REVIEW

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CLEFT LIP AND/OR PALATE: A COMPREHENSIVE REVIEW AND OUR TREATMENT APPROACH

K. Gigov[1,2], I. Ginev[1], M. Miteva[2,3]

[1]Department of Propedeutics of Surgical Diseases, Section of Plastic, Reconstructive and Aesthetic Surgery and Thermal Trauma, Faculty of Medicine, Medical University – Plovdiv, Bulgaria
[2]"Sv. Georgi" University Hospital – Plovdiv, Bulgaria
[3]Department of Endocrinology, Faculty of Medicine, Medical University – Plovdiv, Bulgaria

Abstract. *Cleft lip with or without cleft palate is the most common congenital malformation of the head and neck. Children with cleft anomalies may experience a multitude of physical and developmental challenges. Psychosocial and emotional concerns of the patients and their families can also occur. As such, comprehensive care for the patient with cleft lip and/or palate requires an interdisciplinary team. This article describes epidemiology, embryological developmental processes, known environmental and genetic risk factors, and their interaction, the assessment and current treatment recommendations for children born with cleft lip and/or cleft palate. We review the commonly used surgical techniques for repair, clinical outcomes and complications. Throughout the discussion, we share our experience and identify areas for future study with the focus on cleft palate management.*

Key words: *congenital facial anomalies, surgical techniques, uranoplasty, surgical outcomes*

Corresponding author: *Kostadin Gigov, Department of Propedeutics of Surgical Diseases, Section of Plastic, Reconstructive and Aesthetic Surgery and Thermal Trauma, Faculty of Medicine, Medical University of Plovdiv, Bulgaria; "Sv. Georgi" University Hospital, 66 Peshtersko shosse blvd., Plovdiv, Bulgaria, email: dr.gigov@gmail.com*

ORCID: *0009-0007-2951-1946*

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INTRODUCTION

Orofacial cleft anomalies (OCA) represent a heterogeneous group of disorders affecting the craniofacial area. They may be unilateral or bilateral and involve the lip, the palate, or both. These defects arise in about 1-7 per 1000 live births worldwide, with ethnic and geographic variations. Effects on speech, hearing, appearance, and cognition can lead to long-lasting adverse outcomes for health and social integration. Affected children need multidisciplinary care from birth to adulthood. The guidelines for comprehensive care recommend team members that may include different specialized professionals in anesthesiology, genetics, neurosurgery, nursing, ophthalmology, oral maxillofacial surgery, orthodontics, otolaryngology – head and neck surgery, pediatrics, pediatric dentistry, plastic surgery, psychology, speech – language pathology.

Services and treatment protocols for the management of children with cleft lip and palate (CLP) can differ remarkably within and between developed countries. Various registries of clinical outcomes have emerged and are working independently. In Europe, a networking initiative funded by the European Union

in the late 1990s reached a consensus on a set of recommendations for cleft care delivery [1].

WHO highlighted the need for effective international collaboration on strategies to enhance clinical care, through the interaction of regional cooperatives such as the Eurocran project. It is a prospective registry that enables critical assessment of various kinds of CLP interventions. Different centers submit duplicate records before and after treatment, as a step to minimizing follow-up, analysis, and reporting bias (www.eurocran.net).

The Eurocleft project helped to standardize not only the stages of surgical treatment but also the diagnostic algorithm and monitoring [1]. In Bulgaria, for the last 20 years, within the framework of this project, the results between the European centers were studied and compared, and significant treatment differences were observed [1-3].

In Bulgaria in 1997, a specialized center was established with the collaboration of the non-governmental organization, Association of Patients with Facial Anomalies and Their Parents (ALA), (http://ala-bg.org/); the treatment has been not only surgical but also multidisciplinary [4].

In 2008, a national network of parents, nutritionists, speech therapists, orthodontists, and ENT specialists was developed. In 2010, the team in Plovdiv, in partnership with the ALA, won a project of the Ministry of Education and Science to create a register with a database of patients with facial anomalies. After the end of the project in 2014, the ALA received the rights for the further development of this database and funded a new project to elaborate an Electronic Medical Record for Facial Anomalies (EMRFA). In 2020, Transforming Faces (https://transformingfaces.org/) co-financed a project to upgrade the EMRFA. The data from 500 cases have been collected from the electronic register. Our goal is to exploit this information in the future, thanks to the already built system [5].

