ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 9| Issue: 9| September 2023|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2023: 8.224 || ISI Value: 1.188

CLEFT LIP AND PALATE, SCOPING REVIEW

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Article DOI: https://doi.org/10.36713/epra14264
DOI No: 10.36713/epra14264

ABSTRACT

Introduction: *cleft palate cleft lip is the most common congenital craniofacial defect originated by a disturbed embryonic development of the soft and hard tissues around the oral cavity, as well as the surface of the face, resulting in severe limitations in chewing, swallowing and speaking, besides sometimes generating problems of insufficient space for teeth, adequate breathing and self-esteem problems due to facial appearance.*
Objective: to detail the current information related to cleft lip and palate, description, incidence, epidemiology, etiology, embryology, clinical characteristics and surgical treatment.
Methodology: *a total of 42 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 32 bibliographies were used because the other articles were not relevant for this study. The sources of information were PubMed, Google Scholar and Cochrane; the terms used to search for information in Spanish, Portuguese and English were: cleft lip, cleft palate, cleft palate, malformations, congenital anomalies.*

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Results: the overall incidence of cleft lip and palate is about 1 in 600 to 800 live births (1.42 in 1,000) and cleft palate only occurs in about 1 in 2,000 live births. The incidence is high among Asian individuals at 0.82 - 4.04 per 1,000 live births, intermediate in Caucasians at 0.9 - 2.69 per 1,000 live births and low in Africans at 0.18 - 1.67 per 1,000 live births.

Conclusions: *Cleft lip and/or palate occur in such a strategic area of the orofacial region, at an essential time prior to birth making it a complex congenital deformity. Clefts appear in the fourth stage of embryonic development. The individual affected with orofacial cleft deformity should be treated at the right time and at the right age to obtain functional and esthetic well-being. Clefts of the lip and palate can be solitary or linked in different combinations and/or linked with other congenital deformities. The etiological factors of cleft lip and palate can be associated with genetic and non-genetic factors. Correction consists of surgically fabricating a face that does not attract attention, a vocal apparatus that achieves intelligible speech and a dentition that maintains high quality function and esthetics. To achieve success for the child born with cleft lip and palate requires coordinated collaboration by different specialties, including oral/maxillofacial surgery, plastic/reconstructive, otolaryngology, genetics/dysmorphology, speech/language pathology, orthodontics, prosthetics and others. Currently the use of autogenous bone is the most frequently used type of graft in bone regeneration defects. However, the availability of autogenous bone is limited. Robotic surgery, the use of stem cells and tissue engineering are in development and present a promising vision of the future.*

KEYWORDS: *cleft, cleft lip, cleft palate, malformation, congenital.*

INTRODUCTION

The anomalies of craniofacial bone defects involve both soft and hard tissues and can be originated by different reasons such as bone resections due to tumors or cysts, trauma, as well as congenital origin. Cleft palate-cleft lip is the most common congenital craniofacial defect originated by a disturbed embryonic development of the soft and hard tissues around the oral cavity, as well as the surface of the face, resulting in severe limitations in chewing, swallowing and speaking, also sometimes generating problems of insufficient space for teeth, proper breathing and self-esteem problems due to facial appearance(1).

Orofacial clefts, especially cleft lip (CL) and cleft palate (CP), as mentioned above, are the most common craniofacial birth defects; affected individuals initially experience difficulty swallowing food, speech, hearing and dental problems. Although the clefts can be surgically restored, individuals often undergo multiple craniofacial and dental surgeries, as well as speech and hearing therapy. Individuals become psychosocially disturbed, sometimes lifelong, because of the malformation, and have a higher incidence of mental health problems, as well as a higher mortality rate in all stages of life. Clefting is also associated with a higher risk of different types of cancer, including breast, brain and colon cancers, both in those affected by clefting and in their family members. Clefts of the lip and palate are currently showing great success in the application of modern molecular genetic techniques.

Major advances have been shown in sequencing Mendelian shapes to characterize causal variants and in performing genome-wide linkage and clustering perspectives to identify genes and regions involved in NSCL/P(2).

