22q11.2 Deletion: Surgical and Speech Outcomes of Patients With Velopharyngeal Insufficiency Treated With a Superiorly Based Pharyngeal Flap as the Primary Surgery

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Abstract: The most frequent palate diagnoses in patients with chromosome 22q11.2 deletion syndrome are a classic submucous cleft, occult, and velopharyngeal insufficiency without cleft, which generates alterations in speech that require surgery. Surgical protocols are controversial owing to syndrome characteristics that make their handling more complex. Pharyngeal flap pharyngoplasty is effective for this type of patient. The objective of this study is to examine the surgical management of velopharyngeal insufficiency in patients with chromosome 22 deletion, using a pharyngeal flap as the primary surgery. The clinical records of patients with chromosome 22 deletion and velopharyngeal insufficiency between 2015 and 2017 were analyzed retrospectively. Eight patients underwent pharyngeal flap pharyngoplasty as a primary surgery, including 1 with velopharyngeal insufficiency without a cleft, 1 with a classic submucous cleft, and 6 with occult submucous cleft. The pre- and postoperative protocol performed by speech therapists and surgeons included clinical evaluation of the oral cavity; perceptual, video recording, and nasometry speech evaluation; and videonasopharyngoscopy. All perceptual parameters and nasometry results significantly changed. Of the cases, 88% achieved a flap with the expected width and height and complete closure of the velopharyngeal sphincter. One patient required flap revision. Four of the 8 patients achieved normal resonance, and 2 of 8 showed mild hypernasality. Using the pharyngeal flap pharyngoplasty as a primary technique to correct velopharyngeal insufficiency in patients with chromosome 22 deletion provides satisfactory outcomes and decreases the number of surgeries. Preoperative planning must be conducted carefully and needs to be individualized to be successful.

Key Words: 22 Deletion, pharyngeal flap, submucous cleft, velopharyngeal insufficiency

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22q11 deletion syndrome (22qDS) is one of the most frequent chromosome deletions and has been greatly associated with velopharyngeal dysfunction with or without cleft palate.[1,2] In fact, within the syndromes associated with fissure is the one with the worst velopharyngeal mechanism.[3] Its incidence is estimated to be between 1:2000 and 1:7000 live births.[4] The phenotypic expression of this deletion is highly variable, but palate and nasopharynx expressions have their own characteristics, which have been well defined: small adenoids, hyperplastic tonsils, platybasia, medialization of the carotid arteries, hypotonia, and abnormal pharyngeal muscles.[2,5,6] The most common diagnoses associated with the palate are classic submucous cleft palate (SMCP), occult SMCP (hypoplasia of the muscle of the uvula), and velopharyngeal insufficiency (VPI) without cleft.[5] In total, 8.1% of patients with a cleft palate present the deletion.[7]

The 22qDS often have late diagnoses, mostly determined in early childhood,[8] often because of an unclear or poor visible palatine anatomic defect, the absence of associated cardiopathies, and because health professionals are unaware of the phenotype.[5]

The VPI is the inability of the velopharyngeal sphincter to close completely during the production of speech sounds, generating hypernasal resonance, nasal emission, and compensatory articulations (CAs).[9,10] Between 32% and 74% of patients with 22qDS present with VPI,[11–13] which must be treated surgically.

The above characteristics, combined with learning and behavioral difficulties, complicate the management of speech difficulties in patients with 22qDS.[9,14]

The surgical protocol in this population is controversial. Some teams perform veloplasty or palatoplasty (Furlow or Sommerland) as a primary intervention of the palate, according to the standard treatment for a cleft palate,[1,3,15–19] often with poor postoperative outcomes and a high probability of requirement of further surgery to obtain acceptable velopharyngeal function.[15,17] Other teams propose an algorithm consisting of performing palatoplasty or pharyngoplasty according to individual characteristics such as gap size or palatal mobility,[17,20] or a palatopharyngoplasty, both surgeries performed in the same intervention.[21,22] But in general only good results are obtained when pharyngoplasty is included as a primary or secondary surgery. A last group concludes that the best option is

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to correct the VPI through pharyngoplasty,[1,16,23] considering a different anatomical alteration from that in patients with a cleft palate with VPI without 22qDS,[9,14] usually with a large gap of the velopharyngeal sphincter and severe VPI.[24]

