MARPE—Miniscrew-Assisted Rapid Palatal Expander in young adults: Intermolar width, transverse width of the nasal cavity, complications, and other results. A systematic review

MARPE, Miniscrew Assisted Rapid Palatal Expander, en pacientes adultos jóvenes: Ancho transversal intermolar, ancho transversal de cavidad nasal, complicaciones y otros resultados informados. Revisión sistemática

MARPE, Miniscrew Assisted Rapid Palatal Expander, em pacientes adultos jovens: largura intermolar, largura transversa da cavidade nasal, complicações e outros resultados informados. Revisão sistemática

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Abstract

Objective: To describe the results obtained with MARPE in young adults regarding intermolar width, the transverse width of the nasal cavity, complications, and other results.

Method: We conducted a literature review following Prisma guidelines in Pubmed, SCIELO, Science Direct, Scopus, the System for Information on Grey Literature in Europe, Latin American and Caribbean literature in Health Sciences, and Google Academic. We also conducted a manual search of books and scientific papers. The full articles were analyzed, and nine articles were selected after applying the inclusion and exclusion criteria.

Results: The literature indicates that MARPE increases transverse intermolar width and the transverse width of the nasal cavity. The periodontal and dentoalveolar complications reported are inconclusive. Conclusion: MARPE could be a clinically viable and effective treatment for young adults with transverse maxillary deficiency.

Keywords: maxillary expansion, young adults, palatal expansion technique.

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Resumen

Objetivo: Describir los resultados obtenidos con MARPE en pacientes adultos jóvenes en relación al ancho transversal intermolar, ancho transversal de cavidad nasal, complicaciones y otros resultados informados.

Método: Se realizó un análisis siguiendo la guía Prisma, utilizando bases de datos Pubmed, SCIELO, Science Direct, Scopus, Sistema de información sobre literatura gris en Europa, Literatura Latinoamericana y del Caribe en Ciencias de la Salud, Google Académico, además de una búsqueda manual de libros y artículos científicos. Aplicando los criterios de inclusión y exclusión se analizaron 9 estudios.

Resultados: MARPE aumenta el ancho transversal intermolar y el ancho de la cavidad nasal en pacientes adultos jóvenes. Las complicaciones periodontales y dentoalveolares registradas no son concluyentes. Conclusión: MARPE puede ser un tratamiento clínicamente viable y efectivo para pacientes adultos jóvenes que presenten deficiencia transversal maxilar.

Palabras clave: Expansión maxilar, adulto joven y técnica de expansión palatina.

Introduction and backround

Transverse maxillary deficiency is one of the most frequent skeletal anomalies of the dental arches, regardless of the type of dentition. It can often be accompanied by posterior crossbite and dental crowding.⁽¹⁻²⁾ It is a progressive condition that tends to increase in young people and may be permanent in adults.⁽¹⁾ It has been reported that 9.4% of the population and about 30% of adult orthodontic patients have a transverse maxillary deficiency and a posterior crossbite.⁽³⁻⁴⁾

Multiple etiologic factors have been described for transverse maxillary deficiency. Some causes include developmental disorders such as cleft lip and palate, mouth breathing, and habits such

Resumo

Objetivo: Descrever os resultados obtidos com o MARPE em pacientes adultos jovens em relação à largura intermolares transversais, largura transversa da cavidade nasal, complicações e outros resultados relatados. Método: Foi realizada uma análise segundo o guia Prisma, nas bases de dados Pubmed, SCIELO, Science Direct, Scopus, Sistema de Informação sobre Literatura Cinza na Europa, Literatura Latino-americana e Caribenha em Ciências da Saúde, Google Acadêmico, além da busca manual de livros e artigos científicos. Aplicando os critérios de inclusão e exclusão, 9 estudos foram analisados.

Resultados: MARPE aumenta a largura intermolar transversal e a largura da cavidade nasal em pacientes adultos jovens. As complicações periodontais e dentoalveolares registradas não são conclusivas. Conclusão: MARPE pode ser um tratamento clinicamente viável e eficaz para pacientes adultos jovens com deficiência transversa da maxila.

