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Review

The Tübingen palatal plate approach to Robin sequence: Summary of current evidence☆

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ABSTRACT

Various treatments, many of them considerably invasive, are currently applied to infants with Robin sequence (RS) and accompanying upper airway obstruction (UAO). We present a narrative review of our data on the Tübingen palatal plate (TPP) which show the following: a) in a randomized trial, the TPP was superior to a sham procedure in alleviating UAO; b) children treated with the TPP in infancy showed an intellectual development within the reference range; c) prone positioning is no alternative, as it is ineffective and associated with an increased risk of sudden death; d) the TPP reduces the mixed-obstructive apnea index to near-normal values, both in isolated and most (83%) syndromic RS, e) of 443 infants (129 syndromic) treated with the TPP in our center, 23 (5%) ultimately received a tracheostomy (all with syndromic RS), f) recent data suggest that the TPP may induce mandibular catch-up growth, g) the TPP may also help to reduce respiratory complications following cleft closure in RS, and h) TPP treatment is applied by various centers around the world, although it is unclear if its effectiveness is invariably controlled by endoscopy and sleep studies, although both are necessary. Given these data from peer-reviewed studies, it may be questioned whether the "First do no harm" principle is always adhered to when subjecting RS infants to more invasive procedures such as mandibular distraction osteogenesis or tongue-lip adhesion.

1. Introduction

Robin sequence (RS) is characterized by mandibular retrognathia and micrognathia, glossoptosis and upper airway obstruction (UAO); 80–90% of affected patients also have a cleft palate, i.e. the presence of a cleft is not a prerequisite for the diagnosis. Various treatment approaches exist, ranging from prone positioning, insertion of a naso-pharyngeal tube or application of continuous positive airway pressure (CPAP) to operative procedures such as tongue-lip adhesion, mandibular distraction osteogenesis or tracheostomy (Poets and Bacher, 2011).

Any assessment of the effectiveness of these different treatment approaches should focus on the two main clinical problems in RS: sleep related UAO and feeding problems. A third issue is whether a specific treatment helps to induce mandibular catch-up growth, i.e. will ultimately contribute to correcting the underlying anatomy, and finally, will it impose a significant burden or risk to the patient?

2. Intervention & patients

At Tuebingen University Hospital, an interdisciplinary team consisting of neonatologists, pediatric sleep specialists, neonatal nurses and speech therapists, orthodontists and craniomaxillofacial surgeons developed a treatment approach that is centered around an orthodontic appliance, the Tuebingen Palatal Plate (Fig. 1a) (von Bodman et al., 2003). It consists of a palatal base plate that covers the hard palate and the cleft as well as the alveolar ridges to support a velar extension (spur) of individual length (approximately 3 cm) that is dorsally attached to the plate and ends just above the

☆ This work is dedicated to Margit Bacher, DD – it was her invention and commitment that made everything else possible.

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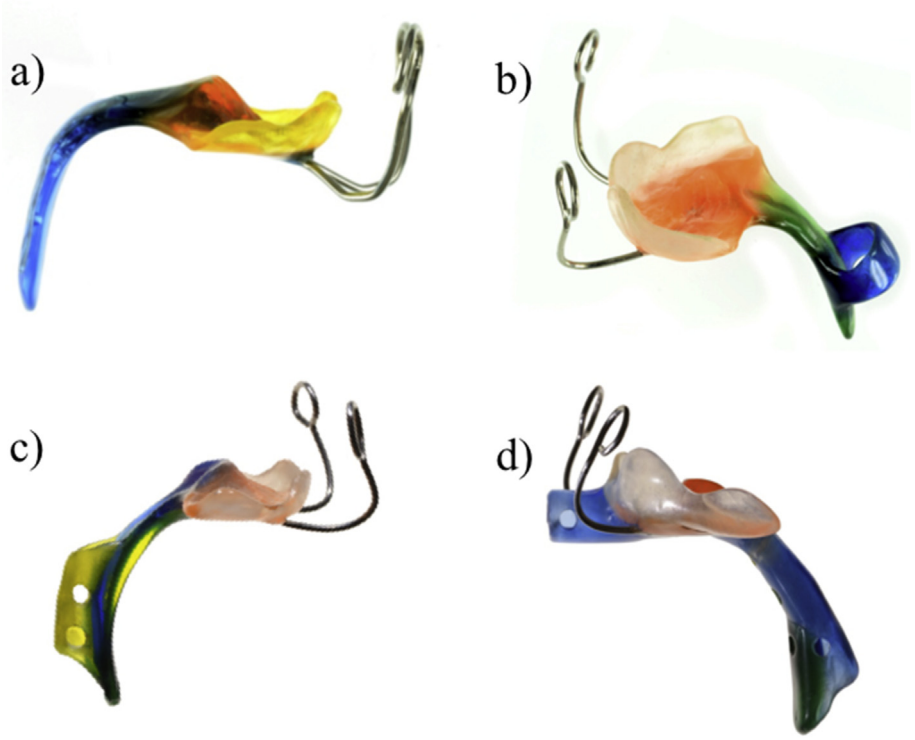

