the grids. Then, head pitch was oriented to Frankfurt horizontal and after that, head roll was done by using the midsagittal plane. Finally, head yaw corrected by using the plane of the forehead from the top-down view. After these steps, the image was saved for future evaluations.

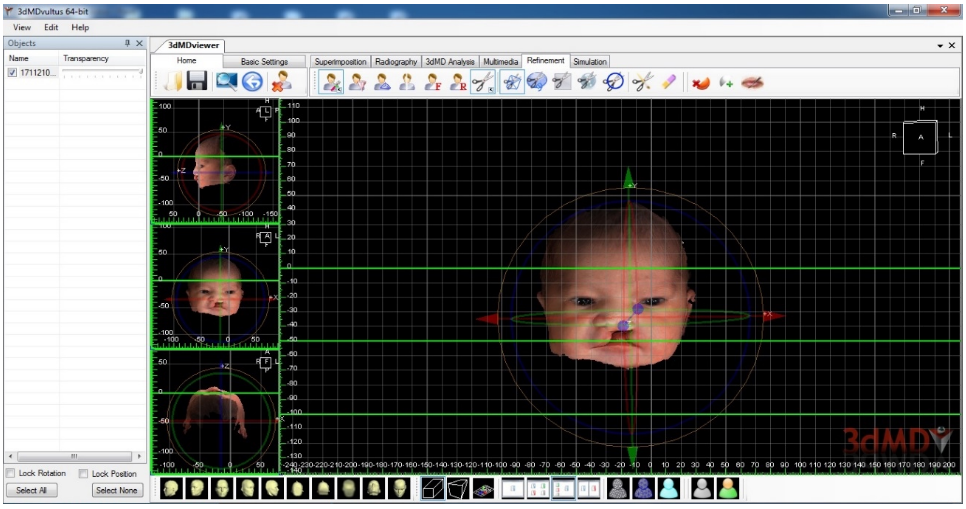

Figure 3.2.5. Use of grids and tools for head orientation.

3.2.3. Evaluating the Images

3.2.3.1. Landmarks

In our study, all landmarks were assigned on three-dimensional images by checking every point on all dimensions separately in order to avoid any mistakes. Twenty-five anatomical landmarks were used in this study. Ten points were used two times as cleft (C) and non-cleft (NC) side and 3 points were only used in NAM group. Also, in control group while choosing the landmarks, left side of the infants were designated to marked as cleft side due to epidemiological studies that were done before (42–47).

All landmarks that we used in our study are listed below (Figure 3.2.6.)

- **Soft Tissue Nasion Point (n):** Deepest concavity point on frontonasal intersection.
- **Endocanthion Point (en):** Inner commissure point of eye fissure.
- **Exocanthion Point (ex):** Outer commissure point of eye fissure.
- **Pronasale Point (prn):** Most protruded point of the nose tip.
- **Subnasale Point (sn):** Junction point between columella and upper lip on the midline.
- **Subnasale Point Cleft Side (snC):** Junction point between columella and upper lip on cleft side.

- **Subnasale Point Non-Cleft Side (snNC):** Junction point between columella and upper lip on non-cleft side.
- **Alar Point (al):** Most lateral point on the alar contour.
- **Nostril Top Point (nt):** Highest point of the nostril aperture.
- **Nostril Base Lateral Point (nbl):** Lowest lateral point of the nostril.
- **Nostril Lateral Point (z):** Most lateral point of outer contour of nostril aperture.
- **Commissure Point (ch):** Junction point of upper and lower lip.
- **Christa Philtri Point Cleft Side (cphC):** Elevated margin of the philtrum on the non-cleft vermillion line facing the cleft.
- **Christa Philtri Point on Lesser Lip (cphC'):** The corresponding point of cphC at the lesser lip.
- **Christa Philtri Point Non-Cleft Side (cphNC):** Elevated margin of the philtrum on the vermillion line on the non-cleft side.
- **Medial Lip Point (ml):** Closest point of lip to lip gap.
- **Labiale Superior Point (ls):** Midpoint of upper vermillion line.

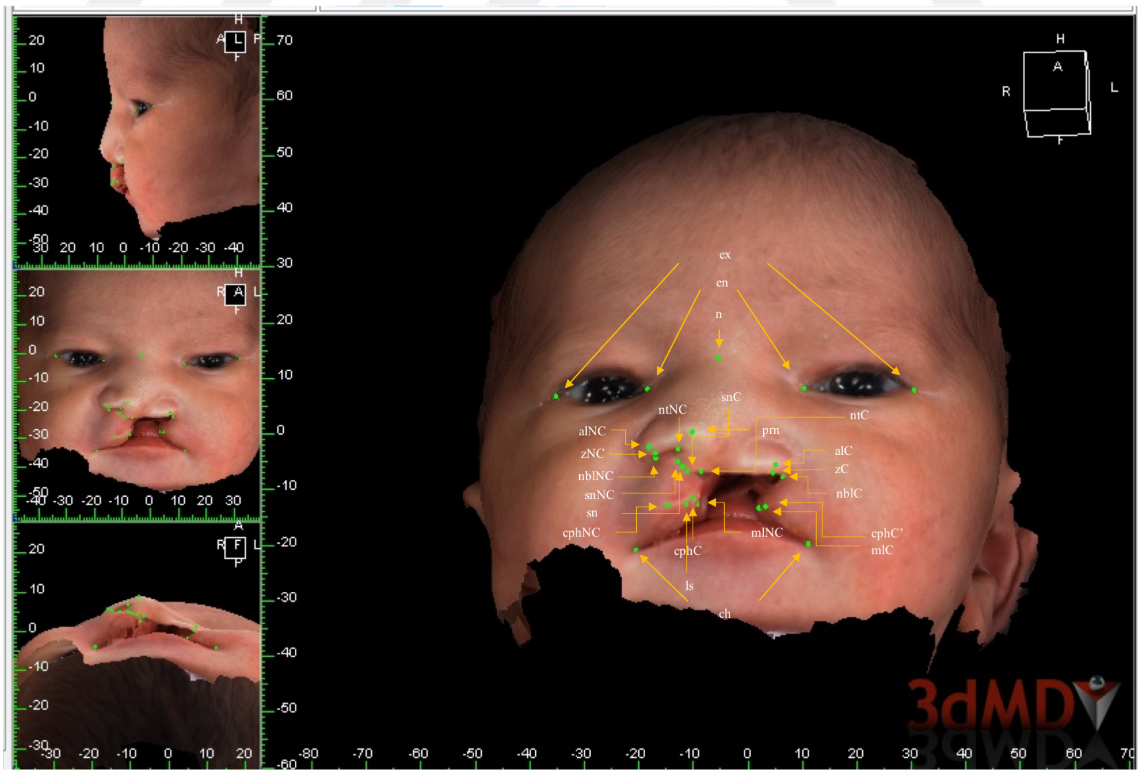

Figure 3.2.6. Landmarks

3.2.3.2. Measurements

3.2.3.2.1. Linear measurements

In this study, 36 linear measurements were used.

- **Biocular width:** The distance between exocanthions (Figure 3.2.7.).
- **Intercanthal width:** The distance between endocanthions (Figure 3.2.8.).
- **Endocanthion distance (en-n C/NC):** The distance between endocanthion and nasion (Figure 3.2.9.).
- **Exocanthion distance (ex-n C/NC):** The distance between exocanthion and nasion (Figure 3.2.10.).
- **Alar width (alC-alNC):** The distance between bilateral alar points (Figure 3.2.11.).
- **Alar distance (al-prn C/NC):** The distance between alare and pronasale (Figure 3.2.12.).
- **Nostril base width (sn-nbl C/NC):** The distance between nostril base lateral point and subnasale cleft/non-cleft (Figure 3.2.13.).
- **Nasal base width:** The distance between nostril base lateral points on both sides (Figure 3.2.14.).
- **Nostril diameter (z-sn C/NC):** The distance between nostril lateral point and subnasale cleft/non-cleft (Figure 3.2.15.).
- **Nostril height (C/NC):** The perpendicular distance between nostril top point to nostril base line (Figure 3.2.16.).
- **Nostril lateral length (nt-nbl C/NC):** The distance between nostril top and nostril base lateral point (Figure 3.2.17.).
- **Columella width:** The distance between subnasale points on cleft and non-cleft side (Figure 3.2.18.).
- **Columella height:** The distance between subnasale and pronasale (Figure 3.2.19.).
- **Columella height C:** The distance between subnasale cleft and pronasale (Figure 3.2.20.).

- **Columella height NC:** The distance between subnasale non-cleft and pronasale (Figure 3.2.21.).
- **Philtral width:** The distance between the christa philtri cleft and non-cleft side (Figure 3.2.22.).
- **Philtral height (C/NC):** The distance between christa philtri and subnasale point on cleft and non-cleft sides (Figure 3.2.23.).
- **Philtral height:** The distance between subnasale and labiale superior (Figure 3.2.24.).
- **Lip gap:** The distance between christa philtri cleft on lesser and greater lips (Figure 3.2.25.).
- **Lip distance (C/NC):** The distance between medial lip point on cleft and non-cleft side to subnasale (Figure 3.2.26).
- **Christa philtri distance C:** The distance between christa philtri on lesser lip and nasion (Figure 3.2.27.).
- **Christa philtri distance NC:** The distance between christa philtri on non-cleft side and nasion (Figure 3.2.28.).
- **Lip height C:** The distance between christa philtri on lesser lip and nostril base lateral cleft (Figure 3.2.29.).
- **Lip height NC:** The distance between christa philtri on non-cleft side and nostril base lateral non-cleft side (Figure 3.2.30.).
- **Mouth width:** The distance between commissure points (Figure 3.2.31.).
- **Lip Length C:** The distance between christa philtri on lesser lip and commissure point on cleft side (Figure 3.2.32.).
- **Lip Length NC:** The distance between christa philtri and commissure point on non-cleft side (Figure 3.2.33.).

Figure 3.2.7. Biocular width

Figure 3.2.8. Intercanthal width

Figure 3.2.9. Endocanthion distances

Figure 3.2.10. Exocanthion distances

Figure 3.2.11. Alar width

Figure 3.2.12. Alar distances

Figure 3.2.13. Nostril base widths

Figure 3.2.14. Nasal base width

Figure 3.2.15. Nostril diameters

Figure 3.2.16. Nostril heights

Figure 3.2.17. Nostril lateral lengths

Figure 3.2.18. Columella width

Figure 3.2.19. Columella height

Figure 3.2.20. Columella height C

Figure 3.2.21. Columella height NC

Figure 3.2.22. Philtral width

Figure 3.2.23. Philtral heights

Figure 3.2.24. Philtral height

Figure 3.2.25. Lip gap

Figure 3.2.26. Lip distances

Figure 3.2.27. Christa philtri distance C

Figure 3.2.28. Christa philtri distance NC

Figure 3.2.29. Lip height C

Figure 3.2.30. Lip height NC

Figure 3.2.31. Mouth width

Figure 3.2.32. Lip length C

Figure 3.2.33. Lip length NC

3.2.3.2.2. Angular measurements

In this study 3 angular measurements were used.

- **Columella inclination C:** The angle between nblC, sn and prn (Figure 3.2.34.).
- **Columella inclination NC:** The angle between nblNC, sn and prn (Figure 3.2.35.).
- **Nasal projection angle:** The angle between sn, n and prn (Figure 3.2.36.).

Figure 3.2.34. Columella inclination C

Figure 3.2.35. Columella inclination NC

Figure 3.2.36. Nasal projection angle

3.2.3.2.3. Proportional measurements

We have used 9 proportional measurement.

- **Exocanthion distance NC/C:** Nasion to ex distances' ratio between non-cleft and cleft side.