METHODOLOGY

A total of 42 articles were analyzed in this review, including review and original articles, as well as cases and clinical trials, of which 32 bibliographies were used because the information collected was not of sufficient importance to be included in this study. The sources of information were Cochrane, PubMed and Google Scholar; the terms used to search for information in Spanish, Portuguese and English were: cleft lip, cleft palate, cleft palate, malformations, congenital anomalies.

The choice of the bibliography exposes elements related to cleft lip and palate in addition to this factor, description, epidemiology, etiology, embryology, clinical characteristics and management and surgical treatment are presented.

DEVELOPMENT

Description

These are the most important congenital anomalies that affect the mouth and related structures. The roof is integrated by the palate and the floor by the constructions of the floor of the mouth. Laterally, it presents a boundary from the cheeks. We refer to a cleft as the congenital abnormal space or place in the upper lip, alveolus or palate, usually the colloquial term for this alteration is cleft lip, however it should be kept in mind that the use of this term may represent a degrading connotation of inferiority that can lead to a major social problem. Cleft lip and cleft palate can be defined as:

- Cleft lip can be referred to the alteration of the fusion of the frontonasal and maxillary processes, resulting in a cleft of different extension crossing the lip, the alveolus and the nasal floor; a complete cleft implies lack of connection between the alar base and the medial labial element, as well as an incomplete cleft does not extend through the nasal floor.
- The term cleft palate refers to the altered fusion of the palatal shelves of the maxillary processes resulting in a cleft of the soft and/or hard palate.

Clefts appear in the fourth stage of embryonic development. The precise site where they appear will be determined by the specific regions where the fusion of multiple facial processes did not occur; influenced by the period of embryological life in which some interference in the development was generated(3,4).

Clefts of the lip and palate can occur alone or linked in different combinations and/or linked with other congenital deformities, especially congenital heart disease. Many authors report that clefts occur due to a combination of genetic and environmental factors, in some countries, especially developed countries, CL/P

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is identified before birth through ultrasound. Early detection allows for parental education regarding the possible origins of CL/P and the procedures that the affected individual may require after birth. In countries where prenatal care is less developed, a CL/P may be unexpected, and in some regions medical answers for clefting are distrusted and instead cultural, religious answers are more accepted to explain the deformity. For example, in some regions a CL/P is thought to be the result of sins from a past life; some other beliefs include witchcraft, God's will and engaging in behavior related to causal power such as closely observing a child with a facial deformity during pregnancy(3,4).

Epidemiology

The overall incidence of cleft lip and palate is about 1 in 600 to 800 live births (1.42 in 1,000) and cleft palate only occurs in about 1 in 2,000 live births. The typical distribution of cleft types is as follows:

1) Cleft lip and palate - 45%.
2) Isolated cleft palate - 40%.
3) Cleft lip alone - 15%.

Among the potential disadvantages of this condition are social disadvantages such as breastfeeding problems and thus growth retardation, malocclusion, severe facial deformity, speech difficulty, deafness and major psychological problems. Cleft lip and/or palate occur in such a strategic area of the orofacial region at an essential time prior to birth, making it a complex congenital deformity(3,4).

Therefore, the individual affected with orofacial cleft deformity should be treated at the right time and at the right age to obtain functional and esthetic well-being. Management is complex, so it must have a multidisciplinary approach. To achieve success in the child born with cleft lip and palate requires coordinated collaboration by different specialties, including oral/maxillofacial surgery, plastic/reconstructive, otolaryngology, genetics/dysmorphology, speech/language pathology, orthodontics, prosthodontics and others. Successful reconstruction requires multiple stages of surgical intervention on an ongoing basis(3,4).

Figure 1. Examples of Nonsyndromic Cleft Lip and Cleft Palate. 1A. Bilateral Cleft Lip Alone. 1B. Unilateral Cleft Lip plus Cleft Palate. 1C. Cleft Palate Alone.