Fig. 1. Modifications of the TPP as used in patients with isolated (a) and syndromic (b–d) RS: a) classical plate with velar extension; b) modified plate with a ring or c) tube attached to the extension; d) modified plate with a tube that has an extra-oral extension. Reproduced from Muller-Hagedorn et al. (2017), with permission.

epiglottis. Its fit is controlled using unsedated fiberoptic nasopharyngoscopy. During this endoscopy, which usually takes only 1–2 min, the tip of the velar extension is checked and its angle, responsible for the forward-shifting of the tongue base, adjusted so that it pushes the tongue base sufficiently forward to erect the epiglottis, thereby widening the pharyngeal space (Fig. 2). If the airway appears endoscopically open, the prototype plate is finished and a strengthening wire incorporated into the extension to safeguard the device against mechanical failure. Plates are held in situ with the help of a fixative cream (Corega Super-Haftcreme Neutral; Procter & Gamble, Cincinnati, OH) and by extraoral wire bows secured to the infant's face using adhesive tape (Steri-Strip and Cavilon-No Sting Barrier Film, Steri-Strip Compound Benzoin Tincture, 3 M Health Care, St. Paul, MN, USA). The TPP is worn continuously and its fit regularly controlled by the nursing staff who instructs the parents on handling and care. The plate is briefly removed once daily to clean the alveolar ridge and to inspect the intraoral soft tissues for pressure marks or decubitus, which almost exclusively develop in the first few days of wearing the plate. If these are present, plates are abraded in these spots. Mean duration of hospital stay in both isolated and syndromic RS is 2–3 weeks. About 3 months after the initial hospital discharge, infants are readmitted for a repeat sleep study; they often also need a larger plate at this time due to cranial growth. Involving parents in handling the plate as early as possible is crucial for treatment success, as they have to learn how to handle and insert the plate

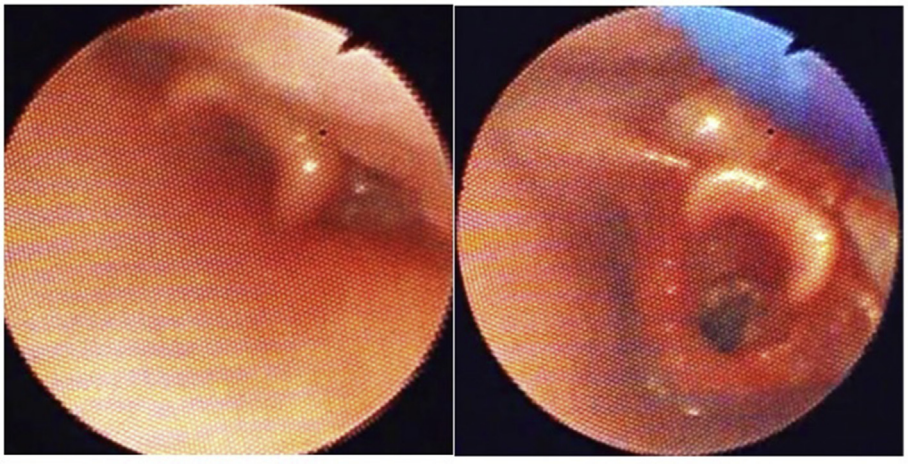

Fig. 2. Endoscopic view with (right) and without (left) the plate in situ.

without dislocating it on the maxilla, how to inspect the gingiva for pressure marks and how to clean the plate. In our experience, early parental involvement is beneficial, as parents become highly motivated once they see how freely their baby can breathe after insertion of the plate.

