

An Oral Appliance With Velar Extension for Treatment of Obstructive Sleep Apnea in Infants With Pierre Robin Sequence

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Objective: A new oral appliance to treat obstructive sleep apnea in infants with Pierre Robin sequence has recently been shown to be superior to a sham procedure. We now investigate safety and long-term effects of this appliance on obstructive sleep apnea in infants with Pierre Robin sequence.

Design: Case series with repetitive follow-up examinations.

Setting: Tertiary neonatal intensive care unit at the University Children's Hospital Tuebingen, Germany.

Patients: Fifteen infants (11 girls and four boys; median age, 5 days) with Pierre Robin sequence and obstructive sleep apnea (i.e., mixed-obstructive-apnea index > 3).

Intervention: A custom-made intraoral appliance with velar extension was used continuously *in situ* from admission until 3 months after hospital discharge.

Main Outcome Measure: The mixed-obstructive-apnea index was determined prior to the intervention at admission, at discharge, and 3 months later using polygraphic sleep studies. The geometric mean of the mixed-obstructive-apnea index and its 95% confidence interval were calculated.

Results: Compared with admission (mean, 17.2; 95% confidence interval, 11.1–26.7), there was a significant decrease in the mixed-obstructive-apnea index to discharge (mean, 3.8; 95% confidence interval, 2.2–6.6) and 3 months later (mean, 1.2; 95% confidence interval, 0.7–2.2; *p* value < .001). No severe adverse events occurred.

Conclusions: This oral appliance was safe and appears to treat obstructive sleep apnea effectively in infants with Pierre Robin sequence.

KEY WORDS: *jaw abnormalities, mandibular advancement, obstructive sleep apnea syndrome*

The Pierre Robin sequence (PRS), characterized by mandibular micrognathia or retrognathia and glossoptosis with or without cleft palate, presents clinically with severe obstructive sleep apnea (OSA) and feeding difficulties

(Robin, 1934). Also in PRS, untreated OSA can lead to cor pulmonale, failure to thrive, neurodevelopmental delay, and even sudden death. Current treatment options range from prone positioning, using a nasopharyngeal tube, surgical tongue advancement (i.e., glossopexy via tongue-lip adhesion), mandibular distraction, and continuous positive airway pressure to performing a tracheotomy.

Endoscopic studies suggested that OSA in PRS may result from the posterior movement of the dorsum of the tongue to the posterior pharyngeal wall and/or an inward movement of the lateral pharyngeal wall (Sher, 1992). Thus, treatment of OSA should stabilize the pharyngeal wall and/or widen the hypopharynx by shifting the tongue forward. Most current treatment options fail to do this or are considerably invasive or inconvenient (Denny et al., 2001; Whitaker et al., 2003).

We recently introduced an oral appliance (i.e., the pre-epiglottic baton plate; PEBP) as a new first-line treatment option for OSA in infants with PRS (von Bodman et al., 2003). The PEBP includes a velar extension, shifting the dorsum of the tongue forward, thereby widening the hypopharyngeal space. In a randomized controlled trial,

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FIGURE 1 The pre-epiglottic baton plate (PEBP) from various perspectives. The length of the baton (here in blue) is adjusted endoscopically (see also Fig. 2).

the PEBP was found to reduce the apnea index by 70% and to be superior to a conventional palatal plate without such extension (Buchenau et al., 2007). The follow-up period ended 36 hours after commencement of the orthodontic treatment in that study. In clinical practice, however, any effect on airway obstruction should last considerably longer. Hence, we aimed to follow up patients undergoing this treatment, hypothesizing that the short-term benefit of the PEBP documented in the controlled trial would continue until hospital discharge and beyond.

METHODS

Patients

Infants up to 3 months of age with isolated PRS who were born at or referred to our department between November 2002 and January 2005 were eligible for enrollment. Other inclusion criteria were (1) presence of OSA, defined as a mixed-obstructive apnea index (MOAI) > 3 upon admission, (2) no previous orthodontic or pharmacologic treatment known to affect respiratory or cardiac control, and (3) written informed parental consent. Exclusion criteria were (1) presence of additional major malformations (e.g., congenital heart disease), (2) presence of a concomitant upper or lower respiratory tract infection upon admission, or (3) OSA-related severe hypoxemia, defined as three or more desaturation events to <60% pulse oximetry-derived arterial oxygen saturation (SpO₂) in the initial sleep study.