Palavras-chave: Expansão maxilar, adulto jovem e técnica de expansão palatina.

as thumb sucking and atypical swallowing. Poor tongue posture, perioral muscle imbalance, and a lack of lip seal, along with labial hypotonicity, may also contribute to maxillary constriction.⁽⁵⁾ It is well documented that correcting transverse maxillary deficiency facilitates other orthodontic/orthopedic mechanics and improves facial and dental esthetics, oral function, nasal mucociliary clearance, and nasal breathing. Therefore, there has been ongoing research to improve treatment modalities for transverse maxillary deficiency and decrease the associated adverse side effects.⁽⁵⁾

Conventional rapid palatal expansion (RPE) has proven to be a reliable treatment method to correct transverse skeletal jaw disharmony in prepubertal patients.⁽⁵⁾ However, in adult patients, the technique has been considered impossible or rarely successful because the mid-palatal suture and adjacent joints begin to fuse and become stiffer in late adolescence.⁽⁶⁾ In particular, the bony palate and the zygomatic buttress show greater resistance to expansion.^(4,7) In adults, it has little or no skeletal effect.⁽⁵⁾ Detrimental dentoalveolar and periodontal effects have been described,⁽²⁻⁴⁾ such as thinning of the buccal alveolar bone plate,⁽⁴⁾ pain, tissue inflammation, unstable results, buccal tipping of crowns, gingival recession, root resorption, and ulcerations.^(6,8)

Surgically assisted rapid palatal expansion (SAR-PE) is a treatment of choice for transverse maxillary deficiency in young adults.⁽³⁻⁴⁾ However, due to the low adherence to complex surgical treatments and the increasing demand for non-surgical treatments,^(4,6,8) the miniscrew-assisted rapid palatal expander (MARPE) is introduced.^(3,8) It is a miniscrew-assisted rapid palatal expansion technique that can be used in young adults to open the midpalatal suture,^(4,8) correct transverse maxillary deficiency in adults,⁽⁵⁾ and maximize the orthopedic separation of the maxilla and overcome the disadvantages of tooth-borne and tooth-and-tissue-borne appliances.^(3,5)

MARPE is a simple modification of RPE technique. Its main difference is the use of miniscrews⁽⁴⁾ anchored to the palate⁽⁵⁾ to ensure the expansion of the basal bone and maintain the separation between the bony structures during the consolidation period.⁽⁴⁾ Most MARPE appliances are tooth-bone-borne,^(2,4,6-7,9) although some are only bone-borne.^(1,3,5,8)

Miniscrews can distribute the stress across the palate, decreasing the stress concentration around the abutment tooth.⁽⁶⁾ However, the information available regarding this novel technique's skeletal, dentoalveolar, and periodontal effects is limited.⁽⁵⁾

To date, most studies have focused on the effectiveness of maxillary expansion in prepubertal patients^{.(5)} This review describes the results obtained with MARPE in young adults regarding intermolar width, the transverse width of the nasal cavity, complications, and other results.

Materials and methods

Search strategy. We conducted a literature review following Prisma guidelines in Pubmed (2010–2021), SCIELO (2010–2021), Science Direct (2010–2021), Scopus (2010–2021), the System for Information on Grey Literature in Europe, Latin American and Caribbean literature on Health Sciences, and Google Academic. We also conducted a manual search of books and scientific papers.

Search terms. The following keywords were used for the search: "maxillary expansion," "young adult," and "palatal expansion technique" related to the boolean operator AND. The DeCs terms used were "maxillary expansion," "young adult," and "palatal expansion technique."

Inclusion/exclusion criteria. The following filters were applied: articles in English, Spanish, and Portuguese published from 2010 to 2021, case reports, clinical trials, cross-sectional studies, systematic reviews, editorials, and clinical guidelines available in full text. Posters, letters to the editor, expert comments, and partial texts were not considered. The last search was conducted on 24 April 2021. The articles included had to mention MARPE and include any of the variables evaluated: transverse intermolar width, the transverse width of the nasal cavity, complications, and other results. All of the above were evaluated in patients with transverse maxillary deficiency aged 18 to 25. The papers including the following exclusion criteria were not considered: patients with systemic disease, craniofacial syndrome, or dentofacial anomalies (cleft lip, cleft palate, or both). Studies where patients had undergone orthopedic, orthodontic, or surgical treatment before MARPE were also excluded.

Selection process. The articles were selected

independently by two reviewers. The titles were selected, and non-relevant publications were removed. The filters of each database were used by selecting the "search by date," "search for clinical trials," and "search for articles" options. The degree of reviewer Kappa concordance was 0.96 for article selection. The disagreements between the reviewers were solved with additional discussion.

