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

Submitted by

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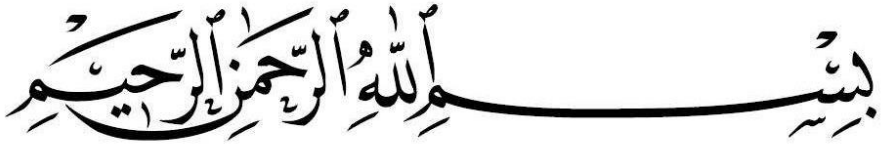

In the name of God, Most Compassionate, Most Merciful

To my Father, and my Father's Father…….

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Table of Contents

List of tables

List of figures

Executive summary

Background

Mandibular distraction osteogenesis (MDO) is becoming increasingly commonly used as the primary surgical option for neonates and infants with upper airway obstruction secondary to micrognathia or to facilitate decannulation for tracheostomy dependent children.

Objectives

The objective of this review was to identify and synthesize the best available evidence on the effectiveness of MDO on airway patency, feeding, gastro-esophageal reflux (GORD) and long-term development in children born with upper airway obstruction secondary to micrognathia. This review also aims to determine the ideal rate of distraction, and compare outcomes of external and internal distractors in this patient group.

Inclusion criteria

The inclusion criterion included studies in children with clinical evidence of micrognathia/Pierre Robin Sequence (PRS) who have failed conservative treatments, including both syndromic (sMicro) and non-syndromic isolated PRS (iPRS) patients. The intervention is patients who have undergone bilateral distraction osteogenesis to prevent a tracheostomy or to facilitate decannulation. The comparator intervention is patients who underwent a tracheostomy alone. The outcomes of interest include relief of airway obstruction with MDO, decannulation of tracheostomy dependent patients, feeding and reflux changes, surgical outcomes such as comparison of rate of distraction and type of distractor. All study designs were included.

Methods

The databases searched included PubMed, Embase, Scopus, Web of Knowledge and grey literature sources. Of the 4815 studies found in the initial search, only 66 were included after critical appraisal. Due to the nature of the studies included, a meta-analysis was not possible. The data was pooled by calculating weighted means.

Results

Primary MDO for the relief of upper airway obstruction was successful in 95% of cases in the literature. Syndromic (sMicro) patients had odds of failure that were four times higher than those of iPRS patients. The most common causes of failure are previously undiagnosed lower airway obstruction, central apnoea, undiagnosed neurological abnormalities and complex multiorgan anomalies. Mandibular distraction osteogenesis (MDO) was less effective (80.3% success rate) at facilitating decannulation of tracheostomy dependent children. Failure in these patients was most commonly due to severe preoperative gastro-oesophageal reflux disease (GORD), swallowing dysfunction and tracheostomy related complications. The failure rate was higher when MDO was performed at an age of ≥24 months for this group of patients. Approximately 84% of children can be exclusively oral fed after MDO. The odds of needing feeding adjuncts were five times higher in syndromic children. There was a trend towards a growth decline in the first six weeks after surgery. MDO relieves GORD in the majority of patients. Patients who were tracheostomy dependent with severe GORD were at higher risk of failure to decannulate after MDO. There was no difference in success rate when comparing a distraction rate of 1mm/day with 2mm/day. External distractors were associated with a higher rate of failure and complications compared to internal distractors. Overall, there was a paucity of long-term results in the literature. Recurrence of airway distress may occur due to a relapse of retrognathia or TMJ ankylosis.

Conclusion

Mandibular distraction osteogenesis is an effective technique for preventing tracheostomy in children with airway obstruction secondary to micrognathia (Level 4 evidence). Thorough airway evaluation and sleep study pre-MDO is necessary to exclude multilevel airway obstruction and central apnoea. Mandibular distraction osteogenesis has a slightly lower success rate at facilitating decannulation. Thorough airway evaluation, assessment for reflux and swallowing dysfunction are necessary prior to surgery. Mandibular distraction osteogenesis is effective at alleviating feeding problems and reflux symptoms in these children. Care needs to be taken to avoid a general growth decline that has been reported in the first six weeks after surgery. Distracting at a rate of 1mm/day or 2mm/day below the age of 12 months is safe. Internal distractors have a higher success rate and a lower rate of complications than external distractors. More studies are needed to evaluate the long-term implications of MDO on facial development and long-term complications.

Chapter 1: Introduction

1.0 Introduction

Micrognathia is a congenital condition characterized by 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 attention.

1.1 Pierre Robin Sequence

In 1923, the French stomatologist was the first to describe a 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, glossoptosis, and in most cases results in a U-shaped cleft palate. There is only limited epidemiological data on this incidence, but it has been reported to range from approximately 1 in 8500 live births in Merseyside[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 literature.

The definition of PRS is challenging due to the wide spectrum of PRS phenotypes, the variation in degree of airway obstruction, feeding difficulties and the need for treatment. This has led to some authors only characterising those with airway obstruction needing treatment as having PRS, [5] while others include all patients with micrognathia and glossoptosis, or limit the PRS diagnosis to those with associated cleft palates as having PRS.[6] Although these clinical features are most commonly seen in isolation[7], they can also occur in association with other clefting conditions of the craniofacial skeleton, for example, Treacher Collins Syndrome, Stickler syndrome and Nager syndrome. Such co-occurrences further complicate the diagnosis. For simplicity, in this review, those without an associated syndrome have been referred to as isolated PRS (iPRS) and those with an associated syndrome referred to as

syndromic micrognathia (sMicro). The varying phenotypes and presumed causes of these anomalies make comparison of the myriad of protocols advocated for management difficult.[8]

1.2 Aetiology of Pierre Robin Sequence

The aetiology of PRS remains a source of considerable debate.[9] The term 'sequence' is preferred over 'syndrome' for this condition because mandibular micrognathia is the primary pathological problem leading sequentially to the other clinical features of PRS. The micrognathia restricts the space for the tongue, leading to glossoptosis. The degree of vertical and posterior position of the tongue determines the interference with the fusion of the palatal shelves prenatally leading to the U-shaped cleft palate.[10-14]

Micrognathia is believed to be either an inherent growth defect or secondary to physically restricted mandibular growth. The inherent defect may be isolated or the small mandible may be part of a craniofacial syndrome.[15] The most common genetic cause is Stickler syndrome. The secondary causes that restrict mandibular growth are usually due to the fetal position at six weeks, which assumes a circular position with the head flexed onto the chest. In the normal fetus, the head is gradually extended and this is completed by the 12th week. If this process does not occur normally, the mandible cannot grow appropriately. This restriction of grown may also be caused by oligohydramnios.[12]

1.3 The potential for 'catch-up' growth

Does micrognathia resolve with growth after birth? This is an important clinical question as it is crucial to the management of these children and may affect the decision for early surgical intervention.

The term 'catch-up' growth implies a faster rate of mandibular growth than average to compensate for micrognathia at birth. It is presumed that those children with inherent growth defects or craniofacial syndromes (sMicro) are unlikely to have any significant catch-up growth of the mandible as they get older due to a genetic growth restriction. In contrast, those with restricted mandibular growth due to secondary causes may have catch up growth once

the cause of the restriction is eliminated (i.e. birth).[16] Those with isolated PRS may fall into either group, and hence it is crucial to identify if these children will have catch up growth.

A number of cephalometric studies have attempted to investigate catch up growth in isolated PRS. Figueroa et al.[17] followed 17 children with isolated PRS, 23 children with isolated cleft palate and 26 healthy children. These authors reported an increase in the rate of mandibular growth in the PRS group initially, but the mandible remained significantly more retrognathic at the end of the observation period in the PRS group compared to the other groups.

Other studies have found limited evidence for catch up growth. A number of cephalometric studies have demonstrated that the rate of growth of the mandible between patients with isolated PRS and isolated cleft lip to be identical by the age of five years[18] and 10.5 years[19] in both groups. This implies that the rate of mandibular growth was not greater in the PRS patients despite a significant micrognathia at birth compared with isolated cleft lip. No catch up growth was observed. This is further supported by the study by Marcovic et al.[20] who followed 15 PRS patients from the age of two to early adolescence. They observed catch up growth in only one patient. The cephalometric studies by Laitinen and Ranta[21] and Daskalogiannakis et al.[16] found no significant improvement in the skeletal pattern of patients with PRS over time again, suggesting no catch up growth. These findings are further supported by results from a large Canadian study designed to assess catch up growth.[22] This study compared the cephalometric tracings of 34 Caucasian subjects with non-syndromic PRS and the same number of unaffected, matched control subjects from birth to adolescence. Subjects with isolated PRS were found to have maxillomandibular retrognathism that persisted throughout life. The pattern of deficient mandibular growth did not improve during pubertal growth, and there was no greater differential adolescent catch-up growth detected.

It is not possible at birth to identify whether micrognathia is secondary or primary unless an obvious syndrome is present. Hence, we cannot predict which child will have catch up mandibular growth and which child will not. Overall, these studies suggest that there is minimal catch up growth seen in children with isolated PRS, so early treatment to correct micrognathia may be warranted.

1.4 Complications of micrognathia

The principal sequel of micrognathia is the inability to effectively breathe or feed due to the airway obstruction.[23, 24] Micrognathia and obstructive apnea contribute to a wide range of clinical problems in these children. Prolonged obstructive apneic episodes can lead to hypercarbia and hypoxia. These children also tend to have higher caloric consumption due to their repeated attempts to clear their upper airway. It is unknown what effect the chronic hypoxia, hypercarbia and increased caloric consumption will have on the growing neonate, particularly on the developing brain.

These infants also have significant feeding and swallowing problems. During the normal swallowing process, breathing is suppressed and a decrease in ventilation occurs during the sucking process.[25] In contrast to normal infants, infants with upper airway obstruction may have to increase the efforts to breathe even at rest, and hence may lack the pulmonary reserve necessary to support the additional respiratory effort required for oral feeding. This may cause failure to thrive.[26, 27]

Another significant complication is the increased incidence of GORD in children with PRS. It is hypothesized that upper airway obstruction results in an increased inspiratory effort to overcome the obstruction, which results in a negative intra-thoracic pressure that can cause a suction type effect on the gastric contents.[28]

All of these complications are secondary to the upper airway obstruction; therefore the priority is to treat the upper airway obstruction. However, it is yet to be determined if relieving the upper airway obstruction will also resolve these complications. Thorough evaluation of the micrognathic child to evaluate these potential clinical consequences of micrognathia is vital for the management of these children.

1.5 Evaluation of the micrognathic child

Current clinical pathways for children born with micrognathia require a comprehensive evaluation by a multi-disciplinary team consisting of a craniofacial surgeon,

pulmonologist, pediatrician, speech therapist, geneticists, otolaryngologists and dietitians.[9] There is no validated method for identifying and quantifying the level of airway obstruction leading to respiratory insufficiency in children with PRS.[29] All children should be evaluated initially with pulse oximetry while awake and asleep. Any evidence of desaturation suggests possible respiratory distress warranting further investigation. Patients who have desaturations include those who have a drop in oxygen saturation during any of the normal activities, namely feeding, sleeping or in wakefulness. Even when no desaturations are found on initial screening, polysomnography (PSG) or a sleep study is still warranted in these patients. Polysomnography can document the frequency and duration of apneic episodes, as well as the severity of desaturations.[23] More importantly, it can determine if the desaturations are mainly obstructive or central in origin. This is crucial to determining the ideal treatment option. Respiratory distress in these children may not be only structural. Thorough neurological examination is necessary to exclude hypotonia or other neurological abnormalities contributing to the distress.

Where a structural cause is presumed to be contributing to the airway obstruction, further investigation with airway endoscopies is warranted. The most important role for airway endoscopies is to evaluate for multilevel obstruction. Laryngoscopies and bronchoscopies are vital to rule out dynamic upper airway obstructive pathologies like laryngomalacia or more distal pathologies like tracheomalacia. When surgical interventions like MDO are being considered, jaw thrust manoeuvres during laryngoscopy can be used to predict the success of the procedure.

Feeding difficulties are defined as either inability to gain weight or a prolonged feeding time. Clinical evaluation of the volume, frequency and quality of successful feeding must be analysed in detail.[30, 31] These children are also assessed with pulse oximetry during feeding to assess for desaturation. Depending on the severity of their feeding difficulty, or evidence of failure to thrive, they may require the use of feeding adjuncts to improve weight gain and growth. These adjuncts may include nasogastric tubes, specially designed bottles, gastrostomy tubes or even total parenteral nutrition (TPN).

Due to the high incidence of GORD and swallowing difficulties in these patients, a diligent assessment of reflux and swallowing dysfunction with pH monitoring and swallow

studies should be performed. This is important even when considering surgical treatment for preoperative planning options because some studies have reported poor postoperative outcomes in children with significant reflux.[23] Some authors advocate video fluoroscopic studies for these children to ensure there is no evidence of significant aspiration.[32]

The severity, nature and cause of the respiratory distress must be identified early in the evaluation of these children. In addition to the airway obstruction, these children tend to have significant feeding and swallowing difficulties as well as a high incidence of reflux, and characterisation of these abnormalities is necessary for determining the appropriate management of the micrognathic child.

1.6 Management of the micrognathic child

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 nasopharyngeal airway or application of nasal continuous positive airway pressure (CPAP). The success of using nasopharyngeal airways is varied in the literature, ranging from 48%[33] to 100%.[34] Large case series looking at children with non-syndromic PRS have determined that less than 10% require surgical intervention.[35]

For neonates with severe respiratory distress, or those who have failed initial conservative treatment, the airway compromise can be a life-threatening emergency. The nasopharyngeal 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.[36] Children who require prolonged treatment with these measures may require more definitive surgical intervention. This decision needs to be made by the multidisciplinary team.

Several surgical treatments have been described for the treatment of the micrognathic child. In 1946 Douglas described the use of tongue-lip adhesion (TLA) for the treatment of upper airway obstruction associated with micrognathia.[37] 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 nine to 12 months of age. Various techniques for TLA have been described.[38] Some advocate this technique as the first line surgical treatment for the majority of children who have failed conservative treatment, and they have reported successful outcomes.[38-40] Others have challenged this approach and found that most children who undergo Tongue-lip adhesion require secondary surgical treatment within four months of treatment.[31] Tongue-lip adhesion is also associated with significant complications including wound dehiscence and feeding difficulties. The swallowing difficulties caused by tethering of the tongue may necessitate the need for nasogastric or gastrostomy feeding tubes.[7, 39] Furthermore, the underlying cause of the obstruction is not fully addressed by TLA, and so many centres have abandoned it as a viable treatment option.[36] Some centres use TLA as a temporary relief of airway obstruction while performing MDO.[41] Other surgical options described include mandibular traction and advancement [42, 43], or subperiosteal release of floor of the mouth musculature.[44, 45] Subperiosteal release of the musculature is based on an observation by Epois in 1983[46] where he suggested that the tightness of the muscular insertion of the tongue on the mandible was responsible for micrognathia, tongue tip elevation and glossoptosis seen in PRS. Hence, releasing the genioglossus attachment from the mandible could allow the tongue tip to move forward into a normal position. These techniques have not been met with widespread success.

The traditional "gold standard" surgical option for micrognathic patients who have failed conservative treatment is tracheostomy.[47] Tracheostomy is a technique that creates an airway within the trachea below the level of an upper airway obstruction leading to immediate relief of the upper airway obstruction. A tracheostomy however is associated with significant morbidity, cost and mortality. Tracheostomy in a neonate is a drastic treatment option that needs careful consideration. Complications are high, with some studies reporting up to 29 per cent tracheostomy related complications including bleeding, pneumonia, tracheostomy tube obstruction and accidental decannulation.[48] Despite this high rate of complications, tracheostomy related mortality is significantly less common (0.5-4%).[49, 50] Complications are compounded by the need to maintain the airway cannulation for years, which leads to a greater incidence of long-term complications such as tracheal hypergranulation, tracheal stenosis and swallowing dysfunction.[51] These complications may often require further surgical intervention. Finally, decannulation can only occur if there is a

degree of catch up growth of the mandible with subsequent enlargement of the airway, which is not always predictable or significant enough to allow for decannulation.

Tracheostomy at a young age can also stunt the development of a child, for example, in the area of normal language skills. Children begin articulation attempts from early infancy, and if they are unable to make these primitive sounds, it is likely that their ultimate speech and language development will be impaired.[52-54] In a study by Singer et al,[55] evaluating the long-term outcomes of neonatal tracheostomy, a follow-up evaluation of language and linguistic competencies of children who had a tracheostomy under 13 months of age found that they functioned at a level below the normal range. In addition other developmental milestones were also found to be impaired. Growth measurements for the otherwise neurologically normal children who underwent tracheostomy before 13 months of age showed a deceleration in growth in relation to the normal distribution of weight for age at birth. The mean percentiles of weight for age were 49.7 with only 10 per cent of children under the 10th centile. At follow-up, the mean percentile of weight for age was 38.6 with 30 per cent under the 10th centiles.[55] Also, based on parental reports in the study, children tracheostomised at infancy had a high incidence of behavioral problems and social isolation compared with a normative group of same-age and same-sex peers. Adult studies have also demonstrated the long-term effects on body image perception and reduced life satisfaction in patients who underwent tracheostomies at a young age.[56]

Parental challenges in caring for the tracheostomy dependent child also need to be considered. Families of children born with disability experience considerable challenges, predominantly emotional and social stresses, as well as financial pressures.[57] A study reported that parents who cared for tracheostomy and/or gastrostomy dependent children experienced a significant disruption of social interactions both within and outside the family, and were cited as a major problem experienced by the caregivers.[58] Furthermore, children with long-term tracheostomy require nursing care at home and in their educational institutions, along with monitoring and suction equipment.[54]

Overall, the prolonged period of having a tracheostomy compounds the developmental delay and also results in a significant negative impact on the psychosocial aspects of the child and the family of the child.[47]

1.7 Mandibular Distraction Osteogenesis

A surgical solution that has recently been proposed and appears to be gaining popularity is MDO. The principles of distraction osteogenesis originated in the early 1900s[59] but only found practical applicability in the 1950s. Ilizarov[60], a Russian orthopaedic surgeon, developed a procedure to lengthen long bones which is based on the "tension-stress" principle. The procedure involves an osteotomy (bony cut) with gradual lengthening of the divided bony segments. Stretching the healing soft tissues between the bony segments into a constant state of tension and stress promotes metabolic activation, angiogenesis and new bone formation.[61]

Since the mid-1980s to early 1990s, this technique has been adapted in the oral and craniomaxillofacial skeleton to deal with various types of reconstructive dilemmas.[62, 63] Mandibular distraction osteogenesis for infants with micrognathia was also first reported during this period, and was initially used for unilateral mandibular lengthening by distraction for cases of hemifacial microsomia[64] and bilateral cases of Treacher Collins Syndrome.[65] In the initial cases, mandibular distraction was used for resolving upper airway obstruction, and also to facilitate the removal of tracheostomy. Since then, it is increasingly being used as the primary surgical option for the management of neonates and infants with micrognathia or PRS with upper airway obstruction.[31]

Mandibular distraction osteogenesis 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. The surgical procedure involves four main phases: osteotomy/corticotomy, latency, distraction and consolidation. Osteotomy involves bony cuts in the mandible bilaterally and distraction devices are inserted which span the proximal and distal bony segments. A latency period is applied to allow for the formation of a soft tissue callous before the segments are distracted. The distraction phase soon follows with activation of the distractor to gradually lengthen the mandible. The distraction is gradual and steady; hence the overlying soft tissues are also stretched to accommodate the changes. The final stage is the consolidation phase. Once the ideal length is

achieved, the distractors are kept in situ until the bone matures and consolidates, which usually takes four to eight weeks. Most children with upper airway obstruction will show 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.

As in all areas of clinical medicine, advances in new technology and experience with the techniques result in modifications to both technique and treatment protocol. External distractors have largely been replaced by internal distractors. The procedure to insert the latter results in a reduction of scarring, nerve damage and infection rate in several studies.[31, 66] Other modifications include use of the corticotomy/osteotomy design, modifying the rate of distraction, various latency and consolidation periods, use of resorbable distraction devices and use of biological adjuncts including bone morphogenic protein (BMP)[67] to enhance bone regeneration in the distracted segment. Lack of longitudinal comparison between these procedures limits the surgeon's ability to select the appropriate procedure. A very important variable is the rate of daily distraction. The recommendation of 1mm per day by Ilizarov is for the treatment of long bones and adult patients, and thus it may not apply for cases involving the craniofacial skeleton of a child. Studies on mandibular distraction vary from distraction at a rate of 1mm per day up to 5mm per day.[68] It is important to determine if there is an ideal daily rate of distraction, and to determine if it differs in certain age groups, as this may directly affect the rate of early reoperation and the rate of complications.

1.8 Methodological approach and aim of this systematic review

Several case series have demonstrated the effectiveness of MDO in alleviating upper airway obstruction in neonates, infants and older children with PRS.[69] Most patients were able to avoid tracheostomies and those who already had traheostomies were able to be decannulated. A systematic review performed in 2008 evaluated the effectiveness of MDO in several clinical applications.[69] This review evaluated 178 studies, comprising 1185 patients. Success in preventing tracheostomies was achieved in 91.3% of patients. Authors of this review however only searched the PubMed database on the applications of unilateral and bilateral mandibular distraction in both children and adults. Limiting to a single database is a significant methodological limitation of this review. In addition this study also included all

possible causes of micrognathia including TMJ ankylosis, hemifacial microsomia and syndromic PRS, which have completely different etiologies 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. The review reported the range of rates of distraction and the variety of distractor types, but did not compare the rate of distraction or distractor type with outcomes and various age groups.

The results of retrospective and prospective case series as well as case reports evaluating MDO in children with micrognathia have been published since the review by Ow and Cheung.[69] In light of the limitations in their methodology and the many recent publications, an update of this systematic review is warranted. Reporting the reasons for failure of distraction may also guide the treating team on the appropriate way to evaluate and treat children with airway obstruction secondary to micrognathia. Identifying those children at high risk of failure may prevent unnecessary operations and interventions. This systematic review also aims to evaluate the success rate of MDO comparing isolated PRS and syndromic micrognathia outcomes and different age groups to identify if there is an appropriate age for surgery.

