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Evaluation of vertical ramus osteotomy for the surgical correction of unilateral mandibular posterior vertical insufficiency: Long-term follow-up results

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ABSTRACT

Purpose: Unilateral posterior vertical insufficiency (PVI) is a growth defect of the mandibular condyle that results in a facial asymmetry. Various surgical procedures can be used to elongate the hypoplastic ramus. The aim of this study was to evaluate long-term aesthetic and architectural outcomes of vertical ramus osteotomy (VRO) in patients with unilateral PVI.
Materials and methods: Patients operated on with unilateral VRO were included in this retrospective study. Aesthetic and architectural parameters were evaluated on frontal photographs as well as on frontal and lateral cephalograms preoperatively, postoperatively, at 1-year and at the end of the follow-up.
Results: A total of 48 patients were analyzed. The aesthetic assessment revealed significant correction of the chin deviation (CD) and of the lip commissural line tilt after VRO ($p1 = 0.0038$ and $p2 = 0.0067$, respectively) with stable results. The architectural analysis revealed significant improvement in the maxillary and mandibular occlusal planes, as well as the chin deviation ($p < 0.0001$). A tendency to relapse was noted for the mandibular canting and the CD during the follow-up. VRO allowed for a mean mandibular lengthening of 8.39 mm (ranging from 2.5 to 14 mm).
Conclusion: VRO allows for immediate restoration of the symmetry of the lower third of the face in patients with unilateral PVI. A revisional procedure may be needed due to a tendency for the chin deviation to relapse.

1. Introduction

Unilateral posterior vertical insufficiency (PVI) of the mandible is due to defective growth of the condyle unit, leading to aesthetic, architectural, and functional alterations. Several etiologies are responsible for this anomaly, dominated by congenital condyle hypoplasia, hemifacial microsomia (HFM), and post-traumatic injury (Mercier et al., 1989). Unilateral PVI is characterized by shortening of the mandibular ramus, thereby causing asymmetry of the lower third of the face. The commissural line is often elevated, while the chin becomes misaligned on the affected side. Elevation of the maxillary occlusal cant is observed, as well as dental class II

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malocclusion on the affected side. When associated with facial syndromes, various facial abnormalities can occur, such as auricular malformation and soft tissue hypoplasia in HFM, cleft lip and/or palate.

Treatment of PVI requires a multidisciplinary approach. An early orthopedic phase can boost condyle growth, but a surgical approach is often necessary to restore facial symmetry (Stoustrup et al., 2013; Leonardi and Barbato, 2007). The surgical therapeutic options differ according to the temporo-mandibular joint (TMJ) function. In the case of an altered or absent TMJ, a costochondral graft (CCG) allows the condyle and ramus to be reconstructed while mandibular growth is promoted (Bertin et al., 2017; Birgfeld and Heike, 2019; Yang et al., 2015). In case of conserved TMJ function, the ramus reconstruction differs according to the center, and can be managed by distraction osteogenesis (DO) or orthognathic ramus elongation procedures. Vertical ramus osteotomy (VRO) aims to restore the ramus length and allow for mandibular advancement to correct a Class II malocclusion, with no alteration of the TMJ function.

To our knowledge, there is no comprehensive study in the literature about the results obtained with the VRO technique. The purpose of this study was to retrospectively evaluate long-term aesthetic, architectural and functional results of VRO for treatment of unilateral mandibular PVI.

2. Materials And Methods

2.1. Data collection

Patients treated by unilateral VRO in the Maxillofacial Surgery and Stomatology Department of the Nantes University Hospital, France, between 1983 and 2017 were included in the study and analyzed retrospectively. The patients' charts were reviewed, and data regarding the date of birth, the affected side (right vs. left), the etiology of the PVI, the dates and types of operations, and additional procedures were compiled. Information regarding TMJ function and potential surgical complications was also collected. In this retrospective study, no change to the current clinical practice or randomization was performed. Approval from an ethics committee was not required in order to use these data in the epidemiologic study, as per French legislation article L. 1121-1 paragraph 1 and R1121-2 of the Public Health Code.