This article describes the epidemiology, known environmental and genetic risk factors, and their interaction, embryological developmental processes, assessment and current treatment recommendations for children born with cleft lip and/or palate. We review the commonly used surgical techniques for repair, clinical outcomes and complications. Throughout the discussion, we share our experience and identify areas for future study with the focus on cleft palate management.

EPIDEMIOLOGY

Orofacial clefts arise in about 1 in 700 live births [6]. According to the WHO, the frequency varies in different parts of the world, with prevalence at birth of cleft lip with or without cleft palate of 3.4-22.9/10,000 births, and an even more pronounced variation for the isolated cleft palate – 1.3-25.3/10,000 births [6]. The average frequency of cleft lip with or without cleft palate was high in parts of Latin America and Asia (China, Japan) and low in Israel, South Africa, and southern Europe. Rates of isolated cleft palate were high in Canada and parts of northern Europe and low in parts of Latin America and South Africa. The incidence of congenital cleft palate in Europe is the highest in Finland (10-14/10,000) and the lowest in Scotland (8/10,000) [7]. Cleft lip with or without cleft palate is most frequent in males, and isolated cleft palate is most typical in females, across various ethnic groups. In white populations, the sex ratio for cleft lip with or without cleft palate is about 2:1 (male:female) [8]. The proportion of individuals with additional anomalies varies between studies, but in general, further defects seem to be more frequent for children with isolated cleft palate than for those with cleft lip with or without cleft palate [8]. In a study of almost 4000 individuals with isolated cleft palate in Europe, 55% of cases were isolated, 18% were recorded in association with other anomalies, and 27% were noted as part of recognized syndromes [9]. For cleft lip with or without cleft palate, in a report of more than 5000 patients, 71% of cases were isolated and 29% were seen in association with other anomalies [10].

Orofacial clefts can be unilateral or bilateral. According to the International Perinatal Database of Typical Orofacial Clefts (IPDTOC), bilateral clefts of the lip without affecting the palate account for 10.3% of cases and 30.2% for anomalies of the lip and palate. Among unilateral cases, 36.9% of cleft lip and 41.1% of cleft lip and palate occur on the right side [11].

The majority of patients with CLP are without concomitant malformations and with preserved intelligence. The most common additional anomalies are vertebral and limb deformities (33%), congenital cardiac defects (28.6%), polydactyly (16.2%), hydrocephalus (11.4%), microphthalmia (8.3%) [2, 12]. Severe malformations such as anencephaly and encephalocele are less common. According to the cited authors, infants with cleft lip and palate may often have concomitant abnormalities more than those with isolated forms [12, 13]. These data do not coincide with our observations: in the patients with cleft lip and palate less common concomitant abnormalities and/or de-

velopmental delay were observed compared to cleft palate-only cases.

Cleft lip and palate and isolated cleft palate are classified as syndromic or nonsyndromic. Nonsyndromic isolated CLP is more common and accounts for over 80% of cases. CLP, as a part of the described over 400 syndromes represent about 4% of all cases [2, 11].

In Bulgaria, according to the web-based national registry (EMRFA) the highest prevalence of cleft anomalies was related to cleft lip and palate. Over 90% of cases in the country have been treated in the last 20 years in the Department of Plastic, Esthetic and Reconstructive Surgery for Children, University Hospital "Sveti Georgi" in Plovdiv. According to EMRFA, every year in Bulgaria, between 60 and 80 new cases of cleft lip and/or palate are born [5].