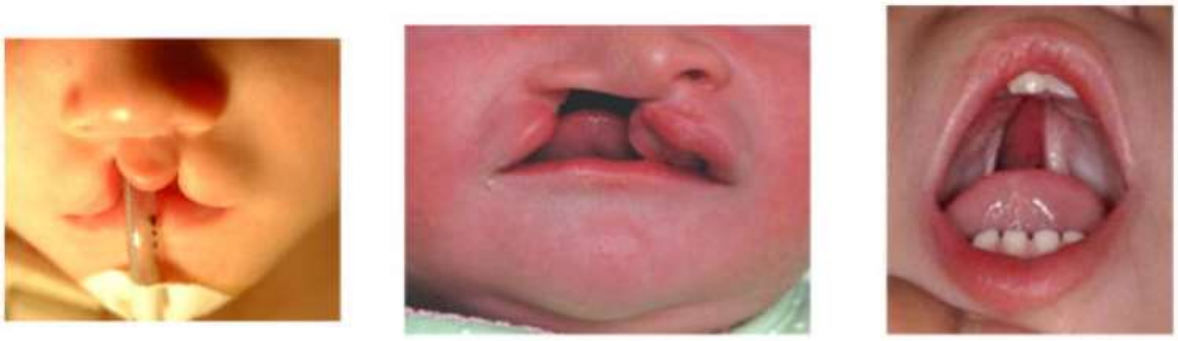

Figure 1A. Figure 1B. Figure 1C.

Source: Leslie EJ, Marazita ML. Genetics of cleft lip and cleft palate: AMERICAN JOURNAL OF MEDICAL GENETICS PART C(2).

Other bibliographies report an overall incidence of orofacial clefting of about 1.5 per 1000 live births, representing about 220,000 new cases every 12 months, with a wide variation among geographic areas, ethnic groups and the nature of the cleft itself. The incidence is high among Asian individuals at 0.82 - 4.04 per 1,000 live births, intermediate in Caucasians at 0.9 - 2.69 per 1,000 live births and low in Africans at 0.18 - 1.67 per 1,000 live births. Chinese showed 1.76 per 1000 live births, on the other hand Japanese reported 0.85 - 2.68 per 1000 live births of orofacial clefting. Solitary CL accounts for approximately 25 % of all clefts, while CL/P together makes up approximately 45 %. CL/P occurs mostly in boys relative to girls. Unilateral clefts are more frequent than bilateral clefts by a ratio of 4 to 1. Unilateral clefts occur about 70% on the left side of the face. Cleft palate is notably more noticeable in females than in males. CL/P is often related to other developmental anomalies and many of these cases are shown as part of a syndrome. Syndromic clefts make up approximately half of all cases in various reports with approximately 300 syndromes described.

All clefts are intended to show an associated familial behavior, however the percentage of cases directly linked to genetic factors is around 40%. Multiple epidemiological publications show that if one of the parents has cleft, there is a 3.2% chance of having a child with cleft lip and palate, and a 6.8% chance of having a child with cleft palate alone. Having cleft in one parent, in addition to a sibling, is linked to a 15.8% chance that the next child will have cleft lip and palate characteristics, as well as a 14.9% chance that the next child will have cleft palate only. Other literature indicates that parents of a cleft child have a 4.4 percent chance of having another child with cleft lip and palate and a 2.5 percent chance of having a child with cleft palate alone(4-6).

Embryology

Over time, the essential morphology of the face is formed through the combination of the five fundamental facial prominences. CLP

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occurs as a result of a combination and partial integration of the rectal protuberances, producing delicate and strong tissues that integrate the palate. Cleft lip occurs due to an alteration between the fourth and sixth month of pregnancy and cleft palate occurs between the sixth and twelfth month of pregnancy. In the first month of pregnancy, and the embryology of the palate is fundamental, this is the period during which human craniofacial morphogenesis is usually vulnerable to the agents that create congenital or teratogenic alterations(4).

Etiology

The etiology of cleft lip and palate is multifactorial and is thought to involve genetic influences with interactions of different environmental factors. The etiological factors of cleft lip and palate can be associated as:

Non-Genetic.

Where it is integrated to multiple environmental-teratogenic risk factors that can develop CL/P, among which we have:

Alcohol consumption : abusive consumption by the mother, in addition to causing fetal alcohol syndrome, also increases the possibility of CLP. Research showed a dose-dependent increase between 1.5 and 4.7 times. However, mild alcohol consumption showed no increase in the risk of orofacial clefts. The relationship between alcohol consumption and genotypes in the risk of CLP has not been demonstrated at this time.