2.2. Surgical protocol

Correction of the PVI was achieved using a VRO according to the Caldwell–Letterman technique (Caldwell and Letterman, 1954). The procedure was performed under general anesthesia with nasotracheal intubation. An extra-oral approach was performed by a low submandibular incision. In most of the cases, it was associated with an intraoral incision for muscular detachment and coronoidectomy. The ramus was sectioned vertically from the sigmoid incisura to the preangular notch, backward the inferior alveolar pedicle and nerve. The ramus could be elongated while the functional mandibular condyle remained in the same location. Osteosynthesis was performed with a 0.8- or 1-mm-thick L-shaped miniplate. A posterior open bite was created on the affected side, and an interocclusal splint was positioned and progressively reduced in length to promote secondary maxillary teeth egression. In some cases, the VRO was associated with other conventional orthognathic procedures such as a Le Fort I osteotomy (LFI), a contralateral sagittal split osteotomy (SSO), and/or a genioplasty. An orthodontic preparation was usually needed, and the postoperative intermaxillary elastic fixation lasted 6 weeks.

2.3. Clinical evaluation

Frontal standardized photographs were analyzed preoperatively, immediately postoperatively, at 1 year postoperatively, and at the end of the follow-up. To assess the chin deviation, the angle α between the facial median line and a line from the glabella to the chin was measured. The angle β of the tilted lip commissure plane was measured using a parallel to pupillary line (Fig. 1) (Bertin et al., 2017; Mouallem et al., 2017). A scar evaluation was performed on the last follow-up photographs by 12 maxillofacial surgeons and non-medical staff members (nurses, administrative assistant) using a visual analog scale that ranged from 0 to 10 (with 0 representing an unsightly scar and 10 corresponding to an invisible scar).

2.4. Radiographic evaluation

Cephalometric analysis was performed on frontal and lateral cephalograms preoperatively, immediately postoperatively, at 1-year postoperatively, and at the last follow-up.

Two reference lines were used for the frontal analysis: the supraorbital line joining the tops of the orbital roofs and a perpendicular line, passing through the crista galli, representing the median facial line. SO was defined as the distance between the supraorbital line and the most prominent cuspid of the second maxillary molar or the occlusal point on the non-affected side. SM was defined as the distance between the supraorbital line and the most prominent cuspid of the second mandibular molar or the occlusal point on the non-affected side. The reference lines in the affected side were designed as SO' and SM'. The SO'/SO ratio was used to assess the maxillary canting of the occlusal plane, while the SM'/SM ratio was used to assess the mandibular occlusal plane tilting in a frontal view. The chin deviation (CD) was defined as the distance between the projection point of the axis of the lower incisors on symphysis and the median facial line (Fig. 1).

For the lateral analysis, the reference line used was the C1 line defined in Delaire's analysis as the line joining the metanasion (M) to the clinoid fossa (Cl). The distance from C1 to the distal cuspid of the last mandibular molar in occlusion (Hmand) allowed the lengthening of the mandibular ramus to be determined and followed postoperatively (Fig. 1).

2.5. Secondary endpoints

The surgical complications were compiled, and they were deemed to be severe if they required the procedure to be stopped or a new intervention (e.g., infection, pseudarthrosis). The other complications were classified as minor (e.g., temporary lip hypoesthesia, facial nerve paresis). The TMJ function was investigated, when possible, in terms of temporomandibular disorders (TMD) (pain, joint cracking, articular locks) and articular amplitudes.

2.6. Statistical analysis

The methodical error of the cephalometric and facial measurements was assessed by Dahlberg's formula (mean square error $[SE^2] = d^2/2n$), where d is the difference between the first and the second measurements, and n is the number of double measurements (Kamoen et al., 2001). To determine the intra-observer error, cephalometric lengths and facial angles were measured twice by the same investigator at 4-week intervals in 10 randomly selected patients.

