Implications from Precision Surgical Anatomy for Modern Craniofacial Pediatrics

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Summary

Orofacial cleft is the most common craniofacial birth anomaly. The comprehensive care of patients with craniofacial anomalies requires a multidisciplinary approach, beginning with prenatal counseling and continuing throughout life.

After birth, presurgical treatments aim to correct the imbalance of forces caused by the cleft. Surgery for cleft repair is usually performed in multiple stages, with cleft lip repair performed first, followed by cleft palate repair. However, several single-stage repair techniques have been developed. This approach involves simultaneous cleft lip and palate repair, thereby reducing the need for additional surgeries. The University Center for Cleft Lip and Palate and Craniofacial Anomalies in Basel has a long-standing history of simultaneous cleft lip and palate repair. However, conducting evidence-based studies on cleft surgery is challenging due to the rarity and variability of the malformation and the many treatment concepts.

As cleft surgery undergoes continuous refinement based on outcome assessment and latest evidence, the primary aim of this PhD project was to quantify the impact on craniofacial growth of simultaneous unilateral cleft lip and palate repair. The study discussed in **section 4** compared two cohorts, one with and one without primary alveolar bone grafting, and evaluated craniofacial growth, dental arch relationship, and palatal morphology. Results showed that omitting primary alveolar bone grafting did not improve craniofacial growth outcomes at the patients’ age of 6-11 years, suggesting that other surgical aspects may have a greater impact on craniofacial growth.

The second study, discussed in **section 5,** aimed to add new evidence for a better understanding of the curved vomerine mucosa in cleft repair. The curved vomer, a key region in unilateral cleft lip and palate, has been a subject of surgical controversy with sparse evidence. The study examined for the first time the histology of curved vomerine mucosa samples and found that they did not exhibit any specific signs of nasal mucosa. This suggests that the use of vomerine mucosa in cleft repair should not be based on fixed physiological beliefs and calls for a rethinking of the anatomy and paved the way for new surgical techniques in this region.

The third study, presented in **section 6,** assessed a new surgical technique, developed on the findings from section 5 and based on pure anatomic rearrangement of curved vomerine tissue for cleft palate closure. By this, a simultaneous continuous circular two-layer closure of unilateral cleft lip and palate has been achieved. The study assessed the safety, wound healing, and cleft width changes with presurgical passive plate therapy in patients undergoing this new surgical method. This study comprehensively demonstrates the potential of a simultaneous continuous circular closure technique for unilateral cleft lip and palate. However, further research is needed to evaluate long-term outcomes.

Overall, this PhD project aimed to contribute to the understanding and improvement of cleft surgery and outcomes in simultaneous cleft lip and palate repair.

Zusammenfassung

Die orofaziale Spaltbildung ist die häufigste kraniofaziale Geburtsanomalie. Die umfassende Betreuung von Patienten mit kraniofazialen Anomalien erfordert einen multidisziplinären Ansatz, der mit der pränatalen Beratung beginnt und sich über das weitere Leben erstreckt.

Nach der Geburt zielen die präoperativen Behandlungen darauf ab, das durch die Spalten verursachte Ungleichgewicht der Kräfte zu korrigieren. Chirurgische Eingriffe zur Behandlung der Spaltfehlbildungen werden in der Regel in mehreren Schritten durchgeführt, wobei zuerst die Lippenspalte und dann die Gaumenspalte operiert wird. Es wurden jedoch auch mehrere einzeitige Operationstechniken entwickelt. Bei dieser Methode werden Lippen- und Gaumenspalte gleichzeitig operiert, wodurch sich die Notwendigkeit zusätzlicher Operationen verringert. Das Universitäre Zentrum für Lippen-Kiefer-Gaumenspalten und Gesichtsfehlbildungen in Basel verfügt über eine langjährige Erfahrung in der gleichzeitigen Versorgung von Lippen-Kiefer-Gaumenspalten. Die Durchführung von evidenzbasierten Studien in der Spaltchirurgie ist jedoch aufgrund der Seltenheit und Variabilität der Fehlbildung und der vielen Behandlungskonzepte eine Herausforderung.

Da sich die Spaltchirurgie auf der Grundlage der Auswertung der Behandlungsergebnisse und der neuesten Erkenntnisse ständig weiterentwickelt, bestand das Hauptziel dieses PhD-Projekts darin, die Auswirkungen auf das kraniofaziale Wachstum bei gleichzeitiger Operation von unilateralen Lippen-Kiefer-Gaumenspalten zu quantifizieren. In der in **Abschnitt 4** beschriebenen Studie wurden zwei Kohorten verglichen, eine mit und eine ohne primäre Kieferspaltosteoplastik, und das kraniofaziale Wachstum, die Zahnbogenbeziehung und die Gaumenmorphologie bewertet. Die Ergebnisse zeigten, dass der Verzicht auf eine primäre Kieferspaltosteoplastik die Wachstumsergebnisse von Patienten im Alter von 6-11 Jahren nicht verbesserte, was darauf hindeutet, dass andere chirurgische Aspekte einen grösseren Einfluss auf das kraniofaziale Wachstum haben könnten.

Die zweite Studie (siehe **Abschnitt 5**) hatte zum Ziel, durch neue Fakten das Verständnis der gekrümmten Vomer-Schleimhaut bei Gaumenspaltoperationen zu erweitern und tradiertes Wissen in Frage zu stellen. Die chirurgische Verwendung der gekrümmten Vomer-Schleimhaut, eine Schlüsselregion bei unilateraler Lippen-Kiefer-Gaumenspalte, wird kontrovers diskutiert. In der Studie wurde erstmals die Histologie von Proben der gekrümmten Vomer-Schleimhaut untersucht und festgestellt, dass die Proben keine spezifischen Anzeichen von Nasenschleimhaut aufwiesen. Dies deutet darauf hin, dass die Verwendung von Vomer-Schleimhaut bei der Gaumenspaltoperation nicht auf starren physiologischen Überzeugungen beruhen sollte, und die Resultate erlauben ein Überdenken der anatomischen Beschreibungen und chirurgischer Techniken in dieser Region.

In der dritten Studie (siehe **Abschnitt 6**) wurde, abgeleitet aus den vorgängigen Studien, ein neues chirurgisches Konzept erarbeitet und für die Verschlussoperation angewendet. Die Spalte wurde nicht mehr durch Verlagerung von Gewebe aus der gesunden Region verschlossen, sondern nur noch durch ausgewogene Umverteilung des gekrümmten Vomer-Gewebes in der Defektzone selbst. Damit konnte ein gleichzeitiger kontinuierlicher, zirkulärer, zweischichtiger Lippen- und Gaumen-Verschluss, bei unilateralen Lippen-Kiefer-Gaumenspalte erreicht werden. Die Studie bewertete die Frühergebnisse der neuen Operationstechnik. Die Studie untersuchte die Sicherheit, die Wundheilung und die Veränderungen der Spaltbreite mit der präoperativen passiven Plattentherapie bei Patienten, die sich einem gleichzeitigen kontinuierlichen zirkulären zweischichtigen Verschluss einer unilateralen Lippen-Kiefer-Gaumenspalte unterzogen. Diese Studie zeigt umfassend das Potenzial einer gleichzeitigen kontinuierlichen zirkulären Verschlusstechnik für unilaterale Lippen-Kiefer-Gaumenspalten. Allerdings sind weitere Untersuchungen erforderlich, um die Langzeitergebnisse zu bewerten.

Insgesamt zielte dieses PhD-Projekt darauf ab, zum Verständnis und zur Verbesserung der Spaltchirurgie und der Ergebnisse bei der gleichzeitigen Operation der Lippen und Gaumenspalte bei Kindern mit Lippen-Kiefer-Gaumenspalten beizutragen.

1. Introduction

1.1 Prevalence of orofacial cleft

Orofacial cleft is among the 10 most common birth anomalies and represents the most prevalent craniofacial anomaly (Dolk et al., 2010). Globally, live birth prevalence of orofacial clefts is 3.4 per 2000 births, with documented variations depending on ethnicity and geography (Mossey et al., 2009). The European Surveillance of Congenital Anomalies (EUROCAT) reports a prevalence of 3 orofacial clefts per 2000 births. When differentiating between types of clefts, the prevalence of cleft lip with or without cleft palate is approximately 1.88 per 2000 births, while cleft palate alone accounts for 1.16 per 2000 (Dolk et al., 2010). In Switzerland, records from the Swiss Cleft Registry (https://swisscleftregistry.org/) indicate an overall incidence of 2 per 2000 births, with 1.16 per 2000 births recorded for cleft lip and palate and 0.86 per 2000 births for cleft palate alone (La Scala et al., 2022). However, underreporting is likely.

Although clefts are among the most common congenital malformations, their phenotypes are diverse, and the numbers of individual variants are low. Rare diseases are defined as having a prevalence of ≤ 1 per 2000 births ("EURORDIS Rare Disease Europe," 2022, "http://www.orpha.net," 2022; Richter et al., 2015).

1.2 Etiology of cleft lip and palate

During embryonic development, fusion of the maxillary lateral processes and medial nasal processes results in the normal anatomy of the upper lip (link: Animation of normal facial development) (Hill, 2022; Stanton et al., 2022). If fusion fails during the period of the 4th to 7th week of embryonic development, a cleft lip and alveolus results. Closure of the primary palate is followed by palatogenesis of the secondary palate by week 12. Midline fusion of the palatal and maxillary processes then occurs (Hammond&Dixon 2021) (link: Animation of palatal development) (Hill, 2022). Failure to fuse the processes results in a cleft palate. **Figure 1** depicts normal facial and palatal development (Stanton et al., 2022).

A quarter of patients with clefts exhibit a syndromic clinical phenotype, with at least 168 different cleft syndromes and 254 cleft loci identified thus far (Calzolari et al., 2007; Kousa et al., 2017; Kousa and Schutte, 2016; "Online Mendelian Inheritance in Man®," 2023). Nonsyndromic clefts are believed to have a multifactorial etiology, involving genetic and environmental risks (Mossey et al., 2017).

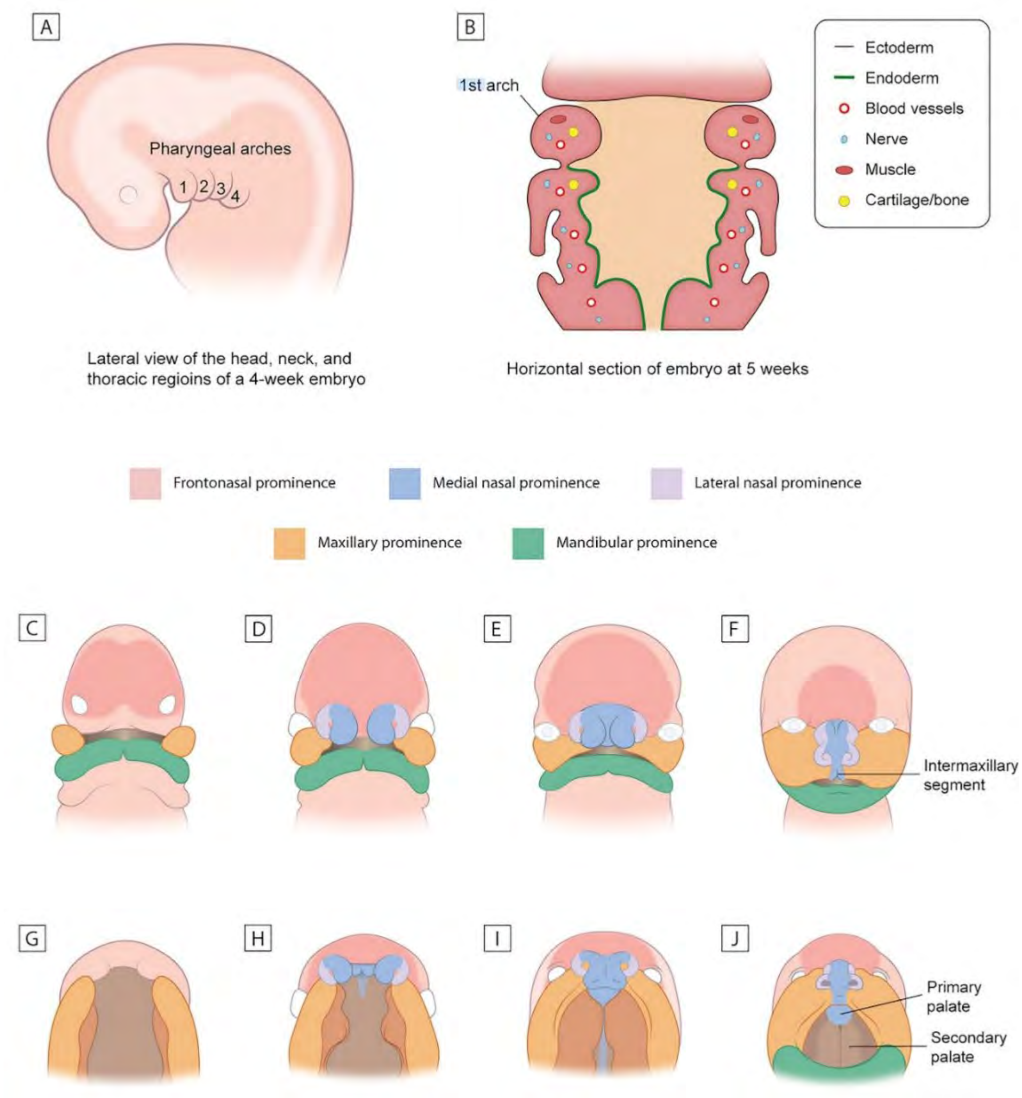
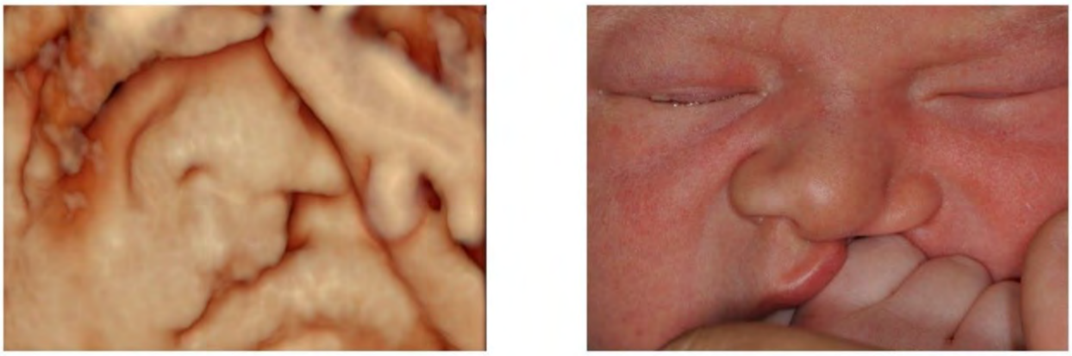


Figure 1. Schematic drawing representing the development of pharyngeal arches and craniofacial complex. (A) and (B) Development of pharyngeal arches and tissue components within each pharyngeal arch in 4-week or 5-week-old embryo. (C)-(F) Development of the frontonasal, bilateral maxillary, and bilateral mandibular prominences (frontal view) into the upper jaw, and lower jaw, respectively. (G)-(J) Development of the primary palate occurs as a consequence of the fusion of the paired medial nasal prominences, forming the intermaxillary segment (axial view). Simultaneously, the secondary palatine processes extend medially from the maxillary prominences, completing palatal shelf fusion. Figure from: Stanton E, Sheridan S, Urata M, Chai Y. From Bedside to Bench and Back: Advancing Our Understanding of the Pathophysiology of Cleft Palate and Implications for the Future. The Cleft Palate Craniofacial Journal. 2022;0(0). doi:10.1177/10556656221142098. Copyright © 2022, American Cleft Palate Craniofacial Association. Reprinted by Permission of SAGE Publications

The importance of fusion of the palate is reflected in its functions in sucking, swallowing, feeding, and phonation. In addition, the muscles of the palate (M. tensor veli palatini, M. levator veli palatini, and M. salpingopharyngeus) participate in the ventilation of the middle ear, thereby affecting hearing function.

1.3 Prenatal diagnosis of cleft lip and palate

The presence of clefts early in fetal development allows to detect orofacial clefts by prenatal ultrasound (Platt et al., 2006; Rotten and Levaillant, 2004). In fetal anomaly screening programs with ultrasound at 18-21 weeks of gestation and up to the 23rd week of pregnancy, the detection rate of cleft lip and palate is reported to be 90.9% (CI 89.4-92.1%) (Aldridge et al., 2022). 3D/4D sonographic modes and fetal dental panoramic techniques have further improved visualizing facial, dental, and palatal malformations (Levaillant et al., 2016; Nicot et al., 2019; Rotten and Levaillant, 2004). This allows for early parental counseling regarding diagnosis and treatment by the craniofacial team (Morales et al., 2022). Although prenatal diagnosis of craniofacial anomalies is a source of parental stress, early parental counseling has been shown to help with coping (Sreejith et al., 2018). **Figure 2** shows a 3D surface-rendering of the fetal face in the 23rd gestational week of a patient with complete unilateral cleft lip and palate and the corresponding clinical image on the first day of life.



A **B**

Figure 2. A, 3D surface-rendering of the fetal face with complete unilateral cleft lip and palate at the 23rd gestational week **B**, clinical image on the first day of life

The occurrence of a cleft during early embryogenesis leads to inhibited tissue fusion, resulting in significant force changes at an early stage in terms of direction and symmetry. The imbalance of forces is attributed to several factors, including the absence of lip ring muscle, disconnected maxillary process, lack of palatal muscle sling, and tongue interposing into the cleft. It is crucial to recognize that these forces are likely to further alter the craniofacial morphology throughout the seven months until birth. A principle described in simplified terms as “form follows function” (Hwang, 2019a). **Figure 3** shows a newborn with a complete unilateral cleft lip and palate on the left side.

A B

Figure 3. Newborn with complete unilateral cleft lip and palate. **A,** front view. **B,** view of the palate with deficiency of the bony nasal floor on the cleft side, thus connecting the oral and nasal cavities**.** Figures derived from Benitez, B. K., Brudnicki, A., Nalabothu, P., Jackowski, J. A. von., Bruder, E., & Mueller, A. A. (2022). Histologic Aspect of the Curved Vomerine Mucosa in Cleft Lip and Palate. Cleft Palate-Craniofacial Journal, 59(8), 1048–1055. https://doi.org/10.1177/10556656211031419

1.4 Postnatal treatment of cleft lip and palate

Due to involvement of multiple specialists in the care and treatment of craniofacial anomalies, a comprehensive network is needed to provide the best possible care. Multidisciplinary attention should begin with prenatal counseling. After birth of a baby with cleft, it is important to ensure feeding and healthy development (Bessell et al., 2011; Glenny et al., 2004). Providing postnatal feeding education is critical as feeding difficulties may lead to malnutrition with failure to thrive and increase the risk of neonatal hypernatremic dehydration, a potentially lethal condition (Livingstone et al., 2000; Pandya and Boorman, 2001). Elective surgical treatment of the cleft is planned after the neonatal period, when the children's risks associated with anesthesia and surgery are reduced.

Even after cleft surgery, the patient and family are ideally accompanied by a multidisciplinary team (Berkowitz, 2014), which includes the transition process into adulthood. In Europe, reference networks for craniofacial deformities (ERN CRANIO) have been established since 2017 ("European Reference Networks," n.d.) to compile and assure highest competence for transdisciplinary treatment for these rare malformations. In Switzerland, the first efforts to accredit rare-disease care networks started in 2023 by the National Coordination Rare Diseases Switzerland (Nationale Koordination Seltene Krankheiten KOSEK) ("https://www.kosekschweiz.ch/," 2023).

1.4.1 Preoperative treatments and orthodontics

Postnatal therapeutic approaches are used as part of preoperative treatment to restore balance among the forces occurring in the region of the cleft. One such approach is lip taping, which counteracts the muscle forces exerted by the separated orbicularis oris muscle (Pool and Farnworth, 1994). Lip taping not only promotes the approximation of the alveolar segments, but has also been observed to reduce the size of the palatal cleft (Abd El-Ghafour et al., 2020). Additionally, nasal molding techniques were utilized in preoperative interventions, either using nasal hooks or fixing different types of nasal stents to a palatal plate (Grayson and Cutting, 2001; Liao et al., 2012). Different orthopedic appliances have been developed to preoperatively modify alveolar and palatal segments. Active appliances, incorporating springs and screws, are specifically designed to apply forces that reposition the segments (Berkowitz et al., 2004; Latham, 1980). Alternatively, semi-active appliances, as originally proposed by McNeil, use a plate to mold and guide the palatal segments towards a desired position (McNeil, 1950). However, there is limited evidence to support the effectiveness of presurgical orthodontics to prevent maxillary arch collapse (Prahl et al., 2003), improve feeding (Masarei et al., 2017; Prahl et al., 2005), or produce long-term effects on maxillary arch dimensions and growth (Bongaarts, Catharina A.M., Martin A. van ’t Hof, Birte Prahl-Andersen, Iris V. Dirks, 2006; Grayson and Cutting, 2001; Noverraz et al., 2015).