Bois et al in 2017 suggest that pharyngoplasty should be the gold standard for the treatment of severe VPI in patients with velocariofacial syndrome.[25] Regarding the type of pharyngoplasty, Ysunza et al in 2009 concluded that individualized pharyngeal flaps seem to be the best option to restore velopharyngeal function in patients with VPI with 22qDS.[23] Similarly, Arneja in 2008 and Filip in 2013, indicated that superior-based pharyngeal flaps generated significant speech improvement in 8 and 12 patients, respectively, with 22qDS and VPI.[16,26] Their unusual anatomy and function of the velopharyngeal mechanism make them ideal candidates for the superiorly based pharyngeal flap.[26] Moreover, Swanson et al in 2011 included 33 patients in a study and concluded that an adapted pharyngeal flap is highly effective for the correction of VPI in patient with the velocardiofacial syndrome, with few complications.[1] In 2012, a systematic review carried out by Spruijt et al concluded that in a heterogeneous group of patients with 22qDS and VPI, a grade C recommendation can be made to minimize the morbidity associated with an additional surgery when pharyngoplasty is directly chosen instead of palatoplasty alone.[24]

On the basis of the available evidence, in January 2015, the medical team of the Gantz Foundation in Santiago de Chile decided to perform pharyngeal flap pharyngoplasty as a primary surgery for patients with classic or occult SMCP with VPI and VPI without cleft palate with 22qDS, analyzing anatomical and functional conditions individually.

There are some previous studies that evaluated the surgical results of direct handling with a pharyngeal flap to treat VPI in patients diagnosed with 22qDS and SMCP, occult SMCP or VPI without cleft. Rottgers et al in 2011 use pharyngeal flap in 4 children with velocariofacial syndrome, SMCP, and "akinetic palate" obtaining 100% success.[17] Currently in The Children's Hospital of Philadelphia primary pharyngoplasty is performed in cases of SVCF with SMCP and severe VPI because, under his experience of 35 years, Furlow is fruitless.[3] But this institution has not yet carried out a formal study. Further, Rouillon in 2009, used a superior pedicle velopharyngoplasty in 8 22q11 patients with severe VPI but without cleft palate or SMCP, with excellent results.[27]

The objective of this study is to examine the surgical management of VPI in patients with 22qDS, using pharyngeal flap pharyngoplasty without having previously performed primary palatoplasty.

METHODS

This retrospective study conducted a review of the clinical records of patients with 22qDS and VPI, who underwent pharyngeal flap surgery as a primary indication to correct VPI between January 2015 and July 2017. All patients were diagnosed using fluorescence in situ hybridization and/or multiplex litigation-dependent probe amplification. The sample included 8 patients, 2 girls and 6 boys. Their clinical characteristics are shown in Table 1.

Chromosome 22 deletion has a diagnostic average age of 4 years, with an age range from newborn to 11 years. Four patients were diagnosed immediately following birth due to cardiopathy observations, and the other 4 patients were diagnosed during their school years. Palate diagnoses were performed by a plastic surgeon using videopharyngoscopy. One patient presented VPI without a cleft, 1 patient with classic SMCP, and 6 with occult SMCP. One patient (case 1) had tonsillectomy. In the other 7 patients, the size of the tonsils did not involve surgical contraindication.

TABLE 1. Consecutive Clinical Characteristics of the Study Patients

Patient	Sex	Diagnostic Age of the 22qDS (y)	Surgical Age	Palate Diagnosis
1	M	6	9	VPI without cleft palate
2	M	NB	6	Occult SMCP
3	M	11	17	Occult SMCP
4	M	NB	6	SMCP
5	M	NB	4	Occult SMCP
6	F	11	12	Occult SMCP
7	F	5	6	Occult SMCP
8	M	NB	14	Occult SMCP

F, female; M, male; NB, newborn; SMCP, submucous cleft palate; VPI, velopharyngeal insufficiency.

The average surgical age was 9 years 3 months, with an age range of 4 to 17 years (Table 1).

This review was approved by the Ethics Committee of the Gantz Foundation.

Pre- and Postsurgical Evaluation Procedures

The clinical and instrumental evaluation protocol performed by speech therapists and surgeons was examined before and 6 months post-VPI surgery of each patient. This included: oral cavity clinical evaluation (veil of palate, uvula, and palpation of the final portion of the hard palate, size of the tonsils), evaluation and video recording of speech and presence and type of CA, nasometry (nasalence percentage obtained by 2 automatic repetitions of the 1–10 numerical series) registered in all patients (Nasometer II Model 6450 equipment; KayPENTAX, Montvale, NJ) and videonasopharyngoscopy evaluation (Fig. 1).

