Long-term effects of nasoalveolar molding in patients with complete unilateral cleft lip and palate

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science (Orthodontics)

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Abstract

To investigate the long-term nasolabial esthetic outcome of nasoalveolar molding (NAM) in comparison to traditional infant orthopedics (TIO), and to no IO in the treatment of patients with complete unilateral cleft lip and palate (CUCLP) at a mean age of 11 years 8 months. Three samples were collected with different infant management protocols, namely NAM, TIO, and no IO. Nasolabial esthetics were assessed based on frontal and cleft-side profile photographs using the Q-Sort modification of the Asher-McDade et al. method. Statistical analysis included the Kruskal-Wallis test and a Bonferroni correction. The use of both types of IO yielded significantly better results in vermilion border and nasal form and profile esthetics of the sample treated with TIO were rated more superiorly. Although direct causation cannot be established given the heterogeneity surrounding cleft care, this study suggests reconsidering the proposed benefits associated with IO in the long-term.
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“If I have seen further, it is by standing upon the shoulders of giants”.

- Sir Isaac Newton

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1 Introduction & Definitions

Cleft lip and palate (CLP) is the most common congenital craniofacial malformation in humans with a prevalence of 6.64 per 10,000 births (Haque and Alam, 2015; Mastroiacovo et al., 2011). Management is complex, involving a multidisciplinary team comprised of various health care practitioners including a psychologist, nurse, pediatrician, plastic surgeon, maxillofacial surgeon, otolaryngologist, speech/language pathologist, pediatric dentist, prosthodontist, geneticist, audiologist, social worker, and orthodontist. There is great variability in treatment procedures and modalities employed in the management of patients with CLP worldwide. In a survey of 201 European cleft centers by the Eurocleft Clinical Network, there were 194 different surgical techniques identified for the primary repair of a complete unilateral cleft lip (CUCL) alone (Shaw, 2000).

The involvement of the orthodontist in the treatment of patients with CLP may begin as early as the first few days of an infant's life. The goal of such early orthodontic intervention is to reduce the severity of the initial cleft, thereby facilitating surgical repair and hopefully enabling a more esthetic outcome of the repair. These interventions are known as infant orthopedics (IO) and can vary from being quite simple (e.g. taping the lip across the cleft) to being more complex or invasive. Nasoalveolar molding (NAM) is a specific type of IO introduced by Grayson et al. in the early 90s (Grayson et al., 1999). Unlike other forms of infant orthopedics NAM includes a nasal stent to enhance the shape of the nostrils and the form of the nose (Grayson et al., 1999).

In 2012, 71% of North American Cleft Centers reported using IO in the treatment of patients with bilateral cleft lip and palate (BCLP) (Tan et al., 2012). Despite its widespread use, controversy remains over the usefulness of IO, with sceptics questioning its long-term benefit, potential inhibition of maxillary growth, and the added cost and burden of care. Similarly, NAM is also a subject of controversy. NAM currently enjoys increasing acceptance within the cleft field. Proponents of NAM highlight its benefits in decreasing the size of the alveolar cleft, improving nasal symmetry, and increasing columellar length, and nostril height (Ezzat et al., 2007). Some also suggest improved feeding and additional psychological benefits to parents who feel as though they are participating first-hand in the treatment of their affected child. On the flipside, critics focus on the increased burden of care, both financial and emotional, related to
the use of NAM, and question its long-term effect on nasolabial esthetics (Singer, 2012). What follows is a review of the literature surrounding cleft lip and palate as well as infant orthopedics with a specific focus on NAM.
2 Review of the literature

2.1 Embryogenesis of cleft lip and palate

Formation of cleft lip and palate occurs due to aberrations in facial development occurring very early on in embryogenesis (Dixon et al., 2011). During the third to fourth week following conception, the notochord forms and induces ectodermal cells to thicken and form the neural plate (Figure 1b). During neurulation, the neural plate elevates, resulting in the neural folds, which then fuse to form the neural tube (Figure 1c). At this time, neural crest cells (NCC) form at the tip of the ectodermal neural folds along the entire length of the neural tube.

NCC delaminate and migrate through mesenchymal tissue into the craniofacial region contributing to facial formation (Figure 1d). The transition from the ectoderm into mesenchyme results in ecto-mesenchyme that provides a lineage of pluripotent cells that give rise to diverse tissues. Neural crest cells migrate from their initially dorsal location on the embryo to ventral destinations that are either predetermined by homeobox transcription factor (HOX) genes or by responding to local cues from epithelia (Figure 1e) (Berkowitz, 2013).
Figure 1 Neural Crest Cell Embryology A) Schematic dorsal view of ten-somite stage chicken embryo, showing the neural crest (green) in the vicinity of the midline. The dotted lines delimit the embryonic region represented in the cross-section (B-E). B) Development of the neural crest begins at the gastrula stage, with the specification of the neural plate border at the edges of the neural plate. C) As the neural plate closes to form the neural tube, the neural crest progenitors are specified in the dorsal part of the neural folds. D) After specification, the neural crest cells undergo epithelium-mesenchyme transition and delaminate from the neural tube. E) Migratory neural crest cells follow stereotypical pathways to diverse destinations, whether they will give rise to distinct derivatives. F) The neural crest is multipotent and has the capacity to give rise to diverse cell types, including cells of mesenchymal, neuronal, secretory and pigmented identity (Simões-Costa and Bronner, 2015).
By week four of embryonic development the neural crest cells specific to the cranium have differentiated and have formed five facial primordia: the frontonasal prominence and the paired maxillary and mandibular prominences, surrounding the primitive oral cavity (Figure 2a). By the end of the fourth week, nasal placodes form, and then sink to form nasal pits resulting in elevated medial and lateral nasal processes (Figure 2b) (Berkowitz, 2013; Dixon et al., 2011).

Figure 2 Embryonic development of lip and palate in humans. A) The developing frontonasal prominence, paired maxillary processes and paired mandibular processes surround the primitive oral cavity by the fourth week of embryonic development. B) By the fifth week, the nasal pits have formed, which leads to the formation of the paired medial and lateral nasal processes. C) The medial nasal processes have merged with the maxillary processes to form the upper lip and primary palate by the end of the sixth week. The lateral nasal processes form the nasal alae. Similarly, the mandibular processes fuse to form the lower jaw. D) During the sixth week of embryogenesis, the secondary palate develops as bilateral outgrowths from the maxillary processes, which grow vertically down the side of the tongue. E) Subsequently, the palatal shelves elevate to a horizontal position above the tongue, contact one another and commence fusion. F) Fusion of the palatal shelves ultimately divides the oronasal space into separate oral and nasal cavities (Dixon et al., 2011).
By week six, intervening epithelium known as a “nasal fin” separates the medial tip of each maxillary prominence from the inferolateral aspect of each medial nasal process (Figure 3). By the end of the sixth week, degeneration of this nasal fin allows for fusion of the two medial nasal processes with the two maxillary processes forming the upper lip and primary palate (located posterior to the gum line and extending to the incisive foramen) (Berkowitz, 2013; Moore et al., 2013). The lateral nasal processes form the nasal alae, and the mandibular processes fuse to form the mandible (Figure 2c) (Dixon et al., 2011). If fusion of the bilateral maxillary and two medial nasal prominences does not occur, cleft lip will form (Berkowitz, 2013).

