Robin Sequence and Mandibular Distraction Osteogenesis: Variations in Craniofacial Morphology and Tooth Development

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Abstract

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Mandibular distraction osteogenesis (MDO) is a treatment option for infants with Robin Sequence (RS) who have severe upper airway obstruction. While this procedure is successful in eliminating airway distress, it can cause changes in craniofacial morphology and tooth development in the growing patient. This study examines the effect of mandibular distraction osteogenesis on craniofacial morphology and tooth development in patients with RS at pre-operative, intra-operative, and mixed dentition timepoints as compared to patients without craniofacial conditions and to patients with RS not treated with MDO.

Fourteen infant patients with RS undergoing MDO from Seattle Children's Hospital met the study inclusion criteria. Pre-operatively at T1, the MDO treatment group was compared to 37 infants without craniofacial conditions. Following MDO at T2, intra-operative and post-operative data was collected from the MDO treatment group. At the mixed dentition follow-up (T3), the MDO treatment group (13 patients) was compared to 19 patients with RS who did not undergo MDO. Data from both groups of patients with RS was compared to norms established by the Michigan Growth Sample. Selected cephalometric linear and angular measurements were assessed at each timepoint and tooth development was evaluated from a panoramic radiograph using a tooth assessment grading scale.

Before surgery, the patients with RS planned for MDO had significantly more obtuse gonial angles and shorter mandibular body lengths. Changes occurring secondary to MDO in patients with RS were increased mandibular body length, a less obtuse gonial angle, and forward rotation of the mandible.

At the mixed dentition timepoint, patients with RS who had MDO had a significantly more obtuse gonial angles (152.5°, p= 0.006) and steeper mandibular plane angles (51.9°, p= 0.0033) than patients with RS who did not have MDO. The RS-affected groups more similarly resembled one another as compared to the normal control, and they demonstrated significant measures of vertical growth.

In the mixed dentition, 30% of RS with MDO patients had one or more teeth with abnormal development as compared to no tooth abnormalities in patients with RS without MDO (p= 0.020). There was no difference in frequency of missing teeth between the groups. There was a low rate of complications associated with MDO in this study, and all patients completed the prescribed course of distraction. No patient with RS required tracheostomy between birth and the time of evaluation in the mixed dentition.

Table of Contents

List of Tables

List of Figures

SPECIFIC AIMS

INTRODUCTION AND STATEMENT OF THE PROBLEM

Robin Sequence (RS) is a congenital condition characterized by mandibular micrognathia, glossoptosis, and potential upper airway obstruction. Posterior displacement of the tongue secondary to a small mandible results in variable degrees of airway obstruction in infants with RS (Dulfer et al., 2006). Non-surgical treatment options are always preferred as a first line of treatment for infants requiring airway support (Lander and Scott, 2015). For those infants with severe base of tongue airway obstruction unable to be stabilized with non-surgical treatments, mandibular distraction osteogenesis (MDO) has evolved into a treatment of choice as it results in less morbidity and mortality than tracheostomy (Lander and Scott, 2015; Resnick, 2018).

When distraction osteogenesis is used to manage airway obstruction in the setting of mandible hypoplasia, an osteotomy is performed through the posterior mandible. Fixed distractors are incrementally activated to move the bone segments apart, allowing osteogenesis to occur along the surgical site. When the anterior-posterior mandible deficiency is corrected by MDO, the tongue attachment to the geniotubercle also moves anteriorly, increasing the airway space behind the tongue and ideally removing the underlying cause of the airway obstruction (Flores, 2014).

Although MDO can be effective in eliminating airway obstruction in 91.3% of infants and obstructive sleep apnea in 97% of children (Ow and Cheung, 2008), more data is needed to fully understand its long-term consequences. Due to the osteotomy location, there can be disruptions of the developing dentition and the mandible morphology (Resnick, 2018; Susarla et al., 2018).

Current literature surrounding this topic is limited by small sample sizes. This study of patients with RS treated with MDO in early life will examine craniofacial morphology at three timepoints: prior to MDO, directly following MDO, and several years post-MDO in the mixed dentition. The patients with RS with MDO will be compared to patients with RS who did not have MDO and to a non-RS reference population. Dental development will be examined in the mixed dentition and compared to patients with RS who did not have MDO.

LIST OF SPECIFIC AIMS

In a sample of patients with Robin Sequence (RS) treated with mandibular distraction osteogenesis (MDO) in infancy:

Aim #1: Examine craniofacial morphology using cephalometric measurements. At the pre-operative timepoint, compare to non-RS infant controls. At the post-operative timepoint, document changes in values between pre- and post-operative images. In the mixed dentition, compare findings to individuals with RS without MDO and to a non-RS reference population.

Aim #2: Assess abnormalities in tooth development following MDO at the mixed dentition timepoint and compare findings to individuals with RS without MDO.

Aim #3: Investigate pre-operative (e.g. age at distraction, BMI at distraction), intra-operative (e.g. estimated blood loss, surgery time), or immediately post-operative factors (e.g. mechanical complication of distractor, failure of distractor, total amount of distraction) that may be associated with changes in craniofacial morphology or tooth development.

BACKGROUND AND SIGNIFICANCE

BACKGROUND, REVIEW OF THE LITERATURE, AND SIGNIFICANCE OF THE PROBLEM

Definition and Prevalence of Robin Sequence

Robin Sequence (RS) is a congenital condition characterized by the triad of mandibular micrognathia, glossoptosis, and ensuing airway obstruction. Evans et al. described a sequence as "a collection of abnormalities that result from previous developmental anomalies or mechanical processes" (Evans et al., 2011). The presentation of RS can vary and the pathogenesis is unclear in many patients. A retrospective cohort study of 191 patients with RS found that a clear etiology could be determined in only 59.7% of patients with RS and of those, pathogenesis was attributed to chromosomal anomaly, Mendelian disorder, connective tissue dysplasia, neuromuscular disorder, or multi-system disorder (Basart et al., 2015). RS is often associated with the presence of a cleft palate, but this feature is not essential for diagnosis (de Smalen et al., 2017). RS can be diagnosed on its own (isolated) or in conjunction with other syndromes and chromosomal anomalies, including Stickler syndrome, Treacher Collins syndrome, and Nager syndrome (de Smalen et al., 2017; Evans et al., 2006).

