European Journal of Orthodontics, 2020, 24–29
doi:10.1093/ejo/cjz078
Advance Access publication 5 October 2019

Randomized Controlled Trial (RCT)

Scandcleft randomized trials of primary surgery for unilateral cleft lip and palate: maxillary growth at eight years of age

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Summary

Objectives: To assess differences in craniofacial growth at 8 years of age according to the different protocols for primary cleft surgery in the Scandcleft project.

Design and setting: Prospective, randomized, controlled clinical trial (RCT) involving 10 centres, including non-syndromic Caucasians with unilateral cleft lip and palate (UCLP). In Trial 1, a common surgical method (1a) with soft palate closure at 3–4 months of age and hard palate closure at 12 months of age was tested against similar surgery but with hard palate repair at 36 months (delayed hard palate closure) (1b). In Trial 2, the common method (2a) was tested against simultaneous closure of both hard and soft palate at 1 year (2c). In Trial 3, the common method (3a) was tested against hard palate closure together with lip closure at 3 months of age and soft palate closure at 1 year of age (3d). Participants were randomly allocated by use of a dice. Operator blinding was not possible but all raters of all outcomes were blinded.

Subjects and methods: The total number of participating patients at 8 years of age was 429. Lateral cephalograms (n = 408) were analysed. The cephalometric angles SNA and ANB were chosen for assessing maxillary growth for this part of the presentation.

Results: Within each trial (Trial 1a/1b, Trial 2a/2c, and Trial 3a/3d), there was no difference in cephalometric values between the common and the local arm. There were no statistically significant differences in the SNA and ANB angles between the common arm in Trial 1a (mean SNA 77.8, mean ANB 2.6) and Trial 2a (mean SNA 79.8, mean ANB 3.6) and no difference between Trial 1a and Trial 3a, but a statistical difference could be seen between Trial 2a and Trial 3a (mean SNA 76.9, mean ANB 1.7). However, the confidence interval was rather large. Intra- and inter-rater reliability were within acceptable range.

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Conclusions: The timing and the surgical method is not of major importance as far as growth outcomes (SNA and ANB) in UCLP are concerned.
Registration: ISRCTN29932826
Protocol: The protocol was not published before trial commencement.

Introduction

This study is part of the Scandcleft multicentre study, which is a prospective, randomized, controlled clinical trial among 10 centres studying non-syndromic Caucasian children with unilateral cleft lip and palate (UCLP) (1). The main aim of the Scandcleft study is to test outcomes of four different surgical protocols for primary surgery of UCLP patients, the main outcome measures being speech and dentofacial development. The protocols include a common surgical method (a) with soft palate closure at 3–4 months of age and hard palate closure at 12 months of age. This protocol was tested in Trial 1 against similar surgery but with hard palate repair at 36 months (delayed hard palate closure) (1b). In Trial 2, the common arm (2a) was tested against simultaneous closure of both hard and soft palate at 1 year (2c); in Trial 3, the common arm (3a) was tested against closure of hard palate together with lip closure at 3 months of age and soft palate closure at 1 year of age (3d). Participants were randomly allocated by use of a dice to one of two arms within their Trial (Figure 1). An envelope assigned to each patient was opened on the day of surgery with information of allocation. Signed consent was obtained from parents in this study. The study was approved by the local ethical committees in all participating countries.

The craniofacial stigmata in children with UCLP is retrusion of both maxilla and mandible with minimal maxillary growth between 5 and 10 years of age (2). It is generally agreed that primary surgery is critical to subsequent maxillary growth and development, but there is a clear lack of evidence for selecting an optimal treatment protocol. This lack of evidence-based criteria for the surgical protocol was seen in the Biomed II project, where 201 cleft teams were asked to describe their UCLP treatment protocol, and 194 different surgical protocols were described (3). The Eurocleft study published their first results in 1992 and found no major differences in the skeletal profile between the six participating North European cleft centres (4). The Slavcleft group published their results in 2016. Like the Eurocleft group, they found no clear difference between the surgical protocols and treatment outcomes in UCLP (5). Several inter-centre comparison studies have come to the same conclusion (6, 7).

