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THERAPEUTIC APPROACHES IN THE SEQUENCE OF PIERRE ROBIN: A SYSTEMATIC REVIEW OF THE LITERATURE

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Abstract — Pierre Robin sequence (PRS) is characterized by micrognathia, glossoptosis and respiratory obstruction with or without cleft palate. These facial abnormalities trigger breathing problems and eating difficulties of varying degrees of complexity. Despite the various therapeutic possibilities currently available, there is the problem of not having a treatment protocol for PRS. The aim of this study is to analyze, through a systematic review of primary clinical studies, the best treatment strategy for SPR. When analyzing surgery risks and postoperative results of surgical interventions to treat patients with SPRS, it is possible to observe that such procedures are safe, in addition to being largely resolutive and effective in the long term, compared to conservative approaches.

Keywords — Pierre Robin sequence, glossoptosis, micrognathia, cleft palate.

I. INTRODUCTION

Pierre Robin sequence (PRS) is a triad of congenital facial abnormalities characterized by: micrognathia, glossoptosis and respiratory obstruction, with or without cleft palate, originally described in 1923 by French stomatologist Pierre Robin [1–2].

PRS, sometimes referred to as a syndrome, is a sequence in which a primary anomaly leads to multiple secondary anomalies. The initial abnormality is believed to be poor growth of the mandible that occurs between the 7th and 11th week of gestation, significantly reducing the oropharyngeal space. Secondary outcomes are glossoptosis and cleft palate, caused by the anatomical readaptation of the tongue in the reduced space [3–4]. In this sense, the organ moves superiorly and posteriorly, causing a mechanical impairment in the fusion of the palatal platforms, preventing the correct closure of the palate [4].

PRS is a rare disease that affects 1:8500 to 1:14000 live births [5]. This congenital condition may present alone or in association with syndromes and other malformations, with Stickler Syndrome, Velocardiofacial Syndrome and Treacher Collins Syndrome being the most prevalent [5–6].

PRS presents in the neonatal period. Anatomical abnormalities manifest with marked clinical features such as respiratory distress, which can range from mild difficulty

breathing to choking attacks, in addition to feeding difficulties that may occur with reduced food intake, prolonged oral feeding (more than 30 min), fatigue, gagging, vomiting, regurgitation and insufficient weight gain which, in combination with other factors, can lead to severe protein-calorie malnutrition [5-6-7].

Early and effective management is decisive in the prognosis and quality of life of patients with PRS. However, the proper conduct of treatment will depend on the severity of the airway obstruction. To perform the risk stratification of symptoms and to outline the best therapeutic approach, classification scales are used [6].

Among the current treatment options, the first line is based on the so-called conservative approaches, which are the prone or lateral postural maneuvers. When positioning fails to help the patient improve, non-surgical invasive alternatives are the next options, such as nasopharyngeal intubation and positive pressure [7]. Approaches such as glossoplexy, palatoplasty and distraction osteogenesis of the jaw are invasive surgical treatments. At the extreme of therapeutic approaches is the tracheostomy, used in patients with a high degree of impairment [7].

Despite the various therapeutic possibilities, there is the problem of not having a treatment protocol for PRS. Therefore, the objective of this study is to analyze, through a systematic review of primary clinical studies, the best treatment strategy for Pierre Robin. In this sense, it is considered from conservative management to current treatments, which present improvements in breathing and eating difficulties and provide an increase in the quality of life for the patient, as well as a decrease in severe and fatal cases of PRS.

II. MÉTHOD

A. Research Strategy

The question that guided this Systematic Literature Review was “What is the best treatment strategy for Pierre Robin Sequence?”. The study was conducted according to the recommendations of the “Cochrane Manual of Systematic Reviews of Interventions” [8].

High sensitivity searches were performed in the following electronic databases: PUBMED, VHL, EMBASE (via ELSEVIER) and COCHRANE, using the following terms: “Pierre Robin Sequence”, “Glossoptosis”, “Micrognathia” and “Cleft Palate” listed in the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH). The combination of descriptors was done using the Boolean operators OR and AND and the high sensitivity strings were built following the particularities of each search engine. No language and time filter was applied, as the study does not aim to limit the search for the best scientific evidence, and articles published until April 2022 were included.

B. Article Selection Criteria

The research results were analyzed individually by two blind researchers, following the inclusion criteria: primary observational cross-sectional studies, cohort, clinical trial and case series dealing with treatment strategy in SPR. Exclusion criteria were: duplicate studies, studies with unavailable full text, publications in which the diagnosis of Pierre Robin was uncertain and articles that did not specifically address Pierre Robin. For the analysis of methodological reliability, only studies with a score > 6 on the PEDro scale were included. The choice of articles took place in three stages: the first selection was based on the title; then, the abstract was read; finally, the articles that remained were selected based on the analysis of the full text. During the screening and selection process of the studies, the RAYYAN software was used in order to guarantee the reliability of the blinding of this step. In cases of disagreement between researchers, texts for which the final decision was consensual were excluded.

