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Non-surgical and surgical interventions for airway obstruction in children with Robin Sequence

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ABSTRACT

There is widespread lack of consensus regarding treatment of airway obstruction in children with Robin Sequence. This study aimed to systematically summarize outcomes of non-surgical and surgical options to treat airway obstruction in children with Robin Sequence. The authors searched the Medline, EMBASE and CENTRAL databases. Studies primarily on mandibular distraction were excluded. Study quality was appraised with the Methodological Index for Non-Randomized Studies (MINORS) score. Forty-eight studies were included, of which 45 studies had a retrospective non-comparative set up, two studies had a prospective design and one study was a clinical trial. The mean MINORS score was 7.3 (range 3–10). The rates of successful relief of the airway obstruction (SRoAO) were: not available for orthodontic appliance (2 studies, n = 24), 67–100% for nasopharyngeal airway (6 studies, n = 126); 100 % for non-invasive respiratory support (2 studies, n = 12); 70–96% for tongue-lip adhesion (11 studies, n = 277); 50–84% for subperiosteal release of the floor of the mouth (2 studies, n = 47); 100% for mandibular traction (3 studies, n = 133); 100% for tracheostomy (1 study, n = 25). The complication rate ranged from zero to 55%. Although SRoAO rates seemed comparable, high-level evidence remains scarce. Future research should include description of the definition, treatment indication, and objective outcomes.

1. Introduction

Robin Sequence (RS) is a congenital facial condition occurring in 1 in 8,500 to 1 in 30,000 newborns (Bushe, 1983; Tolarova and Harris, 1995; Printzlau and Andersen, 2004). The French stomatologist Pierre Robin originally defined RS in 1923 as a triad of mandibular hypoplasia, glossoptosis and airway obstruction. Some clinicians also include cleft palate as part of the definition. However, there is no clear, unanimous definition of RS.

The main problems in RS include airway obstruction and feeding difficulties, both occurring with varying degree of severity. In this review we focus on airway obstruction. Airway obstruction may vary from virtually non-existing to apneas, increased activity of breathing muscles, failure to thrive, cyanosis and ultimately respiratory insufficiency. Patients with RS are frequently diagnosed with obstructive sleep apnea (OSA), which in turn is associated with considerable morbidity. The prevalence of OSA has been reported to be between 46 and 100 % in children with RS (Gilhooly et al., 1993; Wilson et al., 2000; Bravo et al., 2005; Anderson et al., 2011). The current gold standard to diagnose OSA is a nocturnal polysomnography (Section on Pediatric Pulmonology, 2002).

A number of treatment options are available to treat airway obstruction in RS, but there is currently no widely accepted guideline or treatment algorithm. Most clinicians agree that prone

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positioning is the treatment of choice for mild cases, but a large variety of treatment options exist for cases in which prone positioning fails. There is an obvious need for a more evidence-based approach to treatment of children with RS.

The aim of our study was to systematically summarize outcomes of non-surgical and surgical interventions for airway obstruction in children with RS based on effectiveness and safety. This review intends to inform clinicians about the current state of evidence in literature and to highlight research gaps, thereby functioning as a guide in the set-up of future clinical studies.

2. Material and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was adhered to as much as possible in the preparation of this review. No approval was necessary by an institutional review boards due to the nature of this study.

2.1. Search strategy

A detailed systematic review protocol was prepared by all authors. The review was conducted using detailed search and extraction methods for the MEDLINE, EMBASE and CENTRAL databases aimed at studies published after January 1st 2000. The reference list of included studies was checked for additional eligible studies.

2.2. Eligibility criteria

Studies were considered eligible for inclusion if: 1. Study participants had a diagnosis of RS; 2. Study participants were below the age 18 years old; 3. Studies had more than 5 participants; 4. Studies had a focus on non-surgical and/or surgical intervention(s) to manage the airway obstruction; 5. Studies contained original data on treatment outcomes; 6. The study was published in English.

The diagnosis of RS was author-defined to avoid excluding relevant studies. Given the ongoing debate on specific, more or less obligatory features of RS, all definitions were accepted. Children with a diagnosis of mandibular hypoplasia and airway obstruction were also considered to have RS. Children with both isolated and non-isolated forms of RS were included.