ETIOLOGY AND GENETICS

The potential of research on the genetic basis of CLP has increased over the last decade with the development of recombinant DNA technology. In more than 50 craniofacial syndromes, genes involved have been either mapped to a chromosome location or actively isolated and their structure identified. This achievement, however, represents only a fraction of the total number of craniofacial syndromes defined. The pathogenesis of most common forms of CLP, nonsyndromic clefts of lip and/or palate, is challenging because they arise from complex polygenic interactions – gene transmission, chromosomal aberrations, and teratogens with environmental factors [14]. Some gene products studied are growth factors (e.g., TGFA, TGFβ3), transcription factors (e.g., MSX1, IRF6, TBX22), or factors that play a part in xenobiotic metabolism (e.g., CYP1A1, GSTM1 (glutathione S-transferase μ1), NAT2 (N-acetyltransferase 2)), nutrient metabolism (eg, MTHFR (methylenetetrahydrofolate reductase), RARA (retinoic acid receptor α)), or immune response (e.g., PVRL1, IRF6). The most intensively investigated variants have been of the TGFA and MTHFR genes [15, 16].

The potential of research on the genetic basis of CLP has increased over the last decade. The focus is on the role of epigenetic factors, including histone protein modification, chromatin remodeling, post-transcriptional genetic modification by noncoding microRNAs, and DNA methylation, which are essential in the etiology of CLP [17].

DNA methylation, one of the most important epigenetic modifications in mammalian cells, is the process of attaching methyl groups to DNA to regulate gene expression [18]. The process was first identified as a potential mediator of palatal development after a series of studies, in which DNA demethylating agents were used to induce cleft palate in mice [19]. Since then, DNA demethylation has been associated with craniofacial malformations, including cleft palate.

Currently, data strongly suggest that DNA methylation plays a central role in regulating palate development and may serve as a future risk assessment and potential therapeutic goal in patients with orofacial abnormalities [20, 21].

If specific genetic disorders are excluded, the recurrence risk to siblings is greater than that predicted by familial aggregation of environmental risk factors. Concordance rates for cleft lip, cleft lip and palate, and cleft palate alone are higher in the monozygotic than in dizygotic twins. The familial clustering and concordance recorded in twins with CLP are specific for each defect, and, therefore, the anomalies are thought to have heterogeneous causes [14]. The predominance of left-sided clefting and the male excess of cleft lip with or without cleft palate also suggest the importance of genetic susceptibility [8].

In Van der Woude syndrome (1:100,000 live births) de novo mutations with the pathological locus of 1q32-q41 predominate [6, 22]. In non-syndromic isolated forms, the inheritance is according to the multifactorial polygenic model of Falconer. According to this model, exogenous factors cause disease in embryos with inherited additive genes.

Polygenic inheritance is determined by the combined influence of several genes and environmental risk factors in a certain period of pregnancy. The most common syndromes with CLP are Van der Woude, Treacher Collins, ectodermal dysplasia, otomandibular syndrome, Klippel–Feil, Gorlin–Goltz, Stickler, Pierre Robin and others [23].

LIFESTYLE AND ENVIRONMENTAL RISK FACTORS

Accumulated epidemiological and experimental evidence indicates that a variety of environmental influences contribute to the risk of cleft lip and/or palate. Numerous maternal exposures during early pregnancy have been studied, among them tobacco smoking, alcohol consumption, suboptimal nutrition, viral illnesses, medications, and other teratogenic agents. Maternal smoking, in particular, has repeatedly been associated with a higher likelihood of cleft lip with or without cleft palate as well as isolated cleft palate [24].

Observational research also highlights the potential role of maternal nutritional status in orofacial development. The use of multivitamin supplements during the first trimester has been linked with a reduced

risk of craniofacial anomalies; one meta-analysis reported approximately a 25% decrease in the birth prevalence of CLP among women taking multivitamins [25]. The specific effect of folic acid intake – whether dietary or supplemental – remains debated. In regions such as North America, where grain fortification with folic acid has been compulsory since the late 1990s, some studies have suggested a decline in cleft lip with or without cleft palate, whereas similar trends have not been documented in countries like Australia, where fortification was voluntary [26]. When considering overall cleft prevalence, reductions have been reported in the USA but not consistently in Canada or Chile [27].

Zinc, an essential trace element for fetal growth, has also been implicated. Experimental zinc deficiency can produce isolated cleft palate and additional malformations in animal models. Consistent with this, mothers of children with various forms of clefting in the Netherlands were found to have lower erythrocyte zinc concentrations than mothers of unaffected children, and comparable differences were observed in the affected infants themselves [28]. Additional micronutrients – such as riboflavin (vitamin B2) and vitamin A – may also influence orofacial development [29, 30]. Although excessive fetal exposure to retinoid medications is known to cause severe craniofacial abnormalities, the relevance of vitamin A intake from dietary sources is less straightforward. Several commonly used anticonvulsants – including diazepam, phenytoin, and phenobarbital – are associated with elevated clefting risk [31], and some studies have also reported positive associations between maternal corticosteroid use during pregnancy and the presence of orofacial clefts [32].