- **Nostril base width NC/C:** Nostril base widths' ratio between non-cleft and cleft side.
- **Nostril diameter NC/C:** Nostril widths' ratio between non-cleft and cleft side.
- **Alar distance NC/C:** Ratio of the distances between alare and pronasale points on both non-cleft and cleft side.
- **Philtral height NC/C:** Philtral heights' ratio between non-cleft and cleft side.
- **Nostril height NC/C:** Nostril heights' ratio between non-cleft and cleft side.
- **Nostril lateral length NC/C:** Nostril lateral lengths' ratio between non-cleft and cleft side.
- **Lip height NC/C:** Lip heights' ratio between non-cleft and cleft side.
- **Lip Length NC/C:** Lip length ch to cphs' ratio between non-cleft and cleft side.

3.2.4. Method error

In order to evaluate the method error in our study, the same researcher repeated the landmark identification and measurements on three-dimensional images of all study and control subjects with 30-day interval.

3.2.5. Statistical methods

In this study, statistical analyses were performed with the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program.

Descriptive statistics, including means and standart deviations were obtained for the data. The descripted statistics were presented as means and standart deviations for the continuos variables or as percentages for categorical variables. Normal distribution of data was tested using Shapiro-Wilk normality test. For normally distributed variables, independent t-test was used to compare study and control groups, whereas, paired t-test was used to analyze the difference between pre- and post-treatment variables. For variables that were not normally distributed Mann Whitney-U test was used to compare the measurements between two independent groups. Chi-square test was used to compare qualitative data. Significance of the results was evaluated at the level of $p < 0.05$.

Based on the observed effect size of 0.54, experimental statistical power analyses were conducted using G*power 3.1 program (Heinrich-Heine-Universität Düsseldorf, Germany) to determine the power of the study. The sample size was calculated based on the ability to detect 4.01 mm reduction in aperture base on the cleft side after NAM. The expected standard deviation of this reduction was taken from Mancini et al. 's (12) study. The calculation indicated that for a study with a power of 0.80 and alpha of 0.05, we required a total of 23 patients in the study group.

The reliability of measurements was determined by the intraclass correlation coefficient and 95% confidence interval.

4. RESULTS

4.1. Evaluation of Method Error

Intraclass correlation coefficients are considered reliable when over 0.70 (230). In order to evaluate the consistence between the first and second measurements, intraclass correlation coefficients were calculated. In this study, the lowest intraclass correlation coefficient was 0.818 and the highest intraclass correlation coefficient was 0.999. For most of the measurements, the intraclass correlation coefficient was found to be above 0.95 and for some measurements it was found to be above 0.80.

It was observed that intraclass correlation coefficients for linear measurements ranged from 0.818 to 0.999, which were above the acceptance level of 0.700 (Table 4.1.1.).

Table 4.1.1. Intraclass correlation coefficients for linear measurements

Linear measurements	Intraclass Correlation Coefficient	%95 Confidence Interval
Biocular width	0.819	(0.759-0.881)
Intercanthal width	0.818	(0.733-0.952)
Endocanthion distance C	0.857	(0.831-0.975)
Endocanthion distance NC	0.883	(0.825-0.955)
Exocanthion distance C	0.912	(0.882-0.984)
Exocanthion distance NC	0.819	(0.759-0.881)
Alar width	0.847	(0.814-0.969)
Alar distance C	0.832	(0.811-0.916)
Alar distance NC	0.833	(0.809-0.937)
Nostril base width C	0.897	(0.843-0.975)
Nostril base width NC	0.908	(0.875-0.976)
Nasal base width	0.962	(0.931-0.978)

Table 4.1.1. Intraclass correlation coefficients for linear measurements (continued)

Linear measurements	Intraclass Correlation Coefficient	%95 Confidence Interval
Nostril diameter C	0.999	(0.997-0.999)
Nostril diameter NC	0.998	(0.996-0.999)
Nostril height C	0.998	(0.996-0.999)
Nostril height NC	0.902	(0.854-0.934)
Nostril lateral length C	0.995	(0.993-0.997)
Nostril lateral length NC	0.894	(0.842-0.929)
Columella width	0.977	(0.966-0.985)
Columella height	0.992	(0.988-0.995)
Columella height C	0.996	(0.994-0.997)
Columella height NC	0.977	(0.966-0.984)
Philtral width	0.901	(0.864-0.994)
Philtral height C	0.866	(0.745-0.928)
Philtral height NC	0.847	(0.814-0.969)
Philtral height	0.847	(0.814-0.969)
Lip gap	0.943	(0.895-0.982)
Lip distance C	0.867	(0.822-0.934)
Lip distance NC	0.943	(0.895-0.982)
Christa philtri distance C	0.977	(0.966-0.985)
Christa philtri distance NC	0.906	(0.853-0.951)
Lip height C	0.832	(0.811-0.916)
Lip height NC	0.833	(0.809-0.937)
Mouth width	0.897	(0.843-0.975)
Lip length C	0.857	(0.831-0.975)
Lip length NC	0.883	(0.825-0.955)

It was observed that all the angular measurements' intraclass correlation coefficients ranged from 0.849 to 0.995, which were above the acceptance level of 0.700 (Table 4.1.2.).

Table 4.1.2. Intraclass correlation coefficients for angular measurements

Angular measurements	Intraclass Correlation Coefficient	%95 Confidence Interval
Columella inclination C	0.983	(0.970-0.986)
Columella inclination NC	0.995	(0.993-0.997)
Nasal projection angle	0.849	(0.829-0.933)

It was observed that all the proportional measurements' intraclass correlation coefficients ranged from 0.832 to 0.991, which were above the acceptance level of 0.700 (Table 4.1.3.).

Table 4.1.3. Intraclass correlation coefficients for proportional measurements

Proportional measurements	Intraclass Correlation Coefficient	%95 Confidence Interval
Exocanthion distance NC/C	0.991	(0.987-0.994)
Alar distance NC/C	0.943	(0.895-0.982)
Nostril base width NC/C	0.839	(0.806-0.921)
Nostril diameter NC/C	0.871	(0.841-0.908)
Philtral height NC/C	0.841	(0.798-0.923)
Nostril height NC/C	0.913	(0.897-0.970)
Nostril lateral length NC/C	0.866	(0.745-0.928)
Lip height NC/C	0.832	(0.811-0.916)
Lip length NC/C	0.990	(0.985-0.993)

4.2. Comparison of Demographic Data of NAM and Control Subjects

The demographic data of NAM and control group was evaluated (Table 4.2.1.). There was no statistically significant difference in the mean age of the groups at T0, at T1, the treatment duration of NAM group and observation period of control group ($p>0.05$). No significant difference was found in gender distribution between groups ($p>0.05$).

Table 4.2.1. Comparison of demographic data of NAM and control groups with independent t-test and chi square test

		NAM Group (n:39)			Control Group (n:10)			p
		Mean±SD	Min	Max	Mean±SD	Min	Max	
T0 (Day)		23.1±6.5	12	30	23.7±6	14	29	0.785
T1 (Day)		99.3±32.7	68	135	112.5±65.4	44	169	0.369
T1-T0 (Day)		76.2±27.9	46	105	97.8±59.1	39	158	0.094
Gender	Male	20	51.28%		5	50.00%		0.942
	Female	19	48.72%		5	50.00%		

4.3. Comparison of Linear, Angular and Proportional Measurements Between NAM and Control Groups at T0

The comparison of NAM and control groups' measurements at the baseline were given in Table 4.3.1. At T0, in the ocular region, there was no statistically significant differences in biocular and intercanthal widths, endocanthion distance NC, exocanthion distance C and NC measurements between groups ($p>0.05$), whereas endocanthion distance C was significantly greater in the NAM group compared to control group ($p<0.01$).

When the facial middle third was evaluated; alar width, alar distance C, nostril base width C,nasal base width, nostril diameter C and nostril lateral length C were statistically significantly larger in the NAM group ($p<0.001$), whereas nostril diameter NC, nostril height C, columella width, columella height, columella height C and NC were significantly smaller in the NAM group ($p<0.01$, $p<0.001$, $p<0.05$, $p<0.001$, $p<0.01$, $p<0.01$ respectively). On the other hand, no significant differences were found in alar distance NC, nostril base width NC, nostril height NC and nostril lateral length NC between both groups ($p>0.05$).

For the labial complex, philtral height C and NC, philtral height, lip height C values were smaller in the NAM group ($p<0.001$), as well as, christa philtri distance C, lip height NC and lip length C ($p<0.05$, $p<0.01$, $p<0.01$, respectively). In the contrary, mouth width measurement found to be larger in the NAM group ($p<0.05$). The remaining measurements showed insignificant differences between the groups ($p>0.05$).

Table 4.3.1. Comparison of linear measurements at T0 between NAM and control groups with independent t test

Linear measurements (mm)	T0						p
	NAM group (n:39)			Control Group (n:10)			
	Mean±SD	Min	Max	Mean±SD	Min	Max	
Biocular width	64.49±3.71	57.17	73.25	62.72±1.9	59.98	65.25	0.303
Intercanthal width	25.69±2.85	19.34	33.15	23.09±1.27	21.47	23.39	0.052
Endocanthion distance C	15.73±1.86	11.78	22.07	13.28±0.65	12.69	14.3	**0.006****
Endocanthion distance NC	13.96±2.96	10.31	18.59	12.96±0.73	12.05	13.95	0.462
Exocanthion distance C	36.27±2.84	31.15	44.72	33.77±1.47	31.53	35.43	0.061
Exocanthion distance NC	33.21±2.92	27.02	39.74	33.1±2.06	30.8	35.62	0.934
Alar width	23.47±2.02	19.12	27.97	18.58±1.57	16.36	20.6	**0.0001*****
Alar distance C	15.8±1.62	13.42	19.6	11.12±1.24	9.52	12.25	**0.0001*****
Alar distance NC	10.84±1.24	8.6	13.42	10.83±0.8	9.85	12.01	0.987
Nostril base width C	15.39±2.34	9.81	20.15	4.03±0.83	3.2	5.16	**0.0001*****
Nostril base width NC	3.69±0.9	1.35	5.62	3.95±0.93	3.06	5.09	0.543
Nasal base width	21.23±2.46	14.17	25.17	12.51±1.83	10.10	14.49	**0.0001*****
Nostril diameter C	13.85±2.12	9.78	18.1	5.54±0.67	4.91	6.66	**0.0001*****
Nostril diameter NC	4.49±1.01	3.04	7.28	5.86±0.57	5.01	6.41	**0.005****
Nostril height C	1.52±1.14	0.18	5.78	4.2±0.7	3.45	4.97	**0.0001*****
Nostril height NC	3.91±0.98	2.3	6.9	4.16±0.28	3.7	4.38	0.569
Nostril lateral length C	11.26±2.84	7.33	16.75	5.46±0.75	4.22	6.06	**0.0001*****
Nostril lateral length NC	6.11±1.03	4.11	9.03	5.27±0.46	4.71	6	0.084
Columella width	3.75±0.92	2.22	5.73	4.83±0.6	4.04	5.67	**0.014***
Columella height	7.77±1.05	5.57	9.91	9.68±1.1	7.84	10.77	**0.0001*****
Columella height C	8.02±1.09	5.33	10.53	9.6±0.58	8.81	10.41	**0.003****

Table 4.3.1. Comparison of linear measurements at T0 between NAM and control groups with independent t test (continued)

Linear measurements (mm)	T0						p
	NAM group (n:39)			Control Group (n:10)			
	Mean±SD	Min	Max	Mean±SD	Min	Max	
Columella height NC	7.94±1.09	5.7	10.05	9.51±0.55	8.59	10.03	**0.003****
Philtral width	6.39±1.36	3.4	10.43	6.49±0.45	6.09	7.26	0.865
Philtral height	8.04±1.08	6.19	11.21	11.67±1.4	9.2	12.55	**0.0001*****
Philtral height C	4.58±1.17	2.32	7.92	12.1±1	10.44	12.53	**0.0001*****
Philtral height NC	9.78±1.2	7.28	12.39	12.11±0.75	11	12.95	**0.0001*****
Christa philtri distance C	29.82±2.42	26.12	35.48	32.76±2.37	30.11	35.57	**0.014***
Christa philtri distance NC	31.58±2.36	27.85	37	32.86±2.36	30.79	35.47	0.258
Lip height C	6.44±1.75	2.53	10.98	12.2±1.31	10.53	13.76	**0.0001*****
Lip height NC	10.57±1.13	8.07	14.01	12.21±1.39	10.82	14.07	**0.005****
Mouth width	30.26±3.16	24.48	40.16	26.63±0.78	26.1	27.66	**0.015***
Lip length C	11.86±1.71	8.48	15.55	14.57±0.89	13.49	15.52	**0.001****
Lip length NC	12.58±1.74	9.45	17.83	14.09±0.91	13.26	15.51	0.064

(***) p <0.001, (**) p <0.01, (*) p <0.05

The comparison of initial angular measurements between the NAM and control group revealed that, in the NAM group, columella inclination NC was found significantly higher (p<0.001), whereas, nasal projection angle and columella inclination C was smaller (p<0.001, p<0.05, respectively), (Table 4.3.2.).