Earlier studies by Schweckendiek (8), Hotz and Gnoinsky (9), and Friede and Enemark (10) have reported excellent craniofacial morphology in UCLP using delayed palatal closure. These results were discussed when the Scandcleft project was planned and are reflected in Trial 1, which tests early against delayed palatal closure.

The purpose of present part of the Scandcleft project is to evaluate craniofacial growth at 8 years of age. The null hypothesis was that the timing and method of primary surgery have no influence on maxillary growth at this age.

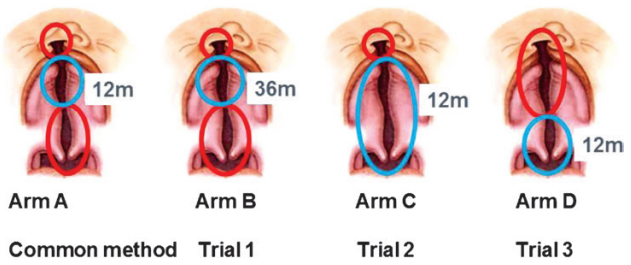

Figure 1. Sequence of closure of unilateral cleft lip and palate (UCLP). From Rautio *et al.* (18). (Reprinted with permission from Rautio *et al.*, 2017, *Journal of Plastic Surgery and Hand Surgery*, Taylor & Frances).

Subjects and methods

The distribution of patients from each centre and the total number of patients included in this study at 8 years of age are shown in Table 1. Flow diagrams for all three trials are shown in Figure 2. One centre discontinued participation after a few years, which means that nine centres contributed with 8 years of registrations. Lateral cephalograms (n = 408) were obtained at 8 years of age, 293 of which were digital and 115 were scanned analogous lateral cephalograms. All cephalograms were traced in the software program FACAD (Ilexis, Linköping, Sweden) by one observer. For intra-observer correlation, 50 lateral cephalograms were traced twice by this observer 2 weeks apart. For intra-observer correlation, 25 lateral cephalograms were traced by two observers.

We chose the cephalometric angles SNA (angle between selle, nasion, and subspinal point) and ANB (angle between maxilla and mandible) to assess maxillary growth in the present study. None of the patients had received any orthodontic treatment or any bone grafting for alveolar cleft closure.

The research protocol was approved by all centres, and local ethical approvals were obtained. The principles outlined in the Declaration of Helsinki were followed.

Statistical analyses

Reliability within and between observers was calculated by assessing the intra-class correlation coefficient (ICC) and the 95 per cent confidence interval (CI) was assessed using a bootstrap model. Bland–Altman plot was used to assess the systematic error of the method and the smallest detectable differences.

Table 1. Total number of patients from each centre as well as total number of available lateral cephalograms.

	Total number of patients from each centre	X-ray not taken	X-ray not eligible	Total number of available lateral cephalograms
Gothenburg	23	0	0	23
Copenhagen	41	0	0	41
Aarhus	83	0	1	82
Helsinki	93	4	2	87
Linkoping	21	0	0	21
Stockholm	36	16	1	19
Oslo	55	0	3	52
Bergen	30	1	0	29
Manchester	47	0	0	47
	429	21	7	401

