THE EFFECT OF INFANT ORTHOPEDICS FROM 4 TO 6 YEARS OF AGE IN CHILDREN WITH UNILATERAL CLEFT LIP AND PALATE

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Chapter 1

General introduction

1.1 Introduction

Clefts of lip, alveolus and palate are among the most common birth anomalies in humans. This congenital malformation develops between the 6th and 12th week of fetal development. There are three categories: isolated cleft palate or lip, lip and alveolus clefts, and combined clefts of lip, alveolus and palate. In each category a complete or incomplete cleft can occur and the condition can be unilateral or bilateral.

The incidence of clefts in the Netherlands is 1.4 - 1.8 of 1000 newborns per year.[1] A combined cleft lip and palate occurs more often in boys and an isolated cleft palate more in girls.[2]

Since the etiology is thought to be multifactorial, it is a complex interplay between genetic and environmental factors.[3] Smoking by both parents tends to increase the CLP risk, as does periconceptional use of medication by both parents.[4] Smaller associations with oral clefts are found for alcohol consumption, drinking tea and drinking cola in the first trimester.[5] An inverse association is found for daily supplementation of folic acid (400 mcg in the first trimester).[5] Mothers of a child with a cleft report significantly more often an illness in the pregnancy compared to mothers with a healthy child.[2] Contributions from single genes, like IRF6, MSX1 en FGFR1 seem to explain 15% of the isolated clefts. Linkage scans, gene expression models and animal models may make it possible to further unravel the causes of clefts in the future.[6]

1.2 Multidisciplinary treatment

A child born with cleft lip, cleft palate, or other craniofacial anomalies may be faced with multiple and complex problems during life such as early feeding and nutritional problems (leading to deficits in growth and development); middle ear problems; hearing loss; deviations in speech and resonance; dento-facial and orthodontic abnormalities; and psychosocial adjustment problems. Interdisciplinary team care should enable most affected children to become functioning and contributing members of society. A cleft palate craniofacial team is a group of experienced and qualified professionals from medical, surgical, dental, and allied health disciplines, working in an interdisciplinary and coordinated system. According to the American Cleft Palate Craniofacial association a team consists of an operating surgeon, orthodontist, speech-language pathologist, and at least one additional specialist from otolaryngology, audiology, pediatrics, genetics, social work, psychology, and general pediatric or prosthetic dentistry, who meet face-to-face to evaluate and develop treatment plans for its patients.[7] The 'Nederlandse Vereniging voor Schisis en Craniofaciale Afwijkingen (NVSCA)' advises a team to include a plastic surgeon, an orthodontist, an ENT-specialist, a speech therapist, a maxillofacial surgeon, a dentist, a geneticist, a psychologist, a social worker and a pediatrician.[8]

Treatment protocols may differ a lot between cleft teams, as was shown in the Eurocleft project where 201 European centers exhibited 194 different treatment protocols,[9] although the main differences concentrated on the cleft palate surgery. In the six-centre Eurocleft study the six participating centers had six different protocols. The Eurocleft studies showed that although the protocol may differ, the result can be the same: the two best performing centers had completely different protocols. The professional quality of care depends partly on the components of the treatment plan, but also on the coordination factors, like timing and sequence of treatment. Another important factor is the surgeon: a high volume surgeon performs better than a low volume surgeon.[10]

This thesis deals with one aspect of the treatment plan: infant orthopedics as performed by the orthodontist in the first year of life. This is a controversial topic in the treatment of babies with unilateral cleft lip and palate and there is no consensus about the effects of infant orthopedics as part of the comprehensive treatment of these children.

1.3 Unilateral cleft lip and palate: Orthodontic concerns

1.3.1 Facial growth

The facial characteristics of a patient treated for a complete unilateral cleft lip and palate have already been described by Dahl in 1970[11] (age group 18-33 years of age). The upper facial height is smaller compared to a normal control group. The maxilla is short, and there is a greater height development in the lower face. Nearly four decades later, Nollet et al.[12] described the UCLP sample born between 1976 and 1986 (aged 8-18 years), treated in Nijmegen. Both the maxilla and the mandible showed a retrusive facial pattern; there was a rather hyperdivergent growth pattern.[12] Ross[13] found that surgery reduced the vertical development of the maxilla and the posterior-anterior development, resulting in more Class III relationships compared to a control group. All studies point in the same direction: the face of a patient treated for a cleft differs in a specific way from individuals without clefts.

These characteristics are caused by intrinsic developmental differences, functional problems, and iatrogenic factors affecting growth. Intrinsic deficiencies are related to the cleft itself. Functional problems are caused by impaired nasal breathing, deviating tongue position, and the cleft lip muscles and their insufficient functioning. The iatrogenic factors are often treatment-induced factors such as scarring due to surgery or the effect of orthodontic treatment.[13]

From the description of unoperated patients with a cleft, the iatrogenic effects of treatment are better understood. Bishara et al.[14] found that unoperated patients with a cleft had a retrusive maxilla and mandible. There was a normal relationship of the untreated cleft maxilla and the cranial base due to the rotated premaxilla combined with the retrusive upper and lower jaw, accompanied by a steep mandibular plane. Mars and Houston[15] showed that Sri Lankan male subjects who had no surgery had a potential for normal maxillary growth. Diah et al.[16] concluded that unoperated patients have a tissue deficiency, mostly in the anterior part, but the sagittal development is comparable to the normal population. In 1991 Kriens[17] found that the midsagittal maxillary length becomes shorter with more severe clefting of the bony palate.

1.3.2 Dental arch relationships

In 1970 Dahl[11] described the incisors as retroclined in treated UCLP patients of 18-33 years of age. In a more recent study it was also found that the interincisal angle was obtuse, as was the nasolabial angle.[12] Also, in these patients more Class III relationships existed. In the Eurocleft study the dental relationships were assessed using the Goslon Yardstick.[18,19] The yardstick is a set of study models arranged in five groups in which score 1 represents the best cases and 5 represents the worst subjects. The Goslon Yardstick scores in Eurocleft varied between 2.5 and 3.5 at 8-10 years of age and the scores varied from 1.7 to 3.4 at 17 years of age for the cleft centers involved, irrespective of treatment protocol.

