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Mandibular distraction osteogenesis for the management of upper airway obstruction in children with micrognathia: a systematic review

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Abstract. Mandibular distraction osteogenesis (MDO) is increasingly used for neonates and infants with upper airway obstruction secondary to micrognathia. This systematic review was conducted to determine the effectiveness of MDO in the treatment of airway obstruction. The databases searched included PubMed, Embase, Scopus, and grey literature sources. The inclusion criteria were applied to identify studies in children with clinical evidence of micrognathia/Pierre Robin sequence (PRS) who had failed conservative treatments, including both syndromic and non-syndromic patients. Overall 66 studies were included in this review. Primary MDO for the relief of upper airway obstruction was found to be successful at preventing tracheostomy in 95% of cases. Syndromic patients were found to have a four times greater odds of failure compared to those with isolated PRS. The most common causes of failure were previously undiagnosed lower airway obstruction, central apnoea, undiagnosed neurological abnormalities, and the presence of additional cardiovascular co-morbidities. MDO was less effective (81% success rate) at facilitating decannulation of tracheostomy-dependent children ($P < 0.0001$). Failure in these patients was most commonly due to severe preoperative gastro-oesophageal reflux disease, swallowing dysfunction, and tracheostomy-related complications. The failure rate was higher when MDO was performed at an age of $\geq$24 months. More studies are needed to evaluate the long-term implications of MDO on facial development and long-term complications.

Key words: mandibular distraction tracheostomy; decannulation; Pierre Robin sequence; upper airway obstruction.

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Micrognathia is a congenital condition involving an abnormally small mandible. This condition tends to occur in conjunction with posterior tongue displacement (glossoptosis), which can lead to physical obstruction of the oropharyngeal and hypopharyngeal regions on inspiration. This upper airway obstruction may be life-threatening and may require urgent medical intervention.

In 1923, a French stomatologist was the first to describe the constellation of symptoms associated with upper airway obstruction in neonates now known as Pierre Robin sequence (PRS).[1] This sequence is a craniofacial anomaly characterized by mandibular micrognathia (mandibular hypoplasia), glossoptosis, and in some cases a 'U-shaped' cleft palate. There is only limited epidemiological data, but the incidence has been reported to range from approximately 1 in every 8500 live births in Liverpool, UK[2] to 1 in 14,000 live births in Denmark.[3] The most recent study from Germany reports an incidence of approximately 1 in 8000 births.[4] This variation in incidence is related in part to the inconsistent definition of PRS in the literature.

The diagnosis of patients with PRS is challenging due to the wide spectrum of PRS phenotypes, variation in degree of airway obstruction, feeding difficulties, and the need for treatment. This has led to some authors only characterizing those with airway obstruction needing treatment as having PRS[5]; others will include all patients with micrognathia and glossoptosis, or limit the PRS diagnosis to those with associated cleft palates.[3] Although these clinical features are most commonly seen in isolation,[6] they can also occur in association with other syndromes of the craniofacial skeleton; for example, Treacher Collins syndrome, Stickler syndrome, and Nager syndrome. Such co-occurrences further complicate the diagnosis. These syndromes differ in pathogenesis from isolated PRS, but all can have micrognathia with glossoptosis and hence airway obstruction. For simplicity, those without an associated syndrome are referred to in this study as having 'isolated PRS' and those with an associated syndrome are referred to as having 'syndromic micrognathia'. The varying phenotypes and presumed causes of this anomaly make comparison of the myriad of protocols advocated for management difficult.[7]

The most important consequences of micrognathia and PRS are the inability to effectively breathe or feed due to airway obstruction. The majority of children born with micrognathia or PRS have no respiratory distress. Those with mild symptoms of respiratory distress can often be treated conservatively with prone positioning or non-invasive techniques, such as a nasopharyngeal airway or the application of nasal continuous positive airway pressure (CPAP). The rate of success with the use of nasopharyngeal airways varies in the literature, ranging from 48%[8] to 100%.[9] A large case series study focusing on children with non-syndromic PRS demonstrated that less than 10% required a surgical intervention.[10]

For neonates with severe respiratory distress, or those who fail initial conservative treatment, the airway dysfunction can be a life-threatening emergency. The nasopharyngeal airway and CPAP can only be tolerated for a limited period of time, and in some cases, children need to be intubated and ventilated to maintain adequate oxygenation.[11] Children who require prolonged treatment with these measures may require a more definitive surgical intervention.

Several surgical treatments have been described for the treatment of the child with micrognathia. In 1946 Douglas described the use of tongue–lip adhesion (TLA) for the treatment of upper airway obstruction associated with micrognathia.[12] This procedure involves surgically fusing the tongue to the anterior lower lip to hold the tongue in an anterior position. The adhesion is usually reversed with another surgical procedure at 9–12 months of age. However, the underlying cause of the obstruction is not fully addressed by TLA, and wound dehiscence and feeding difficulties are common,[6,13] thus many centres have abandoned it as a viable treatment option.[11]

Other surgical options described include mandibular traction and advancement appliances,[14,15] and sub-periosteal release of the floor of the mouth musculature.[16,17] However these procedures have not met with widespread success and have largely been abandoned by the larger centres.

Mandibular distraction osteogenesis (MDO)

Since the introduction of distraction osteogenesis for the craniofacial skeleton in the mid-1980s to early 1990s, it has been used to deal with various types of reconstructive dilemma.[18,19] MDO for infants with micrognathia has been used for unilateral mandibular lengthening by distraction for cases of hemifacial microsomia[20] and bilateral MDO for cases of Treacher Collins syndrome.[21] Initially MDO was used to resolve upper airway obstruction and to facilitate the removal of a tracheostomy. Since then, it has been used increasingly as the primary surgical option for the management of neonates and infants with micrognathia or PRS with upper airway obstruction.[22]

MDO relieves the airway obstruction by lengthening the mandible. This stretches the tongue attachments to the mandible (genioglossus muscle), which positions the tongue more anteriorly, relieving the glossoptosis. Most children with upper airway obstruction have demonstrated an improvement in their respiratory status within a few days of distraction. For those children who are intubated and mechanically ventilated, this may mean extubation and transfer to a regular hospital ward.

Several case series have demonstrated the effectiveness of MDO in alleviating upper airway obstruction in neonates, infants, and older children with PRS.[23] Most patients were able to avoid tracheostomies, and those who already had tracheostomies could be decannulated. A systematic review performed in 2008 evaluated the effectiveness of MDO in several clinical applications.[23] The review evaluated 178 studies including 1185 patients. Success in preventing tracheostomies was achieved in 91.3% of patients. However, the authors of that review searched only the PubMed database on the applications of unilateral and bilateral mandibular distraction in both children and adults. Limiting the search to a single database is a significant methodology limitation of that review. In addition the study also included all possible causes of micrognathia, including temporomandibular joint (TMJ) ankylosis, hemifacial microsomia, and syndromic micrognathia, which have different aetiologies to isolated PRS. No comparative subgroup analyses were performed to differentiate between these groups. Furthermore, the authors did not evaluate any long-term outcomes in children and did not discuss reasons for failure of distraction.

