Timing of Primary Surgery for Cleft Palate

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Abstract

Background

Among infants with isolated cleft palate, whether primary surgery at 6 months of age is more beneficial than surgery at 12 months of age with respect to speech outcomes, hearing outcomes, dentofacial development, and safety is unknown.

Methods

We randomly assigned infants with nonsyndromic isolated cleft palate, in a 1:1 ratio, to undergo standardized primary surgery at 6 months of age (6-month group) or 12 months of age (12-month group) for closure of the cleft. Standardized assessments of quality-checked video and audio recordings at 1, 3, and 5 years of age were performed independently by speech and language therapists who were unaware of the trial-group assignments. The primary outcome was velopharyngeal insufficiency at 5 years of age, defined as a velopharyngeal composite summary score of at least 4 (scores range from 0 to 6, with higher scores indicating greater severity). Secondary outcomes included speech development, postoperative complications, hearing sensitivity, dentofacial development, and growth.

Results

We assigned 558 infants at 23 centers across Europe and South America to undergo surgery at 6 months of age (281 infants) or at 12 months of age (277 infants). Speech recordings from 235 infants (83.6%) in the 6-month group and (81.6%) in the 12-month group were analyzable. Insufficient velopharyngeal function at 5 years of age was observed in 21 of 235 infants (8.9%) in the 6-month group as compared with 34 of 226 (15.0%) in the 12-month group (risk ratio, 0.59; 95% confidence interval, 0.36 to 0.99; P = 0.04). Postoperative complications were infrequent and similar in the 6-month and 12-month groups. Four serious adverse events were reported (three in the 6-month group and one in the 12-month group) and had resolved at follow-up.

Conclusions

Medically fit infants who underwent primary surgery for isolated cleft palate in adequately resourced settings at 6 months of age were less likely to have velopharyngeal insufficiency at the age of 5 years than those who had surgery at 12 months of age. (Funded by the National Institute Dental and Craniofacial Research; TOPS ClinicalTrials.gov number, NCT00993551.)

Isolated cleft palate affects 1 to 25 newborns per 10,000 births worldwide, although the incidence varies internationally.[1-3] Depending on the type and severity of the defect, cleft palate may cause difficulty with communication, owing to abnormal speech development and hearing loss; feeding problems, particularly within the first year of life; aberrant dental development and facial growth; and psychological difficulties. Consequently, treatment and care for a child with an isolated cleft palate require input from a multidisciplinary team of specialists.[4]

For infants with cleft palate, the roles of surgical technique, age at the time of surgery, and number of surgeries in the optimization of speech development continue to be debated.[5,6] Speech is a learned behavior, and much information suggests that the earlier an intact anatomy is established, the greater the benefit to speech development.[7-9] At many cleft palate centers in the United States and Europe, children undergo standard-of-care surgical treatment between 6 and 14 months of age.[10,11] Safety concerns related to airway obstruction and anesthesia are key reasons why some surgeons avoid repair in younger infants. An important aim of primary palatal surgery is normalization of velopharyngeal function — that is, closure between the velum and pharyngeal walls to separate the oral and nasal cavities during speech and swallowing. This closure prevents oral–nasal coupling during speech, enabling intraoral air pressure sufficient for pressure consonants, which is a prerequisite for the normal development of prelinguistic behavior and speech.[12] Despite undergoing surgical repair, approximately 30% of children have symptoms of velopharyngeal insufficiency, which results in hypernasality, audible nasal emission, and inadequate intraoral pressure to produce pressure consonants.[13,14] Although analyses of large cohorts have suggested an association between later repair and poorer speech outcomes during childhood,[15-17] there have been repeated calls for a definitive randomized, controlled trial to assess whether this association exists.[15,18]

In a recent systematic review of randomized, controlled trials, the timing of palatal surgery in various cleft types was compared.[6] Four randomized, controlled trials were identified, but important variations prevented a meta-analysis, which led to the conclusion that further evidence is required.[6] The present trial — the Timing of Primary Surgery (TOPS) trial — was an international, two-group, randomized, controlled trial that assessed whether primary surgery for cleft palate repair, with the use of a standardized technique, produced better speech outcomes when performed at 6 months of age than at 12 months of age.

Methods

Trial Design and Oversight

Our trial was funded by the National Institutes of Health. Full details of the trial design, population, procedures, and statistical analysis plan have been published previously.[11,19] The trial was conducted at 23 centers across Brazil, Denmark, Norway, Sweden, and the United Kingdom. Independent ethics committees in each country approved the protocol (available with the full text of this article at NEJM.org) and amendments. For each patient, a parent or guardian provided written informed consent.