In unoperated UCLP-patients, the smaller cleft segment shows varying degrees of medial collapse, causing crossbite. The non-cleft segment has a tendency to rotate forward.[14] The majority of the unoperated patients with a cleft would need orthodontic treatment but no surgical correction of jaw relationships. Derijcke et al.[20] scored the dental casts of 22 untreated UCLP patients as grade 2 of the Goslon Yardstick (good). According to Liao and Mars[21] upper incisors were more proclined (SN-U1 angle) in unoperated UCLP patients compared to normal controls; lower incisors had less inclination (L1-MP angle). Other studies describe retroclined upper incisors in unoperated UCLP patients.[22] Because of the different racial background of the patients in the different studies, it is hard to give one uniform description of the dental arch relationships and the inclination of the upper incisors of an unoperated UCLP patient.

1.4 History of infant orthopedics

Infant orthopedics (IO) is a therapy also known as presurgical treatment, early orthopedic treatment, presurgical orthopedics, neonatal or early maxillary orthopedics. Although many different appliances can be used, they all include treatment with a maxillary appliance at a very young age. McNeil[23-25] started to advocate infant orthopedics more than half a century ago. He believed that the deficient and retruded face developed because the palatal segments were not attached to the nasal septum. By molding the palatal segments into the correct anatomical position, this would result in a nearly normal maxilla while reducing the size of the cleft. McNeil's appliance was constructed by sectioning and reorienting the maxillary segments on the dental cast; a plate was then made on the reconstructed cast, which forced the palatal segments in the preferred position.

Over the years many CLP teams started to use plates for newborn patients with a cleft. A lot of variation can be seen between the different appliances used: active plates and passive plates, plates with external strapping across the cleft, and plates with nasal extensions (figure 1 and 2).

1.5 Type of appliances

Active appliances are designed with springs or screws to move the maxillary segments into the desired direction. Also described, is a plate made on a reconstructed cast to move the maxillary segments into a predetermined position. Passive appliances induce arch alignment during growth by grinding away material of the plate allowing for a more beneficial orientation of the maxillary segments.[26,27] Beside these appliances, external strapping across the cleft can be part of the treatment protocol.

Specific types of infant orthopedics are described in literature, for example the Kernahan Rosenstein procedure,[28,29] the Latham appliance[30] and the Zürich approach.[26] The Kernahan Rosenstein procedure includes a passive plate (figure 1), lip surgery and primary bone grafting. The plate is worn from just before lip surgery until 6 to 8 weeks after bone grafting. The bone grafting procedure is done with the segments in butt alignment. Another appliance is the one designed by Latham and Millard.[30] This is an active appliance with pins to manipulate the maxillary segments. This treatment is followed by alveolo-periosteoplasty and lip adhesion. The most used method in Europe originates from Zürich. Hotz and Gnoinski[26] proposed a passive plate (figure 2) to take advantage of the intrinsic developmental potentials during the first 18 months after birth. Surgical intervention is postponed to minimize iatrogenic effects of surgery.

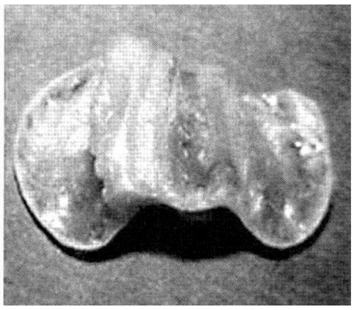

Figure 1
Passive appliance according to Kernahan and Rosenstein (1990)[28,29]

Figure 2
Passive appliance with palatal extension according to Hotz and Gnoinski (1976)[26]

More recently, Grayson and Cutting[31] developed a method to improve the shape of the nose together with molding of the alveolar segments. It is said to reshape and reposition anatomic structures to achieve more symmetrical relationships between the nasal cartilages, columella and alveolar segments prior to lip surgery.

1.6 Benefits and shortcomings of infant orthopedics

The aim of infant orthopedics is to restore the normal relationship of the palatal shelves and to restore normal oro-facial functions.

As noted by Prahl et al. in 2001[32] advocates of IO claim that the presurgical orthopedic plate molds the alveolar segments into a better arch form, and prevents the tongue from positioning in the cleft; it normalizes the pattern of deglutition and facilitates surgery. The dentomaxillary development would improve, resulting in a straighter nasal septum, improved breathing and better speech; it should make feeding easier and have a positive psychological effect on the parents.[24-26,33-42] None of the claimed advantages could be substantiated for children at the age of 1½ years.[43]

Opponents of this therapy claim that lip surgery, will have the same molding effect and that the presurgical orthopedic plate is only an expensive appliance used to comfort the parents by starting treatment at the earliest moment possible. It restricts maxillary growth and makes patients and parents travel a lot.[10,13,18,32,45-49]

1.7 Drawbacks of previous studies

In most of the studies mentioned above, IO was not the only technique used. It can therefore not be concluded that positive effects of the treatment protocol were due to IO alone. Neither can it be concluded that it had negative effects such as anterior crossbite or a retrusive midface. Often non-cleft controls were used instead of patients with clefts. This makes a systematic, evidence based conclusion about any type of infant orthopedic appliance impossible based upon the published retrospective studies available. Besides the study design, long term results of the effect of infant orthopedics are lacking.

For this reason, Dutchcleft was designed as a prospective study: a two-group randomized controlled clinical trial. The trial was started in 1993 in the cleft palate centers of Nijmegen, Amsterdam, and Rotterdam. Short term results on different aspects of this trial have been published in earlier PhD theses.[43,50-51]

1.8 Dutchcleft

1.8.1 Experimental design

A detailed description of the experimental design has been given by Prahl et al.[32] A summary of the most important issues is given. The inclusion criteria were: complete UCLP, infants born at term, both parents Caucasian and fluent in the Dutch language, and trial entrance within two weeks after birth. The exclusion criteria were soft tissue bands, and other congenital malformations. A child entered the study within two weeks after birth. Patients were randomized taking into account birth weight (<3300 g or ≥ 3300 g) and cleft width (< 8 mm, between 8 and 12 mm, and ≥ 12 mm).

