A Randomized Clinical Trial of a New Orthodontic Appliance to Improve Upper Airway Obstruction in Infants with Pierre Robin Sequence

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Objective To test the hypothesis that a new orthodontic appliance with a velar extension that shifts the tongue anteriorly would reduce upper airway obstruction in infants with Pierre Robin sequence (PRS).

Study design Eleven infants with PRS (median age, 3 days) and an apnea index (AI) >3 were studied. The effect of the new appliance on the AI was compared with that of a conventional appliance without a velar extension by using a crossover study design with random allocation.

Results Compared with baseline (mean AI, 13.8), there was a significant decrease in the AI with the new appliance (3.9; *P* value <.001), but no change with the conventional appliance (14.8; *P* = .842). Thus, the relative change in AI was −71% (95% CI, −84-−49) for the new appliance and +8% (95% CI, −52-142) for the conventional appliance, which was significantly different (*P* = .004). No severe adverse effects were observed.

Conclusion This new orthodontic appliance appears to be safe and effective in reducing upper airway obstruction in infants with PRS. *(J Pediatr 2007;151:145-9)*

The Pierre Robin sequence (PRS), characterized by mandibular micrognathia or retrognathia and glossoptosis with or without cleft palate, presents clinically with intermittent upper airway obstruction (UAO) and feeding difficulties, which are most severe during the first months of life.[1-4] PRS can lead to intermittent hypoxia, hypercarbia, cor pulmonale, failure to thrive, neurodevelopmental delay, and even sudden death.[5,6] The incidence of PRS varies between 1 in 8,500 to 14,000 births.[7-10] It is associated with other malformations in about half the cases.[4,6]

Isolated PRS without other malformations does not appear directly to affect neurodevelopment. Active intervention may therefore be required to reduce the risk for neurocognitive impairment resulting from UAO. Endoscopic studies have shown that UAO in PRS results from the reposition of the dorsum of the tongue, an inward movement of the lateral pharyngeal wall, or both.[3] Thus, treatment of UAO should stabilize the pharyngeal wall, widen the hypopharynx, or both by shifting the tongue anteriorly.

Current treatment options for UAO range from prone positioning,[6] use of a nasopharyngeal tube,[11] surgical tongue advancement (ie, glossopexy via tongue-lip adhesion[12]), and mandibular distraction[13,14] to tracheostomy.[15] Some of these treatments are invasive or inconvenient, and none has been subjected to a randomized clinical trial.

An acceptable, convenient, and effective alternative may be an intraoral orthodontic appliance with a velar extension.[16] Our study group has further developed this appliance by repositioning and lengthening the velar extension (the Pre-Epiglottic Baton Plate [PEBP], Figure 1) to shift the tongue anteriorly and thereby widen the hypopharyngeal space. A case study suggested sufficient clinical safety and efficacy.[17] We then evaluated systematically the effect of the PEBP on UAO in a group of infants with isolated PRS. We hypothesized that this new appliance would significantly reduce the frequency of

AI	Apnea index	DI85	Index of all oxygen desaturations to ≤85% SpO_2 per hour of corrected total sleep time
ANOVA	Analysis of variance	MOAI	Index of all mixed and obstructive apneas per hour of corrected total sleep time
CAI	Index of all central apneas per hour of corrected total sleep time	PEBP	Pre-Epiglottic Baton Plate
CPP	Conventional palatal plate	PRS	Pierre Robin sequence
pCO_2	Partial pressure of carbon dioxide	SpO_2	Pulse oximetry-derived oxygen saturation
DI80	Index of all oxygen desaturations to ≤80% SpO_2 per hour of corrected total sleep time	UAO	Upper airway obstruction