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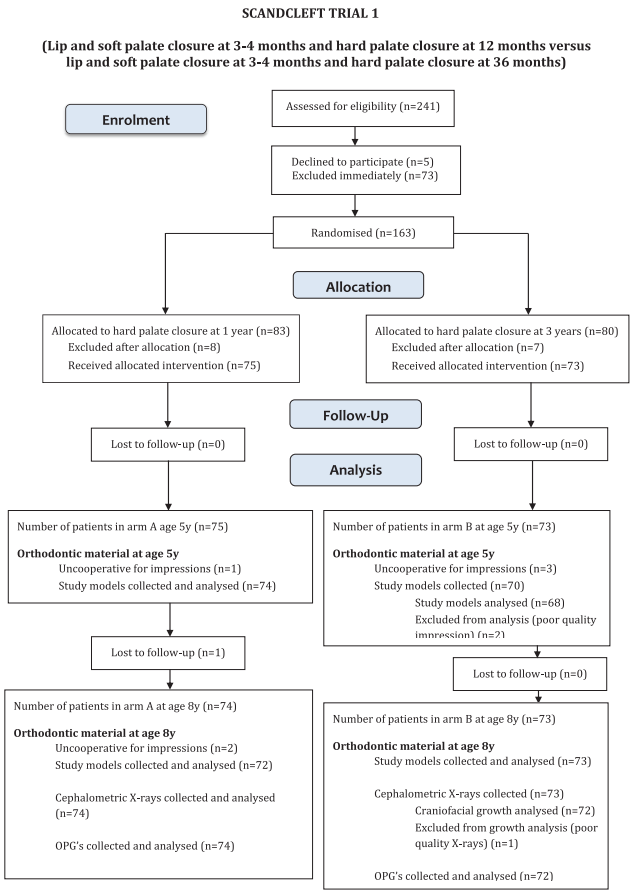

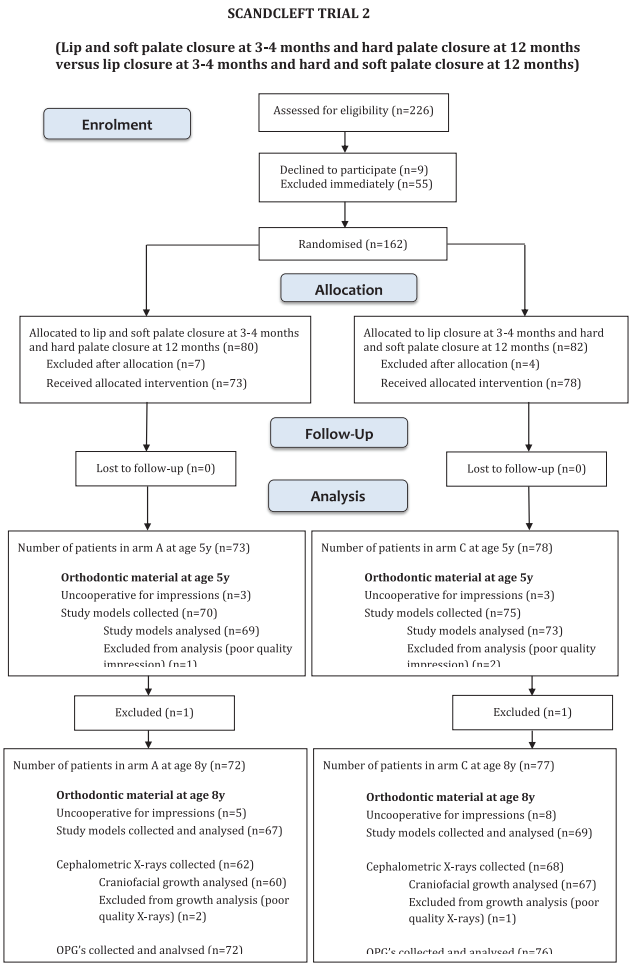

Figure 2. Flowchart of the three Scandcleft trials.

Normality was verified graphically with histograms and QQ-plots.

The outcome was analysed using a mixed model, accounting for the variation between the centres as a random effect.

Test statistics with *P*-values equal to or less than 0.05 were considered significant. CIs were given for the 95 per cent interval.

Results

Table 1 shows the number of lateral cephalograms from each participating centre. Unfortunately, 16 lateral cephalograms from Stockholm were lost/not taken due to merging of two centres some years ago. As shown in Table 1, the total number of available lateral cephalograms was 401 since 7 of the 408 obtained lateral cephalograms were of poor quality and not eligible for analysis. The patients' mean age was 8.1 [standard deviation (SD) 0.27] years. Arm a consisted of 194 patients, arm b 72 patients, arm c 67 patients, and arm d 68 patients (Table 2).