The statistical analysis was performed using GraphPad Prism 5.0 software for Mac (GraphPad Software, La Jolla, CA, USA). Quantitative data were analyzed using a paired t-test when there were more than 30 replicate values and a Wilcoxon test when there were fewer than 30 paired observations. A Mann–Whitney comparison

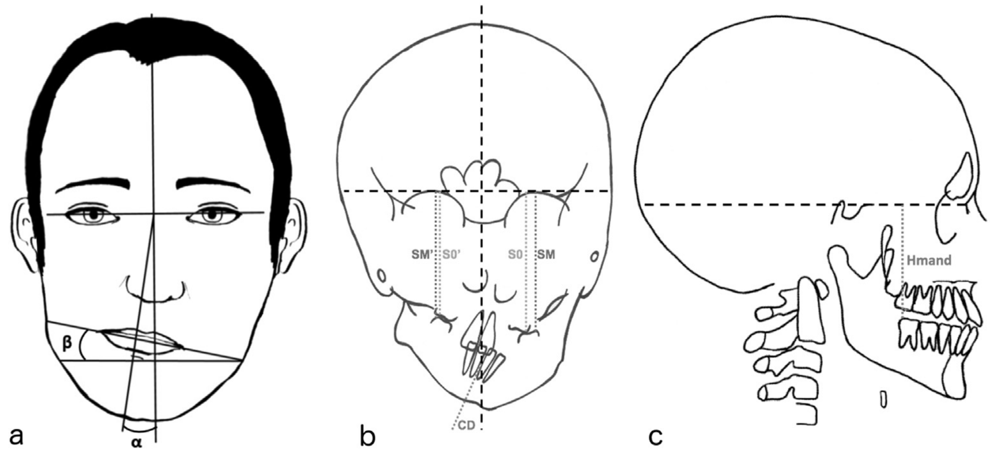

Fig. 1. (a) Clinical evaluation of the facial soft tissues. Angle α: Chin deviation. Angle β: Bi-commissural line tilt. Cephalometric analysis on frontal (b) and lateral (c) X-rays. SO: Distance between the supraorbital line and the maxillary molar occlusal point on the unaffected side. SM: Distance between the supraorbital line and the mandibular molar occlusal point on the unaffected side. SO' and SM': Distance SO and SM on the affected side. CD: Distance between the projection point of the axis of the lower central incisors on symphysis and the medial facial line. Hmand: Distance between C1 and the mandibular occlusal point on the affected side.

test for non-paired observations was used to compare the postoperative results in subgroup analyses. A p-value of less than 0.05 was taken to indicate statistical significance.

3. Results

3.1. Epidemiological data

A total of 52 patients were operated on with a unilateral VRO in our department during the inclusion period. Four patients were excluded due to a lack of medical records.

For the remaining 48 patients, there was a female predominance (32 vs. 16, $p = 0.002$). The left side was affected more often than the right side (28 vs. 20, $p = 0.15$). The mean age at the time of the mandibular surgery was 21.2 ± 10.3 years (7.6–44.3), and the mean follow-up duration was 73.8 ± 60.6 months (Table 1).

In terms of the etiologies (Table 2), we observed a predominance of isolated unilateral PVI represented by congenital condyle hypoplasia, post-traumatic injury, TMJ ankylosis, or condylo-mandibulo-dysplasia. Associated facial malformations were mainly represented by HFM and clefts.

3.2. Surgical protocol

All of the patients underwent a VRO to correct a unilateral posterior-vertical insufficiency. The mean increase in the mandibular ramus, reflected by the Hmand, was 8.39 ± 3.12 mm (2.5–14). A trend of recurrence was observed at 1 year (loss of 2.80 ± 2.58 mm; $p < 0.0001$), with stable results at the last follow-up. The tendency to recur did not correlate with the extent of the lengthening.

In more than half of the patients, a contralateral SSO was associated with the procedure for mandibular derotation and/or advancement. Half of the cases were associated with an LFI osteotomy (23 patients, 4 of whom were less than 18 years of age, where an LF1 was warranted in order to realign the inter-incisor maxillary point and/or to raise the maxillary on the non-affected side) and genioplasty. All of the associated procedures are listed in Table 3. The mean duration of inter-maxillary fixation (IMF) was 1.7 months, and an interocclusal splint was worn for a mean duration of 3.1 months.

A secondary orthognathic procedure was performed in 6 patients, consisting of a genioplasty (5 cases), a contralateral SSO (3 cases), a second VRO (1 case), a homolateral SSO (1 case), and an LF1 osteotomy (1 case). The second intervention was performed on average 25.3 ± 18.9 months (3.1–50.6) after the first procedure, at a mean age of 20.8 ± 10.4 years.

3.3. Aesthetic results

The mean Dahlberg standard errors for the alpha and the beta measurements were 0.19 ± 0.22° (0–0.5°) and 0.21 ± 0.37° (0–2°), respectively.