Data collection. The following variables were searched for in each article: **1.** Transverse intermolar width. **2**. Transverse width of the nasal ca-

vity. 3. Complications. 4. Other results.

Results

One hundred and seventy articles were classified within the search limits described above. Three additional papers were found in the manual search. Of these, 98 that were repeated were eliminated. After analyzing the titles and applying the inclusion and exclusion criteria, nine studies were left for review, as shown in figure 1.

Figure 1: Article selection flowchart. Prisma (2020).



The data were extracted independently using tables 1 and 2 as data collection tools.

MARPE specifications per article are listed in Table 1. The data obtained from each piece for the variables transverse intermolar width, the transverse width of the nasal cavity, complications, and other results are specified in Table 2. We wrote "not mentioned" when the article did not include these variables, we wrote "not mentioned".

Assessing risk of bias

According to The Cochrane Collaboration guideline (2011), the risk of bias for the item "Random sequence generation" was "unclear" for 78% of the studies. (Figure 2). The degree of bias was classified as "low risk" if all criteria were met, "moderate" if only one criterion was missing, and "high" if two or more criteria were missing.

Table 1. MARPE specifications

Reference number	Mean age	Expander used	Miniscrews used	Activation protocol	Retention time
1	23	Rapid palatal expander. Bone-borne.	Four miniscrews: two 11 mm and two 9 mm long. Both are 2 mm in diameter. Spider Screw, Regular plus, HdC, Thie- ne, Italy.	Two activations a day until the midpalatal suture has opened and the maxillary constriction has been corrected.	6 months
2	20	Conventional Hyrax ex- pander with bands on first premolars and first molars. Two anterior hooks were placed on the rugae region, and the other two posterior hooks were placed on the parasagittal area.	Orthodontic miniscrews (Orlus, Ortholution, Seoul, Korea) with a 1.8- mm collar diameter and a 7-mm length.	The screw was turned once a day. The expansion was terminated at six weeks.	3 months
3	Mean age 21.6	Hyrax-type expander: (Hyrax II; Dentaurum, Is- pringen, Germany)	Four miniscrews with a 1.8-mm collar diameter and a 7-mm length. (Or- lus, Ortholution, Seoul, Korea).	The screw was turned once a day (0.2 mm) until the required expansion was achieved. The mean expansion was 6.54 (± 1.35) mm, and the expan- sion duration was five weeks.	4 months
4	Mean age 18± 5.5 years	Hyrax-type expander. Bo- ne-borne.	There are four minis- crews: two between canine and premolar and two between second premolar and first molar. The miniscrews are 10 mm long and 1.6 mm in diameter. (MOSAS self-drilling and self-tap- ping-Dewimed, Gac).	2/4 turn in the mor- ning and 2/4 turn in the evening. The time was calculated based on the expansion required for each patient.	5 months
5	Mean age 20.9 ± 2.9 years	Hyrax type. Four stainless steel bars with hooks solde- red at their base.	Four miniscrews that are 1.8 mm and 7 mm in diameter. Self-drilling. ORLUS, Ortholution, Seoul, Korea	1/4 turn (0.2 mm) every day. The expansion was terminated when the pala- tal cuspid of the perma- nent maxillary first molar came into contact with the tip of the correspon- ding buccal cuspid of the permanent mandibular first molar	3 months
6	Mean age 20.1	Hyrax type. Four rigid bars with 0.8-mm stainless steel wire and hooks soldered to the base. (Hyrax® Click; Dentaurum, Ispringen, Germany). Two hooks were placed on the rugae area and the other two posterior hooks were placed on the parasagittal area. Cemented to the first premolars and molars.	Four orthodontic mi- niscrews with a 1.8 mm collar diameter and a 7-mm length (Orlus; Or- tholution, Seoul, Korea).	One turn per day (0.2 mm) until the required expan- sion was achieved	Not mentioned

8	Group aged 20 to 29	Expander (Peclab, Belo Hori- zonte, Minas Gerais, Brazil).	Four orthodontic mi- niscrews (Peclab, Belo Horizonte, Minas Gerais, Brazil)	2/4 turn immediately after mini-implant placement and 2/4 turn daily, varying from 14 to 18 days until transverse correction was achieved.	4 months
9	Mean age 20.4 ± 3.2 years	Central expansion screw pla- ced in the posterior palate	Four 1.5 x 11 mm minis- crews	Two activations a day (0.40 mm) until a dias- tema appeared. Then, the activation changed to once a day. The ex- pansion was complete when the maxillary basal bone was greater than the mandibular width. The average duration of expansion was 35 ± 10 days.	6 months