DEVELOPMENTAL PATHOGENESIS

Formation of the lip and palate is a complex developmental sequence requiring precise coordination of cell migration, proliferation, differentiation, and apoptosis. Neural crest cells migrate into the craniofacial mesenchyme and, by the fourth week of human embryogenesis, contribute to the formation of the frontonasal prominence and the paired maxillary and mandibular processes surrounding the early oral cavity. As nasal placodes appear toward the end of the fourth week, the lower region of the frontonasal prominence is divided into the medial and lateral nasal processes.

By the close of the sixth developmental week, the fusion of the medial nasal processes with each other and with the maxillary processes leads to the formation of the upper lip and the primary palate. During this interval, the lateral nasal process undergoes a surge in cellular proliferation that makes it particularly vulnerable to teratogenic influences; disturbances at this stage may interfere with normal fusion events and thus give rise to clefting [33].

Secondary palate development begins visibly during the sixth embryonic week, when bilateral palatal shelves extend vertically alongside the developing tongue from the maxillary processes. In the seventh week, these shelves elevate to a horizontal plane above the tongue, subsequently contacting and fusing to create the midline epithelial seam. This seam then disintegrates, enabling mesenchymal continuity across the palate. The mesenchyme differentiates further into the osseous components of the hard palate and the muscular structures of the soft palate. In addition to midline fusion, the secondary palate unites with both the primary palate and the nasal septum, completing these developmental events by the tenth week. This process ultimately separates the oral and nasal cavities, permitting simultaneous feeding and breathing in the neonate [33].

Because the lip/primary palate and the secondary palate have distinct embryological origins, clefts are generally categorized into cleft lip with or without cleft palate and isolated cleft palate, the latter occurring without lip involvement. This classification is supported by genetic observations showing that the two phenotypes do not usually co-occur within the same families. Integration of human genetic data with experimental developmental studies has greatly advanced the understanding of the mechanisms guiding normal facial morphogenesis and the pathways disrupted in these cleft types.

CLASSIFICATION

There are various classification systems of CLP depending on the clinical form and anatomical features. Davis and Ritchie (1922), who based their system on the location of the cleft relative to the alveolar process, used three major headings with some subdivisions [34]. Their classification is still used by some surgeons: group I – prealveolar cleft – cleft lip with subdivisions for unilateral, median, and bilateral; group II – postalveolar cleft – degrees of involvement of the soft and hard palates could be specified, up to the alveolar ridge, submucous clefts could also be included; group III – alveolar cleft – complete clefts of the palate, alveolar ridge, and lip, with subdivisions for unilateral, median, and bilateral.

Clefts from the groups I and II could be reported in the same subject if there was no involvement of the alveolar ridge. There is no opportunity to report a cleft

of the lip and alveolar process under these strict definitions, but Davis and Ritchie recommended adding them to group III. They also suggested this is the best place for a cleft of the palate and alveolar process without lip involvement. Another problem inherent in this form of numbered system is the tendency of users to revert to reporting just numbers.

Veau (1931) described 4 types of cleft [35]: group I – cleft of the soft palate only; group II – cleft of the hard and soft palate to the incisive foramen; group III – complete unilateral cleft of the soft and hard palate, and the lip and alveolar ridge on one side; group IV – complete bilateral cleft of the soft and hard palate, and the lip and alveolar ridge on both sides.

It would be difficult to describe clefts of the lip and alveolar process without palatal clefts using this system.

Fogh-Anderson (1942) modified the Veau classification [36]: (1) cleft lip – unilateral or bilateral; (2) cleft lip combined with cleft palate; (3) isolated cleft palate; and (4) rare atypical clefts.