Table 4.3.2. Comparison of angular measurements at T0 between NAM and control groups with independent t test

Angular (°) measurements	T0						p
	NAM group (n:39)			Control Group (n:10)			
	Mean±SD	Min	Max	Mean±SD	Min	Max	
Columella inclination C	81.21±9.64	58.24	93.74	90.09±5.95	81.09	95.84	**0.048***
Columella inclination NC	110.38±11.31	87.82	142.09	90.69±5.89	82	97.34	**0.0001*****
Nasal projection angle	17.92±2.94	12.44	23.82	26.36±1.74	24.55	28.46	**0.0001*****

(***) p <0.001, (*) p <0.05

NAM and control groups' proportional measurements at T0 were shown in Table 4.3.3. All of the proportional measurements were found to be significantly different between groups (p<0.05), except for exocanthion distance NC/C and lip length NC/C (p>0.05).

Table 4.3.3. Comparison of proportional measurements at T0 between NAM and Control Groups with independent t test

Proportional measurements	T0						p
	NAM group (n:39)			Control Group (n:10)			
	Mean±SD	Min	Max	Mean±SD	Min	Max	
Exocanthion distance NC/C	0.92±0.09	0.52	1.11	0.98±0.04	0.93	1.04	0.145
Alar distance NC/C	0.69±0.1	0.48	0.96	0.97±0.05	0.9	1.03	**0.0001*** **
Nostril base width NC/C	0.25±0.07	0.07	0.41	0.98±0.02	0.95	1	**0.0001*** **
Nostril diameter NC/C	0.33±0.09	0.18	0.6	1.06±0.08	0.98	1.14	**0.0001*** **
Nostril height NC/C	3.88±3.24	0.93	7.9	0.99±0.10	0.86	1.09	**0.048* **
Nostril lateral length NC/C	0.58±0.19	0.32	1.32	0.96±0.05	0.88	1	**0.0001*** **
Philtral height NC/C	2.25±0.57	1.46	4.46	1±0.03	0.97	1.05	**0.0001*** **
Lip height NC/C	1.77±0.67	1.12	5.11	1±0.04	0.95	1.04	**0.014* **
Lip length NC/C	1.07±0.12	0.86	1.43	0.96±0.12	0.88	1.17	0.065

(***) p <0.001, (*) p <0.05

4.4. Comparison of Linear, Angular and Proportional Measurements of NAM Group at T0 and T1

When linear measurements of NAM group at T0 and T1 were evaluated, it was found that in ocular region; biocular width, endocanthion distance NC, exocanthion distance C and NC increased significantly ($p<0.001$, $p<0.05$, $p<0.01$, $p<0.001$ respectively), (Table 4.4.1). However, there was no significant change in intercanthal width and endocanthion distance C ($p>0.05$).

In the nasal region; alar width, alar distance NC, nostril diameter NC, nostril height NC, columella width, columella height, columella height C and NC increased significantly at T1 ($p<0.05$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.05$, $p<0.001$, $p<0.001$ and

$p<0.001$, respectively) while, alar distance C, nostril base width NC and nostril lateral length NC and C did not change ($p>0.05$). On the other hand, nostril base width C, nasal base width and nostril diameter C decreased significantly ($p<0.001$, $p<0.01$, $p<0.001$, respectively). The increase in the nostril height C with a mean value of 2.97±1.71 mm was found to be statistically significant ($p<0.001$).

When the lower third of the facial region was assessed; philtral width and mouth width slightly increased ($p<0.01$ and $p<0.05$); philtral height, philtral height C and NC, lip distance NC, christa philtri distance C and NC, lip height C and NC, lip length C and NC and lastly, lip length C and NC increased significantly ($p<0.001$). Whereas, lip gap and lip distance C decreased ($p<0.001$).

Table 4.4.1. Comparison of linear measurements of NAM group at T0 and T1 with paired t test

Linear measurements (mm)	NAM group (n:39)							p
	T0			T1			T1-T0	
	Mean±SD	Min	Max	Mean±SD	Min	Max	Mean±SD	
Biocular width	64.49±3.71	57.17	73.25	69.05±3.51	59.94	78.24	4.56±2.74	**0.0001*** **
Intercanthal width	25.69±2.85	19.34	33.15	26.12±2.58	20.95	31.65	0.43±2.2	0.23
Endocanthion distance C	15.73±1.86	11.78	22.07	15.6±1.66	12.28	19.22	-0.12±1.72	0.659
Endocanthion distance NC	13.96±2.96	10.31	18.59	14.99±1.85	12.07	19.17	1.03±2.56	**0.016***
Exocanthion distance C	36.27±2.84	31.15	44.72	37.63±2.28	31.02	41.87	1.35±2.45	**0.001****
Exocanthion distance NC	33.21±2.92	27.02	39.74	36.34±2.36	31.72	42.31	3.13±2.44	**0.0001*** **
Alar width	23.47±2.02	19.12	27.97	24.02±1.97	19.89	28.87	0.54±1.62	**0.043***
Alar distance C	15.8±1.62	13.42	19.6	15.79±1.53	12.94	19.49	-0.01±1.49	0.963
Alar distance NC	10.84±1.24	8.6	13.42	12.01±1.5	8.68	15.3	1.18±1.44	**0.0001*** **
Nostril base width C	15.39±2.34	9.81	20.15	13±2.45	10.06	17.7	-2.38±2.93	**0.0001*** **
Nostril base width NC	3.69±0.9	1.35	5.62	4±1.3	1.86	7.22	0.31±1.37	0.159
Nasal base width	21.23±2.46	14.17	25.17	19.86±86	15.63	24.85	-1.37±2.45	**0.001****
Nostril diameter C	13.85±2.12	9.78	18.1	12.47±1.58	9.66	14.97	-1.38±1.95	**0.0001*** **
Nostril diameter NC	4.49±1.01	3.04	7.28	5.48±1.37	3.11	8.62	0.99±1.24	**0.0001*** **
Nostril height C	1.52±1.14	0.18	5.78	4.49±1.55	0.86	7.85	2.97±1.71	**0.0001*** **
Nostril height NC	3.91±0.98	2.3	6.9	4.79±1.12	2.11	6.95	0.88±1.11	**0.0001*** **
Nostril lateral length C	11.26±2.84	7.33	16.75	10.34±2.62	6.51	15.22	-0.92±3.29	0.088
Nostril lateral length NC	6.11±1.03	4.11	9.03	6.39±1.16	2.94	9.2	0.29±1.18	0.135
Columella width	3.75±0.92	2.22	5.73	4.22±1.16	2	6.56	0.47±1.18	**0.018***

Table 4.4.1. Comparison of linear measurements of NAM group at T0 and T1 with paired t test (continued)

Linear measurements (mm)	NAM group (n:39)							p
	T0			T1			T1-T0	
	Mean±SD	Min	Max	Mean±SD	Min	Max	Mean±SD	
Columella height	7.77±1.05	5.57	9.91	9.2±1.32	5.95	11.8	1.43±1.25	**0.0001*** **
Columella height C	8.02±1.09	5.33	10.53	9.76±1.3	6.87	12	1.74±1.19	**0.0001*** **
Columella height NC	7.94±1.09	5.7	10.05	9.42±1.27	6.07	12.48	1.48±1.43	**0.0001*** **
Philtral width	6.39±1.36	3.4	10.43	7.18±1.23	4.72	10.17	0.79±1.39	**0.001** **
Philtral height	8.04±1.08	6.19	11.21	9.68±1.43	7.04	13.54	1.64±1.52	**0.0001*** **
Philtral height C	4.58±1.17	2.32	7.92	6.08±1.45	3.12	9.53	1.5±1.81	**0.0001*** **
Philtral height NC	9.78±1.2	7.28	12.39	11.18±1.54	8.21	14.6	1.4±1.48	**0.0001*** **
Lip gap	14.25±3.36	6.57	20.57	10.12±2.65	5.43	15.82	-4.13±3.46	**0.0001*** **
Lip distance C	16.7±2.24	11.74	22.25	14.57±2.19	10.22	20.15	-2.13±2.45	**0.0001*** **
Lip distance NC	7.85±1.33	6	11.86	9.52±1.28	6.43	11.57	1.67±1.89	**0.0001*** **
Christa philtri distance C	29.82±2.42	26.12	35.48	33.37±2.32	29.57	37.93	3.54±2.73	**0.0001*** **
Christa philtri distance NC	31.58±2.36	27.85	37	36.03±2.48	30.4	41.12	4.45±2.39	**0.0001*** **
Lip height C	6.44±1.75	2.53	10.98	8.07±1.75	4.95	13.44	1.63±1.84	**0.0001*** **
Lip height NC	10.57±1.13	8.07	14.01	11.98±1.21	10.31	14.81	1.41±1.2	**0.0001*** **
Mouth width	30.26±3.16	24.48	40.16	31.9±2.89	25.68	37.35	1.65±4.24	**0.02***
Lip length C	11.86±1.71	8.48	15.55	13.85±2.25	9.03	20.13	1.99±2.79	**0.0001*** **
Lip length NC	12.58±1.74	9.45	17.83	13.98±2.05	10.37	20.09	1.4±2.28	**0.0001*** **

(***) p <0.001, (**) p <0.01, (*) p <0.05

The evaluation of the angular measurements of the NAM group at T0 and T1 revealed that columella inclination C and nasal projection angle was increased (p<0.001 and p<0.01, respectively) (Table 4.4.2.). On the other hand, columella inclination NC did not change significantly (p>0.05).

Table 4.4.2. Comparison of angular measurements of NAM group at T0 and T1 with paired t test

Angular (°) measurements	NAM group (n:39)							p
	T0			T1			T1-T0	
	Mean±SD	Min	Max	Mean±SD	Min	Max	Mean±SD	
Columella inclination C	81.21±9.64	58.2	93.7	90.15±9.19	74.4	118.6	8.94±11.4	**0.0001*** **
Columella inclination NC	110.38±11.3	87.8	142.1	106.93±12.8	74.1	142.4	-3.45±15.3	0.168
Nasal projection angle	17.92±2.94	12.4	23.8	19.27±3.11	11.5	27.5	1.35±3	**0.008** **

(***) p <0.001, (**) p <0.01

The changes in the proportional measurements of the NAM group were given in Table 4.4.3. All of the proportional measurements significantly changed (p<0.05), except for the nostril lateral length NC/C and lip length NC/C (p>0.05).