Intra-observer variability

The ICC for intra-observer was very good [0.98 for ANB (CI 0.96 to 0.99) and 0.96 for SNA (CI 0.93 to 0.98)]. The systematic error of either method was below 0.35 degrees. The smallest detectable difference (limit of agreement) was 1.31 for ANB and 2.02 degrees for SNA.

The lower and upper limit of agreement was −1.63 (CI −1.94 to −1.33) and 1.00 (CI 0.70 to 1.30), respectively, for ANB; and −2.38 (CI −2.84 to −1.91) and 1.66 (CI 1.20 to 2.13), respectively, for SNA.

Figure 2. Continued

Inter-observer

The ICC for inter-observer variability was very good [0.97 for ANB (CI 0.92 to 0.99) and 0.95 for SNA (CI 0.90 to 0.98)]. The systematic error of either method was less than 0.18 degrees. The smallest detectable difference (limit of agreement) was 1.18 for ANB and 2.31 degrees for SNA.

The lower and upper limit of agreement was −1.23 (CI −1.71 to −0.76) and 1.12 (CI 0.64 to 1.60), respectively, for ANB; and −2.49 (CI −3.42 to −1.55) and 2.13 (CI 1.19 to 3.06), respectively, for SNA.

SNA and ANB

SNA and ANB angle values for each trial and trial arm are shown in Table 3. The mean SNA angle was 78.04 (SD 4.08) and the mean ANB angle was 2.85 (SD 3.39) for all 401 patients across the trials (Table 3).

Within-trial differences

As seen in Table 4, no statistical differences in outcome were seen between ANB and SNA angles when the common arm was compared to local arms.

In-between trial differences

Considering the same surgical procedure, i.e. the common method a, we found no statistical difference between arm a in Trial 1 and

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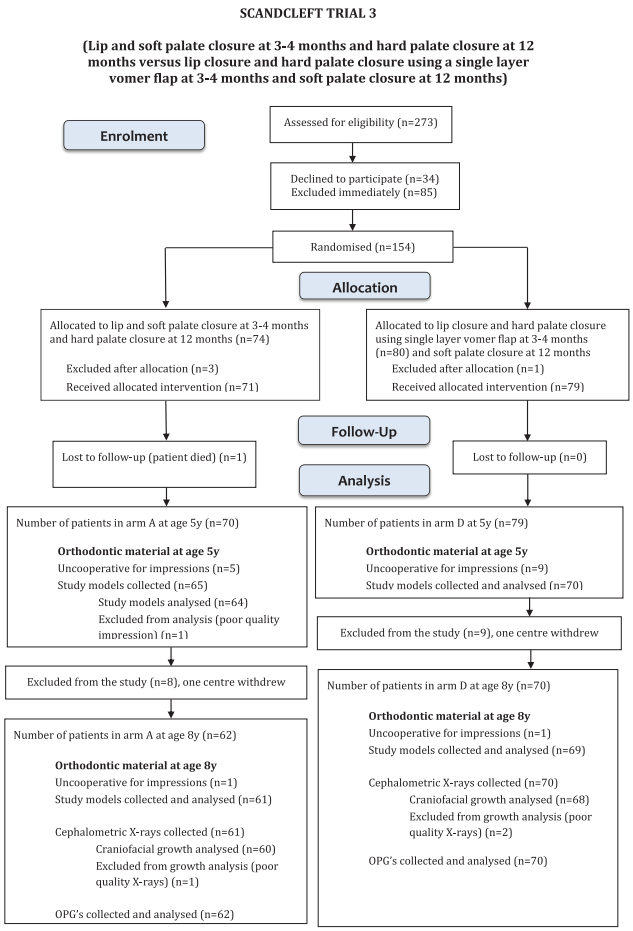

Figure 2. Continued

2 or between Trial 1 and 3, but a statistically significant difference could be seen between arm a in Trial 2 and arm a in Trial 3 (Table 5). However, this difference should be interpreted in the context of the rather large CIs.