For the last 8 months, we have successfully moved to digital scanning (Trios 3 Intraoral Scanner, 3Shape, Copenhagen, DK) and 3D-printing (3Shape Ortho Appliance Designer) to adapt and produce a first TPP prototype (Fig. 3) (Xepapadeas et al., 2018), which is less traumatic to the infant than the traditional imprint taking. The final plate, that also includes the strengthening wire, continues to be fabricated manually. Using this approach, we have now produced 3D-printed prototype plates in >50 infants, 12 of which had RS. The technique, however, yet awaits further evaluation (Xepapadeas et al., 2019).

Clinical effectiveness of the TPP is regularly controlled using sleep studies, performed immediately prior to and a few days after treatment onset, and again at least 3 and 6 months after initiating therapy. The main outcome of interest in these studies is the mixed-obstructive apnea index (MOAI), which should be < 3/hour. We monitor the MOAI as our main outcome as this best reflects the extent of sleep-related upper airway obstruction, and because the more widely used mixed-obstructive apnea-hypopnea index (MOAHI) is difficult to apply in infants, as the hypopnea definition includes cortical arousals, for which no universally accepted definition exists in infants, so that the classification of hypopneas is still considered optional in pediatric patients (Berry et al., 2012) and because we consider central events irrelevant in RS. If this sleep study still shows a MOAI >3, the plate is modified or, in some rare syndromic cases, CPAP or high-flow nasal cannula therapy is added to the TPP. Treatment is usually discontinued at 6–8 months of age, depending on sleep study results (which should show a MOAI $\leq$1) and the facial profile at the time.

Treatment also comprises appropriate feeding techniques (finger feeding and Playtex Drop-Ins®, Playtex Products, Edgewell, North Bergen, NY, USA) and an orofacial stimulation therapy according to Castillo-Morales®. Effectiveness of this orofacial stimulation therapy, however, has yet only been formally studied in older children with Down syndrome (von Lukowicz et al., 2019), so its exact role in infants with RS needs further investigation.

Between 1998 and 2018, 443 infants with RS were treated in our center using the above approach; in 129 (29%) of these, RS was part of an underlying syndrome. None of the 314 infants with isolated RS required a tracheostomy after initiation of treatment with the TPP, but 3 had already arrived with a tracheostomy in place, which could be closed a few weeks after admission. Of the syndromic patients, 23 (17%) ultimately required a tracheostomy, mostly those with a swallowing disorder (e.g., Möbius syndrome) or laryngeal problems, which is a higher rate than that (9.3%) reported in a recent meta-analysis on mandibular distraction osteogenesis (Breik et al., 2016), but does not involve the perioperative risks of the latter procedure. No infant received other surgical intervention(s) for its breathing problems.

3. Study design

In this narrative review of the TPP approach to RS, we will focus on the following questions:

(a) Is the TPP more effective than a sham procedure, i.e. a plate without extension, and what is the best outcome to prove this?
(b) What about non-surgical alternative treatments?
(c) Are patients with isolated RS treated with the TPP in infancy intellectually compromised when reaching school age?
(d) Is the TPP already indicated for mild expressions of RS, e.g. with a MOAI <5, or would a trial of prone positioning be sufficient here?
(e) Is the TPP also effective in severe expressions of RS, i.e. if MOAI is > 10 and/or in syndromic RS, which are otherwise often referred for surgical interventions?
(f) Are there indications that the TPP induces mandibular catch-up growth?
(g) Does the TPP also help to reduce post-operative complications following cleft closure in RS patients?
(h) As most reports on the TPP are from only 1 center, can this treatment also be adopted elsewhere?