Nevertheless, nasoalveolar molding techniques remain highly popular (Grayson et al., 1999) despite criticism of the additional burden of care on parents and patients and the drain on healthcare resources (Alfonso et al., 2020). This criticism even promoted justification of early lip surgery during the vulnerable neonatal period, primarily to alleviate the burden of healthcare costs (Wlodarczyk et al., 2021). Another presurgical treatment approach is the use of passive plates, which requires fewer patient visits (Chen and Liao, 2015; Koželj, 1999). Simplified passive plates aim to create a new balance by keeping the tongue out of the cleft, thereby establishing more favorable conditions for surgery. These plates do not require weekly visits for grinding, thus reducing patient burden and healthcare costs. Furthermore, these passive presurgical plates can be supplemented with a stent for nasal molding (Chen and Liao, 2015; Kozelj, 2007). **Figure 4** illustrates a patient with a unilateral cleft lip and palate undergoing presurgical treatment involving lip taping, nasal stent, and passive palatal plate to rebalance forces and prepare for surgery.

Figure 4. Presurgical re-equilibration of forces in a patient with a unilateral cleft lip and palate with lip taping and nasal stent attached to a passive presurgical plate

1.4.2 Surgical techniques for cleft repair

For cleft repair, various surgical protocols and concepts have evolved. However, conducting evidence-based studies on cleft surgery pose challenges. Firstly, the rarity of the malformation coupled with its substantial variability makes it difficult to obtain necessary sample sizes. Secondly, important outcome parameters such as speech and growth can only be recorded and evaluated in the long term. Moreover, additional treatments administered during this period can act as confounding factors, thus further complicating the studies.

Although some tissues (mucosa, muscle, nasal cartilage, bone, teeth) appear to be missing in the presence of a cleft, the cleft surgeon Victor Veau stated in 1928 that “les structures normales sont présentes sur les berges de la fente, modifiées seulement par le fait de la fente[1]” (Talmant et al., 2007). Others hypothesize that the tissue are hypoplastic depending on the type of cleft, and even sidedness plays a role (Chong et al., 2022).

A reconstructive approach with distinct types of flaps is characteristic of both lip and palate cleft surgery. However, instead of a primary reconstructive approach, anatomic rearrangement using the existing tissue should be planned because most of the tissues are present, but their position has been changed by the cleft. Planning for repositioning is only possible after the extent of tissue displacement has been assessed (Fisher, 2005; Tse et al., 2019). The goal of treatment is to establish the normal form and function by realigning the various tissues that were displaced by the failed fusion during early stages of embryonic development.

[1] “The normal structures are present on either side of the cleft, only modified by the fact of the cleft.”

Traditionally, cleft repair is performed in multiple stages. Most often, the cleft lip is repaired first to reduce the alveolar and palatal clefts by continuous muscle traction from the surgeon's perspective and to satisfy the parents' desire for a rapid correction. Since speech is an important outcome in cleft care, the next step involves restoring normal soft palate anatomy with its associated muscles. Soft palate repair is recommended at the infant's age not later than 12 to 18 months, but the optimal timing for speech outcome remains controversial. Patients undergoing cleft palate repair before the age of 6 months have an increased risk of complications, reoperations and readmission within 30 days (Peck et al., 2021). Therefore, cleft palate repair should be performed after 6 months of age.

In 1958, Farina published a simultaneous cleft lip and palate repair technique for patients with unilateral complete cleft lip and palate (Farina, 1958). In his first description of a simultaneous cleft lip and palate repair, he stated that "on peut très bien tout faire en une seule fois dans certains cas[2]"(Farina, 1958). Simultaneous cleft lip and palate repair facilitates fistula-free closure of the hard and soft palate junction as well as of the alveolar region. These sites are prone to fistula formation in many techniques studied (Tache and Mommaerts, 2019), especially when cleft lip and palate surgery is performed in two stages. This is all the more important because underreporting of fistula formation is likely (Yang et al., 2020), as some studies exclude nasoalveolar fistulas and define them as intentional openings (Cohen et al., 1991; Yang et al., 2020). Farina further mentioned the advantage of reducing the need for a second surgery and avoiding additional general anesthesia.

Since then, various surgeons have developed different concepts to accomplish simultaneous cleft lip and palate repair (Brusati, 2016; Davies, 1966; De Mey et al., 2009; Fudalej et al., 2010; Honigmann, 1996; Kaplan et al., 1974; Torikai et al., 2007). At the Basel cleft center, Honigmann introduced a technique for simultaneous cleft lip and palate repair in 1991. This involved a two-layer palate repair with a cranially pedicled vomer flap and two-flap palatoplasty (Veau's pedicled palatal flaps), primary alveolar bone graft from the rib and lip repair with modified Millard technique (Honigmann, 1998, 1996). Long-term growth analysis of this cohort revealed growth disturbances similar to those seen in external cohorts after staged cleft repair (Mueller et al., 2012). Furthermore, primary alveolar bone grafting had to be abandoned due to inconsistent results and suspected interference with maxillary growth. This indicates clearly that further research is needed on both presurgical and surgical approaches to reduce the treatment burden on the child, thereby reducing healthcare costs, hospitalization, and family burden.

[2] Author translation: "It is possible to do everything at once in some cases."

2. Clinical relevance and aims of the PhD studies

The primary aim of this PhD project was to quantify the effect of two distinct surgical techniques used in simultaneous cleft lip and palate repair with respect to craniofacial growth. The second aim was to study the curved vomer region, a key element in unilateral cleft lip and palate repair. Based on these findings a new surgical technique was introduced and has subsequently been evaluated. The new surgical technique consists of a continuous circular two-layer simultaneous cleft lip and palate repair technique, with a balanced use of curved vomerine mucosa. This makes it possible for the first time to achieve primary wound healing of the entire cleft area without of open sores with secondary wound healing.

2.1 Craniofacial growth after simultaneous cleft lip and palate repair (section 4)

Simultaneous primary cleft lip and palate repair has been debated over many years. Main concerns were growth restriction of the maxilla due to early scarring and secondary wound healing in the hard palate, as well as increased risks of postoperative complications (Kantar et al., 2018). However, these initial concerns regarding the safety of simultaneous cleft lip and palate repair could be allayed when simultaneous repairs were successfully performed in low-resource settings (Hodges, 2010; Hodges and Hodges, 2000). Different surgical techniques have been described for simultaneous cleft lip and palate repair. These techniques may have different effects on maxillary growth. Therefore, long-term follow-up to assess growth outcome is crucial to quantify the impact of previous surgical treatments (Farber et al., 2019). Ideally, growth of the maxilla is assessed at the end of the growth period and then compared with maxillary growth in healthy controls as well as in cohorts who underwent different treatments. However, trends in maxillary growth can already be predicted at the child’s age of 5 to 6 years (Meazzini et al., 2015). **Section 4** deals with the effects on maxillary growth of primary alveolar bone grafting performed during a simultaneous unilateral cleft lip and palate repair in children aged 6-11 years.

2.2 Rethinking cleft anatomy – paradigm of the curved vomerine mucosa (section 5)

Malformation of the curved vomer is specific to the unilateral complete cleft lip and palate. The curved vomer was described as a key element and region for cleft palate closure (Veau, 1931). Literature shows controversies over the use of vomerine mucosa to reconstruct the nasal or oral layer (Abyholm, 1996; Agrawal and Panda, 2006; Delaire and Precious, 1985). We quantify the histopathological morphology of this unique tissue in patients with unilateral cleft lip and palate. Thereupon, we challenge the current paradigm of exclusive use of vomerine tissue to restore the nasal mucosal lining in cleft repair (**section 5**).

2.3 Simultaneous circular cleft lip and palate repair – paradigm of reconstructive cleft surgery (section 6)

Cleft surgery often refers to reconstructing the deformity (Britt et al., 2019) by moving tissue from the healthy area into the defect. However, the tissue barter known as “robbing Peter to pay Paul” (Hwang, 2019b), should be minimized, as it may lead to donor site problems and violates the principle, that normal tissue should remain in its normal position (Gillies and Millard, 1957). We challenge the paradigm of a reconstructive surgery in cleft lip and palate. Instead of a reconstructive approach, we proposed a pure anatomic rearrangement to achieve simultaneous circular two-layer cleft lip and palate closure with a balanced use of vomerine mucosa (**section 6**).

3. Outline of this PhD thesis

This thesis is based on three publications covering the following research questions and topics:

3.1 Craniofacial growth after simultaneous cleft lip and palate repair (section 4)

We investigated whether primary alveolar bone grafting during simultaneous unilateral cleft lip and palate repair negatively affects craniofacial growth as assessed at the children’s age of 6 to 11 years. We compared two cohorts after a single-stage protocol with and without primary alveolar bone grafting at our center to quantify craniofacial growth, dental arch relationship, and palatal morphology. In addition, we compared cephalometric measurements for growth with an external cohort undergoing simultaneous cleft lip and palate repair as well as a heathy control group. We addressed the question whether additional primary alveolar bone grafting, as performed at the Cleft Center in Basel between 1991 and 2002 (Honigmann, 1996; Mueller et al., 2012), influences craniofacial growth as determined at the children’s age of 6–11 years, compared to simultaneous cleft lip and palate repair without primary alveolar bone grafting performed between 2003 and 2014.

Cephalometric results indicated similar sagittal maxillary growth deficits in both protocols compared to the healthy group. Furthermore, dental, and palatal morphology was altered in 70% of patients regardless of primary alveolar bone grafting. Thus, omitting primary alveolar bone grafting under the simultaneous cleft lip and palate repair protocols studied did not improve growth at 6–11 years. Results imply other aspects of surgical technique are more detrimental to growth than primary alveolar bone grafting.

3.2 Rethinking cleft anatomy – paradigm of the curved vomerine mucosa (section 5)

The study presented in **section 5** aimed to challenge the current paradigm of vomerine tissue for cleft repair. The vomer region, which is unique to unilateral cleft lip and palate, is the subject of surgical controversy. Since it represents a key region for cleft palate closure, we histologically examined an excess of curved vomerine mucosa in 8 patients with tissue samples obtained during surgery at 8 months of age. The curved vomerine mucosa comprised a stratified squamous epithelium with numerous seromucous glands. Arrangement of the basal cells were compatible with metaplasia of respiratory epithelium; however, no goblet cells or respiratory cilia were identified. Contrary to common belief, the histopathological findings of curved vomerine mucoperiosteum showed no specific signs of nasal mucosa. Therefore, we concluded that technical use of vomerine mucosa in cleft repair should not follow a fixed physiologic belief. Furthermore, the anatomy of the cleft as well as the surgical techniques in this key region should be rethought.

3.3 Simultaneous circular cleft lip and palate repair – paradigm of reconstructive cleft surgery (section 6)

This study analyzed whether an anatomic rearrangement with a balanced use of vomerine mucosa can achieve a simultaneous circular two-layer closure in unilateral cleft lip and palate. This eliminates the need to move tissue from the healthy area to the clef area. We analyze a cohort of patients after unilateral cleft lip and palate repair with a continuously circular midline suture all along the nasal and oral side. For the primary and secondary outcomes, we assess the safety and reliable wound healing without fistula formation. Furthermore, the effect of 8 months of presurgical passive plate therapy on cleft width was analyzed.

In eleven patients who underwent surgery for unilateral cleft lip and palate repair at the age of 8-9 months, full primary healing occurred without fistula formation. No intra- or postoperative adverse events occurred. Anterior and posterior palatal cleft width decreased significantly from birth to surgery with passive presurgical plate therapy. The preliminary study confirmed the potential for further development of the concept of simultaneous continuous circular closure in patients with unilateral cleft lip and palate. Further investigation is needed, particularly to evaluate subsequent growth and speech outcomes.

4. Craniofacial growth after simultaneous cleft lip and palate repair

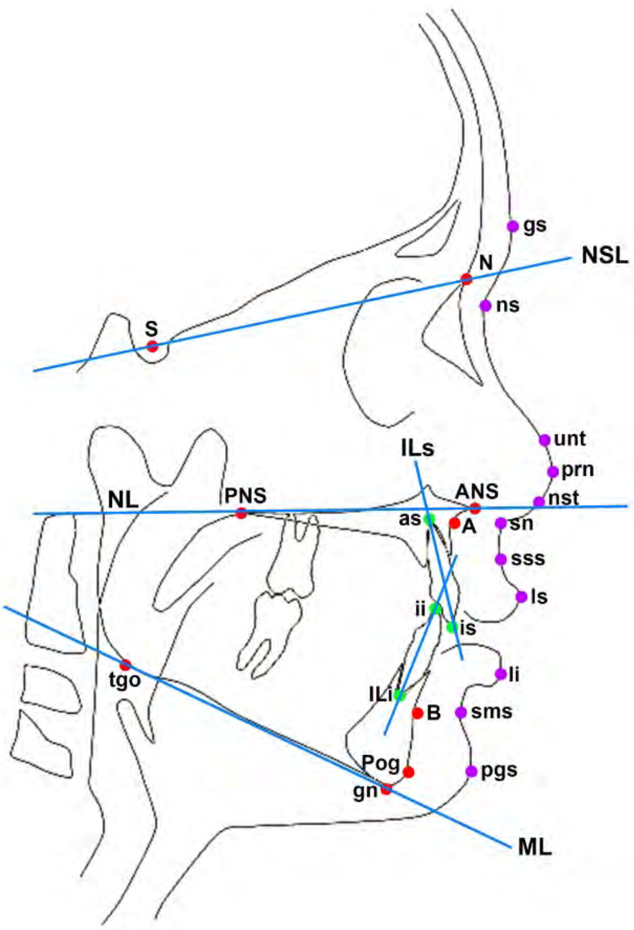


Figure 5. showing skeletal, dental, and soft tissue reference points and lines for cephalometric analysis in Benitez, Benito K., Seraina K. Weibel, Florian S. Halbeisen, Yoriko Lill, Prasad Nalabothu, Ana Tache, and Andreas A. Mueller. Craniofacial Growth at Age 6–11 Years after One-Stage Cleft Lip and Palate Repair: A Retrospective Comparative Study with Historical Controls. Children. 2022; 9(8):1228. https://doi.org/10.3390/children9081228

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Craniofacial Growth at Age 6–11 Years after One-Stage Cleft Lip and Palate Repair: A Retrospective Comparative Study with Historical Controls

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Abstract: Background: Primary alveolar bone grafting inhibits craniofacial growth. However, its effect on craniofacial growth in one-stage cleft lip and palate protocols is unknown. This study investigated whether primary alveolar bone grafting performed during one-stage unilateral cleft lip and palate repair negatively affects growth up to 6–11 years old. Methods: The craniofacial growth, dental arch relationship and palatal morphology at 6–11 years old in children with unilateral cleft lip and palate were compared retrospectively. Two cohorts after a one-stage protocol without (Group A) and with (Group B) primary bone grafting at the same center were compared. Further, cephalometric measurements for growth were compared with an external cohort of a one-stage protocol and a heathy control. Results: Group A comprised 16 patients assessed at 6.8 years (SD 0.83), and Group B comprised 15 patients assessed at 9 years (SD 2.0). Cephalometric measurements indicated similar sagittal maxillary growth deficits and a significant deviation in maxillary inclination in both groups compared to the healthy group. Moderate to severe changes in palatal morphology were observed in 70% of the members in both groups. Conclusion: Omitting primary alveolar bone grafting under the one-stage protocol with two-flap palatoplasty studied did not improve growth at 6–11 years. The results implicate two-flap palatoplasty with secondary healing as having greater adverse effects on growth than primary alveolar bone grafting. Dental and palatal morphology was considerably compromised regardless of primary alveolar bone grafting.

Keywords: cleft lip; cleft palate; growth and development; treatment outcome; cephalometry

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1. Introduction

Unoperated adult patients with unilateral cleft lip and palate (UCLP) show a normal craniofacial growth potential at the expense of persistently wide palatal and alveolar clefts [1]. Cleft surgery, especially on the cleft palate, is known for adverse effects on craniofacial growth [2]. To limit growth inhibition by cleft repair, staged protocols have been developed to postpone surgical interventions to time periods with less of an impact on growth [3]. In contrast, one-stage protocols, combining lip and palate closure, focus on reducing patient and parent burden, early normal function, shortening anesthesia time and lowering overall healthcare costs [4–7]. Technical differences among one-stage protocols might have an influence on craniofacial growth and should therefore be investigated.

Primary alveolar bone grafting, leading to an early connection of the cleft segments, showed negative effects on growth [8–10]. Combining primary alveolar bone grafting with primary cleft repair has been controversial [11], and it has been largely abandoned due to its negative effects on growth [8,9]. However, the influence of additional primary alveolar bone grafting in a one-stage cleft lip and palate protocol has not been evaluated.

The study's purpose and primary objective is to answer the following clinical question: Among patients with UCLP, does primary alveolar rib bone grafting, when compared with no bone grafting at one-stage cleft lip and palate repair, restrict craniofacial growth and affect the dental arch relationship and palatal morphology assessed at 6–11 years.

The secondary objective is to compare craniofacial growth with external historical controls of a one-stage cleft lip and palate surgical protocol and a healthy control group.

The null and alternative hypotheses are as follows:

H_0. *There is no difference in craniofacial growth assessed at 6–11 years of age between patients after one-stage unilateral cleft lip and palate repair with or without primary alveolar bone grafting.*

H_a. *There is a significant difference in craniofacial growth assessed at 6–11 years of age between patients after one-stage unilateral cleft lip and palate repair with or without primary alveolar bone grafting.*

2. Materials and Methods

2.1. Study Design and Setting

A retrospective comparative study between cohorts of children with complete UCLP was performed. The comparison groups were represented by historical controls from the literature. The report follows the STROBE guidelines for observational studies [12]. The setting consisted of two multidisciplinary cleft services in Europe: Group A and Group B—Cleft and Craniofacial Team, University Hospital Basel, Switzerland; Group S—Institute of Mother and Child, Warsaw, Poland.

For Group A and B, the study was approved by the Ethics Commission of Northwest and Central Switzerland (EKNZ) (project-ID 2017-00036 and 2006-00256), and for Group S, the study was approved by the Bioethics Committee at the Institute of Mother and Child, in accordance with the Declaration of Helsinki.

2.2. Participants and Procedures

Patients with complete UCLP after one-stage cleft lip and palate repair who had cephalograms from the age of 6–11 years were included in this study. Children with associated syndromes or a lack of consent for the study were excluded. Table 1 shows all the groups compared, along with their treatment protocol and the healthy control. All surgical procedures were performed differently among the groups, but all were performed by experienced single surgeons.

Table 1. Comparison groups with a summary of the treatment protocols and the healthy non-cleft control group.

Study Population (Publication)	Description	*n*	Age Range [Years]	Treatment Protocol
2003–2014	Group A	16	6–9	One-stage cleft repair: lip, vomer flap and two-flap palatoplasty at 6 months
1991–2002 (Group 1) [13]	Group B	15	6–11	One-stage cleft repair: lip, vomer flap and two-flap palatoplasty with primary rib bone grafting at 6 months
Slav-Cleft (Warsaw) [14]	Group S	35	8–13.6	One-stage cleft repair: lip, vomer flap and bipedicled hard and soft palate repair at 9 months
Healthy control group [15]	Group H	83	6–9	N/A

For the primary objective, the craniofacial growth, dental arch relationship and palatal morphology after one-stage cleft lip and palate repair were compared between the groups without (Group A) and with (Group B) primary rib bone grafting.

The treatment protocol of Group A included passive presurgical orthopedic treatment from birth to surgery [16]. One-stage cleft repair was performed at 4–6 months of age, including primary lip repair, cranial pedicled vomer flap and two-flap palatoplasty with secondary healed lateral relaxing incisions. Group A consisted of consecutive patients operated on by the single surgeon A between January 2003 and December 2014.