C. Data analysis

The selected articles were analyzed according to the following aspects: study design, sample characteristics, type of procedure and intervention characteristics, main results and conclusions.

III. RESULTS

Initially, the high-sensitivity search strategies identified a total of 17,423 articles in the four electronic databases, from which animal, in vitro, simulation and secondary studies were automatically excluded through the filters on the search engines. Thus, 299 articles remained in the selection and then, with the help of the RAYYAN tool, 21 duplicates were eliminated. Still with the help of software developed specifically for screening abstracts and titles of systematic reviews, the blinding step was activated and two reviewers made the selection by title and abstract. At this stage, 201 studies were excluded, leaving a total of 77 articles. There

were disagreements between the evaluators and, after resolving these conflicts, a total of 57 studies were elected to read the full text. After applying the inclusion and exclusion criteria, as well as the methodological reliability analysis score (PEDro Scale), 8 articles were accepted for this review (Figure 1). Table 1 presents a summary of the main information analyzed in each study.

Figure 1. Systematic Review Flowchart recommended by PRISMA.

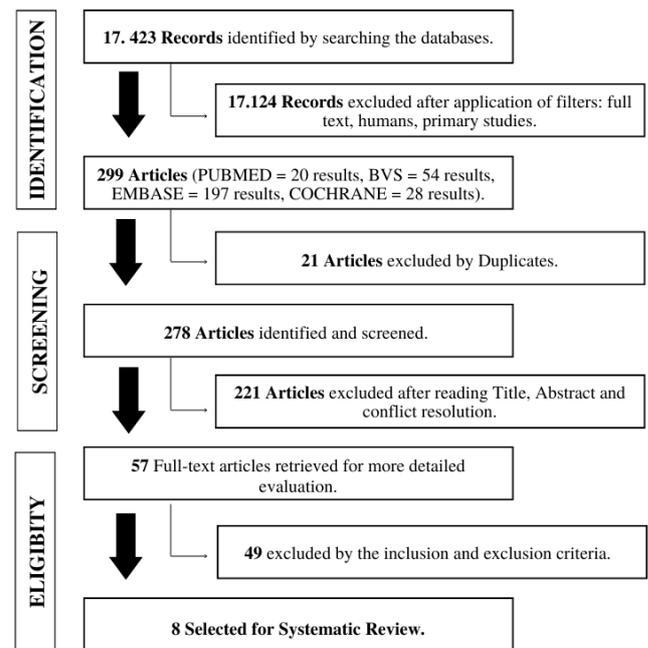


Table 1. List of Articles selected for qualitative analysis.

Author	Sample	Procedure	Conclusion
Marques et al. 2004	9 babies 0 – 6 months old.	Nasopharyngeal Intubation (NPI) and Hypercaloric Diet	The hypercaloric diet led to an improvement in the nutritional status and, probably, in the respiratory conditions of patients with isolated RS, allowing an earlier suspension of NPI.
Bacher et al. 2009	15 babies up to 3 months old.	Oral Device. Pre-epiglottic stick plate (PEBP). Oral Device. Pre-epiglottic stick plate (PEBP).	PEBP with velar extension can be a safe and effective alternative to avoid more invasive interventions until the cleft can be surgically closed.
Poetas et al.	49 babies > 1 year old.	Oral Device.	This study confirms the effectiveness of PEBP

Author	Sample	Procedure	Conclusion
2017		Pre-epiglottic stick plate (PEBP). Oral Device. Pre-epiglottic stick plate (PEBP).	treatment in improving upper airway obstruction and feeding problems, which are the main clinical complications of infants with PRS. Collaborative work is needed to compare this with other treatment approaches.
MorovicI. G.C 2004	31 babies.	Osteogenic Distraction of the Mandible.	Mandibular distraction is a successful method for young patients with PRS to relieve airway obstruction, improve feeding, and prevent early tracheotomy or decannulation in previously tracheotomized patients.
Lozano-Cifuentes et al. 2018	31 babies- 3 – 90 days old.	Osteogenic Distraction of the Mandible.	Patients with PRS treated with mandibular distraction for airway clearance with a maxillomandibular overjet of 7 mm or greater had less treatment failure with $p < 0.01$.
Jiayu et al. 2021	100 babies between 15 days — 14 months of age.	Osteogenic Distraction of the Mandible	Patients' physiques improved after distraction osteogenesis surgery, mainly reflected by weight gain and growth curves in length. Body shape also progressed, indicating that the nutritional status of patients after surgery also improved.
Carpes, Arturo Frick. 2015	53 babies between 10 — 23 months of age.	Palatoplasty. Rating by polysomnography	The prevalence of obstructive sleep apnea found was 61.9% before palatoplasty, and 33.3% postoperatively. Palatoplasty indicated a positive result in relation to sleep-disordered breathing
Cardim et al. 2019	12 babies.	Operative Technique. Orthoglossopelvis-plasty.	Orthoglossopelvisplasty allowed the unlocking of airway obstruction generated by poor lingual positioning, improved feeding function and mandibular development, with low surgical morbidity and few complications.