Figure 3 *Passive plate for infant orthopedics as used in the Dutchcleft study.*

Selected at random, half of the patients were treated with infant orthopedics by means of passive plates (figure 3) until surgical soft palate closure (n=27) (IO+ group); the other half did not get a plate (n=27) (IO- group). The plates were made on a plaster cast using compound soft and hard acrylic. The IO+ children had their plates adjusted every three weeks to guide the maxillary segments, by grinding at the cleft margins; maxillary growth and emergence of upper deciduous teeth indicated the necessity for a new plate. After surgical lip closure the plate was replaced the same day. Checkups were planned every 4 to 6 weeks following lip surgery. The plate was maintained until soft palate closure. The IO- group visited the clinic at 6 weeks of age, and before and after lip surgery and soft palate closure. In both groups, lip surgery was performed at the age of 18 weeks by the Millard technique. At lip surgery, the cleft teams of Amsterdam and Nijmegen used the McComb's technique for repositioning of the nose;[52] the Rotterdam cleft team preferred their own method that combined McComb's with Pigott's technique.[53] Soft palate surgery was performed at the age of about 52 weeks according to a modified Von Langenbeck method including levator muscle repositioning (modification according to Kriens).[17] Hard palate closure was delayed until approximately 9 years of age.

In the trial the following aspects were studied: general variables such as feeding; surgical and orthodontic variables such as facial esthetics and maxillary growth; speech and language development; and cost effectiveness. For all aspects the results until the age of 2 ½ years, are summarized below.

1.8.2 General variables

Feeding (figure 4) was evaluated from birth till 24 weeks of age, measuring daily the total time spent on feeding and the total volume of food intake. The child's length and weight were evaluated regularly until 14 months of age.[54] Feeding velocity increased with time in both groups. There was no significant difference between IO- and IO+. The same was found for weight-for-age, length-for-age and weight-for-length. It was concluded that infant orthopedics with the aim of improvement of feeding and nutritional status in infants with cleft lip and palate, can be abandoned.

Figure 4 *A Haberman squeeze bottle (Mead Johnson or Haberman was advised in Dutchcleft)*

The satisfaction of the motherhood was assessed with questionnaires.[44] For the response a four-point scale was used, with 1 being very satisfactory and 4 being very unsatisfactory. For all variables no differences between IO+ and IO- were found, so it can be concluded that IO has no effect on satisfaction of motherhood.

1.8.3 Surgical and orthodontic variables

The issues that were studied are: facilitation of surgical lip closure, maxillary development, facial appearance, occlusion, and facial growth.
The time needed for the lip surgery did not differ significantly between IO+ and IO-[55]. For IO+ the mean was 57.2 minutes, and for IO- 56.4 minutes. IO did not make surgery easier in such a way that the duration of surgery was reduced.

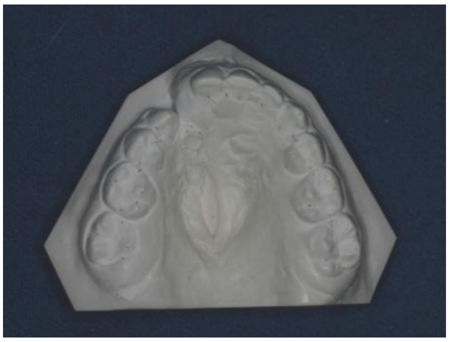

Figure 5 *Maxillary dental arch of a patient with a right-sided UCLP.*

Figure 5 shows an example of the maxillary dental arch in a patient with a complete UCLP. Maxillary dental arch forms were comparable between IO+ and IO- at birth. With time the frequency of segmental collapse increased. IO could not prevent collapse of the maxillary arch.[56] Maxillary arch dimensions were evaluated on dental casts as well. IO had a temporary positive effect on maxillary arch dimensions, which did not last beyond surgical soft palate closure.[32] Cleft width reduced more in the IO+ group before lip closure and more in the IO- group after lip surgery.

Full face and cropped photographs were evaluated by professionals and laymen using a visual analogue scale (VAS) and number scores. To pool the response modalities Z-scores were calculated. The results of the esthetic scores at the age of 1.5 years, showed no significant and relevant effect of IO on facial appearance.[57]

It was concluded that up to the age of 1 ½ year the type of IO as performed in this study had no positive or negative long lasting effect on surgical and orthodontic variables.

1.8.4 Speech and language development

Evaluation of speech and language development (figure 6) showed that at the age of 12 months the IO+ group presented enhanced use of alveolar articulations; however, at the age of 18 months, sound production in babbling was comparable in both groups.[58] The speech results at 2.5 years of age showed differences in intelligibility between the groups. In two different experiments, untrained listeners, as well as experienced speech and language therapists gave higher ratings to the intelligibility of the

IO+ group.[51] However, data obtained by a transcription task indicated no differences in intelligibility.[59] At 2.5 years of age, the phonological development of the IO+ children was normal or delayed, whereas most IO- children had abnormal development. Half a year later it appeared that the IO+ children had acquired more initial consonants than the IO- group.[60] In the same age groups the IO+ children used longer sentences than the IO- children, indicating that their grammatical development was more advanced. At the age of 6 no differences in expressive language skills between the two groups were found. The early speech results show a positive effect of IO on speech. However, this was not seen at six year of age (for the measurements evaluated until now). The effect seems to be temporary.[61]

Figure 6. *Speech test*

1.8.5 Cost-effectiveness

Costs (figure 7) can be divided into medical costs (personnel, materials and overhead costs), direct non-medical costs (travel expenses) and indirect non-medical costs (time investment of parent(s)).