Study Design and Procedures

A prospective, observational study was conducted. All patients underwent the orthodontic treatment without randomization. Following enrollment, patients underwent sleep studies upon admission (baseline assessment), discharge (treatment assessment 1), and 3 months after discharge (treatment assessment 2). Body weight was

measured in weekly intervals. Absolute changes in body weight were calculated upon admission (i.e., actual weight minus birth weight), discharge (i.e., actual weight minus weight upon admission), and follow-up (i.e., actual weight minus weight upon discharge). The study protocol was approved by the institutional review board of Tuebingen University Hospital.

Orthodontic Treatment

Following enrollment, infants had a maxillar cast taken. Using this cast as a model, the PEBP was made from compound soft and hard acrylic (Forestacryl-Strong-S; Foerster, Germany), covering both the palate (including the cleft) and the alveolar ridges. The PEBP was manufactured by our local orthodontic laboratory and inserted within 72 hours following the baseline sleep study. The PEBP had a velar extension of approximately 2 to 3 cm in length; its position (angle and length) was controlled and adjusted using nasal endoscopy (Figs. 1 and 2). A wire structure made from 1.8 × 0.8-mm Remanium strengthener (Dentaurum, Pforzheim, Germany) was incorporated into the velar extension to safeguard the device against mechanical

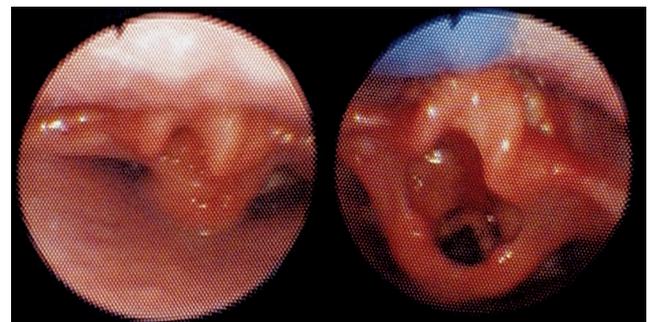


FIGURE 2 Endoscopic view of the larynx without (left) and with the PEBP *in situ*. Without the PEBP, the base of the tongue (i.e., the structure in the upper part of the left picture) obstructs the larynx. The baton (blue structure in upper part of the right picture) pushes the base of the tongue forward, thereby widening the laryngeal entry.



FIGURE 3 Variation of the orthodontic appliance with wires to secure optimal position also in patients with extreme retrogenia.

failure. The PEBP was held *in situ* by suction and adhesion. If necessary, a fixative cream (Corega Super-Haftcreme; Procter & Gamble, Cincinnati, OH) was used to improve retention. In severe cases, extraoral wire bows were added to the PEBP and secured on the infant's face using adhesive tape (Steri-Strip, 3M Health Care, St. Paul, MN; Fig. 3). During the 3-month follow-up period, most infants required a larger version of the appliance, which was manufactured and adjusted according to the same procedures as described above. The appliance was left *in situ* during sleep and wakefulness until the 3-month follow-up sleep study. During this time, it was only removed for cleaning purposes.

Performance of Sleep Studies

Cardiorespiratory sleep studies were performed with a computerized polysomnographic system (Embla N7000 and Somnologica Studio 3.0; Embla, Broomfield, CO). The study montage comprised the following channels, sensors, sampling frequencies, and devices: chest and abdominal wall movements (respiratory inductance plethysmography, 10 Hz; Embla), nasal pressure and linearized nasal airflow (nasal prongs and built-in pressure transducer, 200 Hz; Embla), oral airflow (thermocouple, 10 Hz; Pro-Tech, Mukilteo, WA), snoring (vibration sensor, 10 Hz; New Life Technologies, Glen Burnie, MD), 2-seconds-averaged SpO₂ (2 Hz) and pulse waveform (Radical, 100 Hz; Masimo Inc., Irvine, CA), electrocardiogram and instantaneous beat-to-beat heart rate (100 Hz, Embla), transcutaneous arterial CO₂ pressure (Microgas 7650, 2 Hz; Linde, Basel, Switzerland), and digital video (infrared black/white camera, 5 Hz; Panasonic, Tokyo, Japan). The polygraphic setup did not include electroencephalography, electrooculography, or electromyography. All infants were studied in the supine position during a single night. Recordings commenced in the evening and lasted for at least 8 hours. No sleep study was performed during the daytime. Following completion of the sleep study, a capillary blood sample was taken and analyzed for pH and CO₂ pressure.