This review also aims to determine if the surgical outcomes are affected by the rate of distraction or the type of distractor used. Distracting the mandible by 1mm per day or 2mm per day or more may impact on the rate of complications, the rate of early reoperation, and the length of hospital stay. It is important to determine if there is an ideal rate of distraction for children undergoing MDO and whether the ideal rate varies between age groups.

This systematic review was conducted according the Joanna Briggs Institute (JBI) methodology for performing systematic reviews and meta-analysis. The aim of this systematic review was to gather, synthesize and collate the best available evidence irrespective of type of research. The JBI methodology makes it possible to determine the current evidence based approach to caring for a patient until higher-level evidence is available. This 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 in comparison with

tracheostomy for treating upper airway obstruction in children with micrognathia. It also aims to determine the effects of mandibular distraction on the other complications of micrognathia, including feeding and weight gain, gastro-oesophageal reflux and facial development.

Chapter 2: Systematic review protocol

This systematic review was conducted according the Joanna Briggs Institute (JBI) methods for performing systematic reviews and meta-analysis. This systematic review protocol was prepared and defended in a panel with two experts in the field of craniofacial surgery. It was subsequently peer reviewed and published in the JBI Database of Systematic Reviews and Implementation Reports. [70]

2.1 Objectives and statement of review questions

The objective of this review was to identify and synthesize the best available evidence on the effectiveness of MDO on airway patency and long-term development in children born with upper airway obstruction secondary to micrognathia.

More specifically:

Does mandibular distraction result in improved short and long-term outcomes compared with tracheostomy?

What is the ideal daily rate of mandibular distraction, and does the ideal rate differ between age groups?

2.2 Inclusion criteria

2.2.1 Types of studies

This review considered both experimental and epidemiological study designs, including randomized controlled trials, and in their absence, non-randomized controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, and case control studies. The review also considered descriptive epidemiological study designs, including case series and case reports for inclusion in an effort to inform the effectiveness of

this intervention.

2. 2. 2 Types of participants

This review considered studies that included:

1. Male and female children from birth with clinical evidence of Pierre Robin Sequence or mandibular hypoplasia.

2. Children with upper airway obstruction who have undergone failed conservative treatments.

3. Syndromic and non-syndromic children with micrognathia.

4. Children who have undergone bilateral mandibular distraction for consideration of decannulation and removal of a tracheostomy.

5. Minimum follow-up period of one year

This review did not consider studies that included:

1. Children who have undergone unilateral mandibular distraction.

2. Children with central apnea or acquired conditions that lead to airway obstruction, for example, trauma, iatrogenic injury and tongue disorders.

3. Children with lower airway disorders.

4. Children with Temporomandibular joint TMJ ankylosis, hemifacial microsomia or other mandibular condition leading to airway obstruction.

2.2.3 Types of Intervention(s)/phenomena of interest

This review considered studies that evaluated MDO.

2.2.4 Types of comparisons

The comparator was the use of tracheostomy.

2.2.5 Types of outcomes measured

This review considered studies that included the following outcome measures:

- Primary mandibular distraction osteogenesis (Primary MDO)

- Tracheostomy decannulation (TD)

- Feeding and weight gain

- Gastro-oesophageal reflux (GORD)

- Surgical outcomes

- Long-term facial development.

Primary mandibular distraction osteogenesis and tracheostomy decannulation

The primary MDO outcome is concerned with the reversal of obstructive apnea and the ability of the child to maintain airway patency without airway adjuncts. This was reported in some studies with polysomnographic results, which provide objective evidence of improvement. Other studies reported subjective airway improvement based on the child being able to maintain oxygen saturations without additional airway supports. The tracheostomy decannulation outcome is concerned with children who have already had a tracheostomy to maintain an effective airway. MDO is often used to facilitate decannulation of a tracheostomy dependent child who otherwise cannot be decannulated.

Feeding and weight gain –

As discussed earlier, upper airway obstruction leads to a hypermetabolic state, which often manifests as failure to thrive. Children with micrognathia also tend to have swallowing abnormalities because of abnormal pharyngeal and tongue movements, leading to increased risk of aspiration and inability to tolerate oral intake. Most studies that included this outcome reported the ability to tolerate oral feeding, or if feeding adjuncts were needed to maintain adequate nutritional statusin order to thrive. The most commonly used adjuncts for feeding included nasogastric tube or gastrostomy. Some studies also reported the rate of weight gain preoperatively and postoperatively or results of swallow studies preoperatively and postoperatively.

Gastro-oesophageal reflux

This outcome of interest was reported as a reduction in the symptoms of GORD, or objective evidence of improvement in upper gastrointestinal series or pH monitoring before and after

surgery.

Surgical outcomes

The main outcomes of interest in relation to the surgical procedure were the rate of complications and the need for early re-operation. The main complications for which data was collected included scarring, infections, facial nerve injury, damage to dentition, premature osseous fusion, early-reoperation and damage to the developing dentition.

Long-term facial development

This outcome of interest was included the aim of evaluating the evidence for normal or abnormal facial growth and the need for future mandibular/orthognathic surgery in children who have undergone distraction osteogenesis. Ideally this outcome would be measured by cephalometric measurements compared with normal subjects at skeletal maturity. The minimum follow-up period to include in this outcome analysis was three years.

2.3 Review methods

2.3.1 Search strategy

The search strategy aimed to find both published and unpublished studies. A three-step search strategy was utilised in this review. An initial limited search of PubMed and CINAHL was undertaken followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms was then undertaken across all included databases. Studies published in English were considered for inclusion in this review. Only studies published after 1990 were considered for inclusion in this review, as this was the earliest reported case of the use of MDO in children with airway obstruction.

The databases that were searched include:

PubMed, CINAHL, Embase, Scopus and Web of Knowledge.

Grey Literature was searched through the following databases: Scirus, Mednar, ProQuest Theses and Dissertations, and Index to Theses, Libraries Australia.

The search strategy involved the use of a variety of keywords to ensure complete retrieval of

articles. The search strategy used for searching through PubMed is included in Figure 2.3.1.

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]

Figure 2.3.1: Search strategy used for searching PubMed

mh – mesh heading, tw – text word

There are several terms for each syndrome and condition. A detailed search strategy was required to identify all the relevant studies for this review. The search terms used were translated to other databases to facilitate the search through other databases (Appendix I).

2.3.2 Assessment of methodological quality

Papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix II). Any disagreements that arose between the reviewers were

resolved through discussion, or with a third reviewer.

2.3.3 Data extraction

Data was extracted from papers included in the review into Excel tables (Appendix III). The data extracted included specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. The authors of the included studies were contacted if important data that is relevant to the review was missing from the published papers.

2.3.4 Data synthesis

Individual patient data from the papers included in this review were combined, effectively treating each patient as an independent case report. The categorical data retrieved was then cross-tabulated and expressed as an odds ratio with 95% confidence intervals. The cross-tabulation method allows for comparison of one or more variables. Statistical significance was determined at $p < 0.05$ following a chi-square test. For continuous data, mean differences and standard deviations were calculated. Comprehensive meta-analysis (version 2.2.064, BioStat NJ, USA) was used to establish odds ratios, mean differences and statistical significance. Subgroup analyses were performed where possible to compare surgical protocols, syndromic and non-syndromic children with micrognathia, external and internal distraction, and age at time of surgery, early reoperation rates, and rate of complications. Where statistical pooling was not possible the findings are presented in narrative form including tables and figures to aid in data presentation where appropriate.

Chapter 3: Results

3.1 Description of studies

The search identified a total of 4815 studies. Of these, the total number of studies retrieved based on title was 801. After removal of duplicates, studies not in English, or studies outside the date criteria, there remained only 382 studies. The abstracts of these 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.

Following the review of the full text, an additional 38 studies were excluded, as they did not fully meet the inclusion criteria, resulting in 86 studies that were subjected to critical appraisal resulting in 66 studies included in the final analysis (Figure 3.1)(Appendix IV).

3.2 Methodological quality

Following the search process, 86 studies underwent independent critical appraisal by two reviewers trained in the use of JBI-MAStARI. Any disagreements between the reviewers during the critical appraisal were resolved by discussion, and on two occasions, the opinion of a third reviewer was sought. No specific cut-off figure was required when using the critical appraisal tools by JBI-MAStARI. This was because different studies were measuring a range of outcomes. This heterogeneity made it difficult to decide on a particular cut-off point. Hence, each study was judged on its own merit if it had fulfilled a minimum of five of the possible maximum ten points (Appendix IV). The general quality of the papers was poor with approximately Level 4 evidence (JBI Levels of Evidence 2014).

After critical appraisal, 20 studies were excluded resulting in the selection of the final 66 studies that were included in this review (Appendix V). All studies were descriptive studies and case series (Level 4 evidence). No randomized controlled trials or quasi-randomized trials were found which were related to the review question. The majority of the papers were retrospective case series from a single institution. Of the 66 included studies, 57 were case series, two of which were prospective in design. The remaining nine studies were case reports. These were included after careful critical appraisal to ensure minimal bias in case

selection and outcome data adequate for inclusion in this review. The majority of the papers were originated from centres in the United States (41/66). Of the remaining studies, nine were from Europe, five from Asia, five from the Middle East, three from South America, and three from Australia.

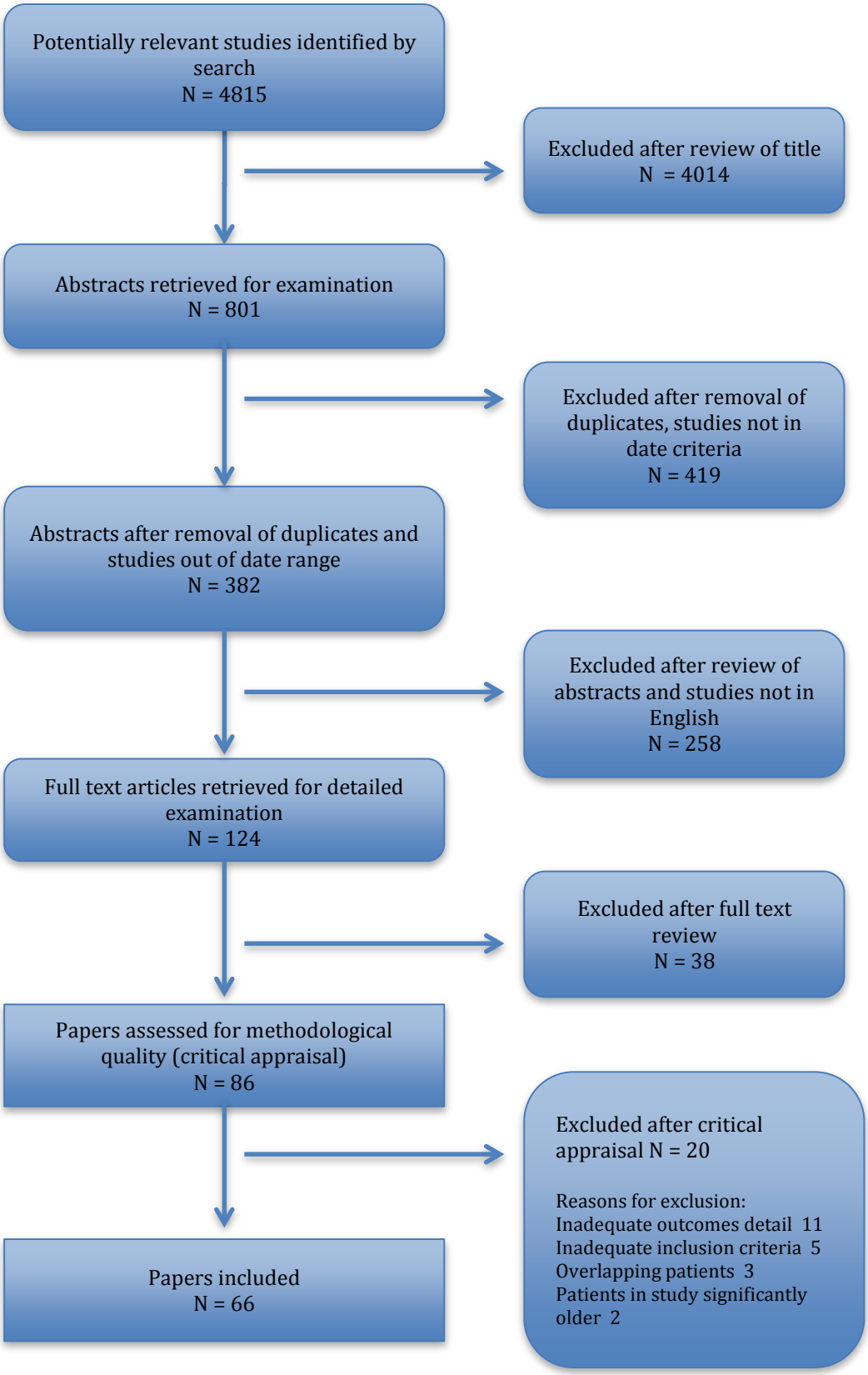

Figure 3.1: Flowchart of search strategy and results

The most common reasons for exclusion were poor reliability of outcome measurement, or lack of outcome reporting (Appendix VI). A poorly defined inclusion criteria was the second most common cause of exclusion. This included papers where airway obstruction was not the reason for MDO, or where there was ambiguity about whether the children included had known lower airway abnormalities or the study explored adequately trialed conservative treatment options (Appendix VI).

Other studies were excluded due to overlap of patients between multiple studies. In such cases, studies were carefully examined, and the most reliable studies were selected. In some of the studies with overlapping patients, 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. For each outcome in this section, studies included for each analysis are detailed in the table of included studies (Appendix V). For the remainder of the results section, each outcome is discussed independently.

3.3 Primary mandibular distraction osteogenesis

Primary mandibular distraction osteogenesis (primary MDO) analysis includes patients who had undergone mandibular distraction as the primary surgical intervention after conservative therapy for upper airway obstruction had failed. All of these patients had undergone failed non-surgical therapy and were being considered for a tracheostomy. A successful outcome was defined as avoidance of a tracheostomy and the relief of upper airway obstruction. In the studies this outcome was reported in a variety of ways. Most reported only subjective improvement in obstructive symptoms (noisy breathing, desaturations) or ability to successfully extubate the patient who was otherwise intubated because of inability to self-ventilate or maintain normal oxygen saturations on room air (Table 3.1 studies without *). Eleven studies included objective evidence of improvement in apnoea with polysomnographic results pre- and post-MDO (marked by * in Table 3.1). Failure was defined as requiring a tracheostomy despite mandibular distraction due to persistent airway obstruction. It is important to note that due to the variable follow-up period between studies, the short-term

avoidance of a tracheostomy (minimum of 1 year follow-up was required for inclusion) was considered a successful outcome.

A total of 51 studies had adequate primary MDO outcome data for inclusion in the analysis (Table 3.1). From the 51 studies, 44 were included in the overall analysis of the success of primary mandibular distraction. The seven excluded papers were likely to have overlapping patients with other papers from the same surgical units. In the subgroup analyses, the reasons for exclusion were either overlap or inadequate distinction between syndromic and non-syndromic patients, or no age-based data available for the age based subgroup analysis. The data extraction table for this analysis is included in Appendix VII.

Table 3.1: Included studies in primary MDO analysis – overall analysis and subgroup analyses with reasons for exclusion for each analysis

Article	Study design	Overall analysis	Syndromic vs non-syndromic	Age based
Al-Samkari 2010 [71]	RR	Excluded – overlap [72]	Included	Excluded – no age data
Andrews 2013 [73]	RR	Included	Excluded – inadequate distinction	Included
Breugem 2012 [74]	RR	Included	Included	Included
Brevi 2006 [75]	CR	Excluded – overlap [76]	Excluded – overlap [76]	Excluded – overlap [76]
Burstein 2005 [77]*	CS	Included	Included	Excluded – no age data
Carls 1998 [78]	RR	Included	Included	Included
Chigurupati 2004 [79]	RR	Included	Included	Included
Chowchuen 2011[80]	RR	Included	Included	Included
Dauria 2008 [35]	RR	Included	Included	Included
Denny and Amm 2005 [81]	RR	Included	Included	Included
Genecov 2009 [82]	RR	Included	Included	Included
Gifford 2008 [83]*	RR	Included	Included	Included
Gözü 2010 [84]	RR	Included	Included	Excluded – no age data
Griffiths 2013 [85]*	CR	Included	Included	Included
Hammoudeh 2012 [86]*	RR	Included	Included	Included
Handler 2009 [87]	CR	Included	Included	Included
Hong 2012 [88]	RR	Included	Included	Included

Article	Study design	Overall analysis	Syndromic vs non-syndromic	Age based
Hong 2012 [89]	RR	Included	Included	Included
Howlett 1999 [90]	CR	Included	Included	Included
Izadi 2003 [91]	RR	Excluded – overlap [73]	Included	Excluded – overlap [73]
Judge 1999 [92]	CR	Included	Included	Included
Kolstad 2011 [93]	RR	Included	Included	Included
Lee 2009 [41]	RR	Included	Included	Included
Lin 2006 [94]*	RR	Included	Included	Included
Looby 2009 [95]*	RR	Included	Included	Included
Mandell 2004 [96]	RR	Included	Included	Included
Miller 2007 [97]*	RR	Included	Included	Excluded – no age data
Miloro 2010 [68]	RR	Included	Excluded – inadequate distinction	Excluded – no age data
Mitsukawa 2007 [98]*	RR	Included	Included	Included
Monasterio 2002 [99]*	RR	Excluded – overlap [32]	Excluded – overlap [32]	Excluded – no age data
Monasterio 2004 [32]	RR	Included	Included	Included
Morovic 2000 [100]	PR	Included	Included	Included
Mudd 2012 [101]	RR	Included	Excluded – inadequate distinction	Included
Murage 2013 [102]*	RR	Included	Included	Included
Olson 2011 [103]	RR	Included	Included	Excluded – no age data
Papoff 2013 [104]	RR	Included	Included	Included
Perlyn 2002 [105]	RR	Included	Included	Included
Rachmiel 2012 [106]	RR	Included	Excluded – inadequate distinction	Included
Sadakah 2009 [107]*	RR	Included	Included	Included
Schaefer 2004 [49]	RR	Included	Included	Included
Scott 2011 [108]	RR	Excluded – overlap [109]	Included	Included
Sesenna 2012 [76]	RR	Included	Included	Included
Sidman 2001 [110]	PR	Excluded – overlap [109]	Included	Included
Smith 2006 [111]	RR	Included	Included	Included
Sorin 2004 [112]	RR	Included	Included	Included
Spring 2006 [113]	RR	Excluded – overlap [103]	Excluded – overlap [103]	Included
Taub 2012 [114]	CR	Included	Included	Included
Tibesar 2006 [115]	CR	Included	Included	Included
Tibesar 2010 [109]	RR	Included	Excluded – inadequate distinction	Excluded – no age data
Wittenborn 2004 [72]	RR	Included	Excluded – inadequate distinction	Included
Zenha 2012 [116]	CR	Included	Included	Included
		44 included	42 included	41 included

Article	Study design	Overall analysis	Syndromic vs non-syndromic	Age based
		(490 patients)	(362 patients)	(408 patients)

RR – retrospective review (case series) CR – Case report PR – prospective review (case series)

** studies which included polysomnographic results pre and post MDO*

3.3.1 Overall primary MDO analysis

This analysis was based on data obtained from 44 papers involving 490 patients. Amongst these patients, 468 had a successful outcome, while 22 required a tracheostomy. This equates to an overall success rate of 95.5 per cent for mandibular distraction preventing tracheostomy in the included studies (Table 3.2). Amongst the successful outcomes, two patients required home oxygen in the short term, but avoided any further surgical intervention and were able to be discharged from hospital. One patient required nocturnal CPAP for three years after distraction, but did not require any further surgical intervention.

Table 3.2: Results of primary MDO overall analysis

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

Studies that included polysomnographic results, the mean obstructive apnoea/hypopnea index (OAHI) was 31.2 preoperatively and 4.34 postoperatively. This statistically significant improvement demonstrates a dramatic clinically significant reduction in hypoxic episodes (Table 3.3).

Table 3.3: Weighted mean and standard deviation calculations for sleep study OAHI results pre- and post-MDO

Parameter	Number of Studies	Number of patients	*Pre-MDO mean (SD)	Post-MDO mean (SD)	Mean difference (95% CI)	*p*-value
OAHI	11	114	31.2 (29.4)	4.34 (2.65)	26.90 (10.67,43.11)	0.002

*OAHI, obstructive apnoea/hypopnea index; *weighted mean and standard deviation [SD]; Mean difference calculated using Comprehensive Meta-analysis (version 2.2.064, BioStat NJ, USA)*

Of the 22 patients with failed MDO, the most common reason (15/22) to avoid tracheostomy 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, or unfavourable mandibular fractures during osteotomy. An additional failure was developing unilateral TMJ ankylosis eight months post-operation, requiring tracheostomy initially followed by repeat MDO which was successful and the patient was subsequently decannulated.

3.3.2 Subgroup analysis 1: Syndromic versus non-syndromic (isolated) Pierre Robin Sequence analysis

This subgroup analysis was based on 42 papers (Table 3.1). The aim of this analysis was to identify if the rate of success was dependent on whether the patient had isolated PRS (iPRS) or PRS associated with a syndrome (sMicro). Among the sMicro 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.[15] 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 was reported in the literature with an estimated 40 syndromes associated with PRS.[117]

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 per cent, which is similar to the result of the overall analysis. Of the 362 patients, 254 were isolated PRS and 108 were syndromic. Of the 16 overall failures, 10 were within the sMicro group. This gives an overall success rate of 97.6 per cent for the iPRS group and 90.7 per cent for the sMicro group (Table 3.4). This difference was found to be statistically significant (p =0.007) implying that

the odds of failure was four times greater when primary MDO to relieve airway obstruction was performed on syndromic patients compared to isolated PRS patients.