The direct medical costs for IO treatment were calculated in 1998 to be US$ 852 for 18 weeks of treatment. The IO- group spent US$ 304 on medical treatment in the same time span. Travel expenses were for IO+ US$ 128 and for IO- US$ 79 and indirect medical expenses were US$ 231 for IO+ and US$ 130 for IO-.[55]

Data published in 2004 show the cost-effectiveness of the speech outcome at the age of 2.5 years: listeners (speech therapists) were asked to rate the speech quality on a 10-point scale of 10 IO+ children and 10 IO- children. The IO+ group had a significant better rating for speech.

The resulting cost-effectiveness ratio was € 1041 for 1.34 point of speech improvement.[62] It was concluded that IO is a very expensive treatment in relation to the effects obtained.

Figure 7 *Costs*

1.9 Objectives

This thesis describes the evaluation of infant orthopedics at the age 4 and 6 years in children with a complete unilateral cleft lip and palate from an orthodontic point of view. At the age of 4 and 6, study casts, photographs and cephalograms were made of the trial children. These materials were used to evaluate the maxillary arch dimensions, occlusion, facial esthetics and facial growth for the IO+ and IO-group. The same methodology as used at earlier ages was adopted for the evaluation of these variables. This made it possible to look at age related changes. For the analysis of 4- and 6-year results also new methods were introduced and tested.

The participating teams in the Dutchcleft-study will continue to document this unique group of patients over a longer period of time.

1.10 Overview of the thesis

The present study is part of Dutchcleft, which is a randomized controlled clinical trial. It describes the effect of Infant Orthopedics (IO) at the age of 4 and 6 years.

In chapter 1 general aspects of the Dutchcleft trial are introduced: the treatment protocol and the type of infant orthopedics.

In chapter 2 the effect of infant orthopedics on the occlusion in the deciduous dentition is discussed.

In chapter 3 maxillary arch dimensions are presented as evaluated on dental casts.

Chapter 4 describes facial appearance measured on full face and cropped photographs.

In chapter 5 a study for alternative landmarks for ANS, PNS and point A is presented because in young patients with a cleft, these landmarks are hard to detect on cephalograms because of the cleft and the rotated unerupted incisors in that area.

In Chapter 6 a cephalometric study is presented evaluating facial growth for the IO+ and IO- group.

In chapter 7 the findings of the previous chapters are discussed in a wider context.

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Chapter 2

The effect of infant orthopedics on the occlusion of the deciduous dentition in children with complete unilateral cleft lip and palate

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Summary

Objective: Evaluation of the effect of infant orthopedics (IO) on the occlusion of the deciduous dentition in patients with unilateral cleft lip and palate (UCLP).

Design: Prospective, two-arm, randomized, controlled clinical trial with three participating cleft palate centers (Dutchcleft).

Setting: Cleft palate centers of the University Medical Center Nijmegen, Academic Center of Dentistry Amsterdam, and Dijkzigt University Hospital Rotterdam, The Netherlands.

Patients: Children with complete UCLP (n=54) were included.

Interventions: In a concealed allocation procedure, half of the patients was randomized to wear a plate till surgical closure of the soft palate (IO+), and the other half (IO-) did not have a plate.

Mean outcome measures: Dental arch relationships were assessed at 4 and 6 years of age with the 5-year-old index; the Huddart-score; and measurements of overjet, overbite, and sagittal occlusion.

Results: There were no significant differences found between the IO+ and IO- groups for the 5-year-old index; the Huddart-score; and overjet, overbite, and sagittal occlusion.

Conclusions: IO had no observable effect on the occlusion in the deciduous dentition at 4 and 6 years of age. Considering the occlusion only, there is no need to perform IO in children with UCLP.

2.1 Introduction

Infant orthopedics (IO) was introduced as a treatment to improve maxillary arch form and the position of the alar base to prevent crossbites and to facilitate surgery.[1,2] Other advantages reported in the literature are straightening of the nasal septum, normalization of the deglutition process, prevention of twisting and positioning of the tongue in the cleft, and better speech development.[3-19] Disadvantages mentioned in literature include maxillary growth restriction, negative influences on speech because of delayed palate closure, the costs of the treatment, and its complexity.[20-24]

Many different appliances, both active and passive, have been described.[10] The so-called Zürich approach, using a passive plate of soft and hard acrylic, has had a major influence on treatment by the European cleft teams.[7] Studies dealing with the effect of (passive) IO on occlusion show different results. Hotz and Gnoinski[3,4] and Gnoinski[7] described that there are less anterior and canine crossbites after presurgical orthopedic treatment with the Zürich appliance combined with delayed surgery, in comparison with their previous treatment procedure, which was the McNiel-type orthopedic treatment with conventional surgery. Huddart found good short-term results for the maxillary arch dimensions, when comparing patients treated with infant orthopedics (IO+) with patients not treated with infant orthopedics (IO-). However, at the age of 5 years, the patient groups were comparable with respect to the number of teeth in crossbite and the severity of the crossbite.[5,21,25] O'Donnell et al.[26] evaluated the occlusion in the deciduous and mixed dentition of patients treated with IO in terms of crossbite malocclusion. A comparison was made with samples of other investigators, some with IO and some without IO. Because of differences in treatment protocol of the samples, the authors concluded that a comparison between IO+ and IO- could not be made.[26] In the Eurocleft studies, the centers that practice passive presurgical orthopedics did not show demonstrable advantages in terms of dental relationship. Here also, other differences in treatment protocols between centers were present.[27-29] One of the few studies with a better research design was conducted by Mishima et al.[11-13] The investigators used a two-group quasi-randomized design, in which twelve were treated with Hotz plate and eight without. At the age of 4 years, they observed larger transverse deciduous canine and second deciduous molar widths for the IO+ group, compared with the IO- group.[11-13]