The prevalence of RS has been estimated to occur in the range of 1 in 5,600 to 30,000 births (Dulfer et al., 2006). Other sources have estimated RS to occur in 1 in 8,500 to 20,000 births (Bush and Williams, 1983; Printzlau and Andersen, 2004). The Dutch birth prevalence of RS was recently estimated to be 1 in 5,600 live births with a slight female predominance. A literature search of 42 studies reporting the birth prevalence for RS, varied between 1:3,900 and 1:122,400 (0.8-32.0 per 100,000), with a mean prevalence of 1:24,500 (8.0 per 100,000) (Paes et al., 2015).

Management of Airway Compromise in Patients with Robin Sequence

Management of airway obstruction in infants with RS is often needed, as failure to treat can result in morbidities including failure to thrive, cyanosis, cerebral hypoxia, and death (Dulfer et al., 2006). A range of non-surgical (prone positioning, nasopharyngeal intubation, positive airway pressure) and surgical managements (tongue-lip adhesion, tracheostomy, mandibular distraction osteogenesis (MDO) have been used to treat airway problems in infants with RS. A retrospective study of 139 patients with RS found that MDO was the treatment of choice by practitioners for 5% of patients (Kam et al., 2015). MDO alleviates upper airway obstruction by increasing the length of the mandible and moving the bony attachment of the tongue forward (Hong et al., 2012). MDO can allow some patients to avoid tracheostomy. A recent systematic review found that primary MDO for the relief of upper airway obstruction was found to be successful at preventing tracheostomy in 95% of cases (Breik, et al., 2016).

Craniofacial Morphology and Dental Development in Patients with Robin Sequence

Craniofacial growth of patients with RS has been described in many prior studies. A cephalometric study of patients with RS (26 isolated, 25 syndromic) compared to a reference population found mandibular morphology and position highly variable. Syndromic patients had significantly shorter ramus length, mandibular length, and more obtuse gonial angles (Rogers et al., 2009). Cephalometric measurements of 34 non-syndromic patients with RS were compared to unaffected matched controls prior to and after orthodontic treatment. Significant differences in patients with RS included smaller cranial base length, shorter maxilla and mandible lengths, increased mandibular plane angulation, and more open mandibular flexure. With growth, the maxilla and mandible remained retrusive and differences in mandibular morphology persisted (Suri et al., 2010). In a study of 61 patients with RS at age 8-9 years, the mean mandibular plane angle of patients with RS was 9.4 degrees greater and posterior facial height 3 mm shorter than normal controls (Wang, 2012).

The reported incidence of tooth agenesis in the general population is 3- 8% and the most commonly missing permanent teeth are third molars, mandibular second premolars, and maxillary lateral incisors (de Smalen et al., 2017). A meta-analysis of 339 patients with isolated RS found an estimated prevalence rate of permanent tooth agenesis was 42% (third molars not included). Mandibular second premolars (26%), and maxillary second premolars (14%) were most commonly missing. Bilateral absence of mandibular second premolars occurred at a rate of 20% in those patients with RS who had tooth agenesis (Antonarakis et al., 2017).

Craniofacial Morphology Following Mandibular Distraction Osteogenesis

MDO is a surgical modality that changes in craniofacial morphology, even in the absence of RS. A 2016 systemic review of eight articles describing patients not diagnosed with RS treated with MDO at ages 7.7 to 29.8 years, reported significant increases in mandibular plane angle, total anterior facial height, and lower anterior facial height following MDO (Rossini et al., 2016).

Ten patients with RS receiving MDO during infancy were described at age 6.8 years and compared to a control group of 10 patients with RS without MDO. Significant differences in the RS with MDO group were: shorter mandibular length, smaller mandibular body, more obtuse gonial angle, more vertically directed growth, longer anterior facial height, and shorter posterior facial height (S-Go). The SNA was similar between the RS groups, but both RS groups had significantly smaller SNA and SNB measurements than normally developing patients (Paes et al., 2016).

In a sample of 17 infants with RS treated with MDO, significant increases were reported in ramus length, gonial angle, mandibular oblique length, and mandibular sagittal length at

8.46 ± 5.99 months after MDO. Distraction resulted in mandibular morphology more similar to age matched non-RS infants and their mandibles were significantly different from non-MDO RS mandibles anterior to the gonial angle. This study did not account for long-term relapse or changes due to growth (Susarla et al., 2018).

A retrospective cohort study of 25 patients with RS treated with MDO found increases in mandibular body length, SNB, and mandibular unit length immediately following MDO, but only two patients (8%) "regained a growth rate in the vector of DO that matched or exceeded normal age- and gender-matched controls" (Peacock et al., 2018). Patients with RS treated with MDO experience significant vertical growth of the mandible.

Effects of Mandibular Distraction Osteogenesis on the Developing Dentition

A potential complication of MDO is disruption of tooth development. The buds of the developing teeth are in close proximity to the bilateral sagittal split osteotomy site and to the location of bone screws anchoring the distractors. During infancy, permanent molar tooth buds occupy a large proportion of the total mandible volume and approximate the inferior mandibular border (Paes et al., 2016).

When preparing for MDO, careful surgical planning is essential to minimize damage to developing tooth buds and the mandibular canal (Rachmiel et al., 2014). In 10 patients with RS treated with MDO in infancy, 8 missing premolars or permanent molars were found in 5 out of 10 patients at five years or longer post-distraction (Paes 2016). A five-year post-MDO follow up of 44 patients with RS found injury to the first permanent molar in 48% of half-mouths with 76% being restorable. Damage or ankylosis of the primary second molar occurred in 14% of the half-mouths with the succeeding second premolars unilaterally absent (22%) or bilaterally absent (17%) (Steinberg et al., 2016). Adverse effects on the teeth proximal to the site of distraction were reported in 40 out of 52 teeth (81%) in a study of 26 patients with RS treated with MDO (Peacock et al., 2018).

The use of internal distractors with inverted L-shaped osteotomy seems to improve dental outcomes. In a retrospective study of 10 children with RS who had MDO using this technique, only 3 patients developed minor dental problems requiring no intervention in 4 primary molars (Hong, et al., 2012).