This current review was performed with the aim of extending the search across multiple databases to include the current available evidence for the effectiveness of mandibular distraction for the treatment of upper airway obstruction in children with micrognathia. This review also reports reasons for failure and compares outcomes between isolated PRS/micrognathia patients and syndromic micrognathia patients. A further aim is to determine the effects of mandibular distraction on the other complications of micrognathia, including feeding and weight gain, gastro-oesophageal reflux,

and facial development. These outcomes will be presented in subsequent papers.

Methods

A research protocol was written and peer-reviewed prior to undertaking this systematic review.[24] The PICO criteria used for this review are listed in Table 1. All of the studies in this review included children with clinical evidence of micrognathia who underwent bilateral MDO and also children who had initially undergone conservative treatment options. This review considered reasons for failure and for the consideration of tracheostomy. Syndromic and non-syndromic children were included, but some particular conditions such as bilateral TMJ ankylosis, hemifacial microsomia, and other conditions that may contribute to the airway obstruction for reasons other than the micrognathia alone, were excluded. In addition, children with known lower airway abnormalities prior to treatment were also excluded.

The types of studies considered included both experimental and epidemiological study designs, including randomized control trials, quasi-experimental studies, prospective and retrospective cohort studies, and case–control studies. The review also considered case series and case reports where higher levels of evidence were not found.

The search strategy included both published and unpublished studies in English, covering the period 1990 to November 2013. The databases searched included PubMed, CINAHL, EMBASE, SCOPUS, Web of Knowledge, and other grey literature databases such as Scirus and MedNar. An example of the strategy used to search through PubMed is given in Fig. 1.

Papers selected for retrieval were assessed by two independent reviewers for methodological validity and were critically appraised using the standardized critical appraisal instruments of the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI). Any disagreements that

Table 1. PICO criteria for the systematic review.

Participants	• Male and female children from birth with clinical evidence of micrognathia • Clinical evidence of upper airway obstruction, who failed conservative treatments • Syndromic and non-syndromic children • Bilateral mandibular distraction • Minimum of 1 year follow-up Exclusion: • Children who underwent unilateral distraction • Children with known preoperative central apnoea/lower airway abnormalities • TMJ ankylosis/hemifacial microsomia or other mandibular condition leading to airway obstruction
Intervention	Bilateral mandibular distraction osteogenesis
Comparator	Tracheostomy
Outcomes	Airway outcomes • Primary mandibular distraction osteogenesis • Decannulation of tracheostomy-dependent patients Long-term outcomes

TMJ, temporomandibular joint.

Child[mh] OR Child*[tw] OR Neonate[mh] OR Neonat*[tw] OR Infant[mh]

Infant*[tw] OR Pediatric[tw] OR Paediatric[tw] OR Newborn[mh] OR Newborn[tw]

AND

Pierre Robin[tw] OR Pierre Robin sequence[tw] OR Robin sequence[tw] OR Micrognathia[tw] OR retrognathia[tw] OR mandibular hypoplasia[tw] OR Goldenhar[tw] OR Treacher Collins[tw] OR Nager[tw] OR Stickler[tw] OR Craniofacial Abnormalit*[tw] OR mandibulofacial dysostosis[mh] OR mandibulofacial dysostosis[tw] OR Jaw Abnormalities[mh] OR Mandibular Diseases/congenital[mh]

AND

Mandibular distract*[tw] OR Mandibular lengthen*[tw] OR Bone lengthening[mh:noexp] OR Osteogenesis, Distraction[mh] OR distraction osteogenesis[tw] OR Tracheostom* [mh] OR Tracheostomy*[tw] OR Tracheotomy[tw] OR Craniofacial Abnormalities/surgery[mh] OR Airway Obstruction/surgery[mh] OR Airway obstruction[tw] OR mandible/surgery[mh] OR surgery[mh] OR mandible[tw]

AND

Apnea[mh] OR Apnea[tw] OR Apnoea[tw] OR Airway obstruct*[tw] OR Airway patency[tw] OR Gastroesophageal reflux[mh] OR Gastro-esophageal reflux[tw] OR Feed*[tw] OR Weight gain[tw] OR Weight[tw] OR Facial growth[tw] OR Facial develop*[tw] OR dentition[tw] OR failure to thrive[tw] OR outcome[tw] OR molars[tw]

Fig. 1. An example of the search strategy used for the PubMed database.

Table 2. Data items collected and recorded for each outcome studied.

Outcome	Success	Failure
Primary mandibular distraction osteogenesis	Relief of upper airway obstruction	Failure: Needing further airway adjuncts due to persistent airway obstruction. The additional interventions needed were also recorded Polysomnography measures: obstructive apnoea/hypopnoea index (OAHI) Reasons for failure
Tracheostomy decannulation	Decannulation was achieved after MDO	Failure: Persistent tracheostomy despite MDO Reasons for failure

MDO, mandibular distraction osteogenesis.

arose between the reviewers were resolved through discussion, or with a third reviewer. Data were extracted from the studies included and entered into study-specific Microsoft Excel tables. A second reviewer checked data extraction.

The data items extracted differed between outcomes. Where available, individual patient data were collected; where not available, the authors were contacted for clarification. For all studies, demographic data and patient characteristics were collected for all patients, including syndromic status. Follow-up periods were also recorded for the long-term outcomes analysis. Other data parameters recorded for each outcome and the definitions used for success and failure of treatment are presented in Table 2.

The quantitative data collected and effect sizes are expressed as odd ratios (OR) with the 95% confidence intervals (95% CI). Subgroup analyses were performed where possible to compare syndromic and non-syndromic children with micrognathia and age at time of surgery. Where statistical pooling was not possible, the findings are presented in narrative form, including tables and figures to aid in data presentation.

Results

The search identified a total of 4815 studies. Out of these, a total 801 studies were retrieved based on title. After removal of duplicates, studies not in English, and studies outside the date criteria, only 382 studies remained. The abstracts were then reviewed to determine their relevance to the review question and objectives. During this process, 258 studies were excluded, leaving 124 studies that were retrieved for full-text examination (Fig. 2).

Following the review of the full text, an additional 38 studies were excluded as they did not meet the inclusion criteria. Eighty-six studies were subjected to critical appraisal resulting in 66 studies included in the final analysis. The analysis included other outcomes not discussed in this paper; these will be presented in subsequent publications.