Because many studies on the effect of IO have a retrospective design, include only a small sample of subjects with unilateral cleft lip and palate (UCLP), lack a control group of UCLP children without IO, do not take confounding variables into account, or measure only at a certain age, uncertainty about the effectiveness of IO remains.[27-33] Therefore, a prospective randomized clinical trial was performed in three cleft palate centers in the Netherlands, i.e., the cleft palate centers of Amsterdam, Nijmegen, and Rotterdam, to investigate the effect of IO in children with complete UCLP (Dutchcleft). The results, until 1½ years of age, showed that IO had a temporary effect on the maxillary arch dimensions, which did not last beyond surgical soft palate closure.[24] Also, it did not prevent collapse of the maxillary arch.[34] Evaluation of speech and language development showed that at the age of 12 months, the IO+ group presented enhanced use of alveolar articulations; however, at the age of 18 months, sound production in babbling was comparable in both groups.[35] The speech results at 2.5 years of age showed differences in intelligibility between the groups. In two different experiments, untrained listeners as well as experienced speech and language therapists gave higher ratings to the intelligibility of the IO+ group.[17] However, data obtained by a transcription task indicated no differences in intelligibility.[16] At 2.5 years of age, the phonological development of the IO+ children was normal or delayed, whereas most IO- children had abnormal development. Half a year later it appeared that the IO+ children had acquired more initial consonants than the IO- group.[19] In the same age groups, the IO+ children used longer sentences than the IO- children, indicating that their grammatical development was more advanced. At the age of 6 years, no differences in expressive language skills between the two groups were found.[18]

The purpose of the part of the Dutchcleft trial presented here was to evaluate the effect of IO on the occlusion of the deciduous dentition in children with UCLP, aged 4 and 6 years. The hypothesis to be tested is that the occlusion is not different between the IO+ group and the IO- group.

2.2 Methods

A detailed description of the experimental design, treatment assignment, treatment protocol, and operators used in this study can be found in Prahl et al.[24] A summary of the most important issues is given below.

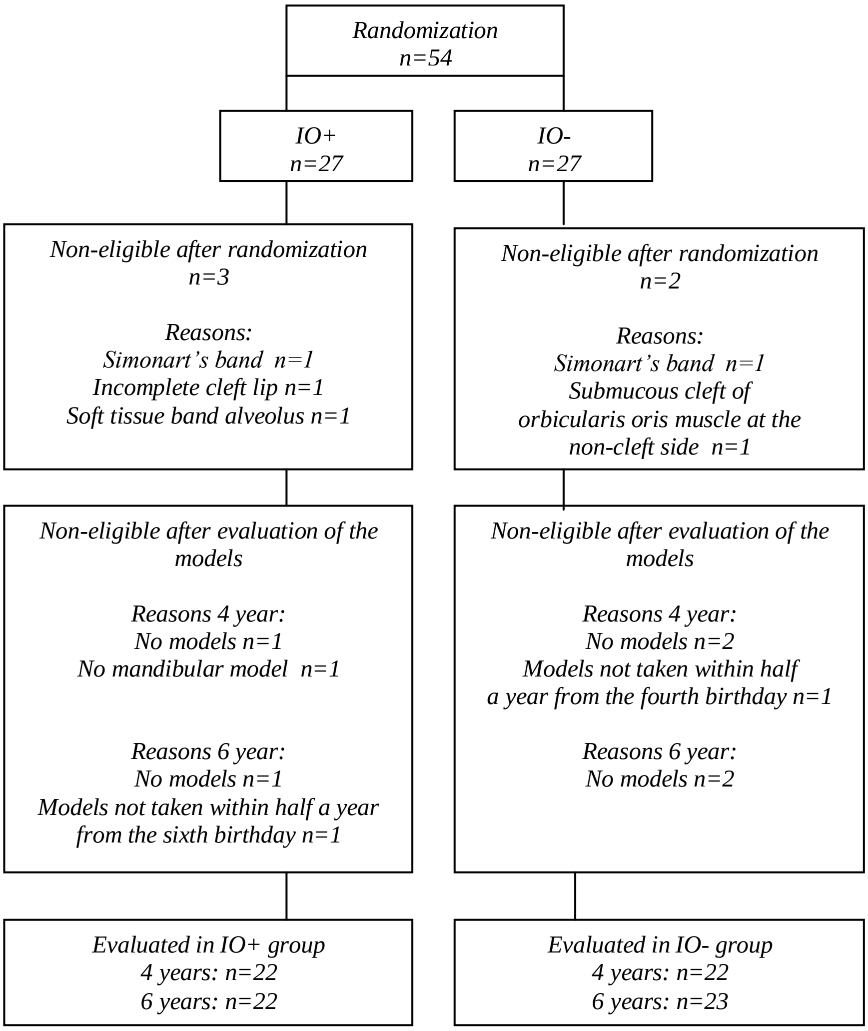

Figure 1 *Flow diagram of trial children with the reasons for exclusion of evaluation.*

The study was designed as a prospective, two-arm, randomized, controlled clinical trial in the cleft palate centers in Nijmegen, Amsterdam, and Rotterdam, The Netherlands. The local ethical committees approved the study protocol. The inclusion criteria were complete UCLP, infants born at term, both parents Caucasian and fluent in the Dutch language, and trial entrance within 2 weeks after birth. The exclusion criteria were soft tissue bands and other congenital malformations. Figure 1 shows the follow-up until the age of 6 years, with the reasons for exclusion of evaluation. When the parents agreed to participate in the study, they were asked to provide informed consent. Between 3 and 6 months of age, all included children were checked by the geneticist of their own cleft lip and palate (CLP) team as being non-syndromic.

2.2.1 Treatment

Half of the patients were treated with IO by means of passive plates until surgical soft palate closure (n=27), and half did not receive a plate (n=27). The plates were made on a plaster cast using compound soft and hard acrylic. The IO+ children had their plates adjusted every 3 weeks to guide the maxillary segments by grinding at the cleft margins; maxillary growth and emergence of deciduous teeth indicated the necessity for a new plate. After surgical lip closure, the plate was replaced the same day. Check-ups were planned every 4 to 6 weeks following lip surgery. The plate was maintained until soft palate closure. The IO- group visited the clinic at 6 weeks and before and after lip surgery and soft palate closure. In both groups, lip surgery was performed at the age of 18 weeks by the Millard technique; soft palate surgery was performed at the age of about 52 weeks according to a modified Von Langenbeck method. In the studied age period (until 6 years of age), other interventions were performed if indicated: pharyngoplasty (n=22), lip revision (n=13), facial mask treatment (n=1), plate to improve speech (n=15), and closure of the anterior palate (n=6). These extra interventions are equally distributed over the IO+ and the IO- group.