The VRO allowed for immediate and significant improvement in the chin deflection and correction of the lip commissural line tilting (Fig. 2), reflected by α and β angles, respectively. The angle α was corrected after the mandibular procedure, from 3.88 ± 2.76° preoperatively to 0.37 ± 1.58° postoperatively; $p = 0.0038$. The angle β was corrected from 4.12 ± 2.29° preoperatively to 2.41 ± 1.86° postoperatively, $p = 0.0067$. The surgical results remained stable over time in terms of bicommissural line tilting, whereas a non-significant trend of relapse was noted at 1 year for the angle α (Fig. 3).

Evaluation of the cervical scar was carried out on 19 lateral photographs at the last follow-up visit. The mean aesthetic score was 8.1 ± 1.5 (3–10), for a mean evaluation time of 4.7 ± 3.9 (1–12.7) years after the surgery.

3.4. Architectural results

The mean Dahlberg standard error for the distance measurements was $2.57.10^{-4}$ ($0\text{-}2.22.10^{-3}$) for the SO'/SO ratio, and $1.78.10^{-4}$ ($0\text{-}9.45.10^{-4}$) for the SM'/SM ratio. The mean error for the distance measurement (CD, Hmand) was 0.64 mm (0–2).

The maxillary occlusal canting reflected by the SO'/SO ratio was significantly improved postoperatively, with a progressive horizontalization over time due to spontaneous egression of the maxillary teeth (0.93 ± 0.03 preoperatively, 0.97 ± 0.04 postoperatively, 0.99 ± 0.03 at 1 year; $p < 0.0001$), and stable results at the last follow-up (0.99 ± 0.03; $p = 0.29$) (Fig. 4). When an associated LF1 osteotomy was performed, the maxillary canting was immediately restored (0.93 ± 0.04 preoperatively vs. 1.00 ± 0.03 postoperatively; $p = 0.0001$), with stable results (Fig. 5). No difference in the maxillary occlusal canting was observed preoperatively and at the last follow-up between the patients who received a concomitant LF1 osteotomy and those who did not.

Fig. 2. Aesthetic results. A young patient exhibiting a right PVI corresponding to congenital condyle hypoplasia, who underwent a VRO and a contralateral SSO at the age of 11 years (top, case no. 1). Frontal photographs preoperatively (a), 3 months postoperatively (b), 1 year postoperatively (c), and 5 years postoperatively (d). A patient exhibiting a left condyle hypoplasia, who underwent a one-stage surgical procedure at the age of 16 years with a left VRO, contralateral SSO, and genioplasty (bottom, case no. 2). Frontal photograph preoperatively (e), 6 months postoperatively (f), 1 year postoperatively (g), and 5 years postoperatively (h).

The frontal mandibular occlusal canting reflected by the SM'/SM ratio was significantly improved and overcorrected after VRO (0.93 ± 0.03 preoperatively vs. 1.01 ± 0.02 postoperatively; $p < 0.0001$), with a slight trend of recurrence of the mandibular asymmetry at 1 year and at the last follow-up (0.99 ± 0.03 and 0.98 ± 0.04, respectively; $p_1 = 0.03$ and $p_2 = 0.01$).

The chin deviation was corrected after VRO (9.74 ± 5.30 mm preoperatively vs. 0.44 ± 4.41 mm postoperatively; $p < 0.0001$). A trend of relapse was noted at 1 year, with stable results at the last follow-up (2.23 ± 4.25 mm and 2.50 ± 5.01 mm; $p_1 = 0.01$ and $p_2 = 0.46$, respectively) (Fig. 5).

3.5. Secondary endpoints

Four severe complications were reported, one of which required the surgical procedure to be stopped due to significant bleeding from a maxillary artery. Three patients needed another procedure (one case of infection, one bad split, and one late pseudarthrosis), with good outcomes.

Ten patients had hypoesthesia in the area of the inferior alveolar nerve, with total recovery in the year following the procedure for 9 patients, and one case of definitive hypoesthesia. Normal sensitivity was noted 6 months after the procedure for the others. Temporary facial paresis with complete recovery 6 months after the surgery was reported in four cases. The other related complications were: intense bleeding controlled with vascular clips in one case, a postoperative infection that was resolved with antibiotic therapy, a case comprising limited opening of the mouth, and condylar resorption.