 Table 2. Addressing each variable: Transverse intermolar width, transverse width of the nasal cavity, complications and other results

Reference number	Title of study	Variables evaluated after implementing MARPE			
		Transverse intermolar width	Transverse width of the nasal cavity	Complications	Other results
1	Class III maloc- clusion and bila- teral crossbite in an adult patient treated with miniscrew-assis- ted rapid palatal expander and aligners.	Increased	Not mentio- ned	Thickness of the buccal alveolar bone plate of the first per- manent molar (M1): Decreased	Orthopedic expansion: Achieved. Gingival recession: Did not increase. Dental tipping: well controlled.
2	Miniscrew-assis- ted non-surgical palatal expan- sion before orthognathic surgery for a patient with se- vere mandibular prognathism.	Increased	Increased	Transitional soft-tis- sue inflammation.	Transverse intercanine width: Increased Separation of midpalatal suture: confirmed. Periodontal tissue: No significant changes
3	Stability of dental, alveolar, and skeletal changes after miniscrew-assis- ted rapid palatal expansion	Increased	Increased	Inclination of M1: Moved buccally. Inclination of al- veolar bone: Moved buccally. Buccal alveolar bone thickness of PM1: Decreased. Buccal alveolar bone thickness of PM1: Decreased. Buccal alveolar crest level of PM1: Towards apical. Buc- cal alveolar crest of PM1: Moved apically.	Increased: Intercusp width of central incisors Intercusp width of canines Intercusp width of PM1 Intercusp width of PM2 Interapex width of incisors Interapex width of canines Interapex width of PM1 Interapex width of PM2 Palatal alveolar bone thickness of PM1 Palatal alveolar bone thickness of PM2 Palatal alveolar bone thick- ness of M1 Statistically not significant: Buccal alveolar bone thickness of PM2

4	Rapid maxillary expansion in young adults: comparison of tooth-borne and bone-borne appliances, a cohort study.	Not mentioned	Not mentioned	Not mentioned	Statistically not significant: Inclina- tion of right PM1 Inclination of left PM1 Inclination of left upper incisor Inclination of left upper incisor Anterior transverse dimension (ATD) Increased: Posterior transverse dimension (PTD) Radiolucency of the midpalatal sutu- re: In 100% of patients.
5	Non-surgical mi- niscrew-assisted rapid maxillary expansion re- sults in accepta- ble stability in young adults	Increased	Increased	Not mentioned	Midpalatal suture opened in a Trian- gular shape. Opening of midpalatal suture: 86% of participants. Increased: Intercanine width Interpremolar width Statistically not significant: Clinical crown height:
6	Skeletal and dentoalveolar changes after miniscrewassis- ted rapid palatal expansion in young adults: A cone-beam computed tomo- graphy study	Increased	Increased	Buccal bone thickness of PM1: Decreased. Buccal bone thickness of M1: Decreased. Buccal alveolar height of PM1: Decreased. Buccal alveolar height of M1: Decreased. Buccal inclination of maxillary M1: Increased	Zygomatic arch width: Increased. Expansion pattern (coronal plane): pyramidal. Expansion pattern (sagit- tal plane): parallel. Opening of midpalatal suture: 84.2% of participants. Skeletal, alveolar, and dental ex- pansion: 37.0%, 22.2%, and 40.7%, respectively.
7	Retrospective Evaluation of Skeletal, Dentoalveolar, and Periodon- tal Changes of Microimplant Assisted Rapid Palatal Expan- sion (MARPE) In Skeletally Matu- red Patients	Increased	The expansion of the nasal cavity areas is equivalent to 45% of the expansion achieved with MARPE.	Buccal alveolar bone thickness of PM1: Decreased. Buccal alveolar bone thickness of M1: Decreased. Dental inclina- tion of left PM1: towards vestibu- lar. Dental inclina- tion of right M1: moved buccally. Dental inclination of left M1: moved buccally.	Opening of midpalatal suture: in 100% of cases and without removing microimplants. Expansion: 41% skeletal, 12% alveolar bone, and 48% tooth tipping. Expansion pattern: parallel in coronal and axial planes. Right zygomatic area: it expanded. Left zygomatic area: it expanded. Left infrazygoma- tic area: it expanded. Left infrazygo- matic area: it expanded.
8	Evaluation of factors related to the success of miniscrew-assis- ted rapid palatal expansion	Not mentioned	Not mentioned	Not mentioned	Increased: Anterior palate trans- verse dimension Posterior palate transverse dimension Midface width (measurement between infraorbital foramens)
9	An assessment of the magnitu- de, parallelism, and asymmetry of microimplant- assisted rapid maxillary expansioni n non-growing patients	Not mentio- ned	Not mentioned	Post-expansion transverse asym- metry: 51% of patients	Increased: Transverse dimension at the anterior nasal spine. Transverse dimension at the posterior nasal spine