2.2.2 Data acquisition

To evaluate the occlusion, impressions were taken at ages 4 and 6 years. In Nijmegen the impressions were made with Cavex CA 37 (Cavex

Holland BV, Haarlem, The Netherlands); in Amsterdam with Lastic (Kettenbach Dental, Eschenburg, Germany); and in Rotterdam with Tetra-chrom (Kaniedenta, London, England and München, Germany). Plaster casts were then fabricated. To eliminate bias, the examiners were able to identify neither children nor the cleft palate center the models came from. Therefore, all models were duplicated and trimmed in the same way.

The dental arch relationship was assessed on the study models using the 5-year-old index.[36,37] This index categorizes arch relationships of patients with UCLP using reference models. The method is comparable with the Goslon Yardstick, used for the late mixed and early permanent dentition.[38] A pilot examination was done by four observers with 10 casts. It appeared necessary to adjust some rules within the original index because many casts were categorized between 1 and 2 or 2 and 3. The adjustments are shown in Table 1. Three examiners, experienced in cleft lip and palate, and one less experienced examiner, assessed all casts twice. For the second scoring, the sequence of the casts was changed to minimize memory effects.

Tabel 1 *A listing of features of the 5-year-old index to be assessed on the study models index.*

1	(excellent) Positive (*normal or enlarged)* overjet with average inclined or retroclined incisors. No crossbites/*crossbite tendency of 1 or 2 teeth in the smaller segment.* No open bites or vertical steps around the cleft site. Good maxillary arch shape and palatal vault anatomy.
2	(good) Positive overjet with average inclined or proclined incisors. Unilateral crossbite/crossbite tendency *of the whole smaller segment.* Open bite tendency around cleft site. *Edge to edge in the front without crossbites in the lateral segments.*
3	(fair) Edge-to-edge bite with average inclined or proclined incisors. Reversed overjet with retroclined incisors. Unilateral crossbite. Open bite tendency around cleft site.
4	(poor) Reversed overjet with average inclined or proclined incisors. Unilateral crossbite/bilateral crossbite tendency. Open bite tendency around cleft site.
5	(very poor) Reversed overjet with proclined incisors. Bilateral crossbite. Poor maxillary arch form and palatal vault anatomy.

* Italic text represents features that were adjusted in the original index.

The overjet and the overbite were measured to the nearest millimeter with a Korkhaus divider at the central incisors of the non-cleft side on the casts. The overbite was calculated as a percentage of the length of central lower incisor of the non-cleft side.

The sagittal occlusion was scored for the deciduous canines and second deciduous molars according to the Angle classification. Class I occlusion was scored as zero; Classes II and III occlusions were scored in premolar widths. A quarter premolar width was scored as 1, half a premolar width was scored as 2, three quarter premolar width was scored as 3, and a full premolar width was scored as 4. A positive sign meant Class II and a negative sign meant Class III.[39] The scoring system is described in Table 2.

Table 2 *Sagittal Occlusion Scoring System*.*

SCORE	*MEANING*	
+4	*1 premolar width*	*Class II*
+3	*¾ premolar width*	
+2	*½ premolar width*	
+1	*¼ premolar width*	
0		*Class I*
-1	*¼ premolar width*	
-2	*½ premolar width*	*Class III*
-3	*¾ premolar width*	
-4	*1 premolar width*	

** + = Angle class II; - = Angle class III; 0 = Angle class I. Every point difference corresponds with one fourth premolar width difference in occlusion.*

Huddart’s scoring system was used to evaluate the severity and location of crossbites. A score, as shown in Figure 2, is given to each tooth in relation to its antagonist. The lateral incisors are not assessed because they are often missing at the cleft side. If another tooth is missing, it will be scored as the mean of the scores of the neighboring teeth. The sum of the scores of all teeth forms the Huddart score.[21,25,39]

To assess the inter- and intraobserver agreement for the overjet, overbite, sagittal occlusion, and Huddart’s score, all measurements at the age of 4 years were done twice by two examiners. The first observer did also do double measurement on 6 years of age.