![Figure 3](image)

**Figure 3 Schematic depiction of breakdown of nasal fin and formation of nostrils. Arrows indicated disintegration of the nasal fin between the medial nasal and maxillary prominences (Losee and Kirschner, 2009)**

Between weeks six to nine, the lateral palatine processes initially grow medially out from the lateral walls of the maxillary processes and then inferolaterally around the tongue (Figure 2d). By the twelfth week the palatine processes elevate as the tongue descends, and finally fuse to form the secondary palate (Figure 2e & 2f). Bone extends from the maxilla and palatine bones into the palatal shelves forming the hard palate, while the posterior section does not ossify and forms the soft palate and uvula (Moore et al., 2013). If fusion does not occur, cleft palate results.

Understanding the embryonic origin of cleft lip and palate allows for enhanced understanding and appreciation of the various severities of the anomaly.
2.2 Classification of cleft lip and palate

Given the many forms of CLP, several classification systems are available for categorizing the malformation. The focus of each classification system often depends on the discipline in which it is being used. Classification systems based on anatomy are useful for dental as well as surgical teams, while classification systems based on embryology are useful for research and genetic counseling. As a result, no classification system is currently universally accepted (Sitzman and Marcus, 2014).

There are approximately one hundred different combinations of CLP; therefore proper classification will allow for better treatment planning. Simply put, classification is based on the severity of the cleft (complete or incomplete), whether it occurs unilaterally or bilaterally, and its possible association with a syndrome. Figure 4 illustrates the various types of CLP.
Figure 4 Types of Cleft Lip and Palate. A) Normal lip and palate. B) Cleft (bifid) uvula. C) Unilateral cleft of the secondary (posterior) palate. D) Bilateral cleft of the posterior part of the palate. E) Complete unilateral cleft of the lip and alveolar process of the maxilla with a unilateral cleft of the primary (anterior) palate. F) Complete bilateral cleft of the lip and alveolar processes of the maxilla with bilateral cleft of the anterior part of the palate. G) Complete bilateral cleft of the lip and alveolar processes of the maxilla with bilateral cleft of the anterior part of the palate and unilateral cleft of the posterior part of the palate. H) Complete bilateral cleft of the lip and alveolar processes of the maxilla with complete bilateral cleft of the anterior and posterior palate (Moore and Persaud, 2008).

2.3 Nasolabial morphology in infants with unrepaired cleft lip and palate

To diagnose and treat cleft lip and palate an understanding of normal morphology as well as the interfering dysmorphology is needed (Mooney and Siegel, 2002). It has been theorized that the role symmetry plays in deeming faces beautiful increases towards the midline of the face (Springer et al., 2007). Patients with CLP have greater asymmetry at the facial midline given their distorted nasomaxillary complex and as a result their facial esthetics can be compromised.

Facial dysmorphology varies by the type of cleft. In patients with CUCLP, the greatest dysmorphology is seen in the nose. A complete unilateral cleft results in a deficiency of bone in the anterior maxilla and alters the insertion points of the circum-oral muscles on the non-cleft side (Figure 5). During muscle contraction in utero, the non-cleft side of the maxilla is rotated away from the cleft, dragging with it the nasal structures and septum. This is unlike the cleft-side alar base which becomes stretched and sits inferior to the alae of the non-cleft side due to muscle activity. The nasal tip and columella base deviate towards the non-cleft side (Figure 6). Given this dysmorphology, regaining nasal symmetry becomes very challenging after birth. The tongue also plays a role by protruding into the cleft and by exerting pressure against the tuberosities, enlarging the width of the posterior maxilla (Lo, 2006; Mooney and Siegel, 2002). Therefore treatment of CLP focuses on restoring this dysmorphology for esthetics, as well as for functionality.
Figure 5 Diagram of the forces acting on the unilateral cleft lip and palate in utero. The effect is mainly on the anterior of the maxilla: the posterior tuberosities are expanded and symmetrical (Mooney and Siegel, 2002).

Figure 6 Characteristic facial morphology of a newborn with complete unilateral cleft lip and palate, showing the deflection of the anterior maxilla and the nasal structures toward the non-cleft side. The cleft-side nostril has been stretched and deformed by muscle activity, which has also caused protrusion of the anterior aspect of the alveolar process on the non-cleft side (Mooney and Siegel, 2002).

2.4 Infant orthopedics

Treatment of CLP is initiated within the first week or two of birth by the clinician performing IO. IO was introduced as a means to facilitate surgical reconstruction and improve its outcome. One of the original IO techniques was introduced by McNeil in the 1950s and further developed by Burston (Burston, 1958). The McNeil approach involves taking a maxillary impression of the newborn to create a plaster cast. This plaster model is then cut and modified with the gap
slightly closed. An acrylic maxillary appliance (“plate”) is fabricated based off of this modified model. This process is repeated re-shaping the plate to the growing patient’s maxilla “molding” the alveolar segments into an ideal position prior to surgery (hence the term “alveolar molding”) (McNeil, 1950). The McNeil approach is considered an active IO as it applies controlled forces to move alveolar segments in a predetermined way. Alternatively, passive IO appliances act as a fulcrum upon which the forces created by surgical lip closure mold the alveolar segments (Suri and Tompson, 2004).

