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EVALUATION OF NASOALVEOLAR MOLDING IN CLEFT CARE: EFFECT ON MAXILLARY GROWTH AND BURDEN OF CARE

Ph.D. thesis

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List of Abbreviations

3D: three dimensional

BCLP: bilateral cleft lip and palate

CBCT: cone beam computed tomography

CLP: cleft lip and palate

ECLR: early cleft lip repair

MTHFR: methylenetetrahydrofolate reductase

NAM: nasoalveolar molding

PRS: Pierre-Robin sequence

RCTs: randomized controlled trials

rhBMP-2: recombinant human bone morphogenetic protein-2

SD: standard deviation

1. Introduction

1.1. Cleft lip and palate

1.1.1. Embryogenesis

Craniofacial development is an intricate process in embryogenesis. It encompasses a sophisticated interplay of transcription factors and molecular signals orchestrating the morphogenesis of craniofacial organs, with the cranial neural crest cells in focus (Chai & Maxson, 2006). Any disruption occurring in the early stages of embryogenesis, particularly between the 4th and 12th weeks, may lead to incomplete fusion of the facial prominences, which results in orofacial clefts. Upper lip, soft- and hard palate development is demonstrated in Figure 1. A coordinated sequence of cellular differentiation and growth, migration and apoptosis occur during the development of the hard- and soft palate, alveolar crest, lips and nose (Compagnucci et al., 2021), and defects in this system could lead to cleft lip or/and cleft palate. Despite their simultaneous occurrence, it is noteworthy that cleft lip and palate have distinct embryonic origins (Babai & Irving, 2023).

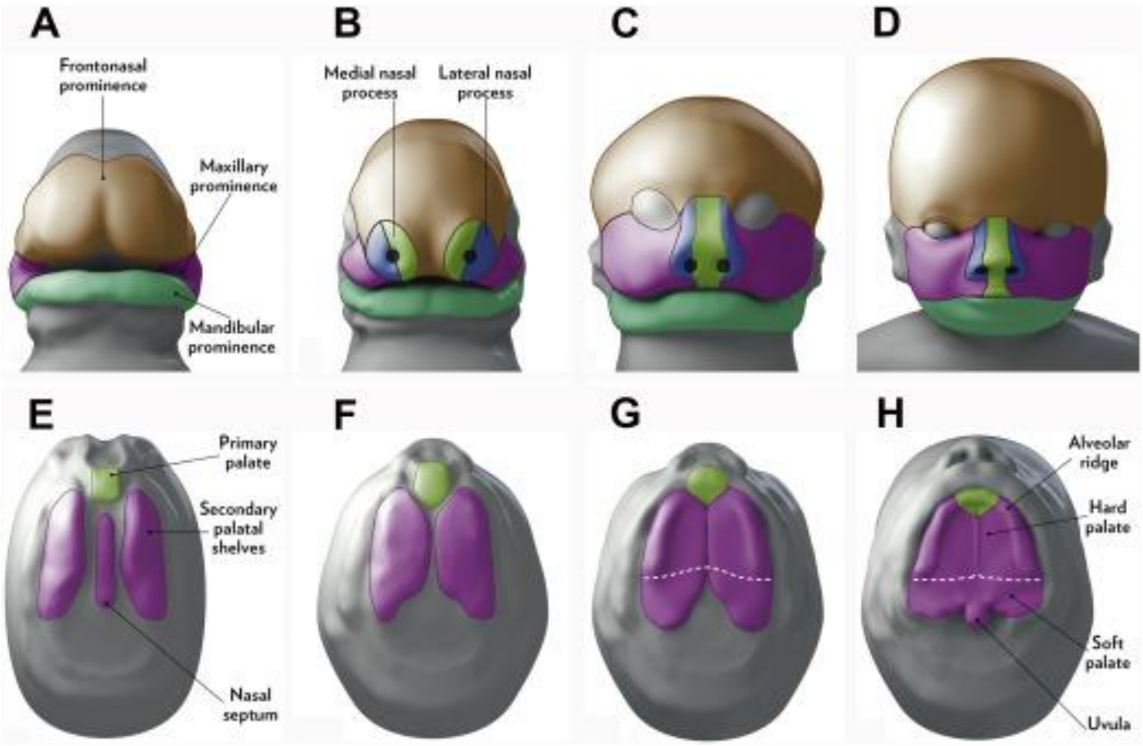

Figure 1 *(A–D) Upper lip development sequence; (E–H) Soft and hard palate development (Worley et al., 2018).*

1.1.2. Prevalence

One of the most common congenital anomalies worldwide are orofacial clefts (OFCs). Their prevalence varies significantly between populations (Dixon et al., 2011): in the Asian population it is as high as 2‰ and in the African population it decreases to 0,4‰ (Babai & Irving, 2023). Disparities in the prevalence of oral clefts are evident at both the national and regional levels, influenced by factors such as racial diversity, climatic conditions, cultural distinctions, and variations in maternal care program. In a meta-analysis, where more than fifty reviews related to the prevalence of orofacial cleft were analyzed, the prevalence of cleft palate was 0.33, cleft lip was 0,3, cleft lip and palate was 0,45 in every 1000 live births (Salari et al., 2022). In Hungary, the prevalence of cleft lip and palate (CLP) is about 2.02‰ (Nagy, 2012).

1.1.3. Risk factors, etiology

Extensive, continuous research is committed to unravel the embryologic development of cleft lip and palate; however, a definitive consensus on their etiology remains elusive (Alois & Ruotolo, 2020). The genesis of CLP is a complex and intricate interaction of genetic, nutritional, and environmental factors, culminating in diverse phenotypes and clinical manifestations of these malformations (Sólya et al., 2015).

Several risk factors play a role in the development of orofacial clefts, including genetic predisposition, exposure to environmental agents such as alcohol consumption, smoking, tobacco use, or secondhand smoke, intake of certain medications (e.g., phenytoin, carbamazepine, oxytetracycline, topiramate, and methotrexate), folate deficiency and maternal metabolic status (diabetes, obesity or low weight) (Shkoukani et al., 2013).

Cleft lip and palate may occur either isolated or as part of various genetic conditions or syndromes (Badovinac et al., 2007). There exist numerous genes associated with syndromic CLP: T-box transcription factor-22, poliovirus receptor-like-1, and interferon regulatory factor-6 play roles in chromosome linked cleft palate, ectodermal dysplasia syndrome, and Van der Woude and popliteal pterygium syndromes (Kohli & Kohli, 2012). Besides the mentioned genes, the enzyme 5,10 methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism raises the risk of neural tube defects. In nonsyndromic cases, it increases the risk of orofacial clefts in offspring by 4.6 times. when coupled with periconceptional folate deficiency, by 10 times (van Rooij et al., 2003).

Additionally, the likelihood of a recurrence of clefts in offspring increases when parents or children have a history of clefts. Nevertheless, in the majority of cases, there is an absence of familial precedent for cleft lip or palate, and there is no recorded history of complicated pregnancies (Alois & Ruotolo, 2020).

1.1.4. Morphology, classification

Facial clefts are characterized by an anomalous opening of variable shape, width, and extent that traverses all layers of the newborn's face, originating from the upper lip and extending towards the forehead, forming a direct passage from the exterior to the oral cavity (Nagy, 2012). Orofacial clefts can be classified based on their location, the degree of involvement of the lip, and the presence of a cleft palate (Alois & Ruotolo, 2020). The various types of oral clefts include cleft lip (CL), complete/incomplete cleft palate (CP), and unilateral/ bilateral cleft lip and palate (CLP) as shown in Figure 2 and Figure 3.

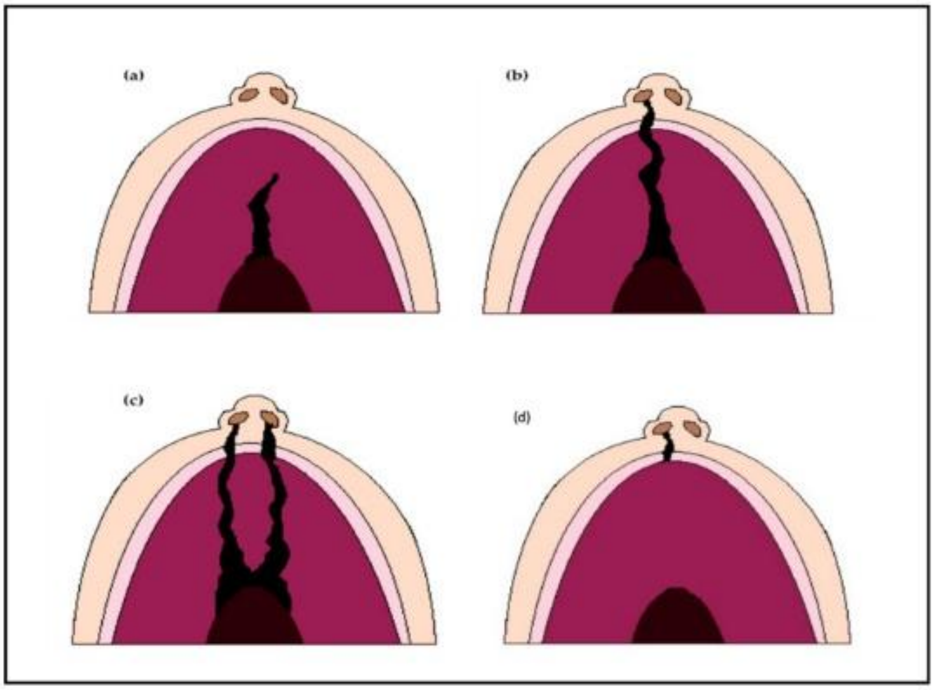

Figure 2 *Types of orofacial clefts: (**a**) Incomplete cleft palate only; (**b**) Unilateral complete cleft lip and palate; (**c**) Bilateral complete cleft lip and palate; (**d**) Cleft lip only (Babai & Irving, 2023).*

Cleft lips are described as complete or incomplete based on the extent of nose involvement, and further categorized as unilateral, bilateral or midline. The most prevalent type is unilateral cleft affecting one side of the lip, which may be combined with cleft palate on the same side (Alois & Ruotolo, 2020).

Cleft palate presents a diverse classification encompassing primary (alveolar arch) and secondary (hard and soft palate) palates, along with distinctions between complete and incomplete, unilateral and bilateral, and submucous clefts. The complete cleft involves the absence of fusion of the palatal shelves, while the incomplete cleft comprises only the secondary palate, demonstrating initial palatal fusion. Further differentiation within the secondary cleft palate is unilateral and bilateral. In unilateral clefts, only one of the palatal shelves fuses with the vomer, while in bilateral clefts, neither palatal shelf fuse to the nasal septum, which leads to defects on both sides of the midline. The cleft can affect not only the soft and hard palate. In approximately 75% of the cases an associated alveolar cleft is present, necessitating subsequent reconstruction of the alveolar bone (Guo et al., 2011). The compromised development of the maxilla leads to the collapse of alveolar bone segments and a reduction in maxillary dimensions (Pálvölgyi, 2024).