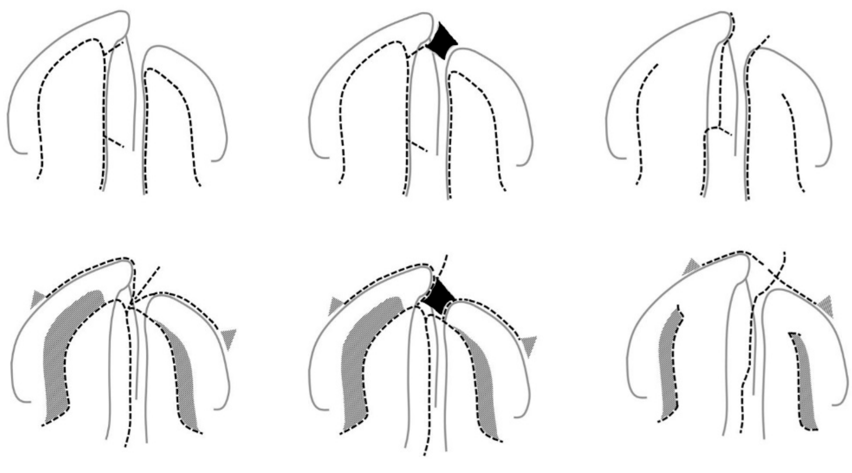
Group B was previously published; the age-matched subgroup 1 (6–11 years) was included for comparison [13]. The treatment protocol of Group B was identical to that of Group A, except for the surgery at 6 months old and additional primary rib bone grafting [6]. This cohort consisted of consecutive patients operated on by surgeon B between January 1991 to December 2002.

For the secondary objective, the comparison included external historical controls.

Group S was previously published by the Warsaw center in the Slav-cleft study [14]. The treatment protocol of Group S included no presurgical orthopedics. The one-stage surgical closure (lip and palate) at 9 months of age by the same surgeon comprised: lip closure (triangular flap), hard and soft palate repair with bipedicled flaps, medial extended vomer flap, hamulus fracture and nasal mucosa and muscle-aponeurosis detachment from the posterior hard palate [17]. The cohort consisted of children with complete UCLP operated on between 1994 and 1996 by a single experienced surgeon. Lateral cephalograms at the age of 8–13.6 years were reported for Group S.

As a healthy non-cleft control (Group H), cephalometric standards out of the Atlas of Craniofacial Growth from the University School Growth Study were included [15]. Lateral cephalograms of children aged 6–9 years without a history of orthodontic treatment were analyzed.

Figure 1 illustrates the surgical procedures for the cleft palate repair of Groups A, B and S with the incision layout and the course of the sutures with secondary healing sites.



(**A**) (**B**) (**C**)

Figure 1. Upper row illustrates incision outlines (dashed line), and lower row illustrates the suture outline for the cleft palate repair of Group A (**A**), Group B (**B**) and Group S (**C**) and the site of secondary healing (gray). In Group B (**B**), primary bone grafting with rib bone (black) is shown in the alveolar cleft.

2.3. Outcome Variables, Data Sources and Measurements

The primary outcome—the craniofacial growth of pre-adolescent children from Groups A, B, S and H—was evaluated based on lateral cephalograms. Figure 2 illustrates the reference points used for cephalometric analysis. To minimize the bias due to different ages, only angular measurements were used. Table A1 in the appendix shows the seven hard tissue and seven soft tissue measurements and their identification in the comparative studies. The lateral cephalograms of Group A were independently assessed by two investigators using OnyxCeph^{3TM} software (Image Instruments, Chemnitz, Germany). This was compared with the previously published results of the lateral cephalometric analysis from Group B with primary rib bone grafting [13], the historical controls of Group S and the healthy control Group H [14,15].

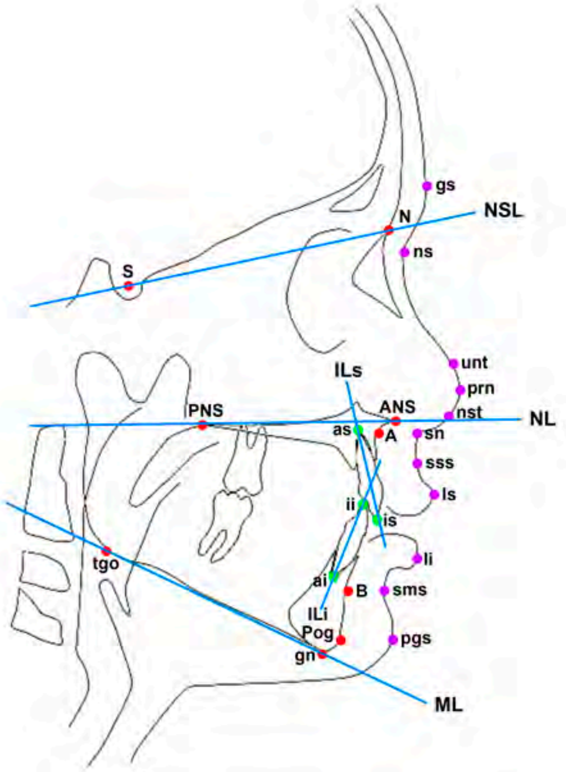


Figure 2. Reference points used for cephalometric analysis: **Skeletal reference points** (red): N—nasion, S—sella, A—subspinale (A-Point), B—supramentale (B-Point), Pog—pogonion, gn—gnathion, tgo—gonion, ANS—spina nasalis anterior, PNS—spina nasalis posterior; **Dental reference points** (green): as—apicale superius, is—inzision superius, ii—inzision inferius, ai—apicale inferius; **Soft tissue reference points** (purple): gs—soft tissue glabella, ns—soft tissue nasion, unt—upper nasal tangent from ns, prn—pronasale, nst—nasal septum tangent point, sn—subnasale, sss—soft tissue subspinale, ls—labrale superius, sms—soft tissue supramentale, pgs—soft tissue pogonion; **Reference lines** (blue): NSL—nasion-sella-line (line through N and S), NL—nasal line (line through PNS and ANS), ML—mandibular line (tangent to the lower border of the mandible trough gn), ILs—axis of upper incisors (line from is to as), ILi—axis of lower incisors (line from ii to ai). Reference points derived from Brattström et al., 2005 [18].

Based on the EUROCRAN Index, we evaluated the dental arch relationship and palatal morphology (EUROCRAN dental and palatal morphology grade) on the dental casts between Groups A and B [19,20]. The absence of the permanent lateral incisor based on photographs, orthopantomography and dental casts was assessed.

2.4. Statistical Methods

Descriptive statistics (means, standard deviation) were calculated for Groups A and B. The primary outcome variables of craniofacial growth were analyzed by one-way ANOVA with Tukey Kramer post hoc pairwise tests to identify intergroup differences for angular and ratio variables. Statistical significance was set at $p < 0.05$. The interrater reliability of the cephalometric measurements in Group A by the two evaluators was determined by the interclass correlation coefficient (ICC). An ICC under 0.5 was interpreted as poor, 0.5–0.75 as moderate, 0.75–0.9 as good and >0.90 as excellent reliability [21]. Bland–Altman plots were used for visual representation. Data analysis was performed using STATA 15.0

(StataCorp LLC, College Station, TX, USA) and R statistical software version 3.5.2 (Boston, MA, USA)

3. Results

For Group A, forty patients were assessed for eligibility based on medical records. Seven patients were excluded due to missing consent, sixteen patients who lacked a lateral cephalogram at 6–9 years were exluded and one patient was excluded due to a low-quality cephalogram. Therefore, sixteen patients were included and analyzed in Group A.

Table 2 shows the baseline characteristics of Group A (without primary bone grafting) compared to those of Group B (with primary bone grafting), as well as Group S as an external control of a one-stage protocol. Group A was younger at both surgery and assessment (on average, 3.9 months and 6.8 years, respectively) than Group B (6 months and 9 years).

Table 2. Baseline characteristics after one-stage repair of unilateral cleft lip and palate without primary bone grafting (Group A) in comparison to (Group B) that with primary bone grafting and Group S.

	Group A (2003–2014) ***n*** **(%)**	**Group B (1991–2002)** ***n*** **(%)**	**Group S (1994–1996)** ***n*** **(%)**
Total patients per group	16	15	35
Female	5 (31.25%)	4 (26.67%)	10 (28.57%)
Male	11 (68.75%)	11 (73.33%)	25 (71.43%)
Cleft			
Left	11 (68.75%)	9 (60%)	N/A
Right	5 (31.25%)	6 (40%)	N/A
Age at study (years) [mean (SD)]	6.8 (0.83)	9 (2)	10.6 (1.2)
Age at cleft repair (months) [mean (SD)]	3.9 (0.62)	6 (1)	9

Data for Group B are derived from Mueller et al., 2012 [13], and data from Group S are derived from Urbanova et al., 2016 [14].

The interrater reliability with ICC for the cephalometric measurements in Group A is shown in Table A2 (Appendix A). The ICC showed a medium to high range (0.57–0.97) of agreement between the two investigators for all variables in Group A. Figure A1 shows the Bland–Altman plots, demonstrating a good agreement between the investigators for the cephalometric variables in Group A, consistent with the findings of the ICC.

3.1. Dental Arch Relationship and Palatal Morphology

Table 3 shows the dental arch relationship and palatal morphology for Groups A and B, quantified by the EUROCRAN index and the status of the lateral permanent incisor. Moderate to severe changes in palatal morphology were observed in 70% of members in both groups. In more than 40%, the non-cleft side lateral permanent incisor was missing.

3.2. Craniofacial Growth

For the primary objective, the measurements of craniofacial growth from Group A (Cohort 2004–2014) and Group B (Cohort 1991–2002) were compared. The children in both groups exhibited a similar and significant ($p < 0.001$) sagittal growth deficit of the maxilla, with a mean SNA of 76.5° (SD 5.9°) and an SNA of 76° (SD 4°), respectively, compared to the healthy non-cleft control Group H (81° (3.1°)). The maxillary inclination showed a significant difference ($p < 0.001$) from the normal cranial relationship. The angle NSL/NL was larger in both Group A (11.7° (4.2°)) and Group B (14° (4°)) than in Group H (6.4° (2.5°)). The intermaxillary relation ANB was similar between Groups A (3.5°) and B (3°). The only significant difference in the hard tissue between Groups A (88.53° (8.1°)) and

B (103° (15°)) was in the inclination of the upper incisor (ILs/NL) ($p < 0.001$). The chin prominence (S-N-Pog) was slightly lower ($p = 0.77$) in Group A (73.9° (4.3°)) than that in Group B (75° (4°)) and Group H (76.1° (2.9°); $p = 0.03$). The nasal profile differed in ns-unt/NSL between Group A (102.4° (7.1°)) and B (107° (4°) ($p = 0.044$)).

Table 3. EUROCRAN Index and status of lateral permanent incisors after one-stage repair of unilateral cleft lip and palate without primary bone grafting (Group A) in comparison to (Group B) that with primary bone grafting.

	Group A (2003–2014) *n* = 16	Group B (1991–2002) *n* = 15
EUROCRAN dental grade [a]		
1	2 (12.5%)	3 (20%)
2	2 (12.5%)	5 (33%)
3	5 (31.25%)	5 (33%)
4a	6 (37.5%)	2 (13%)
4b	1 (6.25%)	
Mean (SD)	3 (1.0)	2.4 (1.0)
EUROCRAN palatal morphology grade [b]		
1	5 (31.25%)	3 (20%)
2	8 (50%)	7 (47%)
3	3 (18.75%)	5 (33%)
Mean (SD)	1.9 (0.7)	2.1 (0.7)
Missing lateral incisors—Cleft side [*n* (%)]		
Yes	8 (50%)	11 (73%)
No	8 (50%)	4 (27%)
Missing lateral incisors—Non-cleft side [*n* (%)]		
Yes	9 (56.25%)	6 (40%)
No	7 (43.75%)	9 (60%)
Missing lateral incisors—Bilateral [*n* (%)]		
Yes	6 (37.5%)	5 (33%)
No	10 (62.5%)	10 (67%)

[a] EUROCRAN index of dental arch relationship. Grade 1: Apical base relationship—skeletal Class I or Class II. Both central incisors have a positive overjet and overbite, or there is a considerably increased overjet with no overbite (note: it is grade 2 if there are obvious dental compensations). Grade 2: apical base relationship is class I. Non-cleft incisor is in a positive overjet and overbite. Tilting or derotation of the cleft-side incisor would achieve a stable overjet and overbite (note: it is grade 3 if there is a moderate open bite). Grade 3: apical base relationship is edge-to-edge or mild skeletal class III. One or both central incisors are edge-to-edge or in a close anterior cross-bite. Tilting or derotation would not achieve a stable overjet and overbite (note: it is grade 4 if there is a severe open bite or if the edge-to-edge position of the incisor in class III is achieved by dental compensation). Grade 4a: apical base relationship is class III. Both central incisors are in an anterior crossbite, or one is in an anterior crossbite with the other being edge-to-edge. Grade 4b: same as grade 3 but with a marked open bite. [b] EUROCRAN index of palatal morphology. Grade 1: Good anterior and posterior height; minor surface irregularities (bumps, crevices); nil or minor deviation of the arch form. Grade 2: Moderate anterior and posterior height; moderate surface irregularities (bumps, crevices); moderate deviation of the arch form (e.g., segmental displacement). Grade 3: Severe reduction in palate height; severe surface irregularities (bumps, crevices); severe deviation in the arch form (e.g., "hourglass" constriction). Data for Group B are derived from Mueller et al., 2012 [13].

Table 4 shows the one-way ANOVA of craniofacial growth in hard and soft tissue among all the groups. Tables A3 and A4 show the results of the pairwise comparison using the Tukey HD post hoc test.

For the secondary aim, the craniofacial growths of historical and healthy controls were included in the comparisons. A comparable restriction of maxillary growth (SNA) with significantly ($p < 0.001$) smaller SNA in all groups was found compared to the healthy control. The rotation of the upper face (NSL/NL) differed in all groups ($p < 0.001$) from the healthy control. The deviations from the norm were the highest in Group B ($\Delta = 7.62$ (5.66–9.58)), followed by Group A ($\Delta = 5.3$ (3.40–7.20)). The angle measurements related to the mandible were comparable across all groups. ANB was larger ($p = 0.02$) in Group A (3.5° (4.3°)) than in Group S (1.33° (2.8°)), which lagged behind the healthy control (4.8°

(2.3°); $p < 0.001$). The interincisal angles (ILs/NL and ILs/Ili) in Group A differed strongly from the others. In the soft tissue morphology, a significantly pronounced facial convexity (gn-sn-pgs) was observed in Group S compared to the other groups ($p < 0.001$).

Table 4. Cephalometric values of Group A without primary bone grafting and Group B with primary bone grafting compared with the mean values of the Slav-cleft study (Warsaw center) and the healthy cephalometric standard control values. Data are presented as the mean (SD). Angles are measured in degrees.

		Group A (2003–2014)	Group B (1991–2002)	Group S (Slav-Cleft)	Healthy Control		
		(n = 16)	Group 1 (n = 15)	Warsaw (n = 35)	(n = 83)		
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p-Value #	Differences *
				Hard tissue			
maxilla	S-N-A	76.5 (5.9)	76 (4)	75.7 (3.6)	81 (3.1)	<0.001	A-H, B-H, S-H
	NSL/NL	11.7 (4.2)	14 (4)	11.2 (4.3)	6.4 (2.5)	<0.001	A-H, B-S, B-H, S-H
mandible	S-N-Pog	73.9 (4.3)	75 (4)	75.4 (4)	76.1 (2.9)	0.022	A-H
	NSL/ML	34.9 (5.5)	35 (4)	37.3 (5.6)	35.1 (4.6)	0.076	-
maxillomandibular	A-N-B	3.5 (4.3)	3 (3)	1.3 (2.8)	4.8 (2.3)	<0.001	A-S, B-H S-H
	ILs/NL	88.5 (8.1)	103 (15)	105 (8.2)	107.3 (7.6)	<0.001	A-B, A-S, A-H
	ILs/ILi	161.1 (11.4)	154 (12)	143 (10.9)	131.7 (11.8)	<0.001	A-S, A-H, B-S, B-H, S-H
				Soft tissue			
maxillomandibular	sss-ns-sms	5.3 (4.1)	6 (3)	5.9 (2.7)	-	0.79	-
	sss-ns-pgs	4.8 (3.5)	5 (3)	4.5 (3.1)	-	0.86	-
	gs-sn-pgs	187.9 (9.5)	187 (7)	173.5 (6.8)	-	<0.001	A-S, B-S
nasal profile	gs-prn-pgs	149.7 (7.4)	150 (5)	147.8 (5.8)	-	0.38	-
	ns-unt/NSL	102.4 (7.1)	107 (4)	105.9 (4.7)	-	0.036	A-B
	ns-prn-sn	107.5 (4.7)	105 (6)	104.5 (5.9)	-	0.22	-
	nst-sn-ls	107.8 (14.8)	102 (11)	101.6 (12.8)	-	0.27	-

One-way analysis of variance (ANOVA) analysis. * Tukey's HSD post hoc test, showing differences between Groups A, B, S and healty control (H). Data for Group B are derived from Mueller et al., 2012 [13], data for Group S are derived from Urbanova et al., 2016 [14] and data for the healthy control are derived from Riolo et al., 1979 [15].

4. Discussion

The study's purpose was to investigate, among patients with UCLP, whether primary alveolar rib bone grafting (Group B), when compared with no bone grafting (Group A), at one-stage cleft lip and palate repair restricts craniofacial growth assessed at 6–11 years of age. The hypothesis—whether there is no difference in craniofacial growth assessed at 6–11 years of age between patients after one-stage UCLP repair with or without primary alveolar bone grafting—was tested. As a secondary aim, craniofacial growth was compared with the external historical controls of a one-stage cleft lip and palate surgical protocol (Group S) and a healthy control group (Group H).

Our results failed to reject the hypothesis, showing comparable craniofacial growth in Group A (without primary alveolar bone grafting) and Group B (with primary alveolar bone grafting). The comparison between the measurements of the cephalometric radiographs of Groups A and B showed a similar relationship of the maxilla to the skull base, with an indication of craniofacial growth inhibition and alteration from the healthy control.

Eliminating primary alveolar bone grafting in the respective one-stage cleft lip and palate protocol did not improve growth at the time point studied. The present study indicates that the impact of primary alveolar bone grafting itself on craniofacial growth, when performed along with the studied one-stage protocol, is negligible. The only significant difference in hard tissue variables was the inclination of the upper incisors (ILs/NL), explained by the younger age in Group A (6.8 years) prior to the eruption of the permanent incisor compared to that in Group B (9 years) at the time of evaluation.

To answer the question of the influence of the treatment protocol on the dental arch relationship and palatal morphology, the plaster casts of Groups A and B were compared. Likewise, the dental arch relationship and palatal morphology based on the EUROCRAN index were equally altered in Groups A and B. These changes must be attributed to the treatment, as no crowding of the teeth and well-aligned dental arches are reported in unoperated patients with UCLP [22]. Additionally, these results implicate a greater impact on growth by other aspects of the surgical technique compared to the intervention in the alveolar cleft.

An increased number of missing lateral permanent incisors on the non-cleft side in both groups (Group A 56%, Group B 40%) was found. Despite the controversial literature regarding missing teeth outside the cleft [23], the lower prevalence in unoperated adult patients with clefts [24] and the natural prevalence of 3.77% [25] indicate a surgical side effect.

We assessed the craniofacial growth after different one-stage protocols in relation to a healthy group based on external historical data. Our data show a significant restriction of maxillary growth (SNA) and rotation of the upper face (NSL/NL) at 6–11 years old in Groups A, B and S after one-stage surgical protocols.

4.1. Clinical Relevance

In summary, these results demonstrate not only sagittal and vertical growth restriction but also the alteration of the transversal growth measured in the dental arch relationship and palatal morphology. As these changes were measured at an age before puberty and the completion of growth, they must be regarded as clinically relevant. Of particular concern is the negative influence of scar formation due to secondary wound healing with the two-flap palatoplasty used in the one-stage protocol in Groups A and B, as depicted in Figure 1. The altered dental arch relationships, as quantified in Groups A and B, might be caused by denuded bony areas in the cleft palate repair [20] influencing subsequent transversal growth, as described in different treatment protocols [26].