Many centers adopted the McNeil approach as a part of their neonatal cleft treatment protocol. Prior to the year 2001, Toronto’s Hospital for Sick Children (HSC) used a modified McNeil version of IO (hereafter termed Traditional Infant Orthopedics, or TIO). TIO treatment begins in the first couple of weeks of birth. The modified approach requires an impression of the neonate’s maxilla to construct a plaster cast. The cleft and any undercuts are filled with wax and an orthopedic plate is fabricated using autopolymerizing acrylic resin. The plate includes .030" stainless steel "outrigger" wires that emerge from the cleft between the lip margins (Figure 7A). Before insertion, the plate is tried in the mouth to ensure an appropriate fit and adequate relief around the labial frenum. Parents are encouraged to keep the plate in 24 hours/day, and to remove it after feedings to clean. Parents are taught the necessary skills to insert, remove, and secure the plate with taping. Transpore tape (3M Health Care, St. Paul, MN) is used to secure the outriggers to Blenderm base tape (3M Health Care, St. Paul, MN) applied to the cheeks of the infant to prevent skin irritation (Figure 7B). Following one week of wear, the patient’s oral cavity is reassessed for sore spots. Parents are further instructed to initiate lip taping. Lip taping involves gently stretching a 3/8” light orthodontic elastic to generate light continuous tension across the gap and using 3M Transpore to tape to the cheeks bringing the segments of the upper lip together. Patients are reassessed at biweekly visits to relieve and adjust the appliance as necessary, while the cleft is reduced in width (Suri and Tompson, 2004).
In the late nineties the Dutchcleft prospective clinical trial investigated the effect of IO on facial appearance of patients with UCLP across three cleft centers in the Netherlands (Prahl et al., 2006). Randomly allocated, half the patients (n=27) were treated with IO until the time of surgical repair of the soft palate at ±52 weeks, and the other half (n=27) received no intervention prior to surgery. Photographs of both the IO and the no-IO groups were evaluated for esthetics using the visual analogue scale at age four (n=24 and 21 respectively) and again at age six (n=22 and 24 respectively) by professionals and laypeople. Results indicated that the use of IO improved facial esthetics at age 4 as detected by both professionals and laypeople. However by age 6, laypeople found no significant differences in facial esthetics between patients treated with IO and those treated without. At age 6, the positive influence of IO was only detectable by
professionals. The Dutchcleft study concluded that the use of IO was irrelevant given that patients with CLP would interact with laypeople and not professionals throughout their lives (Prahl et al., 2006). Interestingly, the results of this study led to the abolishment of IO from the protocols of all Dutch Centers.

Subsequent to Dutchcleft, the Americleft study investigated nasolabial esthetics in patients with CUCLP with an age range of 5 to 12 years amongst four large North American cleft centers. Each center employed a different treatment modality. One center strictly performed surgical repair without the use of IO, while the other three centers used IO, however their protocols varied based on the design of appliance, duration of appliance use, and additional bone grafting. Despite these variations in technique, the Americleft study concluded that there were no significant differences in nasal form, nose symmetry, vermilion border, and nasolabial profile amongst the four centers (Mercado et al., 2011).

Although many centers had adopted the use of IO, in the late 80s, Matsuo and Hirose started considering the elasticity of alar cartilage and began researching the effect of nasal molding in patients with CLP (Matsuo and Hirose, 1988). By the early 90s, Grayson brought this approach to the forefront of cleft lip and palate treatment with a new type of IO termed nasoalveolar molding (NAM). Unlike traditional IO that targeted the position and shape of the alveolar processes only, the NAM technique adds a nasal stent to the molding plate to enhance the position and shape of the nose as well (Grayson et al., 1999).

The NAM process starts with an initial heavy-bodied silicone impression of the infant’s maxillary arch within the first week of birth. The impression is then poured in dental stone resulting in a cast to which the molding plate is fabricated (Grayson and Shetye, 2009). The plate is made of hard, clear self-cured acrylic 2 to 3mm in thickness (Grayson et al., 1999). A retention button (2 buttons in the case of an infant with BCLP) is added to the anterior aspect of the plate, and used to help secure the plate extraorally with the use of surgical tapes (steri-strips) with orthodontic elastics at one end (Grayson and Shetye, 2009). The elastics are stretched approximately twice their diameter to provide roughly 100g of force (Grayson et al., 1999). As the infant’s palate changes, the plate requires weekly or biweekly adjustments. Hard acrylic may be removed in certain spots, while soft denture base is added in others maintaining no more than
1mm of change per visit. Parents are advised that infants should wear the appliance full-time, and remove it only for daily cleaning (Grayson and Shetye, 2009).

According to Grayson, the nasal stent is only added to the NAM appliance after the width of the alveolar cleft has been reduced to 3 to 5mm. That is because attempting to address the nasal cartilage deformity prior to reducing the cleft could result in an undesirable increase in the circumference of the lateral alar wall, producing what has been termed a "mega-nostril". Once the cleft width has been reduced, the nasal stent is fabricated using 0.36-inch diameter round stainless steel wire adapted into a “swan-neck” shape and attached to the labial flange of the plate. The wire extends into the nostril where a bi-lobed hard acrylic portion is covered by soft denture liner. The upper lobe lifts the nasal dome, while the lower lobe lifts the nostril apex and defines the top of the columella (Grayson et al., 1999). The nasal cartilage is then molded using gradual additions of acrylic resin to the stent.

NAM currently enjoys great popularity within the cleft field, especially in North America, yet it is not without controversy. Proponents of NAM highlight its benefits in decreasing the size of the alveolar cleft, improving nasal symmetry, and increasing nostril height (Ezzat et al., 2007). Some also suggest improved feeding and additional psychological benefits to parents who feel as though they are participating first-hand in the treatment of their affected child (which is a claimed benefit of all IO approaches). On the flipside, critics focus on the associated burden of care, both financial and emotional, related to the use of NAM, and question its long-term effect on nasolabial esthetics (Singer, 2012).

Maull et al. reported a significant improvement in nasal symmetry in patients with UCLP treated with NAM at the mean age of 4.5 years (Maull et al., 1999). However the authors acknowledge their limitations in including a control group that is not age-matched (mean age of 9 years-1 month) to the experimental group. Also, the authors realize that their long-term follow-up involves children who have not yet completed growth (Maull et al., 1999).

Currently, the longest follow-up study on NAM available in the literature is 9 years (Barillas et al., 2009). The study suggests greater nasal symmetry in patients who underwent NAM (n=15) versus those who received surgery only (n=10), however the authors conclude by drawing attention to the need for randomized control trials to support their results (Barillas et al., 2009).
There are currently no published randomized clinical control trials involving NAM. Furthermore, the available attempts at systematic reviews and meta-analyses are limited due to the great heterogeneity in cleft treatment and due to the lack of robust studies.

2.5 Primary surgical repair of CUCLP

Another factor contributing maximally to the great heterogeneity in cleft care is surgical repair. Surgeons vary in technique of preference, skill and experience. Primary lip repair and nasal reconstruction generally occurs between the neonatal period to approximately 6 months of age (Campbell et al., 2010). Primary repair of CUCLP involves restoring functionality of the oro-nasal sphincter and soft tissues. Although no universal protocol is in place for the timing of surgical correction, generally the ‘rule of 10s’ (an age of at least 10 weeks, with a weight of 10 lbs and a hemoglobin level of 10g/dl) remains appropriate. Similarly, the stages of surgical repair can vary although two patterns tend to be followed. One pattern involves repair of the lip followed by repair of the hard and soft palate a few months later, while another pattern involves repair of the lip and soft palate followed by delayed repair of the hard palate at approximately 18 months of age (Rohrich et al., 2000).