Since studies specifically on mandibular distraction in children with RS already have been extensively covered in reviews by Ow, Bookman and Paes, we decided to exclude articles solely on mandibular distraction (Ow and Cheung, 2008; Bookman et al., 2012; Paes et al., 2013).

Study quality was appraised with the Methodological Index for Non-Randomized Studies (Slim et al., 2003) and the Oxford Centre for Evidence-Based Medicine (CEBM) scale. MINORS consists of a 12-item checklist. The first eight items focus specifically on non-comparative studies. Each item is scored 0 (not reported), 1 (reported, but inadequate) or 2 (reported and/or adequate). The maximum score is 16 for non-comparative studies and 24 for comparative studies. Primary outcomes included successful relief of the airway obstruction without necessity for further treatment (SROAO), the obstructive apnea hypopnea index (oAHI) and mortality (not disease specific). Secondary outcomes included side effects, complications and improvement of oxygen saturation.

2.3. Selection of studies

Initially, all papers were independently examined on titles and abstracts by two authors (MvL and MvdS). Afterward, the full text manuscript was assessed for eligibility on basis of the defined criteria by the same authors. Any disagreements were resolved by discussion between the two review authors and if needed by involvement of another author of our review group.

2.4. Data extraction and quality appraisal

Data extraction of the manuscripts was performed independently by two authors (MvL and MvdS) using a customized data collection form.

3. Results

Forty-eight studies were included in the qualitative synthesis. All studies except Buchenau et al. were Oxford CEBM Level type IV. We did not find any studies that focused specifically on prone-positioning. The mean MINORS score was 7.3 (range 3–10). Reported outcome measures differed and included: clinical signs of airway obstruction, overnight polysomnography outcomes (oAHI, mixed-obstructive apnea index (mOAI), central apnea index (CAI), oxygen desaturation index (ODI), capillary blood pH, CO_2 pressure), weight velocity, body weight, oxygen saturation, growth, (in-patient) hospital stay, complication rate, need for additional surgery, need for tracheostomy, questionnaires on satisfaction, maxilla-mandibular discrepancy and death. Eleven studies mentioned the use of polysomnography in their clinic, but specific data were not always available (Fig. 1).

3.1. Orthodontic appliance (Table 1) (Two studies with 24 patients in total) (Buchenau et al., 2007; Bacher et al., 2011)

Two studies of the same group on the use of an orthodontic appliance were found. In a prospective observational study and a randomized clinical trial, the study group of the Tuebingen Hospital in Germany described the use of an intraoral orthodontic appliance with velar extension shifting the tongue anteriorly, thereby widening the hypopharyngeal space (Buchenau et al., 2007; Bacher et al., 2011). In the study of Buchenau et al. in 90% of the children in the pre-epiglottic plate group an improvement of mOAI was observed, compared to only 36% of infants in the control group who received a conventional appliance. In the study of Bacher et al. a significant decrease in mean mOAI was noted at the three-month follow-up.

Reported side-effects included soft tender spots. In both studies only children with an isolated RS participated.

3.2. Nasopharyngeal airway (Table 2) (Six studies with 126 patients in total)

Techniques differed in the six available studies, but in general a nasopharyngeal airway was created by modifying an endotracheal tube and position of the distal end of the tube on top of the larynx, bypassing the tongue base. The nasopharyngeal airway permits the child to breathe through the tube, and may break the seal between the posterior placed tongue base and the pharynx wall. The mean duration of the use of a nasopharyngeal airway ranged from 44 days to 8 months. The SROAO rates ranged from 67 to 100%. In the study of Wagener four complications were reported: three patients developed a chest infection and one patient developed right nostril stenosis (Wagener et al., 2003).