Previous studies have reported maxillary retrusion due to primary alveolar bone grafting [8–11,27–30], but others have reported successful outcomes when following presurgical orthopedic therapy [27,29,30]. Presurgical therapy with passive plates is known to reduce the cleft of the palate [13]. Nevertheless, two-flap palatoplasty in the subsequent procedure leads to secondary healing. From a clinical point of view, it needs to be further investigated whether presurgical therapy combined with the incision design used in Group S, allocating parts of the vomerine tissue for oral layer repair, can reduce secondary healing.

Thus, the presented study of Groups A and B prompted changes in the surgical protocol at the study center. Primary alveolar bone grafting [10] and one-stage two-flap palatoplasty with secondary healing of lateral releasing incisions were abandoned. Following passive presurgical therapy, a one-stage protocol with bipedicled palatal flaps was implemented and modified for a continuous two-layer closure and primary healing [7].

Although single-stage lip and cleft palate closure protocols showed a similar growth to multistage surgery [31,32], with the advantage of a reduced treatment burden, further investigation on protocols to reduce the negative effect of cleft surgery on maxillary growth and palatal morphology is warranted [33,34]. In summary, the current findings indicate a greater influence of other aspects of the surgical protocol on growth than the intervention in the alveolar cleft. These results should be considered in the further refinement of one-stage cleft lip and palate strategies to avoid negative effects on craniofacial growth and the dental arch relationship. Henceforth, growth outcomes must be complemented by an assessment of speech and hearing as well as the overall treatment burden [32,35].

4.2. Limitations

The limitations are the retrospective nature and the small sample size. However, the historical control at a single center before the change in surgical protocol and the external historical control with independent sample were evaluated to strengthen the validity and included the comparison with a healthy control. The similar mandibular growth among independent samples validates our comparison. The surgical dexterity of three different surgeons may override the effects of the surgical technique on craniofacial growth.

However, the different cohorts were operated on by the respective experienced surgeons. The unfavorable developmental trend in craniofacial growth was measured at 6–11 years of age and could increase after puberty and later [36]. Speech development and hearing development were not investigated in our study, as Groups A and B used the same hard and soft palate closure technique.

5. Conclusions

Omitting primary alveolar bone grafting in the one-stage cleft lip and palate protocol analyzed did not improve growth at 6–11 years. Dental and palatal morphology was considerably compromised regardless of primary alveolar bone grafting.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Commission of Northwest and Central Switzerland (EKNZ) (project-ID 2017-00036, 8 August 2017) for Group A. The studies for the historical controls (Groups B and S) were approved by the respective ethical review boards.

Informed Consent Statement: Patient consent was waived due to the retrospective nature of the study, using routine clinical data.

Data Availability Statement: Not applicable.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Variables measured in lateral cephalometric analysis and their identification in comparative studies.

	Group A (2003–2014)	Group B (1991–2002)	Group S (Slav-Cleft)	Healthy Control
Hard tissue				
maxilla	S-N-A	S-N-A	s-n-ss (SNA)	A-N-S
	NSL/NL	S-N/ANS-PNS	NSL/NL	N-S/ANS-PNS
mandible	S-N-Pog	S-N-Pog	s-n-pg	PG-N-S
	NSL/ML	S-N/Go-Gn	NSL/ML	N-S/GN-GO
maxillomandibular	A-N-B	A-N-B	ss-n-sm (ANB)	A-N-B
	ILs/NL	ANS-PNS/ILs	Ils/NL	UIE-UIA/PNS-ANS
	ILs/ILi	ILs/ILi	Ils/Ili	LIA -LIE/UIA -UIE
Soft tissue				
maxillomandibular	sss-ns-sms	sss-ns-sms	sss-ns-sms	n/a
	sss-ns-pgs	sss-ns-pgs	sss-ns-pgs	n/a
	gs-sn-pgs	gs-sn-pgs	gs-sn-pgs	n/a
nasal profile	gs-prn-pgs	gs-prn-pgs	gs-prn-pgs	n/a
	ns-unt/NSL	ns-unt/N-S	ns-unt/NSL	n/a
	ns-prn-sn	ns-prn-sn	ns-prn-sn	n/a
	nst-sn-ls	nst-sn-ls	nst-sn-ls	n/a

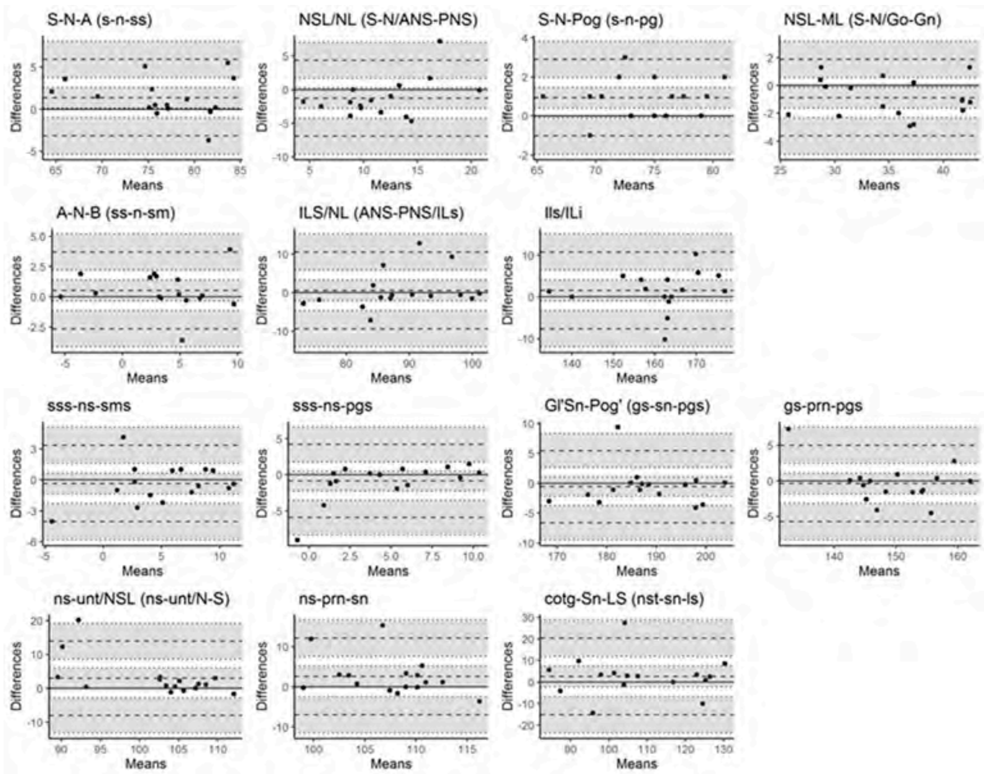

Figure A1. BlandAltman plots demonstrating agreement between the investigators for the cephalometric variables in Group A.

Table A2. Interclass correlation between the investigators in Group A.

		ICC (95% CI)
	Hard tissue	
maxilla	S-N-A	0.92 (0.8–0.97)
	NSL/NL	0.79 (0.5–0.92)
mandible	S-N-Pog	0.97 (0.92–0.99)
	NSL/ML	0.97 (0.91–0.99)
maxillomandibular	A-N-B	0.93 (0.81–0.98)
	ILs/NL	0.82 (0.56–0.93)
	ILs/ILi	0.92 (0.78–0.97)
	Soft tissue	
maxillomandibular	sss-ns-sms	0.9 (0.74–0.96)
	sss-ns-pgs	0.76 (0.44–0.91)
	gs-sn-pgs	0.95 (0.86–0.98)
nasal profile	gs-prn-pgs	0.93 (0.82–0.98)
	ns-unt/NSL	0.73 (0.39–0.9)
	ns-prn-sn	0.57 (0.13–0.83)
	nst-sn-ls	0.83 (0.58–0.94)

Intraclass correlations (ICC) for Group A between the two investigators show a medium to high range of agreement for all variables.

Table A3. Pairwise comparisons of hard tissue variables between the groups using the Tukey HD post hoc test *.

	n	Mean	*n*	Mean	Difference	*p*-Value
			S-N-A			
Group A vs. Group B	16	76.49	15	76	0.49 (−2.62–3.60)	0.98
Group A vs. Group S	16	76.49	35	75.66	0.83 (−1.79–3.45)	0.85
Group A vs. Healthy control	16	76.49	295	81.05	−4.55 (−6.78–−2.33)	<0.001
Group B vs. Group S	15	76	35	75.66	0.34 (−2.34–3.02)	0.99
Group B vs. Healthy control	15	76	295	81.05	−5.05 (−7.34–−2.75)	<0.001
Group S vs. Healthy control	35	75.66	295	81.05	−5.39 (−6.94–−3.83)	<0.001
			NSL/NL			
Group A vs. Group B	16	11.68	15	14	−2.32 (−4.99–0.34)	0.11
Group A vs. Group S	16	11.68	35	11.24	0.44 (−1.80–2.68)	0.96
Group A vs. Healthy control	16	11.68	294	6.38	5.3 (3.40–7.20)	<0.001
Group B vs. Group S	15	14	35	11.24	2.76 (0.47–5.05)	0.01
Group B vs. Healthy control	15	14	294	6.38	7.62 (5.66–9.58)	<0.001
Group S vs. Healthy control	35	11.24	294	6.38	4.86 (3.54–6.19)	<0.001
			S-N-Pog			
Group A vs. Group B	16	73.91	15	75	−1.09 (−4.01–1.82)	0.77
Group A vs. Group S	16	73.91	35	75.41	−1.5 (−3.95–0.94)	0.39
Group A vs. Healthy control	16	73.91	294	76.1	−2.2 (−4.28–0.12)	0.03
Group B vs. Group S	15	75	35	75.41	−0.41 (−2.91–2.09)	0.97
Group B vs. Healthy control	15	75	294	76.1	−1.1 (−3.25–1.04)	0.55
Group S vs. Healthy control	35	75.41	294	76.1	−0.69 (−2.14–0.76)	0.61
			A-N-B			
Group A vs. Group B	16	3.53	15	3	0.53 (−1.78–2.84)	0.94
Group A vs. Group S	16	3.53	35	1.33	2.2 (0.26–4.14)	0.02
Group A vs. Healthy control	16	3.53	294	4.78	−1.25 (−2.90–0.40)	0.21
Group B vs. Group S	15	3	35	1.33	1.67 (−0.31–3.65)	0.13
Group B vs. Healthy control	15	3	294	4.78	−1.78 (−3.48–0.08)	0.04
Group S vs. Healthy control	35	1.33	294	4.78	−3.45 (−4.60–−2.30)	<0.001
			ILs/NL			
Group A vs. Group B	16	88.53	15	103	−14.47 (−21.96–−6.97)	<0.001
Group A vs. Group S	16	88.53	35	105.02	−16.49 (−22.78–−10.20)	<0.001
Group A vs. Healthy control	16	88.53	294	107.25	−18.72 (−24.07–−13.37)	<0.001
Group B vs. Group S	15	103	35	105.02	−2.02 (−8.46–4.42)	0.85
Group B vs. Healthy control	15	103	294	107.25	−4.25 (−9.77–1.27)	0.19
Group S vs. Healthy control	35	105.02	294	107.25	−2.23 (−5.67–1.50)	0.41
			ILs/ILi			
Group A vs. Group B	16	161.15	15	154	7.15 (−3.73–18.02)	0.33
Group A vs. Group S	16	161.15	35	143.03	18.12 (8.98–27.25)	<0.001
Group A vs. Healthy control	16	161.15	293	131.75	29.4 (21.63–37.17)	<0.001
Group B vs. Group S	15	154	35	143.03	10.97 (1.63–20.31)	0.01
Group B vs. Healthy control	15	154	293	131.75	22.25 (14.24–30.27)	<0.001
Group S vs. Healthy control	35	143.03	293	131.75	11.28 (5.87–16.70)	<0.001

* Only for angles with a statistically significant difference in the ANOVA analysis.

Table A4. Pairwise comparisons of soft tissue variables between the groups using the Tukey HD post hoc test *.

	n	Mean	*n*	Mean	Difference	*p*-Value
			gs-sn-pgs			
Group A vs. Group B	16	187.87	15	187	0.87 (−5.57–7.40)	0.95
Group A vs. Group S	16	187.87	35	173.54	14.33 (8.84–19.81)	<0.001
Group B vs. Group S	15	187	35	173.54	13.46 (7.85–19.07)	<0.001
			ns-unt/NSL			
Group A vs. Group B	16	102.38	15	107	−4.63 (−9.15–0.10)	0.044
Group A vs. Group S	16	102.38	35	105.91	−3.54 (−7.33–0.26)	0.07
Group B vs. Group S	15	107	35	105.91	1.09 (−2.79–4.97)	0.78

* Only for angles with a statistically significant difference in the ANOVA analysis.

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5. Rethinking cleft anatomy – paradigm of the curved vomerine mucosa

Figure 6. Cleft Palate Craniofacial Journal Cover August 2022. Image created by Andreas A. Mueller MD DMD PhD and Elisabeth Bruder MD. Description – Histologic aspect of the curved vomerine mucosa in cleft lip and palate. The vomer mucosa showed no specific signs of nasal mucosa (neither ciliated cells nor goblet cells). Use of vomerine tissue in cleft repair protocols should be made by other justifications than the assumption that it is nasal mucosa.

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Histologic Aspect of the Curved Vomerine Mucosa in Cleft Lip and Palate

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Abstract

Background: Common surgical techniques aim to turn the entire vomerine mucosa with vomer flaps either to the oral side or to the nasal side. The latter approach is widely performed due to the similarity in color to the nasal mucosa. However, we lack a histologic description of the curved vomerine mucosa in cleft lip and palate malformations.

Methods: We histologically examined an excess of curved vomerine mucosa in 8 patients using hematoxylin–eosin, periodic acid–Schiff, Elastin van Gieson, and Alcian blue stains. Tissue samples were obtained during surgery at 8 months of age.

Results: Our histological analysis of the mucoperiosteum overlying the curved vomer revealed characteristics consistent with those of an oral mucosa or a squamous metaplasia of the nasal mucosa, as exhibited by a stratified squamous epithelium containing numerous seromucous glands. Some areas showed a palisaded arrangement of the basal cells compatible with metaplasia of respiratory epithelium, but no goblet cells or respiratory cilia were identified. Abundant fibrosis and rich vascularity were present.

Conclusion: The vomer mucosa showed no specific signs of nasal mucosa. These findings should be considered in presurgical cleft orthopedics and palatal surgery for further refinement. Shifting the vomer mucosa according to a fixed physiologic belief should not overrule other important aspects of cleft repair such as primary healing and establishing optimal form and function of palatal roof and nasal floor.

Keywords

craniofacial morphology, palatoplasty, hard palate, surgical technique, nonsyndromic clefting, palatal development, anatomy

Introduction

One in 500 to 1000 newborns (Genisca et al., 2009; Mastroiacovo et al., 2011; Doray et al., 2012; Wang et al., 2017) is affected by cleft deformities of the lip, jaw, or palate. These orofacial clefts constitute the most common congenital disorders in humans that require surgical correction after birth. Cleft deformities are believed to be caused by a combination of genetic factors and yet-to-be identified environmental factors (Mossey et al., 2009). The most common manifestation of cleft deformities involves a complete unilateral cleft lip, jaw, and palate. Complete unilateral clefts typically comprise 30% to 40% of all cleft deformities, occurring in 1 in 1000 to 2000 births (Genisca et al., 2009; Mastroiacovo et al., 2011; Doray et al., 2012; Wang et al., 2017). A unique characteristic of the malformation is the curved vomer that can be already present at week 11 in fetal development and then persists (Atherton, 1967; Latham, 1969). Figure 1 shows the curved vomer where the nasal and palatal mucosa merge.

Understanding the spatial and histological characteristics of the cleft region is crucial when surgically repairing the cleft (Nalabothu et al., 2020). The evolution of cleft surgical techniques has been decisively based on the work of Veau (1931).

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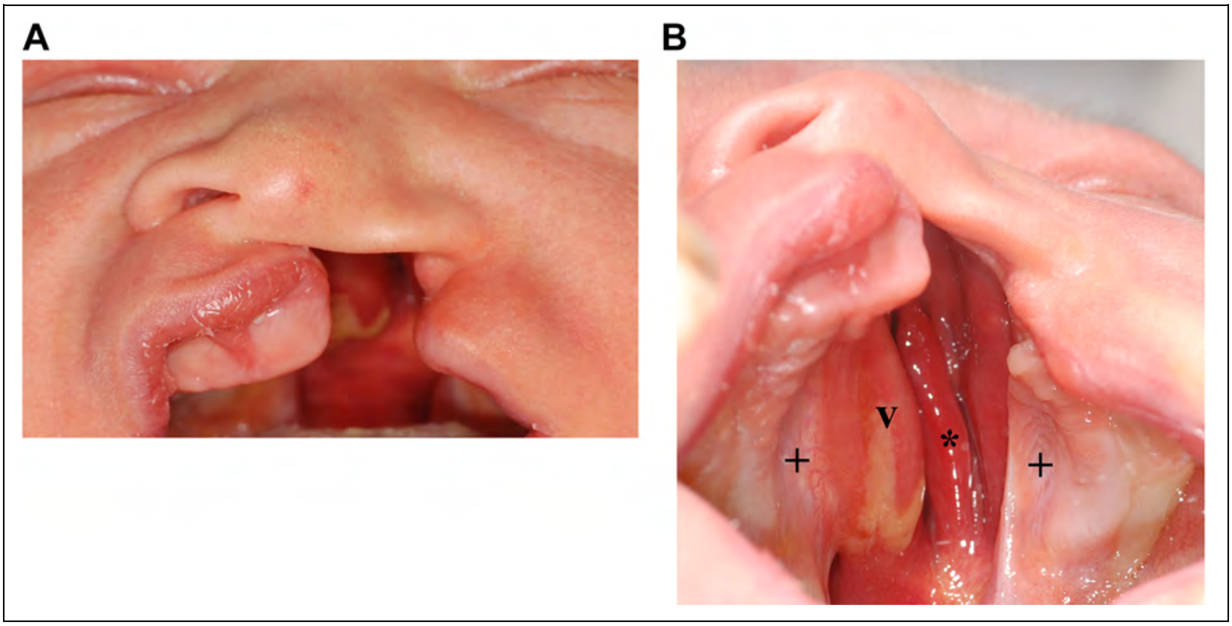

Figure 1. Newborn with complete unilateral cleft lip, jaw, and palate. (A) Front view. (B) View on the palate with deficiency of the bony nasal floor on the cleft side, thus connecting the oral and nasal cavities. This situation results in the nasal concha (*) being visible through the cleft. The hard palate is covered by light pink mucosa in the area of the separated palatal plates (+) and by dark red mucosa in the middle part over the curved vomer bone (v).

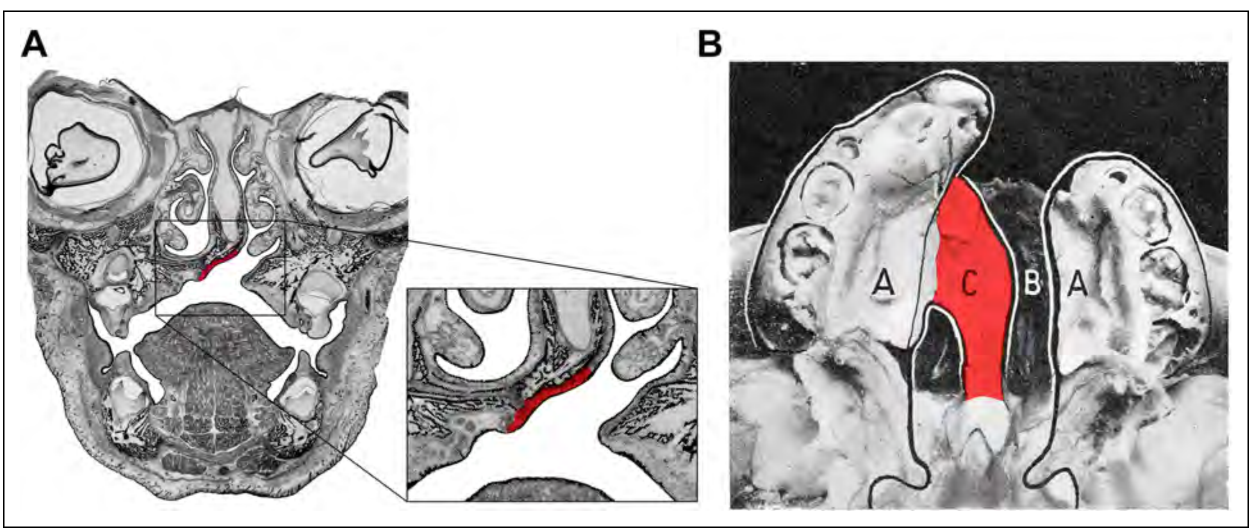

Figure 2. Illustration of a left-sided complete cleft lip and palate. A, Frontal section of a 4-month-old fetus with the mucoperiosteum overlying the curved vomer in red. B, View on the bony palate with the bony part of the curved vomer indicated in red: A = "les lames palatines": "the palatal plates"; B = "la fente vraie": "the true cleft"; C = "portion du vomer incurvé": "curved vomer". The figures in (A) and (B) are derived from figures 79 and 78, respectively, on pages 41 and 42 of reference (Veau, 1931). Division palatine. anatomie. chirurgie. phonétique. V. veau avec la collaboration de Mlle S. Borel, Dijon and Paris: impr. darantière masson et cie éditeurs; 1931. Elsevier did not object to the use of these figures. The creative commons license does not apply to these pictures.