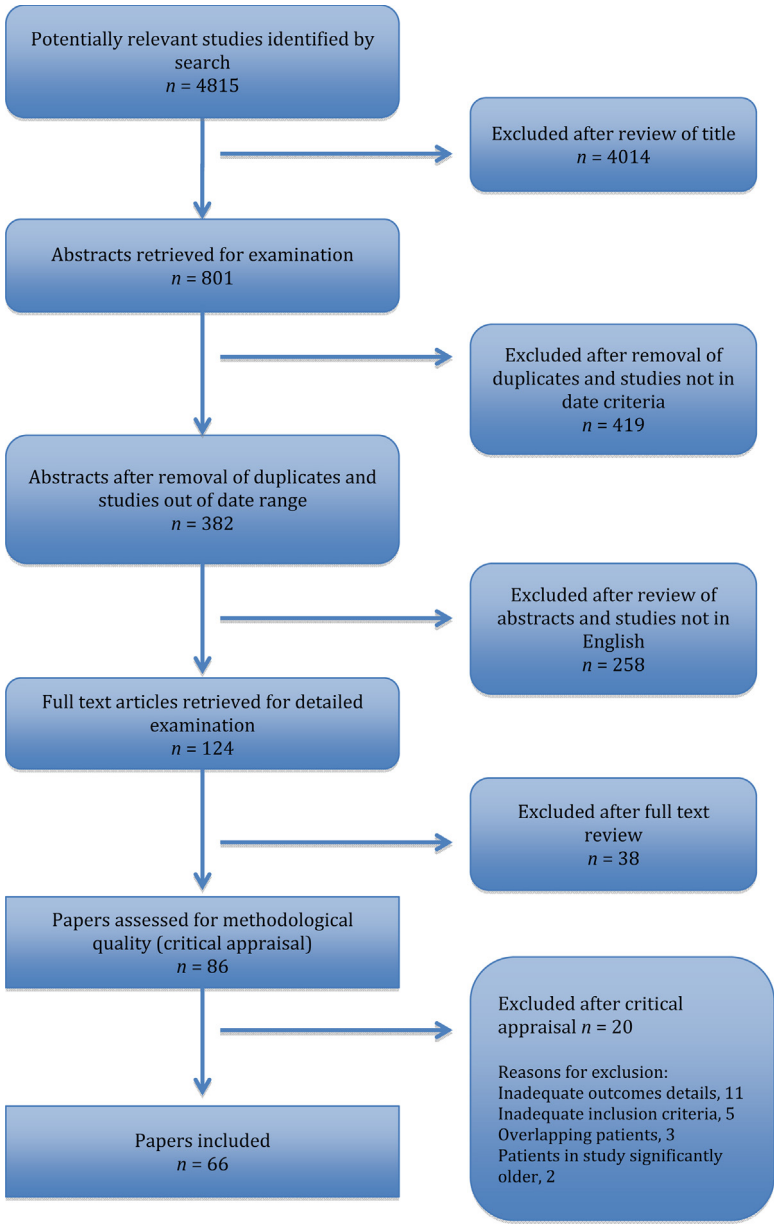

Fig. 2. Flow diagram demonstrating the numbers of studies screened, assessed for eligibility, and included in the review.

Overall, for the primary mandibular distraction outcome, 51 studies were included (Table 3).[10,25–74] The most common reason for exclusion was the potential risk of overlapping patients. In some of the studies with overlapping patients,

Table 3. Studies included in the primary MDO analysis: overall analysis and subgroup analyses including reasons for exclusion for each analysis.

Article	Study design	Overall analysis	Syndromic vs. non-syndromic	Age-based
Al-Samkari 2010[25]	RR	Excluded – overlap[73]	Included	Excluded – no age data
Andrews 2013[26]	RR	Included	Excluded – inadequate distinction	Included
Breugem 2012[27]	RR	Included	Included	Included
Brevi 2006[28]	CR	Excluded – overlap[65]	Excluded – overlap[65]	Excluded – overlap[65]
Burstein 2005[29] *	RR	Included	Included	Excluded – no age data
Carls 1998[30]	RR	Included	Included	Included
Chigurupati 2004[31]	RR	Included	Included	Included
Chowchuen 2011[32]	RR	Included	Included	Included
Dauria 2008[10]	RR	Included	Included	Included
Denny 2005[33]	RR	Included	Included	Included
Genecov 2009[34]	RR	Included	Included	Included
Gifford 2008[35] *	RR	Included	Included	Included
Gözü 2010[36]	RR	Included	Included	Excluded – no age data
Griffiths 2013[37] *	CR	Included	Included	Included
Hammoudeh 2012[38] *	RR	Included	Included	Included
Handler 2009[39]	CR	Included	Included	Included
Hong 2012[40]	RR	Included	Included	Included
Hong 2012[41]	RR	Included	Included	Included
Howlett 1999[42]	CR	Included	Included	Included
Izadi 2003[43]	RR	Excluded – overlap[26]	Included	Excluded – overlap[26]
Judge 1999[44]	CR	Included	Included	Included
Kolstad 2011[45]	RR	Included	Included	Included
Lee 2009[46]	RR	Included	Included	Included
Lin 2006[47] *	RR	Included	Included	Included
Looby 2009[48] *	RR	Included	Included	Included
Mandell 2004[49]	RR	Included	Included	Included
Miller 2007[50] *	RR	Included	Included	Excluded – no age data
Miloro 2010[51]	RR	Included	Excluded – inadequate distinction	Excluded – no age data
Mitsukawa 2007[52] *	RR	Included	Included	Included
Monasterio 2002[53] *	RR	Excluded – overlap[54]	Excluded – overlap[54]	Excluded – no age data
Monasterio 2004[54]	RR	Included	Included	Included
Morovic 2000[55]	PR	Included	Included	Included
Mudd 2012[56]	RR	Included	Excluded – inadequate distinction	Included
Murage 2013[57] *	RR	Included	Included	Included
Olson 2011[58]	RR	Included	Included	Excluded – no age data
Papoff 2013[59]	RR	Included	Included	Included
Perlyn 2002[60]	RR	Included	Included	Included
Rachmiel 2012[61]	RR	Included	Excluded – inadequate distinction	Included
Sadakah 2009[62] *	RR	Included	Included	Included
Schaefer 2004[63]	RR	Included	Included	Included
Scott 2011[64]	RR	Excluded – overlap[72]	Included	Included
Sesenna 2012[65]	RR	Included	Included	Included
Sidman 2001[66]	PR	Excluded – overlap[72]	Included	Included
Smith 2006[67]	RR	Included	Included	Included
Sorin 2004[68]	RR	Included	Included	Included
Spring 2006[69]	RR	Excluded – overlap[58]	Excluded – overlap[58]	Included
Taub 2012[70]	CR	Included	Included	Included
Tibesar 2006[71]	CR	Included	Included	Included
Tibesar 2010[72]	RR	Included	Excluded – inadequate distinction	Excluded – no age data
Wittenborn 2004[73]	RR	Included	Excluded – inadequate distinction	Included
Zenha 2012[74]	CR	Included	Included	Included
		44 included	42 included	41 included