3.3. Non-invasive respiratory support (Table 3) (Two studies with 12 patients in total) (Leboulanger et al., 2010; Girbal et al., 2014)

Only two studies were found on non-invasive respiratory support (Leboulanger et al., 2010). Non-invasive respiratory support

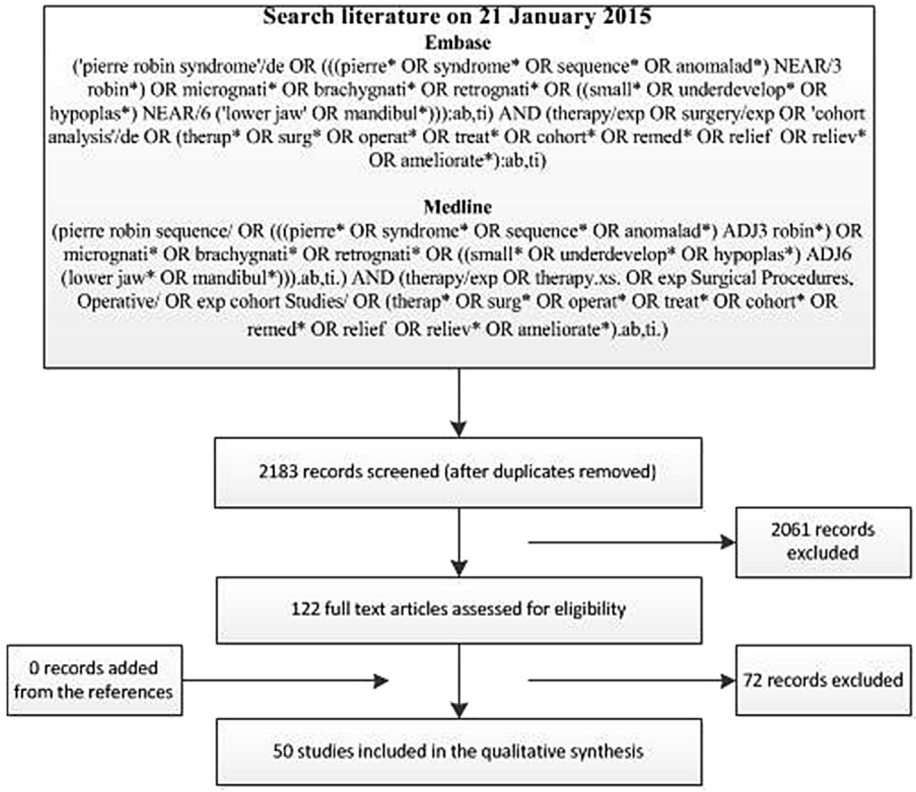

Fig. 1. Flow diagram of literature search and selection process.

Table 1
Orthotic appliance (PEBP: Pre-epiglottic baton plate). *Authors part of the same study group.

First author and year	Design	N	Mean age of the start of treatment	Indication	Primary outcome (1 = SROAO, 2 = AHI, 3 = mortality)	Complication rate	MINORS
Buchenau et al. (2007)[a]	Randomized clinical trial with crossover design.	11	N/A (however article states age at start treatment was below 60 days)	mOAI > 3. Exclusion criteria was (amongst others) OSA-related severe hypoxemia (defined as 3 or more desaturation events to <60% pulse oximetry-derived oxygen saturation (SpO2) in the initial sleep study	1. N/A 2. In 90% an improvement of mOAI was observed in the pre-epiglottic plate group compared to only 36% of infants in the control group who received a conventional appliance. 3. Not reported	N/A	N/A[a]
Bacher et al. (2011)[a]	Prospective, observational study design	15	N/A (however article states age at start treatment was below 60 days)	mOAI > 3. Exclusion criteria was (amongst others) OSA-related severe hypoxemia (defined as 3 or more desaturation events to <60% pulse oximetry-derived oxygen saturation (SpO2) in the initial sleep study	1. N/A 2. N/A in %, but they found a significant decrease in mean mOAI of 17.2 to 1.2 at 3-month follow-up 3. Not reported	N/A	10

[a] Because of its design (RCT) MINORS is not applicable.

includes continuous positive airway pressure (CPAP) and non-invasive positive pressure (NIPP) ventilation. By applying positive pressure during a breathing cycle, the airway patency is maintained. Leboulanger described the use of home ventilation with a custom-molded mask. The mean duration of the home ventilation therapy was 16 months. In this study an SROAO rate of 100% was found. In a large study on non-invasive ventilation by Girbal et al., five patients with RS were described (Girbal et al., 2014). All started non-invasive ventilation at a young age (median 1 month with an interquartile range between 0 and 2 months). Although specific data on RS patients were missing, the study reported non-invasive ventilation led to clinical improvement in all cases and mostly minor complications were reported in 14.7% of the cases including local skin irritation, skin breakdown, conjunctivitis and slight facial deformation.