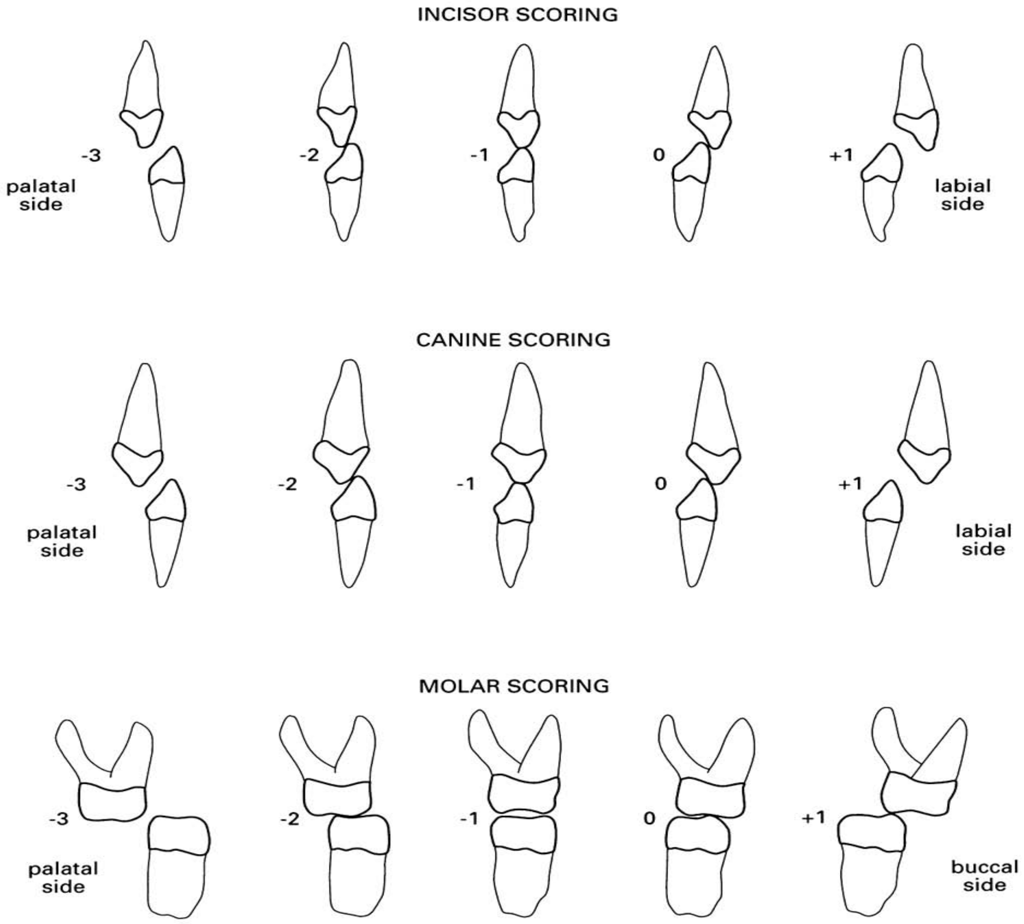

Figure 2 *Huddart's scoring of transverse dental relationship.*

2.2.3 Statistical analysis

For intra- and interexaminer agreement of the 5-year-old index, weighted kappas were calculated at 4 and 6 years of age. Cronbach's alpha was calculated as the reliability coefficient of the mean 5-year-old index score, for 4 and 6 years of age.

For the overjet, overbite, sagittal occlusion according to Angle (overall, cleft side, and non-cleft side), and the crossbite score according to Huddart (overall, cleft side, and non-cleft side), intraexaminer error (duplicate error) was calculated for 4 and 6 years of age. The interexaminer error and the corresponding reliability coefficient (Pearson correlation coefficient) were calculated at the age of 4 years.

To test the differences between IO+ and IO- at ages 4 and 6 years and for the increment, Student's t-tests were used.

2.3 Results

2.3.1 General

At intake, 54 patients participated in the study. An overview of the sample characteristics is given in Table 3. Two IO+ children hardly used the plate, and in one case the plate was mistakenly worn until 78 weeks. These children remained in the IO+ group based on the intention-to-treat principle. The mean duration of IO was 50 ± 16 weeks. Of all children, 44 were available for evaluation at the age of 4 years and 45 at the age of 6 years. The flow diagram in Figure 1 shows the reasons for nonevaluation.

Tabel 3 *Sample Characteristics*.*

Variable	*IO + (n=27)*			*IO- (n=27)*		
Gender: male/female (n)	*20/7*			*21/6*		
Side of cleft: left/right (n)	*17/10*			*18/9*		
Patients per centre: 1/2/3 (n)	*7/11/9*			*7/10/10*		
Age 4-year casts (years.months)	*mean: 4.0 range:3.8-4.4*			*mean: 4.0 range:3.10-4.6*		
Age 6-year' casts (years.months)	*mean: 6.0 range:5.9-6.2*			*mean: 6.0 range:5.11-6.5*		
	IO +			*IO -*		
	P10	*P50*	*P90*	*P10*	*P50*	*P90*
Age at trial entrance (days)	*0*	*3*	*7*	*1*	*6*	*13*
Birth weight (gram)	*2660*	*3350*	*4020*	*2920*	*3600*	*4280*
Cleft width at birth (mm)	*9.5*	*12.5*	*14.4*	*8.6*	*12.4*	*16.4*
Age lip repair (days)	*117*	*127*	*142*	*117*	*125*	*138*
Age soft palate closure (days)	*355*	*375*	*438*	*301*	*367*	*389*

** Some variables are presented in percentiles because of skewness (P10, P50, and P90). IO+ = patients treated with infant orthopedics; IO- = patients not treated with infant orthopedics; P10 = 10th percentile; P50 = 50th percentile; P90 = 90th percentile.*

2.3.2 Reliability of measurements

The kappas for the intraexaminer agreement of the 5-year-old index measurements varied from 0.91 to 0.97. The kappas for the interexaminer agreement of the 5-year-old index measurements ranged from 0.77 to 0.91. A kappa value between 0.81 and 1.00 indicates a very good agreement, whereas a kappa between 0.61 and 0.80 indicates a good agreement. The result of the reliability analysis showed a Cronbach's alpha of 0.97 for the first series of measurements and for the second series of measurements, 0.96.

The interexaminers errors were small: 0.5 mm for the overjet, 13% for the overbite, 0.4 points for the sagittal occlusion, and 1.6 points for the Huddart score. As expected, the intraexaminer errors were lower than the interexaminer errors. The reliability coefficients for the interexaminer errors were between 0.86 and 0.92, indicating a good reproducibility.