MDO, mandibular distraction osteogenesis; RR, retrospective review; CR, case report; PR, prospective review.
* Studies that included polysomnography results pre- and post-MDO.

different outcomes were reported in the different study reports. In these cases, all studies were included and the specific outcome data extracted from the individual studies. Within the subgroup analysis comparing syndromic and non-syndromic children, some studies were excluded due to inadequate distinction of which patients were syndromic and which had isolated PRS. Similarly, for the age-based subgroup analysis, studies were excluded due to limited age-based data to be able to make accurate comparisons.

Primary mandibular distraction osteogenesis

The primary MDO analysis included patients who underwent mandibular distraction as the primary surgical intervention after failing conservative therapy for upper airway obstruction. All of these patients had failed non-surgical therapy and were being considered for a tracheostomy. A successful outcome was defined as prevention of a tracheostomy and the relief of upper airway obstruction. There were a variety of ways in which this outcome was reported in these studies. Most reported only subjective improvements in

Table 4. Overall primary MDO results.

Outcome	Total	Success	Failure	Success rate (%)
Primary MDO	490	468	22	95.5%

MDO, mandibular distraction osteogenesis.

obstructive symptoms, including reduction in noisy breathing and in clinically obvious apnoeic episodes. Other studies reported objective improvements, such as the ability to successfully extubate the patient who was otherwise intubated because of inability to self-ventilate, or to maintain normal oxygen saturation on room air as measured by pulse oximetry. Eleven studies included polysomnography results pre- and post-MDO (marked with an asterisk (*) in Table 3). Failure was defined as requiring a tracheostomy despite mandibular distraction due to persistent airway obstruction.

This analysis was based on data obtained from 44 papers involving 490 patients. The mean age was 10.4 months (range 5 days to 8 years). Amongst these patients, 468 had a successful outcome, while 22 required a tracheostomy. This equates to an overall success rate of 95.5% for mandibular distraction preventing tracheostomy in the studies included (Table 4). Amongst the successful outcomes, two patients required home oxygen in the short term,[50,56] but avoided any further surgical intervention and were able to be discharged home. One patient required nocturnal CPAP for 3 years after distraction, but did not require any further surgical intervention.[45]

For studies that included polysomnography results, the mean obstructive apnoea/hypopnoea index (OAHI) preoperatively was 31.2 and postoperatively was 4.34 (Table 5).

Of the 22 patients with failed MDO, the most common reason (15/22) was undiagnosed lower airway anomalies, including laryngomalacia, tracheal stenosis, or subglottic stenosis. Another reason for failure was undiagnosed central apnoea (4/22). Two failures were due to intraoperative complications, including accidental dislodgement of the endotracheal tube during MDO requiring an emergency tracheostomy,[26] and unfavourable mandibular fracture during osteotomy.[35] An additional failure was due to the development of unilateral TMJ ankylosis 3 years post-operation, initially requiring tracheostomy; this was followed by repeat MDO, which was successful and the patient was subsequently decannulated.[62]

Subgroup analysis 1: syndromic vs. non-syndromic (isolated) PRS analysis

This subgroup analysis was based on 42 papers (Table 3). The aim of this analysis was to identify if the rate of success was dependent on whether the patient had isolated PRS or micrognathia associated with a syndrome (syndromic micrognathia). Among the syndromic micrognathia patients, there was a wide variety of syndromes. The most common were Stickler syndrome, Nager syndrome, Goldenhar syndrome, and Treacher Collins syndrome, which is in keeping with previous studies.[75] Other syndromes included Cornelia de Lange syndrome, Gordon syndrome, orofaciodigital syndrome, chromosome 4q deletion, Catel Manzke syndrome, CHARGE syndrome, Marshall–Stickler syndrome, arthrogryposis, and Smith–Lemli–Opitz syndrome. This wide variety of syndromes has been reported in the literature, with an estimated 40 syndromes associated with PRS.[76]

The total number of patients included in this analysis was 362. Amongst these patients, 346 successfully avoided a tracheostomy, with an overall success rate of 95.6%, which is very similar to the result of the overall analysis. Out of the 362 patients, 254 were isolated PRS cases and 108 were syndromic micrognathia cases. Out of the 16 overall failures, 10 were within the syndromic micrognathia group. This gives an overall success rate of 97.6% for the isolated PRS group and 90.7% for the syndromic micrognathia group (Table 6). This difference was found to be statistically significant ($P = 0.007$), implying that the odds of failure are four times greater when primary MDO to relieve airway obstruction is performed on syndromic patients compared to isolated PRS patients.

Amongst the failures in the isolated PRS group, three were due to previously undiagnosed lower airway abnormalities. Two were in patients with previously undiagnosed neurological conditions (cerebral palsy in one patient and hypotonia in the second).[57] The last failure was in a patient who sustained an intraoperative complication. Reasons for failure in the syndromic micrognathia group were as follows: four had unknown syndromes with other multiple anomalies including congenital cardiac abnormalities, three patients had previously undiagnosed central apnoea,[45,49,50] while an additional three patients had CHARGE syndrome with pulmonary hypertension,[57] velocardiofacial syndrome,[59] and Beckwith–Wiedemann syndrome.[38]

Subgroup analysis 2: age-based analysis

The aim of this analysis was to determine whether the outcome of MDO treatment is dependent on the age of the patient when the MDO is performed. Accordingly three age groups were selected: <6 months, ≥6 to <18 months, and ≥18 months of age at the time of MDO. This analysis involved 41 studies including 408 patients. The reason for exclusion was inadequate details regarding the ages of the patients. The majority of patients were within the <6 months group, accounting for 377 patients; there were 12 patients in the ≥6 to <18 months group and 19 in the ≥18 months group. All 16 failures in this analysis were within the <6 months group, resulting in a success of 95.8%. There was no significant difference in the success rates of primary MDO between the different age groups (Table 7).

A further analysis was then performed within the first group, dividing the patients into those aged <2 months at the time of operation and those aged between 2 and 6 months at the time of operation. The success

Table 5. Comparison of polysomnography results.