Presurgical speech clinical evaluation was performed by a speech therapist with more than 15 years of experience in treating patients with cleft palates. The speech sample included high pressure phonemes in syllables, words, and automatic speech.

Perceptual clinical analysis was performed with the following parameters:

1. Resonance: Normal = 0 (N); Hyponasality = 0 (H); Hypernasality: Mild = 1; Moderate = 2; Severe = 3.
2. Nasal emission: Absent = 0; Mild = 1; Moderate = 2; Severe = 3.
3. Low intraoral pressure: Adequate = 0; Mild = 1; Moderate = 2; Severe = 3.
4. Compensatory articulation: Present = Yes/No
   - Type: Glottal Stop (GS) = Consistent (C GS); Inconsistent (I GS);

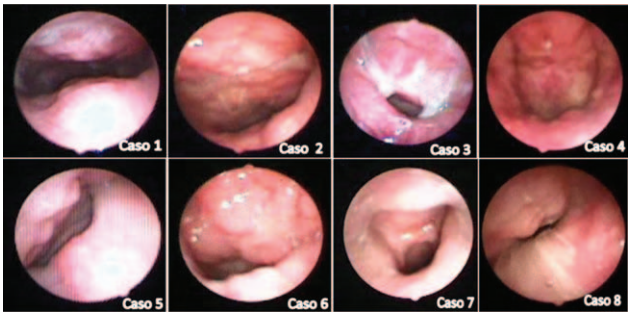

FIGURE 1. Nasopharyngoscopic images of the velopharyngeal sphincter during phonation of the patients in the study.

TABLE 2. Data on Surgical Indication and Preoperative Nasopharyngoscopy Findings

Patient	Velopharyngeal Closure Pattern and Characteristics of the VM	LPWM (%)	VM (%)	GAP (%)	Pulsations	Surgical Indication	CAT NV
1	Coronal, asymmetrical veil, without central notch	10	70	40	Not observed	Wide flap	No relevant findings
2	Coronal, symmetric concave veil, little central notch	10	30	60	Very mild central pulsations	Wide flap	No relevant findings
3	Circular, veil slightly asymmetric, without central cleft	30	50	30	Not observed	Medium flap	No relevant findings
4	Coronal, symmetric concave veil, clear central notch	10	30	70	Not observed	Wide flap	No relevant findings
5	Coronal, symmetric veil, without central notch	10	60	40	Not observed	Wide flap	No relevant findings
6	Coronal, asymmetrical veil, no protrusion of the uvular muscle	10	50	60	Pulsations to the right	Wide flap lateralized to right	Medialization of right carotid artery
7	Circular with slight Passavant's ridge, symmetric concave veil	20	30	50	Intense pulsations to the right and left	Medium flap	Medialization of right carotid artery
8	Coronal, symmetric veil, no protrusion of the uvular muscle	10	80	20	Not observed	Wide flap	No relevant findings

CAT NV, computerized axial tomography of neck vessels; GAP, hiatus or defect in the velopharyngeal sphincter during speech; LPWM, lateral pharyngeal walls movement; VM, velar movement.

- Pharyngeal Fricative (PF) = Consistent (C PF); Inconsistent (I PF);
- Laryngeal Fricative (LF) = Consistent (C LF); Inconsistent (I LF);
- Other_____ = Consistent; Inconsistent

5. Intelligibility: Not affected = 0; Mildly affected = 1; Moderately affected = 2; Severely affected = 3.

Videonasofibroscopy performed with a pediatric nasopharyngoscopy (model FNL-7RP3, diameter 2.4 mm; Pentax, Tokyo, Japan) revealed the velar movement (VM) and pharyngeal wall percentage, as well as the gap location and percentage. It also described the presence and location of beats in the posterior pharyngeal wall (PPW). This result was complemented by a neck vessel computed tomography (CT) to determine the width of the flap. These data are described in Table 2.

The width or cross-sectional dimension of the flap was determined based on the movement of the lateral pharyngeal walls (LPWs) and was proportional to the length of the PPW:

- Narrow flap: with 40% or more LPW movement, using 30% of the PPW cross-sectional length
- Medium flap: with 20% to 30% LPW movement, using 50% of the PPW cross-sectional length
- Width flap: with 20% or less LPW movement, using 90% of the PPW cross-sectional length

The height was defined in relation to the maximum extent of displacement of the soft palate observed in the videonasopharyngoscopy.

A flap review was conducted in patient 1, as this was under the closing level.