3.4. Tongue-lip adhesion (Table 4) (Eleven studies with 277 patients in total) (Hoffman, 2003; Kirschner et al., 2003; Denny et al., 2004; Huang et al., 2005; Cozzi et al., 2008; Bijnen et al., 2009; Rogers et al., 2011; Abramowicz et al., 2012; Mann et al., 2012; Sedaghat et al., 2012; Mokal et al., 2014).

Tongue-lip adhesion is a technique first popularized by Douglas in 1946 in which the tongue is sutured to the lower lip in

Table 2
Nasopharyngeal airway.

First author and year	Design	N	Mean age of the start of treatment	Indication	Primary outcome (1 = SROAO, 2 = AHI, 3 = mortality	Complication rate	MINORS
Chang et al. (2000)	Retrospective study design	6	N/A	N/A	1. 100% (although 4 required supplemental oxygen. Mean follow-up duration not reported) 2. N/A 3. Not reported	During the initial period 2 children had regurgitation of feeding	4
Wilson et al. (2000)	Retrospective study design	7 (late obstruction)	N/A	Differed, but in general poor weight gain and desaturations to 80%	1. 67% (Mean follow-up duration not reported.) 2. N/A 3. Not reported	None reported	3
Wagener et al. (2003)	Case series	20	N/A	Unsatisfactory oxygen saturation and weight gain (moderate obstruction) or in case of severe airway obstruction at rest	1. 100% (Follow-up duration not reported) 2. N/A 3. Not reported	25%	7
Anderson et al. (2007)	Retrospective study design	13	N/A but reported to be close to the median age of admission (6 days, range 1–122 days)	Unsatisfactory oxygen saturation and weight gain (moderate obstruction) or in case of severe airway obstruction at rest.	1. 100% (Mean follow-up duration not reported.) 2. N/A 3. None reported	None reported	5
Parhizkar et al. (2011)	Retrospective case series	18	N/A (no specific data for RS available)	AWO on basis of glossoptosis	1. N/A (no specific data for RS available) 2. N/A 3. Unknown for RS population	None reported	5
(Ook in mix) Abel et al. (2012)	Retrospective study design	63	N/A (Varied from 1 to 330 days)	Sleep study showing moderate of severe UAO (according to Nixon's criteria). moderate UAO for a set of at least three clusters of desaturations with at least 3 dips below 85% (but not below 80%) and severe UAO for a set of at least three clusters of desaturations with atleast 3 dips below 80%.	1. 81,8% with a median follow-up period of 12 months (range 2–30 months) 2. N/A 3. None	None reported	6

Table 3
Continuous positive airway pressure (CPAP) and non-invasive positive pressure (NIPP) ventilation.

First author and year	Design	N	Mean age of the start of treatment	Indication	Primary outcome (1 = SROAO, 2 = AHI, 3 = mortality	Complication rate	MINORS
Leboulanger et al. (2010)	Retrospective study design	7	Median age of 2 months (range 1–10 months)	Symptoms of severe upper airway obstruction (dyspnea, stridor, chest retractions, loud breathing, or failure to thrive) that was responsible for alveolar hypoventilation during sleep, defined on the basis of hypercapnia (transcutaneous carbon dioxide pressure [$PtcCO_2$] of _50 mm Hg for _10 consecutive minutes and/or _10% of sleep time) despite positioning measures and exclusive nasogastric tube feeding.	1. 100% (Mean follow-up duration not reported.) 2. N/A 3. None	None reported	7
Girbal et al. (2014)	Retrospective study design	5	Median age 1 month (Interquartile range 0–2)	Complex OSA	1.N/A 2. N/A 3. N/A	Reported, but no rate available	7

order to advance the tongue. In a second procedure, when the airway is deemed safe, the tongue is released. The eleven studies used different tongue-lip adhesion techniques including those described by Douglas, Argamosa and Routhledge or modified forms. The mean age of release of the tongue-lip plication ranged from 9 to 14.8 months. SROAO rates ranged from 70 to 95%. Non-respiratory related complications included dehiscence and abscesses. Respiratory-related complications included edema, stridor, apnea and a tracheostomy. According to the study of Mann et al., scarring of the lip was insignificant and scarring on the tongue modest. There was no need for scar revisions in any studies. Some studies reported considerable differences in