4. Results

4.1. Short-term outcomes: MOAI and weight gain

Gold standard for effectiveness testing in clinical medicine is the randomized controlled trial design. However, we are aware of only 1 study that applied this design to RS patients. This study compared the TPP against a conventional palatal plate used as a sham

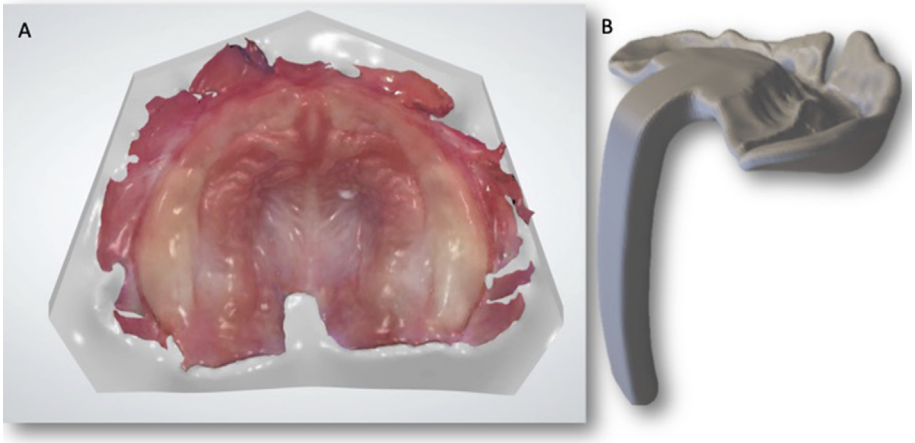

Fig. 3. Tübingen palatal plate, produced through scanning the oral cavity and 3D-printing. a) Digital intraoral scan of the palate, used as the basis for: b) A fully digitally CAD/CAM manufactured plate with velar extension.

procedure in a randomized crossover trial involving 11 infants <3 months of age with isolated RS and a MOAI >3 in a sleep study performed in the supine position. After 48 h of treatment, median MOAI had fallen from 13.8/h to 3.9/h with the TPP ($p < 0.001$), while it remained unchanged at 14.8/h with the sham procedure (Buchenau et al., 2007). In an uncontrolled longitudinal continuation to this study, involving 15 patients (median age at onset of treatment, 5 days), median MOAI fell from 17.2 to 1.2 after 3 months of treatment with the TPP. Notably, all infants had their feeding tubes removed prior to discharge, and continued to gain weight at a mean rate of 24 g/d at discharge and 19 g/d at the 3-month follow-up. All infants continued to be fully orally fed at this follow-up (Bacher et al., 2011).

4.2. Comparisons with other non-surgical treatments

The TPP is the first intervention applied in RS whose effectiveness has been tested against a sham procedure (placebo) using a randomized controlled study design. We compared against a plate without extension rather than another non-surgical treatment such as CPAP or a nasopharyngeal tube based on the principle of using a placebo as comparator treatment in randomized controlled trials. Also, the above alternative treatments, although potentially similarly effective as the TPP, do not correct the anatomical anomalies seen in RS, i.e. do not bring the tongue into a horizontal position (supporting sucking and swallowing), do not induce mandibular catch-up growth (see below), and may not allow families to move around freely with their baby. Obtaining data on a comparison between the TPP and surgical treatments would require large international cohort studies/registries.

4.3. Long-term outcome: intellectual development in children initially treated with the TPP

In studies on the neurocognitive outcome of children with RS, rather severe intellectual impairment is often reported (Caouette-Laberge et al., 1994; Kapp-Simon and Krueckeberg, 2000), with only few exceptions to this rule (Thouvenin et al., 2013). Because our clinical impression was not in line with these data, we hypothesized that this impairment may be a result of frequent exposure to intermittent hypoxia resulting from sleep-related UAO, and that this may be prevented by instituting an effective treatment early in life. We thus determined the cognitive and psychosocial outcome in 34 children with isolated RS aged 4–11 years treated with the TPP in early infancy and 34 aged-matched healthy controls. We also compared results on the Kaufman-Assessment Battery for Children and a self-concept inventory with reference data. Parents rated emotional and behavioral problems of their children. We found no significant differences concerning self-concept, emotional or behavioral problems between cases and controls, but RS children scored lower than controls with regard to their cognitive development. Results, however, were still within the reference range. For example, mean scores on the mental and simultaneous processing scales were at 105 and 108, respectively, in RS vs. 114 and 118 in controls (Drescher et al., 2008). Thus, we conclude that these results do not support the hypothesis that children with isolated RS have a more negative self-concept or severe behavioral or cognitive problems.