The structure of the oversight committee has been described elsewhere.[11] The first author prepared the original manuscript on behalf of members of the writing committee, who vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.[11]

Eligibility and Randomization

Infants referred to participating centers specializing in cleft lip and palate repair were assessed for eligibility. Infants were eligible for inclusion in the trial if they had an isolated cleft palate; were considered to be medically fit to undergo surgery at 6 months of age, corrected for gestational age; and had one parent or caregiver who was a native speaker of the language (Brazilian Portuguese, Danish, English, Norwegian, or Swedish) spoken by the majority of persons in the infant's country of residence. Exclusion criteria were severe developmental delay or syndromic cleft palate, congenital sensorineural hearing loss or structural middle-ear anomalies, and an anatomical

presentation considered to be unsuitable for one-stage closure with the standardized surgical technique for cleft palate repair (see Section S2 in the Supplementary Appendix, available at NEJM.org). The representativeness of the trial participants is summarized in Table S1.

We used a Web-based minimization algorithm that incorporated a random element to randomly assign, in a 1:1 ratio, eligible infants to undergo surgery at 6 months of age (6-month group) or 12 months of age (12-month group), corrected for gestational age. Randomization was stratified according to surgeon and extent of the cleft (soft palate only vs. soft and hard palates).

Standardization of Surgery and Assessments

The cleft palate teams in each center included a surgeon, a speech and language therapist, an audiologist, and an orthodontist. Primary surgery was to occur during the period from 2 weeks before to 4 weeks after the target date. Table S2 provides a summary of the schedule of assessments. Surgery was performed with use of the Sommerlad technique.[20,21] This technique was chosen because of its familiarity to most of the participating surgeons and its association with improved speech outcomes.[22] To standardize the technique among the participating centers, all surgeons received in-person instruction from Mr. Brian Sommerlad, the developer of the technique, in the operating theater. Written descriptions and a video of the surgical procedure were also provided to the surgeons. Table S3 provides a summary of speech assessments according to time point. Speech assessments in children at 5 years of age consisted of phonetic transcriptions of target consonants uttered during a single-word test and ratings of spontaneous speech. The consonants were chosen to minimize the influence of language[23]; the majority were pressure consonants, which are known to be difficult for patients with cleft palate to produce. The speech-assessment methods developed during the Scandcleft study[24-26] were extended to Brazilian Portuguese in the present study. Speech and language therapists from participating centers independently performed standardized assessments, in real time, of quality-checked video recordings of prelinguistic speech in infants at 1 year of age.[27]

Strategies used at each assessment time point to standardize the evaluations by speech and language therapists included theoretical and practical lessons on speech development in infants with and those without cleft palate, online and in-person training with feedback, and a 3-day central standardization meeting, held in the United Kingdom, during which practice recordings were assessed. Central meetings provided a standardized environment for assessment of recordings, with the therapists unaware of the timing of surgery and using software developed as part of the TOPS trial.[28] Single-word tests were assessed by a speech and language therapist who spoke the same language as the patient; recordings of 50% of the tests were assessed by a second speech and language therapist. Assessments of hypernasality and ratings of velopharyngeal competence (VPC-Rate; categorized as competent, marginally incompetent, or incompetent) were provided by three speech and language therapists.

Outcomes

The primary outcome was velopharyngeal insufficiency — defined as a velopharyngeal composite summary score (VPC-Sum) of at least 4[25] — in children at 5 years of age. The VPC-Sum summarizes assessments of measures of hypernasality, symptoms of velopharyngeal insufficiency (nasal emissions, velopharyngeal friction sounds, and weak and nasalized consonants), and nonoral speech errors. Single-word tests were used to assess each of the three measures, with each measure assigned a score of 0, 1, or 2, so that the overall scores ranges from 0 to 6. Higher scores indicate greater severity. Secondary outcomes included velopharyngeal function at 5 years of age, assessed with the use of the VPC-Sum and the VPC-Rate[29]; velopharyngeal function at 3 years of age, assessed with the VPC-Rate and according to the percentage of times that a target consonant was produced with symptoms of velopharyngeal insufficiency; canonical babbling at 1 year of age, assessed according to the presence of canonical babbling (defined as the production of canonical syllables, which consist of ≥1 supraglottal consonant, ≥1 vowel, and a rapid transition between the vowel and the consonant [e.g., “mama”]), the canonical babbling ratio (the ratio of the number of canonical