Figure 2: Assessing risk of bias. The Cochrane Collaboration (2011).

Transverse width of the nasal cavity

This variable increases in all the articles reviewed. The transverse width of the nasal cavity increases 1.07 mm immediately after MARPE removal⁽⁶⁾ to 2.2 mm, a value recorded 10 months post-treatment.⁽⁴⁾

Expansion of the nasal cavity resulted in increased airflow and improved nasal breathing.⁽⁸⁾

Complications

Studies report periodontal and dentoalveolar complications, including:

1. Thinning of the buccal bone plate: Thinning of the buccal bone plate of the first molar.^(3,7) In any case, the teeth still had adequate bone coverage in the roots.⁽³⁾ The same result is reported for the first molar and the first premolar.^(5,7-8)

2. Inflammation: Transitional soft-tissue inflammation surrounding the miniscrews in the palate was recorded during MARPE treatment. This decreased when the device was removed once the budgeted time for expansion had elapsed. There is no indication of treatment interruption.⁽⁴⁾

3. Apical shift of alveolar ridge: An apical shift of the ridge is reported in the first molar and the first premolar.⁽⁷⁻⁸⁾

4. Tooth angulation: There is a change in the tip of the first molar after MARPE treatment.^(5,7-8) It moved buccally by 3.91°.⁽⁷⁾

The angulation of the left first premolar moved buccally. The angulation change of the contralateral tooth was not statistically significant.⁽⁵⁾

5. Movement of alveolar bone: Significant results are recorded for the alveolar bone of the first molar. It varies 1.78° buccally.⁽⁷⁾ This contrasts with another study showing statistically significant results for first premolars and first molars.⁽⁵⁾

6. Transverse asymmetry post-MARPE: 51% of patients had asymmetry of at least 1.1 mm in the expansion of the anterior nasal spine.⁽²⁾

Other results: The literature records other variables.

1. Skeletal expansion: Orthopedic expansion is described, even correcting a bilateral crossbite.⁽³⁾

2. Periodontal tissue: studies do not indicate gingival recession^(3-4;7) immediately after MAR-PE treatment, nor significant changes in dental crown height^(4,6) or bone dehiscence. Periodontal support remained solid and stable.⁽⁴⁾

3. Opening of palatal suture: All studies show opening, achieving an $84.2\%^{(8)}$ and higher success rate. $^{(1,\,5-6)}$

4. Opening pattern: It is pyramidal in the coronal plane,^(6,8) with the smallest increase in the nasal cavity and the most significant increase in intermolar width.⁽⁶⁾ Another author indicates a parallel expansion pattern.⁽⁵⁾ The expansion follows a

parallel pattern in the axial plane.^(5, 8)

5. Transverse measurements: The previous transverse dimension values were not statistically significant.⁽¹⁾ However, Oliveira et al.⁽⁹⁾ report a significant increase. Intercanine width^(3-4; 6) and interapex width of incisors and canines also increases.⁽⁴⁾

6. The posterior transverse dimension increases,^(1, 9) along with the intercuspid width of first premolars and second premolars^(4, 6) and the interapex width of first premolars and second premolars.⁽⁴⁾

7. After MARPE treatment, the studies recorded an increase in the width of the zygomatic arch,⁽⁸⁾ zygomatic area,⁽⁵⁾ infra-zygomatic area,⁽⁵⁾ and the region between the infraorbital foramens.⁽⁹⁾