Table 3.4: Results of primary MDO subgroup analysis: syndromic (sMicro) vs isolated PRS (iPRS)

Variable	Success (%)	Failure (%)	Total	Odds ratio (95% CI)	*p*-value
Primary MDO	468 (95.5)	22 (4.5)	490	-	-
Syndromic analysis					
iPRS	248 (97.6)	6 (2.4)	254	1	
sMicro	98 (90.7)	10 (9.3)	108	4.28 (1.49, 11.92)	0.007

Amongst the failures in the iPRS group, three were secondary to previously undiagnosed lower airway abnormalities. Two were in patients with previously undiagnosed neurological conditions (cerebral palsy in one patient and hypotonia in the other). The last failure was in a patient who sustained an intraoperative complication. The reasons for failure in sMicro group were: four had unknown syndromes with other multiple anomalies including congenital cardiac abnormalities, three patients had previously undiagnosed central apnoea while an additional three patients had CHARGE syndrome with pulmonary hypertension, velocardiofacial syndrome and Beckwith Widemann syndrome.

3.3.3 Subgroup analysis 2: Age based analysis

The aim of this analysis was to determine whether the outcome of MDO treatment was dependent on the age of the patient when MDO was performed. Accordingly three age groups were selected: less than six months, between six to18 months and greater than18 months of age at the time of MDO. This analysis involved 41 studies comprising 408 patients. The reason for exclusion was inadequate detail regarding the age of the patients. The majority of patients were within the less than six months group, accounting for 377 patients, compared with 12 in the six to18 months group and 19 in the greater than 18 months group. All 16 failures in this analysis were within the less than 6 months group, resulting in a success or 95.8 per cent. There was no significant difference between the success rates of primary MDO in different age groups.

A further analysis was then performed within the first group, dividing the patients into those less than two months of age at the time of operation and those between two to six months at the time of operation. The success rates between these groups were equivalent. The difference was not statistically significant (p-value 0.87) (Table 3.5).

Table 3.5: Further analysis comparing outcomes of primary MDO at age <2 months compared with 2-6 months

Variable	Success (%)	Failure (%)	Total	Odds ratio (95% CI)	*p*-value
Age					
<2 mo	169 (96.0)	7 (4.0)	176	1	
2-6 mo	55 (96.5)	2 (3.5)	57	0.88 (0.18, 4.35)	0.87

3.4 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. A successful outcome was removal of the tracheostomy and ability to maintain oxygen saturation at room air. A failed outcome was defined as 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 one year).

A total of 35 studies provided adequate data to be included in this analysis. From these 35 studies, 31 were included in the overall analysis of this outcome (Table 3.6). The four remaining papers were excluded due to its likely overlap with other studies from the same surgical units. For the subgroup analyses, the reasons for exclusion were either overlap of patients, or inadequate distinction between syndromic and non-syndromic patients, or lack of age based data. The data extraction table for this analysis is included in Appendix VIII

Table 3.6: Tracheostomy decannulation analysis – overall analysis and subgroup analyses with reasons for exclusion for each analysis

Article	Study Design	Overall analysis	Syndromic vs non-syndromic	Age based
Ali Bukhari 2011 [118]	CR	Included	Included	Included
Ali Bukhari 2012 [119]	RR	Included	Included	Included
Anderson 2004 [120]	CR	Included	Included	Included
Breugem 2012 [74]	RR	Included	Included	Included
Burstein 2005 [77]	RR	Included	Included	Excluded – no age data
Carls 1998 [78]	RR	Included	Included	Included
Chigurupati 2004 [79]	RR	Included	Included	Included
Chowchuen 2011[80]	RR	Included	Included	Included
Demke 2008 [121]	RR	Included	Included	Excluded – no age data
Genecov 2009 [82]	RR	Included	Excluded – inadequate distinction	Excluded – no age data
Gifford 2008 [83]	RR	Included	Included	Included
Gözü 2010 [84]	RR	Included	Included	Included
Hollier 1999 [122]	RR	Included	Excluded – inadequate distinction	Included
Horta 2009 [123]	CR	Included	Included	Included
Iatrou 2010 [124]	CR	Included	Included	Included
Kolstad 2011 [93]	RR	Included	Included	Included
Lin 2006 [94]	RR	Included	Included	Included
Mandell 2004 [96]	RR	Included	Excluded – inadequate distinction	Included
Miloro 2010 [68]	RR	Included	Excluded – inadequate distinction	Excluded – no age data
Mitsukawa 2007 [98]	RR	Included	Included	Included
Monasterio 2002 [99]	RR	Included	Included	Excluded – no age data
Morovic 2000 [100]	PR	Included	Included	Included
Olson 2011 [103]	RR	Excluded – overlap [111]	Excluded – inadequate distinction	Excluded – no age data
Perlyn 2002 [105]	RR	Included	Included	Included
Rachmiel 2012 [125]	RR	Included	Included	Included
Schaefer 2004 [49]	RR	Included	Included	Included
Scott 2011 [108]	RR	Excluded – overlap [109]	Included	Excluded – no age data

Article	Study Design	Overall analysis	Syndromic vs non-syndromic	Age based
Sesenna 2012 [76]	RR	Included	Included	Included
Sidman 2001 [110]	PR	Excluded – overlap [109]	Included	Included
Smith 2006 [111]	RR	Included	Included	Included
Sorin 2004 [112]	RR	Included	Included	Included
Spring 2006 [113]	RR	Included	Included	Excluded – no age data
Steinbacher 2005 [126]	RR	Included	Included	Included
Tibesar 2010 [109]	RR	Included	Excluded – inadequate distinction	Excluded – no age data
Williams 1999 [127]	RR	Excluded – overlap [112]	Excluded – inadequate distinction	Excluded – no age data
		31 included (152 patients)	28 included (86 patients)	25 included (81 patients)

3.4.1 Overall tracheostomy decannulation analysis

This analysis was based on 31 studies (Table3.7) involving 152 patients. 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% (Table 3.7).

Table 3.7: Overall results of tracheostomy decannulation analysis

Outcome	Total	Success	Failure	Success rate (%)
Tracheostomy decannulation	152	122	30	80.2

A significant number of studies that reported failures did not report the reason for failure.[82, 109, 112, 121] However, when reported the reasons were varied. The most common reported reason for failure was other airway abnormalities which had not been repaired at the time of MDO. These included tracheomalacia, vascular rings and choanal atresia.[77, 79] After MDO and repair of these abnormalities, the patients were able to be decannulated. Severe gastro-oesophageal reflux disease 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 [77, 112], and another study reported that

decannulation was awaiting fundoplication at the time of publication.[77] Five other patients with reported severe reflux and chronic swallowing dysfunction were not able to be decannulated.[80, 96] In one of these studies, hesitancy on the part of the treating team to attempt decannulation was reported as a contributing cause of failure.[96] Six failures were secondary to tracheostomy complications.[112, 122, 123] These included suprastomal granulation tissue, tracheostomy associated tracheomalacia and tracheostomy stoma healing problems that required excision or repair prior to decannulation. Two patients were reported to have failure of decannulation for TMJ ankylosis as a complication of MDO with persistent airway obstruction.[83, 127] Some other patients underwent removal of suprastomal granulation tissue prior to MDO with successful decannulation after MDO.[112, 127]

The mean time to decannulation was also calculated from these studies and it was 28.5 months. It is important to note that a significant number of these patients had other surgical procedures during their childhood to reduce upper airway obstruction. Although poorly reported in the majority of studies, there were more reported surgical interventions in the patients who have had a tracheostomy placed at infancy compared to those who 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 is statistically significant. The odds of failure of MDO when used to facilitate tracheostomy decannulation compared to primary MDO were five times higher (Table 3.8).

Table 3.8: Comparison of success rates of MDO in the primary MDO analysis and the tracheostomy decannulation analysis

Variables	Success (%)	Failure (%)	Total	Odds ratio (95% CI)	*p*-value
Primary MDO	468 (95.5)	22 (4.5)	490	1	-
Tracheostomy decannulation (TD)	122 (80.3)	30 (19.7)	152	5.23 (2.91, 9.39)	<0.0001

3.4.2 Subgroup analysis 1: Syndromic versus non-syndromic Pierre Robin Sequence (tracheostomy decannulation)

This subgroup analysis was based on 28 papers comprising 86 patients (Table 3.6). The most common reason for exclusion was the lack of distinction between syndromic and non-syndromic patients in these papers. Consequently, the results are often presented as a whole cohort. The aim of this subgroup analysis was to identify if having PRS as part of a syndrome affected the rate of success of decannulating tracheostomised patients.

The majority of these patients were syndromic (55/86). The overall success rate in this subgroup analysis was 81.4 per cent. Amongst the 31 iPRS patients, 26 patients were successfully decannulated, with a success rate of 83.9 per cent. Amongst the 55 sMicro patients, 44 were successfully decannulated with a success rate of 80 per cent (Table 3.9). The failures in the iPRS group were secondary to previously undiagnosed severe GORD (two cases)[77, 80], swallowing dysfunction and aspiration (one case)[80] and the last two cases did not have adequate explanation of the reason for failed decannulation.[76] Similarly, the failures in the sMicro group were secondary to: severe GORD awaiting fundoplication (two cases)[77] Choanal atresia awaiting repair (one case)[79], and TMJ ankylosis post MDO (one case)[83]. Other studies did not provide an adequate explanation for failure. The failures occurred in a range of syndromes with no obvious link between specific syndrome and failure except for arthrogryposis. There were only three cases of arthrogyposis who underwent MDO to facilitate decannulation, but all these cases remained tracheostomy dependent despite MDO.[96, 108]

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 per cent.

Table 3.9: Results of tracheostomy decannulation (TD) subgroup analysis: syndromic (sMicro) vs isolated PRS (iPRS)

Variable	Success (%)	Failure (%)	Total	Odds ratio (95% CI)	*p*-value
TD iPRS	26 (83.9)	5 (16.1)	31	1	-
TD sMicro	44 (80.0)	11 (20.0)	55	1.30 (0.41, 4.16)	0.66

3.4.3 Subgroup analysis 2: Age based analysis (tracheostomy decannulation)

This age based subgroup analysis was based on 25 studies comprising 81 patients (Table 3.10). The aim of this analysis was to identify whether the age at which MDO was performed affected the success of decannulation. The reason for excluding certain studies in this analysis was inadequate reporting of the age of the patients. The age based analysis was divided into three groups based on age at time of MDO treatment: less than 12 months, 12 to 24 months and greater than 24 months. The overall success rate was 75.3 per cent. Most of the patients in this analysis were older than 24 months at the time of MDO treatment. The majority of patients had tracheostomy placed at less than three months of age. This analysis is limited due to the poor reporting of duration of tracheostomy. Twelve patients were within the less than 12 months group. Amongst these, there were three failures. One decannulated but needed to be re-cannulated because of previously undiagnosed swallowing dysfunction and aspiration.[80] The second patient had choanal atresia and was awaiting repair.[79] The third patient was a syndromic patient who developed TMJ ankylosis and recurrence of airway obstruction[83]. There were no failures in the 12-24 months group.

In the greater than 24 months group, there were 58 patients. There were 17 failures in this group. 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. For the purposes of statistical analysis, the less than 12 months and 12-24 months groups were combined for comparison with those who underwent MDO at less than 24 months of age (Table 3.10). Although not statistically significant, the odds of failure of MDO at facilitating decannulation were more than 2.5 times greater if MDO was performed at an age of greater than 24 months compared to less than 24 months.

Table 3.10: Results of tracheostomy decannulation (TD) subgroup analysis: age based analysis

Variable	Success (%)	Failure (%)	Total	Odds ratio (95% CI)	*p*-value
TD impact of age					
<24 mo	20 (87.0)	3 (13)	23	1	-
>24 mo	41 (70.7)	17 (29.3)	58	2.76 (0.71, 10.5)	0.137

3.5. Tracheostomy outcomes

This analysis evaluated the results of patients who were confirmed to have PRS and underwent only tracheostomy for the management of iPRS or syndromic micrognathia. The decannulation for this analysis was defined as 'natural' decannulation (with no distraction osteogenesis). For the purposes of simplicity these are referred to as 'natural' decannulation. This analysis was based on six studies comprising of 67 patients (Table 3.11). Overall, these studies contained only very limited information relevant to this review.

Table 3.11: Studies included in the tracheostomy analysis with results

Article	Number of patients	Condition	Mean time to decannulation (months)	Decannulated (number of patients)	Not decannulated (number of patients)	Complications
Andrews 2013 (73)	9	iPRS	27	9	0	Y
	7	sMicro	43.5	5	2	Y
Demke 2008 (121)	10	iPRS	28	8	2	Y
	5	sMicro	29	5	0	Y
Glynn 2011 (128)	6	iPRS	13	6	0	N
	2	sMicro		2		
Han 2012 (129)	14	iPRS	19	11	3	Y
	11	sMicro	73	2	9	Y
Smith 2006 (111)	8	iPRS	17	10*	2*	N

Article	Number of patients	Condition	Mean time to decannulation (months)	Decannulated (number of patients)	Not decannulated (number of patients)	Complications
	4	sMicro	31.7			N
Tomaski 1995 [47]**	10	sMicro	37.2*			N
	1	iPRS				N

** Overall results combined syndromic and non syndromic patients*

*** Did not include specifics about number decannulated from the 11 patients included*

The overall mean time to decannulation was 31.8 months. Five studies included the number of patients decannulated or remained tracheostomy dependent, and this accounted for 76 patients. Among these 76 patients, 58 were decannulated during the follow-up period of the study while 18 patients were still tracheostomy dependent. Among those not decannulated, four died. Details about the reasons for not decannulating or for deaths were often not included in the studies.

A subgroup analysis comparing syndromic versus non-syndromic patients included three studies.[73] [121] [129] The mean time to decannulation for sMicro patients was 48.5 months compared to 24.7 months for iPRS patients. Within this subgroup analysis, eleven patients were not decannulated within the sMicro group, and five patients were not decannulated within the iPRS group. The four reported deaths were all sMicro patients.

3.5.1. Complications of tracheostomy alone

In the studies that reported complications (see Table 3.11 – 'Complications' column), the most common complications reported were pneumonia[73, 121, 128, 129], wound infection[129], bleeding around the stoma[73, 121], tracheitis [73, 121, 129], granulation tissue requiring excision[121, 129], and suprastomal collapse.[121] The incidence of complications was the same for all complications in both syndromic and non-syndromic groups. A study by Han et al.[129] reported greater incidence of organ dysfunction in the sMicro patients compared to the iPRS patients.

3.6. Feeding outcomes

This primary outcome was concerned with assessing the growth and feeding method after successful relief of upper airway obstruction. In some studies, the feeding method preoperatively was also reported and that data was collected where available for comparison. Where available, the weight centiles preoperatively and postoperatively were also extracted. The cases included in this analysis all underwent MDO with successful relief of airway obstruction.

Overall, 21 studies reported adequate information related to feeding and was the basis for this analysis. Five of these were case reports, the remaining 16 were case series. Five of these studies were excluded in the syndromic versus non-syndromic analysis due to inadequate distinction between syndromic and non-syndromic patients. Inadequate information was provided for an age-based analysis to be performed (Table 3.12). The data extraction table for this analysis is included in Appendix IX.

Table 3.12: Feeding outcomes analysis – overall analysis and subgroup analyses with reasons for exclusion

Article	Study design	Overall analysis	Syndromic vs non-syndromic
Al-Samkari 2010 [71]	RR	Included	Included
Breugem 2012 [74]	RR	Included	Included
Brevi 2006 [75]	CR	Included	Included
Chigurupati 2004 [79]	RR	Included	Included
Dauria 2008 [35]	RR	Included	Included
Denny and Amm 2005 [81]	RR	Included	Included
Genecov 2009 [82]	RR	Included	Excluded – inadequate distinction
Griffiths 2013 [85]	CR	Included	Included
Hong 2012 [88]	RR	Included	Included
Howlett 1999 [90]	CR	Included	Included
Iatrou 2010 [124]	CR	Included	Included
Izadi 2003 [91]	RR	Included	Included
Looby 2009 [95]	RR	Included	Included
Miller 2007 [97]	RR	Included	Included
Miloro 2010 [68]	RR	Included	Excluded – inadequate distinction
Mudd 2012 [101]	RR	Included	Excluded – inadequate distinction
Olson 2011 [103]	RR	Included	Included
Scott 2011 [108]	RR	Included	Excluded – inadequate distinction

Article	Study design	Overall analysis	Syndromic vs non-syndromic
Spring 2006 [113]	RR	Included	Included
Tibesar 2010 [109]	RR	Included	Excluded – inadequate distinction
Zenha 2012 [116]	CR	Included	Included
		21 included (246 patients)	16 included (122 patients)

3.6.1 Overall feeding outcomes analysis

Data for this analysis was obtained from 21 studies comprising 300 patients (Table 3.12). The analysis demonstrated that 246 patients out of 300 patients (82%) were feeding completely orally (PO feeding) after mandibular distraction (Table 3.13). The remaining 54 patients still required feeding adjuncts and could not be fed exclusively orally in the short term (average of 12 months follow-up). Of these patients, 13 still required nasogastric (NG) tubes and 41 of them still required gastrostomy tubes for feeding. Most of the children who were able to feed orally were weaned off gastrostomy tubes or NG tubes preoperatively. Two patients were reported to have been fed with TPN (total parental nutrition) before MDO.[35] One of these children was then able to feed orally post-operatively, and the other remained NG dependent.

Evaluation of the available preoperative and postoperative centiles showed a general decline in centiles in the immediate postoperative period. In the first six to eight weeks postoperatively, three studies [35, 90, 113] demonstrated a general decline by one or two centiles in weight gain. After the consolidation period, there was a general improvement in centiles with an average increase of two centiles compared to the preoperative status.

The presence of a cleft palate may also affect feeding in these patients. The majority of larger included studies did not include the number of patients with cleft palates; repaired or unrepaired. The small case series and case reports [74] [75] [79] [35] [85] [88] [90] [124] [116] included whether the patients had an associated cleft palate, but this data was not amenable to further analysis.

3.6.2 Feeding subgroup analysis: Syndromic versus non-syndromic feeding analysis

This subgroup analysis was performed on data obtained from 16 studies involving 122 patients (Table 3.12). The main reason for exclusion was inadequate distinction between sMicro and iPRS children. The objective of this analysis was to identify if having PRS as part of a syndrome affected the feeding outcome after MDO. One-hundred-and-two patients were able to exclusively PO feed (Per oral) after MDO. When comparing sMicro and iPRS patients, most of the patients who needed adjuncts were within the sMicro group. Of the patients with iPRS, 93.7 per cent were feeding orally compared with only 72.9 per cent in the sMicro group. The odds of sMicro patients requiring feeding adjuncts were significantly greater (Table 3.13) despite successful relief of the airway obstruction by MDO.

Table 3.13: Results of feeding outcomes subgroup analysis: syndromic (sMicro) vs isolated PRS (iPRS)

Variable	PO feeds (%)	Adjuncts needed (%)	Total	Odds ratio (95% CI)	*p*-value
All patients	246 (82)	54 (18)	300	-	-
Syndromic					
iPRS	59 (93.7)	4 (6.3)	63	1	-
sMicro	43 (72.9)	16 (27.1)	59	5.49 (1.71, 17.58)	0.004

PO – per oral

3.7 Gastro-oesophageal reflux outcomes

Only four studies comprising 70 patients reported the presence of GORD pre- and post-MDO.[32, 35, 82, 88] These studies reported the GORD outcomes based on pH monitoring. Of the 70 patients with reported preoperative GORD, only four had persistent reflux on pH monitoring post-MDO. No syndromic or age-based subgroup analysis was possible in these studies due to lack of distinction between syndromes and minimal age based data.

3.8 Surgical outcomes

The objective of this evaluation was to identify whether the rate of complications or operative failure was related to the type of distractors or the distraction rate. Overall, 43 studies included adequate surgical outcomes data (Table 3.14). In the overall analysis, three studies were excluded due to likely overlap of patients between studies.[75, 108, 110] The remaining studies involved a total of 417 patients. A variety of surgical techniques were employed to achieve the distraction. Thirty-one of the 40 included studies reported on the type of osteotomy.

Operative failure was defined as failure to achieve the planned advancement or need for early reoperation to achieve the required advancement. In the overall analysis, the most common reason for exclusion was likely due to overlap of patients with other studies. Other studies were excluded due to lack of adequate detail regarding the surgical protocol used. The data extraction tables for these analyses are included in Appendix X and Appendix XI.

Table 3.14: Included studies in the surgical outcomes analysis – overall analysis and subgroup analyses with reasons for exclusion

Article	Overall analysis	Distraction rate analysis	External vs internal analysis	Complications analysis
Ali Bukhari 2011 [118]	Included	Included	Included	Excluded
Ali Bukhari 2012 [119]	Included	Included	Included	Excluded
Anderson 2004 [120]	Included	Included	Included	Excluded
Andrews 2013 [73]	Included	Included	Excluded - mixture	Included
Breugem 2012 [74]	Included	Included	Included	Included
Brevi 2006 [75]	Excluded – overlap [76]	Excluded – overlap [76]	Excluded – overlap [76]	Excluded – overlap [76]
Burstein 2005 [77]	Included	Included	Included	Included
Carls 1998 [78]	Included	Included	Included	Excluded
Chigurupati 2004 [79]	Included	Included	Included	Excluded
Dauria 2008 [35]	Included	Excluded – range of rates	Included	Excluded
Denny and Amm 2005 [81]	Included	Included	Included	Excluded

Article	Overall analysis	Distraction rate analysis	External vs internal analysis	Complications analysis
Genecov 2009 [82]	Included	Included	Included	Included
Gifford 2008 [83]	Included	Included	Included	Excluded
Griffiths 2013 [85]	Included	Included	Included	Excluded
Hammoudeh 2012 [86]	Included	Included	Included	Included
Handler 2009 [87]	Included	Included	Included	Excluded
Hollier 2006 [130]	Included	Included	Included	Included
Hollier 1999 [122]	Included	Included	Included	Excluded
Hong 2012 [88]	Included	Included	Included	Included
Howlett 1999 [90]	Included	Included	Included	Excluded
Iatrou 2010 [124]	Included	Included	Included	Excluded
Judge 1999 [92]	Included	Included	Included	Included
Kolstad 2011 [93]	Included	Included	Included	Included
Lee 2009 [41]	Included	Excluded – range of rates	Included	Excluded
Looby 2009 [95]	Included	Included	Included	Included
Miller 2007 [97]	Included	Included	Included	Included
Miloro 2010 [68]	Included	Excluded – range of rates	Included	Included
Mitsukawa 2007 [98]	Included	Excluded – no rate data	Included	Excluded
Monasterio 2002 [99]	Included	Included	Included	Excluded
Morovic 2000 [100]	Included	Included	Included	Excluded
Mudd 2012 [101]	Included	Included	Included	Included
Papoff 2013 [104]	Included	Included	Included	Included
Rachmiel 2012 [106]	Included	Included	Excluded - mixture	Excluded
Sadakah 2009 [107]	Included	Included	Included	Excluded
Scott 2011 [108]	Excluded – overlap [109]	Excluded – overlap [109]	Excluded – overlap [109]	Excluded – overlap [109]
Sesenna 2012 [76]	Included	Included	Included	Excluded
Sidman 2001 [110]	Excluded – overlap [109]	Excluded – overlap [109]	Excluded – overlap [109]	Excluded – overlap [109]
Spring 2006 [113]	Included	Excluded – range of rates	Included	Included
Steinbacher 2005 [126]	Included	Included	Included	Excluded
Taub 2012 [114]	Included	Included	Included	Excluded

Article	Overall analysis	Distraction rate analysis	External vs internal analysis	Complications analysis
Tibesar 2010 [109]	Included	Included	Included	Included
Williams 1999 [127]	Included	Included	Included	Excluded
Zenha 2012 [116]	Included	Included	Included	Excluded
	40 included (417 patients)	35 included (455 patients)	38 included (413 patients)	16 included

Overall there were only 19 operative failures (Table 3.15). Out of these failures, there was no reported reason for failure in eight patients.[93, 109, 130, 131] The most common reason reported was pin dislodgement and device failure.[68, 74, 81, 83, 99] Pin dislodgement was defined as a cause of failure when it occurred during advancement, requiring a repeat operation and was only a complication of external distractors. Other causes of failure included incomplete osteotomy and premature consolidation, both requiring repeat operation to re-osteotomise the mandible to allow advancement to be completed.[74] In one case, coronoid ankylosis to the posterior maxilla prevented the further advancement of the mandible.[122] This complication was due to not performing a coronoidectomy after an inverted 'L' osteotomy that resulted in the coronoid process of the mandible being advanced with the distal segment of the mandible.