In 1962, the American Cleft-Palate-Craniofacial Association (ACPA) divided the clefts into 4 different groups depending on whether they are prepalatine or palatine [23]: (1) cleft of the lip and alveolar ridge; (2) cleft palate – soft palate only, hard palate only, or cleft that affects the entire palate; (3) clefts of the lip, alveolar ridge, and palate; (4) laterofacial clefts – the most common is the anatomical classification of Tessier (1976) [38].

In addition to the above classifications, CLP can be grouped into unilateral or bilateral, left-sided or right-sided, overt or submucosal. There are also classifications according to the severity and preoperative risk.

In Bulgaria, Kavrakirov (1960) proposed a classification system for cleft lip and palate: (A) incomplete cleft lip and palate – (1) cleft lip – partial, complete, (2) cleft palate – partial, complete, (3) combined (a) partial cleft lip + partial cleft palate, (b) partial cleft lip + complete cleft palate, (c) complete cleft lip + partial cleft palate, and (d) complete cleft lip + complete cleft palate; (B) total cleft lip and palate – (1) cheilognatopalatoschisis – unilateral, bilateral, and (2) cheilognatopalatoschisis with bridge, unilateral [39].

Anastassov (2006) proposed a scored classification for preoperative severity and postoperative defects (Table 1) [2].

Table 1. Preoperative severity groups

Groups	Nose–lip (ASL)	Palate (ASP)	Overall (OASC)
Mild	**1-3**	**1-3**	**1-4**
Average	**4-6**	**4-10**	**5-12**
Severe	**7-11**	**11-13**	**13-21**
Very severe	**12-16**	**14-16**	**22-32**

Acronyms: ASL = assessment of the severity of the cleft lip deformity; ASP = assessment of the severity of the cleft palate deformity; OASC = overall assessment of the severity of the cleft deformity.

This scoring system is integrated into the EMRFA and calculated automatically by the platform.

SURGICAL MANAGEMENT

The focus of the discussion is uranoplasty, its development over the years, and two of the most commonly used surgical techniques – Von Langenbeck and Wardill–Kilner. The technique of Von Langenbeck was described in 1859. The edges of the cleft are adapted to each other by creating bipedicular mucoperiosteal flaps. At the same time, laterally from the defect relieving incisions extend to the alveolar portion of the cleft. The nasal and oral mucoperiosteal layers are formed through the mucoperiosteal flaps (Fig. 1). Numerous modifications of the Von Langenbeck technique include restoration of the m. levator veli palatini [40, 41].

Von Langenbeck technique can also be combined with the Furlow technique, which includes Z plastic to lengthen the palate. A common consequence of uranoplasty is velopharyngeal insufficiency with insufficient mobility of the soft palate. The palate does not reach the posterior pharyngeal wall, which manifests as nasal speech (hypernasality) and/or nasal air emission.The Wardill–Killner technique, created in 1931, is a V-Y “push back” modification of the Von

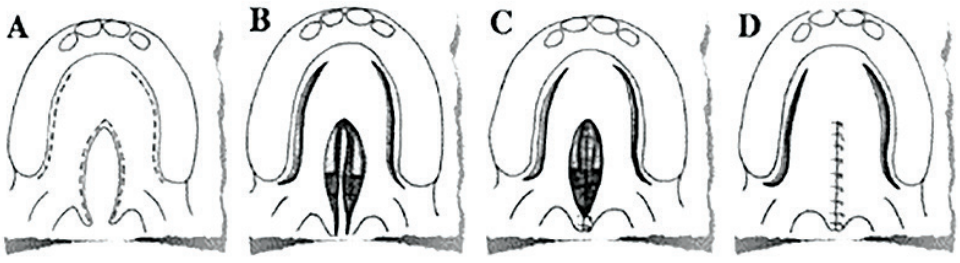

Fig. 1. Palatoplasty by Von Langenbeck technique (1859)