Table 4.4.3. Comparison of proportional measurements of NAM group at T0 and T1 with paired t test

Proportional measurements	NAM group (n:39)							p
	T0			T1			T1-T0	
	Mean±SD	Min	Max	Mean±SD	Min	Max	Mean±SD	
Exocanthion distance NC/C	0.92±0.09	0.52	1.11	0.97±0.04	0.9	1.07	0.05±0.09	**0.001****
Alar distance NC/C	0.69±0.10	0.48	0.96	0.77±0.11	0.51	1.06	0.07±0.12	**0.0001*****
Nostril base width NC/C	0.25±0.07	0.07	0.41	0.32±0.12	0.13	0.62	0.07±0.11	**0.0001*****
Nostril diameter NC/C	0.33±0.09	0.18	0.6	0.45±0.14	0.25	0.81	0.12±0.12	**0.0001*****
Nostril height NC/C	3.88±3.24	0.93	7.9	1.23±0.55	0.62	2.86	-2.66±3.06	**0.0001ǂ*****
Nostril lateral length NC/C	0.58±0.19	0.32	1.32	0.70±0.42	0.33	3.05	0.12±0.45	0.110ǂ
Philtral height NC/C	2.25±0.57	1.46	4.46	1.91±0.38	1.34	2.93	-0.34±0.68	**0.004****
Lip height NC/C	1.77±0.67	1.12	5.11	1.55±0.34	0.77	2.59	-0.23±0.6	**0.024***
Lip length NC/C	1.07±0.12	0.86	1.43	1.02±0.16	0.75	1.41	-0.05±0.19	0.134ǂ

(***) p <0.001, (**) p <0.01, (*) p <0.05

4.5. Comparison of Linear, Angular and Proportional Measurements of Control Group Between T0 and T1

Evaluation of the control group's linear measurements at T0 and T1 showed that nostril base width C, nostril diameter NC, columella width, philtral height C, philtral height, lip height C and NC did not change ($p>0.05$) whereas the other measurements increased significantly ($p<0.05$), (Table 4.5.1.).

Table 4.5.1. Comparison of linear measurements of control group at T0 and T1 with paired t test

Linear measurements (mm)	Control Group (n:10)							p
	T0			T1			T1-T0	
	Mean±SD	Min	Max	Mean±SD	Min	Max	Mean±SD	
Biocular width	62.72±1.9	59.98	65.25	67.46±4.06	62.88	72.36	4.74±2.53	**0.014***
Intercanthal width	23.09±1.27	21.47	23.39	25.63±2.06	23.39	27.87	2.53±1.81	**0.035***
Endocanthion distance C	13.28±0.65	12.69	14.3	14.97±0.63	14.04	15.68	1.69±0.86	**0.012***
Endocanthion distance NC	12.96±0.73	12.05	13.95	14.93±1.22	13.17	16.44	1.97±1.21	**0.022***
Exocanthion distance C	33.77±1.47	31.53	35.43	36.51±1.79	34.19	38.9	2.74±0.64	**0.001****
Exocanthion distance NC	33.1±2.06	30.8	35.62	36.22±2.98	32.82	39.71	3.12±2.07	**0.028***
Alar width	18.58±1.57	16.36	20.6	21.2±1.05	19.42	22.11	2.62±1.27	**0.01***
Alar distance C	11.12±1.24	9.52	12.25	13.01±0.89	11.7	13.48	1.89±1.18	**0.024***
Alar distance NC	10.83±0.8	9.85	12.01	12.71±0.85	11.92	13.64	1.88±0.40	**0.0001*****
Nostril base width C	4.03±0.83	3.2	5.16	4.88±1.28	3.47	6.11	0.85±0.94	0.115
Nostril base width NC	3.95±0.93	3.06	5.09	4.79±0.73	4.02	5.89	0.84±0.49	**0.018***
Nasal base width	12.51±1.83	10.10	14.49	12.81±2.41	1.27	16.15	0.3±1.21	0.608
Nostril diameter C	5.54±0.67	4.91	6.66	6.47±0.54	5.77	7.25	0.93±0.55	**0.019***
Nostril diameter NC	5.86±0.57	5.01	6.41	6.81±0.63	5.99	7.72	0.95±1.05	0.115
Nostril height C	4.2±0.7	3.45	4.97	4.75±0.69	3.94	5.51	0.55±0.11	**0.0001*****
Nostril height NC	4.16±0.28	3.7	4.38	4.72±0.4	4.37	5.25	0.55±0.37	**0.029***
Nostril lateral length C	5.46±0.75	4.22	6.06	6.23±0.81	4.94	6.84	0.77±0.16	**0.0001*****
Nostril lateral length NC	5.27±0.46	4.71	6	6.04±0.69	5.48	6.9	0.77±0.50	**0.026***

Table 4.5.1. Comparison of linear measurements of control group at T0 and T1 with paired t test (continued)

Linear measurements (mm)	Control Group (n:10)							p
	T0			T1			T1-T0	
	Mean±SD	Min	Max	Mean±SD	Min	Max	Mean±SD	
Columella width	4.83±0.6	4.04	5.67	5.28±0.69	4.76	6.44	0.45±0.64	0.192
Columella height	9.68±1.1	7.84	10.77	11.08±1	9.83	12.41	1.4±0.97	**0.032***
Columella height C	9.6±0.58	8.81	10.41	10.76±0.46	10.17	11.24	1.16±0.39	**0.003****
Columella height NC	9.51±0.55	8.59	10.03	10.68±0.48	9.98	11.29	1.17±0.62	**0.014***
Philtral width	6.49±0.45	6.09	7.26	7.13±0.36	6.67	7.67	0.64±0.30	**0.009****
Philtral height	11.67±1.4	9.2	12.55	12.48±1.9	9.21	13.92	0.81±0.75	0.074
Philtral height C	12.1±1	10.44	12.53	12.44±1.13	10.62	13.72	0.34±0.27	0.051
Philtral height NC	12.11±0.75	11	12.95	12.46±0.75	11.49	13.37	0.36±0.28	**0.046***
Christa philtri distance C	32.76±2.37	30.11	35.57	38.09±1.86	35.36	40.03	5.33±2.00	**0.004****
Christa philtri distance NC	32.86±2.36	30.79	35.47	38±1.68	35.44	39.51	5.14±2.12	**0.006****
Lip height C	12.2±1.31	10.53	13.76	13.08±1.16	11.11	13.98	0.88±1.04	0.132
Lip height NC	12.21±1.39	10.82	14.07	13.05±1.00	11.95	14.3	0.84±0.80	0.078
Mouth width	26.63±0.78	26.1	27.66	30.5±2.14	27.17	32.72	3.87±2.38	**0.022***
Lip length C	14.57±0.89	13.49	15.52	16.84±0.41	16.18	17.2	2.27±0.74	**0.002****
Lip length NC	14.09±0.91	13.26	15.51	16.41±0.55	15.86	17.23	2.32±0.67	**0.002****

(***) p <0.001, (**) p <0.01, (*) p <0.05

Evaluation of the angular measurements revealed that columella inclination C and NC increased significantly ($p<0.05$) whereas nasal projection angle decreased ($p<0.05$) (Table 4.5.2).

Table 4.5.2. Comparison of angular measurements of control group at T0 and T1 with paired t test

Angular (°) measurements	Control Group (n:10)							p
	T0			T1			T1-T0	
	Mean±SD	Min	Max	Mean±SD	Min	Max	Mean±SD	
Columella inclination C	90.09±5.95	81.09	95.84	94.65±6.29	85.6	102.39	4.56±2.70	**0.019***
Columella inclination NC	90.69±5.89	82	97.34	95.34±3.91	88.67	98.52	4.64±2.62	**0.017***
Nasal projection angle	26.36±1.74	24.55	28.46	23.83±1.32	21.7	25.33	-2.53±1.36	**0.014***

(*) p <0.05

No significant changes were found for the control group's proportional measurements between T0 and T1 (Table 4.5.3.).

Table 4.5.3. Comparison of proportional measurements of control group at T0 and T1 with paired t test

Proportional measurements	Control Group (n:10)							p
	T0			T1			T1-T0	
	Mean±SD	Min	Max	Mean±SD	Min	Max	Mean±SD	
Exocanthion distance NC/C	0.98±0.04	0.93	1.04	0.99±0.05	0.91	1.02	0.01±0.06	0.648
Alar distance NC/C	0.97±0.05	0.9	1.03	0.98±0.07	0.89	1.07	0.01±0.04	0.505
Nostril base width NC/C	0.98±0.02	0.95	1	0.98±0.02	0.95	1	0.01±0.03	0.697
Nostril diameter NC/C	1.06±0.08	0.98	1.14	1.05±0.16	0.87	1.2	-0.01±0.13	0.899
Nostril height NC/C	0.99±0.10	0.86	1.09	0.99±0.03	0.95	1.02	0±0.10	0.965
Nostril lateral length NC/C	0.96±0.05	0.88	1	0.93±0.08	0.81	1.01	-0.03±0.10	0.530
Philtral height NC/C	1±0.031	0.97	1.05	1±0.026	0.96	1.03	0±0.04	0.918
Lip height NC/C	1±0.04	0.95	1.04	1±0.03	0.96	1.03	-0.01±0.03	0.646
Lip length NC/C	0.96±0.12	0.88	1.17	0.97±0.04	0.92	1	0.01±0.14	0.929

4.6. Comparison of Linear, Angular and Proportional Changes of NAM and Control Group

The changes in interchantal width, endocanthion distance C, alar width, alar distance C, nostril base width C, nasal base width, nostril diameter C, nostril height C and philtral height NC were statistically different between groups ($p<0.05$) (Table 4.6.1.). On the other hand, there was no statistically difference between groups in terms of the other measurements ($p>0.05$).

Table 4.6.1. Comparison of linear changes between NAM and control groups with Mann Whitney U test

Linear measurements (mm)	T1-T0						p
	NAM group (n:39)			Control Group (n:10)			
	Mean±SD	Min	Max	Mean±SD	Min	Max	
Biocular width	4.56±2.74	-1.3	11.37	4.74±2.53	2.11	7.73	0.853
Intercanthal width	0.43±2.2	-5.97	6.23	2.53±1.81	0.61	5.36	**0.033***
Endocanthion distance C	-0.12±1.72	-7.04	2.41	1.69±0.86	0.68	2.99	**0.006****
Endocanthion distance NC	1.03±2.56	-2.96	13.38	1.97±1.21	0.49	3.73	0.085
Exocanthion distance C	1.35±2.45	-7.53	5.71	2.74±0.64	1.74	3.47	0.144
Exocanthion distance NC	3.13±2.44	-0.67	7.68	3.12±2.07	0.97	5.52	0.868
Alar width	0.54±1.62	-3.28	3.65	2.62±1.27	0.6	3.97	**0.011***
Alar distance C	-0.01±1.49	-3.04	2.91	1.89±1.18	0.5	3.39	**0.011***
Alar distance NC	1.18±1.44	-1.54	4.55	1.88±0.40	1.46	2.48	0.365
Nostril base width C	-2.38±2.93	-14.24	3.74	0.85±0.94	0.06	2.2	**0.003****
Nostril base width NC	0.31±1.37	-3.31	3.23	0.84±0.49	0.02	1.26	0.292
Nasal base width	-1.37±2.45	-6.61	1.21	0.3±1.21	-0.61	2.37	**0.032***
Nostril diameter C	-1.38±1.95	-6.82	2.9	0.93±0.55	0.22	1.65	**0.005****
Nostril diameter NC	0.99±1.24	-0.74	4.36	0.95±1.05	0.19	2.71	0.926
Nostril height C	2.97±1.71	-0.64	7.28	0.55±0.11	0.49	0.74	**0.004****
Nostril height NC	0.88±1.11	-1.55	3.24	0.55±0.37	0.1	1.05	0.355
Nostril lateral length C	-0.92±3.29	-12.03	5.25	0.77±0.16	0.62	1.05	0.100
Nostril lateral length NC	0.29±1.18	-3.06	4.07	0.77±0.5	0.25	1.46	0.160
Columella width	0.47±1.18	-2.41	3.19	0.45±0.64	-0.31	1.37	0.839
Columella height	1.43±1.25	-1.02	3.7	1.4±0.97	0.1	2.66	0.956
Columella height C	1.74±1.19	-0.24	4.11	1.16±0.39	0.75	1.64	0.244
Columella height NC	1.48±1.43	-1.24	4.41	1.17±0.62	0.19	1.91	0.542
Philtral width	0.79±1.39	-2.46	3.64	0.64±0.30	0.3	1.07	0.725