Table 3.15: Reported reasons for surgical failure

Reason for failure	Number of patients
Incomplete osteotomy	1
Premature consolidation	1
Pin dislodgement	3
Device failure	2
Exposure of distractor	1
Non union	1
Coronoid ankylosis	1
Mandibular fracture	1
No details provided	8

3.8.1 Distraction rate analysis

This subgroup analysis evaluated the effect of distraction rate per day on risk of failure and complications as shown in Table 3.14. This analysis was based on 35 studies involving 455 patients (Table 3.14). Some authors reported a range of distraction rates for their patients, making it difficult to determine specific distraction rate for each patient. This was the main cause of exclusion from this analysis. Overall, the patients included in this analysis were divided into three main groups based on distraction rate: distraction rate of 1mm per day, 1-2mm per day and 2mm per day.

The majority of patients underwent distraction at a rate of 2mm per day (199 patients), the second most common being 1mm per day (143 patients) and the remaining 113 patients between 1.1-1.9mm per day (Table 3.16).

Table 3.16: Distraction rate analysis with statistical analysis – odds ratios calculated compared with 1mm/day

Variable	Success (%)	Failure(%)	Total	Odds ratio (95% CI)	*p*-value
All patients	436 (95.8%)	19 (4.2)	455	-	-
Distraction rate					
1 mm/d	141 (98.6)	2 (1.4)	143	1	-
1-2 mm/d	106 (93.8)	7 (6.2)	113	4.66 (0.95, 22.86)	0.058
2 mm/d	194 (97.5)	5 (2.5)	199	1.82 (0.35, 9.50)	0.479
>1mm/day	**300 (96.2)**	**12 (3.8)**	**312**	**2.82 (0.62, 12.77)**	**0.1785**

These results show a trend towards higher odds of failure at distraction rate of greater than 1mm/day (Table 3.16). However, on combining the data, no statistically significant association between failure rate and rate of distraction could be observed. Within the included literature, neonates were most commonly distracted at 1.5-2mm/day. By contrast, children older than 12 months of age were more likely to be distracted at 1mm/day.

3.8.2 Distraction rate: complications subgroup analysis

This analysis evaluated the complication rates within each distraction rate group (Table 3.17). Sixteen studies included within the surgical outcomes analysis provided adequate information regarding complications. Scarring includes all significant scars that were reported by the authors and were being considered for scar revision by the treating surgical team. Infection included mild infections that required antibiotics for management, as well as abscesses that required surgical drainage. Facial nerve injury usually corresponds to the marginal mandibular branch that may be damaged during external incisions made near the inferior border of the mandible; injury to the facial nerve includes all reported injuries, even if transient. Due to the lack of long-term data, it is not possible to ascertain the incidence of permanent damage from this analysis. Dental injury corresponds to damage to developing tooth buds during surgical intervention of the mandible. These are likely to be under reported due to the lack of long-term follow-up to the stage of the complete deciduous dentition or permanent dentition. Temporomandibular joint ankylosis corresponds to the bony fusion of the mandibular condyle to the glenoid fossa of the temporal bone. Premature ossification corresponds to the premature healing of the corticotomy or osteotomy before distraction is complete. Technical problems refer to events like device failure, pin dislodgment or fracture of the device.

Table 3.17: Distraction rate complications analysis with statistical analysis

Variable	Complications - No (%)	Complications - Yes (%)	Total	Odds ratio	95% CI	*p*-value
Overall	240 (70.4)	101 (29.6)	341	-	-	-
1mm/d	43 (63.2)	25 (36.8)	68	1	-	-
1-2mm/d	72(73.5)	26 (26.5)	98	0.62	0.32,1.21	0.16
2mm/d	125 (71.4)	50 (28.6)	175	0.69	0.38,1.24	0.22
Scarring (all)	328 (96.2)	13 (3.8)	341	-	-	-
1 mm/d	67 (98.8)	1 (1.2)	68	1	-	-
1-2 mm/d	93 (94.9)	5 (5.1)	98	3.49	0.40,30.55	0.259
2 mm/d	158 (96.0)	7 (4.0)	175	2.97	0.36,24.60	0.313
Infections (all)	306 (89.8)	35 (10.2)	341	-	-	-
1 mm/d	59 (86.8)	9 (13.2)	68	1	-	-

Variable	Complications - No (%)	Complications - Yes (%)	Total	Odds ratio	95% CI	*p*-value
1-2 mm/d	81 (90.8)	9 (9.2)	98	0.73	0.27,1.95	0.527
2 mm/d	158 (90.3)	17 (9.7)	175	0.71	0.30,1.67	0.427
Facial nerve (all)	325 (95.3)	16 (4.7)	341	-	-	-
1 mm/d	62 (91.2)	6 (8.8)	68	1	-	-
1-2 mm/d	91 (92.9)	7 (7.1)	98	0.80	0.26,2.48	0.692
2 mm/d	172 (98.3)	3 (1.7)	175	0.18	0.04,0.74	0.018
Dental injury (all)	330 (96.8)	11 (3.2)	341	-	-	-
1 mm/d	68 (100)	0 (0)	68	1	-	-
1-2 mm/d	94 (95.9)	4 (4.1)	98	6.52	0.35,123.2	0.211*
2 mm/d	168 (96.0)	7 (4.0)	175	6.10	0.34,108.2	0.218*
TMJ – ankylosis (all)	334 (97.9)	7 (2.1)	341	-	-	-
1 mm/d	68 (100)	0 (0)	68	1	-	-
1-2 mm/d	98 (100)	0 (0)	98	-	-	-
2 mm/d	168 (96)	7 (4)	175	6.10	0.34,108.2	0.218*
Premature ossification (all)	340 (99.7)	1 (0.3)	341	-	-	-
1 mm/d	68 (100)	0 (0)	68	1	-	-
1-2 mm/d	98 (100)	0 (0)	98	-	-	-
2 mm/d	174 (99.4)	1 (0.6)	175	1.18	0.05,29.26	0.921
Technical problems (all)	323 (94.7)	18 (5.3)	341	-	-	-
1 mm/d	59 (86.8)	9 (13.2)	68	1	-	-
1-2 mm/d	97 (99.0)	1 (1.0)	98	0.07	0.01,0.55	0.012
2 mm/d	167 (95.4)	8 (4.6)	175	0.31	0.11,0.95	0.023

** These statistical results cannot be interpreted, as there were 0 cases reported at the 1mm/day*

Overall, a distraction rate of 1mm per day had a complication rate of 36.7per cent compared to 26.5 per cent for the 1-2mm per day group and 28.6 per cent when distraction was 2mm per day. A distraction rate of greater than 1mm per day was associated with a significant increase in the odds of technical failures (1-2 mm/d, $p<0.012$ and 2 mm/d, $p<0.023$). No specific details were provided in the studies for the technical failures. Facial nerve injuries

seemed to be less common in patients with a distraction rate of 2mm per day compared with the other two groups ($p<0.018$ compared with 1mm per day). The complications of scarring, infections, TMJ ankylosis, dental injury and premature ossification rates appear not to be statistically related to rate of distraction. TMJ ankylosis was only reported in seven patients in one study included in this analysis and at a distraction rate of 2mm per day[73]. All seven patients were syndromic, and the authors attributed this complication to excessive loading of the condyle during distraction. After instituting the use of class 2 elastics, this complication was no longer observed.[73, 132]

3.8.3 Internal versus external distractor analysis

This analysis was concerned with comparing the surgical outcomes between internal and external distractors. Overall 38 studies with 413 patients were analyzed (Table 3.14). The most common reason for exclusion was overlap of cases between studies, or inadequate reporting of which type of distractor was used. External distractors were used in 206 patients, and internal distractors in 207 patients respectively. There were 15 failures. Failures were defined as incidents requiring early reoperation rather than actual failure of relief of airway obstruction from distraction. Of these 15 failures, 13 were from those in the external distractor group compared to two failures amongst the internal distractor group. This difference was statistically significant (Table 3.18). The most common cause of failure requiring re-operation was pin dislodgement during distraction. Most studies did not include a reason for operational failure.

Table 3.18: Results of internal vs external distractor analysis with statistical analysis

Variable	Success (%)	Failure (%)	Total	Odds ratio	95% CI	*p*-value
All patients	413	15				
External	193 (93.6)	13 (6.3)	206	1	-	-
Internal	205 (99.0)	2 (0.96)	207	0.15	0.03,0.65	0.012

3.8.4 Internal versus external distractors: complications analysis

The complication rates were compared between internal and external distractors. The data were analysed as per previous section and illustrated in Table 3.19.

Table 3.19: Internal vs external distractor outcomes: complications analysis

Variable	Complications No (%)	Complications Yes (%)	Total	Odds ratio	95% CI	*p*-value
Overall (all)	198 (63.2)	115 (36.8)	313	-	-	-
External	99 (66.4)	50 (33.6)	149	1	-	-
Internal	99 (60.4)	65 (39.6)	164	1.30	0.82,2.06	0.27
Scarring (all)	298 (95.2)	15 (4.8)	313			
External	135 (90.6)	14 (9.4)	149	1	-	-
Internal	163 (99.4)	1 (0.6)	164	0.06	0.01,0.45	0.006
Infection (all)	282 (90.1)	31 (9.9)	313			
External	137 (91.9)	12 (8.1)	149	1	-	-
Internal	145 (88.4)	19 (11.6)	164	1.49	0.70,3.19	0.298
Facial Nerve (all)	298 (95.2)	15 (4.7)	313			
External	144 (96.6)	5 (3.4)	149	1	-	-
Internal	154 (93.9)	10 (6.1)	164	1.87	0.62,5.60	0.264
Dental Injury (all)	306 (97.8)	7 (2.2)	313			
External	145 (97.3)	4 (2.7)	149	1	-	-
Internal	161 (98.2)	3 (1.8)	164	0.68	0.15,3.07	0.611
TMJ ankylosis (all)	313 (100)	0 (0)	313			
External	313 (100)	0 (0)	149	1	-	-
Internal	313 (100)	0 (0)	164	-	-	-
Premature Ossif (all)	311 (99.4)	2 (0.6)	313			
External	147 (98.7)	2 (1.3)	149	1	-	-
Internal	164 (100)	0 (0)	164	0.18	0.01,3.77	0.268
Technical problems (all)	295 (94.2)	18 (5.7)	313			
External	136 (91.3)	13 (8.7)	149	1	-	-
Internal	159 (96.9)	5 (3.1)	164	0.33	0.11,0.95	0.039

This analysis demonstrated that patients with external distractors had a complication rate of 33 per cent compared with patients with internal distractors who had a rate of 23 per cent. The odds of developing significant scarring were greater with the use of external distractors compared to internal distractors ($p<0.006$). There were also higher odds of technical failures with use of external distractors compared to internal distractors ($p<0.039$). Internal distractors appeared to cause more infections although this was not statistically significant ($p<0.298$). It is worth noting that there were three cases requiring incision and drainage, and these cases were all in-patients with internal distractors.[95, 101] Generally, infections related to external distractors were managed successfully with oral antibiotics and local wound care. The risk of facial nerve injuries appeared to be unrelated to type of distractor used.

3.9 Long term outcomes

Evidence for long-term outcomes was limited, therefore all studies with a follow-up period of three years or greater were evaluated. There were a total of six studies that were included for long-term data. Three of these studies were classified as intermediate term data (up to five years),[41, 94, 107] and the remaining three were categorized as longer term data (greater than five years).[120] [133] [109]

Sadakah et al.[107] evaluated the outcomes of children who underwent MDO over an average follow-up of 3.7 years. All seven patients demonstrated short-term improvement in airway symptoms that persisted over the follow-up period for six of the seven patients. They reported minimal relapse in six patients, with one demonstrating relapse after three years that was secondary to unilateral TMJ ankylosis. In three other patients, it was observed that there were abnormal changes to the mandibular condyles, but no evidence of ankylosis. Occlusal disturbances was reported in five patients. These were mainly posterior cross bites. Two patients had an anterior open bite which self-corrected. This study also reported premature tooth eruption and occasional dilacerated roots in most patients.

Lee et al.[41] evaluated the outcomes of three patients with PRS who underwent MDO for airway obstruction. To avoid prolonged intubation, tongue-lip adhesion was used during MDO

in this study to provide temporary relief of airway obstruction during the distraction phase. All three children had relief of airway obstruction and prevention of tracheostomy which persisted for the mean follow-up period of 5.4 years.

Lin et al.[94] evaluated the long-term quantitative outcomes of five children treated with MDO for upper airway obstruction. This study had a mean follow-up period from surgery of four years. Four children remained without airway obstruction throughout the follow-up period, which was confirmed on polysomnographic results. One child had a persistent AHI of 20.2, indicating moderate obstructive sleep apnea. This child was the only one from this series who had a previous tracheostomy and had gastro-oesophageal reflux. The authors also reported that two children continued to have clinically severe mandibular retrognathia, while the remaining three children had mild retrognathia but no significant airway obstruction. The author predicted that these children were likely to require orthognathic surgery at adolescence.

Stelnicki et al.[133] compared the outcomes of children after MDO, comparing patients with bilateral mandibular hypoplasia due to PRS, craniofacial microsomia or just developmental micrognathia, with those with micrognathia secondary to Treacher Collins syndrome or Nager syndrome. This study compared the cephalometric changes after mandibular distraction over the period of growth. The average age of the included patients was 5.2 years in the syndromic group compared with 8.4 years in the other group. The ages at distraction were not included. The general outcome of this study was that children with syndromes tended to have relapse to a pre-morbid shape of the mandible (an obtuse gonial angle and a large antegonial notch).

Anderson et al.[120] reported a case study of a child with Treacher Collins syndrome who underwent mandibular distraction osteogenesis at the age of six to facilitate decannulation of a tracheostomy. The treatment that this child received was first reported in a previous study by the same team.[65] The male child had significant relief of his airway obstruction for 18 months before a relapse of his airway symptoms requiring continuous positive pressure airway (CPAP) mask for night time use. However, he did not require the reinsertion of the tracheostomy. He received follow-up up to skeletal maturity and was planned for further orthognathic surgery to correct the persistent mandibular retrognathia. Although mandibular distraction was able to facilitate decannulation, due to the underlying impaired growth

potential secondary to his syndrome, there was inadequate post-distraction growth to maintain the results of the mandibular distraction.

Tibesar et al.[109] evaluated the outcomes of 32 patients who underwent MDO for PRS. The average age at which MDO was performed was 10.4 months of age, with a median age of two months. The average follow-up period was 7.6 years (range of three to 16 years). Overall, only four (12.5%) of the patients remained tracheostomy dependent. Seven of the 11 patients who had tracheostomy prior to MDO could be decannulated and remained free of tracheostomy long-term. One of the children who underwent MDO younger than the age of three months required a later MDO due to failure of mandibular growth and relapsing upper airway obstruction. Tibesar and coworkers[109] also reported long-term complications. Four patients (16%) experienced long-term tooth loss, malformation or dentigerous cyst formation after mandibular distraction. Three patients (9%) sustained long-term marginal mandibular nerve injury. Three patients suffered from hypertrophic scarring. Persistent anterior open bite was the most commonly reported complication (nine patients, 28%). Five of the affected patients had congenitally missing mandibular condyles and underwent costochondral graft condylar reconstruction prior to MDO. These children had persistent anterior open bites after MDO. Of the remaining children with postoperative open bites after MDO, two had a preoperative anterior open bite with associated syndromes; oculo-auricular-vertebral spectrum and arthrogryposis.

Table 3.20: Incidence of airway obstruction recurrences in the long-term studies available

Study	Recurrence	Follow-up (yr)
Sadakah et al., 2009	1/7	3
Lee et al., 2009	0/3	5.4
Lin et al., 2006	1/5	4
Tibesar et al., 2010	5/32	3-16 (average 7.6)
Anderson et al., 2004	1/1	17

Chapter 4: Discussion

MDO for children with airway obstruction secondary to mandibular retrognathia and glossoptosis is a novel technique. However, children with an isolated developmental micrognathia or PRS, or are born with a clefting syndrome that includes micrognathia, glossoptosis and airway obstruction, can often be managed conservatively with prone positioning, nasopharyngeal airways or assisted ventilation techniques until they are able to maintain their own airway.[9] Conservative management is still regarded as the preferred modality of treatment and should always be attempted before considering surgical management.[24, 40, 81] Even patients with severe upper airway obstruction secondary to micrognathia can be managed effectively and safely with a nasopharyngeal airway, or continuous positive airway pressure ventilation and good respiratory physician involvement.[40] Those who fail conservative treatment are considered for surgical intervention. During recent years, MDO has gained in popularity and this systematic review aimed to evaluate the effectiveness of MDO in children with airway obstruction secondary to micrognathia.

4.1 Primary mandibular distraction osteogenesis

Overall, MDO was found to be very successful at preventing tracheostomy in children with micrognathia who had failed conservative treatment. Success in preventing tracheostomy was achieved in 95.5% of neonates and infants. These results are consistent with the results of the previous systematic review in 2008 with a success rate of 91.3%.[69] This was supported by statistically significant improvements in the OAHI. The most common reasons for failure of MDO to relieve the airway obstruction were undiagnosed airway obstruction at other levels such as tracheomalacia, laryngomalacia, or undiagnosed central apnea.

The success rate was higher in isolated PRS patients than in those with associated syndromes. This finding is consistent with other reports in the literature.[23, 134] The patients with iPRS who failed had lower airway abnormalities, and those with sMicro who failed tended to have multi-system congenital anomalies that did not correspond with a particular syndrome. Some

studies called these unique PRS, but in this study they were included under the classification of syndromic. Undiagnosed central apnea was a common cause of failure in both groups.

All children being considered for MDO should have a thorough airway assessment with nasoendoscopy and polysomnographic studies to confirm that the apnea is a primary obstructive apnea, and to exclude lower airway abnormalities. Lower airway abnormalities and central apnea 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 reported the presence of GORD as a relative contraindication for MDO.[23, 91, 102] The findings of this review did not find the presence of GORD to be a cause of failure in the primary MDO patients.

When MDO was first used for neonates with upper airway obstruction, there was concern about the appropriate age to perform surgery. The small size of the mandible and the risk of general anesthetic were reported as reasons to avoid early surgery. However, neonates as young as five days have been successfully managed with MDO.[135] When comparing the results of those younger than two months, two to six months, six to 18 months and greater than 18 months at the time of MDO, there was no significant difference in failure rate. Kolstad and colleagues[93] retrospectively examined the effectiveness and complications of MDO in newborns (<35 days old), early infants (up to five months) and older children (less than five months). They found no significant differences in the success rate between these groups, and MDO was successful in 90 per cent of cases. The results of this review are consistent with these findings. The initial concerns about the size of the neonatal mandible and lack of adequate mineralisation appeared to not be valid, and early surgical intervention seemed to be common, and appeared to be safe and well tolerated by patients.[24]

4.2 Decannulation of tracheostomy dependent patients

A significant number of patients had already undergone tracheostomy because 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 identified one in five patients could not be decannulated after mandibular distraction. This lower success rate compared to primary MDO is consistent with other authors' observations in the literature.[69, 96, 136] The success rate was also not significantly different when comparing syndromic and non-syndromic patients.

Where the cause of failure was reported, the most common reasons were the presence of previously undiagnosed other airway abnormalities, severe gastro-oesophageal reflux disease, chronic swallowing dysfunction and tracheostomy related complications. Those patients with severe GORD could often be decannulated after nissen fundoplication. Approximately 20 per cent 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 to 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 have had a tracheostomy placed at infancy compared to those who 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.[112, 113, 126] 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, closure of tracheostomy stomas.[49, 112, 122, 123]

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 congenital, is a syndrome characterised by multiple joint contractures in the body.[137] There are several subtypes of the disease, some of which have micrognathia and other Pierre Robin Sequence like features, and supraglottic narrowing

similar to laryngomalacia.[137] Often these features are seen in the neurogenic subtype, and so there is also muscular hypotonia contributing to upper airway obstruction.