4.4. Prone positioning as a potential alternative treatment for mild cases

A recent European survey on current practice patterns for RS patients showed that two-thirds of clinicians used prone positioning, especially in mild RS cases (van Lieshout et al., 2015). This practice, however, may be questioned because of the association of the prone sleeping position with an increased risk of sudden death. For example, in a large study involving 745 sudden infant death syndrome infants and 2411 controls across 20 European regions, the prone position was associated with 14-times the risk of death compared to the supine position in multivariate analysis (OR 13.9, 95% CI 8.9–21.6) (Carpenter et al., 2004). As there is nothing to suggest that RS infants are exempt from the mechanisms through which the prone position is thought to increase the risk of death, pediatricians might even face legal problems if they recommend prone positioning for their patients with RS, particularly given that the effectiveness of cardiorespiratory home monitoring in preventing death has never been proven.

Despite these risks, nothing was known about the effectiveness of prone positioning in improving UAO in RS infants. Recently, a French group published a retrospective study involving 18 RS infants who were placed in both positions (no information was provided on the sequence in which positions were applied). The authors reported a higher sleep efficacy in the prone position (mean, 83 vs. 70%, $p = 0.04$), but no significant change in the obstructive apnea-hypopnea index (39 vs. 33/h, $p = 0.13$) (Coutier et al., 2019).

Taken together, prone positioning should be discouraged even for infants with a mild expression of RS because of a lack of evidence for its effectiveness and the above association with a considerably increased risk of sudden infant death.

4.5. Effectiveness of the TPP in severe and/or syndromic forms of RS

As mentioned above, surgical interventions such as mandibular distraction osteogenesis or tracheostomy are often recommended for these infants. We performed two uncontrolled longitudinal cohort studies in this patient group. One was a summary of our 10-year experience with the TPP in 122 infants with *isolated* RS and included 55 infants with a MOAI >10 in their initial sleep study (mean 29, interquartile range (IQR) 15–51); all infants underwent sleep studies at admission, prior to hospital discharge and approximately 3 months after discharge (Buchenau et al., 2017). All infants were treated with the TPP, supplemented by orofacial stimulation therapy. In their pre-discharge recording, median MOAI had fallen to 1.9 (IQR 9.6–5.4); it further decreased to 0.2 (0–1.3) by the time of the 3-month follow-up. The latter results were similar to those seen in infants admitted with a MOAI <5, in whom median MOAI also had fallen to 0.2 at follow-up (IQR 0–0.5). The number of infants receiving nasogastric tube feedings in the total cohort decreased from 66% at admission to 8% at discharge, while Z-scores for weight improved from −0.7 to −0.5 ($p = 0.02$).

The other cohort study involved 68 consecutive patients with *syndromic* RS admitted to our center during a 7-year period (2003-9). Fifty-six patients completed their TPP treatment, while in 4, no TPP was indicated because MOAI was <3 or because of laryngomalacia; 3 infants (4%) ultimately received a tracheostomy (Muller-Hagedorn et al., 2017). The remaining 5 patients did not tolerate TPP treatment, mostly related to problems with swallowing (related to CHARGE association or Wiedemann-Beckwith syndrome as their underlying diagnosis). In contrast to those with isolated RS, the type of TPP used varied in these patients, with 23 patients using a plate with a perforated tube ($n = 20$) or a ring ($n = 3$) attached to the pharyngeal extension to prevent collapse of the lateral pharyngeal or laryngeal wall (Sher types 3–4; Fig. 1b–d).

Underlying diagnoses in the 56 infants tolerating TPP treatment were craniofacial dysostoses ($n = 13$), synostoses ($n = 5$) and yet unclassified dysmorphic syndromes or rare conditions

such as Möbius sequence or single incisor syndrome. Similar to the above patients with severe isolated RS, the syndromic RS patients also had a more than 80% reduction in MOAI between admission and discharge. Also, in the 46 infants in this group with complete data, Z-scores for weight at discharge were comparable to those documented at birth; i.e. postnatal growth failure could be avoided. At the same time, the number of infants who were exclusively fed via nasogastric tube decreased from 23 to 7 (Muller-Hagedorn et al., 2017).