Parameter	Number of studies	Number of patients	Pre-MDO mean (SD)[a]	Post-MDO mean (SD)[a]	Mean difference (95% CI)[a]	*P*-value
OAHI	11	114	31.2 (29.4)	4.34 (2.65)	26.90 (10.67–43.11)	0.002

MDO, mandibular distraction osteogenesis; SD, standard deviation; CI, confidence interval; OAHI, obstructive apnoea/hypopnoea index.
[a] Weighted mean and standard deviation; mean difference calculated using Comprehensive Meta-analysis version 2.2.064 (BioStat, Englewood, NJ, USA).

Table 6. Results of the syndromic vs. isolated subgroup analysis with odds ratios. Results demonstrate a four times greater risk of failure of primary MDO in syndromic children compared to isolated PRS children.

Variable	Success (%)	Failure (%)	Total	OR (95% CI)	*P*-value
Primary MDO	468 (95.5)	22 (4.5)	490	–	–
Syndromic analysis					
Isolated Pierre Robin sequence	248 (97.6)	6 (2.4)	254	1	
Syndromic micrognathia	98 (90.7)	10 (9.3)	108	4.28 (1.49–1192)	0.007

MDO, mandibular distraction osteogenesis; PRS, Pierre Robin sequence; OR, odds ratio; CI, confidence interval.

rates between these groups were almost equal. The difference was not statistically significant ($P = 0.87$) (Table 8).

Tracheostomy decannulation

This outcome was concerned with the ability to remove a tracheostomy from patients with PRS after undergoing mandibular distraction, who otherwise were unable to be decannulated naturally. A successful outcome was the removal of the tracheostomy and ability to maintain oxygen saturation on room air. A failed outcome was defined as an inability to decannulate despite mandibular distraction being successful. Similar to the analysis for primary MDO and due to the variable follow-up data of the studies, the outcomes could only be interpreted as short-term (up to 1 year).

A total of 35 studies provided adequate data to be included in this analysis.[27,29–32,34–36,45,47,49,51–53,55,58,60,63–69,72,77–86] Of these 35 studies, 31 were included in the overall analysis of this outcome (Table 9). The four remaining papers were excluded due to the likely overlap with other studies from the same surgical units. For the subgroup analyses, the reasons for exclusion were overlap of patients, or inadequate distinction between syndromic and non-syndromic patients, or lack of age-based data.

Overall tracheostomy decannulation analysis

This analysis was based on 31 studies involving 152 patients (Table 10). The mean age of this group of patients was 30.4 months (range 6 months to 14 years). Among these patients, 122 were decannulated after mandibular distraction and 30 remained with a tracheostomy *in situ*. The success rate of tracheostomy decannulation after mandibular distraction in patients with micrognathia was 80.3%.

A significant number of studies did not report the reasons for some of their failures.[34,68,72,80] However, when reported, the reasons for failure were varied. The most common reported reason for failure was other airway abnormalities that had not been repaired at the time of MDO. These included tracheomalacia, vascular rings, and choanal atresia.[29,31] After MDO and repair of these abnormalities, the patients could be decannulated. Severe gastro-oesophageal reflux disease (GORD) was also a cause of failure after MDO. A total of eight patients were reported to have severe reflux as a potential cause of failure. In two cases, the patients could be decannulated after a Nissen fundoplication,[29,68] and one study reported that decannulation was awaiting fundoplication at the time of publication.[29] Five other patients with reported severe reflux and chronic swallowing dysfunction were not able to be decannulated.[32,49] In one of these studies, hesitancy on the part of the treating team to attempt decannulation was mentioned as a contributing cause of failure.[49] Five failures were secondary to tracheostomy complications. These included suprastomal granulation tissue, tracheostomy-associated tracheomalacia, and tracheostomy stoma healing problems that required excision or repair prior to decannulation. Only one patient was reported to have failure of decannulation for TMJ ankylosis as a complication of MDO with persistent airway obstruction.

There were 20 cases of failed decannulation post MDO who underwent a second MDO procedure. Among these 20 cases, 14 also failed decannulation after the second MDO; hence the success rate of the second MDO at facilitating decannulation was only 30%.

The mean time to decannulation was also calculated from these studies and was 28.5 months. It is important to note that a significant number of these patients had other surgical procedures performed during their childhood to reduce the upper airway obstruction. Although poorly reported in the majority of studies, there were more reported surgical interventions in the patients who had had a tracheostomy placed at infancy compared to those who had only had primary mandibular distraction. The operations included tonsillectomy and adenoidectomy, uvuloplasties, and suprastomal granuloma excisions.

When comparing the success rate of MDO to prevent tracheostomy with MDO to facilitate tracheostomy decannulation, the difference in success rate was found to be statistically significant. There was a five times higher odds of failure (odds ratio 5.23) of MDO when used to facilitate tracheostomy decannulation compared to primary MDO (Table 10).

Subgroup analysis 1: syndromic vs. non-syndromic PRS

This subgroup analysis was based on 28 papers including 86 patients (Table 9).

Table 7. Results of the age-based subgroup analysis. Odds ratio analysis could not be performed due to 0 failures in the 6–18 months and ≥18 months age groups.

Variable	Success (%)	Failure (%)	Total
Age (months)			
<6	361 (95.8)	16 (4.2)	377
≥6 to <18	12 (100)	0	12
≥18	19 (100)	0	19

Table 8. Results of further subgroup analysis comparing those aged <2 months with those aged 2–6 months for primary MDO. Results demonstrate no significant difference in success rate.

Variable	Success (%)	Failure (%)	Total	OR (95% CI)	*P*-value
Age (months)					
<2	169 (96.0)	7 (4.0)	176	1	
2–6	55 (96.5)	2 (3.5)	57	0.88 (0.18–4.35)	0.87

MDO, mandibular distraction osteogenesis; OR, odds ratio; CI, confidence interval.

Table 9. Studies included in the tracheostomy decannulation analysis: overall analysis and subgroup analyses including reasons for exclusion.