syllables uttered to the total number of utterances), and the consonant inventory; articulation status at 3 and 5 years of age (the percentage of target consonants vocalized correctly,[30,31] the percentage vocalized with the correct place of articulation, the percentage vocalized with the correct manner of articulation, the percentage realized as a nonoral consonant error, and the percentage realized as an oral consonant error); hearing sensitivity at 1 year of age, assessed according to the presence of an abnormal transient otoacoustic emission and the presence of abnormal findings on sound-field audiometry; hearing sensitivity at 3 and 5 years of age, assessed according to the presence of abnormal findings on pure-tone audiometry in at least one ear, the presence of abnormal findings in both ears, and the severity of hearing loss in the ear with better findings; middle-ear function at 1, 3, and 5 years of age, assessed according to the presence of reduced middle-ear compliance (defined as a flat-line tympanogram) in at least one ear and the presence of reduced compliance in both ears; dentofacial development at 5 years of age, assessed according to the soft-tissue ANB angle (which measures the relative position of the maxilla to the mandible)[32] and the maxillary arch constriction score (measured with use of the modified Huddart–Bodenham scoring system[33,34]); growth at 1 year of age (weight without clothes, crown-to-heel length, and occipitofrontal circumference); and postoperative and long-term complications (dehiscence, infection, and fistula). In the 12-month group, assessments at 1 year of age occurred before primary surgery. Detailed descriptions of the relevant scoring systems and outcomes are provided in Section S4 and in Tables S4 through S8.

Statistical Analysis

We calculated, using a chi-square test, that 292 patients per group would provide the trial with 80% power to detect an incidence of insufficient velopharyngeal function at 5 years of age that was lower by 11 percentage points in the 6-month group than in the 12-month group (40% vs. 29%), at a two-sided significance level of 0.05. The effect of variation on the 40% estimate, which was calculated on the basis of a pilot study of 50 children 5 years of age,[24,35] was considered, and the sample size was judged to be sufficient to maintain good statistical power if the event occurred in as few as 20% of the children.[11] The sample size was set at 648 infants to allow for attrition.

Analyses were performed with SAS software, version 9.4 (SAS Institute), at the Liverpool Clinical Trials Centre. Independent statisticians performed randomization, interim analyses, the final analysis, and quality control. The final analysis was performed by statisticians who were unaware of the trial-group assignments. At the end of the trial, a team of speech and language therapists performed standardized assessments of speech recordings at a central facility. Recruitment, safety data, and data quality were described in interim reports. A formal interim analysis with stopping boundaries was not performed. The present trial assessed the effect of primary surgery at 6 months or 12 months of age on speech at 5 years of age. Speech evaluations at 5 years of age were analyzed according to a treatment policy estimand strategy, which did not take into account events that occurred after primary surgery, such as a secondary surgery or speech therapy.[36] Primary analyses included children who had undergone randomization and had outcomes measured, according to their assigned group. The statistical analysis plan has been published elsewhere[19] and is provided with the protocol. We calculated risk ratios and 95% confidence intervals for dichotomous outcomes and differences in means and 95% confidence intervals for continuous data. As part of a sensitivity analysis of the primary outcome, logistic regression was used to adjust for minimization factors, with surgeon treated as a random effect.[19] No adjustment was made for multiplicity in the analysis of secondary outcomes, and the 95% confidence intervals from these analyses should not be used to infer statistical significance. Under a missing-at-random assumption, a post hoc multiple-imputation approach was undertaken to impute missing data for the primary outcome and for the VPC-Rate at 3 and 5 years of age (see Sections S6 and S7).

Results

Recruitment and Patient Characteristics

From September 2010, through July 2015, a total of 558 infants underwent randomization: 281 were assigned to undergo cleft palate repair at 6 months of age and 277 to undergo repair at 12 months of age. The recruitment period —originally proposed to last 3 years — was extended to 5 years. After a review by the oversight committees at year 5, it was agreed to cease recruitment, and we did not request further extension of support from the funders.

Characteristics of the infants were similar in the two groups at baseline (before randomization) (Table 1) and at the time of surgery (Table 2). Details on enrollment, randomization, and follow-up are provided in Figure S1 and Tables S9 and S10. Tables S11 through S13 summarize adherence to the timing of primary surgery, and Tables S14 and S15 provide details on the withdrawal of infants from the trial. The completeness of data is summarized in Tables S16 through S18.