Thus, in this heterogenous group of patients with syndromic RS, TPP treatment was associated with major improvements in sleep study results, but in contrast to our data on infants with isolated RS, some did not tolerate TPP treatment (mainly because of swallowing problems or tongue hyperplasia), and/or ultimately needed a tracheostomy.

4.6. Mandibular catch-up growth during TPP treatment

An important question for any treatment success in RS infants is whether the treatment applied stimulates mandibular growth. Up to now, however, it is undecided whether catch-up growth occurs at all in RS (Purnell et al., 2019). Our personal experience with hundreds of Robin infants suggests, however, that it does, but this needs to be proven objectively, which is difficult to achieve as it usually involves radiation exposure.

Four years ago, we introduced routine determination of the Jaw Index into our clinical protocol for RS infants. It is defined as the alveolar overjet (in mm) times maxillary arch/mandibular arch (also measured in mm) and can quantify the extent of retrognathia in neonates by means of a measuring tape and a micrometer depth gauge (van der Haven et al., 1997). High values indicate a more severe retrognathia (van der Haven et al., 1997). Advantages include its simplicity, applicability as a screening method and suitability for clinical follow-up measurements.

In an evaluation of our data obtained in 31 consecutive RS patients admitted after introducing the Jaw Index (22 isolated, 9 syndromic), we had complete results on the Jaw Index, determined at admission, discharge and 3 months after discharge, in 20. Median values for the Jaw Index decreased from 8.8 (IQR, 6.3–11.3) at admission to 2.1 (2.0–4.0) at the 3-month follow-up ($p < 0.001$). At the same time, the MOAI decreased from 9.7 (4.8–24.2) to 0.0 (0–1.3; $p < 0.002$), although the correlation between both parameters was not significant. There was, however, a positive correlation of the MOAI with the Maxillary/Mandibular Arch Ratio measured as part of the Jaw Index determination ($r = 0.58$; $p < 0.001$). These longitudinal cohort data suggest that TPP treatment may alleviate UAO by promoting mandibular growth (Wiechers et al., 2019). Whether this catch-up growth is sufficient, however, to resolve UAO permanently in RS has yet to be proven.

4.7. Perioperative morbidity after cleft palate repair in RS patients

In a recent study involving 30 children with Robin sequence and 45 cleft palate controls, 26 RS children had been treated by prone positioning, four needed additional treatment. Mean age at cleft closure was 12.4 months for RS, and 10.9 months for cleft patients without RS ($p = .05$). Eight RS patients developed postoperative respiratory distress (PRD) within 48 h, one additional patient after 7 days, while none of the non-RS patients developed this complication. According to these data, almost one third of RS patients may develop PRD following palatoplasty (van Lieshout et al., 2016). In contrast, when we analyzed our data from a retrospective cohort of 234 RS infants admitted in 2003–2018 and treated with the TPP, of the 157 with complete records, cleft palate repair was performed at a mean age of 10 months with only 1 case of PRD in an infant with syndromic RS who needed intubation until day 13 post-operatively (Reinert et al., 2019). These data add yet another aspect to the evidence on the efficacy of TPP treatment.

4.8. Generalizability

Although the majority of studies reported above are from just one center, TPP treatment is also applied elsewhere. In fact, one of the largest case series on RS infants treated with an appliance similar to the TPP, only with a slightly shorter velar extension, comes from a South African group of maxillofacial surgeons (Butow et al., 2016). They reported on 266 RS infants, 187 of which were treated with their modification of the TPP, of which 159 (90%) were reported as treated successfully regarding their breathing problems and 143 (77%) regarding their feeding problems. Plates were used successfully, however, only in infants with a cleft palate.