Veau reported on the morphology of the cleft in detail and also the important characteristics in the vomer region for consideration when performing surgical palatal cleft closure (Veau, 1931). The vomer bone is connected to the palatal plates and premaxilla by the vomeromaxillary and vomeropremaxillary suture with fibrous tissue (Burdi, 1971). The cleft palate can be divided into 3 main parts: the palatal plates, the true cleft, and the curved vomer (Figure 2A and B).

The overlying vomerine mucoperiosteum has long been routinely used as a flap in palatoplasty (Pichler, 1926; Dunn, 1952; Widmaier, 1966), and surgical variants based on its use have been classified (Kumar, 1985; Agrawal & Panda, 2006;

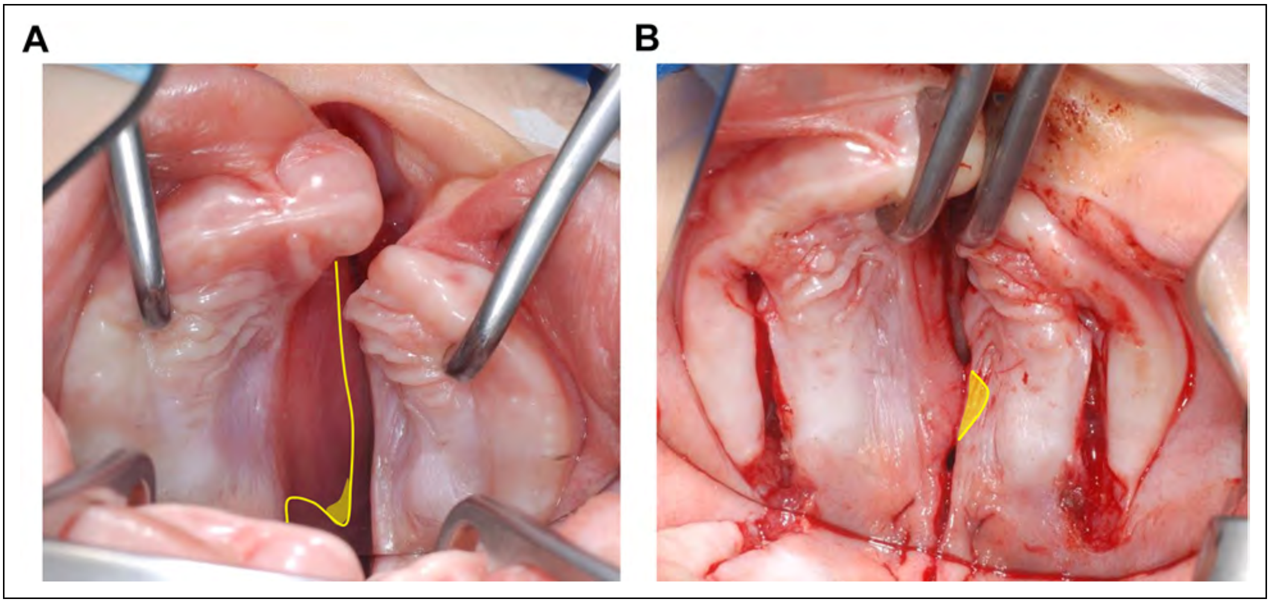

Figure 3. Intraoperative view of the cleft palate. A, Oblique vomer with incision outline (yellow line) and region where a mucosa biopsy was performed (yellow area). B, Incisions made with visible tissue overlap and region of biopsy (yellow area).

Agrawal, 2009). Cleft palate surgical techniques attempt to turn the entire vomerine mucosa either purely to the oral side (Campbell, 1926; Widmaier, 1966; Kobus, 1984; Bütow, 1987) or to the nasal side (Lannelongue, 1872; Veau, 1931; Dunn, 1952; Kobus, 1984; Kumar, 1985; Bardach, 1995; Abyholm, 1996), or its use is advised against (Delaire & Precious, 1985). Veau hypothesized that the vomerine mucosa is embryologically derivated from the nasal mucosa and therefore must be turned into the nose during surgery, and this hypothesis has influenced generations of cleft surgeons despite the lack of any clear supporting evidence (Veau, 1931; Agrawal & Panda, 2006; Ogata et al., 2017). While the vomer region is referred to as "the center of its field of action" for the surgeon (Veau, 1931), we lack a histological description of the vomerine mucosa in cleft lip and palate malformations.

The aim of this study was to histologically characterize the tissue of the vomerine mucosa in cleft lip and palate and to challenge Veau's hypothesis that "... normal structures are present on either side of the cleft, only modified by the fact of the cleft ..." (Talmant et al., 2007).

Material and Methods

Data Collection

This retrospective observational study investigated 8 patients with unilateral complete cleft lip and palate who underwent cleft repair in one surgical procedure comprising full primary healing (clinicaltrials.gov: NCT04108416). All of the parents and their guardians signed an informed consent form for the surgical procedures and for releasing their medical information and photographs for use in scientific investigations. Patients were treated according to the standard cleft treatment at the institute of the author (A.A.M.). The study was performed in accordance with the Declaration of Helsinki after approval from the ethics commission.

Treatment of Cleft Lip and Palate

Presurgical orthopedics using a passive palatal plate were started during the first days after birth and were continued until cleft surgery was performed. The surgical technique consisted of simultaneously repairing the cleft nose, lip, and palate in one single surgical intervention at the age of 8 months (Benitez et al., 2021).

Histology of the Vomer

In 8 patients, an excess of vomerine mucoperiosteum (Figure 3) had to be trimmed off to allow for straight contact between tissue borders. This small pieces of excess tissue were subsequently examined histologically using hematoxylin–eosin, Elastin van Gieson, periodic acid–Schiff, and Alcian blue stains.

Statistical Analysis

Descriptive statistical analysis was applied using Stata (version 15.1; StataCorp) to calculate median and interquartile range (IQR) values of the age at surgery.

Results

Out of 9 patients initially assessed for eligibility, histological analysis of 8 patients could be included in the study (consent not being provided by 1). The median age at surgery was 7 months (IQR = 7-8 months), and 1 patient was female. The histological analysis revealed that the curved vomerine

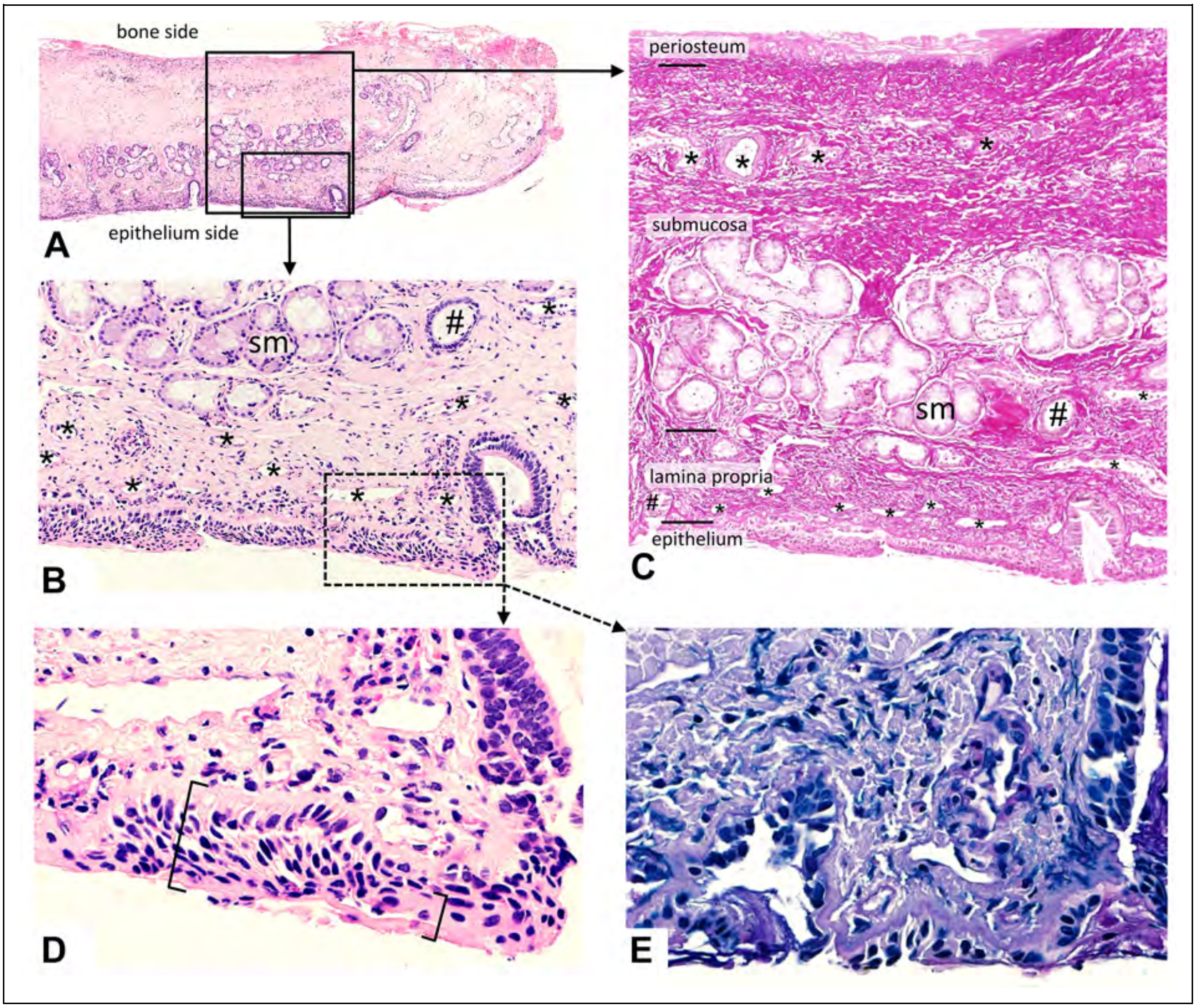

Figure 4. Histology of the curved vomerine mucosa. A, Overview of the curved vomerine mucoperiosteum (compare with the donor site in Figure 3A and B). B, The superficial half of the submucosa contains seromucous glands (sm) and cross sections of the secretory ducts (#). The lamina propria contains multiple small vessels (*). C, The deep half of the submucosa contains a dense network of collagen fibers and some vessels (*). The collagen fiber network reaches from the periosteum to the basal membrane of the epithelium. D, The epithelium appears as a stratified squamous epithelium ([). In some areas, the epithelium shows parakeratosis (]), and the corneal layer therefore contains pycnotic cell nuclei. No ciliated cells were detected. E, No goblet cells with intracellular mucus were detected. A, B, D, Hematoxylin–eosin stain. C, Elastin van Gieson stain. E, Alcian blue and periodic acid–Schiff stain.

mucoperiosteum comprised a stratified squamous epithelium with numerous seromucous glands. Some areas showed a palisaded arrangement of the basal cells compatible with metaplasia of the respiratory epithelium. In none of the 8 samples, goblet cells or respiratory cilia were identified, and abundant fibrosis and rich vascularity were present (Figure 4).

Discussion

Cleft lip and palate in nonsyndromic infants is considered a failure of tissues fusion rather than a consequence of mesodermal deficiency (Veau, 1931; Mulliken et al., 2003; Talmant et al., 2007). Veau hypothesized that " . . . normal structures are present on either side of the cleft, only modified by the fact of the cleft . . . " (Talmant et al., 2007), which implies that the goal of any surgical approach for cleft repair should be to construct the normal anatomy by relocating the present structures. Various approaches of utilizing incisions in the vomer region have been outlined for determining the optimal positioning from a clinical point of view (Veau, 1931; Dunn, 1952). Some authors (including Veau) have argued on a post hoc basis that the exclusive use of the vomerine mucosa for nasal reconstruction is justifiable from an embryological or physiological point of view, in the absence of histological evidence (Veau, 1931; Agrawal & Panda, 2006; Ogata et al., 2017).

Histology of the Vomer

Our histological analysis of the mucoperiosteum overlying the curved vomer revealed no specific signs of the nasal mucosa,

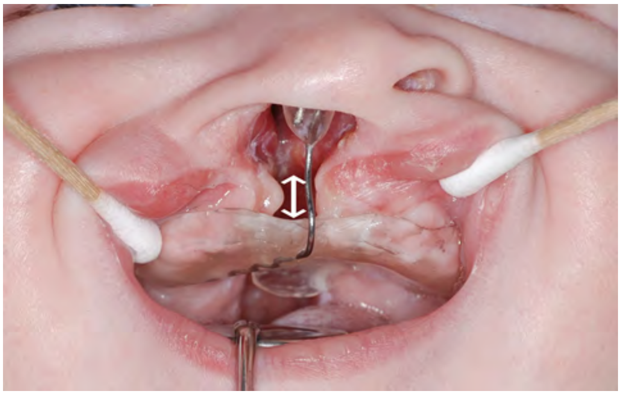

Figure 5. A passive palatal plate with free space (white ↕) between the vomerine mucosa and palatal plate. The plate kept the tongue out of the cleft and thus away from the vomerine mucosa in a newborn with a right-sided complete cleft lip and palate.

Figure 6. Visible difference between the vomer mucosa (v) and the palatal mucosa in a patient with a right-sided complete cleft lip and palate at 3 years of age. The surgical repair was performed at 8 months of age. The primary lateral incisor (tooth 52) is absent. Hard palate repair was performed in 2 layers using bilateral bipedicle flaps, soft palate repair was performed using medial pterygoid detachment and intravelar muscle repair, and lip repair comprising primary rhinoplasty.

with neither ciliated cells nor goblet cells being present. Therefore, the histological findings of the mucoperiosteum are compatible with an oral mucosa or with squamous metaplasia of the nasal mucosa. During the 7 to 8 months of presurgical plate therapy, the vomerine mucosa was not exposed to any physical irritation since the palatal plate did not contact the underlying mucosa and the tongue was kept away from the vomerine mucosa (Figure 5).

Figure 6 shows that during the further postoperative course and normal pediatric development, the vomer mucosa still showed macroscopic differences from the palatal mucosa, as has also been shown by other authors (Ogata et al., 2017). This further highlights that metaplasia of the vomerine mucosa is not reversible. The permanent presence of metaplasia must therefore be assumed, which is analogous to the intestinal metaplasia of the esophagus in gastroesophageal reflux disease (King, 2007).

Clinical Relevance for Cleft Lip and Palate Repair

The vomer mucosa showed no specific signs of nasal mucosa. From this histological point of view, surgical techniques should be reconsidered. We must challenge the pure use of the entire vomer mucosa as a cranial pedicled flap for nasal floor reconstruction (eg, 2-flap palatoplasty) (Bardach, 1995). Veau (1931) has already subdivided the cleft palate into vomer and the true cleft (Figure 2B). The former spanning across the noncleft nasal floor and bottom of the osseous septum, the latter spanning across the absent nasal floor that opens into the nasal cavity on the cleft side. This distinct division of the palatal cleft area has not been given the full attention in surgical and presurgical protocols so far. In staged surgical concepts, typically the first step—whether lip or soft palate repair (Gundlach et al., 2013)—has the mere intention to simplify or make the subsequent hard palate cleft repair less invasive. Whereas cleft orthopedics has shaped the definition and measurements of cleft palate width and cleft area mostly ignoring the vomer region (Berkowitz et al., 2005). The vomer region is more difficult to identify on cleft impressions, even more so after the first step of surgical repair that leads to growth alteration. In contrast, in unilateral clefts without surgical treatment with undisturbed growth after birth until adulthood, the vomer area and true cleft area can be clearly distinguished, as can be seen repeatedly in photographs of unoperated adults (Shetye, 2004). The vomer region has been generally considered as part of the nose without question. This has shaped outcome research to quantify the change in cleft palate morphology (Prasad et al., 2000; Braumann et al., 2002; Neuschulz et al., 2013; Bruggink et al., 2020) as well as led to clinical recommendations for the timing of surgery (Berkowitz et al., 2005). Although this central region of the vomer has not been studied, it has had and continues to have an impact on treatment approaches. Therefore, the concept of the nasal opening "the true cleft" has not been widely used in surgical concepts or in measuring the effect of orthodontic treatment (Nalabothu et al., 2020). Current research on cleft palate morphology and thus surgical concepts still imply that the vomer belongs to the cleft palate. Considering the true cleft described by Veau and the finding that the vomer mucosa is not a nasal mucosa, the exact definition of cleft palate needs to be challenged. What we define as cleft palate and how we translate it into orthodontic research and surgery should be reopened for discussion based on our findings. The clinical relevance of our results will therefore depend on whether we as cleft surgeons and orthodontists have the flexibility to rethink "the center of our field of action" (Veau, 1931). To anatomically reconstruct a symmetrical nasal floor, only a small part of the vomer mucosa is necessary. Figure 3A shows an incision outline on the vomer that contributes minimally to the reconstruction of the nasal layer and leaves substantial tissue for oral closure. We propose allocation of the vomer tissue to reconstruct the oral and nasal layer likewise. If only as little as necessary is used for the symmetrical reconstruction of the nasal floor, most of the vomer mucosa can be used to reconstruct the oral layer. This would support the hypothesis that the structures are present in the case of a cleft and they are only modified by the cleft (Talmant et al., 2007). Technically, a small 5/8 needle with a cone point (eg, FR-10 Art.6O15132 T; Serag Wiessner) is advisable to sew the nasal layer tightly in spite of limited vomer tissue turnover. Without previous lip surgery (Figure 3), the nasal layer can be sutured from the oral side, and especially in the case of narrow clefts, it is technically easier to suture the nasal layer anteriorly from the vestibular (extraoral) side. From a biological point of view, additional tissue to close the oral layer could enable minimal lateral incisions (Karsten et al., 2003) or eliminate the need for lateral relief incisions even in unilateral cleft lip and palate repair (Brusati & Mannucci, 1994; Brusati, 2016). Reduced secondary healing lead to less scarring, having a negative impact on growth (Kim et al., 2002; Pigott et al., 2002). The preservation of vascularity could also facilitate primary wound healing to achieve lower fistula rates (Losken et al., 2011). The amount of tissue required to close the true cleft depends on treatments performed prior to hard palate cleft repair. With passive presurgical orthopedics or lip taping, the true cleft can be reduced in a clinically relevant amount even without prior lip surgery (Abd El-Ghafour et al., 2020; Nalabothu et al., 2020). By combining presurgical reduction of the hard palate cleft and limiting reconstruction to the true cleft by proportional distribution of vomer tissue, cleft palate repair could be facilitated. In this regard, prior lip surgery aiming to reduce the hard palate cleft could be questioned. When the curved vomer mucosa is surgically rotated into the oral cavity, it retains its difference in color from the palatal mucosa. However, it remains uncertain as to whether the vomer mucosa would ever transform into a typical nasal mucosa when it is surgically turned into the nasal cavity. It also remains unclear whether the vomerine mucosa is embryologically formed as a typical nasal mucosa and undergoes reparative adaptive changes or whether it is a mucosal transition zone between the oral and nasal mucosa. This is supported by the common, yet unspecific characteristics of both types of mucosa found in the vomer mucosa. Even if the macroscopic aspect of the vomer mucosa differs from the palatal mucosa (Veau, 1931; Agrawal & Panda, 2006; Ogata et al., 2017), our histological results indicate that the vomerine tissue is adequate for use in oral reconstruction from a histoanatomical point of view. These findings should be considered when further refining the optimal anatomical reconstruction method to apply to cleft palates.