Primary Outcome

The percentage of children with velopharyngeal insufficiency at 5 years of age was significantly lower in the 6-month group than in the 12-month group (8.9% [21 of 235 children] vs. 15.0% [34 of 226 children]; risk ratio, 0.59; 95% confidence interval [CI], 0.36 to 0.99; P = 0.04) (Table 3). Results were consistent when calculated as odds ratios and adjusted for extent of the cleft and for surgeon (Table S19). Analysis with use of multiple imputation under the missing-at-random assumption resulted in a risk ratio of 0.62 (95% CI, 0.37 to 1.03; P = 0.07). Country-specific variation in the percentage of children with velopharyngeal insufficiency at 5 years of age was evident; however, the 95% confidence intervals of odds ratios overlapped, and the reasons for this variation are unclear (Fig. S2 and Table S20).

Secondary Outcomes

Speech Development

Canonical babbling at 1 year of age was present in a greater percentage of children in the 6-month group than in the 12-month group (difference, 20.7 percentage points). There were no clear differences between the groups in other secondary outcomes (Table 3). Analyses performed with the use of multiple imputation are provided in Section S7.

Hearing Sensitivity and Middle-Ear Function

At 1 year of age, hearing sensitivity and middle-ear function appeared to be poorer in the 12-month group than in the 6-month group. These differences were not apparent at 3 and 5 years of age (Table 4).

Growth and Dentofacial Development

No differences between the groups in growth outcomes were apparent at 1 year of age. Assessment of dentofacial development suggested that arch constriction at 5 years of age was greater in the 6-month group than in the 12-month group. The soft-tissue ANB angle at 5 years of age was similar in the two groups (Table 5).

Safety

The percentage of infants with postoperative and long-term complications was similar in the 6-month and 12-month groups (Table 5). Four serious adverse events were reported: three occurred in infants in the 6-month group and one in an infant in the 12-month group (Tables S21 through S25).

Post Hoc Analysis

The number of children requiring a secondary surgery was similar in the two groups, but the reasons for the secondary surgery differed between the two groups (Tables S26 and S27). A larger percentage of children in the 6-month group than in the 12-month group underwent a secondary surgery for velopharyngeal insufficiency (11.5% [27 children] vs. 7.1% [16 children]), whereas more children in the 12-month group required a secondary surgery for fistula. In a post hoc analysis that used a composite

strategy estimand[36] in which children who underwent a secondary surgery for velopharyngeal insufficiency were recategorized as having velopharyngeal insufficiency at 5 years, 41 children in the 6-month group as compared with 45 in the 12-month group were considered to have velopharyngeal insufficiency at 5 years, resulting in a risk ratio of 0.88, with a 95% confidence interval of 0.60 to 1.28, an interval that was wider than that in the primary-outcome analysis.

Discussion

In this international, randomized, controlled trial, we found that velopharyngeal insufficiency at 5 years of age was less common among children who had undergone primary surgery for cleft palate at 6 months of age than among those who had undergone the surgery at 12 months of age. At 1 year of age, canonical babbling (a developmental milestone when present before 10 months of age), hearing sensitivity, and middle-ear function were better in children with earlier repair than in those with later repair, but the benefits related to hearing sensitivity and middle-ear function attenuated over time. Consonant proficiency (assessed as the percentage of consonants vocalized correctly, the percentage vocalized with the correct place of articulation, and the percentage vocalized with the correct manner of articulation) and the percentages of nonoral and oral consonant errors were similar at 3 and 5 years of age. Postoperative and long-term complications were similar in the two groups, and adverse events were few in number. The percentage of children who underwent a secondary surgery was similar in the two groups, but reasons for the secondary surgery varied. More children in the 6-month group required a secondary surgery for velopharyngeal insufficiency, whereas more children in the 12-month group required a secondary surgery for fistula.

The results of our trial are consistent with three of four trials included in a recent systematic review.[6] The included trials were typically of small sample size, differed from each other in eligibility criteria, used heterogeneous methods to assess outcomes, used different surgical techniques and timing of surgeries, and included children with different cleft types.

We addressed some of the limitations of previous trials by standardizing the surgical technique for cleft palate repair and by having a standardized assessment of cross-linguistic speech outcomes performed by a centralized team whose members were unaware of the group assignments. Nevertheless, our trial has several limitations. Not all aspects of palatal repair are amenable to standardization, and some variation in the surgical procedure between surgeons and within surgeons was likely.[37] The trial did not include specific protocols for interventions by otolaryngologists, and the placement of pressure equalization tubes was not recorded. Speech therapy interventions accorded with routine practice and were recorded (Tables S28 to S30). Randomization was stratified by surgeon in order to balance the trial groups with respect to surgeons' experience and level of skill; as a consequence, otolaryngologic interventions in the two groups reflected the balance in routine practice. Children with cleft palate have a high risk of transient conductive hearing loss because of poor eustachian-tube function and middle-ear effusion. The hearing sensitivity and middle-ear function at 1 year of age appeared to be better in children who underwent surgical repair at the age of 6 months than in those who had yet to undergo surgery; this difference had disappeared by the assessment at 3 years of age. The number of children with a hearing test performed was low, and data on hearing sensitivity and middle-ear function are exploratory; however, the percentage of children with conductive hearing loss and middle-ear disease decreased with increasing age, irrespective of the age at primary surgery. Abnormal hearing sensitivity in both ears was observed in 62 of 218 children (28.4%) assessed at 3 years of age and in 77 of 372 children (20.7%) assessed at 5 years of age. Baker and colleagues[38] observed that 54% of children with a cleft palate had received a diagnosis of conductive hearing loss by 18 to 24 months of age.