Table 4
Tongue-lip adhesion (TLA) and other glossopexy techniques.

First author and year	Design	N	Mean age (of the start of) treatment	Indication	Primary outcome (1 = SROAO, 2 = AHI, 3 = mortality	Complication rate	MINORS
Hoffman, (2003)	Retrospective study design	23	38.2 days (range 3–70 days)	Severe or continued respiratory distress despite prone positioning or supplemental oxygen.	1. 70% with a mean follow-up period of 3.3 ± 2.9 years. 2. N/A 3. None	52%	8
Kirschner et al. (2004)	Retrospective study design	29	26.3 days (range 2–129 days)	Not specified.	1. 70%. (Mean follow-up duration not reported.) 2. N/A 3. None	17%	3
Denny et al. (2004)	Retrospective study design	11	16.6 days (range 4–42 days)	Unsuccessful non-operative treatment.	1. 72% with a mean follow-up period of 7.9 years (range 5–15 years) 2. N/A 3. Not reported	27%	8
Huang et al. (2005)	Retrospective study design	14	87.1 days (range 18–348 days)	Unsuccessful non-operative treatment.	1 71%. Follow-up period not specified. 2. N/A 3. Not reported	29%	3
Cozzi et al., (2008)	Retrospective study design	48	120.5 (±22 days)	Severe upper airway obstruction and/or life apparent life-threatening episode and unsuccessful non-operative treatment.	1. 75%. Follow-up period not specified. 2. N/A 3. None	19%	8
Bijnen et al. (2009)	Retrospective study design	22	34.0 days (range 1–98 days)	Unsuccessful non-operative treatment.	1. 80%. Follow up period of minimal 1 year (range 1–9 years) 2. N/A 3. 2 deaths: severe tracheomalacia and a severe cardiac abnormality	55%	10
Rogers et al. (2011)	Retrospective study design	52	24.0 days (range 4–124 days)	Not specified.	1. 89%. Follow-up period not specified. 2. N/A 3. Not reported	4%	5
Abramowicz et al. (2012)	Retrospective study design	22	18.4 days (range 3–45 days)	Not specified.	1. 90%. Follow-up period not specified. 2. N/A 3. Not reported	N/A	8
Mann et al. (2012)	Retrospective study design	22	13.9 days (range unknown)	Type 1 or 2 airway obstructions, verified via bronchoscopy, who experienced desaturations when supine or eating but remained stable when placed prone.	1. 95%, one case required a tracheostomy. Average follow-up duration was 8 years. 2. N/A 3. Not reported	15%	3
Sedaghat et al. (2012)	Retrospective study design	8	29 days (range 15–56 days)	Unsuccessful treatment by conservative measures such as prone positioning and supplemental nasogastric tube feeding.	1. 88% 2. Mean pre-operative oAHI preoperative 52.6, post-operative oAHI 18.1. 7/8 showed improvement. In only 3/8 there was resolution of oAHI below 5. 3. Not reported	None reported	9
Mokal et al. (2014)	Retrospective study design	26	9.7 days (range 3–30 days)	Airway compromise, difficulty feeding, poor weight gain and failure of conservative treatment to relieve symptoms.	1. 96% with a mean follow-up period of 98 months (range 9 months–15 years) 2. N/A 3. Not reported	None	5

management between non-syndromal and syndromal RS children. For example, Rogers et al. found a higher need for preoperative intubation, more average days of intubation, a longer length of intensive care unit and hospital stay and a higher incidence of reintubation (Rogers et al., 2011). In the study of Kirschner et al. management by tracheostomy was more frequently required in patients with RS with multiple anomaly syndromes (Kirschner et al., 2003). Cozzi et al. examined differences in mean body weight or weight velocity percentiles, but did not find significant differences between isolated or non-isolated RS patients (Cozzi et al., 2008).