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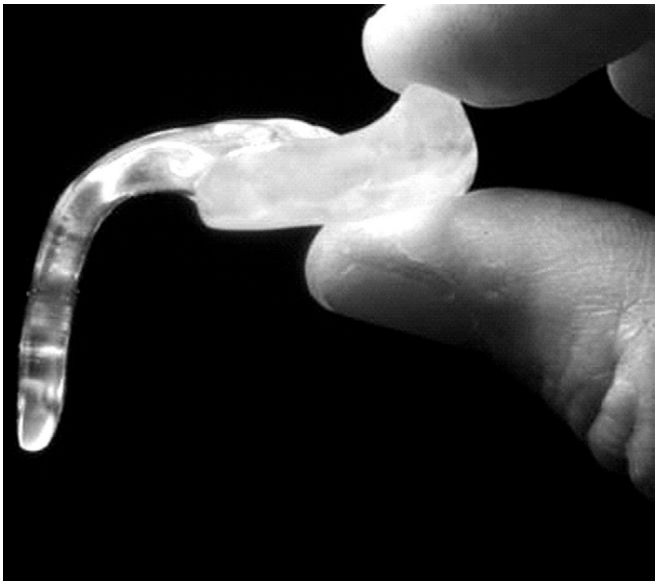

Figure 1. The Pre-Epiglottic Baton Plate with the velar extension.

episodes of UAO during sleep compared with a conventional palatal plate without velar extension (CPP).

METHODS

Patients

Infants up to 3 months with isolated PRS born at our hospital or referred to the neonatal intermediate care unit of our department were eligible for enrollment. They were included when parents or legal guardians gave written informed consent and infants had significant UAO during sleep, defined as a mixed-obstructive apnea index (MOAI) >3 in an initial sleep study performed on the night of admission (baseline assessment). Infants were not included when they had additional major malformations (eg, congenital heart disease), a concomitant upper or lower respiratory tract infection, or severe UAO-related hypoxemia (ie, >3 desaturations to <60% pulse oximetry-derived oxygen saturation [SpO_2] in the initial sleep study).

Study Design

A randomized clinical trial with a crossover study design and 2 study groups was conducted (Figure 2). Patients were enrolled by 1 author (W.B.) and allocated to 1 of the study groups by another author (M.S.U.) not involved in clinical management. The random allocation sequence was generated with random numbers delivered by software. After enrollment, study group 1 received CPP first (study phase 1) followed by PEBP (study phase 2), and study group 2 received PEBP first (study phase 1) followed by CPP (study phase 2). Infants received each appliance for at least 36 hours before the effect on UAO was assessed with a sleep study. During this time, the appliances were removed only for cleaning purposes. This study protocol was approved by the institutional review board of Tuebingen University Hospital.

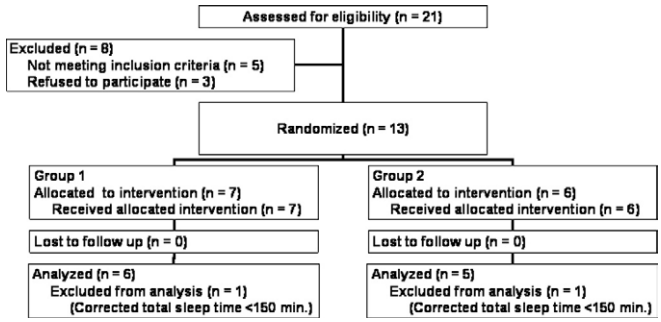

Figure 2. The CONSORT diagram. The chart shows the flow of participants through each stage of the study.

Treatment Modalities

After enrollment, infants had a maxillar cast taken. By using this cast as a model, both types of palatal plates were made from compound soft and hard acrylic (Forestacryl-Strong-S, Foerster, Germany), covering both the palate (including the cleft) and the alveolar ridges. The CPP was chosen for the control phase to enable a blinded analysis. Because we did not expect the CPP to have any beneficial effect on UAO, the CPP was used as a sham procedure. It was designed to reach not more than 3 mm beyond the hard palate. The PEBP had a velar extension of approximately 2 to 3 cm in length. The position of this extension was endoscopically inspected and adjusted when necessary. In severe cases, a wire structure was added to the PEBP and secured on the infant's face with adhesive tape (Steri-Strip, 3M Health Care, USA). Appliances were inserted and kept in situ during sleep and wakefulness. They were held in situ by suction and adhesion; when necessary, an adhesive cream (Corega Superhaftcreme, Procter & Gamble, UK) was used to improve retention.