The TMJ function was known for 12 patients at the end of the follow-up. Six patients exhibited TMJ disorders, four with cracking of the joint, four who were in pain, and two who had joint locking.

Table 1
Patient characteristics.

Patient characteristics	
Gender: female/male, n	32/16 (p = 0.002)
Affected side: left/right, n	28/20 (p = 0.153)
Isolated, associated facial malformations, n	33/15
Age at the time of the surgical procedure (years), mean ± SD (range)	21.2 ± 10.3 (7.6–44.3)
Follow-up duration (months), mean ± S.D. (range)	73.8 ± 60.6 (1.4–255.6)

n, Number of patients; SD, standard deviation.

Table 2
Etiologies of the PVI and associated craniofacial anomalies.

Etiologies and associated craniofacial abnormalities	N = 48
Congenital condyle hypoplasia, n	24
Hemifacial microsomia (types I and IIA), n	9
Post-traumatic injury, n	5
Associated cleft (lip/palate), n	3
Condylo-mandibulo-dysplasia, n	2
Temporomandibular joint ankylosis, n	2
Asymmetric Treacher–Collins syndrome, n	1
Asymmetric Russel–Silver syndrome, n	1
Unilateral Saerthre–Chotzen syndrome, n	1

n, Number of patients; N, total number of patients.

Table 3
Additional associated osteotomies.

Associated orthognathic procedures	
Contralateral SSO, n	26
Le Fort I osteotomy, n	23
Genioplasty, n	24

n, Number of patients; SSO, sagittal split osteotomy.

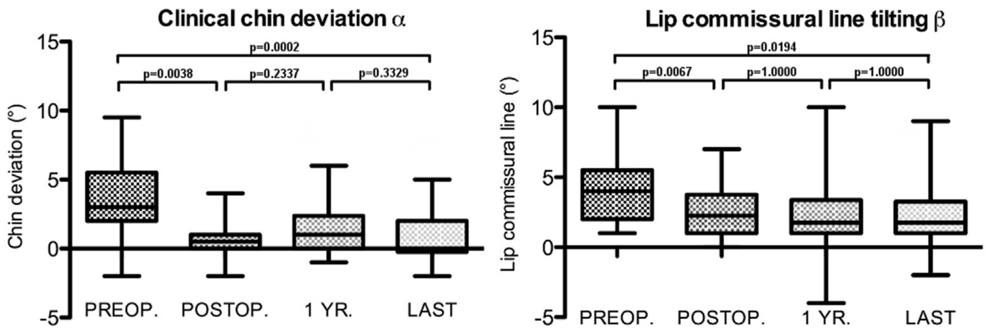

Fig. 3. Variation in the chin deviation and the lip commissural line tilt preoperatively (PREOP.), postoperatively (POSTOP.), at 1 year (1 YR.) postoperatively, and at the last follow-up (LAST) in the patients receiving a unilateral VRO.