Summary

Literature indicates that there may be unfavorable changes in craniofacial morphology and tooth development following mandibular distraction osteogenesis in infants with Robin Sequence. These changes may result in functional deficits and/or unfavorable esthetics that require orthodontic treatment, exodontia, and osseous and/or dental implant reconstruction (Peacock et al., 2018). This topic is pertinent in that by improving a horizontal deficiency of the mandible early in life, altered growth patterns and developmental dental anomalies can persist which may limit or complicate subsequent treatment. Additional research will contribute to improved understanding of long-term craniofacial outcomes and management of patients with Robin Sequence who were treated with mandibular distraction osteogenesis.

PURPOSE OF THE STUDY

The purpose of this study is to investigate craniofacial morphology and tooth development in patients with Robin Sequence (RS) who were treated with mandibular distraction osteogenesis (MDO) in early life and compare findings to 1) patients without craniofacial conditions at infant and mixed dentition stages and 2) patients with RS not treated with MDO at the mixed dentition stage.

RESEARCH DESIGN AND METHODS

RESEARCH QUESTIONS AND HYPOTHESES

The specific aims will be answered through the following questions:

Question #1: Do infants with Robin Sequence (RS) treated with mandibular distraction osteogenesis (MDO) experience changes in vertical and anterior/posterior growth as compared to patients with RS who have not undergone MDO and to patients without craniofacial conditions at the mixed dentition timepoint?

Null Hypothesis #1: Infants with RS treated with MDO will have no difference in vertical and anterior/posterior growth when compared to patients with RS not treated with MDO or to patients without craniofacial conditions at the mixed dentition timepoint.

Anticipated Vertical Findings: Infants with RS treated with MDO will have significantly more vertical growth than comparison groups at the mixed dentition timepoint.

Anticipated Anterior/Posterior Findings: Both infants with RS treated with MDO and patients with RS not treated with MDO will have significant A/P discrepancy compared to patients without craniofacial conditions at the mixed dentition timepoint.

Question #2: Do patients with RS treated with MDO in infancy have a higher frequency of missing or abnormally developing mandibular posterior teeth as compared to patients with RS not treated with MDO, and if so, which posterior teeth are most often affected at the mixed dentition timepoint?

Null Hypothesis #2: At the mixed dentition timepoint, patients with RS treated with MDO in infancy will have no difference in frequency of missing mandibular posterior teeth than patients with RS not treated with MDO.

Anticipated Findings for Frequency of Missing Teeth: At the mixed dentition timepoint, patients with RS treated with MDO in infancy will have significantly more missing mandibular posterior teeth than patients with RS not treated with MDO.

Anticipated Findings for Affected Teeth: At the mixed dentition timepoint, patients with RS treated with MDO in infancy will have significantly more abnormally developing mandibular second primary molars, second premolars, and first molars than patients with RS not treated with MDO.

Question #3: Are any pre-operative, intra-operative, or immediately post-operative factors associated with changes in craniofacial morphology or tooth development in infants with RS treated with MDO?

- Pre-operative factors: age at distraction, BMI at distraction, presence of co-occurring craniofacial/dental condition
- Intra-operative factors: complications during surgery, surgery time, estimated blood loss
- Immediately post-operative factors: mechanical complication of distractor, failure of distractor, lack of compliance, days of distraction, total amount of distraction (mm)

Null Hypothesis #3: There is no association of pre-operative, intra-operative, or immediate post-operative factors with changes in craniofacial morphology or tooth development.

Anticipated Findings: Significant factors which hinder or disrupt the prescribed course of MDO may adversely affect craniofacial morphology (eg: shorter mandibular length) or tooth development (eg: infection-related tooth agenesis).

RESEARCH DESIGN

This retrospective cohort study used data collected from Seattle Children's Hospital (SCH) from 2005 to 2020. Radiographs, computed tomography (CT), and medical records for patients with Robin Sequence (RS) undergoing mandibular distraction osteogenesis (MDO) were evaluated and compared to 1) patients without craniofacial conditions and 2) patients with RS who were not treated with MDO. Evaluation was done at three timepoints: infancy pre-distraction (T1), immediately post-distraction (T2), and at the mixed dentition follow-up (approximately six years later, T3).

Craniofacial morphology was assessed via measurements of lateral cephalograms. Linear and angular measurements commonly used in orthodontic diagnosis were selected in order to assess both anterior-posterior and vertical growth. Tooth development was evaluated using a tooth assessment grading scale on a panoramic image at the mixed dentition timepoint (T3). Pre-operative, intra-operative, and immediately post-operative factors were obtained from the medical records to assess their influence on overall surgical outcome.

METHODS

Sample

All patient records were obtained from Seattle Children's Hospital (SCH) in Seattle, Washington. The sample of patients with Robin Sequence (RS) undergoing mandibular distraction osteogenesis (MDO) included 14 patients treated from 2005 to the present. All patients with RS treated with MDO at SCH with partial or complete records were included. The study was limited to patients treated at SCH for reliable access to medical records, imaging, and consistency of surgical technique. These patients were age matched (and gender matched when possible) to a control group of patients unaffected by craniofacial conditions from SCH for T1 and to the Michigan Growth Sample at T3. The control group of patients without craniofacial conditions at T1 were infants that had head CT imaging for various reasons including trauma, tumors, or airway lesions unrelated to RS (Lee et al, 2016). The study hospital is compiling a collection of infant head CT imaging to use as a research reference sample. Thirty-seven control patients were selected to age approximate the infants with RS planned for MDO. At the mixed dentition T3 timepoint, we identified a comparison group of 19 patients with RS not treated with MDO. This comparison group was not age and gender matched to the RS with MDO group and primarily consisted of less severely affected patients with RS.

Eligibility for the study included partial or complete records pre-distraction, immediately post-distraction, and at the mixed dentition follow-up approximately 6 years later. Subjects having only partial records were included due to the small number of patients with RS having undergone MDO (Table 1).