Article	Study design	Overall analysis	Syndromic vs. non-syndromic	Age-based
Ali Bukhari 2011[78]	CR	Included	Included	Included
Ali Bukhari 2012[77]	RR	Included	Included	Included
Anderson 2004[79]	CR	Included	Included	Included
Breugem 2012[27]	RR	Included	Included	Included
Burstein 2005[29]	RR	Included	Included	Excluded – no age data
Carls 1998[30]	RR	Included	Included	Included
Chigurupati 2004[31]	RR	Included	Included	Included
Chowchuen 2011[32]	RR	Included	Included	Included
Demke 2008[80]	RR	Included	Included	Excluded – no age data
Genecov 2009[34]	RR	Included	Excluded – inadequate distinction	Excluded – no age data
Gifford 2008[35]	RR	Included	Included	Included
Gözü 2010[36]	RR	Included	Included	Included
Hollier 1999[81]	RR	Included	Excluded – inadequate distinction	Included
Horta 2009[82]	CR	Included	Included	Included
Iatrou 2010[83]	CR	Included	Included	Included
Kolstad 2011[45]	RR	Included	Included	Included
Lin 2006[47]	RR	Included	Included	Included
Mandell 2004[49]	RR	Included	Excluded – inadequate distinction	Included
Miloro 2010[51]	RR	Included	Excluded – inadequate distinction	Excluded – no age data
Mitsukawa 2007[52]	RR	Included	Included	Included
Monasterio 2002[53]	RR	Included	Included	Excluded – no age data
Morovic 2000[55]	PR	Included	Included	Included
Olson 2011[58]	RR	Excluded – overlap[67]	Excluded – inadequate distinction	Excluded – no age data
Perlyn 2002[60]	RR	Included	Included	Included
Rachmiel 2012[84]	RR	Included	Included	Included
Schaefer 2004[63]	RR	Included	Included	Included
Scott 2011[64]	RR	Excluded – overlap[72]	Included	Excluded – no age data
Sesenna 2012[65]	RR	Included	Included	Included
Sidman 2001[66]	PR	Excluded – overlap[72]	Included	Included
Smith 2006[67]	RR	Included	Included	Included
Sorin 2004[68]	RR	Included	Included	Included
Spring 2006[69]	RR	Included	Included	Excluded – no age data
Steinbacher 2005[85]	RR	Included	Included	Included
Tibesar 2010[72]	RR	Included	Excluded – inadequate distinction	Excluded – no age data
Williams 1999[86]	RR	Excluded – overlap[68]	Excluded – inadequate distinction	Excluded – no age data
		31 included	28 included	25 included

CR, case report; RR, retrospective review; PR, prospective review.

The most common reason for exclusion was the lack of distinction between syndromic and non-syndromic patients in these papers. The aim of this subgroup analysis was to determine whether having PRS as part of a syndrome affects the rate of success of decannulating tracheostomized patients.

The majority of these patients were syndromic (55/86). Amongst the 31 isolated PRS patients, 26 were successfully decannulated, with a success rate of 83.9%. Amongst the 55 syndromic micrognathia patients, 44 were successfully decannulated, with a success rate of 80% (Table 11). The overall success rate in this subgroup analysis was 81.4%. The failures in the isolated PRS group were secondary to previously undiagnosed severe GORD (two cases)[29,32] and swallowing dysfunction and aspiration (one case)[32]; the last two cases did not have an adequate explanation of the reason for failed decannulation.[65] Similarly, the failures in the syndromic micrognathia group were secondary to severe GORD awaiting fundoplication (two cases),[29] choanal atresia awaiting repair (one case),[31] and TMJ ankylosis post-MDO (one case)[35]; the other studies did not provide an adequate explanation for the failure. The failures occurred in a range of syndromes with no obvious link between a specific syndrome and failure except for arthrogryposis. In the overall tracheostomy-dependent analysis, there were only three patients with arthrogryposis who underwent MDO to facilitate decannulation, but all of these patients remained tracheostomy-dependent despite MDO.[49,64]

Subgroup analysis 2: age-based analysis

This age-based subgroup analysis was based on 25 studies including 81 patients (Table 9). The aim of this analysis was to identify whether the age at which MDO is performed affects the success of decannulation. The age-based analysis was divided into three groups based on age at the time of MDO treatment: <12 months of age, ≥ 12 to <24 months of age, and ≥ 24 months of age. The overall success rate was 75.3%. Most of the patients in this

Table 10. Results comparing the overall success rate of primary MDO with tracheostomy decannulation.

Variable	Success (%)	Failure (%)	Total	OR (95% CI)	*P*-value
Primary MDO	468 (95.5)	22 (4.5)	490	1	–
Tracheostomy decannulation	122 (80.3)	30 (19.7)	152	5.23 (2.91–9.39)	<0.0001

MDO, mandibular distraction osteogenesis; OR, odds ratio; CI, confidence interval.

Table 11. Results of syndromic vs. non-syndromic subgroup analysis for tracheostomy decannulation outcome.

Variable	Success (%)	Failure (%)	Total	OR (95% CI)	*P*-value
Tracheostomy decannulation					
Isolated Pierre Robin sequence	26 (83.9)	5 (16.1)	31	1	–
Syndromic micrognathia	44 (80.0)	11 (20.0)	55	1.30 (0.41–4.16)	0.66

OR, odds ratio; CI, confidence interval.

Table 12. Results of age-based subgroup analysis of tracheostomy decannulation outcome.

Variable	Success (%)	Failure (%)	Total	OR (95% CI)	*P*-value
Tracheostomy decannulation					
Age <24 months	20 (87.0)	3 (13.0)	23	1	–
Age ≥24 months	41 (70.7)	17 (29.3)	58	2.76 (0.72–10.54)	0.137

OR, odds ratio; CI, confidence interval.

analysis were older than 24 months at the time of MDO treatment. The majority of patients had had the tracheostomy placed at less than 3 months of age.

Twelve patients were within the <12 months age group. Amongst these, there were three failures. One was decannulated but needed to be re-cannulated because of previously undiagnosed swallowing dysfunction and aspiration.[32] The second patient had choanal atresia and was awaiting repair.[31] The third patient was a syndromic patient who developed TMJ ankylosis and recurrence of airway obstruction.[35] There were no failures in the 12–24 months age group.

There were a total of 58 patients in the ≥24 months age group, with 17 failures in this group (Table 12). A significant number of these patients needed additional procedures. These children needed more suprastomal granulation tissue removal and repair of tracheostomy-related complications, such as tracheomalacia, before decannulation. Although not statistically significant, the odds of failure of MDO at facilitating decannulation was found to be more than 2.5 times greater if MDO was performed at an age of ≥24 months compared to <24 months.

Long-term outcomes

The long-term outcomes of MDO in children with airway obstruction were evaluated. A total of six studies were included for the analysis of long-term data. Three of these studies included intermediate-term data (up to 5 years),[46,47,62] and the remaining three included longer term results.[72,79,87] The observations from these will be presented in narrative form in the discussion. The incidence of airway recurrences is given in Table 13.

Discussion

This systematic review was designed to evaluate the effectiveness of MDO in children with airway obstruction secondary to micrognathia/retrognathia. This paper discusses the airway outcomes of this systematic review.

Overall, MDO was found to be very successful at preventing tracheostomy in children with micrognathia who have failed conservative treatment. Success in preventing tracheostomy was achieved in 95.5% of neonates and infants. These results are consistent with the results of a previous systematic review performed in 2008, which reported a success rate of 91.3%.[23] This was supported by statistically significant improvements in the OAHI. The most common reason for failure of MDO to relieve the airway obstruction was undiagnosed airway obstruction at other levels, such as tracheomalacia, laryngomalacia, or undiagnosed central apnoea.