Table 4.6.1. Comparison of linear changes between NAM and control groups with Mann Whitney U test (continued)

Linear measurements (mm)	T1-T0						p
	NAM group (n:39)			Control Group (n:10)			
	Mean±SD	Min	Max	Mean±SD	Min	Max	
Philtral height	1.64±1.52	-1.43	4.77	0.81±0.75	0.01	1.98	0.215
Philtral height C	1.5±1.81	-1.18	6.17	0.34±0.27	0.09	0.65	0.125
Philtral height NC	1.4±1.48	-2.64	4.59	0.36±0.28	0.07	0.49	**0.025***
Christa philtri distance C	3.54±2.73	-3.07	9.28	5.33±2	3.01	8.22	0.108
Christa philtri distance NC	4.45±2.39	0.06	10.93	5.14±2.12	2.71	7.97	0.437
Lip height C	1.63±1.84	-2	7.16	0.88±1.04	0.02	2.58	0.275
Lip height NC	1.41±1.2	-1.45	4.14	0.84±0.8	0.17	2.09	0.237
Mouth width	1.65±4.24	-11.08	9.2	3.87±2.38	-0.05	6.16	0.166
Lip length C	1.99±2.79	-4.58	9.36	2.27±0.74	1.68	3.4	0.767
Lip length NC	1.4±2.28	-2.52	8.05	2.32±0.67	1.18	2.83	0.215

(**) p <0.01, (*) p <0.05

The angular changes of both groups were compared (Table 4.6.2.). The change in nasal projection angle was significantly different between groups ($p<0.01$). Other two measurements showed no significant difference between groups ($p>0.05$).

Table 4.6.2. Comparison of angular changes between NAM and control groups with Mann Whitney U test

Angular (°) measurements	T1-T0						p
	NAM group (n:39)			Control Group (n:10)			
	Mean±SD	Min	Max	Mean±SD	Min	Max	
Columella inclination C	8.94±11.39	-6.21	34.68	4.56±2.70	1.58	7.64	0.471
Columella inclination NC	-3.45±15.33	-45.75	26.3	4.64±2.62	0.45	6.67	0.229
Nasal projection angle	1.35±3	-4.05	6.75	-2.53±1.36	-4.35	-0.6	**0.008****

(**) p <0.01, (*) p <0.05

The proportional measurement changes were evaluated and given in Table 4.6.3. The change in nostril height NC/C ratio was significantly different between groups ($p<0.01$), while other changes were found to be insignificant ($p>0.05$).

Table 4.6.3. Comparison of proportional changes between NAM and control groups with Mann Whitney U test

Proportional measurements	T1-T0						p
	NAM group (n:39)			Control Group (n:10)			
	Mean±SD	Min	Max	Mean±SD	Min	Max	
Exocanthion distance NC/C	0.05±0.09	-0.09	0.45	0.01±0.06	-0.06	0.09	0.316
Alar distance NC/C	0.07±0.12	-0.17	0.32	0.01±0.04	-0.01	0.09	0.160
Nostril base width NC/C	0.07±0.11	-0.08	0.36	0.01±0.03	-0.04	0.04	0.134
Nostril diameter NC/C	0.12±0.12	-0.05	0.49	-0.01±0.13	-0.13	0.2	0.062
Nostril height NC/C	-2.66±3.06	-17.51	0.15	0±0.1	-0.1	0.13	**0.001****
Nostril lateral length NC/C	0.12±0.45	-0.68	2.59	0±0.1	-0.19	0.05	0.120
Philtral height NC/C	-0.34±0.68	-2.88	0.78	0±0.04	-0.05	0.05	0.154
Lip height NC/C	-0.23±0.6	-3.28	0.68	-0.01±0.03	-0.03	0.04	0.208
Lip length NC/C	-0.05±0.19	-0.37	0.43	0.01±0.14	-0.24	0.11	0.275

(**) p <0.01

4.7. Comparison of Linear, Angular and Proportional Measurements Between NAM and Control Groups at T1

T1 measurements of both groups were compared (Table 4.7.1.). For the upper third of the face, no significant differences were observed between groups ($p>0.05$).

Alar width, alar distance C, nostril base width C, nasal base width, nostril diameter and lateral height C were smaller in the control group ($p<0.01$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.01$, respectively), whereas nostril diameter NC, columella height NC and columella height measurements were smaller in the NAM group ($p<0.05$, $p<0.05$, $p<0.01$, respectively). On the other hand, alar distance NC, nostril base width NC, nostril height C and NC, nostril lateral length NC, columella width, columella height C did not differ between groups ($p>0.05$).

When the labial measurements were evaluated, philtral height, philtral height C, christa philtri distance C and lip height C were significantly greater in the control group ($p<0.001$). Lip length C was significantly smaller in NAM group ($p<0.01$), whereas christa philtri distance NC, lip height NC and lip length NC were greater in control group ($p<0.05$). Philtral width, philtral height NC and mouth width were not different between groups ($p>0.05$).

Table 4.7.1. Comparison of linear measurements at T1 between NAM and control groups with independent t test

Linear measurements (mm)	T1						p
	NAM group (n:39)			Control Group (n:10)			
	Mean±SD	**Min**	**Max**	**Mean±SD**	**Min**	**Max**	
Biocular width	69.05±3.51	59.94	78.24	67.46±4.06	62.88	72.36	0.353
Intercanthal width	26.12±2.58	20.95	31.65	25.63±2.06	23.39	27.87	0.682
Endocanthion distance C	15.6±1.66	12.28	19.22	14.97±0.63	14.04	15.68	0.407
Endocanthion distance NC	14.99±1.85	12.07	19.17	14.93±1.22	13.17	16.44	0.942
Exocanthion distance C	37.63±2.28	31.02	41.87	36.51±1.79	34.19	38.9	0.301
Exocanthion distance NC	36.34±2.36	31.72	42.31	36.22±2.98	32.82	39.71	0.918
Alar width	24.02±1.97	19.89	28.87	21.2±1.05	19.42	22.11	**0.003****
Alar distance C	15.79±1.53	12.94	19.49	13.01±0.89	11.7	13.48	**0.0001*****
Alar distance NC	12.01±1.5	8.68	15.3	12.71±0.85	11.92	13.64	0.32
Nostril base width C	13±2.45	10.06	17.7	4.88±1.28	3.47	6.11	**0.0001*****
Nostril base width NC	4±1.3	1.86	7.22	4.79±0.73	4.02	5.89	0.193
Nasal base width	19.86±1.88	15.63	24.85	12.81±2.41	10.27	16.15	**0.0001*****
Nostril diameter C	12.47±1.58	9.66	14.97	6.47±0.54	5.77	7.25	**0.0001*****
Nostril diameter NC	5.48±1.37	3.11	8.62	6.81±0.63	5.99	7.72	**0.039***
Nostril height C	4.49±1.55	0.86	7.85	4.75±0.69	3.94	5.51	0.718
Nostril height NC	4.79±1.12	2.11	6.95	4.72±0.4	4.37	5.25	0.89
Nostril lateral length C	10.34±2.62	6.51	15.22	6.23±0.81	4.94	6.84	**0.001****
Nostril lateral length NC	6.39±1.16	2.94	9.2	6.04±0.69	5.48	6.9	0.513
Columella width	4.22±1.16	2	6.56	5.28±0.69	4.76	6.44	0.052

Table 4.7.1. Comparison of linear measurements at T1 between NAM and control groups with independent t test (continued)

Linear measurements (mm)	T1						p
	NAM group (n:39)			Control Group (n:10)			
	Mean±SD	Min	Max	Mean±SD	Min	Max	
Columella height	9.2±1.32	5.95	11.8	11.08±1	9.83	12.41	**0.004****
Columella height C	9.76±1.3	6.87	12	10.76±0.46	10.17	11.24	0.098
Columella height NC	9.42±1.27	6.07	12.48	10.68±0.48	9.98	11.29	**0.035***
Philtral width	7.18±1.23	4.72	10.17	7.13±0.36	6.67	7.67	0.926
Philtral height	9.68±1.43	7.04	13.54	12.48±1.9	9.21	13.92	**0.0001*****
Philtral height C	6.08±1.45	3.12	9.53	12.44±1.13	10.62	13.72	**0.0001*****
Philtral height NC	11.18±1.54	8.21	14.6	12.46±0.75	11.49	13.37	0.074
Christa philtri distance C	33.37±2.32	29.57	37.93	38.09±1.86	35.36	40.03	**0.0001*****
Christa philtri distance NC	36.03±2.48	30.4	41.12	38±1.68	35.44	39.51	**0.043***
Lip height C	8.07±1.75	4.95	13.44	13.08±1.16	11.11	13.98	**0.0001*****
Lip height NC	11.98±1.21	10.31	14.81	13.05±1	11.95	14.3	**0.047***
Mouth width	31.9±2.89	25.68	37.35	30.5±2.14	27.17	32.72	0.304
Lip length C	13.85±2.25	9.03	20.13	16.84±0.41	16.18	17.2	**0.005****
Lip length NC	13.98±2.05	10.37	20.09	16.41±0.55	15.86	17.23	**0.012***

(***) p <0.001, (**) p <0.01, (*) p <0.05

The angular differences between the groups at T1 were shown in Table 4.7.2. Columella inclination NC was higher in NAM group (p<0.001), whereas columella inclination C was higher in control group (p<0.05). Other measurements were found to be insignificant (p>0.05).

Table 4.7.2. Comparison of angular measurements at T1 between NAM and control groups with independent t test

Angular (°) measurements	T1						p
	NAM group (n:39)			Control Group (n:10)			
	Mean±SD	Min	Max	Mean±SD	Min	Max	
Columella inclination C	90.15±9.19	74.39	118.64	94.65±6.29	85.6	102.39	**0.049***
Columella inclination NC	106.93±12.84	74.06	142.44	95.34±3.91	88.67	98.52	**0.0001*****
Nasal projection angle	19.27±3.11	11.48	27.47	23.83±1.32	21.7	25.33	0.088

(***) p <0.001, (*) p <0.05

In T1, alar distance NC/C, nostril base NC/C, nostril diameter NC/C, philtral height NC/C and lip height NC/C were significantly different between groups (p<0.01). (Table 4.7.3.).