Limitations

The number of examined cases is small, but they showed a uniform histological aspect. However, in the area of this malformation, the collection and examination of tissue is limited and can only be done from an ethical point of view as in our case with excess tissue. Since von Langenbeck described the palatal cleft closure in 1861 (Pigott et al., 2002), we are now able to describe to cleft surgeons, on the basis of a small number of cases, the histology of "the center of its field of action" (Veau, 1931) in cleft, lip, and palate malformations, which must be emphasized as a strength. Further analysis of other centers with larger numbers of cases is necessary to confirm the consistency of our findings. Following findings on the histology of the vomer mucosa, different techniques should be investigated for their influence on tissue perfusion and wound healing. We used a presurgical orthopedic plate without any contact with the examined vomer. To exclude the possibility of metaplasia due to presurgical treatment, an external control without any pretreatment is planned. Further evidence of tissue differentiation could be provided by molecular differentiation and testing for specific antigens.

Conclusion

The areas of mucosa analyzed in this study were suggestive of the occurrence of massive regenerative changes. Nonetheless, the histological characteristics of a respiratory epithelium were not present in any of the samples analyzed. The mucoperiosteum overlying the curved vomer did not exhibit any of the specific signs of nasal mucosa, such as ciliated cells and goblet cells. These results substantiate that the curved vomerine mucosa may be used to reconstruct both the nasal floor and palatal roof in cleft lip and palate, since the mucoperiosteum of the curved vomer forms a tissue that is similar (but not identical) to those at the nasal floor and palatal roof. Thus, the distinct use of the vomerine tissue in a cleft protocol should be made by other justifications than the assumption that it is nasal mucosa.

Authors' Note

E.B. and A.A.M. have contributed equally to this work. A.A.M. and B.K.B. were involved in the conception and design of the study and in the drafting of the manuscript. E.B. was involved in the analysis and interpretation of the histological findings. A.B., P.N., J.A.v.J. and E.B. were involved in revising the manuscript critically for important intellectual content. All of the authors have read and approved the final version of the manuscript. This paper was presented at the 24th Congress of the European Association for Cranio-Maxillo-Facial Surgery (EACMFS), 2018, Munich, Germany. The data sets generated and analyzed for this study are available on request from the correspondence author. The study was reviewed and approved by the Ethics Commission of Northwest and Central Switzerland (EKNZ) (project-ID: EKNZ 2020-00739). All parents and their guardians signed an informed consent form for the surgical procedures and for releasing their medical information and photographs for use in scientific investigations.

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Declaration of Conflicting Interests

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6. Simultaneous circular cleft lip and palate repair – paradigm of reconstructive cleft surgery

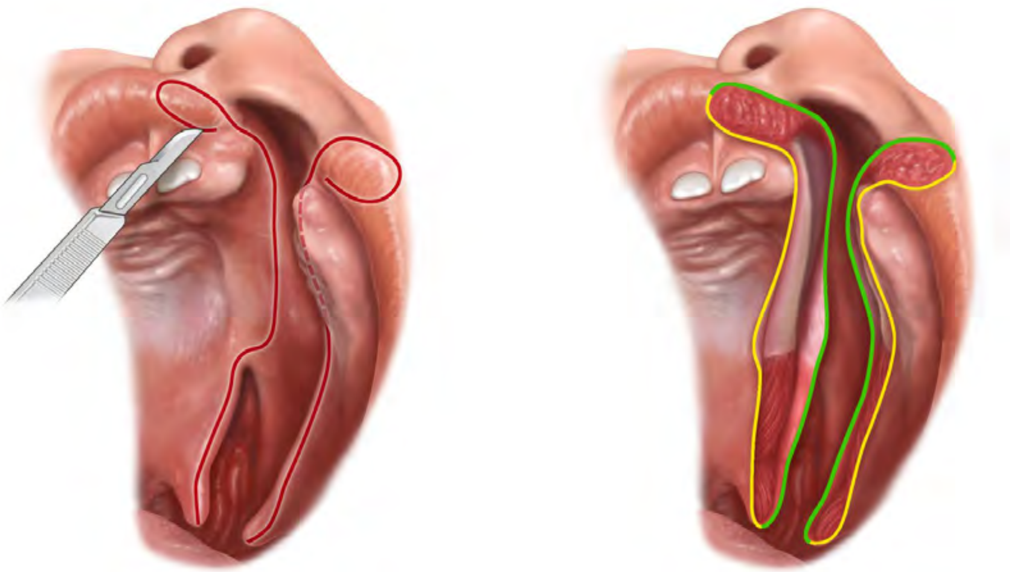

Figure 7. Visualization of a unilateral cleft lip and palate incision outline for a simultaneous circular two-layer closure in the midline and the wound edges for continuous circular suture all along the oral (yellow) and nasal (green) sides in: Benitez, B. K., Brudnicki, A., Surowiec, Z., Singh, R. K., Nalabothu, P., Schumann, D., & Mueller, A. A. Continuous circular closure in unilateral cleft lip and plate repair in one surgery. Journal of cranio-maxillo-facial surgery: official publication of the European Association for Cranio-Maxillo-Facial Surgery, 50(1), 76–85, 2022. https://doi.org/10.1016/j.jcms.2021.07.002

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Continuous circular closure in unilateral cleft lip and plate repair in one surgery

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A R T I C L E I N F O

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A B S T R A C T

The study aims at assessing wound healing and safety of single-stage two-layers continuous closure in patients with unilateral cleft lip and palate (UCLP).

In this retrospective, descriptive cohort study, we assessed wound healing without fistula formation at 1, 3, and 6 months after a single-stage two-layer UCLP repair, in which the midline suture is continuously circular all along the oral and nasal sides. We examined lengths of hospital stay and the incidence of intra- and postoperative adverse events. Furthermore, we compared the cleft width at birth and on the day of surgery, after presurgical orthopaedics.

Eleven UCLP patients underwent one cleft surgery between July 2016 and June 2018 at the age of 8–9 months. Full primary healing occurred in all patients without fistulas. Median length of post-operative hospital stay was 5 days (range = 4–9 days). No intra- or postoperative adverse events above Grade I (according to ClassIntra and Clavien-Dindo, respectively) occurred. Median and interquartile range (IQR) of the palatal cleft width decreased significantly from birth to surgery, i.e., from 12.0 mm (10.8–13.6 mm) to 5.0 mm (4.0–7.5 mm) anteriorly and from 14.0 mm (11.5–15.0 mm) to 7.3 mm (6.0–8.5 mm) posteriorly ($p = 0.0033$ in both cases).

Given these preliminary results, the concept of single-stage continuous circular closure in UCLP has potential for further investigation. However, it remains to be proven that there are no relevant adverse effects such as inhibition of maxillary growth.

Registered in clinicaltrials.gov:NCT04108416.

1. Introduction

There are wide variations in surgical methods to repair complete unilateral cleft lip and palate malformations (UCLP). A survey conducted in 2000 in 201 centers revealed that 194 different UCLP treatment protocols were applied (Shaw et al., 2001; World Health Organization, 2001). Treatment protocols involving two surgeries are the most common, followed by those involving three surgeries. In rare cases (5%), a single surgical intervention for complete closure is performed (Shaw et al., 2001). A goal of single-stage surgery is to reduce the global healthcare burden of craniofacial anomalies. The World Health Organization recognized the need for "the initiation of clinical trials concerning the specifics of surgery in a developing country setting, one-stage operations, optimal late primary surgery, anesthesia protocols (e.g. local anesthetic, inhalation sedation), and antisepsis" (World Health Organization, 2001). Moreover, a simplified surgical strategy would reduce the treatment burden for children suffering from orofacial clefts,

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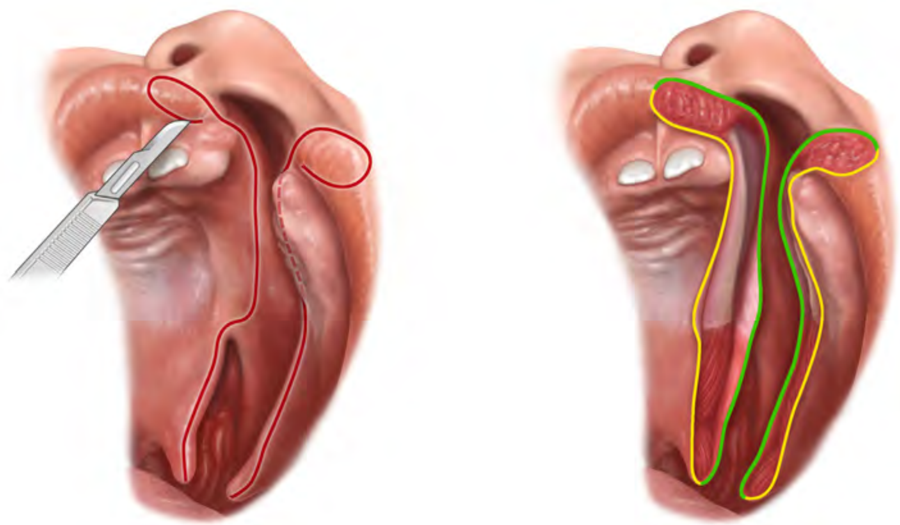

Fig. 1. Visualization of a unilateral cleft lip and palate. (**a**) Incision outline for a single-stage continuous circular two-layer closure in the midline. (**b**) Visualization of the wound edges for continuous circular suture all along the oral (yellow) and nasal (green) sides. (Visualization Andreas A. Mueller and Markus Voll).

psychosocial stress to the families and caregivers, as well as associated healthcare expenditure.

The first techniques for simultaneous repair of UCLP combined lip repair, unipedicled hard-palate repair, and soft-palate repair in adult patients (Farina, 1958). Simultaneous repair is nowadays safely applied in children below 10 months of age also in developing countries (Hodges, 2010). Most surgeons use unipedicled flaps with lateral releasing incisions to close the cleft palate. However, medial transposition of the flaps leads to undesirable raw bone surfaces laterally, with secondary healing (Deng et al., 2002; Guneren et al., 2015; Hodges, 2010; Honigmann, 1996). Even anteriorly, a raw bone surface remains if unipedicled hard-palate flaps are fixed in a pushback position (Savaci et al., 2005).

Bipedicled flaps for cleft palate repair were first described by von Langenbeck (von Langenbeck, 1972). The anterior tips of the bipedicled flaps remain attached to the anterior hard palate even with modern von Langenbeck techniques (Lindsay and Witzel, 1990). The resulting mobility restriction has prompted concerns that bipedicled flaps cannot cover anterior defects or a wide cleft (Losee and Lin, 2014). Furthermore, intentional anterior palatal openings remain after a von Langenbeck procedure (Lindsay, 1971). Nevertheless, bipedicled flap techniques have produced consistently good growth results, as shown in retrospective multicenter studies (Ross, 1987; Shaw et al., 1992) and in a randomized controlled study (Semb et al., 2017). Hence, a novel method of simultaneous lip and palate closure using bipedicled flap designs should allow safe closure of the anterior palate. This is possible using the method described by Dudkiewicz and colleagues (Brudnicki et al., 2014; Fudalej et al., 2010). This technique further allows for a gapless separation of the oral and nasal cavities and primary wound closure over the complete oral layer. However, an open wound remains nasally with a single-layer closure at the transition between the hard and soft palate. This results from the need to transect the nasal mucosa and palatine aponeurosis along the posterior border of the hard palate towards the pterygoid process (Lindsay, 1971). However, complete closure without fistulae depends crucially on the healing of the mucosal layer of the nose.

The rationale of a continuous two-layer separation of the oral and nasal cavities was to avoid two known growth-inhibiting side effects: (1) open wounds as zones of secondary healing and (2) surgical manipulation of the alveolar segments. Fig. 1 shows the single-stage continuous circular two-layer UCLP repair performed in the midline. This contrasts with current concepts of stepwise cleft closure with varying extents of open wounds, secondary healing and concomitant scarring.

We aimed to preliminary evaluate the wound healing and safety of one cleft surgery with a continuous circular two-layer wound closure in patients with UCLP.

2. Patients and methods

2.1. Study design and patient characteristics

The STROBE guidelines for cohort studies were adopted (von Elm et al., 2007). In this retrospective, descriptive cohort study, a single-stage two-layer continuous circular UCLP repair after passive plate therapy was assessed. The included patients had a non-syndromic UCLP without Simonart's band. Patients were operated on by the sinior author (A.A.M.) between July 1, 2016, and June 30, 2018. All parents and guardians signed an informed-consent form for the surgical procedures and for releasing medical information and photographs for scientific purposes. The study was performed in accordance with the Declaration of Helsinki after obtaining approval from the Ethics Committee of Northwest and Central Switzerland (EKNZ; project IDs: EKNZ Req-2017-00902 and 2018-01561). The study was registered in clinicaltrials.gov (NCT04108416), in accordance with the IDEAL recommendations for surgical innovations (McCulloch et al., 2009).

It was assessed if wound healing proceeded without fistula formation. The criterion was the absence of nasal food leakage and inspections at 1, 3, and 6 months, postoperatively. The length of hospital stay and the incidence of intra- and postoperative adverse events were documented. The cleft width was compared between plaster casts at birth and on the day of surgery.

2.2. Surgical procedure

Surgical intervention took place when the infants were at least 8 months old and weighed around 8 kg. We placed the infants in supine position with their head elevated to reduce postural blood stasis in the operation field. We administered a single dose of methylprednisolone (2.5 mg/kg body weight, i.v.) to reduce surgical and laryngeal swelling. Infection prophylaxis consisted of amoxicillin and clavulanic acid (50 mg/kg and 5 mg/kg body weight, respectively) administered for 72 h postoperatively. Cuffed endotracheal tubes were used, with the cuff inflated as little as possible and accompanied by a throat pack. Octenisept® was used for extraoral, intraoral, and endonasal disinfection. At surgery, long-acting anesthetic blocks were administered behind the palatal tuberosity and the infraorbital nerves (0.25% levobupivacaine, maximum 1 mL/kg body weight), and 0.9% saline with adrenaline (10 μg/mL) was administered for hydrodissection underneath the mucosa and periosteum and prior to cleft muscle dissection to reduce bleeding. Appendix A (Detailed surgical procedure) describes the detailed surgical technique with continuous circular two-layer wound closure. Appendix A (Video part 1) provides a video supplement documenting the surgical technique for hard-palate and soft-palate repair.

An incision outline was made to mobilize bipedicled flaps on the cleft and healthy side. On the healthy side, the mucoperiosteal flap was designed to cover the palatal shelf and curved vomer to achieve a balanced split of the mucosa for closure of the nasal and oral layers (Benitez et al., 2021). Medial pterygoid periosteal detachment assured complete mobility of the nasal mucosa at the hard-soft palate junction. Appendix A shows a three-dimensional model of the incision outline. The nasal layer in the hard palate was closed from posterior to anterior direction. Prior to reorientation of the cleft muscles, the nasal mucosa of the soft palate was sutured to the suture of the nasal layer of the hard palate without leaving a gap. The suture ran posteriorly to the uvula. Subsequently, the muscles were dissected, and the palatopharyngeus and levator muscles were reoriented and sutured transversely in the middle third of the soft palate. The oral mucosa of the soft and hard palates as well as the lateral surgical access incisions were sutured to allow primary healing. Fig. 2 illustrates the incision outline, palatal wound closure, and mucosal conditions after primary wound closure.

After removing the mouth gag, we completed two-layer closure in the alveolar cleft area. Cleft lip dissection and reconstruction comprised primary rhinoplasty. Nasal shape definition was supported by nostril stenting by a silicon sheet (0.5 mm) and transmural fixation to eliminate dead space. Appendix A (Video part 2) provides a video supplement with the surgical technique for alveolar, lip, and nose repair. Standard protocol included extubation in the operating room at the end of surgery. After the surgery, children could be fed with milk or porridge immediately. No arm restraints or feeding tubes were used. Nostril retainers placed later than 1 week postoperatively were used for 4 months, but some patients or parents/guardians refused their use. All patients were followed up at 1, 3, and 6 months postoperatively and assessed for nasal food leakage and fistula formation.

Patient records were searched for intra- and postoperative adverse events classified above Grade I, as well as lengths of hospital stay. For classification of intraoperative events ClassIntra (version 1.0) a prospectively validated classification system was used (with a grading from 0 to V, Grade 0 defines no deviation from the ideal surgical course and Grade V defines a deviation leading to intraoperative death of the patient) (Dell-Kuster et al., 2020). For postoperative complications the Clavien-Dindo classification was used (with a grading from 0 to V, Grade 0 defines no complications from the normal postoperative course and Grade V leading to the patient's death) (Dindo et al., 2004).

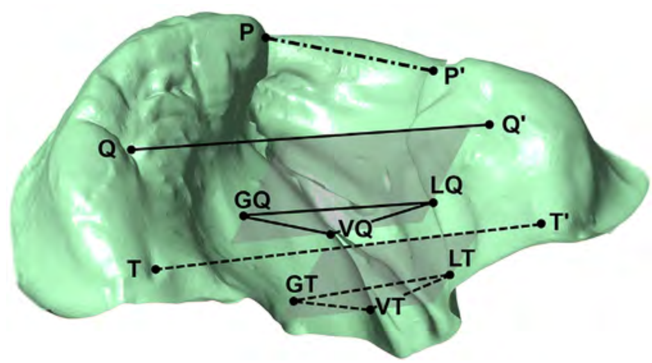

Fig. 3. Three-dimensional surface of a cast with reference points marked. Definitions of the reference points (Braumann et al, 2002, 2003; Nalabothu et al., 2020; Shen et al., 2015): Q and Q′, gingival groove points (intersection of the gingival groove and lateral sulcus); T and T′, posterior shelf pits (posterior end of the lateral sulcus); P and P′, pole points (cleft edges of the alveolar ridges). A midpalatal-section plane through QQ′ (perpendicular to QQ′T) defined: GQ by crossing the greater segment's junction to the vomer, VQ by crossing the vomer edge and LQ by crossing the lesser segment's shelf ridge. In the same way, the posterior-section plane TT′ defined GT, VT and LT. In bilateral pairs of points, the prime (′) indicates the point on the cleft side. T and T′ were allocated in the depth of the lateral sulcus instead of the top of the alveolar ridge for better traceability (Brief et al., 2006; Seckel et al., 1995). The palatal cleft width (pc) was measured from GQ to LQ and from GT to LT, the true cleft width (tc) was measured from VQ to LQ and from VT to LT, and the curved vomer width (cv) was measured from GQ to VQ and from GT to VT.

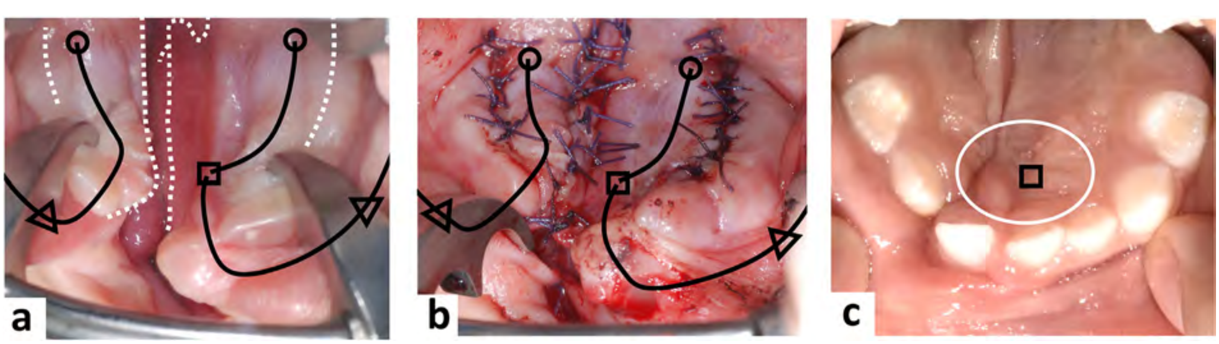

Fig. 2. Cleft palate repair using bipedicled hard-palate flaps and continuous circular two-layer wound closure. (**a**) Complete unilateral cleft lip and palate at surgery at 8 months of age. The palatal vascular territory, supplied by the palatine arteries (**o**) and its nasopalatine artery (NPA) (◘) on the healthy side, connects (—) across the alveolar ridge with the labiofacial vascular territory (**Δ**) on both sides of the cleft. The incision outline (**—**) is shown for a two-layer closure of the hard palate using a vomer turnover flap and bipedicled palatal flaps. Preserving the anterior attachment of the palatal flaps allowed the anastomosing vascular connection between the palate and the labiofacial territory to be maintained. (**b**) Wound conditions at the end of palate repair and before lip repair. Lifting the bipedicled flaps without transposing them allows for complete primary wound closure in the midline and over the lateral surgical access incisions. Posteriorly, the palatine arteries are maintained as well as the nasopalatine artery and nasopalatine nerve at the incisive foramen on the healthy side. (**c**) Palate conditions at 2.5 years of age. No scarring in the anterior junction zone (white circle) around the area of the preserved NPA (◘).