The success rate was found to be higher in isolated PRS patients than in those with syndromic micrognathia. This finding is consistent with other reports in the literature.[88,89] The patients with isolated PRS who failed had lower airway abnormalities, and those with syndromic micrognathia who failed tended to have multi-system congenital anomalies that did not correspond with a particular syndrome. Some studies call these unique PRS, but in this study they were included under the classification of syndromic. Undiagnosed central apnoea was a common cause of failure in both groups.

All children being considered for MDO should have a thorough airway assessment with nasoendoscopy and polysomnography studies to confirm that the apnoea is a primary obstructive apnoea, and to exclude lower airway abnormalities. Lower airway abnormalities and central apnoea are contraindications for early MDO. Lower airway abnormalities will need to be assessed and managed before MDO. Children with multisystem anomalies have a higher risk of failure of MDO, and these children should be evaluated thoroughly and other anomalies repaired before MDO. A tracheostomy can be considered initially until other anomalies have been treated.

Some authors have reported the presence of GORD as a relative contraindication for MDO.[43,57,88] The present findings did not demonstrate the presence of GORD to be a cause of failure in the primary MDO patients.

Although MDO is very effective at relieving airway distress secondary to micrognathia, the optimum age for surgery is yet to be determined. When comparing the results of those younger than 2 months, 2–6 months, 6–18 months, and ≥18 months of age at the time of MDO, there was no significant difference in failure rate. These findings are consistent with those of other studies in the literature.[45,90] The initial concerns about the size of the neonatal mandible and lack of adequate mineralization may not be valid, and early surgical intervention seems to be common, and appears to be safe and well tolerated by patients.[91]

A significant number of patients had already undergone tracheostomy because

Table 13. Summary of airway recurrences in the long-term studies.

Study	Recurrence	Follow-up (years)
Sadakah et al., 2009[62]	1/7	3
Lee and Kim, 2009[46]	0/3	5.4
Lin et al., 2006[47]	1/5	4
Tibesar et al., 2010[72]	5/32	3–16 (average 7.6)
Anderson et al., 2004[79]	1/1	17

of severe apnoea. This outcome evaluated the effectiveness of MDO in facilitating decannulation of these children. All the children included were deemed unfit for decannulation by 'natural' means (i.e., without surgical intervention). This review found that one in five patients were unable to be decannulated after mandibular distraction. This lower success rate compared to primary MDO is consistent with other authors' observations in the literature.[23,49,92] The success rate was also not significantly different when comparing isolated and syndromic micrognathia patients.

Where the cause of failure was reported, the most common reasons were the presence of previously undiagnosed other airway abnormalities, severe GORD, chronic swallowing dysfunction, and tracheostomy-related complications. Those patients with severe GORD could often be decannulated after Nissen fundoplication. Approximately 20% of failures were secondary to tracheostomy-related complications including suprastomal granulation tissue or tracheostomy-associated tracheomalacia.

It is also important to note that a significant number of these patients had other surgical procedures during their childhood in an attempt to relieve the upper airway obstruction. Although poorly reported in the majority of studies, there were more reported upper airway surgical interventions in the patients who had had a tracheostomy placed at infancy compared to those who had only had primary mandibular distraction. A significant number of these operations were upper airway procedures that included tonsillectomy and adenoidectomy, uvuloplasties, and choanal atresia repair to relieve the airway obstruction.[68,69,85] These patients still needed to have MDO to appropriately relieve the obstruction adequately for decannulation. These children also underwent operations to treat the complications of tracheostomy such as suprastomal granulation tissue excision, tracheostomy-related tracheomalacia, and closure of tracheostomy stomas.[63,68,81,82]

No specific syndrome was associated with a higher risk of failure except arthrogryposis. There were no cases of arthrogryposis in the primary MDO group studies. However, the three patients with arthrogryposis all failed decannulation after MDO. Arthrogryposis, also known as arthrogryposis multiplex congenita, is a syndrome characterized by multiple joint contractures in the body.[93] There are several subtypes of the disease, some of which have micrognathia and other Pierre Robin-like features, and supraglottic narrowing similar to laryngomalacia.[93] Often these features are seen in the neurogenic subtype, and so there is also muscular hypotonia contributing to upper airway obstruction. There were some patients with neurological abnormalities who underwent MDO as the primary operation. Although the MDO operation was successful, they still required a tracheostomy.[50,56,57] It is difficult to draw any conclusions on the benefits of MDO in patients with neurological abnormalities from a limited number of patients. Other studies have also reported on the higher risk of failure in children with concomitant neurological abnormalities.[13,64,94,95] Nevertheless, children with neurological abnormalities in the context of glossoptosis and micrognathia are likely to have upper airway obstruction that is multifactorial in nature. The neurological component of their obstruction may not be adequately addressed by MDO alone. Also, the tracheostomy may serve another purpose in these patients such as facilitating pulmonary hygiene. So even though MDO may improve breathing by relieving the upper airway obstruction, the tracheostomy may be kept in place for other reasons.[64] These patients, like other patients with multifactorial airway obstruction, need to be assessed carefully prior to any surgical intervention being offered.

When evaluating the success rate of MDO in facilitating decannulation, the highest rate of success was in the group aged <24 months at the time of surgery. It is hypothesized that this is due to the fact that those children who have a tracheostomy for a longer period of time are likely to have a greater incidence of tracheostomy-related complications.[96] These complications, such as granulation tissue formation, tracheal stenosis, and tracheomalacia, are not resolved by MDO. Prior to MDO, a thorough evaluation of the airway with a panendoscopy/nasoendoscopy should be performed and the treatment of any tracheostomy-related complication should be completed before surgery.

Mandell et al. reported that to achieve the best results in tracheostomized patients with micrognathia and complex airways, adjunctive procedures are often needed.[49] They recommended that the selection criteria for MDO in this group of patients should be limited to patients without a history of severe GORD, chronic swallowing dysfunction, hypotonia, or pre-existing TMJ ankylosis. The results of this current study are in agreement that these factors are associated with a higher risk of failure of MDO in this group of patients.