The size of the gap ranged from 20% to 70%. For the patient with a 20% gap (case 8), the width flap due to the coronal pattern, poor LPW movement, and the gap that increased during spontaneous speech were indicated. A medium flap was scheduled for patient 7 due to the proximity of the carotid arteries. The velum of patient 4, presenting classic SMCP, was repaired in the same surgery, prior to the flap.

Surgical Technique

The flaps were designated by the same surgeon, who used the superior pharyngeal flap technique and de-epithelized the mucosa on the distal third of the flap, where the posterior edge of the velum was excised and the end of the flap was located. The de-epidermization of the distal end of the flap was carried out to optimize the junction of its muscular portion with the velum muscle (see Fig. 2), calibrate the lateral hiatuses with a probe, and to place sutures in 3 planes with absorbable polyglycolic acid suture 4-0.

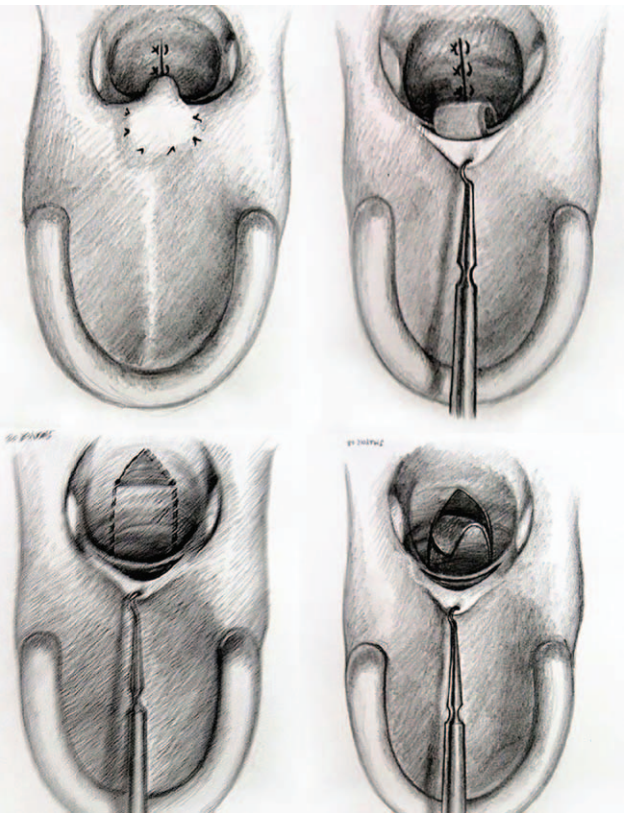

FIGURE 2. Outline of the Hogan's pharyngeal flap, with a de-epidermizated distal end.[28]

After the surgery, all patients were hospitalized for 24 hours, after which they were discharge.

Complications

Data associated with symptoms of obstructive sleep apnea (OSA) related to the surgery: snoring, breath-holding, daytime sleepiness, and fatigue, obtained in consultation with the parents of the patients. This information was analyzed during the presurgical evaluation.

Surgical protocol operative complications and clinical record were reviewed.

Statistical Analysis

The Wilcoxon signed-rank test was used for statistical analysis: Minitab 18 Macro was used to compare pre- and postsurgical perceptual evaluation parameters, as well as nasalance. Confidence interval (CI) was used for median differences, considering significant differences when 95% CI does not contain 0.

RESULTS

The surgery in 88% of the patients (7 of 8) achieved the indicated width and height. In patient 1, the flap was under the closure level, and the patient was referred for additional surgery to correct the height.

In Table 3, the data obtained during the pre- and postsurgical perceptual evaluation and nasalance can be observed.

As shown in Table 4, there were significant changes in all patients; it is found that the CI did not pass through 0 for any sample parameter, with 95% certainty.

Six months after surgery, 4 of the 8 patients achieved normal resonance in perceptual evaluation, 2 presented hyponasality, and 2 presented mild hypernasality. All succeeded in the absence of nasal emission and adequate intraoral pressure when they articulated sounds correctly.

After surgery, patients with CA began to use high-pressure phonemes more consistently. In patients without CA, postsurgical speech therapy was not necessary.

Table 5 shows changes in CA type 6 months after surgery.

There were no complications regarding surgical technique in any patient.

Seven of 8 patients had no symptoms compatible with OSA 6 months postsurgically. Patient 1 was the only patient with a snoring problem postoperatively.