In 2011-13, we did an epidemiological survey in Germany to gather information about the incidence of RS and its initial treatment. Besides confirming that the incidence of RS is approximately 1:8500 life births, we learned that the TPP (or modifications thereof) had been used in 51 of 138 reported infants in 7 centers in Germany (Maas and Poets, 2014). There have also been several case reports from other (international) centers reporting successful treatment results with this approach (Kochel et al., 2011; Gerzanic et al., 2012; Jadhav et al., 2017).

Recently, we performed a 3-center longitudinal cohort study on the effectiveness of the TPP to test the hypothesis that its effectiveness is independent of the team carrying out this treatment. Although one of these centers had difficulties in setting up routine sleep studies, all managed RS patients successfully with the TPP, and the decrease in MOAI in the 2 centers ultimately reporting sleep study results was comparable to that reported in the studies from the inaugurating center (Poets et al., 2017). Although data were not reported separately for each center, the overall decrease in median MOAI from 15.9 (IQR 6.3–31.5) at admission to 2.3 (1.2–5.4) at discharge implies an effectiveness of the TPP in this bicentric study that was similar to that reported in infants only treated in the authors' center (see above), which is particularly noticeable as both syndromic and isolated RS infants were included in this study.

5. Outlook

As shown above, TPP treatment seems effective, both in isolated and syndromic/severe RS, has been successfully used in various centers, and is associated with normal long-term development, at least in patients with isolated RS. The question now is: Despite numerous publications on the effectiveness of this treatment, why has it not yet gained more widespread, particularly international, acceptance? Three aspects may be relevant here:

i) There has been no comparison yet of the TPP with other (surgical or non-surgical) treatments, and there are no treatment guidelines on RS management. This is true, however, for most treatments applied for rare conditions. Nonetheless, the need to adopt a new treatment is less pressing as long is there is no high-quality evidence. As a potential solution, we are currently working on establishing an international data base including a list of core outcome criteria so that all centers around the world can enter results of their treatment approach and compare them with data from other centers using a different approach.

ii) TPP treatment requires a team approach, as it involves various disciplines, including neonatology, pediatric sleep medicine, orthodontics, cranio-maxillofacial surgery,

neonatal nursing and speech therapy. In a country like Germany, 70–80 infants are born annually with RS. Installing such a large team thus only makes sense if focused on 4–5 centers distributed across the country, also because defining the best shape of the plate requires considerable experience, particularly in infants with syndromic RS. Nonetheless, given the comparatively low burden of care associated with TPP treatment, identifying these 4–5 centers would be worthwhile, both from a patients' or parents' point of view, but also economically, as TPP treatment comes at comparatively low cost and usually involves no additional airway management after the initial 6–8 months of wearing the TPP. In Europe, a format for this may be provided by the newly founded reference centers for rare diseases (https://www.eurordis.org/publication/centres-expertise-and-european-reference-networks-rare-diseases), but the situation is less clear in other parts of the world.

iii) Diagnosis of RS is yet mostly made postnatally, potentially confronting physicians and parents with an emergency situation where rapid decisions have to be taken. This situation might be improved with better prenatal detection rates for RS, allowing parents to familiarize themselves with the diagnosis and to arrange for delivery in a setting with experience in the perinatal management of these infants. Most reports on antenatal diagnosis of RS are MR-based, i.e. were not part of prenatal screening (Kaufman et al., 2016), but there are also attempts at diagnosing RS via prenatal ultrasound (Linz et al., 2011; Gueneuc et al., 2019). Improved standards for antenatal screening, including guidelines on RS detection, are urgently needed.

iv) One of the reasons why the situation for TPP treatment is different in Germany may be parental pressure. Parents tend to consult the internet if confronted with a rare disease in their newborn baby, where they may find reports on other parents' experience with TPP treatment, but these are mainly written in German. As 2/3 of RS infants admitted to our center are referred upon parental request, some colleagues in Germany may have been motivated enough by these self-referrals also to install this treatment approach locally, but this is less likely to happen internationally. Thus, RS infants share the fate of many patients with rare diseases: it takes long to disseminate knowledge on new treatment paradigms. Nonetheless, given the “primum nil nocere” principle and the large number of studies demonstrating its effectiveness, we have to ask ourselves why considerably more invasive procedures continue to be recommended for RS infants up to this date (Resnick et al., 2019).

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

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