Table 1
Characteristics of patients with complete unilateral cleft lip and palate (n = 11).

Characteristic	Value
Sex	
Male	8 (73%)
Female	3 (27%)
Side of unilateral cleft lip and palate	
Right	6 (55%)
Left	5 (45%)
Gestational age at birth, weeks	40 (39–41)
Birth weight, g	3500 (3200–3765)
Age at start of plate therapy, days	1 (1–13)
Age at initiation of second plate, weeks	18.4 (15.0–22.4)
Age at surgery, weeks	35.4 (33.0–37.7)
Body weight at surgery, g	8300 (8000–8400)

Data are n (%) or median (IQR) values.

2.3. Presurgical orthopedic treatment with passive plate

After birth, all children underwent passive palatal plate therapy with nasal extension as described previously (Koželj, 1999, 2000; Nalabothu et al., 2020). Lip taping was used in addition (Dyna-Cleft®, Southmedic, Ontario, Canada). The plate typically became unstable after 3–5 months and was renewed. With an orthodontic caliper, we obtained linear measurements on the maxillary impression plaster casts at the beginning and end (day of surgery) of plate therapy (Zurich model®, Art. 215-33, Otto Leibinger, Mühlheim, Germany). Fig. 3 illustrates the palatal cleft width (pc), true cleft width (tc), and curved vomer width (cv) measured in the anterior and posterior cleft areas.

2.4. Statistical analysis

We used Wilcoxon signed-rank test for within-group comparisons of cleft width measurements. Statistical significance was assumed at $p < 0.05$. Statistical analysis was performed using Stata (version 15.1, StataCorp, College Station, TX, USA).

3. Results

From the medical records, eleven patients were assessed as eligible and could be included and analyzed. Table 1 shows the patient characteristics.

3.1. Surgical procedure

Full primary healing occurred in all patients during the early postoperative phase. No fistula was formed, as confirmed by inspections at 1, 3, and 6 months postoperatively and by the absence of any transient nasal food leakage after surgery. Fig. 4 illustrates the healing stages in a representative patient.

Median length of post-operative hospital stay was 5 days (range = 4–9 days). No intraoperative adverse events above Grade I of the ClassIntra classification occurred (any deviation from the ideal surgical course: without the need for any additional treatment or intervention, patient with no or mild symptoms (Dell-Kuster et al., 2020). Postoperative complications showed a maximum of Grade I according to Clavin-Dindo, requiring no pharmacological or surgical treatment besides antiemetic, analgetic or antipyretic drugs (Dindo et al., 2004). Grade II complications such as the need

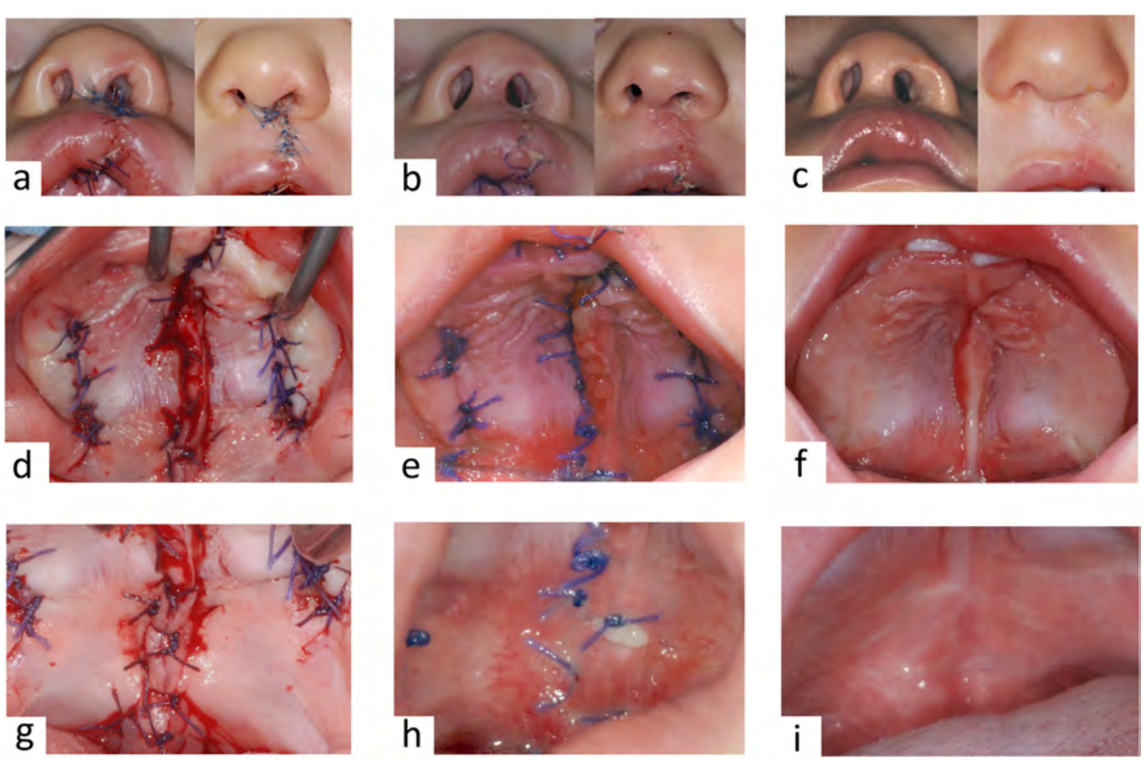

Fig. 4. Postoperative findings after cleft repair in one single surgical intervention with continuous circular closure. Healing conditions at the end of surgery (**a**, **d**, **g**), at 7 days postoperatively (**b**, **e**, **h**), and at 6 months postoperatively (**c**, **f**, **i**). Alar convexity and nostril symmetry and patency were retained at 6 months postoperatively (**a**, **b**, **c**), accompanied by a history of night-time nasal breathing. The palatal vault convexity at 1 week (**e**) and 6 months (**f**) postoperatively was similar to that seen preoperatively. Palatal mucosa relief (rugae palatinae and papilla incisiva) of the anterior palate was fully maintained. Lateral surgical access incisions healed primarily and left inconspicuous scars. Soft palate (**g**, **h**, **i**) healed with a single linear scar.

Table 2
Palatal cast measurements after birth and after preoperative plate therapy at the time of surgery (n = 11).

Variable	Measure	Value after birth+, mm	Value at time of surgery‡, mm	Wilcoxon signed-rank test p-value
Width of alveolar cleft ridges*	P to P′	12.0 (10.8–13.6)	5.0 (4.0–7.5)	0.0044
Width between gingival groove points	Q to Q′	27.0 (25.2–28.5)	26.0 (25.0–27.5)	0.2452
Anterior palatal cleft width*	GQ to LQ	12.0 (11.0–15.0)	5.0 (4.5–7.0)	0.0033
Anterior true cleft width*	VQ to LQ	7.3 (4.0–9.0)	2.0 (0.5–2.5)	0.0038
Anterior curved vomer width	GQ to VQ	6.5 (5.0–7.2)	5.0 (4.0–6.0)	0.0675
Width between posterior shelf pits	T to T′	30.0 (27.5–30.5)	30.0 (28.0–32.0)	0.3025
Posterior palatal cleft width*	GT to LT	14.0 (11.5–15.0)	7.3 (6.0–8.5)	0.0033
Posterior true cleft width*	VT to LT	6.0 (4.3–7.0)	2.5 (1.5–3.5)	0.0066
Posterior curved vomer width*	GT to VT	8.5 (7.5–9.0)	6.0 (5.0–7.0)	0.0044

Data are median (IQR) values. + Age 1 day (1–13). ‡ Age 35.4 weeks (33.0–37.7). * indicate that values after birth and at time of surgery differed at the 0.05 level of significance according to Wilcoxon signed-rank test. Q and Q′, gingival groove points (intersection of the gingival groove and lateral sulcus); T and T′, posterior shelf pits (posterior end of the lateral sulcus); P and P′, pole points (cleft edges of the alveolar ridges). A midpalatal-section plane through QQ' (perpendicular to QQ'T) defined: GQ by crossing the greater segment's junction to the vomer, VQ by crossing the vomer edge and LQ by crossing the lesser segment's shelf ridge. In the same way, the posterior-section plane TT′ defined GT, VT and LT. In bilateral pairs of points, the prime (') indicates the point on the cleft side.

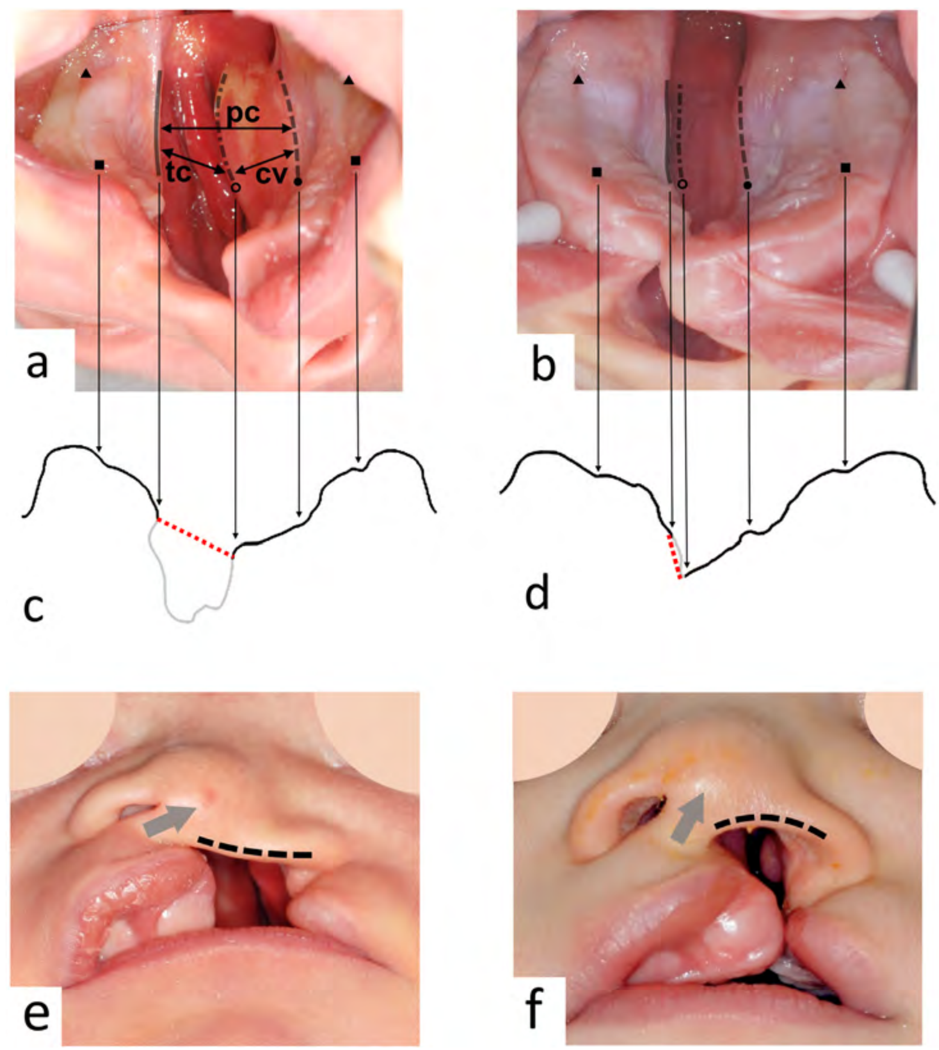

Fig. 5. Morphologic changes during presurgical orthopedic therapy. Cleft morphology at birth (**a**) and at 8 months after passive plate therapy and lip taping (**b**). The palatal cleft width (pc) lies between the lesser segment's shelf ridge (–) and the greater segment's junction to the vomer (– –). This junction is indicated by the transition in the color of the mucosa from pink to red (Veau and Borel, 1931). The true cleft width (tc) lies between the lesser segment's shelf ridge (–) and the vomer edge (– ■ – ■). The width of the curved vomer (cv) comprises the area between the vomer edge (– ■ – ■) and the greater segment's junction to the vomer (– –). Thus, the true cleft denotes the cleft width of the fissure into the nose, whereas the palatal cleft denotes the gap in the palatal mucosa. The cv (○ to ●) and the separation between lateral sulci remained almost stable over time (▲ to ▲, ■ to ■). Coronal cross-section through the corresponding plaster model at birth (**c**) and at 8 months (**d**). The true cleft narrowed significantly, and its entrance plane changed from oblique (**c**, •••) to more vertical (**d**, •••). The shape of the ala on the cleft side changed from a concave (**e**, – –) to a convex (**f**, – –) curvature, and the tilted columella straightened up (**e**, **f**, →).

for nasogastric feeding or blood transfusions did not occur. In particular, there were no adverse events requiring prolonged intubation or reintubation. Median hemoglobin level at end of surgery was 96.0 g/L (IQR = 92.0–98.0 g/L).

3.2. Presurgical orthopedic treatment with passive plate

From birth to surgery, median width of the anterior palatal cleft (pc) decreased by 7.0 mm, and the median width of the anterior true cleft (tc) decreased by 5.3 mm. Both changes were statistically significant (Table 2). In the posterior area, we also achieved statistically significant median reductions of palatal (6.7 mm) and true (3.5 mm) cleft width, respectively (Table 2). In contrast, the widths between the gingival groove points (Q to Q'; $p = 0.25$) and posterior shelf pits (T to T'; $p = 0.30$) remained almost unchanged. Table 2 summarizes the measurements illustrated in Fig. 3.

The reduction of palatal cleft width from birth to the time of surgery mainly occurred anteriorly, due to a marked reduction of true cleft width, while the width of the curved vomer remained almost unchanged. The continuous support of the alar rim by the ovoid acrylic extension led to the alar cartilage maturing into a more convex shape. Fig. 5 illustrates the morphologic changes resulting from presurgical plate therapy.

4. Discussion

UCLP repair is still mostly performed in multiple stages (Shaw et al., 2001). Inevitably, this leads to an opening of the created wound space between the operated and nonoperated areas. There, secondary healing takes place with a tendency to scarring. To prevent secondary healing, combined two-layer closure along the entire cleft lip-alveolar and palate border must be performed in a single surgery. However, with current one-stage techniques, it is not possible to achieve continuous circular two-layer closure of the oral and nasal cavities with primary healing (Brudnicki et al., 2014). Our hypothesis was that simultaneous cleft lip and palate repair can be accomplished in a single surgical intervention with continuous circular two-layer wound closure.

UCLP deformity was reliably closed in one single surgery, followed by continuous circular two-layer closure along the entire oral and nasal surfaces, with preservation of the anterior palatal neurovascular supply. The surgical technique reliably produced a fully closed soft-tissue envelope at the end of surgery. The gingiva-periosteal layer of the alveolar process remained untouched, but oro-nasal communication in the alveolar cleft area was closed in two layers. At surgery, our study patients had a median age of 35.4 weeks and a median weight of 8.3 kg. We refrained from performing simultaneous closure of ULCP in infants before 8 months of age although this is potentially feasible and safe (Hodges, 2010). This was done to facilitate developmental maturation of the child and tissue maturation to cope with surgery, healing, and recovery. Furthermore, between 8 and 10 months of age, the unmineralized, permanent tooth buds within the bone are well protected from surgery-related injury (Broomell, 1910; Lekkas et al., 2000).

The dissection plane in the hard and soft palates along the medial pterygoid plate lay in a subperiosteal plane. However, to simplify our palatoplasty, the soft palate muscle dissection may be further modified, using a small double-opposing z-plasty (Yamaguchi et al., 2016), which has shown favorable healing and speech outcome in a large patient sample. We made no transversal cuts in the anterior palatal region and at the junction between the hard and soft palates. Palatal vascular injections in fetuses (Bosma and National Institute of Dental Research, 1986) and neonates (Wilhelm, 1967, 1969) with and without clefts revealed that there are abundant vascular anastomoses between the nasopalatine and greater palatine artery as well as across the alveolar ridges between the greater palatine artery and vestibular branches of the superior labial artery (Fig. 2a). Thus, our technique maintains the natural connection of the vascular territories between the lip (Mueller et al., 2012), alveolar, and hard-palate and soft-palate regions. In addition, we can assume that the sensitivity of the hard palate is preserved because sensitive nerves run parallel to the nasopalatine and greater palatine vessels. Moreover, the anterior part of the palate is the normal resting position for the tongue. Maintaining full sensation in the anterior palate might facilitate correct tongue position when speaking (Whitehill, 2002), at rest, and when swallowing, and further, the tongue's pressure on the palate is an important natural force for encouraging growth of the face. The anterior part of the palatal shelves has intrinsic tissue deficiency in patients with UCLP even if no surgery is performed (Latief et al., 2012) and is prone to growth inhibition after surgery (Berkowitz et al., 2005; Trotman et al., 1993). Moreover, downward remodeling of the anterior and posterior palatal regions to the same extent is essential for harmonious growth (Enlow, 1996).

Since the curved vomer lies in a more horizontal plane, it does not narrow the anterior region during plate therapy. In contrast, covering the curved vomer with palatal flaps would lead to a lack of tissue and problems for complete wound closure despite preoperative plate therapy (Benitez et al., 2021). To select the optimal time point of hard-palate surgery solely on the basis of the ratio between palatal cleft area and total palate area must therefore be generalized with caution (Berkowitz et al., 2005). Suturing between the edges along the true cleft allows for complete wound closure, minimizes the need for tissue elevation and tissue shifting, minimizing the wound between the curved vomer bone and its overlying mucoperiosteum (Nalabothu et al., 2020). Unnecessary scarring from repetitive surgery or secondary wound healing as well as vascular destruction in the anterior palate must be avoided to minimize interference with the natural growth potential.

Median length of hospital stay of 5 days (range = 4–9 days) after combined UCLP repair compares well with the mean of 5.82 days (range = 1–10 days) reported in a randomized, controlled study of variable two-stage protocols (Bannister et al., 2017) involving mostly lip and soft-palate closure. However, mean postoperative stay was 5.96 days, even in the group receiving isolated lip closure (Bannister et al., 2017). The healthcare system in which the first authors work reimburses cleft surgical procedures to the hospital based on diagnosis-related groups (DRG). Normal reimbursement after palatal surgery occurs if the patient is discharged between postoperative days 1 and 5 (expected mean of 4.2 hospital days). Reimbursement is the same regardless of whether the lip is operated in addition to performing the palate surgery. The healthcare system in which author R.K.S. works does not reimburse combined lip and palate surgery in patients younger than 8 years. Consequently, the DRG system does not reimburse the expenses for prolonged anesthesia due to single-stage UCLP repair. Additionally, single-stage surgery is associated with fewer reimbursements because the patient does not return for a second, third, or fourth step of UCLP repair. The number of reimbursed procedures is reduced by 50%, 66%, and 75% compared to two-stage (Semb et al., 2017), three-stage (Gundlach et al., 2013), and four-stage (Nadjmi, 2018) treatment protocols, respectively. Although the total treatment costs for combined UCLP repair are lower, poor reimbursement strategies clearly hamper implementation of single-stage UCLP surgery.

In total, 5 of the 11 patients came from a place outside our normal referral area. These parents specifically requested a single surgical intervention. The reasons expressed by the parents were to minimize surgical burden for the child and psychosocial stress on the family associated with the upcoming treatment. In our study, parents accepted lip repair at a later time than usual, with the benefit of their child having to undergo only a single surgical intervention.

In our study, patients underwent functional palatal plate therapy with a lower treatment burden compared to presurgical alveolar molding (Alfonso et al., 2020). Median width of the alveolar cleft ridges (P to P′) decreased significantly from 12 mm to 5 mm in the period between birth and surgery onset (Table 2). However, there was a variable residual gap between the alveolar segments (IQR = 4.0–7.5 mm), since passive plate therapy relied solely on the functional interplay of the tongue, palate, and lip. Thus, the margins of the alveolar segments usually do not come into contact before surgery. However, contact of the alveolar segments was not necessary to achieve continuous and complete wound closure in two layers across the alveolar cleft region, since the alveolar mucosa was not implicated for closure.