TABLE 1. Description of Patient Sample

Timepoint	Number of Patients
T1	RS with MDO: 14
	Normal Control: 37
T2	RS with MDO: 12
T3	RS with MDO: 13 (1 patient did not return for records)
	RS without MDO: 19
	Normal Control (Michigan Growth Sample)

Inclusion criteria for cases:

- Diagnosis of Robin Sequence (isolated or with syndrome, for MDO and without MDO groups)
- Partial or complete pre-distraction records: medical history, head/face Computed Tomography (CT)
- Partial or complete immediate post-distraction records: medical history, head/face CT
- Partial or complete mixed dentition records: medical history, dental history, panoramic radiograph, lateral cephalogram
- Treatment provided at Seattle Children's Hospital

Exclusion criteria for cases:

- Patients not treated at Seattle Children's Hospital
- Patients with no imaging available

Inclusion criteria for T1 controls:

- Adequate head CT imaging to assess maxillofacial structures
- Age matched to original cohort

Exclusion criteria for T1 controls:

- Craniofacial diagnosis

Apparatus and Procedures

Infants exhibiting signs of respiratory distress due to severe mandibular retrognathia were identified soon after birth. The tongue-based airway obstruction algorithm was followed and surgical intervention of mandibular distraction osteogenesis (MDO) was recommended based upon clinical protocols if medical management did not yield airway stabilization. Infants planned for MDO received pre-operative head/face computed tomography (CT). From this CT, a lateral cephalogram was constructed. Following osteotomy and placement of fixed distractors, the mandible was distracted until an acceptable bony position was achieved (a typical activation phase is 2-3 weeks). The mandibles were advanced until approximately 2 mm of negative overjet was achieved. Approximately 2 months later at the completion of the consolidation phase, patients would again have a CT from which a lateral cephalogram was constructed. At the mixed dentition follow-up approximately 6 years later, a lateral cephalogram and panoramic radiograph were taken. Measurements and data were taken from each set of radiographs and compared to patients with RS who did not undergo MDO and to control patients.

Data extracted from medical records at the initial timepoint included: age, height, weight, and presence of co-occurring craniofacial/dental condition. Intra-operative data included: complications during surgery, surgery time, and estimated blood loss. Immediate post-distraction data included: mechanical complication of distractor, failure of distractor, lack of compliance, days of distraction, and total amount of distraction (mm).

Data and Analysis

All patient records and radiographic images from Seattle Children's Hospital were imported into Dolphin ImagingPlus™ software for evaluation. Landmarks were identified on the lateral cephalogram by a single examiner trained in landmark identification. The measurements used at all timepoints are defined in Tables 2-4:

TABLE 2. T1 Cephalometric Measurements

Initial (or in treatment group, pre-distraction):

Name of Measurement	Definition	Type of Measurement
Gonial Angle	Intersection of the ramus and mandibular plane using Constructed Gonion	Angular
Ramus Height	Linear distance from Condylion to Gonion	Millimetric/Linear
Mandibular Body Length	Linear distance from Gonion to Pogonion	Millimetric/Linear
Ratio of Ramus Height to Mandibular Body Length	Length of Ramus Height divided by Mandibular Body Length	Percentage/Ratio

TABLE 3. T2 Cephalometric Measurements

Post-distraction:

Name of Measurement	Definition	Type of Measurement
Gonial Angle	Intersection of the ramus and mandibular plane using Constructed Gonion	Angular
Ramus Height	Linear distance from Condylion to Gonion	Millimetric/Linear
Mandibular Body Length	Linear distance from Gonion to Pogonion	Millimetric/Linear
Ratio of Ramus Height to Mandibular Body Length	Length of Ramus Height divided by Mandibular Body Length	Percentage/Ratio

TABLE 4. T3 Cephalometric Measurements

Mixed dentition:

Name of Measurement	Definition	Type of Measurement
Gonial Angle	Intersection of the ramus and mandibular plane using Constructed Gonion	Angular

MP-SN	Intersection of the mandibular plane and Sella-Nasion	Angular
Y-SN	Intersection of the Y-axis (Sella-Gnathion) and Sella-Nasion	Angular
Lower Facial Height as a Percentage of Total Facial Height	Length of ANS to Menton divided by length of Nasion to Menton	Percentage/Ratio
Ramus Height	Linear distance from Condylion to Gonion	Millimetric/Linear
Mandibular Body Length	Linear distance from Gonion to Pogonion	Millimetric/Linear
Ratio of Ramus Height to Mandibular Body Length	Length of Ramus Height divided by Mandibular Body Length	Percentage/Ratio
SNA	Intersection of Sella-Nasion and Nasion-A Point	Angular
SNB	Intersection of Sella-Nasion and Nasion-B Point	Angular
ANB	Intersection of A Point-Nasion and Nasion-B Point	Angular
Posterior Mandibular Height	Distance from the occlusal table of the mandibular first permanent molar to the mandibular body	Millimetric/Linear
Anterior Mandibular Height	Distance from the tip of the lower incisor (L1) to Menton	Millimetric/Linear
Ratio of Posterior Mandibular Height to Anterior Mandibular Height	Posterior mandibular height divided by anterior mandibular height	Percentage/Ratio

The mandibular posterior and anterior height measures were used to assess the relative vertical growth of the anterior versus posterior mandible following MDO, and to quantify clinical observations that first molar root apices approached the mandibular border following MDO.

Development of mandibular second primary molars, mandibular second premolars, and mandibular first permanent molars were evaluated on the mixed dentition (T3) panoramic radiograph by a single calibrated examiner using a tooth assessment grading scale. Maxillary tooth development served as a control for distinguishing tooth development patterns innate to the patient versus abnormalities acquired secondary to MDO.

TABLE 5. Tooth Assessment Grading Scale

Status of Tooth	Definition	Value Assigned
Missing	Tooth is not visible in any available imaging (at any time point) characteristic of agenesis	1
Abnormal Development	Tooth is developing abnormally (either in crown/root morphology and position) in conjunction with patient's age and development	2
Missing due to Caries/Dental Disease/Extraction	Tooth is visible in imaging at an early time point, but has been extracted	3

Intra-examiner reliability was assessed by re-tracing 5 sets of patient records. Cephalometric and panoramic measurements were repeated on 5 patients including 3 RS with MDO and 2 RS without MDO. The intraclass correlation coefficient (ICC) was used to summarize the relative reliability of the cephalometric measures. The reliability was excellent for all measurements (ICC > 0.75) except mandibular body length (ICC= 0.34) and RH/MBL (ICC= 0.32). In the randomly selected individuals, there was little variation in these measures which could explain the poor ICC agreement. The Dahlberg's error, a measure of the absolute measurement error, was also computed and was small for all measures. For example, the measurement error for mandibular body length was ±2.72 mm or ±3.2% around the sample average and the measurement error for RH/BML ±0.03 or ±4.0% around the sample average. There was no evidence of a systematic difference between the first set and second set of measurements. For the panoramic data, there was perfect agreement (100%). The kappa coefficient was used to measure the reliability of categorical variables and was found to be 1.