Discussion

The purpose of this part of the ongoing Scandcleft study was to assess differences in maxillary growth at the age of 8 for different surgical protocols for primary cleft surgery. In this study, we present the result only of the SNA angle as an indicator of maxillary growth in the sagittal plane and the ANB angle as an indicator of craniofacial growth and skeletal relations between the maxilla and the mandible. The SNA is not an ideal maxillary growth indicator at the age of 8 since point A is influenced by the erupting permanent incisors, which might displace point A. When doing the tracing and placing point A, we sought to compensate for this by placing the point on a straight curvature from the anterior nasal spine to prostion. In this way, the position of point A is supposedly more correct and may be interpreted as an expression of sagittal growth. Since lateral cephalograms were obtained at many different centres using different cephalostats, we chose to use only angular measurements to overcome variation in enlargement factor. Although growth has not finished at the age of 8, the advantage of using this age is that no orthodontics or bone grafting have yet been performed at this age, and the position of point A is therefore not influenced by orthodontic

Table 2. Total number of available cephalograms within each arm.

	Arm a	Arm b	Arm c	Arm d	Total number of available lateral cephalograms
Gothenburg	12	11			23
Copenhagen	21	20			41
Aarhus	41	41			82
Helsinki	40		47		87
Linkoping	12		9		21
Stockholm	8		11		19
Oslo	27			25	52
Bergen	12			17	29
Manchester	21			26	47
Total	194	72	67	68	401

Arm a: the common surgical method arm with soft palate closure at 3–4 months of age and hard palate closure at 12 months of age. Arm b: soft palate closure at 3–4 months of age with hard palate repair at 36 months. Arm c: simultaneous closure of both hard and soft palate at 1 year of age. Arm d: hard palate closure together with lip closure at 3 months of age and soft palate closure at 1 year of age.

compensatory movements. A full cephalometric evaluation by use of the Björk analysis has been made and will be used to describe this large UCLP group at 8 years of age in a later publication.

In general, we saw a large variation as verified by the large CIs. This variation among non-syndromic UCLP patients has been documented in other studies (11) as well as in a non-cleft population (12). The mean SNA angle of 78.04 is comparable to that reported by other studies of 8-year-old UCLP patients (2) but lower than seen in healthy age-matched children (12, 13). The mean ANB of 2.85 is larger than the ANB in an age-matched population of healthy children (12, 13). Since the SNA angle indicates maxillary retrognatism, the relatively large ANB angle indicates that the 8-year-old UCLP patients have mandibular as well as maxillary retrognatism.

We found no differences within the individual trials when comparing the common surgical procedure arm a with the local arms b, c, or d. Although the mean ANB and SNA angles varied with each surgical procedure, this difference was not statistically significantly different. As seen in Trial 1, the outcome of delayed hard palate closure (arm b) with closure of the hard palate at 3 years of age was associated with no differences in maxillary growth, which has also been documented in other studies (14, 15). Furthermore, comparison of simultaneous closure of the hard and the soft palate (arm c) with two-stage closure as seen in Trial 2 was associated with no changes in maxillary growth; similarly, hard palate closure before soft palate closure (arm d) in Trial 3 did not affect the outcome at the age of 8. This finding indicates that the method and timing of primary surgery is not the main determinant of craniofacial growth outcome at the age of 8. A main strength of the Scandcleft set-up is that the children are randomly allocated to one of the two surgical trial groups, and both groups are operated by the same surgeon(s), which cancels any influence the surgeon's skills might have when comparing outcomes within the trials. The bias that emerges with the gradual increase in surgical experience as the individual surgeon becomes more skilled can also be ignored, since all participating centres mainly had experienced surgeons.

Other multicentre studies have shown that the surgeon's experience and the volume of operations performed influence the outcome (14, 16). Analysing the results of the same surgical method, arm a (Table 5), we found no differences between Trial 1 and Trial 2 or

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Table 3. Mean ANB and SNA angles. CI, confidence interval; SD, standard deviation.