Various techniques of surgical repair are popular around the world. In the early days, cleft lip repairs followed a straight-line closure technique (Rose, 1891; Thompson, 1912). By the 1950s, a technique using a triangular flap modification became very popular (Blair and Brown, 1930; Brown and McDowell, 1945). Tennison and Randall used this approach to improve the esthetics of the cupid’s bow and the lip tubercle by carrying tissue to the lower part of the lip (Tennison, 1952). Millard developed a rotation-advancement technique that improved esthetics and resulted in an anatomic lip repair and tip rhinoplasty. With time, many modifications have been made to this technique to improve lengthening of the columella and to decrease alar base scarring (Millard, 1957). In the 1970s Delaire re-introduced the straight-line closure technique with the addition of a functional muscle repair, diminishing the risk of lip shortening due to scar contracture (Markus and Delaire, 1993).

Cleft palate repair has also evolved over time. In 1862, Bernhard von Langenbeck demonstrated a cleft palate repair that in principle remains in use today. von Langenbeck used two mucoperiosteal palatal flaps mobilized medially to repair the palate (Von Langenbeck, 1862). In
the 1930s Victor Veau introduced a three-layer closure of the soft palate using nasal mucosa and posterior based unpedicled flaps for velum lengthening using a V-Y closure technique. Given uncertainty surrounding the long-term stability of gained palatal length, Kriens was the first to emphasize the importance of correct anatomical repair of the velar musculature. His concept of intra-velar veloplasty remains in use today (Kriens, 1969). Later, Furlow published his double opposing Z-plasty technique which allows for simultaneous velar closure in addition to lengthening. The Z-plasty technique includes advantages such as velum lengthening and narrowing of the naso-pharyngeal orifice. In addition, the repair offers more anatomically correct positioning of the levator muscles with less muscle dissection, resulting in less scarring around the muscles. Given these advantages, Furlow’s Z-plasty technique is popular today in many cleft centers (Furlow, 1986).

2.6 Secondary unilateral cleft lip and nose deformity

It is an accepted norm that patients that undergo cleft repair will likely require revisions later in life due to secondary deformities. According to Lee et al., (2011), the secondary cleft lip nasal deformity (CLND) is not as much an unsatisfactory outcome of primary surgery, but an inevitable fate (Lee et al., 2011). The same authors recognize that although patients present with varying deformities of the repaired cleft lip and nose, the following seven features are typically observed (Figure 8):

A. Caudal deflection of the nasal septum away from the anterior nasal spine and vomerine groove to the non-cleft side. This results in twisting of the nasal tip and influences symmetry (Byrd et al., 2007; Cutting, 2000).

B. Deviation of the nasal dorsum to the non-cleft side and fusion with the upper lateral cartilage results in nasal tip and dorsum bending to the non-cleft side (Byrd et al., 2007; Cutting, 2000).

C. The medial crus is set lower on the cleft side. This results in inferior positioning of the alar dome on the cleft side and a shorter columella on the cleft side (Byrd et al., 2007; Kim et al., 2008; Park et al., 1998).

D. The cleft-side lateral crus is attached in a lower position to the piriform aperture. This causes flattening and lateralizing of the cleft-side alar cartilage and lowering of the alar dome (Stenstrom and Oberg, 1961).
E. Given the repeated action of the lip elevator muscles, some discontinuity of the orbicularis oris muscle is observed (Fára, 1968).

F. Inappropriate preoperative primary lip repair design can result in a short or long upper lip (Stal and Hollier, 2002).

G. Deformity of the orbicularis oris muscle can cause absence of the philtral column on the cleft side (Briedis and Jackson, 1981; Latham and Deaton, 1976).

Figure 8 Seven common features of secondary cleft lip nasal deformity: A. Caudal deflection of nasal septum to non-cleft side. B. Deviation of nasal dorsum. C. Low setting of medial crus. D. Tethering deformity of lateral crus. E. Discontinuity of orbicularis oris muscle. F. Short or long upper lip. G. Absence of philtral column. (Lee et al., 2011)

Recognizing and appreciating the secondary CLND has led to several modifications of techniques of surgical repair to improve treatment for patients. Furthermore, understanding the secondary CLND allows researchers to have a better appreciation of treatment outcomes when evaluating various treatment protocols and their limitations.

2.7 Methods of assessment of the cleft-related facial deformity

In order to determine the most appropriate evidence-based course of treatment, an objective set of criteria needs to be applied to evaluate the cleft-related facial deformity. To date, two-
dimensional media, including photographs and video recordings, are the most commonly used stimulus media for assessing cleft-related deformities (Al-Omari et al., 2005). Various forms of photographs have been used including color (Glass and Starr, 1979), black and white (Glass et al., 1981), projected color transparencies (Schneiderman and Harding, 1984), and on-screen digital (Becker et al., 1998). Several facial areas have also been investigated including frontal and lateral facial views (Eliason et al., 1991), views cropped below the eyes, nasolabial area only views (Tobiasen et al., 1991), and inferior views of the nose showing the upper nasal perimeter below the eyebrows and above the canthi (Cussons et al., 1993). Although video recordings have also been investigated, pitfalls surrounding inter-rater reliability and reproducibility of images from video were found (Benson and Richmond, 1997; Morrant and Shaw, 1996; Russell et al., 2000).

Given that cleft centers’ records readily include photographs, Asher-McDade et al. focused on using these images to develop a standardized rating scheme to evaluate the soft tissue anomalies associated with clefts. Asher-McDade et al. realized that rating full face photographs involved great bias from features not affecting the cleft, such as hair, eyes, and overall attractiveness. As a result, photographs were cropped to show only the nasolabial area (Figure 9). Raters were made familiar with all the images prior to rating by completing a practice rating task. Furthermore, in order to improve inter-rater reliability, a graduate ordinal scale was proposed from 1 (“very good” appearance) to 5 (“very poor” appearance) to describe the nasolabial esthetics. Four features were assessed individually including nasal form, nasal symmetry, vermillion border, and nasal profile including the upper lip. Feature-specific scores offered clinicians the ability to assess these categories individually (Asher-McDade et al., 1991). Kuijpers-Jagtman et al. further introduced one example photograph to represent each score per nasolabial feature being rated (Figure 10). These reference photographs were made available to raters to view in comparison to the patient being rated (Kuijpers-Jagtman et al., 2009).
Figure 9 Cropped photographs

Figure 10 Reference photographs for rating the nasolabial area in UCLP. One reference photograph is provided to represent each score from 1 to 5 per feature (Kuijpers-Jagtman et al., 2009).
Building upon the work of Asher-McDade et al. and Kuijpers-Jagtman et al., the Americleft group suggested three further modifications. Firstly, the Americleft group expanded the reference photographs to include multiple examples representing the range of possibilities for each score in each category (Figure 11). Secondly, in order to shorten and simplify the ratings the nasal form and nasal symmetry categories were consolidated into one nasal frontal group. Lastly, the Q-Sort method (Stephenson, 1953) for assessing smile esthetics was adopted, meaning that each rater is provided unlimited time to sort through the entire set of photographs and could divide them into five piles from most (rated 1) to least (rated 5) esthetically pleasing. Raters are additionally given the liberty to go back and re-rate photos if necessary. As a result of these modifications, the Americleft group has shown improved reliability of the Asher-McDade methodology in rating nasolabial esthetics (Mercado et al., 2016).