Statistical methods of comparison between RS with MDO patients and control patients at T1 were: the proportion of females to males using the chi-square test; average height, weight, and BMI using the two-sample t-test; and median age using the Wilcoxon rank sum test. The average gonial angle, ramus height (RH), mandibular body length (MBL), and RH/MBL ratio were compared between the two patient groups using a two-sample t-test and linear regression, which adjusted for patient age, sex, and BMI. Ninety-five percent confidence intervals for the unadjusted and adjusted difference between the groups' means were computed.

The gonial angle, ramus height (RH), mandibular body length (MBL), and RH/MBL ratio were compared between T1 and T2 for the RS with MDO patients using the mean (SD) at T1 and T2, the mean (SD) and 95% confidence interval for the mean change, and the paired t-test. Similar comparisons were done for the RS with MDO patients between T2 and T3.

Statistical methods for comparing RS with MDO patients and RS without MDO patients at T3 were: the proportion of females to males using the chi-square test; average age, height, weight, and BMI using the two-sample t-test; cephalometric measurements using a two-sample t-test and with linear regression, which adjusted for patient age, sex, and BMI. Ninety-five percent confidence intervals for the unadjusted and adjusted difference between the groups' means were also computed. The ninety-five percent confidence intervals were used to compare the RS with MDO patients to the normative values from the Michigan Growth Sample. A 95% confidence interval that does not include the normative value for a cephalometric measurement indicates a significant difference at two-sided 0.05 significance level. The data was analyzed in this way so as to not compare two sample groups to a single value.

At T3, data was collected from panoramic images in the RS without MDO and RS with MDO groups. Maxillary and mandibular teeth were graded on a scale with the patient's maxillary teeth serving as the control. Due to the small sample size, the options for statistical testing were limited. To compare the two groups, the percentage of the subjects with any missing teeth (value=1), any abnormalities (value=2), and any missing due to caries/dental diseases/extraction (value=3) were compared. Comparisons were done separately for mandibular and maxillary teeth, and the Fisher's exact test was used to compare percentages between the two groups. All statistical analyses were done using R statistical software.

RESULTS

T1

The mandibular distraction osteogenesis (MDO) treatment group at T1 included 14 patients with Robin Sequence (RS). The control group at T1 consisted of 37 comparison control patients who had received head CT imaging for a reason unrelated to RS. Patient demographics at T1 are displayed in Table 6:

TABLE 6. T1 Demographics for Control Patients and Patients with RS Planned for MDO

Sex	**Group**	**N**	**Female N (%)**	**Male N (%)**	**P-value***
	Control	37	23 (62.2%)	14 (37.8%)	0.7444
	MDO	14	10 (71.4%)	4 (28.6%)	
Age at CT months	**Group**	**N**	**Median (IQR)**	**P-value***	**Difference (95% CI)****
	Control	37	2.8 (1.1, 18.4)	0.1482	1.7 (-3.9, 11.9)
	MDO	14	1.1 (0.4, 10.9)		
Height at CT cm	**Group**	**N**	**Mean (SD)**	**P-value**	**Difference (95% CI)**
	Control	31	68.4 (19.0)	0.1812	7.3 (-3.6, 18.3)
	MDO	14	61.0 (15.5)		
Weight at CT kg	**Group**	**N**	**Mean (SD)**	**P-value**	**Difference (95% CI)**
	Control	31	8.1 (4.9)	0.1051	2.3 (-0.5, 5.0)
	MDO	14	5.8 (3.9)		
BMI at CT	**Group**	**N**	**Mean (SD)**	**P-value**	**Difference (95% CI)**
	Control	31	15.6 (2.1)	0.0186	1.5 (0.3, 2.8)
	MDO	14	14.1 (1.8)		

Mean values were used to describe all findings excluding age at CT imaging. One patient received his initial CT scan several years after birth, which greatly affected the mean. The median value for age at CT more accurately represents the sample.

More female than male patients were included in the study. The control group was slightly older than the treatment group, this difference was not statistically significant. Height, weight, and BMI data were unavailable for 6 control patients. BMI was significantly lower in the patients with RS at T1 (p= 0.0186).

The median age for initial imaging at T1 was 1.1 months. Significant differences in cephalometric measurements at T1 between patients with RS and controls were increased gonial angle (p=0.044) and decreased mandibular body length (p= 0.0013). Although ramus height was decreased in the RS group, the ratio between ramus height and mandibular body length was not significantly different from the control group. The mandible in the patients with RS was deficient in height and length, but proportionally so (Table 7).

TABLE 7. T1 Initial Cephalometric Values for Control Patients and Patients with RS Planned for MDO

	Control	**MDO**	**Control versus MDO**			
	N= 37 Mean (SD)	N = 14 Mean (SD)	Difference (95% CI)	P-value	Adjusted difference* (95% CI)	P-value*
Gonial Angle	136.6 (7.3)°	144.6 (9.6)°	-8.0 (-13.9, -2.1)°	0.011	-6.1 (-12.1, -0.2)°	0.044
Ramus Height	26.0 (8.7) mm	20.8 (7.8) mm	5.2 (0.0, 10.4) mm	0.0488	2.2 (-0.4, 4.9) mm	0.0989
Mandibular Body Length	40.6 (7.9) mm	31.5 (8.6) mm	9.1 (3.6, 14.6) mm	0.0025	5.3 (2.2, 8.5) mm	0.0013
RH/MBL	0.63 (0.12)	0.66 (0.16)	-0.03 (-0.13, 0.07)	0.5324	-0.05 (-0.15, 0.05)	0.2749

T2

Twelve patients with RS treated with MDO had both imaging and surgical data available at the T2 timepoint. The majority of patients (58.3%) had a co-occurring condition with cleft palate (57.1%), Stickler syndrome (21.4%), and obstructive sleep apnea (21.4%) most often present. The median patient age at distraction was 1.5 months. The distractors were in place for 76.0 days with T2 CT imaging performed 86.0 days after the initial surgery date. The median value was used to assess any data pertaining to dates/time as the sample was highly variable and the median was more representative of this data.