In the studies there were some patients with neurological abnormalities who underwent MDO as the primary operation. Although MDO operation was successful, they still required a tracheostomy.[97, 101, 102] 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 also reported on the higher risk of failure in children with concomitant neurological abnormalities.[38, 39, 108, 138] 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 toilet. So even though MDO may improve breathing by relieving the upper airway obstruction, the tracheostomy may be kept in place for other reasons.[108] These patients, like other patients with multifactorial airway obstruction, need to be carefully assessed 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 below the age of 24 months at the time of surgery. It is hypothesied 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.[139] These complications such as granulation tissue formation, tracheal stenosis and tracheomalacia are not resolved by MDO. Prior to MDO, it is important that a thorough evaluation of the airway with a nasoendoscopy be performed and treatment of any tracheostomy related complications is completed before surgery.

Mandell et al.[96] reported that to achieve the best results in tracheostomised, micrognathic patients with complex airways, adjunctive procedures are often needed. They recommended that the inclusion 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.

4.3 The comparator: Tracheostomy patients

Limited studies evaluated the children with upper airway obstruction secondary to micrognathia who underwent tracheostomy alone. Six studies comprising 77 patients were analysed in this review. [47, 73, 111, 121, 128, 129]

The average time to decannulation overall was 31.8 months. On average, syndromic patients were tracheostomy dependent for twice as long as the non-syndromic patients. There was a high incidence of complications in these children, with a substantial number suffering from respiratory infections and complications of long-term tracheostomies, including suprastomal collapse, granulation tissue formation and tracheomalacia.[139] There was a 5 per cent mortality rate for patients who underwent tracheostomy for upper airway obstruction secondary to micrognathia. There were no reported deaths in the patients who underwent MDO.

These six studies contained limited information about individual patients, and hence the information was difficult to interpret. In addition, the protocols for decannulation were vague or non-specific. As a consequence decannulation that was considered 'natural' may have also included those patients who had undergone other surgical procedures that were not reported. These surgical procedures may have included laryngeal reconstructions for laryngomalacia or other upper airway procedures that may have contributed to their ability to be decannulated. Hence, the results need to be interpreted with caution.

The mean age for decannulation between the patients who were tracheostomy dependent and then underwent MDO and those who were tracheostomy dependent and awaited natural decannulation was only four months (28.5 months and 31.8 months respectively). However, this difference would have been much greater if MDO was carried out at an earlier age. As discussed above, the success rate of MDO at facilitating decannulation seems to be better before 24 months of age. Thus if medically stable, these children could undergo MDO before the age of 24 months facilitating earlier decannulation. Early decannulation will provide an

environment for the child to develop speech and language skills that will be otherwise hindered by having a tracheostomy.

4.4 Feeding outcomes

Feeding abnormalities in children with micrognathia appear to be closely related to the upper airway obstruction. In this review, one in five patients was able to feed exclusively orally after MDO. Most of these children were weaned from gastrostomy or enteric feeding before MDO to oral feeding after MDO. It is hypothesised that this good outcome is due to improvement in the upper airway caliber, allowing the child to breathe adequately and maintain oxygenation while feeding. In addition the improved facial skeletal profile will improve lip approximation, facilitating a better sucking reflex after the healing phase is complete. Syndromic patients were more likely to require feeding adjuncts despite MDO compared with non-syndromic children with micrognathia. This may have been due to concomitant subtle neurological or swallowing abnormalities in syndromic patients that may have contributed to the feeding difficulties.[30, 113] Overall, micrognathic children managed with distraction had improved outcomes in oral feeding and many patients could avoid enteral feeding via nasogastric or gastrostomy tubes.

When evaluating preoperative and postoperative growth centiles, a general trend was noted which showed a decline in centiles in the immediate postoperative period in several studies.[35, 90, 113] The consequences of this early growth decline are not yet known. The reasons for this immediate decline may be related to an abnormal sucking and swallowing reflex due to daily movement of the mandible and tongue structures. The anatomical changes caused by MDO to the tongue base and pharyngeal wall position may precipitate a feeding disorder due to a dysfunctional and disorganized feeding mechanism.[113] Although most of the studies reported complete oral feeding postoperatively, it is important for clinicians to be aware of this potential early growth decline. Clinicians should consider continuing feeding with the preoperative feeding adjuncts initially, until after completing the consolidation period or until removal of the distractors to avoid this decline in growth.

Although the swallowing functional improvement after MDO was not specifically included in this review, the findings support other studies that have demonstrated significant improvement in swallowing function after MDO. In the study by Hong et al, significant improvements in feeding and swallowing function were noted in all of their patients after MDO and this was confirmed by video fluoroscopic swallow studies.[88] The authors of that study felt that although the cleft palate of these patients may have also contributed to the feeding problems, it was only afterl MDO that improvement in swallowing and feeding was noted.

The contribution of an associated cleft palate in the feeding difficulties in these patients remains unclear. The presence of a cleft palate alone is associated with a lag in growth in the first few years of life compared to noncleft children[140, 141]. In children with PRS however, it is presumed that airway obstruction is the main reason for the feeding difficulties[9, 142]. The studies included in this systematic review often did not report the number of patients with cleft palates, repaired or unrepaired. In the study by Hong et al., 2012[88], all 6 patients had a cleft palate, and the authors reported that all children had attempted standard cleft palate feeding strategies such as the use of nipples and bottles. These children had no significant improvements in feeding until after relief of the airway obstruction by mandibular distraction. The study by Spring et al.,[113] reported that the 3 patients who had growth decline after MDO had an associated cleft palate and this may have contributed to their persistent feeding difficulty. However the study did not report if the other 7 patients had cleft palates and so it is difficult to determine the association of the cleft palate to the persistent feeding difficulties in those patients. Overall, this systematic review supports the hypothesis that the airway obstruction is the main cause of feeding difficulties in children with micrognathia. However, it is important for clinicians managing these children to consider the role of the cleft palate during treatment and early involvement of a paediatric dietitian and speech pathologist is imperative.

The age at the time of MDO may also affect feeding outcomes, but due to the lack of adequate reporting in the included studies, it was not possible to do an age based analysis on outcomes. The mean age of patients included in this study was 7 months with ages ranging from 5 days of age at the time of surgery to 6 years of age. It can be extrapolated however from our findings that early MDO was successful at improving feeding, and this in turn may affect long term growth of the child. This is consistent with another study by Lidsky et al.,[30] 2008 which found that children who

underwent early airway interventions (less than 3 months of age) were less likely to need feeding assistance compared to those who underwent delayed airway intervention despite syndromic status.

4.5 Gastro-oesophageal reflux outcomes

This review found that the majority of patients with confirmed preoperative GORD had significant improvement in reflux on pH monitoring after MDO. These findings are consistent with the hypothesis that the cause of GORD in these patients is airway obstruction, which leads to negative intrathoracic pressure causing a suction effect on gastric contents. Some recent studies have suggested that GORD and the need for Nissen fundoplication are associated with failure of distraction osteogenesis.[102] The findings of this study were not consistent with this observation for primary MDO. The presence of severe GORD however was associated with increased risk of failure of decannulation of tracheostomy dependent patients after MDO. Often these children can be decannulated after nissen fundoplication. Tracheostomy dependent patients who are being considered for MDO should have formal pH monitoring preoperatively. If severe reflux is diagnosed, referral to the paediatric general surgeons is required for consideration of nissen fundoplication. Ideally, this should be performed before MDO.

4.6 Surgical outcomes

There are a variety of surgical protocols for MDO reported in the literature. It is generally an effective operation with a high success rate in the literature. Nevertheless, it is expected that operative failures are likely to be under-reported in the literature. The most common reported reasons for failure were pin dislodgement or device failure. These problems are easily corrected, but will often require a return to the operating theatre for correction. Rarely, failure was attributed to incomplete osteotomy, premature consolidation and intra-operative complications, such as mandibular fracture or airway complications.

4.6.1 Distraction rate analysis

The ideal rate of distraction is yet to be determined. Anecdotal reports in the literature suggested that a faster rate of distraction was just as effective in neonates and may lead to a lower rate of premature consolidation in the rapidly healing neonates.[130] The findings of this review showed no significant different in failure rate between a distraction rate of 1mm per day or 2mm per day.

Because of the limited information from the included studies, it is difficult to draw conclusions about these results. It would be best to perform this analysis with age matching and also a comparison of syndromic versus non-syndromic patients. However, it was not possible to perform any further sub-analysis. It is important to also note that the majority of patients who were included in the 1mm per day group were older than those who underwent between 1-2mm per day or 2mm per day (mean of 27 months and a mean of six months respectively). Due to this wide discrepancy, it is difficult to draw conclusions from the above data.

When evaluating the complications and attempting to relate those with rate of distraction, no specific association was found between rate of distraction and incidence of premature consolidation. In the study by Miloro[68], premature consolidation was reported in one case while distracting at 3 mm per day, further highlighting that rate of distraction is unlikely to significantly contribute to the development of premature consolidation. The craniofacial skeleton appears to be able to tolerate rates of distraction that are greater than 1mm per day. This is likely due to the smaller overall final length of distraction and the improved vascularity of the craniofacial skeleton compared to long bones.[130] Children also have a greater propensity for healing, and so it is likely that they can tolerate faster rates of distraction without complications.

A distraction rate of 1mm/day seems to be associated with a greater incidence of technical failures. It is hypothesised that this is due to the older age of the children undergoing distraction at 1mm/day. Older children are likely to move more and hence are more likely to dislodge the external devices. Infection rates were not affected by rate of distraction.

Overall, the results of this review suggest that there is no significant difference in outcomes between those children who underwent distraction at a rate of 1 mm per day or 2 mm per day. Distracting at a rate of 2 mm per day appeared to be safe in neonates and shortened the distraction phase of the treatment. Few studies included in this analysis had older children distracted at 2 mm per day, so it is not possible to extrapolate if it is safe to distract children older than two years at a rate faster than 1 mm per day. When evaluating complications, there was a slightly higher risk of infection and risk of technical failures in those undergoing distraction at 1 mm per day.

Clinically, being able to distract the mandible at a faster rate with predictable results is in the best interests of the child. New studies are using adjuncts such as bone morphogenic protein (BMP) to encourage bony growth and maturity in a more rapidly distracted segment.[67] Further research is needed to determine if these techniques are effective and that the quality of the bone produced with these adjuncts is adequate.

4.6.2 External versus internal distractors analysis

There are two main types of distraction devices used for MDO: external and internal. This review compared these two different distraction devices. Overall, there was a high rate of reoperation within the external distractor group compared with the internal distractor group. The most common reason for reoperation was pin dislodgement, which often needed a general anesthetic for repositioning of the pin. This carried additional risk to the neonate/infant.

The complication rates for external distractors were higher than internal distractors. Hypertrophic scarring was more common in patients who had external distractors inserted (9.40% in external distractor patients compared with 0.61% in internal distractor patients). Technical problems were also more common in external distractors compared with internal distractors (8.72% compared with 3.05% respectively). Infections were found to be as common in external distractors and internal distractors. These results differ from the results of some other studies. Genecov et al.[82] reported that external distractors had almost double the number of infections compared to internal distractors. This contradiction may be due to

the underreporting of mild infections. In the studies included in this review, serious infections were more common with the use of internal distractors compared with external distractors, requiring incision and drainage. Infections in patients with external distractors were often managed with oral antibiotics and wound care. Temporomandibular joint ankylosis and dental injuries were likely to be underreported for both internal and external distractor groups. This was due to the lack of long-term follow-up of these patients as both TMJ ankylosis and dental injuries occur during development, or manifest later.

A systematic review based on 12 studies was undertaken by Paes et al., 2013[66] who compared the outcomes of internal and external distractors. The results of their review favoured better outcomes and fewer complications with internal distractors. The results of this current systematic review are in agreement with the results of Paes et al. regarding the higher rate of complications in external distractors and the increased risk of scarring when using external devices. However, the results of this review differ from the one of Paes et al. in that facial nerve injuries were reported to be more common when using external devices due to the inability to directly visualise the marginal mandibular nerve. The results of this current review found no statistically significant difference in facial nerve injuries between internal and external devices.

4.7 Long-term outcomes

The data on long-term outcomes were heterogeneous and hence quantitative comparison was not possible. They have been presented in narrative form in the results section. There was a distinct lack of studies regarding long-term outcomes of children who underwent MDO for airway obstruction secondary to micrognathia.

Overall the studies showed relatively stable results of relief of airway obstruction in the intermediate term with minimal relapse of the airway obstruction observed. Relapse was seen secondary to late development of TMJ ankylosis[107] or failure of mandibular growth. The incidence of recurrence in these studies is summarized in Table 3.20. In the study by Stelnicki et al, [133] it was found that children with sMicro tended to have relapse of the shape of the mandible to the pre-morbid shape. This study suggests a potential genetic predisposition to

relapse after MDO. This is consistent with other studies such as the study by Gürsoy et al, [143] who reported on excellent short-term structural changes in syndromic children after MDO, but during a five-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 were likely to have a persistent deformity requiring further surgical intervention in the future. Both studies however still considered MDO at a young age indicated for severe airway obstruction, but the effects on facial esthetics were transient.

The study by Anderson et al, [120] of a child with Treacher Collins with airway obstructive symptoms recurring 18 months after MDO shows that this relapse potential may lead to further airway obstruction. This patient's airway obstruction 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 they may not correspond with recurrent airway symptoms. These patients should be considered like any patient with a class II skeletal profile and managed accordingly.

When evaluating complications, it was noted that occlusal abnormalities were more commonly reported in these longer follow-up studies. Anterior open bite and long standing posterior cross bite were the most commonly reported occlusal abnormalities[107, 109]. Some cases of anterior open bite spontaneously resolved with further facial growth, but in other cases they persisted. Persistence of the anterior open bite seems to be more common in syndromic patients[109], but this finding needs longer-term studies to be confirmed. This observation has guided some surgeons to consider ways to reduce the risk of long-term malocclusion. McCarthy et al. described a technique for moulding the distraction regenerate (the mineralising healing callous) which has been very successful at achieving a good functional occlusion and avoid anterior open bite from developing.[144]

Other complications such as dental injuries and inferior alveolar nerve injuries require long-term follow-up to accurately evaluate and so are likely underreported in the literature. Most odontogenic abnormalities caused by disruption of the tooth bud can only be seen later in life. Examples include dentigerous cysts[109] and dental hard tissue abnormalities like dilacerations which may only be diagnosed if there is a failure of tooth eruption, or after

commencement of tooth eruption or from serial imaging. The long-term studies in this systematic review showed a high incidence of dental abnormalities that were only noticed during dental development. An important study by Kleine-Hakala found that the mandibular molars were affected by MDO in 13 out of 17 patients. The effects included root malformations, hindered tooth development, destruction of tooth follicles and positional changes.[145] This study also reported that about a third of all dental malformations were not identified until the second postoperative year. Further long-term studies are needed to determine the long-term effects of MDO on the primary and permanent dentitions and then strategies can be designed to avoid injury. Some authors are advocating pre-distraction enucleation of tooth follicles to avoid difficulties with distraction and tooth malformations after distraction[146].

Condylar changes and ankylosis after MDO have also been reported, and can lead to recurrence of airway symptoms. In the study by Sadakah et al,[107] three out of seven patients had condylar changes after MDO over time and one patient developed ankylosis at three years postoperatively. Andrews et al.[73] similarly reported cases of postoperative TMJ ankylosis after MDO, with a higher incidence in syndromic patients. During the distraction process, posterior cephalic forces are transmitted from the condyle to the TMJ and glenoid fossa. When these forces exceed the regenerative ability of the condyles, erosion of the articular cartilage occurs and this may lead to ankylosis over time. It has been reported to be more common in syndromic patients,[132, 147, 148] and this may be related to altered TMJ anatomy in syndromic patients, who often have hypoplastic condyles. Hence, the load per unit area is greater on the smaller, deformed condyles. Some authors suggest that ankylosis may be prevented by techniques to unload the condyles during distraction and the consolidation phase. In a study by Fan et al, the use of class II elastics to unload the condyles has led to no further cases of TMJ ankylosis.[132] These should be considered in all syndromic patients undergoing mandibular distraction, and in non-syndromic patients with evidence of preoperative TMJ abnormalities.

Our findings should guide the surgical team to carefully follow up these patients through their childhood until adolescence. Persistence of retrognathia or relapse can lead to recurrence of airway obstruction. These children should be assessed clinically, and should have polysomnographic analysis if there is suspicion of relapse of airway symptoms.

Temporomandibular joint ankylosis should always be considered as a possible long-term complication of MDO and it may lead to airway obstruction. Syndromic patients or patients with preoperative condylar abnormalities should be monitored for TMJ ankylosis, and techniques for unloading the condyles be considered. Children with a concurrent syndrome should be monitored closely with serial lateral cephalograms to assess for evidence of relapse of skeletal abnormality and the upper airway caliber. Furthermore, currently available long-term studies demonstrate that patients will often have a persistent skeletal and occlusal discrepancy into adolescence. These children will often need to be considered for Orthognathic surgery at skeletal maturity.

4.8 Other outcomes of mandibular distraction osteogenesis

Throughout the literature, there were other aspects and outcomes of MDO in children with airway obstruction that did not satisfy the inclusion criteria for this systematic review.

4.8.1 Aspiration risk

The most commonly reported complication in children with tracheostomies for upper airway obstruction in children with retrognathia was pneumonia.[47] Pneumonia and other respiratory infections seem to be rare in children undergoing MDO. The most likely reason for pneumonia and other lower respiratory tract infections after MDO would be aspiration. The study by Monasterio, [32] and Hong,[88] discussed the role of aspiration during pre-and post-operation periods. Monasterio reported, in a retrospective series of 18 patients, that 66 percent had barium penetration into laryngeal vestibule, 50 percent had stasis of residual material in the pharyngeal recess, 28 percent had pharyngeal transit of less than one second and five percent had bronchial aspiration on barium swallow preoperatively. Post-MDO, none of the patients demonstrated barium aspiration and there was normal pharyngeal transit of less than one second in all patients.[32] Despite MDO significantly disrupting the tongue and oropharyngeal musculature, these patients tended to not develop aspiration.

4.8.2 Intubation during anaesthesia

Due to the anatomical abnormalities in the upper airways of these children, it would be expected that there would be significant anaesthetic consequences. These children often require multiple operations during infancy, and so difficulty of intubation can pose a significant risk to these children. In children with PRS, a study by Marston et al.[149] found that only 37 per cent of children could be intubated with direct laryngoscopy. The remaining 63 per cent could not be intubated by direct laryngoscopy and needed more advanced techniques to be successfully intubated. By advancing the tongue with the mandible, MDO would improve visual access to the larynx during induction of anaesthesia. In a study by Frawley et al, [150] prior to MDO, the incidence of difficult intubation was approximately 71 per cent. After MDO, the incidence dropped to 8 per cent. The dramatic changes were statistically significant in those without a concomitant syndrome (in this study Treacher Collins Syndrome was the comparator). Hence, due to the overall anatomic changes with MDO, the ease of intubation and therefore the safety of anaesthesia were improved in children with micrognathia.

4.8.3 Financial comparison between MDO and tracheostomy

Overall when comparing tracheostomy and MDO from a financial perspective, studies have demonstrated a clear financial advantage of MDO over tracheostomy. In a study by Kohan et al., [151] the total per patient treatment cost in the tracheostomy group was two times greater than in the distraction group. A Canadian study by Hong et al.[27] had similar findings with an average per-patient cost being 1.6 times greater in the tracheostomy group compared to the MDO group. The reason for the financial difference relates to the long-term complications associated with tracheostomy. After tracheostomy, a prolonged hospital stay is expected for tube changes and appropriate education of parents and caregivers on how to manage a tracheostomy at home.[55, 152] Although the equipment needed for MDO are expensive, the children often spend less time in intensive care and hospital compared to children who undergo tracheostomy, and have no long-term costs associated with treatment.[27]

4.9 Limitations of the study

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 randomised 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. I have divided this section into the specific stages of the systematic review and the limitations encountered in each section.

4.9.1 Study inclusion and search strategy

This review excluded studies that were not in English. There was a substantial amount of literature in Chinese and Japanese and some European studies that may have had relevant results for this review. Excluding these papers reduced the risk of misinterpretation, inaccurate translation and the risk of introduction of bias. Every attempt was made to find an English version of the article, and some Chinese language papers were obtained in this way.

This systematic review's inclusion criteria required clear case selection criteria from the included studies to ensure that the correct population was included in the review. The significant and fundamental difficulty was defining the clinical condition of the patients. Some studies would define any patient with micrognathia and airway obstructive symptoms as having PRS, while others would only include those with an associated cleft palate as having PRS and those without as congenital micrognathia. Also, in those with an associated clefting syndrome and micrognathia, the pathology is different and hence it is vital to have that distinction for most of the analyses. Another example of a challenge encountered during this study was the quality and consistency in reporting of previous treatments. Documentation of attempts in conservative management or treatment for these patients was required. Only patients who were being considered for tracheostomy (ie. those children that had failed conservative treatment) could be included in this review. Otherwise, the outcomes of MDO may have been skewed towards more positive results, as those with less severe airway

obstruction may have been operated on unnecessarily. These challenges led to several studies being excluded purely for poor reporting.

4.9.2 Critical appraisal

A significant number of studies did not include their selection criteria and inclusion criteria. After retrieval of studies, a significant number of studies were actually technical papers with no or minimal reporting of outcomes. A significant number of studies also grouped all patients into one group, making specific comparisons difficult. Although some of these studies could be included for specific analyses, it was not possible to include them fully due to their limited details regarding patients.

The methodology of the considered studies was heavily scrutinised to ensure that biased reporting was minimised. In the methods section of this systematic review retrospective case series were included, but the period of retrospective review in the particular unit as well as details of which patients were excluded needed to be mentioned to ensure that all relevant patients were included in the analysis and not only the good outcomes.

4.9.3 Data extraction

During the data extraction phase of the study, several challenges were encountered. Occasionally the same authors published results on the same cohort of patients at different times, or when looking at different outcomes, or they were publishing the same outcomes and results but in different journals. It was a challenge to identify these studies, and sometimes it was necessary to contact the authors to confirm that the patient cohort between studies was the same. Some studies with the same cohort of patients were included where different outcomes were reported, and care was taken to ensure that only the outcomes needed from each study were included in the individual analyses. Some multicentre case series were excluded because of potential overlap with other studies by the same authors from their respective centres.[23] Despite care being taken to identify these overlapping results, it is possible that there may have been some overlap of patients in the studies analysed in this review.