Discussion

Chronological age is a good predictor of MARPE success (disjunction), showing a negative Pearson correlation. This means that the older the patient, the lower the chances of MARPE success and the less opening and skeletal expansion.⁽⁹⁾ However, age should not be the only factor to consider.⁽⁹⁾

The literature is contradictory: the data show intrasutural and interindividual variability in the developmental stages of the midpalatal suture, which is not directly related to chronological age.⁽⁵⁾ Midpalatal suture fusion varies with gender and age. Fusion of the midpalatal suture has been reported in patients aged 15 to 19, and lack of fusion has been reported in patients aged 32, 54, and 71.⁽⁵⁾ This would explain the different MARPE success rates and the variable increases post-MARPE. The most significant increase in transverse intermolar width immediately after MARPE removal is 8.32 mm,⁽⁶⁾ followed by 8.3 mm,⁽⁴⁾ and 6.26 mm.⁽⁵⁾ The greatest increase in transverse width of the nasal cavity recorded is 2.2 mm.^(4,7)

The decision to use appliances such as MARPE or tooth-borne devices in young adult patients should be based on patient characteristics: skeletal maturity, palate shape, hygiene, teeth present, condition of dental crowns, and orthodontist's preferences.^(1,5) Therefore, anchoring MARPE to the palate with miniscrews⁽⁴⁾ can be very useful in patients who have missing or compromised posterior teeth.⁽¹⁾

Miniscrews allow clinicians to perform orthodontic therapy and expansion simultaneously, which reduces treatment times.⁽¹⁾ In addition, skeletally-anchored expanders produce more significant orthopedic expansion than tooth-borne devices.^(1, 6) Both show an increase in the anterior transverse dimension. However, on average, this is greater in patients treated with 2.4 mm versus Hyrax 1.9 mm miniscrews.⁽¹⁾

Four of the nine articles reviewed use bone-borne MARPE devices.^(1, 3, 5, 8) The rest of the MARPE devices are bone-tooth-borne. It would be interesting to compare the results obtained with these two devices in young adults.

Only one study⁽²⁾ refers to the symmetry of the resulting expansion. Considering the records obtained, it would be useful to conduct further studies on the expansion of the anterior nasal spine. ⁽²⁾

No study has recorded clinically significant gingival recession immediately after MARPE use. However, in the future, this should be monitored, given the changes in the alveolar bone, apical migration of the alveolar ridge, and inflammation. (7-8)

Only one study mentions the millimeters of transverse discrepancy for which MARPE is effective. MARPE corrects mild to moderate maxillary transverse discrepancies of less than 7 mm in skeletally mature patients with a healthy periodontium.⁽⁵⁾

Regarding maintaining the results obtained with MARPE, a post-treatment relapse of 0.07 mm in the intermaxillary width was recorded.⁽⁹⁾ More long-term studies are needed to evaluate this item.

One of the potentia limitations of this review is that we included studies with patients of different races, skeletal maturity, and craniofacial anatomy. The number of microimplants varied, and there was a lack of long-term follow-up because MARPE was continued with orthodontic or surgical treatment. The degree of activation and containment of each device was different for each patient. The lowest activation frequency was one turn per day and the highest was two turns per day. The longest activation time reported was seven weeks.⁽⁵⁾ This study reports that the expansion of the nasal cavity areas is equal to 45% of the expansion achieved with MARPE.⁽⁵⁾

Conclusion

The studies reviewed indicate that MARPE could be a clinically viable and effective treatment for young adults with transverse maxillary deficiency. After separation of the palatal suture, intermolar transverse width and the transverse width of the nasal cavity increase.

Periodontal and dentoalveolar complications reported in the literature are mild in magnitude and inconclusive. Among them, the most common are thinning of the buccal plate of the alveolar bone of the first molar and first premolar, and tipping of the first molar.

Recent literature suggests that chronological age should not be the only factor to consider in evaluating the prognosis of this treatment.

Randomized clinical trials involving more patients and long-term follow-up are required to assess the success of MARPE and the stability of post-treatment expansion.

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Authorship contribution

- 1. Conception and design of study
- 2. Acquisition of data
- 3. Data analysis
- 4. Discussion of results
- 5. Drafting of the manuscript
- 6. Approval of the final version of the manuscript

APF has contributed in: 1, 2, 3, 4, 5, 6. JSS has contributed in: 1, 2, 3, 4, 5, 6.

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