No patient had intraoperative complications during MDO surgery. Blood loss was minimal, estimated at 10mL (median value). Mean surgery time was 159.1 minutes (SD= 46.8). Post-operative complications were infrequent. Three patients had mechanical issues with the distractor (25%). One distractor failed and was replaced in a second operation. One patient had a second operation because the osteotomy on one side did not open. Other complications included backward auto-rotation of the distractor arms and a stuck ratchet. Two patients had post-operative methicillin resistant staphylococcus aureus superficial infections which resolved without early removal of hardware.

Distractors were activated to achieve a target of 2mm of negative overjet between the maxillary and mandibular anterior alveolar processes. The mean mandibular advancement during MDO was 22.0 mm (SD= 2.7). The amount of distraction recorded in patient records was more than measured on the cephalograms due to limitations of using a two-dimensional measurement to assess a curvilinear trajectory.

Differences between the T1 and T2 imaging can be attributed both to growth and the effects of MDO. Significant increases were recorded in mandibular body length (14.0 mm, p= <0.0001) and ramus height (4.5mm, p= 0.0026). Gonial angle changes were variable and not significant. Although statistically significant, the small change in ratio of ramus height to mandibular body length (-0.07) is not clinically significant (Table 8).

TABLE 8. Cephalometric Changes Between T1 and T2 for 12 Patients with RS Treated with MDO

	T1	**T2**	**T2 – T1 Change**		
	Mean (SD)	Mean (SD)	Mean (SD)	95% CI	P-value
Gonial Angle	145.7 (9.8)°	141.3 (8.5)°	-4.4 (11.5)°	-11.7 to 3.0)°	0.2171
Ramus Height	20.1 (7.9) mm	24.6 (6.7) mm	4.5 (4.1) mm	2.0 to 7.1 mm	0.0026
Mandibular Body Length	31.7 (9.1) mm	45.8 (9.7) mm	14.0 (4.5) mm	11.2 to 16.9 mm	<0.0001
RH/MBL	0.63 (0.16)	0.56 (0.13)	-0.07 (0.10)	-0.14 to 0.00	0.0414

T3

Between the T2 imaging and mixed dentition follow-up T3 imaging, both linear and angular measures changed significantly for the RS with MDO group. Vertical growth tendencies persisted as described by significant increases in both gonial angle and the ratio of ramus height/mandibular body length (Table 9).

TABLE 9. Cephalometric Changes Between T2 and T3 for 12 Patients with RS Treated with MDO

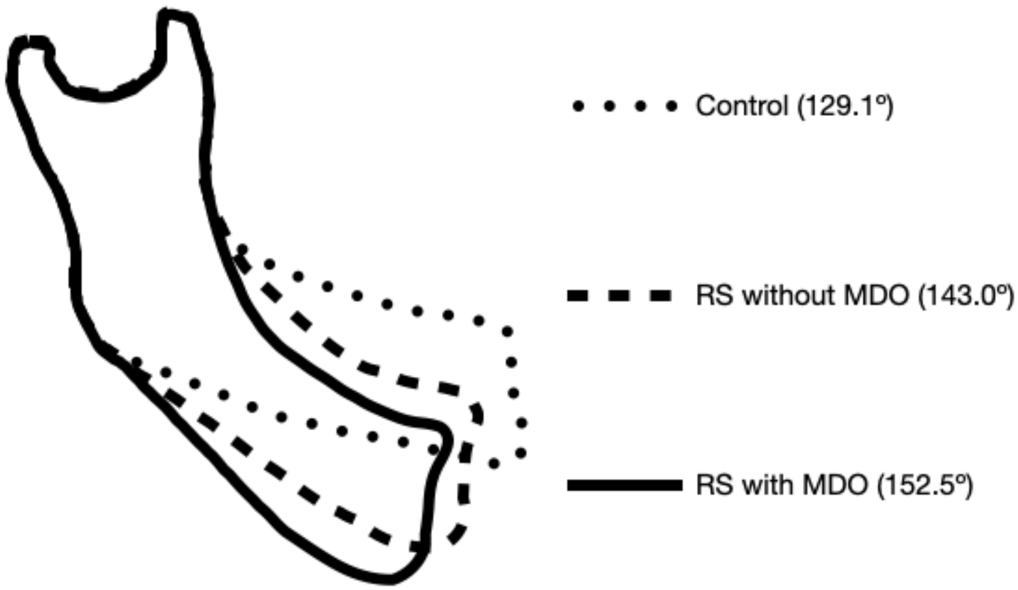
	T2	**T3**	**T3 – T2 Change**		
	Mean (SD)	Mean (SD)	Mean (SD)	95% CI	P-value
Gonial Angle	140.2 (7.7)°	152.8 (10.5) °	12.6 (6.9)°	12.6 (7.3, 17.9)°	0.0006
Ramus Height	24.1 (7.6) mm	37.6 (5.0) mm	13.5 (6.8) mm	13.5 (8.3, 18.7) mm	0.003
Mandibular Body Length	47.0 (10.9) mm	54.0 (6.9) mm	7.1 (8.3) mm	7.1 (0.7, 13.4) mm	0.0333
RH/MBL	0.54 (0.14)	0.70 (0.07)	0.15 (0.13)	0.15 (0.05, 0.25)	0.0080

Cephalometric measurements were examined for three groups at the T3 timepoint: 19 patients with RS without MDO (age= 8.4 years [SD=1.6]), 13 patients with RS with MDO (age= 7.8 years [SD=1.9]), and non-RS control patients sourced from the Michigan Growth Sample (age=8 years) (Table 10).

The first comparison was made between RS groups with and without MDO. Statistically significant differences in patients with RS with MDO were more obtuse gonial angle (+10.6 degrees, p= 0.006) and steeper mandibular plane angle (+9.9 degrees, p= 0.003), indicating a greater vertical growth trajectory of patients with RS with MDO. Although the mean distance from incisal edge of the mandibular incisor to menton (anterior mandibular height) was 3.5 mm increased in the RS with MDO group (p = 0.044), neither the mean distance from the molar occlusal surface to mandibular body (posterior mandibular height) nor the posterior/anterior ratio was statistically significant.

Both RS without MDO and RS with MDO groups were compared to control patients sourced from the Michigan Growth Sample. A 95% confidence interval was established for each measurement collected for the RS without MDO and RS with MDO groups. Statistically significant differences between both RS groups and normal controls were found for all measures except ANB (both RS groups), RH/MBL (RS with MDO), and anterior mandibular height (RS with MDO).