Often the studies included had incomplete data, making the specific inclusion for each individual analysis more complex as can be seen in the results section. Where data needed for the study was incomplete, attempts were made to contact the authors. However frequently there was no response from the authors. Where the particular outcomes and results were unclear in those situations, the data was excluded.

4.9.4 Data analysis

Some of the studies included in this review were heterogenous, making arithmetic and statistical analysis difficult. Different studies reported outcomes differently, and hence it was important to critically evaluate the results and undertake specific analyses for different aspects of the same outcome. For example, with the primary MDO analysis, the main outcome was subjective improvement in respiratory symptoms avoiding the need for a tracheostomy. If polysomnographic evidence of improvement was necessary for this outcome, only 11 from the 31 included studies would have been finally included.

Due to the nature of the studies and evidence available for this analysis, a meta-analysis could not be performed on this data.

For surgical analyses, most papers omitted the identity of the surgeon who performed the procedures and it remained unknown whether there was a single surgeon performing all the operations or if there were several surgeons involved in the study. Every centre would likely perform the procedure slightly differently, and this makes overall analysis difficult, as subtle differences in technique may be significant to the surgical outcome. This is unlikely to affect the airway outcomes, but may affect the surgical failure results.

4.9.5 Gap analysis

All current data is in the form of case series and the occasional comparative case series. Although valuable, they provide a low level of evidence (Level IV - JBI Levels of Evidence

2014). Randomised controlled trials are difficult to accomplish in rare conditions and are difficult to ethically consider in the paediatric population, but they can help provide answers to clinical questions on which better treatment for these children may hinge. Even if only Level III evidence was available on this treatment option, with good quality research and reporting, the indications and contraindications for MDO may have been made clearer.

This current review showed that there is unlikely to be a significant difference in surgical outcomes when distracting at 1 mm per day or 2 mm per day. A well designed case control study or if possible a randomised controlled trial with two age groups divided into 1 mm per day and 2 mm per day distraction and comparing surgical outcomes, such as failure, reoperation rate and rate of complications, would provide higher level of evidence than is presently available in the literature.

To answer the primary question of this current systematic review, the ideal study would be a randomised controlled trial grouping children who have failed conservative treatment and have confirmed upper airway obstruction (with no airway obstruction below the tongue base) into the MDO group or the tracheostomy group. The children will be followed until adolescence. Serial cephalometric radiographs, speech assessments, developmental evaluations, psychological growth, requirement for further surgery and complications can all be resolved by a long-term randomised controlled trial like this. This study would be particularly valuable because it would provide better long-term outcomes of those children who undergo tracheostomy alone. There are no current studies that have evaluated the long-term outcomes of children with micrognathia related upper airway obstruction who underwent tracheostomy at a young age. Although there are studies looking at the paediatric population in general who have undergone tracheostomy at a young age, it would be valuable to evaluate the outcomes of this particular group and compare them to children who underwent MDO.

If randomised controlled trials cannot to be performed, then authors should aim to perform prospective multicentre studies comparing treatment protocols of different centres. Even future case series, if done prospectively combining results of multiple units, can shed light on which patients will benefit from MDO and which patients will not.

Despite the large number of case series and reports of MDO in children with micrognathia and airway obstruction, there are few long-term studies monitoring these children into adolescence. Although our results suggest that MDO is effective in alleviating airway symptoms, we have very little long-term data to determine the long-term consequences of MDO.

Chapter 5: Conclusions and clinical recommendations

Although not a direct outcome of this study, it is important to emphasise that there are still significant challenges in diagnosing children with micrognathia and airway obstruction. These children need to be treated by a multidisciplinary team consisting of surgeons, paediatricians, respiratory physicians, dieticians, speech pathologists and social workers. The first line of treatment, where possible, should be conservative non-surgical treatment. Although our results show a good success rate for primary mandibular distraction, this is no substitute for good paediatric respiratory support from expert physicians. Good effective conservative treatment may avoid the need for surgery or provide an opportunity to appropriately evaluate the children before surgical intervention is performed. Thorough evaluation of the children to exclude multilevel obstruction and other comorbidities that may contribute to their respiratory distress may result in more predictable results from MDO. Despite the number of studies in the literature, the indications for MDO remain unclear. From the results of this systematic review and analysis of the literature, the following clinical recommendations can be made:

Recommendation 1: Primary mandibular distraction osteogenesis

Mandibular distraction osteogenesis is a successful technique in alleviating upper airway obstruction secondary to micrognathia and preventing tracheostomy. The most common causes of failure of MDO are undiagnosed lower airway obstruction, central apnoea or additional cardiovascular comorbidities. All children being considered for MDO should hence have a thorough airway assessment with nasoendoscopy and polysomnographic 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 risk of failure four times greater compared to isolated PRS patients. The success rate of primary MDO is not influenced by age or the time of surgery. This review 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 hypotonia is likely to be contributing to the airway obstruction.

Recommendation 2: Mandibular distraction osteogenesis to facilitate decannulation of tracheostomy dependent children

Children who are tracheostomy dependent secondary to upper airway obstruction from micrognathia can be successfully decannulated after MDO in approximately 80.3% of cases. It is interesting to find that the odds of failure of MDO are four times greater when it is used for the purpose of facilitating decannulation compared to primary MDO performed to prevent a tracheostomy. The success rate may be higher for isolated PRS patients compared to syndromic patients, although the difference was not statistically significant. The most commonly reported reasons for failure include previously undiagnosed additional airway abnormalities, gastro-oesophageal reflux disease and chronic swallowing dysfunction. Children with neurological complications are also at higher risk of failure of MDO to facilitate decannulation. This is likely due to the multifactorial nature of the airway obstruction.

Age-based analysis also revealed that the success rate of MDO at facilitating decannulation was best when performed before the age of 24 months. This is likely due to tracheostomy related complications that develop from long-term tracheostomy. 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 are attempted to determine the presence of additional lower airway abnormalities or tracheostomy related complications (Table 5.1). Children who have severe gastro-oesophageal reflux on pH monitoring should be referred for consideration of treatment of the reflux prior to MDO.

Without MDO, the average time to 'natural' decannulation is 32 months. And these tracheostomy dependent children suffer from significant complications related to tracheostomies including pneumonia, wound infection, bleeding around the stoma and development of granulation tissue.

Table 5.1: Table summarizing higher risk of failure and recommended interventions for primary MDO, tracheostomy decannulation and feeding outcomes

	Higher risk of failure	Recommended interventions
Primary MDO	- Syndromic patients - Additional airway abnormalities - Central apnoea - Multisystem comorbidities - Neurological abnormalities	- Attempt conservative treatment - Pulse oximetry - Airway assessment – nasoendoscopy/laryngoscopy - Polysomnographic studies - Neurological assessment
Tracheostomy Decannulation	- Syndromic patients - Additional airway abnormalities - Gastro-oesophageal reflux disease - Chronic swallowing dysfunction - Long-term tracheostomy - Neurological abnormalities	- Airway assessment – nasoendoscopy/laryngoscopy - Exclude lower airway abnormality or tracheostomy related complications - Neurological assessment - pH monitoring – consider Nissen fundoplication prior to MDO - Swallow studies – videofluoroscopy to exclude swallowing dysfunction
Feeding	- Syndromic patients - Early removal of feeding adjuncts	- Maintain feeding adjuncts for 6-8 weeks post-op

Recommendation 3: Feeding after mandibular distraction osteogenesis

After MDO, approximately 82 percent of children are exclusively orally fed. Those with associated syndromes tend to have a five times higher odds of requiring feeding adjuncts after MDO and hence should be monitored closely by a dietitian and speech pathologist if the feeding adjuncts are removed. Some children suffer from a decline in growth in the first six to eight weeks post-operatively and hence should be continued on feeding adjuncts during this period to ensure appropriate nutritional status during this period of increased stress.

Recommendation 4: Gastro-oesophageal reflux outcomes after mandibular distraction osteogenesis

Relief of the upper airway obstruction by MDO is effective at relieving GORD symptoms in children with micrognathia. In the studies reviewed, those who were tracheostomy dependent with GORD were associated with an increased risk of failure to decannulate after MDO. It is recommended that tracheostomy dependent patients who are being considered for MDO should have formal pH monitoring and evaluation of their reflux prior to surgery.

Recommendation 5: Surgical factors

Despite the variety of reported surgical techniques, MDO is successfully completed in 96 per cent of patients. The most common reasons for failure were technical problems related to distractors such as pin dislodgement or device failure. Regarding the rate of distraction, there was no difference in the success rate between 1 mm per day and 2 mm per day. Due to the more rapid distraction and shorter period of treatment, distracting at a rate of 2 mm per day should be considered in children younger than one year of age. The role of adjuvants such as BMP is yet to be proven and require further research. More studies are required to evaluate the rate of distraction in older children as most patient's included in this review were neonates at the time of surgery.

Recommendation 6: External versus internal distractors

Both techniques provide predictable results. There is a higher incidence of failure with the use of external distractors and this is most commonly due to technical difficulties that require a

return to the operating theatre. Scarring is also more common when external distractors are used compared to internal distractors. Where available, internal distractors should be used.

Recommendation 7: Long-term outcomes

There are few studies evaluating the long-term outcomes of MDO. Although recurrence of airway symptoms is uncommon in the currently available evidence, it is important that these children are monitored carefully. Recurrence of airway symptoms may occur which may be secondary to failure of progressive mandibular growth or TMJ ankylosis. More studies are needed to evaluate the long-term facial changes after MDO and the long-term occlusal and dental complications of MDO. Long-term evaluation of facial development after MDO will guide the development of different distractor devices to help prevent occlusal and skeletal abnormalities that seem to be prevalent in these children after MDO in the long-term.

Conclusions regarding study design and quality

There is a lack of good quality research in the literature on the use of MDO in children with upper airway obstruction secondary to micrognathia. Randomised controlled trials comparing the rate of distraction are needed to determine the ideal rate of distraction in different age groups. . The effects of tracheostomy and MDO on development of speech and language are also required to determine if MDO creates an environment that facilitates development of speech and language at a rate similar to normal children without these complications. The psychological and social implications of early treatment may be crucial to the wellbeing of these children but this is not yet known. Despite the number of studies reporting successful treatment of airway obstruction with MDO, there is a lack of availability of long-term data with follow-up of these children into adolescence.

The application of JBI methodology for systematic reviews has allowed synthesis of current knowledge based on case series and case reports only. Although causal relationships cannot be confirmed with case series and case reports, synthesising the current evidence from them may still help inform clinical decisions until further higher level evidence is available.

In conclusion, MDO is an effective technique for preventing tracheostomy or facilitating decannulation in children with severe airway obstruction secondary to micrognathia when

used in the correct patient. Thorough evaluation preoperatively is needed before embarking on MDO to achieve more predictable results. More studies are needed to provide higher levels of evidence than is currently available and to evaluate the long-term implications of MDO on facial development and long-term complications and the ideal surgical protocol to achieve the best outcomes.

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Appendices

Appendix I – Search Strategies for different databases

PubMed (Medline)

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]

Embase

'child'/exp OR 'children'/exp OR 'neonate'/exp OR 'infant'/exp OR ('paediatric') OR ('pediatric') OR 'newborn'/exp AND ('pierre robin'/exp OR 'robin sequence'/exp OR 'pierre robin syndrome'/exp OR 'micrognathia'/exp OR 'micrognathia'/syn OR 'retrognathia'/exp OR

'craniofacial malformation'/syn OR 'jaw malformation'/exp OR 'jaw malformation'/syn OR ('nager') OR ('stickler') OR ('treacher collins') OR ('goldenhar')) AND ('distraction osteogenesis'/exp OR ('mandibular distraction') OR ('mandibular lengthening') OR 'tracheostomy'/exp OR 'tracheotomy'/exp OR ('airway obstruction surgery') OR 'bone lengthening'/exp OR 'surgery'/exp) AND ('airway obstruction/exp' OR 'apnea/exp' OR ('apnoea') OR 'newborn apnea/exp' OR 'gastroesophageal reflux/exp' OR ('feeding') OR 'child nutrition/exp' OR 'weight gain/exp' OR ('facial growth') OR 'face growth/exp' OR 'facial development'/exp OR ('dentition:de,ti,ab') OR 'failure to thrive'/exp OR ('outcome')) AND [humans]/lim

Scopus

(ALL("Child" OR "Children" OR "Neonate" OR "Neonatal" OR "Infant" OR "Infants" OR "Pediatric" OR "Paediatric" OR "Newborn") AND ALL("Pierre Robin" OR "Pierre Robin sequence" OR "Robin sequence" OR "Micrognathia" OR "retrognathia" OR "mandibular hypoplasia" OR "Goldenhar" OR "Treacher Collins" OR "Nager" OR "Stickler" OR "Craniofacial Abnormality" OR "mandibulofacial dysostosis" OR "Jaw Abnormality") AND ALL("Mandibular distraction" OR "Mandibular lengthening" OR “distraction” OR "Bone lengthening" OR "distraction osteogenesis" OR "Tracheostomy" OR "Tracheotomy" OR "Airway Obstruction") AND ALL("Apnea" OR "Apnoea" OR "Airway obstruction" OR "Airway patency" OR "Gastroesophageal reflux" OR "Feeding" OR "Weight gain" OR "Weight" OR "Facial growth" OR "Facial development" OR "dentition" OR "failure to thrive" OR "outcome" OR "molars"))

Web of Knowledge

Child OR Children OR Neonate OR Neonatal OR Infant OR Infants OR Pediatric OR Paediatric OR Newborn
AND

Pierre Robin OR Pierre Robin sequence OR Robin sequence OR Micrognathia OR retrognathia OR mandibular hypoplasia OR Goldenhar OR Treacher Collins OR Nager OR Stickler OR Craniofacial Abnormality OR mandibulofacial dysostosis OR Jaw Abnormality
AND
Mandibular distraction OR Mandibular lengthening OR distraction OR Bone lengthening OR distraction osteogenesis OR Tracheostomy OR Tracheotomy OR Airway Obstruction
AND
Apnea OR Apnoea OR Airway obstruction OR Airway patency OR Gastroesophageal reflux OR Feeding OR Weight gain OR Weight OR Facial growth OR Facial development OR dentition OR failure to thrive OR outcome OR molars

Grey Literature

Mednar/OpenGrey/GreyMatters/Scirus

Child, pierre robin, micrognathia, mandibular distraction, tracheostomy, tracheotomy

Index to Theses

Mandibular distraction osteogenesis, distraction osteogenesis

Appendix II: Appraisal Instruments

MAStARI Descriptive/case series critical appraisal checklist

JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was study based on a random or pseudo-random sample?	☐	☐	☐	☐
2. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
3. Were confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
4. Were outcomes assessed using objective criteria?	☐	☐	☐	☐
5. If comparisons are being made, was there sufficient descriptions of the groups?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____

_____

_____

Appendix III: Studies selected for retrieval

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Appendix IV: Number of included studies and results of critical appraisal checklist

Number of studies included and excluded

Number of studies included	Number of studies excluded
66	20

Descriptive /case series studies

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Mitsukawa, N., Satoh, K., Suse, T., Hosaka, Y., 2007	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Al-Samkari, H. T., Kane, A. A., Molter, D. W., Vachharajani, A., 2010	N	Y	Y	Y	Y	U	N/A	Y	Y
Ali Bukhari, S. G., Khan, S., Ahmed, W., Ashfaq, M., Khan, S. I., Abdullah,, 2011	N	Y	N/A	Y	N/A	Y	N/A	Y	N/A
Ali Bukhari, Syed Gulzar, Ahmed, Waseem, Janjua, Omer Sefvan, Waheed, Ashar, Junaid, Muhammad, Khan, Sarfaraz, 2012	N	Y	U	Y	Y	Y	N/A	Y	Y
Andrews, Brian T., Fan, Kenneth L., Roostaeian, Jason, Federico, Christina, Bradley, James P., 2013	N	Y	Y	Y	Y	Y	N/A	Y	U
Breugem, C., Paes, E., Kon, M., van der Molen, A. B., 2012	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Brevi, B., Lagana, F., Piazza, F., Sesenna, E., 2006	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Burstein, F. D. & Williams, J. K., 2005	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Carls, F. R. & Sailer, H. F., 1998	N	Y	Y	Y	Y	Y	N/A	Y	N/A
Chigurupati, R., Massie, J., Dargaville, P., Heggie, A., 2004	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Chowchuen, B., Jenwitheesuk, K., Chowchuen, P., Prathanee, B., 2011	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Dauria, D. & Marsh, J. L., 2008	N	Y	Y	Y	Y	U	N/A	Y	N/A
Demke, J., Bassim, M.,	N/A	Y	Y	Y	Y	Y	N/A	Y	N/A

Patel, M. R., Dean, S., Rahbar, R., van Aalst, J. A., Drake, A., 2008									
Denny, A. & Amm, C., 2005	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Genecov, D. G., Barcelo, C. R., Steinberg, D., Trone, T., Sperry, E., 2009	N	Y	Y	Y	N	U	N/A	Y	N/A
Gifford, T., Park, A., Muntz, H., 2008	N	Y	Y	Y	Y	Y	N/A	Y	N/A
Glynn, F., Fitzgerald, D., Earley, M. J., Rowley, H., 2011	N	Y	Y	Y	N	Y	N/A	Y	N/A
Gozu, A., Genc, B., Palabiyik, M., Unal, M., Yildirim, G., Kavuncuoglu, S., Ozsoy, Z., 2010	N	Y	Y	Y	Y	Y	N/A	Y	N/A
Griffiths, Amanda Louise, Heggie, Andrew, Holman, Sarah, Robertson, Stephen P., White, Susan M., 2013	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Gursoy, S., Hukki, J., Hurmerinta, K., 2008	N	Y	Y	Y	Y	Y	N/A	Y	Y
Hammoudeh, J., Bindingnavele, V. K., Davis, B., Davidson Ward, S. L., Sanchez-Lara, P. A., Kleiber, G., Nazarian Mobin, S. S., Francis, C. S., Urata, M. M., 2012	N	Y	Y	Y	N/A	Y	N/A	Y	Y
Han, K. D., Seruya, M., Oh, A. K., Zalzal, G. H., Preciado, D. A., 2012	N	Y	Y	Y	Y	Y	N/A	Y	Y
Handler, M. Z., Alabi, O., Miller, J., 2009	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Hollier, L. H., Jr., Higuera, S., Stal, S., Taylor, T. D., 2006	N	Y	Y	Y	Y	U	N/A	Y	N/A
Hollier, L. H., Kim, J. H., Grayson, B., McCarthy, J. G., 1999	N	Y	Y	Y	Y	Y	N/A	Y	N/A
Hong, P., Brake, M. K., Cavanagh, J. P., Bezuhly, M., Magit, A. E., 2012	N	Y	Y	Y	Y	Y	N/A	Y	N/A
Hong, Paul, Graham, Elise,	N	Y	Y	Y	N/A	Y	N/A	Y	N/A

Belyea, James, Taylor, S. Mark, Kearns, Donald B., Bezuhly, Michael, 2012									
Horta, R., Marques, M., Gomes, V., Rebelo, M., Reis, J., Amarante, J., 2009	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Howlett, C., Stavropoulos, M. F., Steinberg, B., 1999	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Iatrou, I., Theologie-Lygidakis, N., Schoinohoriti, O., 2010	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Izadi, K., Yellon, R., Mandell, D. L., Smith, M., Song, S. Y., Bidic, S., Bradley, J. P., 2003	N	Y	Y	Y	Y	Y	N/A	Y	N/A
Judge, B., Hamlar, D., Rimell, F. L., 1999	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Kolstad, C. K., Senders, C. W., Rubinstein, B. K., Tollefson, T. T., 2011	N	Y	Y	Y	Y	Y	N/A	Y	U
Lee, J. H. & Kim, Y. H., 2009	N	Y	N	Y	N/A	Y	N/A	Y	N/A
Looby, J. F., Schendel, S. A., Lorenz, H. P., Hopkins, E. M., Aizenbud, D., 2009	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Mandell, D. L., Yellon, R. F., Bradley, J. P., Izadi, K., Gordon, C. B., 2004	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Miller, J. J., Kahn, D., Lorenz, H. P., Schendel, S. A., 2007	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Miloro, M., 2010	N	Y	Y	Y	Y	Y	N/A	Y	N/A
Monasterio, F. O., Drucker, M., Molina, F., Ysunza, A., 2002	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Monasterio, F. O., Molina, F., Berlanga, F., Lopez, M. E., Ahumada, H., Takenaga, R. H., Ysunza, A., 2004	N	Y	Y	Y	Y	Y	N/A	Y	N/A
Morovic, C. G. & Monasterio, L., 2000	N	Y	Y	Y	U	Y	N/A	Y	U
Mudd, P. A., Perkins, J. N., Harwood, J. E., Valdez, S., Allen, G. C., 2012	N	Y	Y	Y	Y	Y	N/A	Y	N/A

Olson, T. P., McMurray, J. S., Mount, D. L., 2011	N	Y	Y	Y	Y	Y	N/A	Y	Y
Perlyn, C. A., Schmelzer, R. E., Sutera, S. P., Kane, A. A., Govier, D., Marsh, J. L., 2002	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Rachmiel, A., Emodi, O., Aizenbud, D., 2012	N	Y	N	Y	Y	Y	N/A	Y	N/A
Rachmiel, A., Srouji, S., Emodi, O., Aizenbud, D., 2012	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Sadakah, A. A., Elshall, M. A., Farhat, A. A., 2009	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Schaefer, R. B., Stadler, J. A., 3rd, Gosain, A. K., 2004	N	Y	Y	Y	Y	Y	N/A	Y	N/A
Scott, A. R., Tibesar, R. J., Lander, T. A., Sampson, D. E., Sidman, J. D., 2011	N	Y	Y	Y	Y	Y	N/A	Y	N/A
Sesenna E, Magri A S, Magnani C, Brevi B C, Anghinoni M L. , 2012	N	Y	Y	Y	Y	Y	N/A	Y	N/A
Sidman, J. D., Sampson, D., Templeton, B., 2001	N	Y	Y	Y	Y	Y	N/A	Y	N/A
Smith, M. C. & Senders, C. W., 2006	N	Y	Y	Y	Y	Y	N/A	Y	Y
Spring, M. A. & Mount, D. L., 2006	N	Y	Y	Y	Y	Y	N/A	Y	U
Steinbacher, D. M., Kaban, L. B., Troulis, M. J., 2005	N	Y	Y	Y	Y	Y	N/A	Y	Y
Stelnicki, E. J., Lin, W. Y., Lee, C., Grayson, B. H., McCarthy, J. G., 2002	N	Y	Y	Y	Y	Y	N/A	Y	N/A
Taub, P. J., Wolfeld, M., Cohen-Pfeffer, J., Mehta, L., 2012	N	Y	N/A	Y	N/A	Y	N/A	Y	N/A
Tibesar, R. J., Price, D. L., Moore, E. J., 2006	N/A	Y	Y	Y	N/A	Y	N/A	Y	N/A
Tibesar, R. J., Scott, A. R., McNamara, C., Sampson, D., Lander, T. A., Sidman, J. D., 2010	N	Y	Y	Y	N/A	Y	Y	Y	N/A
Tomaski, S. M., Zalzal, G. H., Saal, H. M., 1995	N	Y	Y	Y	Y	Y	N/A	Y	N/A
Williams, J. K., Maull, D.,	N	Y	Y	Y	Y	Y	N/A	Y	N/A