Recruitment into the present trial was challenging. We ended recruitment before the target sample size was reached; this decision reduced power but did not introduce bias. The trial restricted eligibility

to infants who, at the discretion of the participating surgeon, were considered to be medically fit for repair at 6 months of age; 369 infants were excluded from the trial because they were not considered to be medically fit, with similar numbers excluded because of syndromes or developmental delay. Just over one third of eligible families (299 of 857) declined to participate: more than half of these families (160 of 299) did not provide a reason for declining, whereas nearly one third stated a preference for the timing of the procedure (85 families preferred surgery at 6 months of age, and 11 families preferred surgery at 12 months of age) (Table S10). Although recruitment could have included additional countries with a high incidence of cleft palate, difficulty in standardizing the language assessments and surgical intervention would probably have increased the variation in treatment effect.

Language is a background variable in cross-linguistic studies of speech outcomes, and the influence of cleft palate on a speech sound is determined by the phonetic characteristics of the sound.[23] Because languages differ according to these phonetic characteristics, the quality of speech in persons with cleft palate is language-dependent. In our trial, we minimized language differences by assessing single-word tests, rather than spontaneous speech, a choice that aligns with recent recommendations.[24,35,39] In addition, extensive strategies were undertaken to standardize the assessments. Despite our effort, it is possible that levels of language dependency remained, but they are unlikely to explain the variation in treatment effect observed among the trial countries.

The TOPS trial assessed the effect of primary surgery on speech at 5 years of age among children who underwent surgery at 6 months or 12 months of age. Given that a multidisciplinary team is involved in cleft palate treatment, we did not determine the success of the primary outcome in isolation. The children's speech at 5 years of age was evaluated without regard for intercurrent events, such as secondary surgery for velopharyngeal insufficiency or speech therapy.[36] Use of the composite estimand strategy led to a wider 95% confidence interval than use of the treatment policy estimand strategy, but it did not change the direction of the effect.

Concern has been raised about the effect of earlier surgery on facial growth.[7] Maxillary arch constriction appeared to be greater in the 6-month group than in the 12-month group, but this finding was not considered to be clinically meaningful. The timing of surgery did not affect other growth outcomes. Postoperative and long-term complications were similar in the two groups, and the number of adverse events was low; however, the TOPS trial was not powered to detect differences in safety end points. Ongoing debate about the effects of general anesthesia on global functioning and development, which may be greater at younger ages, should be considered in interpreting the results.

Several studies have reported differences in outcomes among infants with anatomically different cleft types, and care should be taken in generalizing these results beyond infants with isolated cleft palate. The TOPS trial excluded infants with syndromic cleft palate or additional diagnoses that may influence speech outcomes. In these infants, the beneficial effects of earlier surgery on speech and hearing outcomes may still be present, but such effects might be more difficult to measure because of the clinical characteristics associated with these diagnoses.

This trial provides evidence that primary palatal repair at 6 months of age results in a lower risk of velopharyngeal insufficiency at 5 years of age than repair at 12 months of age. Additional benefits of early surgery include canonical babbling, hearing sensitivity, and middle-ear function at 1 year of age. Risks associated with earlier repair may include maxillary arch constriction and the need for secondary surgery for velopharyngeal insufficiency.

Our trial included medically fit infants with isolated cleft palate who underwent palate repair at 6 months of age or 12 months of age in adequately resourced, high-volume centers. Velopharyngeal function at 5 years was better in the children who had undergone surgery at 6 months of age than in

those who had undergone surgery at 12 months of age.