Performance of Sleep Studies

Cardiorespiratory sleep studies were performed with a computerized polysomnographic system (Embla N7000 and Somnologica Studio 3.0 software, Embla, Canada). The study montage comprised these channels and sensors: chest and abdominal wall movements (respiratory inductance plethysmography, Embla), nasal pressure and linearized nasal airflow (nasal prongs and built-in pressure transducer, Embla), oral airflow (thermocouple, Pro-Tech, USA), snoring (vibration sensor, New Life Technologies, USA), pulse waveform and 2-seconds-average SpO_2 (Radical, Masimo, USA), electrocardiography and beat-to-beat heart rate (Embla), transcutaneous carbon dioxide partial pressure (pCO_2, Microgas 7650, Linde, Switzerland), and digital video (infrared black and white camera, Panasonic, Japan). An electroencephalogram was not recorded so as to interfere as little as possible with the infants' sleep. Recordings commenced in the evening and lasted for at least 8 hours. All infants were studied in the supine position. After the completion of the sleep study, a capillary blood sample was taken and analyzed for pH and

pCO_2. Infants underwent sleep studies at admission (baseline assessment) and after the appliance of the CPP and the PEBP (study phase 1 and 2).

Analysis of Sleep Studies

Recordings were made anonymous by 1 author (M.S.U.) and analyzed by another author (J.S.), who was also not involved in clinical management and blinded to treatment allocation. First, the total recording time was determined, and sleep was distinguished from wakefulness by assessing the infant's behavior for each 60-second epoch of the video recording. Prechtl's behavioral states were assigned to each epoch.[18] State 1 and 2 were regarded as sleep; states 3 through 5 were regarded 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 re-analyzed 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 when they lasted for >5 minutes, and the corrected total sleep time (ie, 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.

Third, recordings were manually re-analyzed for the presence of respiratory events by using standard criteria.[19] In brief, an apnea was scored when: 1) the amplitude of the nasal airflow fell to <20 % of the average amplitude of the 2 preceding breaths; 2) no airflow was detected at the mouth; and 3) the event comprised at least 2 breath cycles (ie, approximately 4 seconds). An obstructive apnea was scored when: 1) criteria for apnea were fulfilled and 2) out-of-phase movements of the chest and abdominal wall were present. For central apneas, we used a definition apart from the guideline. This was done to enhance sensitivity to possible adverse effects of the appliances. Thus, a central apnea was scored when criteria for apnea were fulfilled and no chest or abdominal wall movements were present. Mixed apneas were defined as apneas with both central and obstructive components, each lasting at least 2 breath cycles. The MOAI (ie, index of all mixed and obstructive apneas per hour of corrected total sleep time) and a central apnea index (CAI; index of all central apneas per hour of corrected total sleep time) were calculated.

Fourth, desaturation events were visually confirmed to exclude spuriously low values. Events with a distorted pulse waveform signal within 7 seconds before their onset were considered to be artifactual and were excluded. The occurrence of desaturation events to <80% and <85% SpO_2 was counted, and indices, defined as events per hour of corrected total sleep time, were then calculated for desaturation events to <80% (DI80) and <85% SpO_2 (DI85).

Statistical Methods

The primary study variable was the MOAI, which was a right-skewed variable. For sample size calculations and statistical hypothesis tests, the MOAI was log-transformed to achieve a normally distributed test variable. Because the geometric mean corresponds to the arithmetic mean after log-transformation, descriptive statistics for the untransformed MOAI are given as the geometric mean and its 95% CI.

Sample size calculations on the basis of a pilot study comprising 3 patients revealed that 11 study participants would be sufficient to detect a decrease in the geometric mean from 20 to 5 MOAI with 0.05 type I and <0.2 type II error (ie, actual power, 83.7%). This calculation was based on an estimated SD of 1.4 for the paired difference between the log-transformed baseline and PEBP MOAI.

Except for the MOAI, descriptive statistics such as numbers and percentages and median, minimum, and maximum were used to summarize demographic and other clinical characteristics. Comparisons between baseline and treatment phase stratified by type of treatment were made with the Student *t* test for paired data. Comparisons between treatment modalities (ie, CPP and PEBP) adjusted for study phase, interaction (study phase times treatment), and random effects (ie, individuals) were done with analysis of variance (ANOVA). To adjust for group differences at baseline, the paired difference between baseline and treatment phases was used as the dependent variable in the ANOVA. All statistical tests were performed with the aforementioned log-transformed test variable.