3.5. Subperiosteal release of the floor of the mouth (Table 5) (Two studies with 47 patients in total) (Breugem et al., 2008; Caouette-Laberge et al., 2012)

Two studies were included on subperiosteal release of the floor of the mouth. The procedure is based on the theory that the muscular insertion of the tongue on the mandible is under increased tension, creating the glossoptosis and elevation of the tip of the tongue (Epois, 1983). Both Breugem et al. and Caouette-Laberge used the technique according to Delorme (Breugem et al., 2008; Caouette-Laberge et al., 2012). In the study of

Table 5
Subperiosteal release of the floor of the mouth.

First author and year	Design	N	Mean age of the start of treatment	Indication	Primary outcome (1 = SROAO, 2 = AHI, 3 = mortality	Complication rate	MINORS
Breugem et al. (2008)	Retrospective study design	14	15 weeks (range 1–68 weeks)	Failure of traditional management such as prone positioning and nasopharyngeal intubation and indicators of continued respiratory distress such as desaturations, elevated carbon dioxide levels, cardiac abnormalities and failure to thrive	1. 50% 2. N/A 3. Not reported	None reported	6
Caouette-Laberge et al. (2012)	Retrospective study design	31	33 days (range 3–188 days)	Failure of conservative measures as ventral positioning or a nasopharyngeal airway	1. 84% 2. Early postoperative recordings mean AHI of 17.4, compared to mean 46.5 preoperatively. 3. One death. Circumstances unclear.	None reported	7

Table 6
Mandibular traction.

First author and year	Design	N	Mean age of the start of treatment	Indication	Primary outcome (1 = SROAO, 2 = AHI, 3 = mortality	Complication rate	MINORS
Pradel et al. (2009)	Retrospective study design	8	Not reported	Failure of conservative management (lateral or prone positioning, acrylic plate) failed and resulted in hypercapnia> 60 mm Hg, acidosis PH < 7.2 and pure oxygenation <85%	1. 100% with a follow-up period of 11 years. 2. N/A 3. One patient died of an aspiration pneumonia	None reported	5
Baciliero et al. (2011)	Retrospective study design	118	22 days (range 2–64 days)	Neonates who had experienced even a single episode of desaturation or respiratory obstruction, and babies with feeding difficulties.	1. 100% 2. N/A 3. None reported	25%	6
Dong et al. (2014)	Prospective study design	7	13.7 days	Surgery was performed if the mean transcutaneous oxygen saturation was less than 90% after a 24-h monitoring period in the lateral/prone position, or if the transcutaneous oxygen saturation decreased continuously due to dyspnea during the monitoring period and manual intervention/rescue was required.	1.100% 2.N/A 3. Not reported	No major complications reporter.	6

Table 7
Tracheostomy.

First author and year	Design	N	Mean age of the start of treatment	Indication	Primary outcome (1 = SROAO, 2 = AHI, 3 = mortality	Complication rate	MINORS
Han et al. (2012)	Retrospective study design	25	N/A	Not specifically specified	1. 100% with a mean follow-up of 4 years. 2. N/A 3. 2 children died.	52%	7

Breugem et al. children remained intubated for one week post-operatively to allow for weight gain, swelling of the floor of the mouth to subside and the endotracheal tube to splint the tongue in a forward direction. In this study a SROAO rate of 50% was found, considerably lower than the 84% SROAO rate as reported by Caouette-Laberge.