Analysis of Sleep Studies

Recordings were pseudonymized by one author (M.S.U.) and analyzed by another (J.S.); neither was involved in clinical management. First, total recording time was determined and sleep distinguished from wakefulness by assessing the infant's behavior for each 60-second-epoch of the video recording. Precht's behavioral states were assigned to each epoch (Precht, 1974). States 1 and 2 were regarded as sleep; states 3 through 5 as wakefulness. Recording periods during which the infant was taken out of bed, fed, or otherwise cared for were not considered. Total sleep time was then calculated as total recording time minus all periods of wakefulness. Second, within total sleep time and without considering the video, recordings were reanalyzed for artifactual or uninterpretable readings on the nasal flow, thoracic or abdominal effort, or oximetry channel. Artifactual/uninterpretable recording periods were excluded from the total sleep time if they lasted for more than 5 minutes, and the corrected total sleep time (i.e., total sleep time without artifactual/uninterpretable recording periods) was then calculated. Recordings with a corrected total sleep time <150 minutes were excluded from further analysis because they likely did not comprise three full sleep cycles. Third, recordings were then manually reanalyzed for the presence of respiratory events using standard criteria (American Thoracic Society, 1996). In brief, an apnea was scored if (1) the amplitude of the nasal airflow fell to <20% of the average amplitude of the two preceding breaths, (2) no airflow was detected at the mouth, and (3) the event comprised at least two breath cycles (i.e., approximately 4 seconds). An obstructive apnea was scored if (1) criteria for apnea were fulfilled and (2) out-of-phase movements of the chest and abdominal wall were present. A central apnea was scored if (1) criteria for apnea were fulfilled and (2) no chest and abdominal wall movements were present. Mixed apneas were defined as apneas with both central and obstructive components, each lasting at least two breath cycles. The MOAI (i.e., sum of mixed and obstructive apneas per hour of corrected total sleep time) and a central apnea index (CAI; i.e., sum of all central apneas per hour of corrected total sleep time) were calculated. Fourth, oxygen desaturation events, defined as fall in SpO₂ to ≤80%, were visually confirmed to exclude spuriously low values. Events with a distorted pulse waveform signal within 7 seconds prior to their onset were considered artifactual and were excluded. The number of desaturation events was counted and an oxygen desaturation index (ODI), defined as events per hour of corrected total sleep time, was calculated.

Statistical Methods

The primary study variable was the MOAI. This was not normally distributed in our study. To obtain a normally distributed test variable for parametric statistical testing, the MOAI was transformed using the natural logarithm.

TABLE 1 Demographic and Clinical Characteristics of Study Subjects (n = 15)

Characteristic	Definition		Results
Gender	Male	n	4
Gestational age at birth	wk	Median (minimum to maximum)	39 (36 to 41)
Birth weight	g	Median (minimum to maximum)	3330 (2300 to 4150)
Age at admission	d	Median (minimum to maximum)	5 (0 to 60)

The advantage of log-normally distributed test variables is that the arithmetic mean (i.e., the “simple” mean) of the log-transformed test variable corresponds to the geometric mean of the untransformed original variable. This enables easy calculation of confidence intervals. The geometric mean is the *n*th root of the product of *n* individual values. Descriptive statistics for the untransformed MOAI were given as geometric means and their 95% confidence intervals (95% CI). Differences on the log-scale were expressed as quotients on the untransformed scale. Comparisons between assessments (i.e., baseline versus treatment assessments) were done using univariate analysis of variance (ANOVA). *Post hoc* pairwise comparisons with baseline as reference category were done using Dunnett’s *t* test if the global test was significant.