The CAI, DI80 and DI85, and the capillary blood pH and pCO_2 were secondary study variables and not transformed for analysis. Non-parametric tests for paired data (ie, Friedman and Wilcoxon test on ranks) were used for secondary study variables. Pair-wise comparisons with the Wilcoxon test were performed when the global test (ie, Friedman test) revealed significant differences in the study phases. A *P* value <.05 was considered to be statistically significant. No adjustment for multiple testing was performed for secondary study variables. All analyses were completed with statistical software packages: sample size calculations were done with SAS version 9.1 for Windows (SAS Institute, Cary, NC), the remaining analyses were done with SPSS version 12.0.1 for Windows (SPSS, Chicago, IL).

RESULTS

Between November 2002 and January 2005, 21 infants with isolated PRS were born in or transferred to our department. Of these, 5 infants had an MOAI <3 at baseline; 3 parents refused to give consent, and 2 infants were subsequently excluded because 1 sleep study did not comprise sufficient corrected total sleep time (Figure 2). Finally, 11 infants (6 in study group 1 and 5 in study group 2) completed the study. Their demographic and clinical characteristics are given in Table I.

All infants tolerated the study procedures well and underwent the allocated interventions according to the pre-

Table I. Demographic and clinical characteristics of study subjects (N = 11)

Characteristics	Results
Sex (male/female)	3/8
Gestational age at birth (weeks)	39 (36–41)
Birth weight (gm)	3430 (2300–4150)
Length at birth (cm)	50 (47–57)
Head circumference at birth (cm)	34 (32–39)
5 minutes APGAR score	10 (8–10)
Age at admission (days)	3 (0–60)
Duration of stay in hospital (days)	23 (19–71)

Values given as median (minimum-maximum).

defined sequence. No protocol deviations occurred, and an intention-to-treat analysis was performed. Severe adverse events like bleeding, systemic infections, or aspiration were not observed. The most frequent adverse effect was the occurrence of tender spots on the hard or soft palate. They, however, improved in all affected infants after manually reshaping the plate.

Descriptive statistics for the primary and secondary study variables are shown in Table II. In 10 of 11 infants, the MOAI decreased with PEBP, whereas such an improvement was observed in only 4 infants with CPP. The Student *t* test for paired data revealed a statistically significant decrease ($P = .0007$) in the MOAI from baseline (geometric mean, 13.8; 95% CI, 7.5-25.4) to the PEBP phase (geometric mean, 3.94; 95% CI, 1.6-9.5). No such change was observed for the CPP phase (geometric mean, 14.8; 95% CI, 5.4-41.0; $P = .842$). With ANOVA, a statistically significant difference in the change of MOAI by type of treatment was found ($P = .004$). The relative change (95% CI) in MOAI compared with baseline was +8% (−52-142) for CPP and −71% (−84-−49) for PEBP.

However, there was a concern about the presence of a carryover effect. The interaction term between study phase and treatment explained a significant part of the variance of the test variable ($P = .0435$). We, therefore, repeated the analysis after excluding the second study phase (ie, the crossover phase), which did not change the results. The effect of type of treatment on MOAI was still statistically significant ($P = .003$). For secondary study variables, there were no statistically significant differences in treatment phases.

DISCUSSION

In a sample of infants with PRS and clinically significant UAO, we found that a new orthodontic appliance, in contrast to a conventional one, significantly reduced the frequency of mixed and obstructive apneas during sleep. Even mild UAO only recognizable by sleep studies improved after 2 days of treatment. This new orthodontic appliance may thus offer a convenient and effective treatment option for UAO in infants with PRS.

UAO is the predominant clinical problem for infants with PRS. It may lead to intermittent hypoxia, failure to thrive, mental retardation, and even sudden death. The genioglossus muscle normally protrudes and depresses the tongue. In PRS, it is displaced posteriorly, thereby forcing the tongue into the palatal defect and obstructing the nasal passage, the hypopharynx, or both. Earlier attempts to treat UAO in PRS were either invasive (eg, nasopharyngeal tubes or mandibular distraction) or only effective in mild cases and fraught with an increased risk of sudden infant death syndrome (eg, prone positioning). However, most of these treatments were not directed at the cause of UAO or have not been evaluated in a randomized clinical trial.