Figure 11 Multiple reference photographs are provided representing a score of 1 for vermillion border (Mercado et al., 2016).
3 Statement of the problem

Over the past two decades the NAM technique has become routine practice in more than one-third of US cleft centers (Sischo et al., 2012). In a systematic review of the literature of 134 publications narrowed down to 12, van der Heijden et al. concluded that NAM outcomes indicated a positive trending effect (van der Heijden et al., 2013). Grayson reported that most of the literature, including the 12 publications reviewed by van der Heijden et al. either showed “significant positive effects of NAM on nasal symmetry, nasal tip projection, and columella elongation” or showed "a mix of positive change in some variables and no change in others". Few articles show no positive outcomes from the use of nasoalveolar molding” (Grayson, 2013). Despite these positive trending findings, the evidence supporting NAM mainly consists of assessments performed at a young age. Of the 12 articles reviewed by van der Heijden, 11 studies investigated results following NAM ranging from before lip repair to 5.1 years after lip repair. Only one of the 12 publications reported a later follow-up period at a mean age of nine years (Barillas et al., 2009). Although some studies justify the use of NAM in the short-term, more research is necessary on its long-term benefits to patients.

Given the limited literature available to support NAM’s long-term benefits, we have decided to conduct a scientific investigation of this topic. Toronto’s HSC offers a unique opportunity to study the effects of NAM. Up to the year 2000, the management protocol of infants with UCLP included TIO. In 2001 the protocol changed to include NAM instead of TIO. No other major protocol changes have been implemented in the interim. The same group of surgeons, with few changes, have been involved in cleft treatment prior to and following 2001. This offers a relatively homogenous landscape to compare the effects of NAM versus TIO by studying a similar substrate (patient population) with the involvement of a similar surgical team utilizing more or less similar surgical approaches.
4 Objective of study

To investigate the long-term nasolabial esthetic outcome of NAM, TIO, and no IO in the treatment of patients with CUCLP, at the mean age of 11 years 8 months.

5 Hypothesis

- Null Hypothesis: There is no significant difference at a mean age of 11 years 8 months in the nasolabial esthetics of patients with CUCLP that were treated with NAM, TIO, and no IO.

- Alternate Hypothesis: There are significant differences at a mean age of 11 years 8 months in the nasolabial esthetics of patients with CUCLP that were treated with NAM, TIO, and no IO.
6 Samples & Methods

6.1 Samples

Three different cohorts of patients with CUCLP were compared with regard to their nasolabial appearance. The three groups comprised of 30-40 patients between the ages of 10 to 14 years, treated with three different management protocols at infancy, namely using NAM, TIO, and no IO at all. The groups were derived as follows:

1. Group I (n = 37)
   CUCLP treated with NAM
   Hospital for Sick Children, Toronto, Ontario (Date of birth after 2001)

2. Group II (n = 39)
   CUCLP treated with TIO
   Hospital for Sick Children, Toronto, Ontario (Date of birth before 2001)

3. Group III (Control, n = 33)
   CUCLP treated without any IO
   Lancaster Cleft Palate Clinic, Lancaster, Pennsylvania

The Research Ethics Board of each participating center provided approval for use of clinical records and standardized photographs prior to initiating the investigation.

6.2 Inclusion criteria

1. Only Caucasian patients were included as to avoid racial variations in craniofacial form.
2. Patients diagnosed with complete unilateral cleft lip and palate (CUCLP) with no associated anomalies or syndromes.
3. All cleft treatment including infant orthopedics or surgery were performed at the institution of record, and complete records were available.
4. Good quality extraoral photographs including frontal view of the face with lips in repose and the cleft-side profile were available for patients between ages 10 to 14 years.
5. None of the patients in any of the groups underwent GPP or primary alveolar repair.
6.3 Descriptive data

The following descriptive data were recorded for each patient included in the study:

1. Gender
2. Date of birth
3. Side of Cleft
4. Age at the time that the photographs being used for assessment were taken
5. Type of infant orthopedic appliance (if used)
6. Lip repair technique and surgeon performing repair
7. Hard palate repair and surgeon performing repair
8. Age at secondary alveolar bone grafting (ABG), if applicable
9. Age at lip/nose revision (if applicable) and surgeon performing the revision

6.4 Sample sizes

1. Group I
   a. N = 37
   b. 29 (78%) were male
   c. 8 (22%) were female
   d. Left side clefts occurred in 27 subjects (73%)
   e. Right side clefts occurred in 10 subjects (27%)
   f. NAM was used
   g. Surgical repairs were performed by 4 different surgeons
   h. Photographs were taken at a mean age of 11y 10m
   i. All patients had cleft-side photographs available

2. Group II
   a. N = 39
   b. 22 (56%) were male
   c. 17 (44%) were female
   d. Left side clefts occurred in 28 subjects (71%)
   e. Right side clefts occurred in 11 subjects (29%)
   f. TIO were used
g. Surgical repairs were performed by 3 different surgeons
h. Photographs were taken at a mean age of 12y0m
i. All patients had cleft-side photographs available

3. Group III
   a. N = 33
   b. 20 (60%) were male
   c. 13 (40%) were female
   d. Left side clefts occurred in 17 subjects (52%)
   e. Right side clefts occurred in 16 subjects (48%)
   f. No IO were used
   g. Surgical repairs were performed by 1 surgeon
   h. Photographs were taken at a mean age of 11y 3m
   i. All patients had cleft-side photographs available

The sample demographics are depicted in Table 1 and protocol details per center are described in Table 2.