Smoking: the association between maternal smoking and CLP is statistically significant, but lacks strength, with multiple studies consistently presenting a relative risk of about 1.3 to 1.5. When analyzing maternal smoking indexed to positive genetic history, a significant association was found. Other studies showed that maternal smoking and infant MSX1 genotypes acted equally to increase the risk of CLP by 7.16 times.

Other factors that could be related to the condition are:

- Maternal illness.
- Stress in pregnancy.
- Chemical exposure: fetal exposure to drugs such as retinoids can cause severe craniofacial anomalies.
- Reduced blood supply to the nasomaxillary region.
- Age: Increasing maternal and paternal age increases the risk of cleft lip with and without palate, while advanced parental age has been related only to cleft palate.

Genetic Factors

Can be divided into:

Syndromic form of cleft lip and cleft palate: here the cleft is related to another malformation. Usually with monogenic or Mendelian cause there are more than 400 known syndromes and several of them present the classic Mendelian inheritance pattern. Some of the syndromes with cleft lip and palate are listed in Table 1.

Table1. Syndromic form of cleft and palate.

Syndromes	Gene name (symbol)	Location on chromosome	Inheritance
Waardenburg syndrome, type II A	Microphtalmia associated transcription(MLTF)	3p14,1-12,3	AD
Di George syndrome	Di George syndrome chromosome region (CATCH 22)	22g11	AD
Treacher - Collins mandibulofacialdysostosis	Treacle (TCOF1)	5q32-q33,1	AD
Van der woude syndrome	Interferor regulatory factor - 6 (IRF 6)	1q32-q41	AD
CLP-Ectodermal dysplasia syndrome	Poliovirus receptor related-1(PVRL-1)	11q23,3	AD
Ectrodactyly, ectodermal dysplasia orofacial cleft syndrome	P 63	3q27	AD
Zollinger syndrome-3	Peroxisomalmembrame protein-3 (PXMP3)	8q21,1	AD
Diastrophic dysplasia	Diastrophic dysplasia sulphate transporter(DTDST)	5q32-q33,1	AD
Gorlin syndrome (Basal cell nevus syndrome)	Patched (PTCH)	9q22,3	AD

Source: Vyas T, Gupta P, Kumar S, Gupta R, Gupta T, Singh H. Cleft of lip and palate: A review. J Fam Med Prim Care(4).

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Non-syndromic form of cleft lip and palate: in this form the cleft is essentially a solitary feature and occurs in the vast majority of individuals who have cleft lip or palate in approximately 70% of cases of CL/P and 50% of all cases of CPO. So here a cleft is not a recognized pattern of malformation nor can an explanation for the disorder be known for certain. Related studies have identified several genes responsible for clefting, because a mutation in them can generate non-syndromic cleft lip and palate, as shown in Table 2(4,7-10).

Table 2. Possible genes whose mutation may result in non syndromic clefting

Name of gene	Symbol	Chromosome location
Transforming growth factor - alpha	TGFA	2p13
Transforming growth factor - 133	TGF 133	14q24
Methylene tetra - hydrofolateReductase	MTHF3	1p36,3
Blood clotting factor XIII gene	ET1	6p24
Endothelin - 1 gene	ET1	6p24
Proto-oncogene BCL3	BCL3	19q13,2
Retinoic acid receptor alpha gene	RARA	17(t15/17)
MSX-1	MSX-1	4q25

Source: Vyas T, Gupta P, Kumar S, Gupta R, Gupta T, Singh H. Cleft of lip and palate: A review. J Fam Med Prim Care(4).

Clinical Characteristics

At the moment there are not several studies evaluating the knowledge and experience of primary care physicians regarding the physical, dental and behavioral and emotional needs of an individual with cleft mouth.

Dental Problems in Cleft Lip and Palate

Natal and neonatal teeth: Several studies report that the presence of neonatal teeth does not appear to influence the primary or secondary dentition in clefts. Most of the natal teeth with clefts are located on the lateral margin of the premaxillary and maxillary segments, unlike in newborns without clefts.