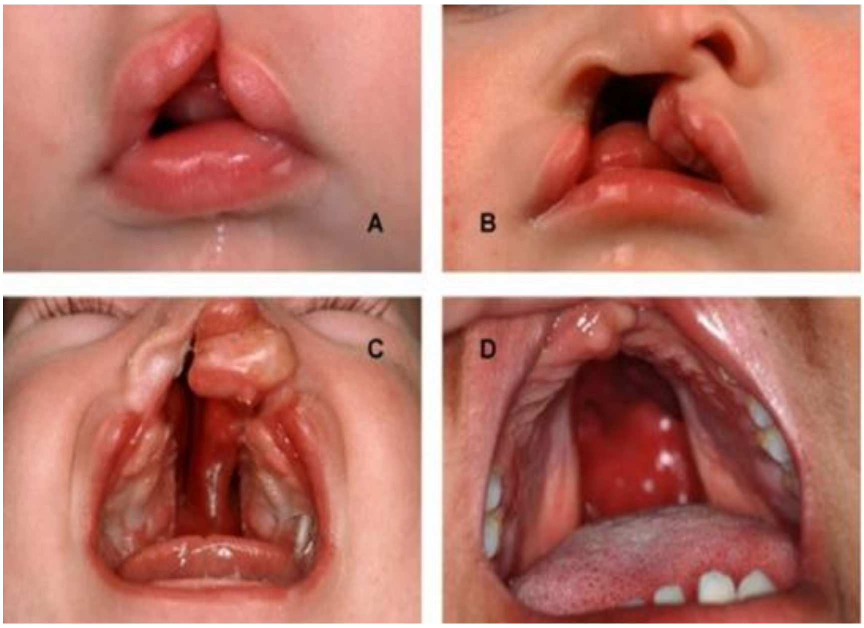

Figure 3 *(A) Unilateral cleft lip; (B) Unilateral cleft lip and palate; (C) Bilateral cleft lip and palate; (D) Midline cleft palate (Magyar et al., 2024).*

Submucosal cleft, characterized by a less pronounced manifestation, is situated beneath the mucous membrane of the soft palate, leading to inadequate function of the levator muscles. The diagnosis of submucosal cleft poses greater challenges during examination, as it may go unnoticed due to the seemingly intact appearance of the soft palate. Detection may be delayed until the child starts to speak.

Fissures may also manifest in other regions of the face, including the periorbital area, ears, nasal region, cheeks, and forehead.

Clefts can be classified as **syndromic** as part of Mendelian diseases, or they may be linked to a chromosomal defect and appear in the clinical phenotype. In contrast to cleft lip and palate, cleft palate only (CPO) is more often linked with a syndrome or genetic disorder. Nevertheless, it is important to note that most of cases involving CLP do not present with other birth defects (Alois & Ruotolo, 2020).

The following syndromes are associated with oral cleft: Stickler or Pierre-Robin sequence (PRS), Van der Woude, Goldenhaar, Treacher-Collins, ectrodactyly-ectodermal dysplasia-clefting, and velo-cardio-facial syndrome (Strong & Buckmiller, 2001). PRS and Van der Woude syndrome are autosomal dominant conditions. Children with PRS often have a cleft palate, a small lower jaw (micrognathia), glossoptosis, collagen disorder, and airway obstruction (Gundlach & Maus, 2006). Children diagnosed with Van der Woude syndrome frequently exhibit cleft lip, pits of the lower lip, and urogenital problems. Cleft palate is commonly associated with Velo-cardio-facial syndrome, which is characterized by cardiovascular abnormalities, including ventricular septal defects, along with distinctive facial features (Alois & Ruotolo, 2020).

The presence of genetic syndromes can aggravate not only the incidence of CLP but also the management and treatment of cleft patients.

1.2. Modern guidelines for the care of cleft patients

The management strategy for cleft lip and palate adopts a multidisciplinary approach, necessitating the inclusion of various specialists such as cleft surgeon, pediatrician, ENT specialist, geneticist, anesthesiologist, speech therapist, nutritionist, oral and maxillofacial surgeon, orthodontist, prosthodontist, psychologist, and ophthalmologist within the cleft team. The objective is to provide comprehensive, long-term care during the child's facial development. The treatment goals encompass the normalization of facial aesthetics, ensuring proper neonatal feeding, preserving the structural integrity of the soft and hard palate, establishing and maintaining optimal speech and hearing, ensuring patency of the airways, achieving a normocclusion with normal mastication, promoting optimal dental and periodontal health, supporting psychosocial development, and enhancing overall well-being. Figure 4 shows the surgical and non-surgical interventions in modern cleft care in chronological order.

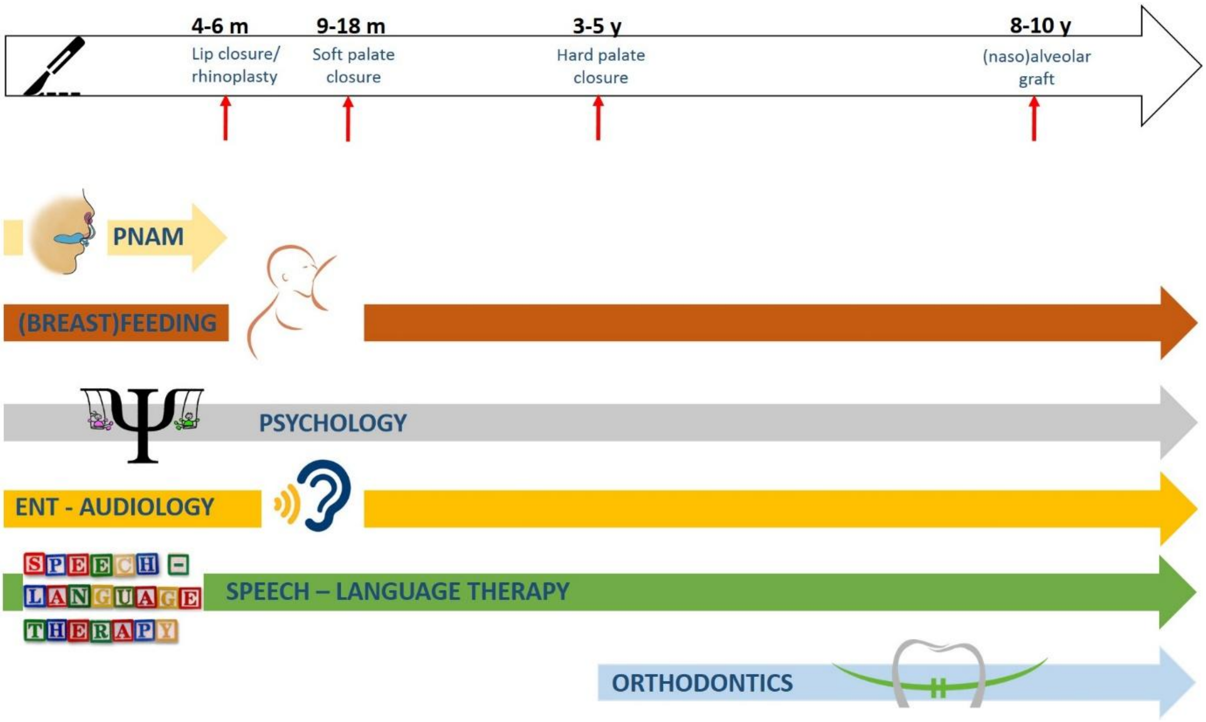

Figure 4 *Timeline of the surgical and non-surgical interventions in modern cleft care (Nagy, 2021).*

Cleft lip and palate (CLP) management lacks universally accepted, standardized approach across the cleft centers, highlighting a notable diversity in clinical practices within this domain. There is a lack of the high level of evidence in the treatment of cleft patients. Numerous clinical decisions are reliant on evidence derived from biased sources, including case reports or retrospective studies (Wadde et al., 2023).

One of the most important aspects of surgical treatment is, that from the first intervention to the entire treatment protocol, the treatment is managed by an oral surgeon who understands and is able to accompany the entire rehabilitation process of the child. The cleft team follows the child's entire pre and postnatal life, thereby supporting his recovery. Surgeries can be divided into primary and secondary surgeries.

1.2.1. Primary surgical interventions

Presurgical nasoalveolar molding (NAM)

To achieve tension-free surgical adjustment of the lip segments and to avoid scar tissue during cheiloplasty, presurgical infant-orthopedic techniques are often performed in cleft lip and palate patients. In our center at Semmelweis University we apply the so called nasoalveolar molding technique described by Grayson et al. (Grayson et al., 1999). With this technique perioral structures and the nasolabial and maxillary segments are brought together with the help of a palatal plate, nasal support and adhesive tapes. The non-surgical intervention starts during the first weeks of life and takes approximately 3-4 months.

Surgical nose/lip adhesion

The surgical nose and lip adhesion is required when the cleft is too wide. The intervention supports that the deformed nose and the jawbone are placed in the correct position. A long-term study demonstrated that lip adhesion is a reasonable alternative to presurgical molding in the case of a wide complete cleft lip (Lee et al., 2021). The optimal timing of surgery is 6 to 8 weeks after the birth.

Definitive lip closure

Cleft lip repair techniques center around the restoration of lip continuity, achieving symmetry in the cupid's bow and nasal structures, and repairing the deficient orbicular muscle of the mouth. Typically, these procedures are performed at 4 to 6 months age (Millard & Latham, 1990; (Nagy & Mommaerts, 2009).

In the case of unilateral cleft lip repair, two techniques are the most commonly used: the Millard technique (rotation-advancement technique) and Tennison-Randall technique (triangular flap technique) (Rossell-Perry, 2016). Bilateral cleft lip represents a particular challenge for surgeons. There are so many different techniques ranging from 2-stage to single-stage surgical repair, such as Millard-Mulliken, Fisher, Pfeiffer, and Delaire's classical or modified procedures. The primary goal of surgical repair is to restore the lip and nasal symmetry through the formation of the philtral column, especially the cupid's bow, and reshape the orbicularis oris. Moreover, it is required to lengthen the columella and close the nasal floor (Chen et al., 2005). In unilateral cleft cases our surgeons at the cleft center perform mostly a combination of several techniques, called modified Millard-Mohler-Fisher-Noordhoof technique (see Figure 5).