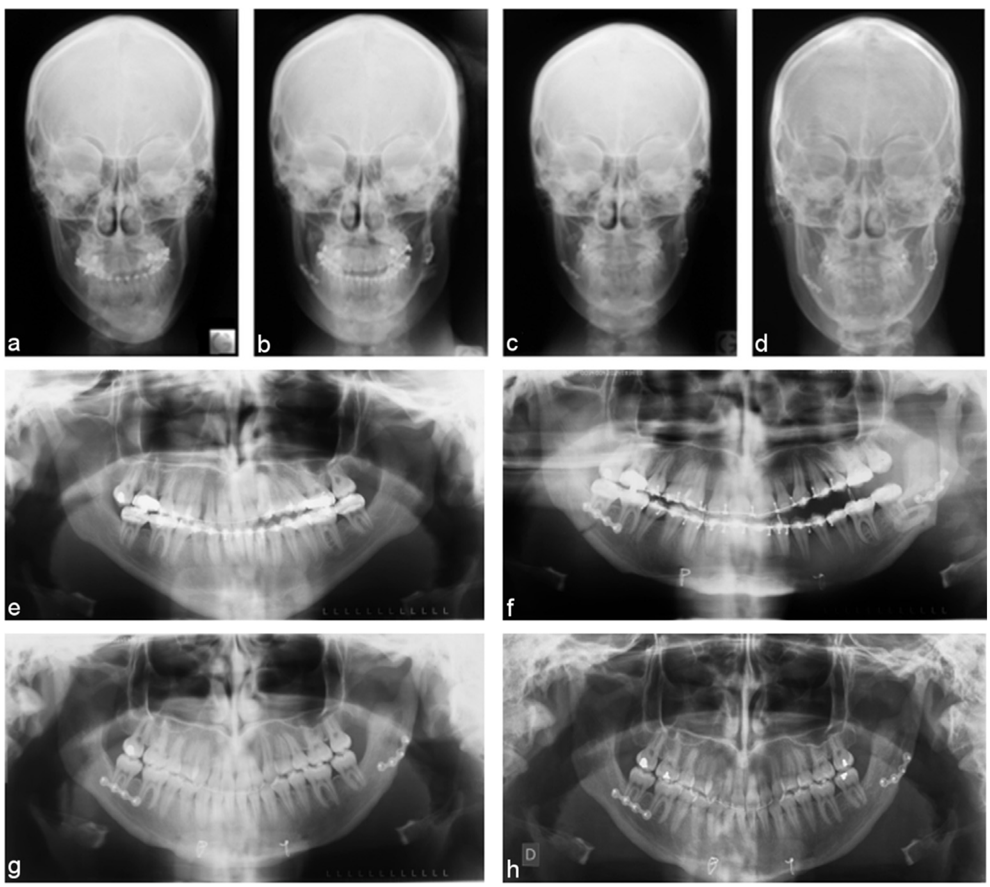

Fig. 4. Architectural results. Case patient who underwent a left VRO, contralateral SSO, and genioplasty. Frontal cephalograms and panoramic x-rays preoperatively (a, e), 3 months postoperatively (b, f), 1 year postoperatively (c, g), and 5 years postoperatively (d, h). Note the spontaneous closure of the left open-bite.

4. Discussion

Based on analysis of the literature, the posterior vertical dimension is less studied than the anterior vertical height. PVI correlates with a growth defect of the condyle unit. It can be acquired (Chouinard et al., 2018), such as after a condyle fracture (Mercier et al., 2000), TMJ ankylosis, or juvenile idiopathic arthritis (El Assar de la Fuente et al., 2016). The other cause is congenital condyle hypoplasia, isolated or associated with a craniofacial malformation such as HFM (Mercier et al., 1989). The treatment of PVI can be challenging both for orthodontists and for maxillofacial surgeons. Surgical treatment aims to achieve facial symmetry and normal occlusion, as well as functional and aesthetic outcomes after completion of growth. CCG remains the gold standard for replacement of the TMJ in HFM Prusansky–Kaban types IIB and III (Birgfeld and Heike, 2019), in case of TMJ ankylosis, or degenerative joint disease (Bertin et al., 2017; Pluijmers et al., 2014; Al-Moraissi et al., 2015). It allows for restoration of normal function and substantial growth potential in children (Birgfeld and Heike, 2019; Castellon et al., 2017). When the TMJ function and anatomy are preserved, a ramus osteotomy is more suitable to provide facial symmetry (Mercier et al., 1989). The VRO technique was first described by Caldwell and Letterman in order to set back the mandibular ramus for the