Microdontia: Small teeth or microdontia are largely shown with CL/P. It tends to be more common in patients with missing lateral incisors. Peg-like upper lateral incisors are commonly seen.

Taurodontism: reported to be related to some syndromes and disorders of dental development.

Ectopic eruption: primary lateral incisors may erupt palatally adjacent to or within the cleft side, while the permanent canine on the side of the alveolar clefts may erupt palatally. Delayed eruption of the permanent incisors may be noted.

Enamel hypoplasia: occurs mostly in individuals with CL/P compared to populations without clefts, primarily in the upper central incisors.

Related Conditions

Speech difficulties: phonation dysfunction due to involvement of the levator palatinius veli muscle, as well as delayed consonant sounds (p, b, t, d, k, g) which is most common. Abnormal nasal resonance and complexity in the articulation of words are another characteristic in individuals with cleft lip and palate.

Ear infection: due to dysfunction of the tensor muscle of the palatine velum, which opens the Eustachian tube. Otitis media can be seen, if they occur repeatedly they can generate hearing loss. However, the incidence increases when there is submucous cleft palate.

Feeding problems: due to difficulty sucking on a regular nipple. A baby's ability to suck is essentially associated with 2 factors, the first is the ability of the lips to do the necessary sucking and the second the ability of the palate to allow the required agglomeration of pressure inside the mouth so that food can be propelled into the mouth. Most babies need a customized or special nipple for feeding. Infants usually learn to feed quietly with a cleft palate nipple(4,15-17).

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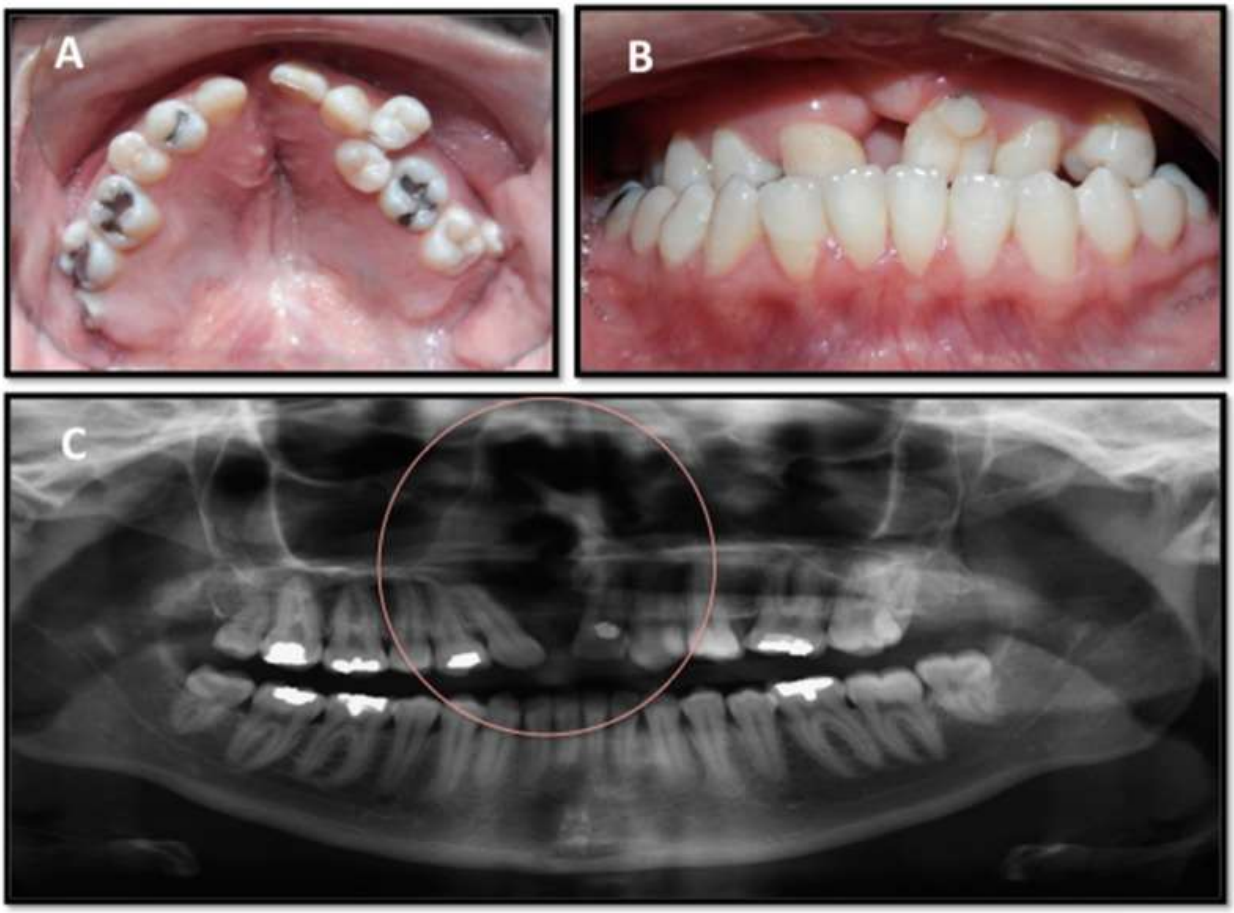
Cleft lip and palate treatment.
Correction consists of surgically fabricating a face that does not attract attention, a vocal apparatus that achieves intelligible speech, and dentition that maintains high quality function and esthetics.