TABLE 3. Pre- and Postoperative Nasalence and Perceptual Evaluation Data

	Resonance		Audible Nasal Emission		Weak Pressure Consonants		Intelligibility		Nasometer: 1–10	
No Patients	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	3	1	1	0	2	0	3	2	75	37
2	2	0 (N)	2	0	2	0	3	1	54	47
3	1	0 (N)	2	0	1	0	1	0	54	54
4	2	0 (H)	2	0	2	0	2	0	70	37
5	2	0 (N)	2	0	1	0	1	0	59	18
6	2	1	2	0	2	0	3	2	46	41
7	2	0 (N)	2	0	2	0	3	1	49	19
8	2	0 (H)	2	0	1	0	1	0	35	21

H, hyponasal; N, normal; Post, postoperative result; Pre, preoperative result.

TABLE 4. Nonparametric Test Results for Paired Samples Confidence Index for Medians Difference

Pre- and Postanalysis Surgical	N	Median	CI for η	Confidence Achieved
Resonance	8	2	(1, 5; 2)	94.13%
Nasal emission	8	2	(1, 5; 2)	94.13%
Low intraoral pressure	8	1.5	(1; 2)	94.13%
Intelligibility	8	1.5	(1; 2)	94.13%
Nasalence	8	21	(6; 35.5)	94.13%

N, data number; n, median difference.

DISCUSSION

The 22q11.2 deletion syndrome is the most common chromosome microdeletion in humans.[29] However, late diagnoses prevails, especially when no important cardiopathy presentations are found.[8,30] In our case, half of the patients had a 22qDS diagnosis in their school years, delaying surgical indication to correct VPI to an average age of 9 years and 3 months. Unfortunately, at this age, children have entered the school system, and their social skills may be affected by their nasal voice and unintelligibility. Patients admitted to our institution at an older age were derived from their school site, and the ones admitted early suffered from cardiopathy. The average surgical age at our research center is similar to that at others.[24,27]

Although 22qDS is associated with anatomophysiologic characteristics, typical in the palate and pharynx, a detailed evaluation of each patient must be considered to define special features. This sample included patients with VPI without cleft, and classic and occult SMCP. The palate diagnosis, indicating appropriate palate or pharyngeal flap repair, must be considered as the first step in the management of VPI.[4,20]

Veloplasty or Furlow's techniques performed by experienced surgeons have excellent results for the management of VPI in patients with nonsyndromic SMCP,[31,32] as they correct the symptoms efficiently. However, the results in patients with 22qDS are poor, even in the presence of good palate mobility,[17,20] and especially in patients with severe VPI,[9,23] where the improvement degree does not resolve the social stigma caused by a nasally voice.

Another type of procedure used to treat VPI in patients with SVCF is autologous fat grafting, having the benefit of being less invasive than pharyngoplasty, but good results are obtained only in cases with mild VPI.[33] This option could also be useful in case of

TABLE 5. Pre- and Postsurgical Compensatory Articulation Data

	CA Type	
Patient	Pre	Post
1	IGS, IFP	IGS
2	CGS	NO
3	NO	NO
4	CGS	NO
5	NO	NO
6	CGS	IGS
7	CGS, CFP	IGS, IFP
8	NO	NO

CA, compensatory articulation; CFP, consistent fricative pharyngeal; CGS, consistent glottal stop; IFP, inconsistent fricative pharyngeal; IGS, inconsistent glottal stop.

aberrant carotids arteries, but the same author points out that it should be considered only if pharyngoplasty is not feasible.[25]

This study is retrospective, so the sensitivity of detection is limited in relation to OSA. The symptoms were known based on what was expressed by the parents in at the time of postsurgical evaluation. In our study, no patient with OSA was detected compared to 2 other studies that used pharyngoplasty as a primary surgery.[17,27] In both studies, individual characteristics of the patients were taken in consideration to perform the surgical treatment. Future studies analyzing the impact of individual characteristics in patients to make a surgical decision and the incidence of OSA after surgery needed to be done.

Regarding the performance of primary palate surgery in patients with 22qDS, classical palate cleft diagnosed at birth is not discussed. By contrast, a patient with occult SMCP, VPI without cleft or even classic SMCP, frequently have a late diagnosis.[8] Therefore, VPI treatment must be conducted efficiently to achieve integration into the school system without a nasally voice.

Commonly, patients with 22qDS suffer from severe VPI and speech disorders, affecting intelligibility.[31] The work published by Jiramongkolchai et al in 2016 concluded that it is less likely to have good results in patients with severe presurgical hypernasality than in those with moderate hypernasality.[10] In our sample, 6 patients suffered from moderate hypernasality; 1, severe; and 1, mild, according to the preoperative evaluation. The results were positive for all moderate cases. The patient in case 1 with severe hypernasality required flap revision.