3.6. Mandibular traction (Table 6) (Three studies with 133 patients in total) (Robinson, 1923; Pradel et al., 2009; Baciliero et al., 2011; Dong et al., 2014)

Three studies on mandibular traction were included (Pradel et al., 2009; Baciliero et al., 2011; Dong et al., 2014). During

mandibular traction the tongue and mandible are forced in a forward position, while slowly lengthening the mandible and the soft tissues, thus creating a larger oropharyngeal space and relief of the airway obstruction. Mandibular traction was described in a group of eight RS children by Pradel et al., for a period of two to five weeks using 50–200 g weights (Pradel et al., 2009). Traction was stopped when the infant no longer showed signs of airway obstruction, and blood gas analysis showed normal values during observation. Baciliero et al. performed mandibular traction surgery according to the Stellmach & Schettler technique (Baciliero et al., 2011). Traction was discontinued on the basis of oxygen saturation values and the degree of correction of mandibular deficiency. The oxygen saturation values had to be stable and >96% in room conditions without traction for 72 h. The maxilla-mandibular discrepancy had to be less than 3 mm. The mean period of traction treatment was 44 days. Dong et al. followed the same surgical technique as Baciliero (Dong et al., 2014). In this study of seven patients the mean duration of traction was 26.6 days. All studies reported a SROAO rate of 100%. In the study of Baciliero et al. complications were reported in 25% of patients including transient infection at the site of the wires. In three patients loss of one of the wires was reported. No evident scars were reported. In the study of Dong et al. no severe complications were reported, but there was note of minor complications such as increased oral secretion after surgery.

3.7. *Mandibular distraction (Ow and Cheung, 2008; Bookman et al., 2012; Paes et al., 2013)*

As stated in the method section, mandibular distraction in children was already elaborated by a number of review studies. Therefore, publications solely on this topic were excluded from our analysis (Ow and Cheung, 2008; Bookman et al., 2012; Paes et al., 2013).

3.8. *Tracheostomy (Table 7) (One study with 25 patients in total) (Han et al., 2012)*

One study reported specifically on the use of a tracheostomy, a technique usually performed in patients with a life-threatening airway obstruction who are in need of immediate treatment (Han et al., 2012). Han et al. found the median time to 'natural' decannulation was 97 months without further surgical intervention. Patients with syndromic RS had a significantly longer median time to decannulation than did those with isolated RS. The mean follow-up was 4 years and a SROAO rate of 100% was found. Complications were noted in 52% of patients such as tracheïtis, pneumonia, wound breakdown, wound infection and hematoma. One patient died due to a tracheostomy tube occlusion early in the study period. Long term-outcomes such as developmental delay, organ system dysfunction and death were also recorded.

3.9. *Studies describing a mix of treatments (21 studies) (Marques et al., 2001; Van Den Elzen et al., 2001; Li et al., 2002; Hamdi et al., 2004; Schaefer et al., 2004; Evans et al., 2006; Lin et al., 2006; Smith and Senders, 2006; de Buys Roessingh et al., 2007; Meyer et al., 2008; Butow et al., 2009; Genecov et al., 2009; Gozu et al., 2010; Chowchuen et al., 2011; Glynn et al., 2011; Daniel et al., 2013; Handley et al., 2013; Papoff et al., 2013; Flores et al., 2014; Maas and Poets, 2014; Van Lieshout et al., 2014; Filip et al., 2015)*

Twenty-one studies reported on multiple techniques simultaneously in case series of children with RS in their institution. Most studies reported successful treatment of the airway obstruction by 'prone positioning only' in the majority of RS patients (Marques et al., 2001; Van Den Elzen et al., 2001; Li et al., 2002; Hamdi et al., 2004). In a number of studies a difference in children with an isolated RS and children with non-isolated RS was reported (Marques et al., 2001; Van Den Elzen et al., 2001). For example, the study of Marques et al. reported on the clinical course of 62 patients during the first six months of life and found prone positioning treatment or a nasopharyngeal airway to be the definitive treatment in 75,8% in children with probable isolated RS and in 52% of the cases of syndromes or other malformations. In contrast some studies did not find such a difference. A large study by Evans et al. among 115 RS patients showed no statistical difference between syndromic and non-syndromic patients regarding operative treatment (Evans et al., 2006). In this study 44% of patients in total underwent any form of operative treatment. Handley et al. reported a significant difference in need for a surgical intervention between children with and without cleft palate. Handley et al. also identified a number of factors that may predict need for a definitive airway intervention (Handley et al., 2013).