Disclaimer
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Table 1. Characteristics in the Intention-to-Treat Population at Baseline.*

Characteristic	Surgery at 6 Mo (N = 279)	Surgery at 12 Mo (N = 273)
Sex — no.(%)		
Male	114 (40.9)	111 (40.7)
Not recorded	1 (0.4)	1 (0.4)
Race or ethnic group — no. (%)†		
Asian	4 (1.4)	7 (2.6)
Black	2 (0.7)	8 (2.9)
Chinese	0	0
Mixed race	13 (4.7)	16 (5.9)
White	256 (91.8)	238 (87.2)
Other	3 (1.1)	1 (0.4)
Not stated	1 (0.4)	3 (1.1)
Gestational age at birth		
Mean — wk	39.27±1.75	39.30±1.81
Not recorded — no. (%)	1 (0.4)	2 (0.7)
Cleft extent — no. (%)		
Soft palate only	93 (33.3)	93 (34.1)
Soft and hard palates	186 (66.7)	180 (65.9)
Weight without clothes		
Mean — kg	5.29±1.13	5.34±1.13
Not recorded — no. (%)	5 (1.8)	5 (1.8)
Crown-to-heel length		
Mean — cm	59.08±5.08	59.29±4.55
Not recorded — no. (%)	10 (3.6)	10 (3.7)
Occipitofrontal circumference		
Mean — cm	39.99±2.36	39.94±2.18
Not recorded — no. (%)	7 (2.5)	8 (2.9)
DDST II assessment — no. (%)‡		
Normal	251 (90.0)	247 (90.5)
Suspect	26 (9.3)	21 (7.7)
Untestable	1 (0.4)	3 (1.1)
Not recorded	1 (0.4)	2 (0.7)

* Plus–minus values are means ±SD.

† Race or ethnic group was reported by the clinician after discussion with the parent or guardian.

‡ The Denver Developmental Screening Test (DDST) II assesses 125 items in four domains of child development: personal–social, fine motor and adaptive, language, and gross motor. Each item is scored as pass (the child successfully performs the task or the caregiver reports that the child can perform the task), fail (the child does not successfully perform the task, the caregiver reports that the child cannot perform the task, or both), no opportunity (the child has not had the opportunity to perform the task because of restrictions), or refusal (the child refuses to attempt the task and the caregiver cannot report whether the child can perform the task). Items that can be completed by 75 to 90% of children but are assigned a score of "fail" are termed "cautions," and items that can be completed by 90% of children but are assigned a score of "fail" are termed "delays." Development is classified on the basis of the scores as normal (no delay and a maximum of 1 caution), suspect (≥2 cautions with or without ≥1 delay), or untested (refusal on ≥1 item).

Table 2. Characteristics of the Intention-to-Treat Population at the Time of Surgery.*

Characteristic	Surgery at 6 Mo	Surgery at 12 Mo
Patients who underwent surgery		
Total no.	266	255
Cleft palate severity at surgery — no. (%)†		
Grade 1	39 (14.7)	35 (13.7)
Grade 2	100 (37.6)	91 (35.7)
Grade 3	82 (30.8)	96 (37.6)
Grade 4	43 (16.2)	31 (12.2)
Not recorded	2 (0.8)	2 (0.8)
Sommerlad technique used		
Yes	261 (98.1)	250 (98.0)
Not recorded	2 (0.8)	1 (0.4)
Cleft shape		
U-shaped	102 (38.3)	105 (41.2)
V-shaped	160 (60.2)	149 (58.4)
Not recorded	4 (1.5)	1 (0.4)
Patients with cleft palate dimensions assessed‡		
Total no.	236	216
Soft-tissue width at posterior hard plate		
Median (IQR) — mm	7.0 (4.0–9.0)	7.0 (4.0–9.0)
Not recorded — no.	21 (8.9)	13 (6.0)
Bony width at posterior hard palate		
Median (IQR) — mm	10.0 (7.0–13.0)	11.0 (8.0–13.0)
Not recorded — no.	15 (6.4)	14 (6.5)
Width at uvula base		
Median (IQR) — mm	9.0 (7.0–11.0)	10.0 (8.0–12.0)
Not recorded — no.	12 (5.1)	11 (5.1)
Soft palate length§		
Median (IQR) — mm	16.0 (14.0–20.0)	17.0 (14.0–21.0)
Not recorded — no.	16 (6.8)	17 (7.9)

* IQR denotes interquartile range.
† Grade 1 severity is defined as a cleft extending into the soft palate only, grade 2 as a cleft extending into less than one third of the hard palate, grade 3 as a cleft extending into more than one third of the hard palate but not reaching the foramen incisivum, and grade 4 as a total cleft extending to the foramen incisivum.
‡ Excluded are 30 patients in the 6-month group and 29 patients in the 12-month group who had alternative cleft dimensions.
§ The soft palate length was measured from the distal base of the uvula to the hard palate.