<table>
<thead>
<tr>
<th>Group</th>
<th>Sample total</th>
<th>Male</th>
<th>Female</th>
<th>Left-sided Cleft</th>
<th>Right-sided Cleft</th>
<th>Mean age (ym)</th>
<th>Age range (ym)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 – NAM</td>
<td>37</td>
<td>29</td>
<td>8</td>
<td>27</td>
<td>10</td>
<td>11y10m (142m)</td>
<td>9y8m – 14y10m (116m-178m)</td>
</tr>
<tr>
<td>Group 2 – TIO</td>
<td>39</td>
<td>22</td>
<td>17</td>
<td>28</td>
<td>11</td>
<td>12y0m (144m)</td>
<td>9y11m – 15y9m (119m-189m)</td>
</tr>
<tr>
<td>Group 3 – no IO</td>
<td>33</td>
<td>20</td>
<td>13</td>
<td>17</td>
<td>16</td>
<td>11y3m (135m)</td>
<td>10y0m – 13y6m (120m-162m)</td>
</tr>
</tbody>
</table>

Table 1 Sample Demographics
<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of IO</td>
<td>NAM</td>
<td>TIO</td>
<td>None</td>
</tr>
<tr>
<td>Lip repair technique</td>
<td>4-5 months, Modified Straight Line Closure +/- Inferior Triangle</td>
<td>3 months, Modified Millard</td>
<td>3 months, Tennison</td>
</tr>
<tr>
<td>Hard palate repair</td>
<td>18 months, Modified Von Langenbeck/Veau +/- Vomer flap</td>
<td>12-14 months, Modified Von Langenbeck/Wardill-Kilner/Veau +/- Vomer flap</td>
<td>12 months, Vomer flap</td>
</tr>
<tr>
<td>Soft palate repair</td>
<td></td>
<td></td>
<td>18 months, Median suture with Intravelar Veloplasty</td>
</tr>
<tr>
<td>Age at secondary bone grafting</td>
<td>8-10 years</td>
<td>9-12 years</td>
<td>9 years</td>
</tr>
<tr>
<td>Number of surgeons</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 2 Protocol table per cleft center**
6.5 Methods

The study was retrospective in nature, utilizing patient records previously obtained for treatment as per each cleft center’s protocol. Records were gathered and evaluated at a single site twice on two days by 6 blinded raters, including orthodontists and oral surgeons, experienced in cleft treatment and in assessment of its outcomes using a nasolabial esthetic rating scale.

Nasolabial esthetics were assessed based on cropped frontal and cleft-side profile photographs. Depending on when the photographs were taken, photographs were available in either photographic slide or digital format. If a photograph was available in slide format it was scanned at the highest possible resolution and converted to digital. The orientation of all profile photographs were in accordance with the North American standard of the right sided profile view. As such, all left-sided cleft photographs were flipped to the right. Photographs were prepared in accordance with the Americleft Study Guide, as follows:

- Photos were taken on a single color, well-lit, non-textured background with eye-glasses, hats and nose jewelry removed.
- Full-face frontal photo taken at repose (not smiling), without strain on the lip musculature and keeping the inter-pupillary plane parallel to the floor.
- Patient’s head should be oriented at natural head position. If the camera has a single point flash, it should be oriented 90° so the flash is on the same side of the nose. The 90° profile photos must be taken from both the right and left side of the patient’s full face. Lips should be at rest.
- Each patient must have a complete set of quality photos. If a patient has one image in the set that is not of adequate quality, the patient must be excluded from the study.
- Photos were scanned and saved as JPEG images with at least a 1400dpi resolution.
- Frontal images - Adobe Photoshop was used to tilt the image so that the inter-pupillary plane is horizontal. This corrected for canting on the face due to posturing. Following this step, a small white circle was used to block or cut out individually both irises of the eyes, while preserving the inner canthi of the eyes visible in the image. The nasion area (between the eyes) was not blocked.
- Profile images – a small white triangle was used to block out the eye on each image. The profile images were not tilted clockwise or counterclockwise.
- Adobe Photoshop software was used to crop all images. The only areas to show were the nasolabial area, inner canthus, nose bridge, nostrils, philtrum and upper lip.

- Any background shown on the profile images was standardized to the same color.

The method used for the rating of the photographs was the Q-Sort modification of the Asher-McDade method (as suggested by the Americleft group). The 3 nasolabial categories evaluated were the vermillion border, nasolabial frontal, and nasolabial profile. Photographs were printed on 4 x 6 inch index cards and labeled randomly with case numbers. Prior to assessment, raters went through a 45-minute training and calibration session. During the assessment each rater was provided unlimited time to sort a set of photographs into five piles from most (rated 1) to least (rated 5) esthetically pleasing. Raters were able to go back and re-rate photos if needed, until they were satisfied with the way they classified the photographs into 5 “stacks”. Raters were provided written criteria and a visual yardstick demonstrating what constitutes a rating of 1, 2, 3, 4, and 5 for each of the categories of vermillion border, nasolabial frontal, and nasolabial profile. The visual yardsticks were derived from photographs that were uniformly rated by previous raters and in previous studies. Once a rater was finished rating all photographs for a particular category he/she would write the rating scores on a recording sheet for data collection (Figure 12) (Mercado et al., 2011).
6.6 Statistical analysis

In order to analyze the non-parametric categorical nasolabial esthetic scores, a Kruskal-Wallis test with a Bonferroni correction for pairwise comparisons was used. Power analysis calculations were also performed with the type I error rate (α) set at 0.05 and the statistical power (1-β) set at 0.80 in order to detect a reasonable departure from the null hypothesis.
7 Results

7.1 Nasolabial esthetic scores

Following data collection, one hundred and nine (109) patient photographs were evaluated. Figure 13, Figure 16, and Figure 19 illustrate the percentage distribution of scores from 1 to 5 for the three categories of vermilion border, nasolabial frontal, and nasolabial profile respectively, for each group.

7.1.1 Vermilion border

Significantly superior scores for vermilion border were detected (p=0.002) for Group 1 – NAM (median score = 2.833) and Group 2 – TIO (median score = 2.917), compared to Group 3 – no IO (median = 3.583) (Figure 13, Figure 14, Figure 15).

![Figure 13 Percentage distribution of vermilion border scores for each group](image-url)
Figure 14 Vermilion border means and 95% CI's by group

Figure 15 Pairwise comparisons of the three groups with respect to their vermilion border ratings. On the right side of the figure is a graphic representation of the degree of statistical significance as per the Kruskal-Wallis test. When the blue dot at the end of the horizontal blue line lies beyond the outer (left or right) interrupted red lines this denotes a significant difference between the two groups being compared.
7.1.2 Nasolabial frontal

Significantly favorable frontal-view nasal form and symmetry (p=0.015) were found in Group 1 – NAM and Group 2 – TIO cohorts (both median scores = 3.00) over Group 3 – no IO (median = 3.417) (Figure 16, Figure 17, Figure 18).