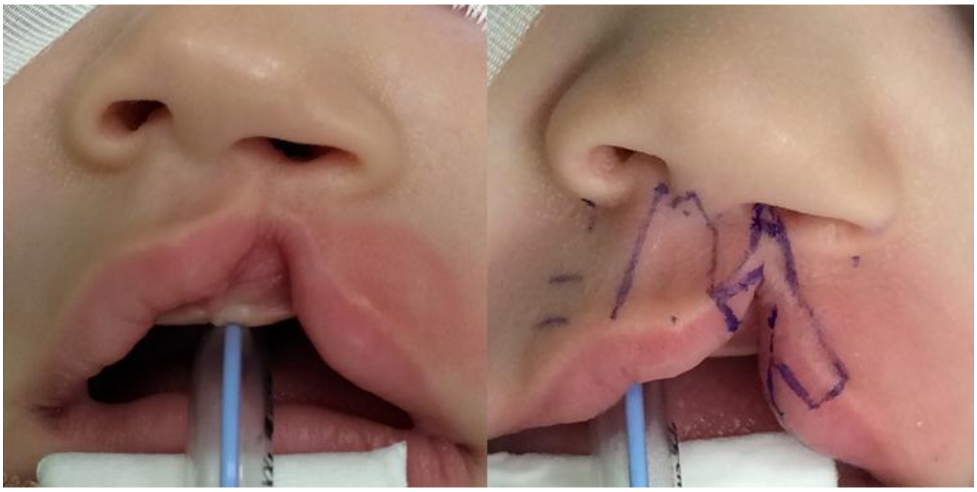

Figure 5 *Modified Millard-Mohler-Fisher-Noordhoof lip closure technique (Nagy, 2023).*

Closure of the soft palate cleft

Cleft palate repair is usually performed nine months after the cheiloplasty. It is crucial in reorienting the abnormally positioned musculature of the soft palate, the levator veli palatini, in closing the oronasal fistula, and in ensuring adequate palate length for normal speech development. The following surgical techniques provide these 3 aspects: Furlow's, Sommerlad's technique and their combinations, or various push-back techniques. In addition, a relatively new technique was described by Nagy and Swennen (Nagy & Swennen, 2015). This procedure combines the principles of an oral mucosal Z-plasty, Sommerlad's intravelar veloplasty, and a nasal straight-line closure as seen in Figure 6.

Figure 6 *Closure of the soft palate: Z-plasty and intravelar veloplasty (Nagy, 2022).*

Repairing the hard palate simultaneously can significantly limit maxillary growth. To address this issue, a two-stage palate repair technique is suggested. In this approach, the soft palate is repaired first to promote normal speech development. The hard palate repair is then postponed to reduce the adverse effects on upper jaw growth that occur due to periosteum stripping (Wadde et al., 2023).

Closure of the hard palate cleft

If the palatal cleft is closed in the two-stage method, the closure of the hard palate cleft is recommended to be performed at 2 to 4 years old. The timing of the surgery depends on the speech development and facial growth. Delaying hard palate cleft repair was described to result in significant deterioration of speech development. On the other hand, facial growth could be intact if the hard palate cleft is reconstructed later than the soft palate cleft. There are several competing surgical approaches aiming to close the hard palate, each with their own strengths and limitations. The surgical approach chosen must consider the size of the defect, the available soft tissue, the prospect of scarring and maxillary growth deficit following surgery. There are also differences in speed of speech development depending on the surgical technique used (Naidu et al., 2022). In Figure 7 the hinge-door flap technique for hard palate closure can be observed.

Figure 7 *Hard palate cleft closure: Hinge-door flaps (Nagy, 2021).*

Closure of the alveolar cleft

Alveolar bone grafting (ABG) is carried out to close communication between the oral and nasal cavity, enhance alar symmetry, restore the alveolar crest, and facilitate the eruption of the permanent canine and the lateral teeth. The optimal timing for ABG is a subject of prolonged discourse. It can be performed in the decidual, in the mixed dentition stage, or during the permanent dentition (Ganesh et al., 2015). ABG can be carried out using two primary approaches: autogenous bone grafts harvested from the patient's own iliac crest or rib, or allogenic bone substitutes (Magyar et al., 2024). Autogenous bone grafts have demonstrated favorable success rates, when combined with bone morphogenic proteins. These grafts are effective in supporting tooth eruption, establishing desirable nasal bone morphology, and ensuring the stability of orthodontic treatment. Allogenic bone substitutes can also be used as an alternative (Wahaj et al., 2016). Advancements in biomaterials, such as collagen membranes, hydroxyapatite, and tricalcium phosphate have expanded the possibilities for repairing alveolar clefts (Kraut, 1987). In terms of radiological evaluation, cone beam CT (CBCT) is a low-dose and effective method used for planning of the alveolar graft dimensions (Figure 8). Furthermore, it can be used postoperatively to evaluate the formation of bone, assessing both the quality and quantity of bone. Orthodontic treatment with the utilization of CBCT imaging provide valuable aid in the dental preparation and assessment of patients with alveolar cleft deformity (Zhou et al., 2015).

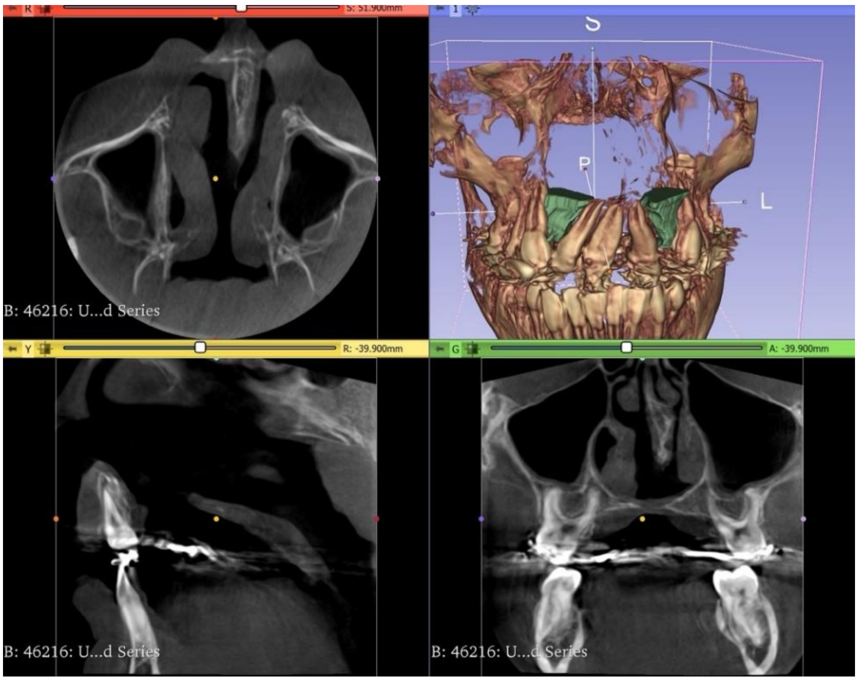

Figure 8 *Planning of the nasoalveolar graft in 3D Slicer. 3D models of the grafts are shown in green (Magyar et al., 2024).*

1.2.2. Secondary surgical interventions

In some cases, the initial procedure may not achieve the desired outcome due to factors such as surgical complications, healing issues, or unexpected changes in the patient's condition. Secondary operations can then be performed to address these concerns and improve the overall result. It's important to note that the need for secondary operations can vary greatly depending on individual circumstances, the specific procedure performed, and the goals of treatment. The decision to pursue additional surgical interventions is typically made in consultation between the patient and their healthcare provider, considering the desired outcomes, potential risks, and available treatment options.

Pharyngoplasty/speech correction surgeries

In cases where a patient's speech remains unsatisfactory despite appropriate speech therapy and clinical or radiological examinations reveal an anatomical issue such as a short, scarred, or non-moving palate, secondary speech correction surgery may be considered. There are several surgical procedures available to address these anatomical problems and improve speech outcomes (Ysunza et al., 2004). Some of the commonly used techniques for secondary speech correction include Hynes pharyngoplasty, Sanvenero-Roselli pharyngoplasty, Orticochea pharyngeal flaps, and reoperations according to Furlow or Sommerlad (Pálházi et al., 2014). During these surgical procedures, the goal is to create a new anatomical situation that improves the function of the soft palate and addresses specific speech defects. The decision to perform secondary speech correction surgery is typically made collaboratively between the surgeon, speech therapist, and the patient, considering the individual's needs and goals (Khafagy et al., 2021).

Rhinoplasty

Rhinoplasty or nasal reconstruction surgery can help improve the appearance and function of the nose in individuals with cleft lips. It is typically recommended to perform rhinoplasty after the completion of primary surgeries, such as cleft lip repair, and after the insertion of a nasoalveolar graft if necessary. The timing of rhinoplasty is often suggested during puberty, typically after the age of 14, when the nasal growth is closer to completion. Given the complexity and diversity of rhinoplasty techniques, as well as the significant psychological impact associated with nasal deformities, it is important to have an experienced surgeon perform these surgeries. An experienced surgeon can assess the individual's specific nasal anatomy, determine the appropriate techniques, and work toward achieving the desired aesthetic and functional outcomes (Nagy & Mommaerts, 2009).

Orthognathic surgeries

Cleft lip and palate conditions can often lead to disturbances in the development of dental arches, which can impact the occlusion (the contact between teeth). In cases where classic orthopedic and orthodontic treatments do not provide adequate results in terms of occlusion, surgical and adjunctive interventions may be necessary. These interventions primarily focus on the maxilla to address crossbite, vertical, and sagittal positional disorders. There are several surgical techniques commonly used in such cases, including SARPE (Surgically Assisted Rapid Palatal Expansion), premaxilla osteotomy, Le Fort I type osteotomy (Mommaerts, 2017; (Suri & Taneja, 2008). The timing of the surgeries depends on the individual's growth and development, as well as the treatment plan determined by the orthodontist and surgeon. According to professional guidelines, various diagnostic tools and analyses are utilized before proceeding with the actual surgery. These may include Cone Beam Computed Tomography (CBCT)/Digital Volumetric Tomography (DVT) radiological examinations, cephalometric analyses (which involve measuring and analyzing the skull and facial structures), and virtual surgery planning. These pre-operative assessments help in treatment planning, visualization of the anatomical structures, and precise surgical execution (Bahmanyar et al., 2021).

Scar corrections

If there are minor scarring disorders or aesthetically disturbing wound healing defects resulting from previous surgeries, it may be necessary to perform surgical interventions for correction. However, it is generally recommended to proceed with surgical intervention only when there are objectively, clearly defined and realistically correctable problems. Serial surgeries in the same anatomical area can indeed be unpredictable and may negatively affect the development of the tissues. It is important to carefully evaluate the potential risks and benefits before deciding to undergo additional surgical procedures. Psychological aspects are also significant in these cases, as the patient's self-perception and emotional well-being can be affected by aesthetic concerns. Surgical moderation and the use of minimally invasive techniques should be considered to address these concerns. In some cases, the use of fillers or other non-surgical approaches may be appropriate to improve the appearance of scars or correct minor defects (Bartkowska & Komisarek, 2020).

1.3. Presurgical nasoalveolar molding (NAM)

1.3.1. History of NAM, development of the devices

The clinical approaches and the benefits of presurgical infant orthopedics have undergone considerable changes since their initial development. Numerous techniques have emerged over the years to enhance the alignment of cleft alveolar segments (Berkowitz, 1996).

In 1686, Hoffman introduced an extraoral device, a head cap with extended arms, to retract the premaxilla and reduce cleft severity. Despite many advancements, this technique of using the head for extraoral anchorage is still employed (Berkowitz, 1996).

McNeil later developed an intraoral device to align cleft alveolar segments using acrylic plates to mold them into their optimal position (McNeil, 1950). Then Georgiade and Latham invented a pin-retained appliance for the retraction of the premaxilla and expansion of the posterior segments at the same time (Georgiade & Latham, 1975). Due to controversies surrounding active premaxilla retraction, Hotz suggested a passive method to gradually align cleft segments with an orthopedic plate without retracting the premaxilla, believing the face would naturally balance with the premaxilla by age 10 (Hotz et al., 1987).