IV. DISCUSSION

This study reaffirms the need to develop an internationally recognized clinical protocol in order to guide the various health services for the treatment of patients with Pierre Robin sequence. Most of the articles qualitatively analyzed in this systematic review highlighted the need for new studies of high value in scientific evidence involving all the therapeutic approach strategies used in PRS. One of the characteristics of this condition is the heterogeneity of clinical manifestations, which is hardly addressed in clinical studies due to strict methodological criteria.

The choice of the best therapeutic approach is directly related to the degree of respiratory function impairment and feeding difficulties. The literature, in general, mentions the use of prone and lateral positioning maneuvers as the first line of treatment. However, probably because it is a very conservative procedure, no clinical studies were found in this regard. In a study developed at the Hospital for Rehabilitation of Craniofacial Anomalies of Bauru (HRAC-USP) by Marques et al. [9], thirty children with PRS, were treated with prolonged nasopharyngeal intubation (NTI) in order to test the best type of diet. One group of infants received a high-calorie diet (milk formula supplemented with 5% to 7% polymers of glucose and 3% to 5% medium-chain triglycerides), and another group of infants received formula alone. The choice of diet for each infant was randomized. In both groups, the children started the diets before 1 month of age and were maintained until 6 months of age. The study showed, through the analysis of weight and length, that children with a high-calorie diet showed an improvement in their nutritional status and, consequently, in their respiratory conditions, allowing for an earlier suspension of NTI.

NTI is an invasive and temporary treatment, as there may be improvement in the condition or the need for more invasive measures. Devices like the epiglottic plate show promise. And it was analyzed in two studies as an alternative to NTI.

Bacher et al. [10] carried out a study showing that the preepiglottic stick plate (PEBP) with velar extension can offer a safe and effective alternative capable of avoiding more invasive interventions until the cleft palate can be surgically closed. The prospective and observational study included 15 babies up to 3 months of age undergoing orthodontic treatment without randomization. Using a maxillary plaster used as a mold, the PEBP was custom built, covering both the palate, including the cleft, and the alveolar ridges.

The oral appliance included a velar extension of about 2 to 3 cm in length, moving the dorsum of the tongue forward, thus widening the hypopharyngeal space. Positioning in terms of angle and length was controlled and adjusted by nasal endoscopy. Patients underwent sleep studies at admission, at discharge and after three months of discharge, and body weight was monitored weekly. The study suggests

that this protrusion is sufficient to reduce the frequency of apneas not only in the acute phase, but also up to 3 months after the initial admission.

A cohort study conducted in Germany by Poetas et al. [11] reaffirms the effectiveness of PEBP in improving upper airway obstruction and weight gain in PRS infants. The median length of stay for orthodontic treatment was 3 weeks, the effectiveness of the plaque in relieving upper airway obstruction was confirmed by additional sleep studies, and 69% of babies were discharged without a feeding tube after starting PEBP treatment. Both INF with a high-calorie diet and the pre-epiglottic stick plate are temporary alternatives pending a definitive therapeutic option, such as a surgical technique. The surgical procedure of mandibular distraction is widely studied in the literature, as well as in several case reports in which the technique proved to be beneficial in the resolution of respiratory obstruction and feeding difficulties. The objective of jaw distraction osteogenesis (MDO) is to induce tissue neof ormation between two segments of a bone and trigger bone neof ormation from the surgical separation of two structures.

Morovic [12] submitted 31 patients with PRS to mandibular distraction, which resulted in relief of airway obstruction in all cases. Two cases underwent tracheotomy at birth, which was removed during the process and two other patients had pulmonary hypertension and clinical signs also reversed after distraction. Her weight charts improved significantly after the surgery. Post-distraction feeding was greatly facilitated, with reduced time (average of 20 minutes) due to more effective swallowing. In the long-term follow-up, they did not present respiratory obstruction, and in all cases early distraction was the only and definitive treatment. The nutritional evolution of 100% of the patients was positive.