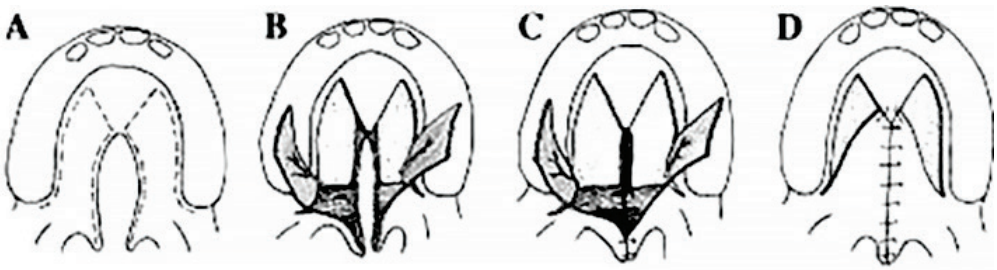

Fig. 2. Palatoplasty by Veau–Wardill–Kilner technique (1937)

Langenbeck technique [42]. It is used for incomplete hard palate clefts (Fig. 2).

The V-Y incision provides more length of the palate than the Von Langenbeck technique, velopharyngeal insufficiency is prevented, speech function is improved and hypernasality cases are reduced [44, 43]. The Wardill–Killner modification is more traumatic than Von Langenbeck's technique due to two additional incisions connecting the lateral ones with the cleft. In a higher percentage of cases, palatal fistulas occur and maxillofacial growth is affected [43, 45, 46].

Another technique for cleft palate repair was developed by Janusz Bardach and involves the formation of two flaps separating the oral and nasal layers. This modification is applicable to small defects [48]. The Furlow technique is used in combination with the von Langenbeck palatoplasty. In 1978, Furlow offered his technique of double Z plastic. It is a Z-shaped incision with transposition of the flap, thus achieving elongation of the palate and proper repositioning of muscle fibers. This technique eliminates the need to dissect a large part of the mucoperiosteal layer which is less traumatic for patients. Other advantages are normal speech development and low risk of maxillofacial deformity [40, 47].

Since the beginning of the 20th century, in addition to surgery for cleft repair, treatment plans routinely involve multiple interventions to achieve speech improvement, a short recovery time with minimal surgical trauma, which affects maxillofacial growth. The current treatment approach is multidisciplinary and multi-stage, involving different types of specialists: surgeons, anesthesiologists, speech therapists, nutritionists, orthodontists, and postsurgical outcomes are reported for different periods of development of the individuals.

Until 1980, in Bulgaria the Limberg flap technique was used for surgical cleft repair. In addition to retroposition of the oral layer, the neurovascular bundle is moved by interlaminar osteotomy, performed at about 10 years of age. Subsequently, according to the suggestion of Kavrakirov, Yovchev, Georgiev, and Anastassov, the operation was performed at the age of 6 years using the Wardill–Kilner palatoplasty. Earlier palate surgery with the elevation of mucoperiosteal flaps affects the maxillary growth due to scarring at an early age, but a late primary palate repair has also a negative impact on speech, which may stay affected even with a long speech therapy.

From 1996 to 2010 the surgical team in the Department of Plastic, Esthetic and Reconstructive Surgery for Children, University Hospital "Sveti Georgi" in Plovdiv, used the Wardill–Kilner modification with transverse incision of the nasal layer. Since 2010, a modified uranoplasty technique is performed without lateral releasing incisions, but with the section of the nasal layer and the same muscular repair as in the modified Wardill–Kilner technique. The difference with other techniques is the transverse section of the already restored nasal layer. Bilateral hamulutomy is not always applied. The surgical correction is performed at the age of 9-12 months [2, 4]. Anastassov used his own technique with minimal incisions for clefts on the soft palate first, then for the hard palate defects, searching to determine the limit, at which the technique can be successful in the incidence of fistulas. However, the comparisons of the two modifications regarding speech outcomes, the number of reoperations, pharyngoplasties and maxillofacial growth are of major importance.

An important stage in the modified technique is the restoration of the nasal layer with the available nasal mucosa in the area of the hard and soft palate, which is precisely dissected by the muscles and bone of the palate. This allows the formation of a nasal layer in any type of cleft, without a need for a vomer flap (described by Pilcher in 1926), used by other authors. We, as well as other teams, believe that the creation of an additional wound surface, therefore scarring and retraction of the vomer and nasal airway impairment, affects the maxillofacial growth. This is followed by a transverse incision of the already restored nasal layer at the border of the hard and soft palate. This stage is the most important and distinguishes our modification from any other described

operative technique for correction of congenital cleft palate. This step allows intraoperative lengthening of the soft palate and is one of the main factors for favorable speech outcomes (Fig. 3).