Although various appliances were created to correct alveolar clefts, addressing the cleft nasal deformity posed a significant aesthetic challenge.

Matsuo's pioneering work on molding nasal cartilage identified that newborn cartilage is soft and lacks elasticity due to high maternal estrogen levels, which increase hyaluronic acid and inhibit cartilage matrix linking. This adaptation helps relax ligaments, cartilage, and connective tissue for childbirth. Matsuo used a silicone tube stent to shape the nostrils, though it required an intact nasal floor and had limitations in force direction (Matsuo et al., 1989).

In 1993, Grayson et al. introduced a new technique called nasoalveolar molding (NAM). He adapted a nasal stent to extend from the anterior flange of an intraoral molding plate. The greatest advantage of this technique is that it enables the practitioner to apply force to precisely shape the nasal cartilage. In bilateral cleft cases, it enables to lengthen the columella (Grayson et al., 1993). In addition, since the stent is extended from a molding plate, an intact nasal floor is not required (Grayson & Maull, 2004).

1.3.2. Grayson's nasoalveolar molding technique

Since the 1950s, presurgical infant orthopedics have been used as an adjunctive therapy for orofacial cleft correction. Grayson et al. introduced a significant shift from the traditional methods in 1993, addressing issues such as nasal cartilage deformities in unilateral and bilateral clefts and columella tissue deficiency in bilateral clefts (Grayson et al., 1993).

The NAM technique uses acrylic nasal stents attached to an oral plate to mold nasal alar cartilages during the neonatal period, capitalizing on the malleability of immature cartilage for permanent correction. Additionally, nonsurgical columella construction is achieved through tissue expansion principles by elongating nasal stents and applying elastic forces to the prolabium as seen in Figure 9. This method has replaced surgical columella reconstruction, avoiding scar tissue (Grayson et al., 1999).

The combination of presurgical nasal and alveolar molding (nasoalveolar molding) in the infant orthopedic field has resulted in measurable long-term benefits to the patient (Cutting et al., 1998; (Maull et al., 1999; (Santiago et al., 1998) and to medical economics (Pfeifer et al., 2002).

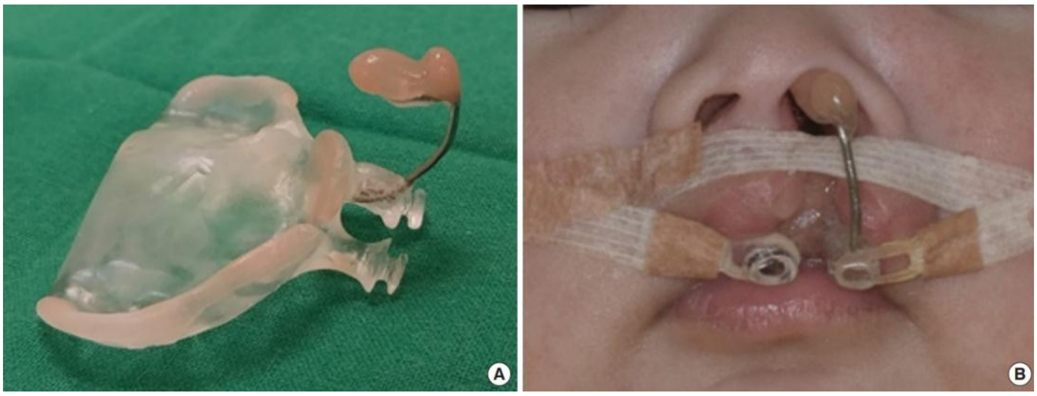

Figure 9 *Nasoalveolar molding device and its application: acrylic palatal plate with nasal stents (A); device in mouth and fixed with elastic lip tapes (B) (Oh & Kim, 2023).*

Treatment with NAM in unilateral clefts

Unilateral cleft lip and palate show notable abnormalities in the form of the nose, alar base symmetry and columella. To align and approximate the alveolar cleft segments and to correct the nasal soft tissue deformity a nasal stent is added to the labial part of the acrylic intraoral molding plate (Grayson & Cutting, 2001).

The NAM appliance is adjusted over approximately three months until nasal tip projection, nasal symmetry and alveolar segment alignment are achieved. The intraoral plate is secured with hypoallergenic tapes and elastics applied to the cheeks and lip segments (Grayson & Cutting, 2001). The esthetic result of nasoalveolar molding and cheiloplasty can be observed in Figure 10.

Figure 10 *Patient with unilateral cleft lip and palate (UCLP) before NAM treatment (left), after NAM treatment (middle), and after cheiloplasty (right) (Magyar et al., 2022).*

Treatment with NAM in bilateral clefts

Addressing bilateral facial cleft deformities involves unique challenges to achieve a successful surgical outcome. Typically, the surgical correction of a bilateral cleft lip requires a two-phase procedure to address the shortened or missing columella and the overly broad prolabium. However, presurgical techniques that elongate the columella, along with orthopedic retraction of the premaxilla and active alveolar molding, have rendered the conventional surgical reconstruction of the columella unnecessary (Cutting et al., 1998).

In the technique of nasoalveolar molding and columella elongation, the rear lateral alveolar ridges are shaped to the correct width to accommodate the premaxilla. Then the premaxilla is drawn back with the molding plate and an elastic tape, which should be changed daily. Nasal stents extend from the vestibular part of the plate into both nostrils. This combination of pushing the nasal tip forward and applying pressure on the nasolabial fold gradually expands the tissue and lengthens the columella. The lower lateral nasal cartilages are brought together in the midline, and the intranasal lining is expanded. (Grayson & Cutting, 2001).

Preoperative retraction of the premaxilla significantly aids in achieving tension-free muscle repair and narrowing the alar bases. The integration of presurgical nasoalveolar molding with nonsurgical columella elongation permits a single-stage correction of bilateral cleft lip and nose. This approach has demonstrated enhanced aesthetic results and a decreased necessity for surgical revisions prior to secondary bone grafting (Lee et al., 1999). Figure 11 demonstrates the esthetic outcome of nasoalveolar molding and cheiloplasty in a BCLP patient.

Figure 11 *Patient with bilateral cleft lip and palate (BCLP) before NAM treatment (left), after NAM treatment (middle) and after cheiloplasty (right) (Magyar et al., 2022).*

1.4. Difficulties affecting cleft patients

Orofacial anomalies significantly impact the quality of life, imposing significant psychosocial challenges on affected individuals, particularly before undergoing treatment or among adults, who are not content with their facial look. Managing orofacial clefts places a substantial financial strain on both the healthcare system and society (Wehby & Cassell, 2010). Individuals with cleft lip or palate face numerous challenges beyond facial deformity. Feeding difficulties can result in failure to thrive, and CLP can also impede speech development or hearing, when left untreated. Dental malocclusion and jaw discrepancies are also important to diagnose and treat later in childhood. The broader spectrum of consequences encompasses social stigmas and potential declines in self-esteem among children with cleft anomalies (Babai & Irving, 2023). Therefore, children with orofacial clefts require long-term complex and coordinated care with a multidisciplinary team, in order to deal with the different issues associated with CLP and ensure optimum management (Taib et al., 2015).

1.5. Parents' burden of care in nasoalveolar molding therapy

NAM treatment holds potential to enhance the surgical outcomes of cleft lip repair in infants with cleft lip. Nevertheless, patients may encounter a lot of challenges, such as difficulties in feeding, skin irritations, and challenges faced by caregivers in accurately positioning and stabilizing the NAM appliance (Magyar et al., 2022). To ensure successful treatment, the cleft team should consider the parents' economic and social circumstances, as these can impact the physician-patient relationship. Furthermore, external factors such as travel distance, the financial position of the caregivers, and the level of parental engagement can influence the effectiveness of the therapy (Alfonso et al., 2020). It is essential to identify factors that may diminish the effectiveness of NAM therapy, causing inconvenience for both caregivers and the child (Sischo et al., 2015; (Sischo et al., 2012).

2. Objectives

The aim of my dissertation is to review the cleft care at the Centre of Facial Reconstruction, Semmelweis University, Department of Pediatrics, focusing on presurgical nasoalveolar molding (NAM) treatment, setting two main goals:

1. To evaluate the effectiveness of nasoalveolar molding therapy in improving the alignment of the maxillary cleft segments before cleft lip surgery in patients with BCLP.
2. To reveal the burden of care in nasoalveolar molding therapy from the parents' perspective.

3. Methods

3.1. Evaluating changes in the maxillary arch following NAM in BCLP patients

A total of 18 patients with bilateral cleft lip and palate were included in the study, 12 males and 6 females, with a mean age of 12 ± 5 days. All participants underwent preoperative nasoalveolar molding (NAM) therapy prior to cheiloplasty at Semmelweis University. The therapy started before the infants reached 6 weeks of age, taking advantage of the flexibility of the nasal cartilages.

Nasoalveolar molding technique

The molding procedure began by making an alginate impression of the palate shortly after the birth of the infant (first 2 weeks). A plaster cast of the infant's palate was crafted in the laboratory on which the palatal guidance plate was made from acrylic resin. The nasoalveolar molding (NAM) plate was firmly affixed on the infant's palate using denture adhesive along with two adhesive tapes secured to the cheeks. An extra tape aided in bringing the upper lip segments and premaxilla together, thereby reducing the fissure size. Nasal stents were incorporated into the plate to elongate the columella, with the goal of achieving an ideal nasal tip projection (see Figure 12). Alginate impressions were promptly taken following the conclusion of NAM therapy, and casts were created for further analysis (Nemes et al., 2013).

Figure 12 *Nasoalveolar molding device (left) and attachment of the device on a BCLP patient (right) (Magyar et al., 2024).*

All NAM devices were crafted manually in a dental laboratory by a dedicated team of dental technicians. Daily application of the NAM device was mandatory, with caregivers assuming a crucial role. Their duties included the consistent replacement of adhesive tapes and the ongoing maintenance and repositioning of the palatal plate. During follow-up appointments, an orthodontist made essential adjustments to the device, with the aim of directing the growth of the lateral maxillary segments and contouring the nasal cartilages (Magyar et al., 2024).

Maxillary arch analysis

The plaster casts of the patients' maxilla were scanned pre-NAM (T0) and post-NAM (T1) using a D500 3D dental scanner (3Shape GmbH, Düsseldorf, Germany) with a resolution of 0.1 mm. Subsequently, virtual models of the casts were imported into Blender software (Version 3.6.5, Blender Foundation, Amsterdam, Netherlands) for evaluating dimensional changes in the maxillary arch at T0 and T1 time-points. The morphometric analysis followed the method proposed by Mazaheri et al. (Mazaheri et al., 1971), involving the annotation of 12 landmarks on the digital models for conducting linear and angular measurements (see Figure 13). The measured parameters, based on these landmarks, included premaxilla width, right and left alveolar cleft width, right and left molar region length, intercanine width, intermolar width, intertuberosity width, palatal length, and anterior basal angle (see Figure 14). Figure 15 illustrates an example of a patient with linear and angular dimensional measurements at T0 and T1 points.