Although there is a paucity of long-term studies available, the current literature provides some clinically relevant information to consider. Overall the studies included in this review showed relatively stable results for the relief of airway obstruction in the intermediate term, with minimal relapse of the airway obstruction. Relapse was observed secondary to the late development of TMJ ankylosis, [62] or failure of mandibular growth. The incidence of recurrence in these studies is summarized in Table 13. Stelnicki et al. reported that children with syndromic micrognathia tended to have relapse of the shape of the mandible to the pre-morbid shape.[87] A potential genetic predisposition for this relapse after MDO was suggested. This finding concurs with that of Gürsoy et al., who reported excellent short-term structural changes in syndromic children after MDO.[97] However during a 5-year follow-up period, there was persistent impaired mandibular growth and hence recurrence of deformity. Whether this affects airway outcomes was not reported, but this indicates that these children are likely to have a persistent deformity requiring further surgical intervention in the future. Both studies, however, still considered MDO at a young age as an indicator for severe airway obstruction, but not for facial aesthetics.

Anderson et al. reported the results of a child who underwent MDO to facilitate decannulation.[79] This child developed recurrence of obstructive apnoea 18 months after MDO that was successfully managed with CPAP without the need for further surgery until adolescence. Skeletal surgery is not necessary for all patients with persistent retrognathia after MDO, as this may not correspond with recurrent airway symptoms. These patients should be considered similar to patients with a class II skeletal profile and managed accordingly. Condylar changes and ankylosis after MDO have also been reported, and can lead to recurrence of airway symptoms. Sadakah et al. reported that three out of seven patients had condylar changes after MDO over time and one patient developed ankylosis at 3 years postoperatively with recurrence of airway distress.[62] Andrews et al. also reported cases of TMJ ankylosis after MDO in mainly syndromic patients.[26] These complications may be prevented by techniques to unload the condyles; such a technique was introduced by Guerrero in 1999, and was used during the distraction and consolidation phases of treatment.[98] Using class II intermaxillary elastics

alleviated strain on the TMJ and reduced postoperative condylar changes. These unloading regimens have been found to reduce the incidence of TMJ ankylosis after MDO.[99,100]

These studies should highlight the importance of carefully following up these patients through their childhood until adolescence. The persistence of retrognathia or relapse can lead to recurrence of airway obstruction. These children should be assessed clinically and should undergo polysomnography analysis if there is a suspicion of relapse of airway symptoms. TMJ ankylosis should always be considered as a possible long-term complication of MDO and it may lead to recurrence of airway obstruction.

It is imperative to mention here that where possible, conservative treatment should always be trialled first before surgical intervention is considered. When considering MDO in any infant or child, the risk versus benefit of surgery must always be considered. It is important to remind the reader that as with all surgical interventions, there is the potential for long-term morbidity associated with MDO. In a recent systematic review by Verlinden et al., MDO was associated with long-term complications such as facial scarring, facial nerve palsy, neurosensory disturbances of the inferior alveolar nerve, occlusal abnormalities such as an anterior open bite, and dental damage.[101] The dental damage ranges from dilacerations and hindered tooth development, to failure to erupt.[102] Dentigerous cysts forming in the distracted segment from stretching of the tooth follicle have also been reported.[81] Although these are uncommon, further studies are needed to determine the ideal osteotomy technique, ideal type of distractor, and the best treatment protocol for different age groups (latency period, distraction rate, consolidation time). Longer-term studies are needed to determine the overall incidence of these complications and the consequences of them.

Systematic reviews by nature are retrospective and observational. They are heavily reliant on the data reporting of others, and hence are at risk of replicating biased results. When comparing randomized controlled trials, it is easier to compare inclusion and exclusion criteria and to identify ways in which bias is avoided, but when comparing clinical case series and case reports, it is difficult to identify and avoid biased reporting. Authors like to report positive results, and hence systematic reviews on case series are prone to providing conclusions and clinical advice based on this reporting.

Often the studies included had incomplete data, making their specific inclusion for each individual analysis more complex. Where data needed for the study were incomplete, attempts were made to contact the corresponding authors; however, confirmatory details were not available at the time of writing. Where the particular outcomes and results were unclear in those situations, the data were excluded.

For the purposes of statistical analysis, all studies were treated as case reports. This allowed the odds ratio to be calculated by univariate analysis. Ideally, a multivariate analysis would be performed to help determine a weighting to what characteristics have the most influence on the outcome.

A wide variety of syndromes were associated with the micrognathia, glossoptosis, and upper airway obstruction in the studies included in this systematic review. These syndromes are a very heterogeneous group of syndromes with varying spectrums of severity and additional co-morbidities. Hence, there is always an inherent difficulty in trying to group them into a single group – syndromic micrognathia. Even isolated PRS has a wide variety of phenotypes and sometimes additional co-morbidities that do not fit within the characteristics of any known syndrome. Hence, the syndromic analysis needs to be interpreted with caution, and each patient needs to be treated as an individual. The findings of this review provide a guide to what factors are associated with a higher chance of failure and which overall groups of patients are at risk of further problems.

In conclusion, MDO is a successful technique in alleviating upper airway obstruction secondary to micrognathia and has a success rate of approximately 95% in preventing tracheostomy. The most common causes of failure of MDO were found to be undiagnosed lower airway obstruction, central apnoea, and additional cardiovascular co-morbidities. All children being considered for MDO should have a thorough airway assessment with nasoendoscopy and polysomnography studies to confirm that the apnoea is a primary obstructive apnoea, and to exclude lower airway abnormalities. Syndromic patients should be investigated more carefully as they have a four times greater chance of failure compared to isolated PRS patients. The success rate of primary MDO is not influenced by age at the time of surgery. This study did not find the presence of GORD to be a contraindication to primary MDO for children with micrognathia. Patients with neurological abnormalities are more likely to still require a tracheostomy despite successful MDO, as the airway obstruction is likely to be multifactorial.

Children who are tracheostomy-dependent secondary to upper airway obstruction from micrognathia can be successfully decannulated after MDO in approximately 81% of cases. The success rate was found to be slightly higher for isolated PRS patients compared to syndromic micrognathia patients, although the difference was not statistically significant. The most commonly reported reasons for failure included previously undiagnosed additional airway abnormalities, GORD, chronic swallowing dysfunction, and tracheostomy-related complications. Children who have severe gastro-oesophageal reflux on pH monitoring should be referred for consideration of treatment of the reflux prior to MDO. Children with neurological complications are also at higher risk of failure of MDO to facilitate decannulation.

The success rate of MDO at facilitating decannulation was higher when performed before the age of 24 months. This is likely due to the tracheostomy-related complications that develop from long-term cannulation. The failures at an age of less than 24 months were due to untreated additional abnormalities and were all in syndromic patients. Hence caution should to be taken in decannulating syndromic patients and a thorough airway assessment is needed before MDO and decannulation is attempted to determine the presence of additional lower airway abnormalities or tracheostomy-related complications.

There are few studies evaluating the long-term outcomes of MDO. More studies are needed to evaluate the long-term facial changes after MDO and the long-term occlusal and dental complications following MDO.

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