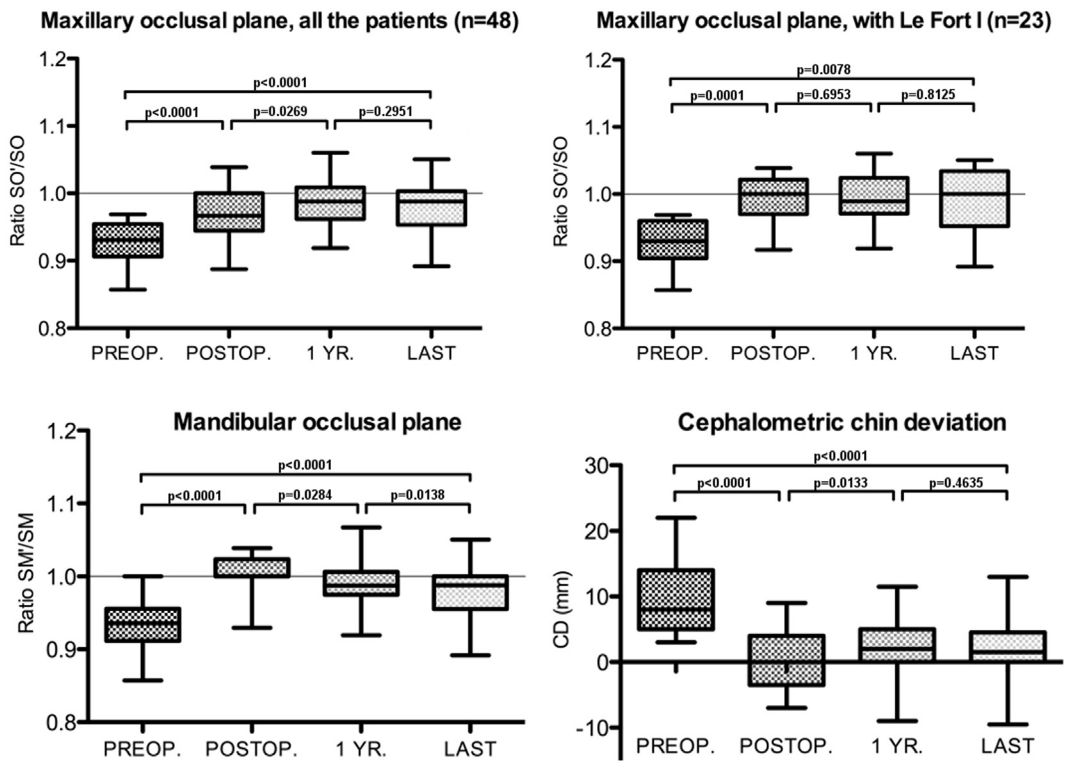

Fig. 5. Variation of the maxillary occlusal plane preoperatively (PREOP.), postoperatively (POSTOP.), at 1 year postoperatively (1 YR.), and at the last follow-up (LAST) in all of the patients and in the patients with LF1. Variation of the mandibular occlusal plane and the cephalometric chin deviation preoperatively (PREOP.), postoperatively (POSTOP.), at 1 year postoperatively (1 YR.), and at the last follow-up (LAST).

correction of prognathism (Caldwell and Letterman, 1954). Most of the literature about the procedure is related to the treatment of Class III malocclusions of mandibular origin (Ghali and Sikes, 2000; Iwanaga et al., 2017). In our practice, we have been using the VRO technique for many years to correct unilateral and bilateral PVI with a normal TMJ.

We reported the aesthetic and the architectural results obtained with VRO in a series of 48 patients. Most of the patients exhibited an isolated unilateral PVI of congenital or acquired origin, whereas one-third of the patients exhibited an associated craniofacial abnormality, mainly types I and IIA HFM. The procedure was made available to pediatric patients once they reached 7 years of age, because it does not interfere with mandibular growth, as well as to the adult population. VRO provided immediate restoration of the symmetry of the lower third of the face, evidenced by photographic and cephalometric analyses. A trend of relapse was noted at 1 year postoperatively in terms of the mandibular canting and the chin deviation, with stable results thereafter with a mean follow-up duration of 6 years after the procedure. These outcomes are consistent with those obtained by Bertin et al. in 15 patients treated by VRO for a type IIA HFM (Bertin et al., 2017). A revisional procedure may be needed after several years, mainly for chin repositioning, which is an issue that patients need to be made aware of. The procedure allowed for significant ramus lengthening, ranging from 2.5 to 14 mm without using a bone graft, with a 33% loss of height at 1 year after the procedure, and stable results at the last follow-up. Nevertheless, this measurement does not represent the actual bone lengthening, which is more substantial but difficult to assess due to the remodeling of the mandibular angle. Partial relapse did not correlate with the degree of lengthening, and it can be explained by the action of the masticatory muscles, the potential condyle resorption, or it can be due to the soft tissue hypoplasia in patients with HFM (Ferri et al., 2008). This loss is clinically barely discernible and corresponds to overcorrection of the lengthening and the effect of relapse. In our practice, we perform a large soft tissue detachment with sectioning of the pterygomasseteric muscular strap, as well as a superior coronoidectomy, to retain the ramus height and to minimize recurrence of the PVI. Furthermore, a hypercorrection of the mandibular lengthening is performed to prevent potential relapse. For greater stability, a notch can be made on the posterior side of the distal fragment to lock the ramus proximal fragment, as described by Mehnert (Mercier et al., 1989). One-stage correction of the maxillary occlusal canting was obtained either by a concomitant Le Fort I osteotomy (half cases) or by the spontaneous dentoalveolar adaptation of the maxillary bone in response to the generated open bite. This highlights the importance of the progressive shortening of the occlusal splint and release of the maxillary molars from the orthodontic arch to guide the vertical movement of the maxilla. These results remained stable over time.