Table 4.7.3. Comparison of proportional measurements at T1 between NAM and control groups with independent t test

Proportional measurements	T1						p
	NAM group (n:39)			Control Group (n:10)			
	Mean±SD	Min	Max	Mean±SD	Min	Max	
Exocanthion distance NC/C	0.97±0.04	0.9	1.07	0.99±0.05	0.91	1.02	0.247
Alar distance NC/C	0.77±0.11	0.51	1.06	0.98±0.07	0.89	1.07	**0.0001*****
Nostril base width NC/C	0.32±0.12	0.13	0.62	0.98±0.02	0.95	1	**0.0001*****
Nostril diameter NC/C	0.45±0.14	0.25	0.81	1.05±0.16	0.87	1.2	**0.0001*****
Nostril height NC/C	1.23±0.55	0.62	2.86	0.99±0.03	0.95	1.02	0.343
Nostril lateral length NC/C	0.7±0.42	0.33	3.05	0.93±0.08	0.81	1.01	0.236
Philtral height NC/C	1.91±0.38	1.34	2.93	1±0.03	0.96	1.03	**0.0001*****
Lip height NC/C	1.55±0.34	0.77	2.59	1±0.03	0.96	1.03	**0.001****
Lip length NC/C	1.02±0.16	0.75	1.41	0.97±0.04	0.92	1	0.420

(***) p <0.001, (**) p <0.01

4.8. Correlations

In this study, the correlations between T0 lip gap and the changes in nostril base width C, nasal base width, nostril height C, columella height, columella height C, philtral width, philtral height and lip gap were evaluated with pearson correlation test (Table 4.8.1.). T0 lip gap showed statistically significant negative correlation with nostril base width C, nasal base width and lip gap changes (r=-0.526, p=0.001, r=-0.611, p=0.0001 and r=-0.662, p=0.0001). T0 lip gap showed statistically significant positive correlation with columella height C and philtral height changes (r=0.351, p=0.029 and r=0.447, p=0.004)

Table 4.8.1. Correlation of NAM group's lip gap T0 values to T1-T0 measurements evaluated with Pearson correlation test

Linear measurements (T1-T0)		Lip gap (T0)
Nostril base width C	r	-0.526
	p	**0.001**
Nasal base width	r	-0.611
	p	**0.0001**
Nostril height C	r	0.296
	p	0.067
Columella height	r	0.290
	p	0.073
Columella height C	r	0.351
	p	**0.029**
Philtral width	r	-0.076
	p	0.643
Philtral height	r	0.447
	p	**0.004**
Lip gap	r	-0.662
	p	**0.0001**

Other than correlations based on initial lip gap measurements, the coorelations between the initial nostril height C and linear measurement changes were evaluated

(Table 4.8.2.). Two significant correlations were found: nostril base width C was positively and nostril height C was negatively correlated with T0 nostril height C measurements (r=0.531, p=0.0001 and r=-0.568, p=0.0001).

Table 4.8.2. Correlation of NAM group's nostril height C T0 values to T1-T0 measurements evaluated with Pearson correlation test

Linear measurements (T1-T0)		Nostril height C (T0)
Nostril base width C	r	**0.531**
	p	**0.0001**
Nostril height C	r	**-0.568**
	p	**0.0001**
Columella height	r	0.18
	p	0.216
Columella height C	r	0.059
	p	0.687
Philtral width	r	0.2
	p	0.168

Correlations between T0 lip gap and angular measurement changes (T1-T0) of NAM group were given below in Table 4.8.3. Positive correlations were found between T0 lip gap measurement and the changes in columella inclination C and nasal projection angle (r=0.399, p=0.012 and r=0.319, p=0.047).

Table 4.8.3. Correlation of NAM group's lip gap T0 values to angular T1-T0 measurements evaluated with Pearson correlation test

Angular measurements (T1-T0)		Lip gap (T0)
Columella inclination C	r	**0.399**
	p	**0.012**
Columella inclination NC	r	0.062
	p	0.707
Nasal projection angle	r	**0.319**
	p	**0.047**

The correlations between lip gap change and linear measurement changes were also evaluated (Table 4.8.4.). Change in lip gap showed statistically significant positive correlation with the change in nostril base width C and nasal base width (r=0.468, p=0.003 and r=0.723, p=0.0001). Whereas, columella height, columella height C and philtral height changes showed negative correlation with lip gap change (r=-0.387, p=0.015, r=-0.430, p=0.006, r=-0.500, p=0.001, respectively).

Table 4.8.4. Correlation of NAM group's lip gap T1-T0 values to T1-T0 measurements evaluated with Pearson correlation test

Linear measurements(T1-T0)		Lip gap (T1-T0)
Nostril base width C	**r**	**0.468**
	p	**0.003**
Nasal base width	**r**	**0.723**
	p	**0.0001**
Nostril height C	**r**	-0.250
	p	0.125
Columella height	**r**	**-0.387**
	p	**0.015**
Columella height C	**r**	**-0.430**
	p	**0.006**
Philtral width	**r**	0.018
	p	0.912
Philtral height	**r**	**-0.500**
	p	**0.001**

The correlation between lip gap change and angular changes of NAM group was evaluated (Table 4.8.5.). A negative correlation was found between the change in columella inclination C (r=-0.339, p=0.035).

Table 4.8.5. Correlation of NAM group's lip gap T1-T0 values to angular T1-T0 measurements evaluated with Pearson correlation test

Angular measurements (T1-T0)		Lip gap (T1-T0)
Columella inclination C	r	**-0.339**
	p	**0.035**
Columella inclination NC	r	-0.087
	p	0.599
Nasal projection angle	r	-0.290
	p	0.073

5. DISCUSSION AND CONCLUSION

5.1. Discussion of Purpose and Methods

Preoperative orthopedic treatments primarily aim to correct the distorted alveolar segments and minimize the severity of the cleft deformity to enable surgeons to operate in a better environment and achieve optimal results under minimal tension of the soft tissues. However, Dr. Grayson and Dr. Cutting added another aspect to this treatment modality by addressing the nasolabial complex in addition to the alveolar structures (125,129). This new approach called NAM is used to correct the nasal deformity characterized by depressed alar cartilage and deviated columella in unilateral CLP, taking advantage of ability of molding nasal cartilages due to the increased plasticity caused by the high levels of maternal estrogen in infants in the early post-natal period (8,148,149). During the past three decades, the efficacy of NAM has been evaluated in many scientific studies (9,10,11–13,154,157,158,160,234). The results of these studies confirmed an improvement in the shape of nasolabial complex following NAM in patients with UCLP. On the other hand, Laverde et al. (14) followed the facial growth and development of children with unilateral cleft lip from birth to six-months of age and found that facial growth caused a natural improvement in the nasolabial structures of these patients without the need of presurgical molding. This reveals the necessity of conducting studies including control groups to eliminate the effects of growth and development from that of the NAM therapy. However, most of the studies assessing short-term effects of NAM did not include control subjects (9,10,13,152,156,231). The absence of a control group was reported as a weakness of their study design by several authors (10,12,156,232). The only study comparing soft tissue nasal changes following NAM used a historical control group composed of non-cleft infants aged between 0 to 5 months (12). The authors mentioned the use of a historic control group as a limitation of their study because of the possibility of secular changes in craniofacial size or form of the subjects and errors due to different examiners and measurement techniques. Furthermore, the age range of their control group was not matching that of the study group. They proposed to use a modern control group of unaffected infants to be able to assess the absolute treatment effects. Therefore, in our study we tried to compose a control group including age-matched healthy subjects, evaluated by the same procedures and examiner, and compare that normative data with that of NAM group to assess the true correction of the nasolabial deformity by NAM.

The timing of NAM is of utmost importance in terms of the critical neonatal period where the plasticity of the cartilage tissue is high. It is suggested to start molding the nose as early as possible after birth (8,148,149). Mastuo et al. postulated that the high degree of plasticity in neonatal cartilage is due to high levels of hyaluronic acid, which is a component of the proteoglycan aggregate of the intercellular matrix in the cartilage. Estrogen increases the level of hyaluronic acid, which subsequently increases the level of plasticity in the cartilage (233). With neonatal levels of maternal estrogen highest immediately after birth, the period of plasticity is slowly lost during the first months of postnatal life (7,148,234). Active soft tissue and cartilage molding plate therapy is most successful during these first 3 to 4 months after birth. The benefit from continued nasal orthopedics in the infant with a unilateral cleft is reduced after 12 weeks, because the cartilage becomes less able to maintain a permanent correction of its initial deformity (7). Therefore, in our study, the cleft patients presurgical treatment started within the first month and was completed in three months. The mean age at the onset of the treatment was approximately 23 days ranging from 12 to 30 days similar to other studies (9,10,12,152,163). On the other hand, the treatment duration was approximately 76 days, slightly shorter than reported in the previous studies with an average ranging from 95 to 110 days (9,12,152,163). The difference of the treatment duration between studies may be due to needs of the patient, the initial severity of the deformity and the timing of the surgical intervention independent from the orthodontist.

In order to compose an age-matched control group, every effort was made to collect facial records of the healthy subjects at the corresponding record collection periods of cleft patients at the beginning and end of NAM therapy. The statistical analysis revealed that there was no difference between the ages of the control and NAM subjects at each data collection time.

In our study, the power analysis showed that a minimum of 23 subjects with CLP was required in the study group. Our study group was consisted of 39 subjects who were treated between years of 2016-2018, thus this requirement was met. For the control group, the healthy infants of volunteer families were involved. Although, a non-invasive and practical method was used to take 3d facial photographs of the control subjects, we experienced difficulties to convince the parents to participate to this study or to take the records in appropriate time. Therefore, the number of control subjects was smaller than expected.

There is an increasing number of studies focusing on facial esthetic outcomes of the treatments (9,11,237–242,12,50,172,223,227,228,235,236). In order to evaluate the facial changes, researchers used many methods, such as direct or indirect anthropometric measurements. Direct anthropometric evaluation of the patients with cleft is the oldest method. However, it causes problems in terms of being time consuming, requirement of the presence of the patient and difficulty in patient cooperation especially in infants. On the other hand, some of these problems have been overcome by indirect methods. To be able to make indirect anthropometric measurements, researchers need to obtain records of the patient's face. For this purpose, several methods have been described over the years. As a simple, economic and practical way, conventional photography of the face or facial models have been used in many studies (10,11,14,49,50,152,155,158). However, the measurements made on 2d photographic images can not represent the realistic 3d characteristics of the nasolabial unit and might have some inherent errors (155). Facial photography is limited by the patient's head position, standardization of the records, parallax phenomenon and calibration problems (12). Another method for facial structure documentation is taking impression of the face, which enables 3-dimensional measurements (9,172,243). However, soft tissue deformation is likely to occur because of the tension and weigth of the impression material (12,183). Holberg et al. (183) reported 1 to 3 mm of soft tissue deformation caused by alginate impression. Impression errors are most evident in the lower facial third including the nasal tip and the subnasal region, which may cause more measurement problems in patients with cleft where there is no integrity of the soft tissues. In addition, a baby can not stay still during this procedure unless this record is taken under sedation or anesthesia, which will cause further distortion of the nasolabial soft tissues during crying. Furthermore, extraoral impression taking requires safeguarding the respiratory system because it is likely that the operators could encounter complication such as cyanosis of the infant (244,245). Nur-Yılmaz et al. (184) reported that oxygen saturation of the infants may decrease significantly during extraoral impression taking.

In recent years, with the development of computer technology three-dimensional imaging systems such as laser surface scanner or stereophotogrammetry have become popular. Stereophotogrammetry as a gold standard of capturing 3d images has several advantages over other imaging techniques, such as being non-invasive, contact free, reliable, accurate, reproduciable and having short capture time (13,21,24,29,172,192,212,246). These properties are particularly important in youngest child when movements may cause motion artifacts. Another advantage of this technique is color identification in surface texture. This specification facilitates landmark identification in the cleft region. On the other hand, the cost and requirement of a special software programme are the main disadvantages of this system. Taking into consideration the pros and cons of the imaging systems, we used stereophotogrammetry to capture 3d facial images of the subjects as proposed by many authors (9,12,13,24,172,192,212,241,246). Furthermore, by using stereophotogrammetry as a non-invasive method we eliminated the concerns about collecting records of a healthy control group by facial impressions as reported by Keçik and Enacar (10).

While the acquisition of the 3d images of infants, it is important to have the subject at a relaxed position in order to eliminate tissue tension caused by crying. In order to do so, in our study we paid attention to take all the records when the infant is relaxed. Furthermore, the display of the images was checked immediately after every capture and if an image with poor quality was detected the image was recaptured. Only the high-quality images were used in our study.

We used linear, angular and proportional measurements to evaluate nasolabial changes. The identification of the landmarks composing these measurements is very important for reliable results. This depends on good description of the landmarks, morphology of the anatomic surface, examiner factors and image quality (172,247). Therefore, the most reproducible landmarks were chosen according to the literature (192). The high reproducibility of our landmarks proven by the results of intraclass coeffiecient correlations further confirms it. As the experience and skill of the examiner is an important factor, all the landmarks were marked by the same examiner who had a training about 3-dimensional image manipulation and data processing with 3dMd camera and 3dMd Vultus software. The landmark identification differs greatly when working on 2d or 3d images. On 3d images, the essential is to check the correct position of the landmark from different aspects. Therefore, each landmark was first positioned from frontal view and then checked from basillar and saggital views.