The correction is to surgically fabricate a face that is inconspicuous, a vocal apparatus that achieves intelligible speech and a dentition that maintains high quality function and aesthetics. The concept of the cleft palate team has evolved from that need, as excellence in care is obtained through multiple types of clinical expertise, the team may be comprised of:
Dental specialties: pediatric dentistry, orthodontics, oral surgery and prosthodontics.
Medical specialties: pediatrics, plastic surgery, genetics, otolaryngology, and psychiatry.
Related health care fields: psychology, social work, audiology, nursing and speech pathology(4).
Several tissues, such as bone, dental organs and soft tissues of the respiratory system, are greatly altered in CL/P reconstruction, so there is a need to standardize the perioperative management of these individuals. In the reconstruction of alveolar cleft defects, the most accepted approach is secondary alveolar cleft osteoplasty in the mixed dentition phase, whose mission is to obtain a normal facial appearance, as well as the ability to feed, speak and hear without affecting the final facial shape of the affected individual. For this the most frequently accepted palatoplasty techniques currently used are the von Langenbeck technique, Veau-Wardill-Kilner closure, Bardach 2-flap palatoplasty, 2-stage palatoplasty and Furlow palatoplasty. There is variability in the best time to do the palate repair. Because transverse facial growth is not completed until 5 years of age, several surgeons have opted to delay cleft palate repair until 8 to 10 years of age, reducing the potential risk of midface hypoplasia; however, other surgeons use an earlier repair, with the goal of improving speech development and achieving greater integration into society, as well as decreasing the psychosocial impact on both the affected individuals and their families. Using an intermediate option, there are those who obtain cleft palate repair in 2 steps, with soft palate repair between three and six months and hard palate repair between 15 and 18 months, as well as those who opt for a single-step repair, simultaneously repairing the soft and hard palate(1,18-20).

Figure 2. Deformation of the arch and dental crowding (A), crossbite dental malposition (B), and the deviated nasal septum (C) as revealed by panoramic radiographs showing the maxillary defect (circle).



Source: Martín-del-Campo M, Rosales-Ibañez R, Rojo L. Biomaterials for Cleft Lip and Palate Regeneration(1).

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Surgery

Contrary to the artistic nature needed for cleft lip repair, cleft palate repair should be more functional in its approach, as well as maintain good teamwork, which reduces morbidity and secondary deformities caused by the cleft and focuses especially on speech quality. Soft palate repair techniques can be used separately on their own or in conjunction with other hard palate procedures, and some variant of an intravelar veloplasty is frequently performed in place of a two-flap palatoplasty with an opposing double z-plasty to obtain a repositioning of the levator muscle. Maxillary distraction is increasingly used for the correction of severe maxillary retrusion in individuals with cleft lip and palate. The literature suggests that children with cleft lip and palate with nasoalveolar molding (NAM) benefit from the special treatment requirements of the team approach. Published studies on NAM present evidence of benefits to the individual, caregivers, surgeon and society, such as documented decrease in the severity of the cleft deformity prior to surgery and consequently better surgical outcomes, as well as less burden on caregivers. Robotic cleft surgery is a new area, which offers several advantages, but the use of surgical robots currently presents economic challenges for its implementation due to the longer surgical time and high costs, although this will probably not be a drawback in the future(4,21-25).