In Buenos Aires, Argentina, Lozano-Cifuentes et al. [13] performed a prospective randomized comparative study in patients diagnosed with PRS undergoing osteogenesis by mandibular distraction. Through the maxillomandibular discrepancy, the study found that there was an association between greater or lesser success in the outcome of the procedure. Patients with PRS treated with mandibular distraction for airway clearance with a maxillomandibular overjet of 7 mm or more had fewer treatment failures with $p < 0.01$.

Recently, a study carried out in Malaysia by Jiayu et al. [14] showed that bilateral distraction osteogenic surgery of the mandible also has a positive effect on the nutritional status of children with PRS. In this study, all patients were fed whole milk and t tests for independent samples were used to analyze pre- and postoperative indicators. The WFA percentile increased from 14.16 ± 2.17 to $15.01 \pm 1.85\%$ ($P = 0.0048$), the WFA z score increased from -2.40 ± 0.18 to -1.90 ± 0.14 after surgery ($P = 0.0010$), the LFA percentile increased from 20.04 ± 3.48 to $33.67 \pm 4.29\%$ ($P = 0.0098$), the LFA z score increased from -2.09 ± 0.19 to -1.42 ± 0.23 ($P = 0.0009$), the BMI z score increased from -1.95 ± 0.22 to -1.39 ± 0.16 ($P = 0.0408$), ALB increased from 37.06 ± 0.51

to 42.85 ± 0.30 g/L ($P < 0.001$), which indicates that the physique of patients improved after distraction osteogenesis surgery, reflected mainly by weight lifting and growth curves in length; body shape also improved, indicating that the nutritional status of patients after surgery also improved.

The osteogenic distraction of the mandible was used in most studies as a permanent and resolute procedure, however, in some cases a new procedure is necessary to correct any problems.

Carpes [15] evaluated the effects of palatoplasty on obstructive sleep apnea using polysomnography (PSG) in 53 patients diagnosed with PRS. The prevalence of obstructive sleep apnea found was 61.9% before palatoplasty, and 33.3% postoperatively. Palatoplasty indicated a positive result in relation to sleep-disordered breathing, reducing both the rates of respiratory events and their severity.

A Brazilian study carried out at the Benefício Portuguesa Hospital of São Paulo, Núcleo de Cirurgia Plástica Avançada developed a new operative technique for lingual repositioning of PRS patients with glossoptosis. Cadim et al. [16] followed 12 patients, previously submitted to conservative treatment with postural maneuvers of lateral/ventral decubitus, use of nasopharyngeal cannula and speech therapy without success. The surgical indication for muscular and functional reorganization of the tongue with the "Orthoglossopelvelplasty" technique was given by physical and speech-language examinations. The results were analyzed in relation to the evolution of the treated patients, in terms of morbidity and mortality data, and the need for tracheostomy and/or gastrostomy.

Four patients were operated on with this technique and 8 associated with osteogenic distraction of the mandible. The evolution of the patients was as follows: 3 cases evolved with no need for tracheostomy and gastrostomy; 2 cases, with the need for postoperative tracheostomy (due to laryngomalacia and tracheal stenosis); in 1 case it evolved with the need for postoperative gastrostomy (due to Edwards syndrome); 2 cases, with the need for postoperative tracheostomy and gastrostomy (due to laryngomalacia); in 4 cases that had previous tracheostomy and gastrostomy evolved with: tracheostomy and gastrostomy removal, tracheostomy removal programming, gastrostomy removal and death (died during cardiac surgery) respectively. The study states that the performance of orthoglossopelvelplasty is effective, functional and anatomical, with less surgical extension and complications. It is important to highlight that there are positive and negative aspects of both conservative and surgical approaches. Surgical interventions are shown to be safe, resolute and effective, compared to conservative actions. In the studies of high methodological qualities selected in the present systematic review, there is a lack of information to establish specific protocols, due to the great variability of symptoms and clinical manifestations, which makes it difficult to establish restrictive methodologies.

V. CONCLUSION

When analyzing surgery risks and postoperative results of surgical interventions to treat patients with PRS, it is possible to observe that such procedures are safe, in addition to being largely resolutive and effective in the long term, compared to conservative approaches.

Due to the diversity of approaches in the treatment of PRS, observed in most of the articles analyzed in this systematic review, as well as the heterogeneity of clinical manifestations of this condition, the relevance and urgency of establishing a clinical protocol for elaboration, analysis and international recognition is evident, which seeks to allocate, in the various health sectors, a gold standard treatment for patients with PRS.

The cost-benefit of the numerous therapeutic procedures for SPR must be considered. In addition, it is suggested the integration and partnership of international and national health reference centers in the elaboration of the protocol, in order to analyze, through sleep studies and weight and growth charts, which treatment approaches are suitable for each patient. more effectively and efficiently in its patient population.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest in carrying out this study.

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