Table 3. Primary Outcome and Speech Development.*

Outcome	Surgery at 6 Mo	Surgery at 12 Mo	Risk Ratio (95% CI)	Difference (95% CI)†
Primary outcome				
VPC-Sum ≥4 at 5 yr of age — no./total no. (%)‡	21/235 (8.9)	34/226 (15.0)	0.59 (0.36 to 0.99)§	—
Secondary outcomes related to speech development				
At 1 yr of age¶				
Canonical babbling present — no./total no. (%)	204/242 (84.3)	154/242 (63.6)	1.32 (1.19 to 1.48)	—
Canonical babbling ratio				
No. of patients	242	242	—	—
Ratio	0.41±0.22	0.28±0.21	—	0.13 (0.09 to 0.17)
Canonical babbling consonant inventory				
No. of patients	242	242	—	—
No. of consonants	4.54±2.34	2.91±1.68	—	1.63 (1.26 to 1.99)
At 3 yr of age				
Velopharyngeal function				
VPC-Rate — no./total no. (%)‖				
Incompetent	25/228 (11.0)	19/223 (8.5)	1.29 (0.73 to 2.27)	—
Marginally incompetent	28/228 (12.3)	33/223 (14.8)	—	—
Competent	175/228 (76.8)	171/223 (76.7)	—	—
Velopharyngeal insufficiency symptoms**				
No. of patients	218	215	—	—
No. of symptoms — median (IQR)	3.33 (0.0 to 12.5)	3.33 (0.0 to 13.3)	—	0.00 (0.0 to 0.00)††
Articulation‡‡				
No. of patients	218	215	—	—
Percent consonants correct	73.7 (53.6 to 88.5)	70.0 (55.0 to 86.7)	—	1.72 (−2.62 to 6.19)
Percent correct placement	82.5 (64.0 to 92.3)	80.0 (63.3 to 90.0)	—	1.11 (−1.90 to 4.10)
Percent correct manner	93.3 (80.8 to 100.0)	93.3 (80.0 to 96.7)	—	0.00 (0.00 to 2.76)
Nonoral consonant errors	0.0 (0.0 to 6.7)	0.0 (0.0 to 5.3)	—	0.00 (0.00 to 0.00)††
Oral consonant errors	0.0 (0.0 to 3.5)	0.0 (0.0 to 3.6)	—	0.00 (0.00 to 0.00)††
At 5 yr of age				
Velopharyngeal function				
VPC-Sum‡				
No. of patients	235	226	—	—
Value	0.93±1.47	1.17±1.69	—	−0.24 (−0.53 to 0.05)
VPC-Rate — no./total no. (%)‖				
Incompetent	21/236 (8.9)	20/221 (9.0)	0.98 (0.55 to 1.76)	—
Marginally incompetent	38/236 (16.1)	45/221 (20.4)	—	—
Competent	177/236 (75.0)	156/221 (70.6)	—	—
Articulation‡‡				
No. of patients	235	226	—	—
Percent consonants correct	88.9 (77.8 to 97.2)	88.9 (77.8 to 94.4)	—	0.00 (−2.78 to 2.78)
Percent correct placement	94.4 (83.3 to 97.2)	91.7 (83.3 to 97.2)	—	0.00 (0.00 to 2.78)
Percent correct manner	97.2 (94.4 to 100.0)	97.2 (94.4 to 100.0)	—	0.00 (0.00 to 0.00)††
Nonoral consonant errors	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	—	0.00 (0.00 to 0.00)††
Oral consonant errors	0.0 (0.0 to 0.0)	0.0 (0.0 to 2.8)	—	0.00 (0.00 to 0.00)††

* Plus–minus values are mean ±SD.

† Differences are for the 6-month group as compared with the 12-month group. The difference in medians was calculated as the Hodges–Lehmann estimate of the location shift.

‡ For calculation of the velopharyngeal composite summary score (VPC-Sum), investigators used single-word tests to assess hypernasality, symptoms of velopharyngeal insufficiency, and nonoral speech errors, with each component assigned a score of 0, 1, or 2. The VPC-Sum ranges from 0 to 6, with higher scores indicating greater severity

§ P = 0.04 for the comparison of the 6-month group with the 12-month group.

¶ For the 12-month group, assessments at 1 year of age occurred before primary surgery.

‖ The rating of velopharyngeal competence (VPC-Rate) is an auditory assessment of velopharyngeal function, categorized as competent, marginally incompetent, or incompetent.

** Symptoms of velopharyngeal insufficiency were defined as nasal emissions, velopharyngeal friction sounds, and weak and nasalized consonants.

†† The upper and lower boundaries of the 95% confidence interval are equal to 0 because of a high proportion of tied values in the Hodges–Lehmann estimate of the location shift.