Grayson, B. H., Longaker, M. T., McCarthy, J. G., 1999									
Wittenborn, W., Panchal, J., Marsh, J. L., Sekar, K. C., Gurley, J., 2004	N	Y	Y	Y	Y	Y	N/A	Y	U
Zenha, H., Azevedo, L., Rios, L., Pereira, A., Pinto, A., Barroso, M. L., Costa, H., 2012	N	Y	Y	Y	Y	Y	N/A	Y	N/A
Murage, K. P., Tholpady, S. S., Friel, M., Havlik, R. J., Flores, R. L., 2013	N	Y	Y	Y	Y	Y	N/A	Y	Y
Papoff, P., Guelfi, G., Cicchetti, R., Caresta, E., Cozzi, D. A., Moretti, C., Midulla, F., Miano, S., Cerasaro, C., Cascone, P., 2013	N	Y	Y	Y	Y	Y	N/A	Y	Y
Lin, S. Y., Halbower, A. C., Tunkel, D. E., Vanderkolk, C., 2006	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Anderson P J, Netherway D J, Abbott A, Moore M, David D J, 2004	N	Y	Y	Y	N/A	Y	N/A	Y	N/A
Sorin, A., McCarthy, J. G., Bernstein, J. M., 2004	N	Y	Y	Y	U	Y	Y	Y	Y
%	0.00	100.00	95.38	100.00	89.47	94.03	100.00	100.00	68.75

Appendix V: Table of included studies

	Study	MDO – overall	MDO - syndromic	MDO – age based	Tracheostomy only	TD - overall	TD - syndromic	TD – age based	Feeding – overall	Feeding - syndromic	Surgical – overall	Surgical – distraction rate	Surgical – internal vs external	Surgical - complications
1	Ali Bukhari 2011[118]					☐	☐	☐			☐	☐	☐	
2	Ali Bukhari 2012 [119]					☐	☐	☐			☐	☐	☐	
3	Al-Samkari 2010 [71]		☐						☐	☐				
4	Anderson 2004 [120]					☐	☐	☐			☐	☐	☐	
5	Andrews 2013 [73]	☐		☐	☐						☐	☐		☐
6	Breugem 2012 [74]	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	☐
7	Brevi 2006 [75]								☐	☐				
8	Burstein 2005 [77]	☐	☐			☐	☐				☐	☐	☐	☐
9	Carls 1998 [78]	☐	☐	☐		☐	☐	☐			☐	☐	☐	
10	Chigurupati 2004 [79]	☐	☐	☐		☐	☐	☐	☐	☐	☐	☐	☐	
11	Chowchuen 2011 [80]	☐	☐	☐		☐	☐	☐						

12	Dauria 2008 [35]	☐	☐	☐					☐	☐	☐		☐	
13	Demke 2008 [121]				☐	☐	☐				☐	☐	☐	
14	Denny and Amm 2005 [81]	☐	☐	☐					☐	☐	☐	☐	☐	
15	Genecov 2009 [82]	☐	☐	☐		☐			☐		☐	☐	☐	☐
16	Gifford 2008 [83]	☐	☐	☐		☐	☐	☐			☐	☐	☐	
17	Glynn 2011 [128]				☐									
18	Gözü 2010 [84]	☐	☐			☐	☐	☐						
19	Griffiths 2013 [85]	☐	☐	☐							☐	☐	☐	
20	Hammoudeh 2012 [86]	☐	☐	☐							☐	☐	☐	
21	Han 2012 [129]				☐									
22	Handler 2009 [87]	☐	☐	☐							☐	☐	☐	
23	Hollier 1999 [122]					☐		☐			☐	☐	☐	

24	Hollier 2006 [130]										□	□	□	□
25	Hong 2012 [88]	□	□	□					□	□	□	□	□	□
26	Hong 2012 [89]	□	□	□										
27	Horta 2009 [123]					□	□	□						
28	Howlett 1999 [90]	□	□	□					□	□	□	□	□	
29	Iatrou 2010 [124]					□	□	□	□	□	□	□	□	
30	Izadi 2003 [91]		□						□	□				
31	Judge 1999 [92]	□	□	□							□	□	□	□
32	Kolstad 2011 [93]	□	□	□		□	□	□			□	□	□	□
33	Lee 2009 [41]	□	□	□							□		□	
34	Lin 2006 [94]	□	□	□		□	□	□						
35	Looby 2009 [95]	□	□	□					□	□	□	□	□	□
36	Mandell 2004 [96]	□	□	□		□		□						

37	Miller 2007 [97]	□	□						□	□	□	□	□	□
38	Miloro 2010 [68]	□				□			□		□		□	□
39	Mitsukawa 2007 [98]	□	□	□		□	□	□			□		□	
40	Monasterio 2002 [99]					□	□				□	□	□	
41	Monasterio 2004 [32]	□	□	□										
42	Morovic 2000 [100]	□	□	□		□	□	□			□	□	□	
43	Mudd 2012 [101]	□		□					□		□	□	□	□
44	Murage 2013 [102]	□	□	□										
45	Olson 2011 [103]		□						□	□				
46	Papoff 2013 [104]	□	□	□							□	□	□	□
47	Perlyn 2002 [105]	□	□	□		□	□	□						
48	Rachmiel 2012 [125]					□	□	□						

49	Rachmiel 2012 [106]	☐		☐							☐	☐		
50	Sadakah 2009 [107]	☐	☐	☐							☐	☐	☐	
51	Schaefer 2004 [49]	☐	☐	☐		☐	☐	☐						
52	Scott 2011 [108]		☐	☐			☐		☐					
53	Sesenna 2012 [76]	☐	☐	☐		☐	☐	☐			☐	☐	☐	
54	Sidman 2001 [110]		☐	☐			☐	☐						
55	Smith 2006 [111]	☐	☐	☐	☐	☐	☐	☐			☐		☐	☐
56	Sorin 2004 [112]	☐	☐	☐										
57	Spring 2006 [113]			☐					☐					
58	Steinbacher 2005 [126]					☐	☐	☐			☐	☐	☐	
59	Stelnicki 2002 [133]													
60	Taub 2012 [114]	☐	☐	☐							☐	☐	☐	

61	Tibesar 2010 [109]	☐				☐			☐		☐	☐	☐	☐
62	Tibesar 2006 [115]	☐	☐	☐										
63	Tomaski 1995 [47]				☐									
64	Williams 1999 [127]										☐	☐	☐	
65	Wittenborn 2004 [72]	☐	☐	☐										
66	Zenha 2012 [116]	☐	☐	☐					☐	☐	☐	☐	☐	

MDO – Primary mandibular distraction osteogenesis analysis

TD – Tracheostomy decannulation analysis

Appendix VI: Excluded studies

Benjamin, B. and Walker, P., Management of airway obstruction in the Pierre Robin sequence

Reason for exclusion: Inadequate outcomes data. Patients were recruited from 1977-1987 before the period of inclusion in the study.

Cheng, A. T., Corke, M., Loughran-Fowlds, A., Birman, C., Hayward, P., Waters, K. A., Distraction osteogenesis and glossopexy for Robin sequence with airway obstruction

Reason for exclusion: Known lower airway abnormalities were an exclusion criterion for the current systematic review.

Cohen, S. R., Simms, C., Burstein, F. D., Mandibular distraction osteogenesis in the treatment of upper airway obstruction in children with craniofacial deformities

Reason for exclusion: Inadequate separation of patients for specific outcomes data.

Cruz, M. J., Kerschner, J. E., Beste, D. J., Conley, S. F., Pierre Robin sequence: Secondary respiratory difficulties and intrinsic feeding abnormalities

Reason for exclusion: No outcomes detail included in this paper.

Da Silva Freitas, R., Tolazzi, A. R. D., Alonso, N., Cruz, G. A. O., Busato, L., Evaluation of molar teeth and buds in patients submitted to mandible distraction: Long-term results

Reason for exclusion: Most of the included cases were craniofacial microsomia. Although there was one case of Treacher Collins syndrome, there was no separation of outcomes.

Daniel, M., Bailey, S., Walker, K., Hensley, R., Kol-Castro, C., Badawi, N., Cheng, A., Waters, K., Airway, feeding and growth in infants with Robin sequence and sleep apnoea

Reason for exclusion: Details of feeding and growth outcomes in patients who underwent mandibular distraction were not clearly specified. Additional information was sought, but there was no response.

Denny, A. D., Talisman, R., Hanson, P. R., Recinos, R. F., Mandibular distraction osteogenesis in very young patients to correct airway obstruction

Reason for exclusion: Multiple patients from multiple centres. Inclusion criteria not rigorous enough to ensure bias was eliminated. Also,

likely overlap of some patients with other Denny et al. papers.

Evans, A. K., Rahbar, R., Rogers, G. F., Mulliken, J. B., Volk, M. S., Robin sequence: A retrospective review of 115 patients

Reason for exclusion: No outcomes reported.

Farina, R., Castellon, L., Nagelash, E., Valladares, S., A new way to anchor the external device in mandibular distraction: three case reports with a Pierre Robin sequence

Reason for exclusion: Inclusion criteria did not stipulate if these cases were the only cases done with this technique. Risk of bias.

Gursoy, S., Hukki, J., Hurmerinta, K.. Five year follow-up of mandibular distraction osteogenesis on the dentofacial structures of syndromic children.

Reason for exclusion: Did not undergo distraction for airway obstruction.

Klein, C. and Howaldt, H. P., Correction of mandibular hypoplasia by means of bidirectional callus distraction

Reason for exclusion: The included subjects did not have their operation for airway obstruction.

Kleine-Hakala, M., Hukki, J., Hurmerinta, K., Effect of mandibular distraction osteogenesis on developing molars

Reason for exclusion: The age of the patients included in this study did not correspond with the average age of children undergoing mandibular distraction because of airway obstruction. Comparison was not possible.

Li, H. Y., Lo, L. J., Chen, K. S., Wong, K. S., Chang, K. P., Robin sequence: review of treatment modalities for airway obstruction in 110 cases

Reason for exclusion: No outcomes data provided.

Lin, Samuel J., Roy, Saswata, Patel, Pravin K., Distraction osteogenesis in the pediatric population

Reason for exclusion: Inadequate outcomes data.

McCarthy, J. G., Katzen, J. T., Hopper, R., Grayson, B. H., The first decade of mandibular distraction: Lessons we have learned

Reason for exclusion: Overlap of patients with subsequent papers.

Meyer, A. C., Lidsky, M. E., Sampson, D. E., Lander, T. A., Liu, M., Sidman, J. D., Airway interventions in children with Pierre Robin Sequence

Reason for exclusion: No clear outcomes provided.

Molina, F. M., Morales, C., Taylor, J. A., Mandibular distraction osteogenesis in a patient with melnick-needles syndrome

Reason for exclusion: Rare syndrome, single case report, patient included was older than most included papers making comparison very difficult.

Perkins, J. A., Sie, K. C. Y., Milczuk, H., Richardson, M. A., Airway management in children with craniofacial anomalies

Reason for exclusion: No adequate outcomes detail provided for analysis.

Rodriguez, J. C. and Dogliotti, P., Mandibular distraction in glossoptosis-micrognathic association: preliminary report

Reason for exclusion: No adequate outcomes data provided.

Senders, C. W., Kolstad, C. K., Tollefson, T. T., Sykes, J. M., Mandibular distraction osteogenesis used to treat upper airway obstruction

Reason for exclusion: Overlap of cases with another included paper – Kolstad 2011.

Appendix VII: Primary MDO data extraction table

Article	Study design	Country/unit	number of patients	Age (months) mean	Syndrome	Success	Failures	PSG Pre (OAHI)	PSG Post	Other comments
Al-Samkari 2010 [71]	RR	St Louis	7		iPRS	7	0			
			5		sMicro	4	1			Tracheostomy in pt with Chromosome 4q deletion
Andrews 2013 #[73]	RR	Los Angeles	73	1.5	Mixture	72	2			Tracheostomy – accidental displacement during MDO
Breugem 2012 [74]	RR	Netherlands	6	1	iPRS	6				
			5	1	sMicro	5				
Brevi 2006 [75]	CR	Italy	2	1	iPRS	2				
Burstein 2005 [77]	RR	Atlanta	12		iPRS	12		15.36	1.11	
			2		sMicro	2				
Carls 1998 [78]	RR	Switzerland	1	48	iPRS	1				
			2	54	sMicro	2				Syndromes: Treacher Collins, Goldenhar
Chigurupati 2004 [79]	RR	Australia	1	4	iPRS	1				
			1	4	iPRS	1				
Chowchuen 2011[80]	RR	Thailand	1	3	iPRS	1				
Dauria 2008 [35]	RR	St Louis	4	1 month	iPRS	2	2			Failures: 1 tracheomalacia/subglottic stenosis. 2. Laryngomalacia(3) Gastrostomy tubes. 1 success still needed nasal cannula oxygen

Denny and Amm 2005 [81]	RR	Wisconsin	4	16 days	iPRS	4	0			
			7	20 days	sMicro	7	0			
Genecov 2009 [82]	RR	Texas	26	<6 months	iPRS	25	1			
Gifford 2008 [83]	RR	Utah	6	1 month	iPRS	6	0	57.7+/-15	3.6 +/- 1.5	
			1	21 days	sMicro	0	1			Failed case is because of intraoperative dislodging of endotracheal tube, mandible fracture and subsequent tracheostomy
Gözü 2010 [84]	RR	Turkey	3		iPRS	3				
			2		sMicro	2				Both Sticklers
Griffiths 2013 [85]	CR	Melbourne	1	5	Skeletal dysplasia	1		39.2	0	Developmentally normal at 3.5 years. No recurrence of OSA
Hammoudeh 2012 [86]	RR	California	19	2.7	iPRS	19		46.25	3.92	
			6	5.04	sMicro	4	2	19	4.14	1 Cornelia De Lange - expired because of co-morbidities – successful distraction. 2. Beckwith-Widemann – interstitial lung disease and central apnoea
			3	4.36	Micrognathia	3		34	15.4	
Handler 2009 [87]	CR	Omaha	1	4 days	sMicro	1				Treacher Collins with Diamond Blackfan anaemia
Hong 2012 [88]	RR	Nova Scotia Canada	2	2	iPRS	2				
			4	2.5	sMicro	4				Otopalatodigital, 2 stickler, 4p deletion

Hong 2012 [89]	RR	Nova Scotia Canada	3	2.5	iPRS	3				
Howlett 1999 [90]	CR	Florida	1	2	iPRS	1				
Izadi 2003 [91]	RR	Los Angeles	7	8.5 days	iPRS	7				Stickler (2) Treacher Collins (2) Nager (2) Cornelia De Lange (1) Unknown (1)
			8	8.5 days	sMicro	7	1			Failed pt was one with unknown syndrome and multiple co-morbidities including facial dysmorphology, degenerative encephalopathy, VSD, obstructive and central apnoea (underappreciated before operation)
Judge 1999 [92]	CR	Minneapolis	1	6 days	sMicro	1				Klippel Feil syndrome
Kolstad 2011 [93]	RR	California	4	19 days	iPRS	4				
			6	19 days	sMicro	5	1			Unknown syndrome – Failed due to undiagnosed central apnoea, other syndromes: oto-palatal-digital syndrome, moebius, sticklers, 3 undetermined
			3	3.3 months	sMicro	3				1 needed CPAP for 3 yrs post MDO but successful, TCS, Cornelia De Lange, 1 undetermined
			5	10 months	iPRS	5				
			1	7.2 months	sMicro	1				
			2	60 months	sMicro	2				Sticklers, moebius, Goldenhar, 3 undetermined

Lee 2009 [41]	RR	Korea	2	5 months	iPRS	2				
			1	2.5 years	iPRS	1				
Lin 2006 {#957)		Baltimore	3	1 month	iPRS	3			0.3	
			1	13 month	iPRS	1			0.9	
Looby 2009 [95]	RR	California	12	105 days	iPRS	12		10.57	2.21	
			5		sMicro	5				Nager, Stickler, Gordon, TCS, Torrielo-Carey and Townes-Brock syndromes
Mandell 2004 [96]	RR	Los Angeles	3	69 months	iPRS	3				
			3		sMicro	2	1			Goldenhar, Cornelia De Lange, Trisomy 2
Miller 2007 [97]	RR	Stanford	7		iPRS	7		19.2	1.5	
			3		sMicro	2	1			non-specific syndrome but with neurologic impairment
Miloro 2010 [68]	RR	Chicago	23	3.5months	Mixture	22	1			Failure – distress 1 yr post MDO – undiagnosed laryngomalacia
			3		iPRS	3				
Mitsukawa 2007 [98]	RR	Japan	1	8 months	Micrognathia	1		12.2	0.8	
			4	2.5 months	iPRS	4		12.6	4.6	
			2	1.5 years	iPRS	2		11.8	1	
			1	3 years	sMicro	1		14.5	0.5	Treacher Collins Syndrome
Monasterio 2002 [99]	RR	Mexico	4	7 days	iPRS	4				
			4	?	iPRS	4				
			4	older	iPRS	4				

Monasterio 2004 [32]	RR	Mexico	17	120 days	iPRS	17		18.3	Not reported - noted as "no episodes of apnoea or hypopnea"	17 iPRS, 1 Orofaciodigital syndrome
			1		sMicro	1				Orofaciodigital syndrome
Morovic 2000 [100]	Prospective	Chile	4	2.75 months	iPRS	4		Not reported with exact figures		1 pt had facial clefts
			1	5 months	sMicro	1				Treacher Collins Syndrome
Mudd 2012 [101]	RR	Colorado	25	30 days	Mixture	25				No airway failures, but 1 pt needed home O2 as he lived at a high altitude
										7 pts non iPRS: Femoral hypoplasia, Chromosome 4Q deletion, Wiskott-Aldrich, Treacher Collins, Stickler, Velocardiofacial, Freeman-Sheldon syndrome
Murage 2013 [102]	RR	Indianapolis	39	<6 months	iPRS	36	3	37.8 +/- 25.6	6.5 +/-8.03	Failures: 1. CHARGE syndrome with pulmonary hypertension, ASD and chronic lung disease. 2. Laryngomalacia and tetraology of Fallot. 3. Cerebral palsy and laryngomalacia. 4.