To ensure the reliability of the measurements, all assessments were conducted twice by a single observer with over 5 years of experience in orthodontics, with an interval of 1 week to evaluate interobserver reliability (Magyar et al., 2024).

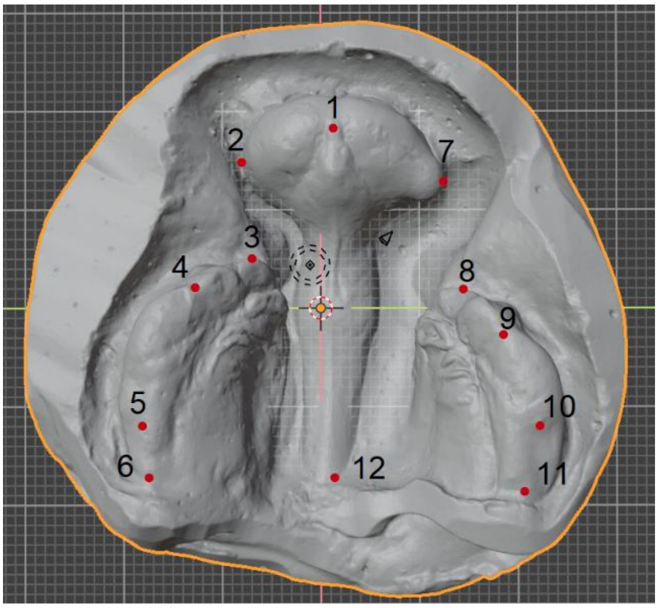

Figure 13 *Landmarks of the maxillary arch:*
1. apex of ridge situated on line demarcating labial frenulum and incisive papilla, 2. rightmost boundary of premaxilla, extending from alveolar ridge, 3. Anterior most point on right maxillary segment, 4. distal boundary of canine protuberance on right maxillary segment, 5. Distal boundary of molar protuberance on right maxillary segment, 6. tuberosity point on right maxillary segment, 7. leftmost boundary of premaxilla, extending from the alveolar ridge, 8. Anterior most point on left maxillary segment, 9. distal boundary of the canine protuberance on the left maxillary segment, 10. distal boundary of molar protuberance on right maxillary segment, 11. Tuberosity point on left maxillary segment, 12. reference point located at base of a perpendicular line drawn from landmark 1 to line connecting segments from reference points 6 and 11 (Magyar et al., 2024).

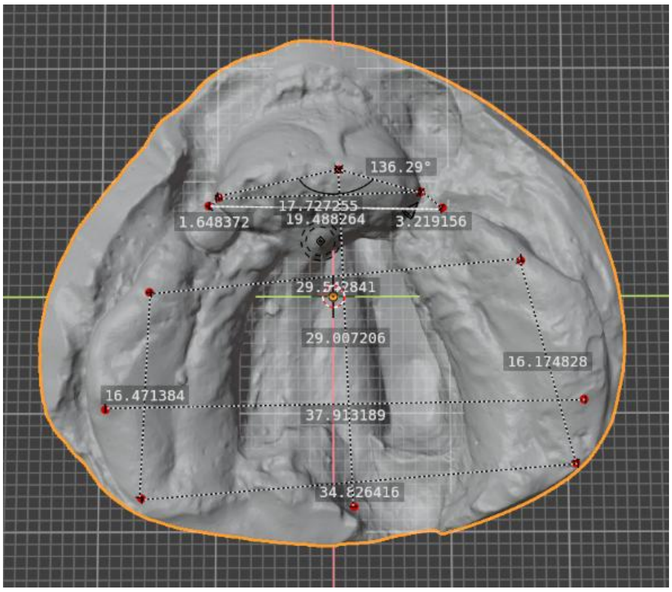

Figure 14 *Measurements based on maxillary arch landmarks:*
premaxilla width (2-7), right (2-3) and left (7-8) alveolar cleft width, right (4-6) and left (9-11) molar region length, intercanine width (4-9), intermolar width (5-10), intertuberosity width (6-11), palatal length (1-12), and anterior basal angle (3-1-8.) (Magyar et al., 2024).

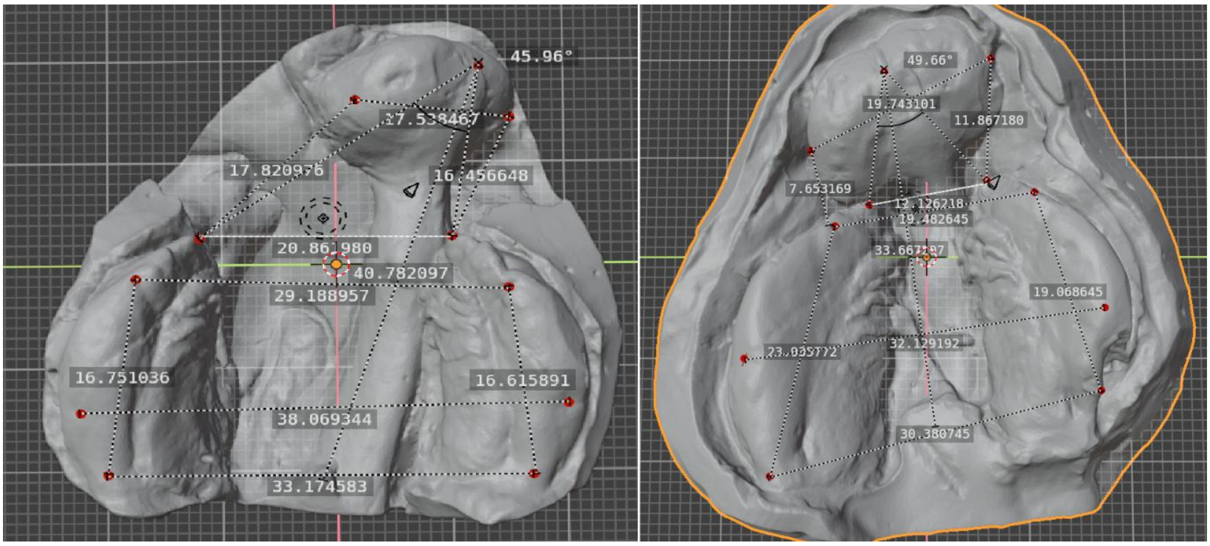

Figure 15 *Maxillary dimensional analysis before (left) and after (right) nasoalveolar molding therapy (Magyar et al., 2024).*

Statistical analysis

The analysis of data was carried out utilizing R Studio 3.4.2 (Boston, MA, USA). Mean and standard deviation values were computed for maxillary arch dimensions at both T0 and T1 timepoints. A paired T-test was utilized to compare the variances between T0 and T1. Furthermore, a two-way analysis of variance (ANOVA) was employed to assess maxillary arch dimensions concerning the alveolar cleft width. A p-value below 0.05 was considered statistically significant.

Ethical approval

Ethical approval was acquired from the Medical Ethics Committee of Semmelweis University and St John’s Hospital Bruges-Oostende (No. 265/2019). Written informed consent was obtained from the guardians of all patients before enrolment in the study.

3.2. Assessing parents’ burden of care in nasoalveolar molding treatment

The continuous use of the nasoalveolar molding (NAM) device and regular medical check-ups can impose a significant burden on the lives of caregivers. Additionally, the perceived burden of care may impact the effectiveness of NAM treatment (Levy-Bercowski et al., 2009). In order to identify factors influencing the consistent use of oral and nasal palates during NAM therapy, a survey-based pilot study was conducted using a 32-item questionnaire.

The questionnaire design drew inspiration from previous surveys conducted by (Dean et al., 2019). Most of the questionnaire consisted of multiple-choice or single-answer questions. However, some sections permitted caregivers to openly share their experiences in their own words. Our aim with the questionnaire was to assess the effectiveness of NAM therapy from the perspective of patients and caregivers. However, our questionnaire has not yet been validated.

The questionnaire was distributed to families whose children underwent NAM therapy at Semmelweis University between 2013 and 2020, and we expanded the survey to include patients between 2022 and 2024. Twenty-three caregivers completed the questionnaire. Ethical approval for this study was obtained from the Medical Ethics Committee of Semmelweis University (No. 265/2019).

The survey was structured into four main sections. The first section focused on socio-economic factors, such as financial, educational, and social aspects that could influence caregivers' ability to successfully navigate NAM therapy. The second section explored the origins of the disease and any concurrent genetic disorders or malformations, including monogenic or chromosomal syndromes. The third section investigated potential challenges associated with NAM therapy, encompassing difficulties in breathing, feeding, wounds, and allergies. Finally, the fourth section comprised a self-assessment of caregivers' overall satisfaction with the outcome of NAM therapy. The survey did not include an objective evaluation of clinical success (physical, functional, or aesthetic).

Statistical analyses, including Fisher's exact probability test or one-way ANOVA with post hoc Tukey's multiple comparison test were performed as needed. A p-value of less than 0.05 was considered statistically significant. Statistical analysis and diagnosis were conducted using R Studio 3.4.2.

4. Results

4.1. Changes in maxillary arch dimensions following NAM in BCLP patients

NAM therapy lasted for 3-4 months, concluding when patients reached an average age of 6 months. By this point, the length of the columella had increased, indicating optimal alignment of the alveolar segments, and lip segments had come together without tension. For visual representation, Figure 16 illustrates an example of a BCLP patient before and after NAM therapy.

Figure 16 *Patient with bilateral cleft lip and palate before (left) and after (right) nasoalveolar molding treatment (Nagy, 2020).*

On the digital casts, all landmark placements and measurements showed excellent reliability, as evidenced by the intraclass correlation coefficient (ICC) of 0.99. Table 1 presents the mean changes in maxillary dimensions during the T0-T1 intervals. Both left ($p= 0.047$) and right ($p= 0.019$) alveolar clefts demonstrated a significant reduction in size at T1 (after NAM). Additionally, a significant increase in premaxillary width was observed ($p=0.037$), accompanied by a slight non-significant reduction in palatal length ($p=0.305$). Except for intermolar width ($p=0.045$), no significant changes were observed for intercanine, intermolar, and intertuberosity widths. Notably, NAM therapy resulted in a significantly high change in the anterior basal angle ($p=0.043$).

When assessing the influence of cleft severity on maxillary dimensions, the results indicated that a decrease in cleft size corresponded to a significant reduction in premaxilla width (p-value < 0.001). Moreover, the decrease in cleft size was linked with a significant increase (p-value < 0.001) in the anterior basal angle.