Regarding the presence of CA, 5 patients who had preoperative CA experienced modified CA 6 months postoperatively, from CA to without CA or consistent to inconsistent CA. All of them remained under speech therapy, which is necessary to eliminate CA and to learn how to use the new anatomy appropriately.[21] The therapy improved all cases, since the flap helped to increase the intraoral pressure. The 8 patients improved intelligibility by 1 or 2 points, according to the perceptual evaluation scale.

Sphincter or Hynes pharyngoplasty is also suggested for the management of cases with moderate and/or severe VPI.[24] Losken et al demonstrated that this technique was safe and efficient for patients with 22qDS, but the number of surgical revisions was significantly higher in patients without deletion.[34] Significant improvements are observed in components such as hypernasality, nasal emission, and intelligibility, but normal voice is not achieved.[18,20] There is imaging and historical evidence that argues that the superior constrictor muscle is thinner in patients with chromosome 22 deletions,[35] which could affect the efficiency of a technique who need a good VM.[26] The proximity of the carotid arteries may also be a risk factor for this technique.

In 2012, Spruijt et al performed a systematic review of the most effective surgical treatments to correct VPI in 22qDS. Twenty-seven articles were selected that analyzed resonance, intelligibility, and the need for additional surgeries. The best results for perceptual parameters and intelligibility were found in patients who underwent the pharyngeal flap procedure. In addition, they also required fewer surgery review and additional surgeries.[24]

As a secondary surgery, in 2002, Tatum et al reported that 90% of VPI corrections were successful when using the pharyngeal flap.[36] In 2007, Chegar et al noted that pharyngeal flap is the most effective technique for the treatment of patients with VPI not requiring a prior veloplasty in cases with a submucous cleft and chromosome 22 deletions.[37]

As a primary surgery, Rottgers et al used pharyngeal flap as a primary surgery in 4 children with SVCF, SMCP, and ''akinetic palate'' obtaining 100% success.[17] Rouillon et al used a superior pedicle velopharyngoplasty in 11 22q11 patients with IVF but without cleft palate with 91% of excellent results (normal/inconsistent) and 9% of mild IVF.[27] This is comparable to our results, as this type of technique was successful in 88% of the patients and only 1 patient required revision.

As mentioned earlier, the velopharyngeal anatomy of patients with chromosome 22 deletion includes: hypotonia, platybasia or base of skull flattening with basal angle increase,[2,38] more obtuse and voluminous airway, wider velopharyngeal space, and a shorter, harder palate.[39] Park et al also described that the levator veli palatini muscle is thinner compared to that in patients with nonsyndromic SMCP. In addition, they noted asymmetry in the left and right levator muscles.[4]

As reported by Chegar et al in 2006,[40] and in our series, 4 patients presented asymmetry in the elevation of the velum during speech.

However, the lateralized flap was indicated only in patient 6, who presented greater velar asymmetry and a clearer lateralized gap. This allowed for complete closure of the velopharyngeal sphincter during speech, since the flap was planned according to the anatomic defect.

Our group of patients received individualized surgical management, considering: LPW movement, VM (considering symmetry/asymmetry), defect size, and position of the carotid arteries (determined in neck vessels CT). None of the patients, informed through CT of the neck vessels, were suspended for presenting medialized carotid arteries. In case of unilateral aberrant carotid artery, an asymmetric pharyngoplasty is an option to consider.[22] In our case, the width of the flap in patient 7 was modified without affecting the results.

Arneja et al mentions that to performing a successful pharyngeal flap requires precise height and great firmness, otherwise, dehiscence or an insufficient velopharyngeal closure may occur.[26] This generates the need to continue in the search of multiple variants of the technique to find the perfect fit. With regard to the surgical technique of the pharyngeal flap procedure performed in this institution, there were no cases of dehiscence. Apparently, introducing the flap in the muscular pocket made in the velum reduced the loss of the flap. To assess this clinical observation, a larger group of patients and comparison with the traditional technique performed in a control group are required.

CONCLUSION

Pharyngeal flap pharyngoplasty as a primary technique to correct VPI in patients with 22qDS must be performed carefully and individually to be successful. It is suggested that the cleft type, patient age, speech characteristics, previous surgeries, tonsils size to reduce the risk of obstructive apnea, location of the carotid arteries, symmetry of the VM during speech, movement of the lateral walls, and gap size be evaluated before the procedure.

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