										Hypotonia and no gag reflex noted at birth
			11	< 6 months	sMicro	10	1			Stickler (4), Treacher Collins (2), Duplicated X15 (2), CHARGE syndrome (1), Fragile X (1), 4p deletion (1)
Olson 2011 (103)	RR	Wisconsin	6	237 days	iPRS	6				
			8		sMicro	8				velocardiofacial, orofacial digital, VATER association, Treacher Collins, 6q deletion, Stickler(3), Smith-Lemli-opitz, unspecified/unknown
Papoff 2013 (104)	RR	Italy	4	24 days	iPRS	4				
			5		sMicro	4	1			Failure: velocardiofacial syndrome – failed MDO, TLA then needed Tracheostomy and gastrostomy
										Stickler, velocardiofacial, larsen, 7p deletion, lymphoedemadistichiasis
Perlyn 2002 (105)	RR	St Louis	1	68 months	Nager	1				Initially had tracheostomy, decannulated but developed OSA again
Rachmiel 2012 (106)	RR	Israel	12		Mixture	12				Minimal detail provided

Sadakah 2009 [107]	RR	Egypt	1	7 months	iPRS	1		60+/- 7.25	1.57+/-1.61	Developed relapse of retrognathia and airway symptoms at 3 years, found to be due to unilateral ankyolsis – repeat MDO with good results
			2	20 months	iPRS	2				
			4	5.9 years	iPRS	4				
Schaefer 2004 [49]	RR	Wisconsin	1	11 months	iPRS	1				Successfully avoided tracheostomy Needed tx of GORD and enlarged adenoids as well
			1	30 months	iPRS	1				
Scott 2011 [108]	RR	Mineapolis	14	4.8 weeks	iPRS	14				All were able to avoid tracheostomy
			3		sMicro	3				Stickler syndrome, Marshall-Stickler syndrome, Catel Manzke syndrome
Sesenna 2012 [76]	RR	Italy	8	2.3 months	iPRS	8	0			
Sidman 2001 [110]	Prospective	Mineapolis	1	8 months	iPRS	1				excluded one patient because of likely inclusion in Scott 2011 paper - <3 months old
Smith 2006 [111]	RR	California	1	<6 weeks	iPRS+	1				
			2	<6 weeks	sMicro	2				Both Stickler syndrome
Sorin 2004 [112]	RR	New York	1	2 months	sMicro	1				Goldenhar
			1	18 months	sMicro	1				Stickler
Spring 2006 [113]	RR	Wisconsin	1	1 week	iPRS	1				10 patients syndromes: 3 TCS, 1 Trisomy 18 mosaic, Orofacialdigital, VATER, velocardiofacial, 4q chromosome deletion

			4	3 months	sMicro	4				
			2	>2 years	sMicro	3				
Taub 2012 (114)	CR	New York	1	15 days	sMicro	1				4q deletion
Tibesar 2006 (115)	CR	Rochester	1	9 days	iPRS	1				
Tibesar 2010 (109)	RR	Mineapolis	21		Mixture	19	2			Failure: ended up with a tracheostomy. Another patient needed repeat MDO due to failure of mandibular growth and relapsing upper airway obstruction
Wittenborn 2004 (72)	RR	St Louis	17	29 days	Mixture	14	3		55% improvement	Failures: 1 had undiagnosed tracheal stenosis. Decannulated after repair of trachea. 2 failure of extubation post-op. 3. tracheostomy 4 months post MDO for persistent obstruction
Zenha 2012 (116)	CR	Portugal	1	9 days	iPRS	1				
			1	11 days	sMicro	1				Weissenbacher-Zweymuller syndrome

Appendix VIII: Tracheostomy decannulation outcome data extraction table

Article	Study Design	Unit	Number	Condition	Age (months) mean	Success	Failure	Comments
Ali Bukhari 2011 [118]	CR	Pakistan	1	Micrognathia	48	1	0	
Ali Bukhari 2012 [119]	RR	Pakistan	1	Micrognathia	24	1	0	
Anderson 2004 [120]	CR	Adelaide	1	Treacher Collins	72	1	0	Required CPAP after 18 months
Breugem 2012 [74]	RR	Netherlands	1	Stickler	2.7	1	0	Decannulated after 7 months of age - unsure if MDO is the reason
Burstein 2005 [77]	CS	Atlanta	3	iPRS	9	1	2	2 failures - 1. vascular ring - decannulated after reconstruction. 2. GORD - decannulated after fundoplication
			3	sMicro		2	1	1 failure -Opitz syndrome + severe GORD - awaiting fundoplication
Carls 1998 [78]	RR	Switzerland	1	Treacher Collins	84	1	0	
			1	Amnion Band syndrome	18	1	0	
Chigurupati 2004 [79]	RR	Australia	1	Treacher Collins	39	1		
			1	Treacher Collins	10		1	Choanal atresia – awaiting repair
			1	Tessier Cleft	20	1		
Chowchuen 2011[80]	RR	Thailand	1	iPRS	1.5	1	0	
			1	iPRS	3		1	Initially decannulated, but subsequently needed it replaced because of swallowing and aspiration

Demke 2008 [121]	RR	North Carolina	3	iPRS		2	1	Failure and Re-operation - requiring redo tracheostomy and second distraction – still has tracheostomy in place – unsure of reason
Genecov 2009 [82]	RR	Texas	41	Mixture		38	3	No details on what those who failed needed
Gifford 2008 [83]	RR	Utah	1	Nager	0.5	0	1	Still tracheostomy in place because of TMJ ankylosis and persistent airway obstruction
Gözü 2010 [84]	RR	Turkey	1	iPRS		1		Good outcomes
			1	Skeletal dysplasia	5	1		
Hollier 1999 [122]	RR	New York	4	Mixture	41	3	1	Needed suprastomal granulation tissue removed, then decannulated. MDO successful, 3 Treacher Collins, 1 Nager
Horta 2009 [123]	CR	Portugal	1	iPRS	48	1	0	Needed closure of tracheostomy stoma with rib graft
Iatrou 2010 [124]	CR	Greece	1	iPRS	8	1		
Kolstad 2011 [93]	RR	California	2	iPRS	15	2		
			1	Goldenhar	49	1		
Lin 2006 {#957)	RR	Baltimore	1	iPRS	1	1		Initially decannulated, after 1 year began to develop symptoms of OSA again
Mandell 2004 [96]	RR	Los Angeles	10	Mixture	33	2	8	Failures: 1 developed TMJ ankylosis, 7 had chronic swallowing dysfunction and gastrostomy tube dependence, 4 had previous nissen fundoplications for severe GERD. Syndromes: 1 Arthrogryposis, 3 iPRS, 3 nager, 2 Goldenhar, 1 TCS, 1 Lowe, 1 Marden Walker syndrome

Miloro 2010 [68]	RR	Chicago	9	Mixture		9	0	
Mitsukawa 2007 [98]	RR	Japan	1	iPRS	8	1		
			1	Cerebrocostomandibular	48	1		
Monasterio 2002 [99]	RR	Mexico	2	iPRS	?	2		
Morovic 2000 [100]	Prospective	Chile	1	iPRS	8	1		
			1	Treacher Collins	18	1		
Olson 2011 [103]	RR	Wisconsin	2	sMicro		2		
Perlyn 2002 [105]	RR	St Louis	2	Treacher Collins	19	2		Delay in decannulation was due to distance from center, ENT consultation, parental resistance because of fear of death
			1	Nager	64	1		
Rachmiel 2012 [125]	RR	Israel	11	sMicro	33	11		
Schaefer 2004 [49]	RR	Wisconsin	1	iPRS	33	1		Tracheomalacia – needing reconstruction
Scott 2011 [108]	RR	Mineapolis	1	iPRS		1		
			1	sMicro			1	arthrogryposis patient failed decannulation
Sesenna 2012 [76]	RR	Italy	1	iPRS	5	1		
			1	Goldenhar	24	1		needed repeat MDO – no explanation given
Sidman 2001 [110]	Prospective	Mineapolis	3	iPRS	27.6	3	0	Needed repeat MDO because of inadequate osteotomy. Failure secondary to death from pulmonary bleed from a vascular malformation - unrelated to the operation or post-op recovery. Otherwise, advancement was adequate and endoscopic review showed good relief of tongue based obstruction
			4	sMicro	24	4		

Smith 2006 [111]	RR	California	1	iPRS	4	1		
Sorin 2004 [112]	RR	New York	1	sMicro	8	1		Additional procedures: Tonsillectomy, fundoplication, suprastomal granuloma excision. Syndrome: Stickler
			5	sMicro	25.6	5		Additional procedures: Tonsillectomy and adenoidectomy (4), suprastomal granuloma (3), Choanal atresia repair (3). Syndromes: Goldenhar (2), TCS, Unknown (2)
			4	sMicro	46.5	4		
			6	sMicro	42.2		6	Additional Procedures: Choanal atresia repair, tonsillectomy and adenoidectomy, suprastomal granuloma excision, cleft nose repair
Spring 2006 [113]	RR	Wisconsin	3	sMicro		3		Unsure which syndromes
Steinbacher 2005 [126]	RR	Boston	3	iPRS	31	3		Additional procedures: TLA, Tonsillectomy and adeniodectomy (2) Uvuloplasty
			1	sMicro	96	1		Additional procedure: Choanal atresia repair. Syndrome: CHARGE syndrome
			1	iPRS	168	1		Additional Procedure: Tonsillectomy and adenoidectomy
Tibesar 2010 [109]	RR	Mineapolis	11	Mixture		7	4	No explanation given for failures
Williams 1999 [127]	RR	New York	4	sMicro	32	3	1	Additional Procedures: Tonsillectomy and adenoidectomy (1), suprastomal granuloma excision (2). Syndromes: TCS (3), Nager (1)

Appendix IX: Feeding outcomes data extraction table

Article	Study Design	Country/Unit	number of patients	Syndrome	Pre-MDO feeding	PO feeds	Feeding adjuncts	Centile pre	Immediate	Centile Post	Other comments
Al-Samkari 2010 [71]	RR	St Louis	7	iPRS		6	1		Improved		1 needed NG tube for feeding
			5	sMicro		2	3		Improved		3 Gastrostomy tubes - 1 required a Nissen fundoplication (Trisomy 8 mosaicism). Tracheostomy in pt with Chromosome 4q deletion
Breugem 2012 [74]	RR	Netherlands	6	iPRS	6 (NG tube)	6	0				
			5	sMicro	5 (NG tube)	4	1				Needed NG tube
Brevi 2006 [75]	CR	Italy	2	iPRS		2	0				
Chigurupati 2004 [79]	RR	Australia	1	iPRS	1 NG tube	1	0				
			1	iPRS	1 NG tube	1	0				
			1	TCS	Gastrostomy	1	0				
			1	TCS	Gastrostomy	0	1				Needed persistent gastrostomy
			1	Tessier facial cleft	Gastrostomy	1	0				
Dauria 2008 [35]	RR	St Louis	1	iPRS+	TPN	0	1	11-25th		5-10th	Digital malformations
			1	iPRS+	Gastrostomy	0	1	11-25th		11-25th	Craniosynostosis, ambiguous genitalia, diaphragmatic hernia

			1	iPRS	Gastrostomy	0	1	11-25th		5-10th	3 adjuncts needed - gastrostomy
			1	iPRS	TPN	1	0	26-50th		51-75th	
Denny and Amm 2005 [81]	RR	Wisconsin	4	iPRS		4	0				
			7	sMicro		6	1			(10) - >50th centile	Feeding adjuncts - gastrostomy in 1 pt with Sticklers. Went to PO feeding by 1 year. 1 patient still not thriving - not due to airway obstruction – pt has velocardiofacial syndrome and severe cardiac malformations
										(1) - <3rd	
Genecov 2009 [82]	RR	Texas	67	Mixture		61	6				No details about feeding adjuncts needed
Griffiths 2013 [85]	CR	Melbourne	1	Skeletal Dysplasia	Haberman feeder	1	0	<3	9/12 - 10th	12 months 25th	Normal developmentally at 3.5 years
Hong 2012 [88]	RR	Nova Scotia Canada	2	iPRS	NG tubes	2	0				
			4	sMicro	NG tubes (3) ND tube(1)	4	0				All patients had no evidence of aspiration post-op either
Howlett 1999 [90]	CR	Florida	1	iPRS		1	0	25	3/52 - <5	8/52 - 25th	Drop in weight centile for first 5 weeks post-op due to impraired suck reflex. Improved after removal of distractors

Iatrou 2010 [124]	CR	Greece	1	iPRS	Gastrostomy	1	0	4.8kg at 8/12		13.5kg at 22/12	Pre-MDO tracheostomy in place
Izadi 2003 [91]	RR	Los Angeles	7	iPRS	NG tube	7	0				
			8	sMicro	NG tube	6	1				Failed pt was one with unknown syndrome and multiple co-morbidities including facial dysmorphology, degenerative encephalopathy, VSD, obstructive and central apnoea (underappreciated before operation)
Looby 2009 [95]	RR	Israel	12	iPRS	8 gastrostomy	12	0				
			5	sMicro	=	4	1				1 gastrostomy tube kept in place. 4 patients had evidence of aspiration pre-op. Average time to full PO feeding after MDO was 3.5 months
Miller 2007 [97]	RR	Stanford	7	iPRS	2 NG tube	7	0				2 patients could only feed with NG feeds, now PO feeding completely
			3	sMicro	3 NG tube	0	3				3 couldn't be weaned off NG feeds. 1 airway failure due to central apnoea.
Miloro 2010 [68]	RR	Chicago	35	Mixture	13 gastrostomy, 18 NG tube, 4 PO	35	0			Improved	These 3 pts had previous failed MDO - at redo was successful

Monasterio 2004 [32]	RR	Mexico	18	Mixture							Pre-op pH monitoring showed overall duration of pH episodes below 4 over 24 hrs was 7.7% compared with 0.3% after distraction osteogenesis (statistically significant)
											Also reported pre-op 66% barium penetration into laryngeal vestibule, 50% had stasis of residual material in the pharyngeal recess, 28% had pharyngeal transit >1 second, 5.5% bronchial aspiration. Post-MDO normal pharyngeal transit <1sec and no barium aspiration seen in any patient
Mudd 2012 [101]	RR	Colorado	25	Mixture		13	12	Just above 5	first 10/52 - 5	between 5-25	No airway failures, but 1 pt needed home O2 as he lived at a high altitude. Feeding adjuncts: 8 NG feeds. 4 gastrostomy tubes (2 placed prior to MDO, 1 for failure to thrive post MDO)
											After follow-up, only 2 needed G tubes, both syndromic with neurological deficits

											Initial growth decline until completed MDO and completed consolidation
Olson 2011 (103)	RR	Wisconsin	6	iPRS		6					
			8	sMicro		6	2				2 required gastrostomy tubes – developmental delays because of Smith-lemli-opitz, other needed because of severely impaired jaw motion and oral aversion – unknown syndrome
Scott 2011 (108)	RR	Boston	19	Mixture		13	6				13 on full PO feeding. 6 needed G tube feeding. By 3 yr follow-up, only 3 needed G tubes
Spring 2006 (113)	RR	Wisconsin	1	iPRS		1		Have individual centile charts			
			4	sMicro		1	3	Have individual centile charts			2 gastrostomy tubes, 1 NGT – all 3 patients eventually went to oral feeding. Also important to note that 1 pt had an endocrinopathy and the other had a heart anomaly – likely further contributing to the growth decline post-op

			5	sMicro		5		Have individual centile charts			Same 3 patients had evidence of aspiration on post-op videosfluoroscopic assessment which resolved within a year for most patients
Tibesar 2010 (109)	RR	Mineapolis	32	Mixture	17 (Gastrostomy) 15 (PO)	22	10				In the 10 still needing a gastrostomy tube,
Zenha 2012 (116)	CR	Portugal	1	iPRS	Orogastric tube	1					
			1	sMicro	PO	1					

Appendix X: Surgical outcomes extraction table

Article	Number of patients	Age at operation (months) mean	Condition	Distractor Type	Latency period (days)	Distraction rate (mm/day)	Times a day	Consolidation phase (weeks)	Failures
Ali Bukhari 2011 (118)	1	24	Micrognathia	Internal	3	1	Twice	8	
Ali Bukhari 2012 (119)	1	48	Micrognathia	Internal	3	1	Once	4	
Anderson 2004 (120)	1	72	Treacher Collins	External	5	1	Once	6	
Andrews 2013 (73)	73	1.5	Mixture	Mixture	1	2	Once	12	
Breugem 2012 (74)	12	1	Mixture	Internal - resorbable	2	2	Twice	4	1
Brevi 2006 (75)	2	20 days	iPRS	Internal	1	1	Once	5	
Burstein 2005 (77)	15	3	?	Internal	2	2	Once	4	
	5	5.5 years	?						
Carls 1998 (78)	1	48	iPRS	External	5	1	Twice	3	
	1	18	Amnion Band Syndrome	External	0	1	Twice	0	
	1	84	Treacher Collins	Internal	3	0.8	Twice	2	
	1	54	Goldenhar	Internal	4	0.8	Twice	1	
	1	54	Treacher Collins	Internal	0	0.8	Twice	2.5	
Chigurupati 2004 (79)	2	4	iPRS	Internal	0	1.5		6.5	

	3	23	sMicro	Internal	0	1.5		7	
Dauria 2008 [35]	4	0.9	iPRS	Internal - resorbable	1	1.5-2.0			
Denny and Amm 2005 [81]	11	20 days	Mixture	External	0	2		4	
Genecov 2009 [82]	33	16 months	Mixture	Internal	1-4 days	1		8	
	34			External	1-4 days	1		8	
Gifford 2008 [83]	4	1	Mixture	External - wire	3	1.5	Twice	4-6 weeks	1
	4	1		External - screw	3	1.5	Twice	4-6 weeks	
Griffiths 2013 [85]	1	5	Skeletal Dysplasia	Internal	0	1.5	Three	12	
Hammoudeh 2012 [86]	28	4.5	Mixture	Internal	1	1.5	Three	several	1
Handler 2009 [87]	1	4 days	Treacher Collins	Internal Curvilinear	<24 hours	2		16	
Hollier 2006 [130]	15		Mixture	External	<24 hours	2			
Hollier 1999 [122]	1	35	Micrognathia	External	5-7 days	1	Twice	6-8 weeks	
	1	39	Nager	External	5-7 days	1	Twice	6-8 weeks	
	3	42	Treacher Collins	External	5-7 days	1	Twice	6-8 weeks	
Hong 2012 [88]	5	2	iPRS	Internal	1	2		6-8 weeks	
	4	2.5	sMicro	Internal	1	2		6-8 weeks	
Howlett 1999 [90]	1	2	iPRS	Internal	3	1	Twice	5	
Iatrou 2010 [124]	1	8	iPRS	Internal	4	1		8	
Judge 1999 [92]	1	6 days	Klippel-Feil Syndrome	External	5	1	Twice	3	

Kolstad 2011 [93]	10	12 days	Mixture	External	1	2		4	1
	5	3.8 months	Mixture	External	1	1.6		4	1
	8	14 months	Mixture	External	1	1.9		6	
Lee 2009 [41]	2	5 months	iPRS	External	1	1-2mm	Twice	3-9 weeks	
	1	2.5 years	iPRS	External	1	1-2mm	Twice	3-9 weeks	
Looby 2009 [95]	12	105 days	iPRS	Internal Curvilinear	1	2		12	
	5		sMicro						
Miller 2007 [97]	10	3.5 months	Mixture	Internal Curvilinear	1	2	Twice	8-12 weeks	
Miloro 2010 [68]	35	3.5 months	Mixture	External	0	4	Twice	4	1
Mitsukawa 2007 [98]	2	8 months	Micrognathia +PRS	Internal				4 months	
	4	2.5 months	iPRS	Internal				4 months	
	2	1.5 years	iPRS	Internal				4 months	
	2	years	sMicro	Internal				4 months	
Monasterio 2002 [99]	15	3.2 years	iPRS	External	5	1		8-10 weeks	1
Morovic 2000 [100]	4	3 months	iPRS	External	3	1		4	
	1	5 months	sMicro	External	3	1		4	
	1	8 months	iPRS	External	3	1		6	
	1	18 months	sMicro	External	3	1		6	
Mudd 2012 [101]	25	30 days	Mixture	Internal	1-3 days	1.8	Twice	12	
Papoff 2013 [104]	9	24 days	Mixture	External	2	2	Twice	4	
Rachmiel 2012 [106]	22		Mixture	Mixture	4	1		10	

Sadakah 2009 [107]	1	7 months	iPRS	Internal	3	1	Twice	4	long-term (1)
	2	20 months	iPRS	Internal	3	1	Twice	4	
	4	5.9 years	iPRS	Internal	3	1	Twice	4	
Scott 2011 [108]	14	4.8 days	iPRS					4-8 weeks	
	5		sMicro					4-8 weeks	
Sesenna 2012 [76]	9	2.3 months	iPRS	Mixture	0	2		8	
	1	2 years	Goldenhar	External	0	2		8	1
Sidman 2001 [110]	1	8 months	iPRS	External	3-5 days	1.5	Twice	4-8 weeks	
	1	11 months	Down Syndrome	External	3-5 days	1.5	Twice	4-8 weeks	
	2	31 months	iPRS	External	3-5 days	1.5	Twice	4-8 weeks	1
	3	28 months	sMicro	External	3-5 days	1.5	Twice	4-8 weeks	
Spring 2006 [113]	10	32.68 months	Mixture	Internal	1	1-1.5	Twice	6	
Steinbacher 2005 [126]	3	2.6 years	iPRS	Internal	2	1		8 weeks	
	1	8 years	sMicro	Internal	3	1		8 weeks	
	1	14 years	iPRS	Internal	3	1		8 weeks	
Taub 2012 [114]	1	15 days	sMicro	Internal	1	2	Three		
Tibesar 2010 [109]	32	10.4 months	Mixture	External	2	1.5	Twice	6 weeks	4
Williams 1999 [127]	4	2.7 years	sMicro	External	5	1	Twice	8 weeks	
Zenha 2012 [116]	1	9 days	iPRS	Internal	1	1.8		6 weels	
	1	11 days	sMicro	Internal	1	2		12 weeks	

Appendix XI: Surgical complications data extraction table

Article	No. of patients	Scarring	Infection	Facial nerve	Dental injuries	TMJ ankylosis	Premature osseous fusion	Technical failure	Other complications	Comments
Andrews 2013 #[73]	73	6	4	0	4	7 (all syndromic)				2 tracheostomy (1 central apnoea, 2 displaced ETT during operation). Wound infections managed by oral antibiotics, Dental injuries included: accidental tooth bud loss, wide gap between molars
Breugem 2012 [74]	12		3					2 (incomplete osteotomy, failed screw 5 weeks)		Initially failed decannulation until 7 months
Burstein 2005 [77]	15		3							2 failed decannulation. Wound infections managed with antibiotics
	5									
Genecov 2009 [82]	33		3	3?				2		
	34		6	3?				7		
Hammoudeh 2012 [86]	28		1	1				1	Exposure of distractor	Replacement for unilateral failed distractor. Exposure of distractor. Facial nerve – recovered in 1 week
Hollier 2006 [130]	15		2				1			Non-union – grafted patient. Infection patients recovered with oral antibiotics
Hong 2012 [88]	5				0					
	4		2		3					Dental injuries: Minor positional changes x2, Minor root malformations and shape deformity x 2 – all still

										erupted normally
Judge 1999 (92)	1	1							Excessive upper airway secretions	
Kolstad 2011 (93)	10	1	2	1	0	0	0	2		Repeat MDO - no detail. Pin mobility
	5	1	2	1	0	0	0	0		Repeat MDO - no detail
	8	1		0	0	0	0	0		
Looby 2009 (95)	12		1	1						facial nerve resolved within 2/12. Wound infection resolved with antibiotics and early removal of distractor - didn't affect outcome
	5									
Miller 2007 (97)	10			1						Facial nerve recovered within 2 months
Miloro 2010 (68)	35	7		0	0	0	1	Device not long enough (1), pin exposure (2)	Anterior open bite (18)	Re-fracture (1) – premature consolidation. All open bites resolved within 3 months, one case of premature ossification - at a rate of <3mm
Mudd 2012 (101)	25		6	2						Incision and drainage for abscess. 1 marginal Md branch – temp, 2 complete facial nerve palsy from compression of posteriorly placed distraction arm, partially recovered function
Papoff 2013 (104)	9				0			4		Pin lost needing repositioning - in consolidation phase.
Spring 2006 (113)	10	1		2					3 had limited mandibular range of movement	Both transient facial nerve weakness

Tibesar 2010 (109)	32	3		3	4				9 had residual open bites (5 of these had congenitally missing condyles for which they had reconstruction prior to MDO). 2 others had pre-existing open bites - oculo-auricular-vertebral spectrum and arthrogryposis	4 needed re-MDO. No details given about why needed repeat MDO and if they were successful. Dental: tooth loss, malformation, or dentigerous cyst formation. Facial nerve - long-term injury. 3 had hypertrophic scarring