Table 1 *Maxillary arch dimensional changes following nasoalveolar molding.* ***Bold values indicate standard deviation (SD), p<0.05*** *(Magyar et al., 2024).*

Maxillary arch dimensions	T0 (mean ± SD)	T1 (mean ± SD)	Mean difference (T1-T0)	p-value
Premaxilla width (mm)	15.4 ± 3.2	17.4 ± 3.4	2.0 ± 3.3	**0.037**
Right alveolar cleft width (mm)	9.6 ± 4.8	6.4 ± 4.0	-3.2 ± 4.4	**0.019**
Left alveolar cleft width (mm)	9.7 ± 3.4	7.3 ± 3.6	-2.4 ± 3.5	**0.047**
Right molar region length (mm)	17.0 ± 2.2	17.4 ± 3.1	0.4 ± 2.7	0.332
Left molar region length (mm)	16.4 ± 2.2	17.3 ± 2.8	0.9 ± 2.5	0.137
Palatal length (mm)	31.6 ± 3.9	30.9 ± 2.2	-0.7 ± 3.2	0.305
Intercanine width (mm)	28.5 ± 3.2	28.7 ± 3.8	0.2 ± 3.5	0.411
Intermolar width (mm)	36.4 ± 3.0	38.2 ± 3.0	1.8 ± 3.0	**0.045**
Intertuberosity width (mm)	33.3 ± 3.5	34.3 ± 4.4	1 ± 3.9	0.22
Anterior basal angle (°)	80.1 ± 6.7	84.9 ± 9.3	4.8 ± 8.1	**0.043**

4.2. Parents' burden of care in nasoalveolar molding treatment

Socio-economic factors

The majority of patients lived in two-parent families with one sibling. In 44% of the families, the firstborn child was affected by CLP. In 69% of the cases NAM therapy started when the patients were between 1 week and 1 month old. 57% were male, and 43% were female patients. Most families lived more than 60 km away from their cleft center, resulting in over 60 minutes of travel time (52%). However, the duration of hospital visits was generally less than 30 minutes (61%). Patients made approximately 10 trips between their residence and the cleft center. Health insurance covered NAM therapy for the majority (83%) of patients. About 49% of the caregivers could receive paid or sick leaves.

Cleft types and associated malformations

Unilateral cleft lip and palate (UCLP) occurred in 52% of the cases, while bilateral (BCLP) occurred in 48%. The defects mainly affected firstborns (44%). No correlations were found between dentofacial deficiency distribution and its occurrence among siblings ($p = 0.29$). 26% of patients had associated health problems, such as atrial septal defect, renal developmental abnormality, optic nerve coloboma, or corpus callosum agenesis.

Difficulties of the treatment

Overall, the therapy was successful in 91% of the cases. Allergic reactions against the adhesive tapes were reported in 26% of the cases. Similarly, 30% of patients experienced wounds on their lips or noses during therapy. Feeding methods varied among caregivers, with 61% using a feeding bottle, 22% opting for a Haberman feeder, and another 17% using a different special feeder. Only 13% of the mothers were able to breastfeed, and 21% reported difficulties with feeding or breathing. No correlation was found between feeding or breathing difficulties and the method of feeding ($p = 0.67$). Unfortunately, 48% of caregivers did not receive feeding guidance from the cleft team.

Self-assessment

Patients obtained information about the process from treating specialists and social media (78%). In every instance, parents reported satisfaction with the therapy and would recommend NAM therapy to other caregivers of CLP patients.

The results of the pilot survey are summarized in Table 2.

Table 2 *The main findings of the survey (Magyar et al., 2022).*

Variables	**Summary of statistic**
Total participants (n)	23
Age of patient at the start of NAM	
less than 1 week old	9% (n=2)
between 1 week and 1 month old	69% (n=16)
between 1 and 2 months old	9% (n=2)
more than 2 months old	13% (n=3)
Gender (n)	
female	43% (n=10)
male	57% (n=13)
Type of the dentofacial deficiency (n)	
unilateral cleft and lip palate	52% (n=12)
bilateral cleft and lip palate	48% (n=11)
Patient with cleft (n)	
first born	44% (n=10)
second born	30% (n=7)
third born	26% (n=6)
Distance between the cleft center and residence (n)	
more than 60 km	61% (n=14)
less than 60 km	39% (n=9)
Travelling time to the cleft center (mins)	
more than 60 mins	52% (n=12)
less than 60 mins	48% (n=11)
Number of the travelling (n)	
1-5 times	17% (n=4)
6-10 times	49% (n=11)
11-15 times	17% (n=4)
15 times <	17% (n=4)
Duration of the visit (mins)	
less than 30 mins	61% (n=14)

30 – 60 mins	39% (n=9)
Associated health problem (n)	26% (n=6)
NAM treatment covered by health insurance (n)	83% (n=19)
Receive paid or sick leave (n)	49% (n=11)
Successfulness of the NAM therapy (n)	91% (n=21)
Allergic reaction against the adhesive (n)	26% (n=6)
Wounds on the lip or nose following the therapy (n)	30% (n=7)
The way of feeding (n)	
feeding bottle	61% (n=14)
Haberman feeder	22% (n=5)
other special feeder	17% (n=4)
Breastfeeding (n)	13% (n=3)
Difficulty feeding (n)	26% (n=6)
Difficulty breathing (n)	17% (n=4)
Knowledge of the NAM therapy by the specialists (n)	87% (n=20)
Usage of other source for advisements, like social media (n)	78% (n=18)
Recommendation of NAM therapy	100% (n=23)

5. Discussion

The scarcity of randomized controlled trials (RCTs) focusing on the management of cleft patients has posed challenges in determining the optimal timing and techniques for various procedures employed in their treatment. A variety of techniques have been experimented with over the years, and the diversity in outcome and measurement tools used across studies adds to the complexity. Additionally, most available studies have relatively short follow-up durations. Given that cleft treatments have long-term implications, reaching conclusions on the most effective treatment modality becomes challenging in the absence of information on prolonged effects (Wadde et al., 2023).

The American Cleft Palate-Craniofacial Association highlights the crucial role of a multidisciplinary approach in the treatment of cleft patients. According to their suggestion, the basic cleft care should consist of following interventions (ACPA, 2024):

- prenatal genetic counseling and feeding consultation;
- 0-5 months: consultation for feeding and growth, hearing monitoring, NAM, cleft lip repair, inserting ear tubes in case of otitis media;
- 9-12 months: palatoplasty, inserting ear tubes when otitis media is present;
- 1-4 years: introduction to pediatric dentist, assessment of language development;
- 4-6 years: assessment of velopharyngeal dysfunction, corrective speech surgery, lip revision if needed, minor nasal surgery if needed;
- 6-12 years: orthodontics, alveolar bone grafting;
- 12-21 years: orthodontics, orthognathic surgery, definitive rhinoplasty.

Surgical correction plays a pivotal role in the modern multidisciplinary approach to treating clefts. An optimal surgical plan aims to effectively restore essential functions such as speech, chewing, breathing, and appearance, while also maintaining the natural growth potential of the affected area. However, despite these efforts, postoperative issues like an underdeveloped upper jaw, a concave mid-face, and an abnormal dental arch frequently occur, and no existing surgical method can fully prevent these complications. There is a pressing need for more meticulously designed multicenter RCTs.

The complex treatment based on the above-mentioned principles has been applied since 2010 at Semmelweis University, Department of Paediatrics. During this time, more than 800 patients were treated. A significant (p-value < 0.001) increase in cleft patient numbers can be observed (see Figure 17). As the prevalence of cleft anomalies doesn't show any consistent linear decreasing or increasing pattern (Heydari et al., 2024), this increase in patient numbers might be an issue of the formation of a new cleft team at the clinic in 2010, and since then patients are looking up the institute from all over the country.

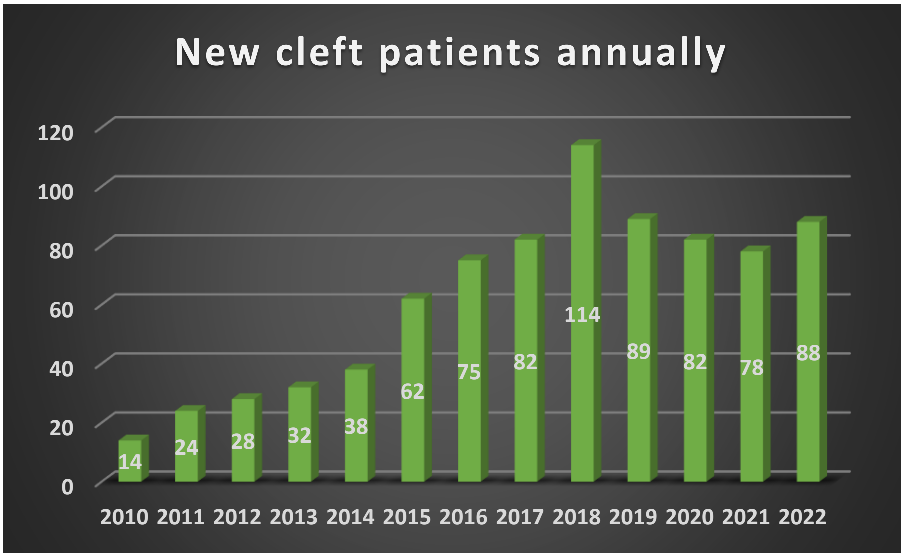

Figure 17 *Cleft patient number changes at Semmelweis University between 2010 and 2022 (Magyar et al., 2024).*

Among this number of patients, between 2017 and 2022, it can be observed that we treated an average of 47 patients with cleft lip, 35 with cleft soft palate, 20 with cleft hard palate, and 11 with alveolar cleft. Our department offers the opportunity for all surgical interventions in cleft care. The entire spectrum of primary and secondary surgeries required for the treatment of cleft lip, cleft palate and alveolar cleft, are performed following the newest professional guidelines. The number of total surgeries has also increased significantly (p-value < 0.001) in the last 10 years as a consequence of growing patient numbers (Figure 18). Among primary surgeries, cheiloplasties accounted for approx. 43% of the annual cases, and palatoplasties for 50% of the cases. Alveolar bone grafting (ABG) was less common at 7%, because this intervention is done at an older age, and children who started the complex cleft treatment in the beginning of our study period, have turned to the optimal age for ABG recently.

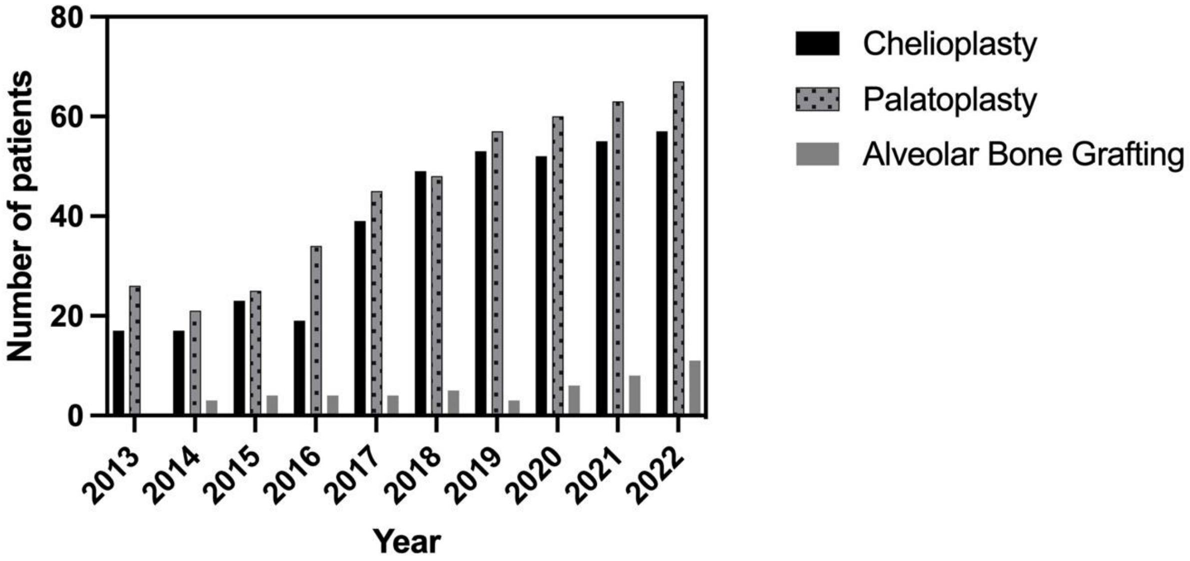

Figure 18 *Number of cleft surgeries annually at Semmelweis University between 2013 and 2022 (Nagy, 2022).*

The specialists working in our center share their knowledge and experience with their colleges, ensuring the flow of information between the different disciplines of medical care.