Trial	Arm	Mean ANB	CI	Mean SNA	CI
1	a	2.88	1.68 to 4.07	78.42	76.63 to 80.20
2	a	3.89	2.73 to 5.05	80.05	78.45 to 81.66
3	a	1.67	0.44 to 2.90	76.78	75.16 to 78.40
1, 2, 3	a	2.80	1.96 to 3.63	78.38	77.10 to 79.66
1	b	3.55	2.44 to 4.67	78.90	77.28 to 80.52
2	c	3.43	2.28 to 4.58	77.78	76.17 to 79.39
3	d	2.53	1.31 to 3.74	77.62	76.01 to 79.12
All patients		2.85 (SD 3.39)		78.04 (SD 4.08)	

Table 4. Within-trial differences. CI, confidence interval.

	ANB		SNA	
Trial	*P*-value	CI	*P*-value	CI
1a versus 1b	0.12	−0.19 to 1.66	0.41	−0.69 to 1.69
2a versus 2c	0.69	−0.88 to 1.34	0.15	−2.31 to 0.34
3a versus 3d	0.72	−1.02 to 1.47	0.56	−1.73 to 0.93

1a versus 1b: the common surgical method with soft palate closure at 3–4 months of age (1a) against similar surgery but with hard palate repair at 36 months (1b). 2a versus 2c: the common arm (2a) was tested against simultaneous closure of both hard and soft palate at 1 year (2c). 3a versus 3d: the common arm (3b) was tested against closure of hard palate together with lip closure at 3 months of age and soft palate closure at 1 year of age (3d).

between Trial 1 and 3; however, a statistically significant difference could be seen between Trial 2 and 3. Still, because of the large CI, we cannot conclude whether differences in surgeon's skills may have affected the outcome concerning craniofacial growth.

Previous studies have shown varying maxillary growth outcomes in patient populations operated by the same surgeons (11, 17). One factor contributing to such variation in maxillary growth may be the initial severity of the cleft at birth. Hence, cleft deformity exhibits large phenotypic variation and various degrees of soft tissue deformity and displacement, which may in turn affect how the initial cleft surgery affects subsequent growth. The relationship between cleft severity and maxillofacial growth remains unknown, and a survey of this relationship in a standardized material like the Scandcleft material is needed. Besides initial cleft width, other factors contributing to soft tissue hypoplasia such as agenesis of cleft side laterals have also been shown to be important non-iatrogenic factors (11).

Differences in craniofacial growth related to the method and the timing of primary surgery should ideally be based on records made when the patients have finished growth in their late teens, as several studies have shown that maxillary retrusion measured by the SNA angle becomes more and more apparent with age (2). However, since the patients in the present report had not yet received any orthodontic treatment, the influence of orthodontic compensations and/or orthognatic surgery did not influence the result. The Scandcleft study continues until the patients have stopped growing; and craniofacial growth in this large patient group will be re-evaluated at a later time point.

Conclusion

The result of this study on 8-year-old UCLP patients offers no indications that surgical method or timing influences the maxillary growth. The null hypothesis was hence accepted. Other outcomes, such as speech development, surgical complications, dental development, and occlusion, will be addressed in other papers.

Table 5. Differences between the common arm a between the trials (soft palate closure at 3–4 months of age and hard palate closure at 12 months of age). CI, confidence interval.

	ANB		SNA	
	P-value	CI	*P*-value	CI
Trial 1a versus 2a	0.21	−0.58 to 2.61	0.21	−0.88 to 4.02
Trial 1a versus 3a	0.14	−2.99 to 0.40	0.17	−4.20 to 0.71
Trial 2a versus 3a	0.01*	0.63 to 3.99	0.01*	1.00 to 5.62

Acknowledgements

We thank Professor Helen Worthington for statistical advice.

Conflicts of interest

The authors declare that there is no conflict of interest regarding this research. The authors alone are responsible for the contents and writing of the paper.

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