![Figure 16 Percentage distribution of nasolabial frontal scores per group](image-url)
Figure 17 Nasal frontal means and 95% CI’s by group

Figure 18 Pairwise comparisons of the three groups with respect to their nasal frontal ratings. On the right side of the figure is a graphic representation of the degree of statistical significance as per the Kruskal-Wallis test. When the blue dot at the end of the horizontal blue line lies beyond the outer (left or right) interrupted red lines this denotes a significant difference between the two groups being compared.
7.1.3 Nasolabial profile

The Group 2 – TIO sample demonstrated a significantly (p<0.001) favorable nasal profile appearance (median score = 2.917) in comparison to the NAM and no IO samples (median scores of 3.250 and 3.917, respectively) (Figure 19, Figure 20, Figure 21).

![Percentage distribution of nasolabial profile scores per group](image)

*Figure 19 Percentage distribution of nasolabial profile scores per group*
Figure 20 Nasal profile means & 95% CI's by group

Figure 21 Pairwise comparisons of the three groups with respect to their nasal profile ratings. On the right side of the figure is a graphic representation of the degree of statistical significance as per the Kruskal-Wallis test. When the blue dot at the end of the horizontal blue line lies beyond the outer (left or right) interrupted red lines this denotes a significant difference between the two groups being compared.
7.2 Mean scores

The mean scores across all three cohorts for each individual category along with the mean cumulative total scores are depicted in Table 3.

![Mean Scores per Nasolabial Esthetic Category and Total Cumulative Scores](image)

**Table 3 Mean Scores for each Nasolabial Esthetic Category per Center and Total Cumulative Scores**

7.3 Median values

The median values for each cohort across the esthetic categories and the results of the Kruskal-Wallis multiple and pairwise comparisons are summarized in Table 4.

<table>
<thead>
<tr>
<th></th>
<th>Vermillion Border</th>
<th>Nasolabial Frontal</th>
<th>Nasolabial Profile</th>
<th>Total Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 - NAM</td>
<td>2.833</td>
<td>3.000</td>
<td>3.250</td>
<td>3.000</td>
</tr>
<tr>
<td>Group 2 - TIO</td>
<td>2.917</td>
<td>3.000</td>
<td>2.917</td>
<td>2.917</td>
</tr>
<tr>
<td>Group 3 - no IO</td>
<td>3.583</td>
<td>3.417</td>
<td>3.917</td>
<td>3.583</td>
</tr>
<tr>
<td>Kruskal-Wallis (Multiple Comparisons)</td>
<td>p = 0.002</td>
<td>p = 0.015</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

**Table 4 Median scores for each nasolabial esthetic category per group and the significance of their differences as per the Kruskal-Wallis test for multiple comparisons**
7.4 Intra- and Inter-rater reliabilities

The intra and inter-rater agreement in the ratings was assessed by calculating Cohen’s kappa coefficient for categorical measurements. In order to better communicate kappa statistics, Landis and Koch arbitrarily established the following classification system to ascribe a strength of agreement to an associated kappa value (Landis and Koch, 1977):

<table>
<thead>
<tr>
<th>Kappa Statistic</th>
<th>Strength of Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.00</td>
<td>Poor</td>
</tr>
<tr>
<td>0.00-0.20</td>
<td>Slight</td>
</tr>
<tr>
<td>0.21-0.40</td>
<td>Fair</td>
</tr>
<tr>
<td>0.41-0.60</td>
<td>Moderate</td>
</tr>
<tr>
<td>0.61-0.80</td>
<td>Substantial</td>
</tr>
<tr>
<td>0.81-1.00</td>
<td>Almost perfect</td>
</tr>
</tbody>
</table>

Table 5 Strength of agreement labels for Kappa Statistics (Landis and Koch, 1977)

Based on the above “benchmarks” set by Landis and Koch (1977), the strength of intra- and inter-rater reliability when assessing all three categories in the present study should be considered substantial. Table 6 reports the specific mean weight intra- and inter-rater kappa statistics and ranges for each category of nasolabial esthetics:

<table>
<thead>
<tr>
<th>Nasolabial Esthetic Variable Evaluated</th>
<th>Mean Weighted Intra-rater Kappa Statistic (and ranges)</th>
<th>Mean Weighted Inter-rater Kappa Statistic (and ranges)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vermillion Border</td>
<td>0.747 (0.598 – 0.836)</td>
<td>0.616 (0.455 – 0.726)</td>
</tr>
<tr>
<td>Nasolabial Frontal</td>
<td>0.766 (0.620 – 0.832)</td>
<td>0.627 (0.422 – 0.753)</td>
</tr>
<tr>
<td>Nasolabial Profile</td>
<td>0.753 (0.699 – 0.810)</td>
<td>0.596 (0.489 – 0.639)</td>
</tr>
</tbody>
</table>

Table 6 Mean weighted intra- and inter-rater reliability kappa statistics (and ranges) among six raters for three variables of nasolabial esthetics
8 Discussion & Study Limitations

The growing popularity of NAM intensifies the need for scientific evidence to help determine its efficacy and usefulness amongst the many infant management protocols available. This investigation evaluated the long-term nasolabial results following NAM, TIO, and no IO by presenting data at the mean age of 11 years 8 months. To our knowledge, this represents the longest follow-up period that has been published on NAM to date.

Applying the pre-specified selection criteria we were able to generate three cohorts of patients from 2 different centers that represented three different approaches of cleft infant management. The two cohorts came from the same center before and after the change in protocol. This change offered a unique opportunity to study the effects of NAM while most of the remaining variability was controlled to the extent possible. The NAM and TIO samples followed the typical 2:1 gender distribution generally seen in patients with UCLP. However, this was not true for the no-IO group. This was reconfirmed and attributed to the number of patients from this group that were excluded due to lack of the required records. The results showed that patients treated with NAM and TIO at infancy presented with improved outcomes in vermilion border and nasolabial form by the mean age of 11 years 8 months when compared to patients that were treated without IO. This comes in contrast with the results of the Dutchcleft study that found no long-term esthetic difference at a mean age of 6 years between patients treated with IO and those treated without IO (Prahl et al., 2006). NAM’s superior vermilion border and nasolabial frontal esthetic scores are echoed by others such as Barillas et al., who also found better nasal symmetry in patients (mean age of 9 years) that were treated with NAM compared to those who had surgery alone with no IO treatment (2009).