5.2. Discussion of Results

Nasoalveolar molding therapy starts with alignment and approximation of the alveolar segments by negative sculpting then continued with reshaping of the nostril area using plate-nasal stent-lip tape combination. As the alveolar gap and nasal base width are reduced by the movement of the underlying bone, the overstreched alar rim shows some laxity enabling elevation of the nose (4). Afterwards, the nasolabial changes become obvious as improved nasal shape and approximated lips enabling a surgical closure with less tension and optimal results. In our study, lip gap decreased significantly with a mean value of 4 mm after NAM as a result of alveolar molding and lip taping (151,169). Also, nostril base width on the cleft side, which was greater (approximately 11 mm) than the control group at the beginning of the NAM therapy, decreased significantly with treatment by approximately 2.5 mm whereas, in the control group a slight increase was noted in nostril base width measurements due to growth. Our finding was in accordance with the findings of the previous studies evaluating the short-term nasolabial effects of NAM (9,12,152). Nur-Yılmaz and Germeç-Çakan (9) reported a reduction of 1.5 mm, measured on 3d images of facial casts. Ezzat et al. (152) noted a 1.7 mm decrease although it was not found significant. On the other hand, Mancini et al. (12) showed approximately 4 mm of reduction at the nostril base on the cleft side. This greater amount of improvement may be due to the longer treatment period (95 days) compared to that of our study (76 days), the age at the beginning of treatment or patient cooperation. The effectiveness of NAM therapy is related to the age of the patient at the onset of the therapy and the treatment duration. Better results are expected with earlier intervention and extended treatment time (11,149,152,248). Ezzat et al. (152) and Gomez et al. (11) proposed extending the NAM treatment as much as possible as longer treatment results in better nose symmetry.

Similar to nostril base width and lip gap changes on the affected side, the nasal base width (the distance between nostril base lateral points on both sides) reduced after NAM by the approximation of the alveolar bones. In the literature, there are controversial findings about the changes of the nasal base width following NAM. In accordance with our study, Keçik and Enacar (10) reported a significant reduction of the nasal base following approximately six months of NAM therapy. Moreover, Singh et al. (13) found a decrease of 2 mm after 4 months of nasoalveolar molding in their study conducted on

3-dimensional facial images captured by stereophotogrammetry. On the other hand, Gomez et al. (11) noted an increase of 2.75 mm in the width of the base of the nose. This result might be related to the differences in treatment techniques. The authors mentioned that the lip taping was only used in severe cases and concluded that the insufficient lip taping may be responsible from their poor results. As pointed out previously, in a successful NAM therapy, the molding of the alveolus by the adjustments of the plate and forces exerted by the extraoral taping reduces the alveolar gap thus, approximates the edges of the nostrils and narrow down the nostril floor (4). In our study, despite its reduction with NAM, the nasal base width remained wider post-treatment compared to the control group.

As expected, similar to nostril base width on the cleft side, nostril diameter, which was larger at the beginning compared to the control group, showed improvement with NAM treatment. In the study group, this measurement decreased 1.4 mm whereas in the control group it increased with 1 mm. The comparison of the groups revealed a significant difference showing the positive effects of NAM in the presence of growth. The improvement of the nostril diameter may be explained by elevation of the alar rim and repositioning of the nasal bases leading to closure of the cleft by NAM. This finding is in accordance with the findings of Nur-Yılmaz and Germeç-Çakan (9) and Liou et al. (158). On the other hand, Gomez et al. (11) found an insignificant increase. A possible explanation of this difference between studies may be the evaluation method. The authors used 45° basillar photographic views and 2d measurements. In addition, it seems that there are methodological differences between their and our treatment approaches. They used a larger nasal stent lobe covering the whole nostril area whereas, in our protocol, a smaller bi-lobed intranasal portion was positioned at the nostril apex to lift the dome.

When the nostril diameter on the non-cleft side was evaluated, it was found that it was initially smaller than the control group and increased by growth. The reason of the smaller diameter on the unaffected side is the displacement of the insertion of the columella toward this side. We expected a normalization in this measurement with the correction of the columellar inclination. We further evaluated the symmetry of bilateral structures by dividing non-cleft to cleft measurements thus obtaining a basic symmetry index. Values approximating 1 signify symmetry whereas diverging values signify asymmetry. The proportional measurements regarding nostril diameter revealed a significant asymmetry at the beginning of the treatment: in the NAM group the proportion was 0.33, whereas in control group it was 1 indicating complete symmetry between the nostril diameters. At the end of treatment period, there was a significant improvement in NAM group although it did not reach the ideal symmetry as previously reported by several authors (155,158). In accordance with our findings, Pai et al. (155) also showed that nostril width ratio changed positively although the nostril on the affected side was still wider after NAM therapy. They explained this result by the missing or lowered nasal floor. The deviation of the nasal floor can be corrected only by cheiloplasty which would make the nostrils even more symmetrical in terms of width, height and columella angle (155). Liou et al. (158) also questioned the need to mold the nose completely symmetrical before primary cheiloplasty and concluded that, NAM is an adjunctive therapy for facilitating primary repair but not a definitive treatment for the nasal asymmetry in cleft patients. In addition, when primary gingivoperioplasty was not an objective during lip repair, the remaining gap between the alveolar segments because of incomplete approximation may be responsible of the persisting nasolabial asymmetry (158).

One of the purposes of NAM therapy is to increase the nostril and columella height for reshaping the depressed alar cartilage and the nose (150). Our study showed that this objective was met as the nostril height on the cleft side increased approximately 3 mm following the use of the nasal stent producing pressure on the alar dome. The nasal stent serves as a custom tissue expander for the columella on the cleft side (7). When compared to the control group, it is evident that this increase exceeds the changes due to growth which counts for 20% of the improvement. Besides, the comparison of T1 measurements between groups showed that the nostril height on the cleft side reached the normal values. On the non-cleft side, nostril height changed parallel to the control group. The symmetry index changed from 3.9 to 1.2, showing achievement of symmetry of the nostril heights. Gomez et al. (11), Liou et al. (158) and Ezzat et al. (152) also reported an increase in nostril height. Furthermore, similar to our proportional findings, Pai et al. (155) found that nostril height ratio (affected/non-affected side) changed from 0.5 to 0.8, indicating improvement of the nostril height symmetry. In addition, in the NAM group, columella heights at T0 were smaller than that of the control group. Following NAM therapy, approximately 2 mm of increase was observed whereas, in the control group due to growth approximately 1 mm of increase was noted. Although, the elongation of the columella was greater in the NAM group compared to the control group, no statistically significant difference was found between groups. However, at the end of treatment and the observation periods, columella heights were similar to the control group. In accordance with our findings, Gomez et al. (11) and Liou et al. (158) showed increased columellar height after NAM but they did not have a control group to compare their findings.

Nasal tip projection which is always diminished in patients with CLP as a characteristic of nasal deformity was also observed in our patients (135). The nasal projection angle which was used to evaluate the nasal projection showed that there was a significant difference between groups in the first month after birth. Following NAM, this angle significantly increased in the study group whereas it decreased in the control group. It appears that the nasal morphology changes during growth while this angle is becoming more acute (249). On the other hand, elevation of the nasal cartilage and correction of the columella deviation by the nasal stent helped to increase nasal projection. To our knowledge, the only study evaluating the nasal tip projection after NAM on a short-term basis is the study by Mancini et al. (12). The authors used pronasale-subnasale distance as an indicator of nasal tip projection. They concluded that the nasal tip projection significantly increased (approximately 2 mm) with NAM. In our study, although we could not reveal any significant columella height increase apart from the growth effects, columella deviation showed a significant improvement which may explain the positive effects of NAM therapy on the nasal projection.

Philtral heights of the patients with CUCLP were found to be shorter at T0 probably due to soft tissue deficiency and pull of the muscles. However, the changes occured in the NAM group were greater than the control group, which could be related to the usage of lip tapes (7). Moreover, after NAM therapy, philtral height of the non-cleft side was comparable to the control, eventhough philtral height on the cleft side remained significantly shorter. The reason of this difference between both sides was the presence of aparted and rolled-up lip segments, which could only be corrected with surgical intervention. Similar findings were also reported by Nur-Yılmaz and Germeç-Çakan (9). Furthermore, the symmetry index of the philtral heights improved significantly by treatment although did not reach the complete symmetry.

The nasal symmetry greatly depends on the inclination of the columella as well as bilateral dimensions of the nostrils. The columella inclination differed significantly between groups at T0 showing a significant asymmetry. At the muscular level, the interruption of the orbicularis oris affects the nasal morphology by displacing the insertion of the columella to the non-cleft side and the nasal tip to the opposite side, thus creating an asymmetry. With the molding of the greater alveolar segment in medio-posterior direction by the plate and the lip tapes, at the insertion of the columella, subnasale moved medially, thus correcting the columella deviation approximately by 9°. Our findings confirmed the findings of the previous studies (10–12,152,155,163), although the correction was slightly smaller. This may be explained by several factors such as methodological differences (selecting different landmarks or using 2d evaluation) or treatment duration. Improvement of the columellar deviation angle by premaxillary and nasal cartilage repositioning with NAM was reported by many authors (152,163). Primary factor could be the movement of the subnasale point toward the midline following the correction of the greater alveolar segment's displacement (7,106). As the lower midface skeletal elements improve relationship, the overlined soft tissues also improve (4). Fuchigami et al. (156) found a correlation between the improvement of alveolar and columellar measurements on 2d images and concluded that alveolar and nasolabial changes are dependent on each other. In a study where the horizontal deviation of the subnasale from the midsaggital plane was evaluated on 3d stereophotogrammetric images, Mancini et al. (12) found approximately 3 mm movement of the subnasale point toward the midsaggital plane of the face.

When the morphological changes of the nose were evaluated in our control group, it was seen that the columella angle widened approximately 5° with growth, indicating nasal reshaping (249). Eventhough the changes between groups showed no statistically significant difference, the change in the NAM group almost doubled the change in control group. This insignificance may be due to high standard deviations in the NAM group. In NAM therapy, meeting the objectives depends on the severity of the initial deformity and the response of the infant to the treatment. It is known that the babies with UCLP show a great individual variability in terms of lip and nose deformity and the success of the treatment relies on the adaptation capacity of the infants to the reshaping of the alveolar and nasolabial structures and compliance factor. Unfortunately, not every patient's response to treatment is the same as documented by the -6° to 35° change in the columella deviation on the cleft side following NAM. This showed that, in some of the patients, the inclination did not improve at all, whereas in others there was a significant improvement showing the effectiveness of the treatment. On the other hand, the variability of the changes in the control group was very limited ranging between 1.5° to 7.5°. Therefore, we can assume that the correction of columellar inclination in NAM group is partly due to the treatment effects and the growth. Furthermore, when evaluating the data of the present study, one should consider the effects of the possible growth impairements of the infants with UCLP, which may differ from the normal growth of the nasolabial structures

(250,251). At that point, an untreated cleft group could serve as a control group to compare the findings. However, due to the ethical reasons, we could not collect untreated subjects with UCLP.

With growth and development, alar distance increased approximately 2 mm in the control group, whereas in NAM group this distance remained the same on the cleft side. This finding proves that nasal shaping was achieved despite the continued growth of the alar rim and tip of the nose and the increase in nasal projection due to treatment. Furthermore, the alar width which is the distance between bilateral alar points slightly widened in NAM group whereas, the control group showed a greater increase. Similar findings were reported in the literature (9).