Oral appliances have been used for >30 years in PRS to facilitate bottle-feeding and to keep the tongue out of the cleft.[20-22] In contrast to these goals, the PEBP aims to push the base of the tongue anteriorly to widen the hypopharynx and promote mandibular catch-up growth. Conventional palatal plates may even be harmful in PRS, because CPP treatment was associated with an increase in the frequency of mixed and obstructive apneas during sleep in 7 of 11 infants.

Severe UAO can cause failure to thrive by either an increased energy expenditure or sleep disturbance.[23] In PRS, failure to thrive may also result from feeding difficulties, necessitating nasogastric tube feeding in 30% to 50% of patients,[10,24] sometimes even despite apparently successful positional treatment or mandibular distraction.[25] In our study, nasogastric tubes could be removed in all infants during PEBP. This may indicate that PEBP does not interfere with, but may even help to promote, oral feeding.

We only enrolled infants with isolated PRS, yet approximately 50% of infants with PRS have it as part of other malformations. We refrained from studying such infants because of the heterogeneous pathogenesis of their UAO. Our own unpublished data, however, suggest that the PEBP is equally effective in relieving UAO in those infants.

We chose a crossover study design despite presence of a (previously unknown) carryover effect. This most likely biased our data. The positive long-lasting effect of PEBP on UAO influenced the following CPP treatment phase in 1 study group. Thus, the results for the CPP treatment would be even worse without this carryover effect. To account for this problem, we re-analyzed our data according to a parallel-group design. This, however, did not change the main finding of this study.

Sleep studies were performed in the supine position. This prevented us from demonstrating that positional treatment alone was insufficient to treat UAO. Although positional treatment has been reported as successful in 70% of infants with UAO,[26,27] it rarely proved to be an adequate long-term treatment in severe cases.[3] In our study, most infants had been referred to our department after prone positioning had failed. We caution against using prone positioning on a routine basis because of its association with the sudden infant death syndrome.

Sleep staging was based on behavioral criteria only, but these are validated and commonly used in neonates.[28] Our decision not to record the electroencephalogram, however,

Table II. Results for the primary and secondary study variables (N = 11)

Variable	Results		
	Baseline	CPP	PEBP
Total recording time (minutes)	667 (604–834)	712 (567–789)	663 (349–939)
Total sleep time (minutes)	344 (300–538)	391 (218–568)	389 (293–389)
Sleep efficiency (%)	51 (36–90)	59 (39–78)	58 (40–84)
Corrected total sleep time (minutes)	333 (279–486)	391 (218–568)	385 (262–573)
MOAI (apneas per hour)	13.8 (7.5–25.4)	14.8 (5.4–41.0)	3.9 (1.6–9.5)
CAI (apneas per hour)	7.1 (0.6–45.2)	9.5 (1.4–19.7)	12.1 (4.2–33.1)
DI85* (desaturation events per hour)	0.7 (0.0–46.8)	0.4 (0.0–71.6)	0.1 (0.0–21.4)
DI80† (desaturation events per hour)	0.0 (0.0–18.3)	0.0 (0.0–42.6)	0.0 (0.0–8.8)
Blood pH	7.37 (7.26–7.46)	7.38 (7.31–7.42)	7.38 (7.35–7.46)
Blood pCO_2 (mm Hg)	45 (31–71)	46 (38–63)	46 (35–56)

Values are given as geometric mean (95% CI; MOAI) or as median (minimum-maximum; the remaining variables).
*Index of desaturation events ≤85% oxygen saturation.
†Index of desaturation events ≤80% oxygen saturation.

prevented us from identifying arousals. Theoretically, the decrease in MOAI thus could have been the result of a reduction in total sleep time, but this was not the case. Recent work from our group has shown that the PEBP leads to improved sleep quality and fewer arousals (unpublished data). Also, we did not identify hypopneas, but these are uncommon in neonates, and there are no standard criteria yet for this age group.

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