Use of an external approach can represent a limitation in terms of the scar and the potential for nerve damage in the area of the facial nerve. In our experience, all of the patients recovered from facial paresis, and the cervical scarring was satisfactory at the last follow-up according to the 12 evaluators. An intraoral strategy is used by various teams to prevent any cutaneous or nerve damage (Ghali and Sikes, 2000; Choi et al., 2016; Greaney et al., 2015; Grimaud et al., 2017).

Other orthognathic procedures have been described to lengthen the mandibular ramus. An L-inverted osteotomy can yield good results but requires bone grafting, thereby resulting in donor site morbidity (Medeiros and Ritto, 2009). Ferri et al. described how it is possible to achieve mandibular lengthening with a conventional Epker-modified-Wolford osteotomy after complete sectioning of the pterygomasseteric sling, thereby avoiding extraoral procedures

(Ferri et al., 2008). Grimaud et al. proposed a different type of intraoral osteotomy that allows for lowering of the mandibular angle and lengthening of the ramus without a coronoidectomy (Grimaud et al., 2017). Due to the paucity of long-term data with these procedures, it is not known whether stable outcomes are achieved over time. Other teams prefer to perform a DO for ramus elongation, particularly in case of PVI with a normal TMJ associated with HFM (i.e., type I and IIA). DO has the advantage of an intraoral device and minimally invasive surgery, as well as the concomitant expansion of the surrounding soft tissues (Meazzini et al., 2012; McCarthy et al., 2001; Molina, 2001). However, long-term relapse is frequently described, thus requiring further procedures.

To assess the efficacy of VRO, we used standardized photographic and posteroanterior cephalograms for more reliability with the measurement of distances. The mandibular lengthening was evaluated by the variation of the distance between a reference cranial line C1 and the cuspid of the last mandibular molar in occlusion. While other authors prefer the use of the Gonion point to evaluate ramus elongation (Ferri et al., 2008), we consider this point to be variable due to remodeling of the mandibular angle after ramus elongation. The SO'/SO and SM'/SM ratios, reflecting the frontal maxillary and mandibular canting, respectively, were used to eliminate the variability between radiographs. A three-dimensional analysis would be more relevant to assess the cephalometric changes and could be part of further studies. Furthermore, a double measurement of the clinical and radiographic parameters by two examiners would have provided our results with a greater degree of reliability.

The patients included in this work were heterogeneous in terms of the cause of the PVI, making it difficult to draw conclusions regarding the impact of soft tissue hypoplasia (observed in HFM) in partial relapse of the deformity. Moreover, this study focused on PVI cases with preserved TMJ function, excluding the most severe cases of shortened mandibular ramus. Further studies are needed to compare VRO to DO in unilateral PVI, and the analysis has to be extended to bilateral cases of PVI.

5. Conclusion

The Caldwell–Letterman VRO technique belongs to the therapeutic arsenal for lengthening of the mandibular ramus. It allows for immediate restoration of the symmetry of the lower third of the face in patients with unilateral PVI. A revisional procedure may be needed after several years due to a tendency for the chin deviation to relapse.

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Author contributions

All the authors mentioned in this manuscript contributed to the work reported, have read and approved the final version of this manuscript, and agree to be accountable for all aspects of work ensuring integrity and accuracy. The authors contributed as follows: Conceptualization, M.A., J.M., P.C., and H.B.; Methodology, M.A. and H.B.; Acquisition/Investigation, M.A., S.L., S.M., and H.B.; Writing: Original Draft Preparation, M.A., and H.B.; Writing: Review and Editing, JP.P., JM.S., T.D., P.C., and H.B.

Declaration of Competing Interest

None.

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