Presurgical palatal plate treatment led to significant narrowing of the anterior and posterior true cleft widths before surgery (anterior, $p = 0.0038$; posterior, $p = 0.0066$). In addition, plate therapy provided the possibility of using a nasal stent to improve nasal symmetry (Kozelj, 2007). However, long-term effects of the presurgical nasal molding remain controversial (Van Der Heijden et al., 2013). The anterior palatal cleft (GQ to LQ) was reduced significantly before surgery, but this was caused by the significant reduction of the true cleft (VQ to LQ), while the curved vomer (GQ to VQ) remained unchanged. The width of the true cleft was consistently reduced to less than 3 mm (IQR = 0.5–2.5 mm). Thus, maximal benefit from presurgical plate therapy increased if surgical closure was restricted to the true cleft. Because the plane of entrance was almost vertical, only minimal transversal tissue shift was necessary (Fig. 3b, d). Presurgical passive plate therapy reduced the need for tissue mobilization during palatal surgery and made it unnecessary to perform an early lip surgery to narrow the cleft palate. Therefore, we could perform lip surgery in conjunction with palatal surgery. This improved the benefit–burden ratio of UCLP management compared to staged protocols.

In the present study the fit of the plate was maintained well over several months without having to perform regular plate adaptations. This is in contrast to other forms of orthopedic plates applied presurgically, such as the Hotz plate (Hotz et al., 1978), dentomaxillary advancement appliance of Latham (1980), or nasoalveolar molding appliances (Grayson et al., 1999; Grayson and Cutting, 2001). These appliances and their modifications aim to actively mold the alveolar arches by performing regular grinding and adaptation of the plate every few weeks. This requires frequent consultations, which increases the overall treatment burden for patients and their families (Singer et al., 2018).

In the present study, transversal width of the alveolar segments between QQ′ and TT′ remained constant during the period of plate therapy. Thus, three-dimensional position of the main contact zone of the plate remained stable. In terms of plate stability, the narrowing of the segments towards each other was compensated by expansive bone remodeling (Enlow, 1996). The plate prevented the tongue from entering the fissure of the true cleft. This led to new force equilibrium of the lip, tongue, and palate segments and the observed morphological adaptation. However, in the first months, the volume of the alveolar ridge itself increases. After 4–5 months, this resulted in instability of the plate, which required its renewal.

The findings of the present study are consistent with those of investigations using the same type of preoperative therapy (Koželj, 1999). In patients with palatal cleft, transversal dimensions of the alveolar segments are wider than normal at birth. Koželj showed that without plate therapy, there is no spontaneous narrowing in the period up to 6 months of life.

To bring the alveolar segments into contact before primary surgery, additional extrinsic forces are required (Grayson et al., 1999). This leads to an increased treatment burden with frequent visits for plate adjustments, risk of tissue pressure sores (Levy-Bercowski et al., 2009), or interventions under general anesthesia (Shay et al., 2015). The attempt to bring the alveolar segments into contact before primary repair is meaningful if gingivoperiosteoplasty is planned at the same time (Hopper and Al-Mufarrej, 2014). However, gingivoperiosteoplasty (Wojtaszek-Slominska et al., 2010) and early alveolar ossification (Berkowitz et al., 2004; Eppley, 1996) have been reported to increase the risk of a negative growth effect. Furthermore, the effectiveness of gingivoperiosteoplasty for promoting bone formation remains uncertain (El-Ashmawi et al., 2018; Wang et al., 2016). We therefore refrained from performing gingivoperiosteoplasty, even in cases where the alveolar segments were in contact after passive plate therapy.

The Dutchcleft study tested the effects of a preoperative Hotz-type plate in a randomized controlled trial in 24 patients (Prahl et al., 2001). In contrast to traditional assumptions, plate therapy did improve neither feeding (Prahl et al., 2005) nor parent satisfaction (Prahl et al., 2008). Furthermore, in a protocol using staged repair of UCLP, plate therapy had neither a positive nor a negative influence on the maxillary form (Bongaarts et al., 2006; Noverraz et al., 2015). In a randomized, controlled study, using a nasoalveolar molding plate is expected to have a lasting positive effect on maxillary form (Shetty et al., 2017). Therefore, no negative permanent effect is to be expected from the plate itself. The Dutchcleft study concluded that plate therapy to improve the form of the maxillary arch can be abandoned because combined lip and palate surgery overrides the effect of preoperative plate therapy (Prahl et al., 2001). This recognizes, that preoperative plate therapy followed by isolated lip surgery does not contribute anything to the palate surgery. However, before lip surgery they found significant reductions of the alveolar, midpalatal, and posterior cleft widths when using plate therapy (Prahl et al., 2001).

4.1. Limitations and strengths of the study

The impact of the present study is limited by the small number of patients, short follow-up period, and retrospective nature of this investigation. Comprehensive analysis of advantages and disadvantages of a specific treatment protocol requires assessment of all aspects of the final outcome (Allori et al., 2017) up to the end of growth and treatment. An intercenter study (Fudalej et al., 2019; Urbanova et al., 2016) using a similar single-surgery method without oral lateral raw surface but involving a raw surface in the soft-palate nasal layer showed a slightly more favorable growth outcome than staged lip and palate repairs at the patients' age of 10 years. Although the age of 10 years is too early to predict final growth outcome, relative growth ranking between the protocols used in intercenter studies remained stable between the ages of 9 and 20 years (Brattstrom et al., 2005; Semb et al., 2005). It can be assumed that without preoperative plate therapy, the same surgical technique would necessitate undesirable broader tissue mobilization with a larger wound. However, it remains unclear as to what effect wider tissue mobilization, necessary to achieve tension-free closure of the cleft, will have on short- or long-term results.

In terms of study strengths, the chosen surgical technique respected the blood microcirculation in the palate, especially in the anterior palate and labioalveolar junction. Further, it combined minimal tissue tension and primary healing. Long-term follow-up is needed to verify whether our surgical technique is consistent with the conclusion of Ross that "there is every indication that for facial growth the most simple treatment is as effective as any other"(Ross, 1987). As the lateral access incisions were completely closed at the end of surgery, it seems technically feasible to avoid these incisions (Brusati, 2016; Brusati and Mannucci, 1994; Li et al., 2021; Ogata et al., 2017) and replace them with submucosal periosteal incisions (Kobayashi, 2010).

5. Conclusions

Within the limitations of this preliminary study it seems that the concept of single-stage continuous circular closure in UCLP has potential for further investigation. However, it remains to be proven that there are no relevant adverse effects such as inhibition of maxillary growth.

Author contributions (CRediT)

Benito K. Benitez: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Writing − Original draft preparation. **Andrzej Brudnicki:** Conceptualization, Methodology, Writing-Review and Editing. **Zbigniew Surowiec:** Conceptualization, Methodology, Writing-Review and Editing. **Ravi K. Singh:** Writing-Review and Editing. **Prasad Nalabothu:** Writing-Review and Editing. **Dieter Schumann:** Supervision, Writing-Review and Editing. **Andreas A. Mueller:** Conceptualization, Methodology, Formal Analysis, Investigation, Resources, Visualization, Writing − Original draft preparation.

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Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2021.07.002.

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7. Conclusion and outlook

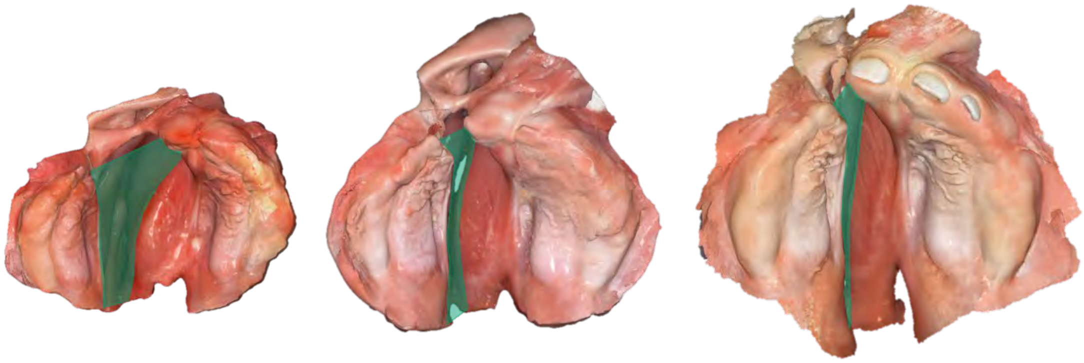
7.1 Overall approach

The first study included in this thesis compared two simultaneous cleft lip and palate repair techniques performed in Basel. The study evaluated the effects of these techniques on maxillary growth as well as dental and palatal morphology. Similar alterations were observed in both techniques using unipedicled palatal flaps. In the subsequent study we assessed the histopathology of the curved vomer area, to work out the foundations for a need-based use of curved vomer mucosa to close the cleft palate in two-layers Furthermore, a preliminary study assessed a simultaneous continuous circular closure technique in two-layers with bipedicled palatal flaps in patients with unilateral cleft lip and palate.

7.2 Presurgical treatment

Presurgical treatment with passive palatal plates has been a consistent component of the treatment protocols at the Cleft Center in Basel since 1991. However, presurgical treatment remains controversial and leads to additional burden on patient, family, and healthcare costs. Thus, the benefit of presurgical treatments must be proven and logically aligned with the surgical concept. In our cohorts, presurgical treatment with a passive plate for period up to 8 months decreased the cleft width and the true cleft area defined as the area connecting the oral and nasal cavities (Benito K. Benitez et al., 2022a; Nalabothu et al., 2020). In addition to the morphologic benefits for surgery, functional improvements were observed, thus adjusting the anatomy and functions to those seen in healthy individuals without clefts (Koželj, 1999).

In our future research, we will compare our results to those obtained in an external control group undergoing a similar surgical concept (Benitez et al., n.d.). This analysis will provide further evidence whether presurgical passive plate therapy can substitute early isolated lip surgery, to facilitate subsequent simultaneous cleft lip and palate repair. In addition to reducing surgical burden by presurgical treatment, refinement of the presurgical treatment burden will be of substantial interest. **Figure 8** depicts the reduction in true cleft area after 4 months of passive plate therapy and indicates minimal changes until primary cleft closure at 10 months. Therefore, the stability of the reduction of cleft widths after early discontinuation of presurgical treatment must be investigated. Such studies would shed light on the possibility of reducing the burden of presurgical treatment while still achieving the desirable outcomes to facilitate surgery. Additionally, potential inhibitory effects of presurgical therapy on maxillary growth should be investigated.



A **B** **C**

Figure 8. Digital maxillary impression in a patient with unilateral cleft lip and palate with true cleft area highlighted in green: **A** at birth, **B** at 4 months and **C** at 10 months after passive presurgical plate treatment.

To measure morphological changes under treatment and to fabricate presurgical plates, impressions of the maxilla are necessary in newborns and throughout the course of treatment. Conventional impressions are described to involve risks (Chate, 1995; Reichert et al., 2017), resulting in inconsistent documentation of the pretherapeutic malformation anatomy. Use of the latest technology with intraoral scanners for digital impression taking can remedy this situation (Benito K. Benitez et al., 2022b; Weise et al., 2022). The 3D digital models obtained by intraoral scanners not only necessitate but also enable new designs and manufacturing processes for presurgical treatment. Design methods will change from physical to digital approaches, ultimately progressing towards automated and data-driven techniques (Schnabel et al., 2023). Concerning manufacturing, 3D printing will allow for manufacturing presurgical plates at the point-of-care (Aretxabaleta et al., 2021; Xepapadeas et al., 2020; Zarean et al., 2022).

7.3 Surgical treatment

In the primary treatment of clefts, most patients undergo staged surgeries, involving two to four individual surgeries (Shaw et al., 2001). Despite the World Health Organization (WHO) recommendation to assess ways of reducing the burden of care, including the evaluation of simultaneous cleft lip and palate (WHO, 2002), the practice of simultaneous cleft lip and palate repair remains the exception. Currently, such surgeries are performed in only about 5% of cleft centers in Europe (Shaw et al., 2001). The timing of cleft palate repair has been the subject of discussion, aiming to balance between early surgery to optimize speech outcome and late surgery to minimize detrimental effects on maxillary growth (Gundlach et al., 2013).

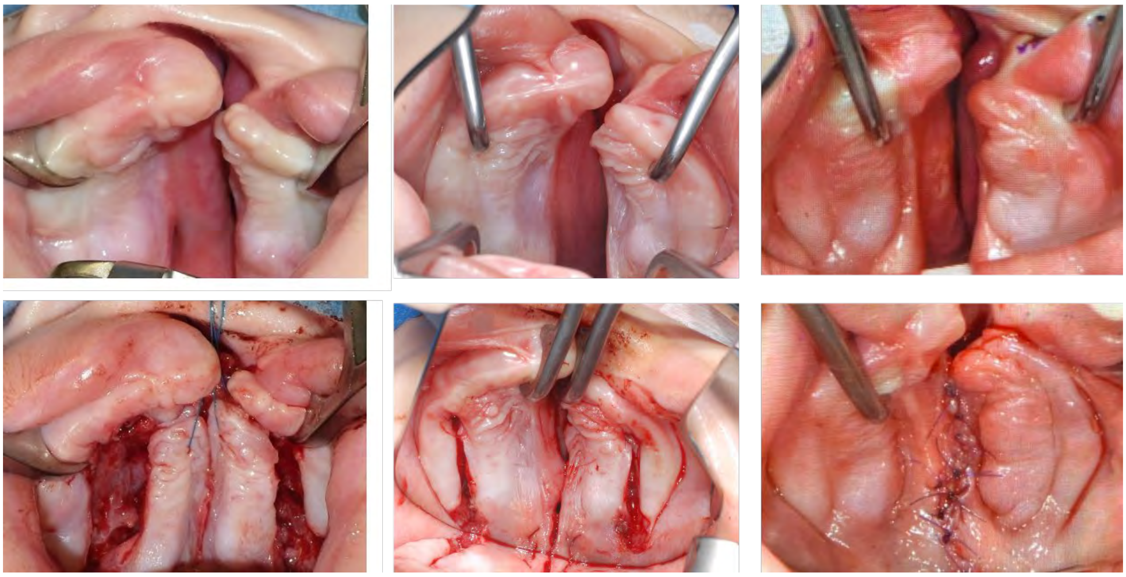
Since its first description in 1958 (Farina, 1958), simultaneous cleft lip and palate repair with various presurgical and surgical concepts has evolved at different craniofacial centers (Brusati, 2016; Davies, 1966; De Mey et al., 2009; Fudalej et al., 2010; Honigmann, 1996; Kaplan et al., 1974; Torikai et al., 2007). In Basel, Honigmann initiated a simultaneous cleft lip and palate repair approach in 1991 (Honigmann, 1996) to reduced the surgical burden. From 1991-2002 unilateral cleft lip and palate repair in Basel comprised two-layer palate repair with cranially pedicled vomer flap and two-flap palatoplasty, primary alveolar bone graft from the rib and lip repair using the modified Millard technique (Honigmann, 1998, 1996). From 2003-2014 the surgical protocol was modified, to abandon primary alveolar bone grafting due to inconsistent ossification results and suspected interference with maxillary growth (Mueller et al., 2012). Compared to healthy controls, both protocol showed deficits in maxillary growth, as well as altered dental and palatal morphology (Benito K Benitez et al., 2022). In 2014, Mueller revisited the surgical concept at the Basel center inspired by the methods and results of Dudkiewicz and colleagues (Brudnicki et al., 2014; Fudalej et al., 2010). The long-term results of their simultaneous cleft lip and palate repair using bipedicled palatal flaps was thoroughly studied (Brudnicki et al., 2014; Fudalej et al., 2011, 2008, 2019; Hortis-Dzierzbicka et al., 2012; Offert et al., 2012; Urbanova et al., 2016). From 2016 onwards the technique with bipedicled flaps was further modified to achieve a simultaneous circular two-layer closure also on the nasal side. Furthermore, the use of presurgical treatment with passive palatal plates proved to reduce cleft width. This combined presurgical and surgical technique permits smaller lateral incisions that can be closed primarily, thus avoiding growth inhibiting side effects of secondary healing.

Within this thesis, several measures were described to limit the need for tissue displacement which negatively affects maxillary growth. Firstly, the cleft was narrowed over the course of presurgical treatment. Secondly, the necessary tissue shift was reduced by a balanced use of vomerine mucosa for both, nasal and oral layer closure. Short-term follow-up confirmed primary healing possibility without fistula formation. Lateral access incisions for bipedicled flaps as described in s**ection 6**

(Benito K. Benitez et al., 2022a) were closed at the end of the operation. However, the necessity for bipedicled palatal flaps in cleft palate closure is questionable because several authors have reported the successful omission of lateral incisions (Brusati and Mannucci, 1994; Torikai et al., 2007). Limiting lateral access incisions and primary wound closure may result in reduced scarring. Thus, a positive impact on maxillary growth can be expected (Brusati, 2016). Consequently, future efforts to optimize maxillary growth outcome should focus on surgical techniques that involve minimal incisions and less tissue displacement.

Based on the available literature, the simultaneous circular cleft closure described in s**ection 6** was refined in 2022, aiming for a minimal incision palatoplasty without lateral incisions (Mendoza et al., 1994; Ogata et al., 2017; Pan et al., 2014; Seo et al., 2019). **Figure 9** depicts the evolution in cleft palate repair in simultaneous cleft lip and palate repair protocols at the cleft center in Basel, evolving from two-flap palatoplasty with unipedicled palatal flaps (practiced from 1991 to 2014) to modified von Langenbeck bipedicled palatal flaps (practiced from 2015 to 2021) to continuous circular closure with midline incision palatoplasty (practiced since 2022).

Our data of the histology of the curved vomer obtained in the framework of this PhD project confirmed that the tissue of the curved vomer can be used for both oral and nasal layer repair. While continuous circular closure in two layers appears promising, open questions regarding long-term maxillary growth and speech outcome remain.



A **B** **C**

Figure 9. Evolution in the simultaneous two-layer cleft palate repair in unilateral cleft lip and palate in Basel **A,** two-flap palatoplasty (unipedicled palatal flaps) with secondary healing on the lateral side (1991 to 2014) **B**, modified von Langenbeck palatoplasty (bipedicled palatal flaps) and use of vomerine tissue (2015-2021) **C**, two-layer continuous circular closure with midline incision palatoplasty (since 2022)

Using vomerine tissue to cover the transversal lack of fusion and distance mainly addresses the hard palate closure. However, omitting lateral incisions on the hard and soft palate junctions might lead to a better preservation of tissue perfusion and thus healing, also on the soft palate.

To achieve intelligible speech, a velopharyngeal function with sufficient cranial suspension, lengths, volume, and muscle function of the soft palate is necessary (Kobayashi et al., 2021, 2020; Randall et al., 2000). Here, the combination of a circular closure with a Furlow-type double-opposing z-plasty has been described (Kobayashi, 2010; Torikai et al., 2007). Others have reduced the double-opposing z-plasty to a minimal z-plasty, however not incorporated into simultaneous cleft lip and palate repair (Seo et al., 2019; Yamaguchi et al., 2016). Cleft surgeons have proposed a case-based decision on the staging and technique depending on cleft palate width, balancing the risk of tension, wound healing and fistula formation against the effect of lateral incisions and secondary healing (Brusati, 2016; Brusati and Mannucci, 1994; Kobayashi, 2010). Further techniques for using buccal fat pad, buccal flaps and other regional flaps have been described (Adekunle et al., 2023; Adeyemo et al., 2019; Lo et al., 2022; Mann et al., 2017). However, in primary cleft repair, these techniques do not follow the principle of restoring the anatomy with tissue locally displaced by the cleft malformation (Talmant et al., 2007), but follow a reconstructive paradigm using other distant tissues.

Ongoing studies by our group (ClinicalTrials.gov Identifier: NCT03877666), will assess the change in tissue perfusion due to the surgical intervention in the palate. We aim to give preliminary data on palatal perfusion to be compared with different techniques. The studies aim to prove that limiting incisions and tissue mobilization will positively affect maxillary growth and speech outcomes in the long-term, while still achieving reliable cleft palate closure.

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Benito K. Benitez: Postgraduate online-lecture: «Reinventions in Cleft and Craniofacial Surgery», Universidade Federal De Pelotas, Brasil, 20. April **2023.**

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Benito K. Benitez. Full digital workflow: from intraoral scan to 3d design and 3d printing in cleft care. *Symposium Lecture at the 26th Congress of the European Association for Cranio Maxillo Facial Surgery EACMFS 2022;* Madrid, Spain, September **2022.**

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