Our center has established a close relationship with both the Catholic University of Leuven (Belgium) and the HRAC-USP University (Bauru, Brazil), which provided an opportunity to share our surgical protocol and to exchange knowledge and information internationally. Our goal is to reform cleft care and emphasize personalized therapy, which enables us to compete with the best cleft centers in Western Europe and the United States.

Presurgical nasoalveolar molding

Presurgical infant orthopedics constitute a diverse category of devices that are utilized for varying durations and can yield different outcomes that cannot be generalized. While numerous studies indicate their effectiveness in reducing the cleft gap, uncertainties persist regarding their potential adverse effects on maxillary growth (Matsuo & Hirose, 1988).

Nasoalveolar molding is the most commonly employed presurgical orthopedic treatment in early cleft management to align the alveolar segments and improve nasal symmetry of the patients (Siriwiroj et al., 2023). It has become a standard part of the treatment protocol in a lot of cleft centers to improve the outcome of cheiloplasty in infants (Shiva et al., 2019). In the cleft center at Semmelweis University, it is also part of the early cleft management, which is unique in Hungary.

A statistically significant reduction in the cleft gap and improvement in nasal symmetry were observed with nasoalveolar molding in a review on six studies (Wadde et al., 2023). Best results were seen with patients less than 1 month of age when initiating NAM therapy, but effects are evident even when starting up to 5 months of age (Wadde et al., 2023).

In a comparison different molding techniques, the Grayson type showed the best results in the esthetic outcome, but had high chances of developing of ulcers around the mouth (Singh et al., 2018). Patients who didn't undergo NAM therapy showed minor increase in cleft gap (Saad et al., 2020). Our cleft center applies the Grayson molding technique, which is proved to be efficient and widely accepted.

The short-term benefits of NAM before lip surgery are generally acknowledged, yet its enduring impacts are still uncertain. Despite the existence of numerous differing opinions about the prolonged effects of NAM on maxillary development post-surgery, it continues to be a standard procedure in many medical facilities (Nayak et al., 2021). Research assessing the long-term impacts of NAM on maxillary growth has identified enhancements in both horizontal and vertical dimensions up to 18 months of age, with no adverse effects on maxillary growth observed. By the age of 6, children who did not receive NAM exhibited a higher risk of anterior segment collapse. This indicates that NAM may help prevent arch collapse (Shetty et al., 2016).

Opponents of NAM contend that it raises both costs and the burden of care, and they argue that it negatively affects maxillary growth. Nonetheless, clear benefits of NAM include a reduced number of nasal surgeries and a decreased need for secondary bone grafting. These advantages can ultimately lessen the burden of care for caregivers and streamline healthcare delivery (Patel et al., 2015).

The alignment facilitated by this device could lead to superior surgical outcomes by enabling a tension-free closure of the lip segments. The limited sample size due to the low incidence of the deformity and short-term follow-up necessitates further multicenter studies to evaluate long-term outcomes of NAM with a larger sample size.

Changes in maxillary arch dimensions following NAM in BCLP patients

Patients with bilateral cleft lip and palate (BCLP) often require a combination of surgical and non-surgical interventions to achieve optimal functional and aesthetic outcomes (McIntyre et al., 2016). Various presurgical procedures are implemented to mitigate the deformity, with nasoalveolar molding (NAM) playing a crucial role in defect correction (Shetye & Grayson, 2017). While NAM can bring the cleft segments in unilateral cases closer together, its impact on the maxillary arch in BCLP patients warrants thorough evaluation. However, due to the relatively low incidence of BCLP, limited studies have addressed this aspect (Ocak et al., 2024). Consequently, our study aimed to investigate the changes in maxillary dimensions following NAM therapy in bilateral cases. The analysis of the maxillary arch utilized laser-scanned digital models, a methodology known for its high reliability and validity in such evaluations (Verma et al., 2022).

The impact of nasoalveolar molding (NAM) therapy on midface and maxillary arch parameters remains a subject of ongoing discussion. Research by Tankittiwat et al. indicated that NAM therapy might increase the length of the alveolus (Tankittiwat et al., 2021). Conversely, Ross proposed that orthopedic correction could enhance transversal maxillary growth, leading to a reduction in cleft size (Ross, 1995). In a long-term study spanning 18 years, Grayson and colleagues found that this non-surgical intervention did not impede maxillary arch growth (Grayson & Shetye, 2009). Similarly, Lee et al. in a study monitoring patients from ages 9 to 13 years, concluded that NAM therapy had no discernible effect on midface growth and promoted normal facial growth in 60% of cleft patients (Lee et al., 2004). However, contrasting findings were presented by Ras et al., who suggested that the forces exerted during distraction might disrupt the premaxilla's growth center, potentially hindering normal midface growth (Ras et al., 1995). A long-term study by Alhayyan et al., affirmed that NAM therapy did not impact midface symmetry (AlHayyan et al., 2018).

The results of our study revealed a significant increase in premaxilla width, consistent with prior research indicating a notable influence of alveolar bone apposition on premaxilla dimensions. In their research, long term effects of NAM showed significant reduction in cleft size, which leads to improved, symmetric arch form. In the control group, whom NAM was not performed, anterior arch collapse leading to dental crossbite was observed (Shetty et al., 2017). Furthermore, we observed enlargements in both intermolar and intertuberosity widths. Comparison with a study by Heidbuchel et al. (Heidbuchel et al., 1998), investigating maxillary arch development in children with BCLP and those without clefts, showed increased intertuberosity width in both cohorts, suggesting that the NAM appliance likely does not hinder maxillary arch growth. Conversely, the intercanine width in our study exhibited a negligible and statistically insignificant increase, aligning with earlier studies reporting minor changes in intercanine width in BCLP patients and slight width alterations in children without clefts. Kiya et al., in their investigation of a fixed active plate combined with an elastic chain, also reported an insignificant rise in intercanine width (Kiya et al., 2015). The most plausible explanation for these observations could be that the cleft defect potentially restricts growth in the anterior region compared to the posterior region. Furthermore, our study found an increase in the anterior basal angle and a significant enhancement in angulation due to cleft defect reduction, subsequently improving premaxilla rotation. These findings suggest that the premaxilla might have moved closer to the palate medially, thereby reducing the size of the cleft (Magyar et al., 2024).

In terms of cleft width, a decrease was observed at T1, consistent with findings from previous studies utilizing NAM devices and fixed molding plates with elastic chains, as seen in Grayson's presurgical NAM for BCLP treatment. The reduction in cleft severity may primarily be attributed lip strapping and a retraction plate (Pool & Farnworth, 1994). Simultaneously, a slight decrease in palatal length was noted, potentially resulting from the elongation of the alveolar ridge due to maxillary growth. However, the precise impact of NAM remains unclear, given the challenge in distinguishing between therapeutic effects and natural growth, especially because of the lack of a control group and ethical constraints (Rossell-Perry et al., 2020).

In our study, NAM therapy was initiated before the six-week mark, as it is believed to be most beneficial when started as soon as possible after birth (Rau et al., 2015). The high concentration of hyaluronic acid in newborns renders the cartilage extremely flexible, making it highly susceptible and adaptable to new positions. The surgical protocol outlined in our study is both straightforward and effective in managing the premaxilla, and it has demonstrated satisfactory results in addressing the dental arch. Despite the labor-intensive nature of this treatment sequence, it offers a solution for the complex task of treating bilateral cleft lip and palate (BCLP). The NAM protocol could be a valuable addition in order to achieve a more successful lip closure surgery (Nagy & Mommaerts, 2011).

Medical institutions that forego presurgical orthopedic therapy before primary lip surgery have observed that approximately 83% of patients may develop a noticeable anterior overbite between the ages of 5 and 7 years. This overbite is attributed to the downward shift of the premaxilla and could potentially increase the need for surgeries to reposition the premaxilla during secondary alveolar bone graft procedures (Traube et al., 2023). Some researchers have reported that around half of their patients with BCLP require surgery to reposition the premaxilla.

However, nasoalveolar molding (NAM) therapy can pose several challenges, including feeding difficulties, skin irritation, and caregivers' difficulty in correctly positioning and securing the appliance. These factors can highly impact the expected outcomes of the treatment. Despite these challenges, prior studies indicate that although the care burden for patients undergoing NAM treatment is relatively high, caregivers remain committed to improving the therapy's effectiveness (Magyar et al., 2022).

Our study faced several limitations. Firstly, its retrospective design inherently introduced potential confounding bias. Additionally, the absence of a control group might have inadvertently biased the findings. Including a group without NAM at the same time points would have provided more robust results, but this was not possible because of ethical reasons. Secondly, the study's generalizability may be limited because it recruited only 18 patients with BCLP from two craniofacial centers following similar treatment protocols. Continuously collecting data on current and future patients will enhance the statistical robustness of this study. Thirdly, performing intraoral impressions on infants carries risks to the patient and may also lead to precision variations. The development of small intraoral scanning devices may offer a safer and more precise alternative, eliminating the need for physical impressions. Lastly, the study only focused on evaluating the maxillary arch. Future research could explore both short- and long-term aspects such as nasolabial soft tissue morphology, dentition emergence, occurrence of impacted or ectopic tooth buds, and occlusal function, which would provide a more comprehensive understanding of the treatment outcomes (Magyar et al., 2024).

The burden of care in nasoalveolar molding treatment from the parents' perspective

Individuals with cleft lip and palate often undergo multiple surgical procedures to achieve the desired nasal and lip aesthetics. Numerous presurgical interventions have been developed to mitigate the severity of labial and nasal deformities (Latham et al., 1976; (McNeil, 1950). Nevertheless, among these approaches, the nasoalveolar molding (NAM) technique has demonstrated notable reliability.

Upon literature review, numerous articles delve into NAM therapy and its contexts (Dean et al., 2019; (Levy-Bercowski et al., 2009). Beyond the clinical accomplishments of NAM, several studies have investigated the sociographic, economic, and satisfaction-related aspects of the therapy from the perspective of caregivers. It is imperative to engage caregivers in counseling sessions regarding the NAM process, giving them information on the success or failure of the therapy and potential complications.