Whether the advantage lies in improving arch form, facilitating surgical repair, refining nasal symmetry, or enhancing lip esthetics (Berkowitz et al., 2004; Konst et al., 2004; Kuijpers-Jagtman et al., 2009; Kuijpers-Jagtman and Ross E. Long, 2000; Mishima et al., 2000; Prahl et al., 2001; Ross and MacNamera, 1994), these data suggest that long-term, both NAM and TIO provide a more pleasing nasolabial appearance. Although opponents emphasize the complexity, cost, and associated burden of care linked to IO (Konst et al., 2004; Prahl et al., 2001; Severens et al., 1998), this study draws attention to its lasting esthetic benefit.
Grayson et al. further emphasizes that the “major intraoral benefit of NAM is its ability to guide the alveolar segments into a normal position prior to surgery” (1999). However, this ability is not unique to NAM. Improvement in maxillary arch form through alveolar molding to facilitate lip and nasal repair is the main goal and outcome of most presurgical infant orthopedic approaches (Berkowitz, 2013; Kuijpers-Jagtman et al., 2009; Mishima et al., 2000; Prahl et al., 2006; Prahl et al., 2001; Ross and MacNamara, 1994). The results of our study demonstrated that the vermilion border was improved by both NAM and TIO, with no significant difference between the two. With respect to the vermilion border this was not surprising, as this is the category that is thought to mainly depend on surgical skill rather than approximation or preparation of the segments via IO.

Our results also indicated that there was in fact no significant difference in nasal form from the frontal view between patients who were treated with NAM versus TIO in the long run. This comes in contrast with the findings of Maull et al., that NAM significantly improves nasal symmetry from the frontal view when compared to TIO (Maull et al., 1999). Maull et al.’s methodology was significantly different, their follow-up was shorter, and their control group was not age-matched. However, the contrast between the two studies may stem from the fact that they targeted different aspects of the nose based on their methodology. The Maull study strictly looked at symmetry (through a mirror image superimposition), whereas our study looked at overall nose shape from the front, long axis deviations differences in the alar base position and dome symmetry.

The main distinguishing feature of NAM is the presence of the nasal stent. It is with the nasal stent that NAM is purported to aid in repositioning the columella and septum from an oblique position to an upright one, and in lifting the alar dome to improve the appearance of the, yet unrepaired, cleft nose. It is expected and hoped that this change would result in an improved nasal tip projection and greater symmetry in the alar bases after the repair of the lip and nose and beyond. Unexpectedly however, in this investigation, it was TIO and not NAM that demonstrated superior esthetics in nasal profile, whereas no significant difference was detected between the NAM and no-IO groups. In other words, our study suggests that NAM may not offer a significant long-term benefit on nasal profile esthetics regardless of the use of a nasal stent. These findings may mean that it may be alveolar molding that plays a more critical part in
improving the bony foundation for a more symmetrical nose with better projection, rather than the addition of a nasal stent.

In addition to the proposed benefits of nasal molding, Grayson et al. suggest that NAM will result in a reduction in the number of surgeries required over a patient’s lifetime (Grayson et al., 1999). In an attempt to test this hypothesis we went back to review the charts of the patients in our samples. Unfortunately this information for the TIO cohort was unavailable as many of their charts had been purged following electronic conversion. Obviously, there is a fair amount of subjectivity that is exercised in the decision to revise a nasal repair, and the criteria likely vary among individual surgeons. Given the limitations of the available records, it was not possible to evaluate the claimed benefit of NAM over TIO in reducing secondary surgeries.

Our data suggest that NAM reduces the size of the cleft pre-surgically and demonstrates improved nasal symmetry from the frontal view. However, TIO offers similar outcomes without the increased burden of care that accompanies NAM. In addition, although the potential role of growth and/or future surgical procedures must be considered, the claimed superiority of NAM in enhancing the nasal profile is not supported, especially when compared to the outcomes of TIO.

Like all multicenter cleft studies, several confounding variables must be considered when interpreting the results. Given that the duration of cleft treatment is lengthy and involves several surgeries from birth to adulthood, the compound effect of various interventions other than the type of neonatal presurgical management could affect the presentation by age 10-14 years. Thus, attributing the findings directly to the type of IO is not sensible. Also, given the multidisciplinary approach to cleft treatment, proficiency bias, including surgical skill and technique used, can influence our results. Further, owing to the lengthy follow-up period as well as the broad age range assessed, the role of maturation, or the lack thereof, must be considered when interpreting the results. When studying patients in the 10-14 year age range, many fall in the pre-pubertal or pubertal stage and as such can vary greatly in terms of maturation. Although this age range is the longest follow-up period reported studying NAM, follow-up to the end of puberty or beyond, would be preferable. However, given the difficulty of collecting retrospective records and the relatively low prevalence of complete unilateral clefts such records were simply not available at the time of our data collection. Lastly, although the Asher-McDade
methodology is one of the most widely used for the assessment of nasolabial esthetics, it has some inherent limitations. This method cannot isolate the specific aspect or feature in a nose (i.e. alar base, nasal tip) that resulted in a good or poor rating. It also assesses vermillion border but does not evaluate the remaining elements of the lip (e.g. philtrum, scar elevation, vermilion thickness). The decision to employ this method was made because it is the most recognizable method to date and we wanted to make the results comparable to previous studies.
9 Conclusions

Under the conditions and limitations of this study, the following conclusions could be reached:

1. NAM and TIO result in improved vermillion border and nasolabial frontal esthetics in the treatment of non-syndromic patients with CUCLP between the ages of 10-14 years in comparison to patients who had no IO.

2. TIO results in improved nasolabial profile esthetics in the treatment of non-syndromic patients with CUCLP between the ages of 10-14 years in comparison to patients who had NAM or no IO.

3. No significant difference was found in nasolabial profile esthetics between the NAM and no-IO group in the treatment of non-syndromic patients with CUCLP between the ages of 10-14 years.
10 Future directions

This study had several obvious limitations, owing to the nature of the existing retrospective data, the large variability in cleft treatment and the differences among centers, and to the methodology applied in the assessment of facial esthetics. It is hoped that in the not-too-distant future the conditions will be such that will allow the organization and execution of a prospective randomized controlled trial on the topic of NAM, similar to the Dutchcleft trial. This study could potentially not be limited to static photography, but rather be based on 3D photography or an advanced color version of a surface scan. The cohorts that would be followed prospectively could be operated on by the same surgeons using the same surgical repair, and the remainder of the protocol be kept standardized. A detailed comprehensive assessment method could be employed, considering specific aspects of the vermilion and cutaneous portions of the lip, as well as the nasal morphology, and how they contribute to the overall esthetic appearance of the face. It should be noted here that the Americleft surgical group is currently working on developing such a systematic evaluation of various components from static photographs. The assessment ideally should not be limited to static views but instead include a dynamic evaluation of the repaired facial muscles during movements and function of the lips and nose.

Even though the above scenario currently seems to belong in the sphere of science fiction, it is sincerely hoped that future generations of cleft researchers will someday be able to contribute to the literature studies like that. Only then will we be able to make definitive statements about the true value of NAM in comparison with other types of presurgical infant management and their long-term implications.
11 References


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