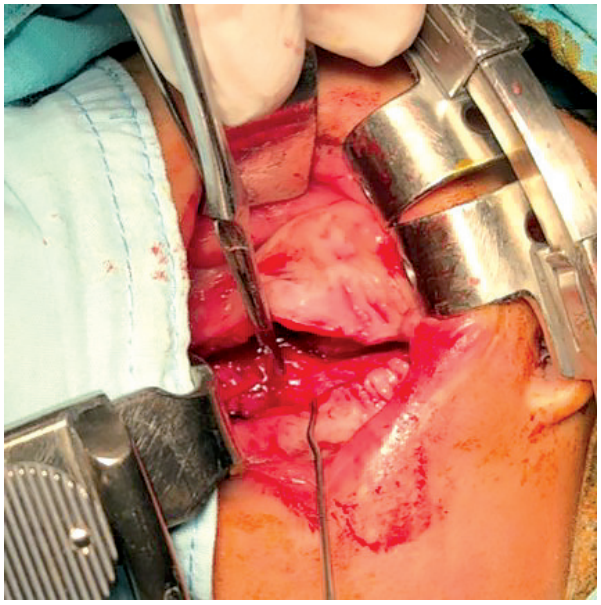

Fig. 3. Transverse incision of the restored nasal layer with lengthening and elevation of the palate.

The evaluating system of postoperative results was proposed by us. It is cited and used by other authors in their research.

In our EMRFA we are scoring the surgery procedure, the speech outcomes, the maxillofacial growth, the hearing, and the psychological outcomes. The postoperative defects are scored by anatomical areas, types, and degrees. Depending on the type and preoperative severity of the defect, the number of points is awarded. A sum of points on the scale determines five groups of postoperative results: (1) excellent, (2) very good, (3) medium, (4) bad, and (5) very bad [2]. The corresponded points to each outcome are presented in Table 2. The absence of postoperative defect brings 0 points [2]. For the palate score, the surgical preoperative severity cannot be a prognostic factor, as the minimal cleft of the palate is not correlating with the postsurgical outcomes, especially in speech. The fistula rates and the number of operations can correlate with the severity of the cleft, but the paramount principle for optimal care in facial anomalies is the follow-up of the patients through an electronic record system, which contains a wide range of data, including comprehensive care, not only the surgical outcome.

Table 2. Degrees of postoperative outcome

Groups	Lip–Nose (LRE)	Palate (PRE)	Total (ORE)
Excellent	0-1.5	0-1.5	0-2
Very good	2-3.5	2-5	2.5-6.5
Medium	4-5.5	5.5-7	7-10
Bad	6-8	7.5-8	10.5-16
Very bad	> 8.5	> 8.5	> 16.5

Acronyms: LRE = Lip-nose result evaluation; ORE = Overall cleft result evaluation; PRE = Palate result evaluation.

CONCLUSIONS

Clefts of the lips and/or palate are a significant social problem, affecting almost 1 million people in Europe and about 20,000 people in Bulgaria. There is no well-established, optimal treatment protocol (surgical technique, chronology of operations, multidisciplinary treatment) to ensure excellent results with optimal number of surgery procedures and comprehensive care. We are still witnessing cases of permanent disability, despite considerable resources and treatment efforts. Understanding and analyzing the muscle pathology of the cleft palate allowed us to change our behavior in clinical forms with a smaller cleft width so that surgery is less traumatic. We set out to study the fistula rates, reoperations, pharyngoplasty, and speech outcomes in our classic technique compared to the new one, with fewer incisions. To enable such an analysis, we created a survey methodology by introducing standardized speech and orthodontic diagnostics under international standards. This analysis could help us to measure the percentage of all clefts on the lip and/or palate, in which the less traumatic techniques are applicable. Does it lead to the same, better, or worse outcomes according to the fistulas rates, reoperations, speech results, dental and maxillofacial development? This assessment will standardize diagnostic protocols in speech therapy and orthodontics in patients with CLP and we will obtain information about the speech outcomes and dental results of patients with cleft palate operated in the last 20 years in Bulgaria.

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