FIGURE 1. Mean Gonial Angle Measurement at Mixed Dentition (T3)



Tooth development data was collected from panoramic images for both RS groups at T3. The percentages of patients with any missing teeth, any abnormalities of tooth morphology, and any missing teeth due to extraction were compared between RS with MDO and RS without MDO groups. The only statistically significant finding was that RS with MDO patients experienced more frequent abnormalities in mandibular posterior tooth morphology than RS patients without MDO (Table 11).

TABLE 10. T3 Cephalometric Values and Comparison of RS with MDO, RS without MDO, and Reference Control Patients

	RS Without MDO		RS With MDO		Reference Control	RS Without MDO versus RS With MDO				Is the difference between RS affected groups and the reference control statistically significant?	
Variable	N= 19 Mean (SD)	95% CI	N = 12 Mean (SD)	95% CI	Mean (SD)	Difference (95% CI)	P-value	Adjusted difference* (95% CI)	P-value*	RS Without MDO	RS With MDO
Gonial Angle	143.0 (6.5)º	139.9 to 146.2º	152.5 (10.7)º	145.7 to 159.3º	129.1 (4.7)º	-9.5 (-16.7, -2.2)º	0.014	-10.6 (-17.9, -3.33)º	0.006	Yes	Yes
MP-SN	43.3 (8.4)º	39.8 to 48.0º	51.9 (5.7)º	49.1 to 56.8º	35.2 (4.8)º	-8.6 (-13.9, -3.3)º	0.0024	-9.6(-15.7, -3.5)º	0.0033	Yes	Yes
Y-SN	71.8 (6.0)º	68.9 to 74.7º	75.2 (4.6)º	72.1 to 78.3º	66.9 (3.4)º	-3.5 (-7.5, 0.6)º	0.0898	-4.3 (-9.1, 0.6)º	0.0824	Yes	Yes
LFH/TFH	56.7 (3.9)	54.8 to 56.5	54.6 (2.2)	53.1 to 56.1	58.0	2.1 (-0.2, 4.3)	0.0733	1.3 (-1.5, 4.0)	0.3415	Yes	Yes
Ramus Height	40.9 (4.8) mm	38.6 to 43.2 mm	37.5 (4.6) mm	34.6 to 40.4 mm	50.2 (3.0) mm	3.4 (-0.1, 7.0) mm	0.0576	3.4 (-0.7, 7.5) mm	0.0969	Yes	Yes
Mandibular Body Length	54.0 (5.0) mm	51.6 to 56.5 mm	53.3 (6.5) mm	49.2 to 57.5 mm	70.8 (3.6) mm	0.7 (-3.9, 5.3) mm	0.7528	0.3 (-4.5, 5.1) mm	0.9044	Yes	Yes
RH/MBL	0.76 (0.09)	0.72 to 0.80	0.71 (0.07)	0.66 to 0.75	0.71	0.05 (0.00, 0.11)	0.0576	0.06 (-0.01, 0.13)	0.0864	Yes	No
SNA	78.1 (4.4)º	76.0 to 80.3º	77.3 (4.5)º	74.4 to 80.1º	81.1 (3.2)º	0.9 (-2.5, 4.3)º	0.6056	0.6 (-3.4, 4.7)º	0.7500	Yes	Yes
SNB	73.2 (4.6)º	71.0 to 75.4º	70.7 (4.8)º	67.5 to 73.9º	76.5 (3.1)º	2.5 (-1.2, 6.2)º	0.1798	2.6 (-2.2, 7.3)º	0.2799	Yes	Yes
ANB	4.9 (4.7)º	2.7 to 7.2º	6.0 (3.0)º	4.0 to 8.0º	4.7 (2.3)º	-1.1 (-3.9, 1.8)º	0.4531	-1.4 (-4.8, 1.9)º	0.3889	No	No
Posterior Mandibular Height	21.0 (2.4) mm	19.9 to 22.2 mm	20.6 (2.2) mm	19.2 to 22.1 mm	29.7 (1.8) mm	0.4 (-1.4, 2.2) mm	0.6411	0.03 (-2.0, 2.0) mm	0.9747	Yes	Yes
Anterior Mandibular Height	34.0 (3.1) mm	32.5 to 35.5 mm	36.7 (4.2) mm	34.0 to 39.4 mm	38.9 (2.3) mm	-2.6 (-5.6, 0.3) mm	0.0786	-3.4 (-6.7, -0.1) mm	0.0436	Yes	No
Ratio of Posterior Mandibular Height to Anterior Mandibular Height	0.62 (0.05)	0.60 to 0.64	0.57 (0.05)	0.53 to 0.60	0.77	0.05 (0.01, 0.09)	0.0104	0.05 (0.01, 0.10)	0.0830	Yes	Yes

TABLE 11. Tooth Development Abnormalities for 19 Patients with RS without MDO and 13 Patients with RS with MDO

	Without MDO (N=19) n (%)	**With MDO (N=13) n (%)**	**P-value***
Mandibular 2nd primary molars, 2nd premolars, and first molar			
Any missing	8 patients (42.1%)	4 patients (30.8%)	0.713
Any abnormal development	0 patients (0%)	4 patients (30.8%)	0.020
Any missing due to caries/dental disease/extraction	1 patient (5.3%)	1 patient (7.7%)	1.000
Maxillary 2nd primary molars, 2nd premolars, and first molar			
Any missing	6 patients (31.6%)	2 patients (15.4%)	0.420
Any abnormal development	0 patients (0%)	1 patient (7.7%)	0.406
Any missing due to caries/dental disease/extraction	0 patients (0%)	2 patients (15.4%)	0.157

DISCUSSION

Mandibular distraction osteogenesis (MDO) is a treatment alternative to long-term tracheostomy in patients with Robin Sequence (RS) with severe isolated base of tongue airway obstruction. Ideally, the horizontal deficiency of the mandible corrected by MDO would be maintained throughout growth, resulting in normalized craniofacial morphology. This study examines cephalometric measurements pre- and post-surgery and in the mixed dentition for a sample of patients with RS treated with MDO in infancy.