Cleft lip and palate deformities are mainly a variation of midline defects in the craniofacial region and such deformity might affect the upper facial structures as well because of the problematic underlying bones. In the present study, we also evaluated the ocular region in patients with CUCLP and healthy infants. According to our findings, the endocanthion distance was increased on the affected side of the patients with CUCLP when compared to the control subjects at T0. This increase might be caused by the affected bony structures. Anchlia et al. (252) explained this deformity as defective development of palatal and maxillary processes in patients with CLP, resulting in eye ball migration thus causing hypertelorism. However, there was a significantly greater change in the control group whereas NAM group's measurements almost remained the same. Therefore, initial difference between groups disappeared at the end of observation period.

Columella width and the labial soft tissue dimensions measurements were generally smaller at T0 in patients with UCLP. As well as hard tissue deficiency, the soft tissue may be insufficient to some extent in subjects with cleft deformity (135). Following NAM and the observation period, these measurements increased in both groups due to growth. Although, columella and philtral widths reached the control group's values, the lip dimensions remained smaller in NAM group despite the use of lip tapes. This finding is also supported by the symmetry index (lip height proportion), which was enhanced during treatment but failed to achieve symmetry. The reduced labial tissue dimensions may be partly due to soft tissue deficiency because of cleft as mentioned previously, partly caused by remaining cleft deformity despite the improvement by NAM and partly due to growth impairments. In a study where weight and length gain of the infants with CLP were evaluated, it was revealed that children with CLP had smaller body dimensions and presented impaired weight gain compared with typical children in the first 5 months of age (251).

In our study, the correlations between the initial deformity and the changes in measurements were also evaluated. The results of correlation tests revealed that there was a strong correlation between the initial lip gap and decreases in the nasal base width, lip gap and nostril base width on the cleft side. The initial nostril height on the cleft side was found to be correlated with the reduction of the nostril base width on the same side. Futhermore, the initial nostril height was negatively correlated with the nostril height changes on the affected side. It appears that as the initial severity of the deformity is higher, the benefit and efficacy of the treatment increases as well as the observed changes. Similarly in a study where alveolar changes were evaluated in UCLP patients after NAM therapy, Altay-Burgaz (106) found that larger the initial alveolar gap, greater the reduction of the cleft and correction of the alveolar misalignment.

When the angular measurements were evaluated, a weak and positive correlation was detected between initial lip gap and the changes in columella inclination on the cleft side and nasal projection angle. Again, similar to linear, the angular measurements improved more when the initial deformity was more severe.

The reduction of the lip gap may be explained partly by repositioning of the alveolar segments (posteromedial movement of the greater segment and the growth of the lesser segment directed to the greater segment) and partly by elongation of the lips due to lip taping, which is supported by our correlation findings. The lip gap changes due to treatment were correlated with the treatment changes of other nasolabial measurements. It was revealed that the reduction of the lip gap was correlated with the reduction of the nasal base width and the nostril base width on the cleft side. The soft tissue landmarks of nasal base width and nostril base width are projecting the underlying hard tissue changes because they are in close proximity with the alveolar bone. Therefore, as Fuchigami et al. (156) showed previously in their study, we could assume that the alveolar changes are correlated with nasolabial changes as well. In addition, as philtral heights increased as a result of soft tissue growth and expansion caused by lip tapes, this helped the reduction of the lip gap, which was supported by the negative correlation between these measurements. On the other hand, the clinicians treating nasolabial cleft deformity with NAM should consider that soft tissues might not follow the hard tissues 1:1 ratio although a correlation between these structures was shown in the literature (156). Our clinical impression is that in most of the patients the improvement of the labial deformity is parallel to hard tissue changes whereas in some patients the soft tissue improvements are less than ideal and does not perfectly follow the alveolar changes (Figure 5.2.1.).

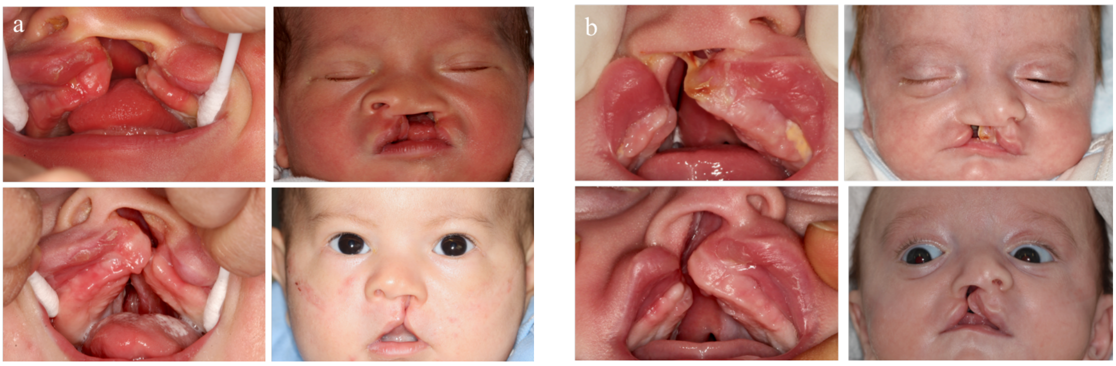

Figure 5.2.1. Patients with CUCLP treated with NAM (a) Soft tissues following underlying hard tissue (b) Soft tissues are not adequately following hard tissue

In this study, where 3d stereophotogrammetry was used to evaluate the nasolabial morphology in infants with CUCLP before and after NAM and to compare the changes with a control group, significant improvements in lip gap, nostril dimensions, columella deviation and nasal projection were observed as a result of NAM therapy. Therefore, based on our results, we recommend the use of this method in cases with CUCLP to decrease the severity of nasolabial cleft deformity prior to primary lip and nose surgery. However, the clinicians should consider the interindividual variability in the response to treatment. The compliance of the caregivers is another important determinant of the successful results (50,161). The clinicians should also be aware of the complications which may occur during NAM treatment. Intraoral and nasal soft tissue complications have mainly two reasons, over activation and rough surfaces of the NAM appliance. These issues could cause tissue irritations, bleeding or in more severe cases ulceration. However, these two problems may be easly eliminated by the experience of the clinician. When occurred, deactivation or trimming of the appliance will solve these complications and soft tissues will recover soon. Other than these, also caregivers might cause unwanted problems such as fungal infections due to lack of hygiene. Also, while using extraoral tapes, caregiver should be aware of the consequences of constant removal and application of the tapes could cause contact dermatitis. As a solution, there are base tapes which could affixed to the cheeks for 4 to 5 days, protecting the fragile skin of the infants. Furthermore, missed appointments or improper usage of tapes might end up with poor results.

Limitations of this study include the absence of an untreated CUCLP group, disregarding the growth percentile of both groups and evaluation of short-term effects. As mentioned previously, our craniofacial clinic provides NAM treatment for infants with cleft. The selection criteria for treatment is based on the general health status of the infant and the consensus between the surgeon and the orthodontist about the possible benefits to the patient. Except for the patients with compromised health problems and parents rejecting the treatment for several reasons such as living abroad, increased burden of care, financial issues, etc., all the patients with CUCLP are offered to undergo NAM therapy in our clinic. Therefore, we found it unethical to compose an untreated cleft group for comparison. To overcome this problem, conducting intercenter studies may be suggested. For further studies, the growth percentiles and birth weights of the infants should also be taken into consideration.

In the literature, the importance of long-term 3d morphological and functional studies of NAM treated patients with CUCLP was emphasized because, it is suggested that the effects of NAM are transient and subjected to relapse after the primary surgeries (158). Furthermore, some authors were not able to find any significant difference in lip and nose anatomy of patients with UCLP who received or not received NAM in the long-term (164). In 2013, a systematic review revealed that nasoalveolar molding seems to be beneficial for achieving nasal symmetry in patients with unilateral cleft however, the evidence level was low (253). Although, this is a controversial issue, the recent studies have started to provide evidence about the long-term benefits of NAM on nasolabial outcomes (49,151,153,155,158). An intercenter comparison recently revealed that the use of NAM as part of an infant management protocol produced significantly more favorable nasolabial appearance scores when compared with the outcomes resulting from primary surgery only (49). Therefore, there is an increasing need for controlled randomized clinical long-term trials which, excluding the variability of initial deformity, experience of the surgeon and orthodontist, variations in surgical approach and number of surgical interventions before the termination of the growth and the patient's genetic background.

6. CONCLUSION

The results of our study evaluating the nasal changes of infants with CUCLP revealed that at the beginning of treatment and observation period:

- The cleft patients showed increased alar and nostril widths with lateraly displaced alar cartilage and lesser alveolar bone, diminished nostril and columella heights, shorter philtrum and lip on the cleft side, decreased nasal projection, deviated columella to the non-cleft side, reduced nostril diameter on non-cleft side compared to the control infants.
- Proportional measurements indicated a significant nasolabial asymmetry in the cleft group whereas, control group was greatly symmetrical.

Following NAM treatment;

- Lip gap reduced and the lip segments approximated to each other.
- Nostril base width and diameter decreased on the cleft side.
- Nostril height increased and became more symmetrical.
- Columellar inclination was improved.
- Nose projection increased.
- The improvement of the nasolabial structures was mainly correlated with the severity of the initial deformity.

Following observation period of the control group;

- Most of the nasolabial measurements increased due to growth.
- Nasal projection decreased.
- Proportional measurements remained the same.

At the end of NAM and observation period;

- Nose projection and the nostril height of the patients with cleft reached the normal values. However, alar and nostril base widths were greater, nostril diameter was larger on the cleft side whereas slightly smaller on non-cleft side, columella and lip was shorter, and columella was still deviated compared to the control subjects.
- Proportional measurements indicated a nasolabial asymmetry except for the nostril height in NAM group compared to the control group.

As a conclusion, NAM is an effective method to reduce the severity of the nasolabial deformity and improve the symmetry before primary cheiloplasty in infants with CUCLP however a residual asymmetry may be observed at the end of the treatment.

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8. CURRICULUM VITAE

Personal Informations

Name	Alp Doruk	**Surname**	Birli
Place of Birth	Bakırköy / İstanbul	**Date of Birth**	11/07/1989
Nationality	Turkish	**TR ID Number**	31702068838
E-mail	alpbirli@gmail.com	**Phone number**	+905387705758

Education

Degree	Department	The name of the Institution Graduated From	Graduation year
Doctorate	Orthodontics	**Yeditepe University**	2019
Master	Faculty of Dentistry	**Istanbul University**	2012
University	Faculty of Dentistry	**Istanbul University**	2012
High school		**Adnan Menderes Anatolian Highschool**	2007

Languages	Grades (#)
English	IELTS GT (8/9), ALES (78.5)

Work Experience (Sort from present to past)

Position	Institute	Duration (Year - Year)
		-
		-

Computer Skills

Program	Level
MS Office	Good

9. ETHICAL COMMITTEE REPORT

T.C. YEDİTEPE ÜNİVERSİTESİ

Sayı : 37068608-6100-15-1201 **21/04/2016**
Konu: Klinik Araştırmalar
Etik kurul Başvurusu hk.

İlgili Makama (Alp Doruk Birli)

Yeditepe Üniversitesi Diş Hekimliği Fakültesi Ortodonti Anabilim Dalı Doç. Dr. Derya Germeç Çakan'ın sorumlu olduğu **"Dudak Damak Yarıklı Bebek Hastalarda Nazoalveolar Şekillendirmenin Hastaya Özel Plak Uygulanması İle 3 Boyutlu Değerlendirilmesi"** isimli araştırma projesine ait Klinik Araştırmalar Etik Kurulu (KAEK) Başvuru Dosyası (**1208** kayıt Numaralı KAEK Başvuru Dosyası), Yeditepe Üniversitesi Klinik Araştırmalar Etik Kurulu tarafından **20.04.2016** tarihli toplantıda incelenmiştir.

Kurul tarafından yapılan inceleme sonucu, yukarıdaki isimi belirtilen çalışmanın yapılmasının etik ve bilimsel açıdan uygun olduğuna karar verilmiştir (**KAEK Karar No: 600**).

Prof. Dr. Turgay ÇELİK
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