Supplement 1 shows the ratio between the MINORS score, type of treatment and SROAO success percentage.

4. Discussion

The total number of studies with original data on treatment in RS was low, as well as the mean number of patients participating. Although we found two prospective studies and one clinical trial, most studies had a retrospective non-comparative character. To appreciate methodological quality differences between CEBM level IV studies, the MINORS score was applied. The mean MINORS (range 3–10) score was 7.3 out of 16 (non-comparative studies). The large majority of scores ranged between 5 and 8. Therefore, unfortunately the MINOR scores did not provide much guidance in differentiating between outcomes of studies. Low scores were especially found on items 3 (prospective collection of data) and 5 (unbiased evaluation of endpoints). These scores indicate there is still a lot to gain in reporting outcome for rare diseases using case series. We advocate the usage of objective descriptions of indication and the pre-treatment airway status. Only 11 out of 48 studies reported use of polysomnography, the gold standard to diagnose OSA. All other studies used fairly subjective measures or none at all for means of indication.

In most studies there seemed to have been a stepwise treatment approach, in which the indication for a certain treatment is failure of another. This makes it difficult to generalize results to the entire RS population due to selection bias. Generating a treatment protocol on the basis of these studies for any newborn child with syndromic or non-syndromic RS is therefore difficult. Nonetheless, there seems to be agreement that prone positioning, although not substantiated by specific scientific evidence, is the first step in the treatment cascade with exception of RS cases with acute life-threatening respiratory distress. Remarkably, we did not find any notions on the relation between prone positioning in children with RS and the possibly increased risk on SIDS.

As in all conditions, preference should be given to a treatment which is most effective and least invasive. Therefore, when prone positioning fails, other non-surgical therapies may be applied, such as a nasopharyngeal airway, non-invasive respiratory support or an orthodontic plate. All these measures give temporary support to the airway. The included studies in this review showed similar success rates for SROAO with few complications. One can argue that the choice of any of these non-surgical does not matter, since results on outcomes seemed almost the same.

When prone positioning or other non-surgical therapies fail to relieve airway symptoms, a multitude of surgical options is available. On the basis of this review, given the quality of studies and the impossibility of a fair comparison (due to incompatible outcome

reporting and selection bias), one cannot warrant a consensus recommendation for clinical practice. In reviews conducted on mandibular distraction, levels of evidence and effectivity appeared to be similar to our findings (Ow and Cheung, 2008; Bookman et al., 2012; Paes et al., 2013). Therefore, local circumstances and experience of the practitioner or clinic rightfully guide treatment decisions.

Finally, there is an ongoing discussion regarding what the natural course of RS is. Since most of the described measures give temporary airway support and probably do not have much (or any) long-term influence on the anatomical or physiological situation after the treatment has been stopped, this implies presence of a natural improvement of the airway obstruction in time. Some studies found that more permanent invasive surgical measures were more often needed in children with non-isolated RS, suggesting the natural improvement in airway dimensions may be less in these children. Unfortunately, in most studies data on long-term outcomes, when the child has overcome the critical first years were missing.

During the preparation of this systematic review, we noted a few recurring complicating factors one comes across quite often while doing research in children with RS, such as variety in RS definition, the heterogeneity of the RS population and lack of a reliable and uniform outcome measures. In this review we used SROAO as our primary endpoint, but this was not always clearly mentioned in the articles and therefore sometimes interpreted by the researcher from the text. However, SROAO was available across all studies and therefore enabled us to compare outcome. Also, absence of need for further treatment does not necessarily mean that OSA is absent. To investigate this, post-operative PSG studies are needed.

5. Conclusion

This systematic review revealed the current state of literature on treatment in RS. Despite growing attention, high-level evidence on treatment outcomes remains scarce. On the basis of this review, given the quality of studies and the impossibility of a fair comparison (due to incompatible outcome reporting and selection bias), a consensus recommendation for clinical practice is not warranted. Future research should include description of the definition, treatment indication, and objective outcomes. Although challenging, there is a clear need for prospective and comparative studies to assess the different treatment modalities and their follow-up.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jcms.2016.06.021.

Conflicts of interest

None.

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