Of utmost significance to the child, their family, and healthcare providers is that the treatment pursued is safe and effective. Complications should be minimized and more aggressive interventions (i.e. tracheostomy) avoided, if possible. In this sample of infants with

RS, MDO was successful in alleviating severe airway obstruction, and no patient required tracheostomy. There was no mortality associated with the procedure and morbidity was minimal. All patients completed their planned course of mandibular distraction.

At T1, infants planned for MDO had a lower BMI than the control infants, which may reflect feeding difficulties in these infants with RS and airway compromise. Other growth measures did not differ from control patients, indicating that there were no inherent negative physical growth patterns to consider outside of mandibular retrognathia. The RS-affected infants had a significantly more obtuse gonial angle and smaller ramus height (RH) and mandibular body length (MBL). The ratio between the linear measurements (RH/MBL) was similar to normal infants, indicating that RS-affected infants had smaller, but normally proportioned mandibles. Infants with RS demonstrated a significant vertical growth tendency prior to surgical intervention.

With MDO, mandibles were advanced from a severely retrognathic position to a target of 2mm negative overjet. Both ramus height (RH) and mandibular body length (MBL) increased significantly, and the increased RH/MBL ratio resulted in a favorable forward rotation of the mandible. These results echo the significant increase in ramus length, gonial angle, mandibular oblique length, and mandibular sagittal length previously reported for patients with RS with MDO (Susarla et al., 2018) (Rossini et al., 2016). The T2 measurements were taken an average of 10 days following distractor removal and reflect the mandibular shape and position obtained with distraction prior to surgical relapse or craniofacial growth. It would be misleading to claim that infants with RS undergoing MDO have corrected mandibular morphology as there is significant uncertainty in their ability to maintain growth with a favorable trajectory.

In the years between completion of MDO and the mixed dentition (T2 to T3), the original vertical growth tendencies resurfaced in the RS with MDO group. The gonial angle significantly increased 12.6 degrees on average. The ramus length and mandibular body length increased, as would be expected with normal growth, but the increased ratio between them indicates backward (unfavorable) growth rotation of the mandible. The positive cephalometric outcomes found immediately following MDO were not maintained at the mixed dentition timepoint as illustrated in figure 1.

It is important to consider if the RS with MDO group more closely resembles patients with RS who did not have MDO or children without craniofacial conditions at the mixed dentition timepoint. MDO did not create more normal mandibles in our sample. Vertical measures significantly increased in the RS with MDO group as compared to the RS without MDO sample included gonial angle, MP-SN, and distance between incisal edge and menton (anterior mandibular height). Although not quantified in this study, the mandibles in the RS with MDO group had deep antegonial notching and irregular contours of the mandibular border. All other cephalometric measurements were similar between the two groups of patients with RS.

In comparison to reference controls, both RS groups were significantly different in almost every measurement assessed except ANB. Only RH/MBL and anterior mandibular height in the RS with MDO group were similar to the normal control. MP-SN was 16.7° higher in the RS with MDO group as compared to the normal control and notably larger than the 9.4° increase previously reported for patients with RS not treated with MDO (Wang, 2012).

A concern with MDO is the effect on developing mandibular posterior teeth. The osteotomy location is near the buds of developing mandibular posterior teeth. Studies from other centers report a high frequency of missing or damaged mandibular posterior teeth. At Seattle Children's Hospital, the technique for MDO includes bilateral submandibular incisions and inverted -L corticotomies with horizontal and vertical cuts superior and posterior to the lingula (Susarla et al., 2021). We expect that corticotomy location influences the likelihood of damage to developing tooth buds in the posterior mandible. The only significant difference in tooth development in this study between RS groups with and without MDO was abnormal morphology of at least one posterior mandibular tooth in 30% of RS treated with MDO patients. This indicates that the surgical technique used for MDO influences the type and extent of adverse consequences to mandibular posterior teeth.

The orthodontist overseeing care at the mixed dentition for patients with RS treated with MDO must understand the challenges that accompany future treatment. These patients do not have a normalized or predictable growth trajectory, and they would not be appropriate candidates for Phase I Class II correction with headgear, Herbst appliance, or mandibular anterior repositioning appliance (MARA). MDO temporarily corrects an anterior-posterior deficiency in the mandible, but the inherent growth potential associated with an RS diagnosis is not eliminated. The striking vertical growth vector that exists at T3 may presumably worsen with time and growth during puberty as well. These patients will most likely need surgical skeletal correction with comprehensive orthodontic treatment, not dental compensation.

Patients with RS may also have congenitally missing teeth or missing/damaged teeth following MDO that must be considered in the creation of a comprehensive orthodontic treatment plan. Recognition of dental anomalies or agenesis would allow for selection of the most appropriate treatment plan which may include exodontia or dental implants. It is critical that orthodontists aim to reduce the burden of care for the patient and time treatment for when it can be most efficiently and effectively delivered.

Limitations of this study are due to the small number of infants with RS receiving MDO at the study hospital, inconsistency in timing and quality of imaging prior to and following MDO, and heterogeneity of the sample which included patients with isolated and non-isolated RS. Images varied in clarity, particularly at T1 and T2, making landmark identification challenging. The control group at T1 may not be representative of the general population, but it would be unethical for healthy infants to undergo CT imaging. The non-distracted patient group with RS is not directly comparable to the RS with MDO group because the non-distracted patients with RS likely had milder craniofacial presentations of RS. This retrospective study was not randomized; randomization to MDO or non-MDO is impractical as infants in respiratory distress imminently need surgical intervention. It would not be ethical to assign less severely affected infants to MDO treatment if non-surgical methods would be effective in airway management.

Continued research on this topic should evaluate different surgical techniques and include more well-phenotyped patients with longer-term follow-up intervals. It would be interesting to following a sample of patients into adolescence and adulthood to track the additional surgical procedures needed to meet the functional needs and esthetic desires of patients with RS.

CONCLUSION

Mandibular distraction osteogenesis (MDO) prevented the need for tracheostomy and produced some positive mandibular morphological changes in the short-term for this sample of infants with Robin Sequence (RS). At the mixed dentition, the craniofacial morphology of patients with RS with MDO resembles patients with RS managed without MDO, demonstrating a significantly more vertical mandibular growth vector than patients without craniofacial conditions. Tooth morphology abnormalities in mandibular posterior teeth were uncommon in this sample of patients with RS treated with MDO in early life.

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