‡‡ The values are median (IQR), with the percent consonants correct calculated as the percentage of consonants vocalized correctly, the percent correct placement as the percentage of consonants vocalized with the correct place of articulation, the percent correct manner as the percentage of consonants vocalized with the correct manner of articulation, nonoral consonant errors as the percentage of consonants vocalized with a nonoral error, and oral consonant errors as the percentage of consonants vocalized with an oral error.

Table 4. Secondary Outcomes Related to Hearing Level and Middle-Ear Function.

Outcome	Surgery at 6 Mo	Surgery at 12 Mo	Risk Ratio (95% CI)*
	no. of patients/total no. (%)		
At 1 yr of age			
Hearing sensitivity			
Abnormal transient otoacoustic emission	20/51 (39.2)	50/64 (78.1)	0.50 (0.35–0.72)
Abnormal findings on sound-field audiometry	51/174 (29.3)	87/173 (50.3)	0.58 (0.44–0.77)
Middle-ear function			
Flat-line tympanogram in at least 1 ear	122/175 (69.7)	177/201 (88.1)	0.79 (0.71–0.88)
Flat-line tympanogram in both ears	96/167 (57.5)	158/197 (80.2)	0.72 (0.62–0.83)
At 3 yr of age			
Hearing sensitivity			
Abnormal findings on pure-tone audiometry in at least 1 ear	94/171 (55.0)	101/174 (58.0)	0.95 (0.79–1.14)
Abnormal findings on pure-tone audiometry in both ears	30/109 (27.5)	32/109 (29.4)	0.94 (0.62–1.43)
Hearing sensitivity assessed as below normal in ear with better findings	67/169 (39.6)	72/170 (42.4)	0.94 (0.72–1.21)
Middle-ear function			
Flat-line tympanogram in at least 1 ear	109/173 (63.0)	95/180 (52.8)	1.19 (1.00–1.43)
Flat-line tympanogram in both ears	80/165 (48.5)	61/162 (37.7)	1.29 (1.00–1.66)
At 5 yr of age			
Hearing sensitivity			
Abnormal findings on pure-tone audiometry in at least 1 ear	78/195 (40.0)	70/184 (38.0)	1.05 (0.82–1.35)
Abnormal findings on pure-tone audiometry in both ears	46/191 (24.1)	31/181 (17.1)	1.41 (0.94–2.11)
Hearing sensitivity assessed as below normal in ear with better findings	36/194 (18.6)	21/182 (11.5)	1.61 (0.98–2.65)
Middle-ear function			
Flat-line tympanogram in at least 1 ear	82/189 (43.4)	72/179 (40.2)	1.08 (0.85–1.37)
Flat-line tympanogram in both ears	41/173 (23.7)	39/167 (23.4)	1.01 (0.69–1.49)

* The risk ratios were calculated for the 6-month group as compared with the 12-month group.

Table 5. Secondary Outcomes Related to Safety, Growth, and Dentofacial Development.

Outcome	Surgery at 6 Mo	Surgery at 12 Mo	Risk Ratio (95% CI)	Difference (95% CI)*
Postoperative and long-term complications — no./total no. (%)				
Dehiscence	24/265 (9.1)	23/255 (9.0)	1.0 (0.58 to 1.73)	—
Infection	12/259 (4.6)	13/246 (5.3)	0.88 (0.41 to 1.88)	—
Evidence of fistula	40/266 (15.0)	33/256 (12.9)	1.17 (0.76 to 1.79)	—
Growth at 1 yr of age				
Weight without clothes				
No. of patients	236	241	—	—
Mean — kg	9.5±1.15	9.5±1.1	—	0.01 (−0.19 to 0.21)
Crown-to-heel length				
No. of patients	238	237	—	—
Mean — cm	75.1±3.6	75.1±3.1	—	−0.05 (−0.65 to 0.55)
Occipitofrontal circumference				
No. of patients	234	235	—	—
Mean — cm	46.4±1.8	46.3±1.7	—	0.11 (−0.20 to 0.42)
Dentofacial development at 5 yr of age				
Soft-tissue ANB angle†				
No. of patients	181	180	—	—
Angle	8.6±2.6	8.6±2.4	—	−0.03 (−0.55 to 0.48)
Maxillary arch constriction score				
No. of patients	188	172	—	—
Score	−2.6±4.0	−1.6±3.7	—	−1.02 (−1.83 to −0.21)

* Differences are for the 6-month group as compared with the 12-month group.
† The ANB angle measures the relative position of the maxilla to the mandible as measured on a profile photograph.