The CAI, ODI, the capillary blood pH and CO₂ pressure, and weight gain were secondary study variables and were not transformed for analysis. Except for the MOAI, descriptive statistics as numbers and percentages and median, minimum, and maximum were used to summarize demographic and other clinical characteristics, as well as sleep study results. Nonparametric tests for paired data (i.e., Friedman test and Wilcoxon’s signed rank test) were used for secondary study variables. Pairwise comparisons using the Wilcoxon test were performed if the global test (i.e., Friedman test) revealed significant differences between study phases. A *p* value of <.05 was considered statistically significant. No adjustment for multiple testing was performed for secondary variables. All analyses were done with SPSS 12.0.1 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

A total of 21 infants with isolated PRS were born at or transferred to our hospital between November 2002 and

January 2005. Of these, 15 met inclusion criteria and had interpretable sleep studies at baseline, discharge, and follow-up. The remainder were not included or were subsequently excluded from the study because parents refused consent (*n* = 3) or a sleep study did not comprise sufficient corrected total sleep time. Demographic and clinical characteristics of participating infants are presented in Table 1. The median duration of hospital stay was 23 days (minimum was 19, maximum was 71). All infants tolerated the study procedures well. Severe adverse events like bleeding, systemic infection, aspiration, or suffocation were not observed. The only side effect observed was the occurrence of tender spots on the hard or soft palate, which improved after manually reshaping the plate (e.g., rounding some of the plate’s edges or shortening the velar extension).

Results for the primary study variable are presented in Table 2 and Figure 4. The corrected total sleep time ranged from 248 to 486 minutes in the baseline recordings, from 166 to 601 minutes in the recordings at discharge, and from 221 to 592 minutes in the recordings at follow-up. There was a clear decrease in the MOAI from baseline (geometric mean, 17.2; 95% CI, 11.1–26.7) to discharge (geometric mean, 3.8; 95% CI, 2.2–6.6) to follow-up (geometric mean, 1.2; 95% CI, 0.7–2.2). The distributions were statistically significantly different on the log-scale (ANOVA: *F*-value = 25.07; *df* = 2; *p* value < .0001). Dunnett’s *t* test revealed a statistically significant mean decrease (95% CI) in MOAI from baseline to discharge of –77% (–41% to –91%) and from baseline to follow-up of –94% (–85% to –98%). In fact, all infants but one had a MOAI <3 in the 3-month follow-up sleep study.

Results for the secondary study variables are also presented in Table 2. The Friedman test revealed significantly different distributions between treatment assessments for ODI (*p* value = .027), capillary blood CO₂ pressure (*p* value = .002), and weight gain (*p* value < .0001). Pairwise comparisons revealed statistically significant differences between baseline and discharge for ODI (*p* value = .007), between baseline and follow-up for capillary blood CO₂ pressure (*p* value = .006), and between baseline and discharge as well as between baseline and follow-up for weight gain (*p* value < .001 for both comparisons). All infants had their feeding tubes removed prior to hospital discharge; none was tube fed between discharge and the 3-month follow-up.

TABLE 2 Results for the Primary and Secondary Study Variables (n = 15)

Variable	Definition	Time of Sleep Study			
		Baseline	Discharge	3-Month Follow-Up	
MOAI†	Apneas per hour	Geometric mean (95% CI)	17.2 (11.1–26.7)	3.8 (2.2–6.6)*	1.2 (0.7–2.2)*
CAI	Apneas per hour	Median (minimum to maximum)	7.1 (0.6 to 105.2)	11.6 (2.5 to 28.4)	7.6 (2.1 to 18.9)
ODI	Events per hour	Median (minimum to maximum)	0.6 (0.0 to 18.3)	0.0 (0.0 to 2.2)*	0.0 (0.0 to 6.8)
Capillary blood pH		Median (minimum to maximum)	7.37 (7.26 to 7.46)	7.40 (7.36 to 7.45)	7.40 (7.33 to 7.43)
Capillary blood CO ₂ pressure	mm Hg	Median (minimum to maximum)	45 (31 to 71)	41 (36 to 50)	35 (31 to 49)*
Weight gain	g/day	Median (minimum to maximum)	–20 (–234 to 19)	24 (6 to 34)*	19 (4 to 27)*

* *p* value < .05 for the comparison with baseline as reference category.

† 95% CI = 95% confidence interval; MOAI = mixed-obstructive-apnea index; CAI = central apnea index; ODI = oxygen desaturation index.