Caregivers frequently express concerns regarding the success of nasoalveolar molding, including stress related to lip taping, the possibility of the appliance causing sores in their child's mouth, and the logistical challenges of weekly appointments (Sischo et al., 2015). The parents in our pilot study also reported allergic reactions of the skin and wounds on the chin or noses of the babies, but these difficulties didn't affect the end result of NAM therapy in our cases. Consequently, it is crucial to develop and communicate evidence-based guidelines effectively. This is essential not only to alleviate barriers to care but also to enhance the likelihood of successfully completing nasoalveolar molding treatment (Dean et al., 2019).

Compliance-related challenges are a notable concern, as evidenced by an incidence of approximately 30% for missed appointments and an incidence of 26% for the removal of the NAM appliance by the tongue, as indicated in Levy-Bercowski's research (Levy-Bercowski et al., 2009). In our survey, we did not encounter severe issues with caregiver compliance regarding check-ups or the use of the NAM plate. However, in one instance, the infant was unable to wear the plate, and only the lip tape could be applied (Magyar et al., 2022).

In all of our cases, the parents completed NAM therapy and, based on their subjective assessment, they rated the therapy as successful in 91% of the cases. They reported only partial failures. In the study of Dean et al. the non-completion rate was higher. They identified 94 patients that had initiated NAM therapy. 13.8% failed to complete the entire prescribed therapy. Complications, such as device intolerance and rash, were listed as the primary reason (Dean et al., 2019). In the survey of Herman et al., almost a quarter (23.4%) of 47 patients experienced early termination of their NAM treatment. They had a greater likelihood of additional unscheduled NAM visits, presence of siblings, non-Caucasian race, and history of social work visits. A larger total number of comorbidities, preterm birth, greater days inpatient after birth were correlated with noncomplete NAM treatment (Herrman et al.)

In a retrospective study by Park et al. physical, psychosocial, and financial factors of NAM therapy were assessed. The treatment lasted 13.6±8.8 weeks consisting of 15±6 check-ups. Mean travel distance for families was 28.6±37.1 miles. Though more than half of the families had private insurance, the rest of the patients received charity support for their treatment. They concluded, that the decision to pursue NAM should be evaluated in conjunction with the burden of care required for caregivers to complete the treatment (Park et al., 2024).

In a systematic review of 114 articles, analyzing difficulties around NAM treatment, parents reported financial burden in 10 percent of the articles, which has influence on the success of NAM therapy. In the USA, insurance companies can partially or fully cover the costs in 85% of cases, so families often consider whether they can afford the treatment and the associated financial burden (Alfonso et al., 2020).

In our findings almost one third of the cleft babies were born with associated health problems affecting the cardiovascular system, renal system or the optic nerve. This percentage is very similar to the ones found in the literature. Summarizing the data of 14 European countries, between 1980 and 2000, approx. in 5,500 cases of cleft lip and/or palate, 29.2% had other associated anomalies (Calzolari et al., 2007). A similar rate of 29.8% in 739 cases was registered in Italy between 2001 and 2014 (Impellizzeri et al., 2019). At the Charité University in Berlin, between 1999 and 2000, 27.8% of 266 patients had defects associated with clefts (Bartzela et al., 2021). Looking at Japan, between 1967 and 2020 at Tottori University, the percentage was lower, 14.5%, in 739 patients (Fujii et al., 2023).

Early cleft lip repair (ECLR) presents an alternative protocol for the treatment of children with cleft lip and palate. In this case cleft lip repair surgery occurs without a presurgical infant orthopedic treatment. A previous study has demonstrated that ECLR can effectively reduce the burden of health costs (Wlodarczyk et al., 2021). In our study, state insurance provided coverage for NAM therapy, including the travel costs of public transport. As compared to ECLR, NAM therapy emerged as a more cost-effective option, as it did not necessitate subsequent expensive secondary surgical procedures in the nasal area (Patel et al., 2015).

A study, which surveyed parents of orofacial cleft children, yielded findings aligning with our research group's conclusions. Both studies indicated that parents generally hold a positive attitude toward presurgical orthopedic treatment. Drawing on the literature, Alquadi et al. recommend that presurgical orthopedic treatment be regarded as a routine approach in the early management of orofacial clefts (Alqadi et al., 2023).

Our findings align with the observations from a previous project by Raina et al. in pediatric literature, indicating a positive correlation between the quality of caregivers' social support system and their coping mechanisms as well as psychosocial functioning during their infant's medical treatment (Raina et al., 2004).

Our results align significantly with the outcomes reported by Sischo et al., wherein caregivers faced challenges in coping with their primary role in preventive nasoalveolar molding therapy without sufficient social or appropriate assistance. Undoubtedly, the psychosocial well-being of caregivers emerges as a critical factor influencing effective treatment and clinical outcomes (Sischo et al., 2016).

Our study has several limitations. While caregivers were well-informed about the treatment process and potential challenges of NAM therapy, they did not receive nutrition counseling in half of the cases. Additionally, methodological limitations include the fact that data was obtained from a single institute with a limited number of cases. A multi-institutional study would be necessary to elucidate the relationship between caregivers' attitudes and the efficacy of NAM therapy.

Moving forward, our primary objective is to implement a fully digital workflow for nasoalveolar molding therapy in Hungary. The utilization of prefabricated palates would enable caregivers to easily manage the therapy in their home environment, leading to reduced travel time and a more tranquil atmosphere (Magyar et al., 2022).

5. Conclusions

Based on the limited number of RCTs and existing literature, we have formulated a clinical decision protocol in cleft care regarding the timing and specific interventions. Our cleft team highlights the inclusion of nasoalveolar molding as a key non-surgical approach in the thorough management of cleft patients during the first 6 months of life.

1. The NAM therapy demonstrated a substantial decrease in the maxillary arch deformity associated with BCLP. Moreover, this device played a crucial role in aligning the premaxilla without hindering short-term maxillary growth.
2. Our pilot study, centered on utilizing a quality-of-life questionnaire to assess both the success of NAM and the impact on caregivers' quality of life, underscores the crucial role played by caregivers in the therapy process. Furthermore, our findings indicate a relatively high burden of care for NAM-treated patients; however, caregivers exhibit a steadfast commitment to enhancing the therapy's effectiveness.

6. Summary

My thesis presents modern guidelines in cleft treatment protocol and explores different aspects of nasoalveolar molding therapy to improve the overall care and treatment success for patients with CLP at the Centre of Facial Reconstruction, Semmelweis University.

Cleft lip and palate are the most prevalent facial developmental anomalies. Addressing these conditions in children requires a series of complex surgical interventions over several years. The combined expertise and teamwork of a multidisciplinary group are essential to deliver optimal care for children with CLP. Although the standard sequence of surgical and non-surgical treatments is generally accepted, individual clinical judgment remains a key factor in treatment decisions. In my thesis surgical treatment steps of modern cleft management are described in chronological order while underlining the importance of nasoalveolar molding therapy (NAM), a presurgical infant orthopedic technique, which enhances the success of the lip closure, forms the nasal cartilages and directs the growth of the cleft alveolar segments.

The first aim of my study was to evaluate the short-term influence of preoperative NAM therapy on maxillary arch dimensions in bilateral cleft lip and palate infants. BCLP are severe congenital anomalies. The cleft interferes with the normal growth of the maxilla, leading to deficient midfacial development. Digital maxillary casts of 18 BCLP infants were analyzed before and after NAM therapy. The detected significant changes were the reduction of the alveolar cleft size, the expansion of premaxilla width and an increase of the anterior basal angle. NAM therapy could potentially serve as an effective tool in mitigating the severity of bilateral cleft deformities in the short term without interfering with maxillary growth.

While NAM seems to be a successful tool in the management of cleft patients, still, families may face various difficulties during treatment. My second aim was to reveal the burden of care of NAM therapy from the caregiver's perspective. A 32-item questionnaire was distributed to families whose children received NAM therapy. The survey focused on 4 main parts: socio-economic, origin of the cleft, difficulties of treatment and self-assessment. Although most of the families reported challenges including feeding difficulties, long travel distances, high number of checkups, allergic skin reactions and wounds caused by the applied adhesive tapes, in all instances, caregivers were satisfied with the aesthetic outcome of NAM. Our study emphasized the importance of parents' roles in NAM therapy. Despite the high burden of care, families demonstrated high compliance and were committed to enhancing the therapy's effectiveness.

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8. Bibliography of the candidate's publications

Publications related to the thesis

Articles:

MAGYAR, D., BODROGHELYI, M., PÁLVÖLGYI, L. & NAGY, K. 2024. [Modern management of children with cleft lip and palate]. Orv Hetil, 165, 163-170. (Q3; IF: 0,8)

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MAGYAR, D., PÁLVÖLGYI, L., SWENNEN, G., SHUJAAT, S. & NAGY, K. 2024 -b. Alteration in maxillary arch dimensions following preoperative nasoalveolar moulding therapy in bilateral cleft lip and palate patients. Clinical and Investigative Orthodontics, 1-7. (Q3; IF: 0,5)

Poster presentations:

VII. Tóth Pál wandering assembly [Pécs, Novembre 2019]. Application of 3D technology in presurgical nasoalveolar molding (NAM) for patients with clefts. Magyar Dominika, Würsching Tamás, Nagy Krisztián.

Oral presentations:

Oftex presentation [30th September 2021]. The role of nasoalveolar molding in the care of patients with cleft lip and palate.

Semmelweis University, Department of Paediatrics, Referee meeting [Budapest, 26th November 2020]. The role of nasoalveolar molding in the care of patients with cleft lip and palate.

Other publications

Conference papers:

Changes in the physical properties of orthodontic archwires to use mouthwashes. D Magyar, L Nádai, E Bognár, G Fábián (2014); In L.A. Gömze (Editor) 3rd International Conference on

Competitive. Materials and Technology Processes, Miskolc-Lillafüred, Hungary, pp., ISBN 978-963-12-0334-9.

Changes in the physical properties of orthodontic archwires with the use of mouthwashes [Budapest, 2014]. Magyar Dominika, Képes Dániel, Pammer Dávid, Nádai Lilla, Fábián Gábor; Dental Mini conference abstract booklet.

Poster presentations:

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92nd European Orthodontic Society Congress [Stockholm, June 2016]. The effect of mouthrinses on the material composition of orthodontic archwires. D Magyar, L Nádai, E Bognár, and G Fábián.

8th International Orthodontic Congress [London, September 2015]

Surface changes of orthodontic archwires under using mouthwashes;

D Magyar, L Nádai, E Bognár, and G Fábián

Oral presentations:

Semmelweis University, Medical, Dental and Pharmacy Student Conference [Budapest, April 2014]. Changes in the physical properties of orthodontic wires with the use of mouthwashes. III. place; Department of Paedodintics and Orthodontics special award.

Dental Mini conference [Budapest, January 2014]. Changes in the physical properties of orthodontic wires with the use of mouthwashes. Budapest University of Technology and Economics Faculty of Mechanical Engineering, Student Conference [Budapest, November 2013].

Changes in the physical properties of orthodontic wires with the use of mouthwashes. I. place; Department of Materials Science and Technology special award.

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Sincerely,

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