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META-ANALYSIS
Craniofacial Anomalies

The effects of clinical factors on airway outcomes of mandibular distraction osteogenesis in children with Pierre Robin sequence

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Abstract. Mandibular distraction osteogenesis (MDO) is an effective treatment for tongue-based airway obstruction in children with severe Pierre Robin sequence. An investigation was performed to determine whether certain clinical factors influence the airway outcomes of MDO. A literature search of several databases was performed to identify studies providing individual patient data. Data extracted from the studies included patient sex, age at distraction, disease type, experience of any previous surgery on the airway, length of distraction, pre- and postoperative blood oxygen saturation nadir, and osteotomy design. Non-parametric tests and multivariate logistic regression analysis were conducted to investigate the potential interaction between these clinical factors and the efficacy of surgery. Five studies met the inclusion criteria, with data available for 73 individual patients. The results of the statistical analysis revealed that few of the factors investigated influenced the surgical efficacy in children with Pierre Robin sequence; the effect of the length of distraction was regarded as uncertain because of the limited amount of individual data available. In conclusion, no influencing factors were found, and according to this analysis, mandibular distraction may be a widely effective procedure. However, more well-designed studies and more individual data are needed to strengthen the results of this meta-analysis.

Key words: mandibular distraction osteogenesis; Pierre Robin sequence; airway obstruction; children.

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Pierre Robin sequence (PRS) is characterized by micrognathia, glossoptosis, and commonly a cleft of the palate[1]. This condition occurs in approximately 1 in 8500 births[2]. It can be isolated or found in association with other congenital anomalies such as Stickler syndrome, 22q11.2 deletion, Treacher–Collins syndrome, and others[3]. As a result of the micrognathia and glossoptosis, many children with PRS experience tongue-based airway obstruction (TBAO) and accompanying respiratory

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distress to varying degrees. In addition, the secondary effects of airway obstruction include failure to thrive, developmental delay, CO_2 retention, feeding difficulties, heart failure, brain damage, and sudden death, leading to a mortality of 1.7% to 65%[4–6].

Although most children born with PRS are either asymptomatic or can be treated conservatively, some have severe TBAO that necessitates more aggressive interventions. Tracheostomy is a direct and effective procedure for establishing a stable airway[7]. However, considering the associated frequent morbidity, high cost, and occasional mortality[8–10], other procedures have been proposed as alternatives to tracheostomy. By gradual lengthening of the mandible, simultaneously advancing the soft tissues and tongue, mandibular distraction osteogenesis (MDO) can increase the upper airway size and relieve the airway obstruction safely and effectively. In recent years, it has become one of the most popular alternatives to tracheostomy[11].

Thus far, many studies have demonstrated the effectiveness of MDO in treating TBAO in children with severe PRS, and several meta-analyses synthesizing the results have been published[12–14], particularly related to the avoidance of tracheostomy, successful decannulation, and polysomnography (PSG) data, among others. Unfortunately, although many studies have emphasized that proper patient selection and an appropriate surgical protocol are key to surgical success[12,15,16], there have been few evidence-based analyses evaluating the effects of patient factors (e.g., age, sex) and therapeutic factors (e.g., osteotomy design, length of distraction) on TBAO improvement. In addition, it is not certain whether different population or different surgical details influence the efficacy of MDO. Therefore, several basic factors discussed in previous studies that are thought to possibly influence the outcomes were selected, and this meta-analysis was performed to investigate the potential influence of these clinical factors on the efficacy of MDO in the paediatric PRS population.

Materials and methods

A systematic protocol was developed in advance. Two reviewers independently identified studies for inclusion and data extraction. Any disagreements between the two reviewers were discussed with a third reviewer and a consensus on inclusion reached.

Inclusion and exclusion criteria

The following inclusion criteria were applied: (1) patients: subjects aged younger than 18 years, diagnosed with PRS and TBAO, who had failed conservative treatment; (2) intervention: bilateral MDO; (3) data variables: individual patient characteristics, surgical details, and pre- and post-MDO airway outcomes.

The exclusion criteria were as follows: (1) adults, (2) airway obstruction resulting from other diseases such as temporomandibular joint ankylosis; (3) children with PRS treated conservatively; (4) interventions other than MDO; (5) review articles and duplicate publications; (6) articles without individual patient or surgical data.

Search strategy

An electronic search of the MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and BIOSIS databases was conducted for articles published up to March 2016. Medical subject heading (MeSH) terms and free-text words were combined in the search strategy, including ''osteogenesis, distraction'', ''obstructive sleep apnoea'', ''upper airway obstruction'', ''Pierre Robin sequence'', ''child'', etc. Reference lists of the identified articles were also checked. The titles and abstracts were first assessed independently by two reviewers. The full-text articles of all relevant studies were obtained for final consideration. Studies meeting the inclusion criteria underwent data extraction and studies not meeting the inclusion criteria were excluded.

Data extraction

Studies that reported individual patient data were identified. A customized data extraction form was developed. The following data were extracted: patient sex, age at distraction, disease type (isolated PRS or syndromic PRS), experience of any previous surgery on the airway (yes or no), pre- and post-MDO blood oxygen saturation nadir (SpO_2 nadir), osteotomy design (inverted-L osteotomy of the mandibular ramus or vertical/slightly oblique osteotomy of the mandibular body), and length of distraction. When individual patient data were not available, the authors of the articles were contacted for clarification.

Statistical analysis

The Shapiro–Wilk normality test was employed to examine continuous variables. If the results accorded with the normal distribution, then the means of the two groups (e.g., male vs. female) were compared using the *t*-test. If not, the two groups were compared using the non-parametric Wilcoxon rank sum test. Linear regression analysis was conducted with the least-squares method. When using the stepwise regression analysis method to screen the independent variables, the level of significance was set at 0.1 for inclusion and 0.05 for elimination. All data were analyzed using IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA).

Results

A total of 1277 studies were identified through the electronic and manual search. After screening the article titles and abstracts, 72 studies were considered eligible, and the full-text articles were retrieved. Subsequently, 67 studies were excluded for particular reasons. Finally, five studies met the inclusion criteria, with data available for 73 individual patients[15,17–20]. A flow diagram of the study inclusion process is given in Fig. 1. The distribution of the diagnoses of patients with syndromic PRS is shown in Fig. 2.

For continuous variables, the results of the Shapiro–Wilk test showed that the data did not have a normal distribution, thus the non-parametric test was employed for comparisons. The results of the influence of the different binary variables on the post-MDO SpO_2 nadir by univariable regression analysis are shown in Table 1. Patient sex, disease type, experience of any previous surgery on the airway, and osteotomy design had no statistically significant influence on the post-MDO SpO_2 nadir ($P > 0.05$). Since the *P*-value for experience of any previous surgery on the airway was relatively close to 0.05 ($P = 0.106$), further analysis was required.

The results of the influence of the continuous variables on the post-MDO SpO_2 nadir are shown in Table 2. Age, length of distraction, and the pre-MDO SpO_2 nadir had no statistically significant influence on the post-MDO SpO_2 nadir ($P > 0.05$). However, the *P*-value for length of distraction was close to 0.05 ($P = 0.073$). Of note, the scatter plot appeared to reveal a certain linear relationship between the post-MDO SpO_2 nadir and the length of distraction (Fig. 3). Therefore the variable of length of distraction also needed further analysis.

In the multivariate regression analysis, all of the factors were first included in the regression model; the results are shown in Table 3. None of the variables included was found to have a statistically significant influence on the post-MDO SpO_2 nadir. When adding them into the stepwise

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