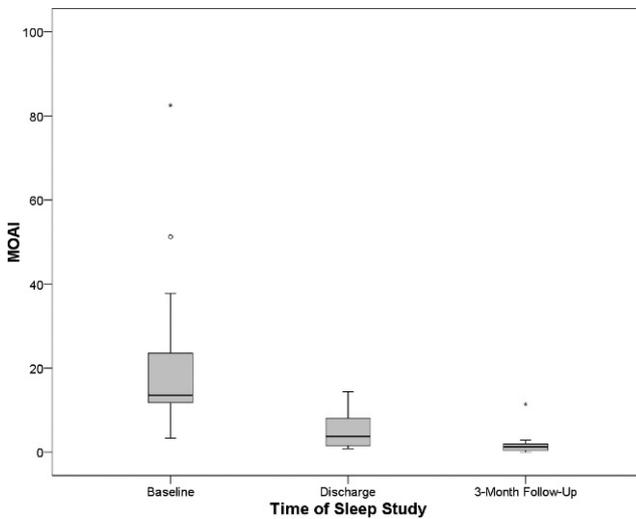


FIGURE 4 Box-and-whisker plots of the primary study variable (i.e., mixed-obstructive-apnea index) stratified by time of sleep study.

DISCUSSION

Though the problems associated with PRS may be numerous, the most pressing problem is upper airway obstruction, which may be severe and usually persists for several months. The genioglossus muscle normally protrudes and depresses the tongue. In PRS, it is displaced posteriorly, thereby forcing the tongue into the palatal groove and obstructing the nasal passage and/or the hypopharynx. Treatment options attempting to treat airway obstruction have traditionally been considerably invasive or only effective in mild cases. The primary aim of the PEBP is to move the base of the tongue forward to widen the hypopharynx. Our data from the trial (Buchenau et al., 2007) and the current study suggest that this protrusion is sufficient to reduce the frequency of apneas not only in the acute phase but also until 3 months after the initial hospital stay. We speculate that the protrusion may also promote mandibular catch-up growth, but this has yet to be proven.

The mandibular distraction technique is the only other approach aimed at advancing the mandible to correct for retrogenia (Denny et al., 2001). This intervention, however, is considerably invasive and associated with several risks, including permanent damage to the inferior alveolar nerve and disturbed intrinsic mandibular growth (Garcia et al., 2002; Hurmerinta et al., 2004; Schaefer et al., 2004). In contrast to this treatment, use of the PEBP was not associated with any significant side effects. Thus, our oral appliance offers a safe, effective, curative, and noninvasive treatment alternative for the time gap between birth and surgical cleft closure.

Severe OSA can cause failure to thrive via either an increased energy expenditure or sleep disturbance (Shprintzen and Singer, 1992). In PRS, failure to thrive may also result from feeding difficulties, necessitating nasogastric

tube feeding in 30% to 50% of patients (Schaefer and Gosain, 2003). This may happen despite apparently successful positional treatment or mandibular distraction. In our study, nasogastric feeding tubes could be removed during PEBP treatment and the infants still showed adequate weight gain 3 months after discharge (Table 2), which appears better than the growth recently reported for a group of infants with PRS treated with a nasopharyngeal airway and a hypercaloric diet (Elliott et al., 1995), although we acknowledge that the observation period in the latter study (Elliott et al., 1995) was longer.

Sleep studies were performed in the supine position. This prevented us from demonstrating that positional treatment alone was insufficient to treat OSA. Although positional treatment has been reported as successful in 70% of infants with OSA (Tomaski et al., 1995), it rarely proved to be an adequate long-term treatment in severe cases. Most infants in our study had been referred to our department after prone positioning had failed. We caution against using prone positioning on a routine basis due to its association with sudden infant death. We also failed to randomize the PEBP to more established treatments such as the pharyngeal tube. In a previous study, however, we compared it with a palatal plate without a velar extension and found the PEBP to be superior. We used the MOAI as our primary outcome parameter. This happened because in neonates, obstructive and mixed apneas share the same pathophysiology (Mathew, 1985), that is, a narrow upper airway, which we hoped to widen with the PEBP. A further limitation includes the fact that treatment of infants with PRS in our department includes not only the PEBP but also the use of suitable feeding techniques (finger feeding, Playtex® Drop-Ins®, Playtex Products, Neenah, WI) and orofacial stimulation (Boiron et al., 2007). This may have introduced bias because it may have contributed to the improvement in OSA seen over the 3-month study period. Given its striking effect on upper airway obstruction in our controlled study occurring within 2 days (Buchenau et al., 2007), we are confident that the PEBP was also the primary cause of the improvement seen over the more extended period covered by the present study.

CONCLUSION

A PEBP with a velar extension was shown to be effective for OSA in infants with PRS. It may offer a safe and effective alternative that helps to avoid other, more invasive interventions until the cleft can be closed surgically.

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