Currently the use of autogenous bone is the most frequently used type of graft in bone regeneration defects. However, the availability of autogenous bone is limited and not without major drawbacks. Thus, it may not be the ideal graft for alveolar bone reconstruction. The method is often invasive and can generate significant morbidities at the donor site, such as paresthesia, postoperative pain, infection and healing problems.tissue engineering strategies offer the possibility of using individualized artificial carriers for tissues and cells with the mission of applying them to the affected site to promote the regeneration of missing or lost tissues(1,26-28).

Current bioartificial tissues designed for cleft palate reconstruction are essentially based on isolated inserted granules with a single layer of tissue; however, the alveolar cleft defect traditionally constitutes a 2-walled bony defect in which mucoperiosteal flaps are sutured in 2 layers to form a new nasal floor and a continuous oral mucosa. Therefore, the free movement of the inserted granules adversely affects the dimensional stability and biomechanical qualities of the reconstructed sites, conflict with the adequate closure of these mucoperiosteal flaps and retraction of microorganisms that could infect the graft(1,29-31).

Adult stem cells are considered a cornerstone in cell therapy because of their remarkable ability to self-renew and differentiate into different phenotypes, as well as to be derived from different tissues. They have been used for the regeneration of craniofacial defects in tissue engineering. Adipocyte stem cells (ADSCs) are especially desirable candidates for musculoskeletal tissue engineering applications, such as cleft lip and palate. Biomaterials have a unique role in tissue engineering for reconstruction of missing tissue in addition to their function. Advances in bone regeneration by means of 3D biomimetic scaffolds made of polymers, bioceramics and composites, using various fabrication strategies such as 3D printing, cryopolymerization, synthesis, and others allow us to delve into new alternatives for tissue restoration in CL/P treatment(1,29).

Finally, regarding the impact of cleft lip and palate repair on maxillofacial growth and development, several bibliographies show that early palatoplasty leads to inhibition of maxillary growth in all dimensions; furthermore, secondary alveolar bone grafting had no influence on sagittal maxillary increment. Cleft lip repair inhibited the sagittal length of the maxilla in individuals with cleft lip and palate. We can also say that some authors evidenced that Veau's retrograde palatoplasty and Langenbeck's palatoplasty with relaxing incisions became more detrimental to growth and Furlow's palatoplasty resulted with less detrimental effect on maxillary growth(32).

CONCLUSIONS

Cleft lip and/or palate occur in such a strategic area of the orofacial region, at an essential time prior to birth making it a complex congenital deformity. Clefts appear in the fourth stage of embryonic development. The individual affected with orofacial cleft deformity should be treated at the right time and at the right age to obtain functional and esthetic well-being. Clefts of the lip and palate can be solitary or linked in different combinations and/or linked with other congenital deformities. The etiological factors of cleft lip and palate can be associated with genetic and non-genetic factors. Correction consists of surgically fabricating a face that does not attract attention, a vocal apparatus that achieves intelligible speech and a dentition that maintains high quality function and esthetics. To achieve success for the child born with cleft lip and palate requires coordinated collaboration by different specialties, including oral/maxillofacial surgery, plastic/reconstructive, otolaryngology, genetics/dysmorphology, speech/language pathology, orthodontics, prosthetics and others. Currently the use of autogenous bone is the most frequently used type of graft in bone regeneration defects. However, the availability of autogenous bone is limited. Robotic surgery, the use of stem cells and tissue engineering are in development and present a promising vision of the future.

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ISSN (Online): 2455-3662
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Conflict of Interest Statement

The authors report no conflicts of interest.

Funding

The authors report no funding by any organization or company.