2.3.3 Treatment effects

Mean values and SDs for all variables describing the occlusion are given in Table 4 for both ages. Because there were two extreme positive overjet measurements in the 4-year group, the distribution for the variable overjet was not normal. Winsorization was applied as a transformation to normality; values larger than 5 mm were reduced to 5 mm. For the 5-

Table 4 *Means and SD of the measured variables for IO+ at age 4 and 6y*.*

	IO+ Age 4 y			*IO- Age 4 y*			
Variable	*n†*	*Mean*	*(SD)*	*n†*	*Mean*	*(SD)*	*p*
5-y-old index (group)	*21*	*2.01*	*(0.73)*	*22*	*1.98*	*(0.81)*	*.89*
Overjet (mm)	*21*	*1.35*	*(1.25)*	*22*	*2.08*	*(2.44)*	*.23*
Overbite(%)	*21*	*32.45*	*(41.94)*	*22*	*23.50*	*(35.99)*	*.46*
Sagittal occlusion, overall (pt)	*22*	*0.93*	*(1.10)*	*22*	*1.28*	*(1.01)*	*.28*
Sagittal occlusion, cleft side (pt)	*22*	*1.39*	*(1.48)*	*22*	*1.79*	*(1.38)*	*.36*
Sagittal occlusion, non-cleft side (pt)	*22*	*0.48*	*(0.90)*	*22*	*0.77*	*(0.86)*	*.28*
Transverse occlusion, overall (pt)	*22*	*-1.44*	*(3.28)*	*22*	*-2.46*	*(4.22)*	*.37*
Transverse occlusion, cleft side (pt)	*22*	*-1.81*	*(2.33)*	*22*	*-2.52*	*(3.02)*	*.39*
Transverse occlusion, non-cleft side (pt)	*22*	*0.37*	*(1.66)*	*22*	*0.06*	*(1.59)*	*.53*
	IO+ 6 y			*IO- Age 6 y*			
Variable	*n†*	*Mean*	*(SD)*	*n†*	*Mean*	*(SD)*	*p*
5-y-old index (group)	*20*	*2.23*	*(0.84)*	*21*	*2.16*	*(0.85)*	*.80*
Overjet (mm)	*20*	*1.30*	*(1.15)*	*20*	*1.30*	*(1.68)*	*1.00*
Overbite(%)	*17*	*23.97*	*(34.90)*	*20*	*15.17*	*(39.87)*	*.48*
Sagittal occlusion, overall (pt)	*22*	*1.02*	*(1.14)*	*23*	*1.21*	*1.21*	*.56*
Sagittal occlusion, cleft side (pt)	*22*	*1.57*	*(1.77)*	*23*	*1.68*	*1.68*	*.80*
Sagittal occlusion, non-cleft side (pt)	*22*	*0.47*	*(0.78)*	*23*	*0.74*	*0.74*	*.38*
Transverse occlusion, overall (pt)	*22*	*-3.02*	*(3.34)*	*23*	*-3.52*	*-3.52*	*.64*
Transverse occlusion, cleft side (pt)	*22*	*-2.63*	*(2.51)*	*23*	*-2.76*	*-2.76*	*.86*
Transverse occlusion, non-cleft side (pt)	*22*	*-0.40*	*(7.75)*	*23*	*-0.76*	*-0.76*	*.48*

** The differences between IO+ and IO- were tested with t-tests. The level of significance is indicated with p values.*
† n may vary because of incidental missing values (e.g, shedding of incisors). IO+ = patients treated with infant orthopedics; IO- = patients not treated with infant orthopedics.

year-old index, the overjet, the percentage overbite, the sagittal occlusion (overall, cleft side, and non-cleft side), and the transverse occlusion (overall, cleft side, and non-cleft side), no significant differences were found between IO+ and IO- (all $p > .05$).

Table 5 shows the results of the Student's t-tests for the increments between 4 and 6 years. No significant differences between the IO+ and IO- group were found for any of the variables.

The distribution of subjects over the five categories of the 5-year-old index at the age of 4 years and 6 years is shown in Figure 3 for IO+ and IO-.

Table 5 *Mean and SD of the increments from 4 to 6 y of the measured variables for IO+ and IO-*.*

	IO+ Increment			IO- Increment			
Variable	*n†*	*Mean*	*(SD)*	*n†*	*Mean*	*(SD)*	*p*
5-y-old index (group)	*20*	*0.22*	*(0.32)*	*21*	*0.13*	*(0.45)*	*.49*
Overjet (mm)	*18*	*-0.18*	*(1.02)*	*19*	*-0.25*	*(0.92)*	*.81*
Overbite(%)	*15*	*-21.29*	*(21.87)*	*19*	*-8.76*	*(23.03)*	*.12*
Sagittal occlusion, overall (pt)	*20*	*0.07*	*(0.61)*	*21*	*0.05*	*(0.48)*	*.88*
Sagittal occlusion, cleft side (pt)	*20*	*0.13*	*(0.94)*	*21*	*0.05*	*(0.96)*	*.78*
Sagittal occlusion, non-cleft side (pt)	*20*	*0.01*	*(0.87)*	*21*	*0.04*	*(0.57)*	*.87*
Transverse occlusion, overall (pt)	*20*	*-1.67*	*(1.47)*	*21*	*-0.70*	*(1.91)*	*.07*
Transverse occlusion, cleft side (pt)	*20*	*-0.93*	*(0.84)*	*21*	*-0.00*	*(1.87)*	*.06*
Transverse occlusion, non-cleft side (pt)	*20*	*-0.74*	*(0.89)*	*21*	*-0.70*	*(1.80)*	*.94*

** The differences between IO+ and IO- were tested with t tests. The level of significance is indicated with p values.*

† n may vary because of incidental missing values (e.g., shedding of incisors). IO+ = patients treated with infant orthopedics; IO- = patients not treated with infant orthopedics.

2.4 Discussion

To compensate for shortcomings of earlier studies, the design of the present study was a prospective, two-armed, randomized, controlled clinical trial.[24] The number of patients involved in the study decreased from 54 to 44 in the 4-year-old age group and from 54 to 45 in the 6-year-old group. Still, the number was larger than most previous studies. For example, Mishima et al.[11-13] had a sample of 12 IO+ and 8 IO- patients, Huddart[25] had 34 IO+ patients and 13 IO- patients, Pruzansky and Aduss[20] studied 33 patients, and the Eurocleft centers had samples of

19 to 30 patients.[28] But none of these studies was designed as a randomized clinical trial.

To evaluate occlusion in patients with CLP, different methods have been used in the past. Mostly, these methods describe the transverse (e.g. Huddart score),[21] vertical (e.g. overbite), or sagittal relationship (e.g. occlusion according to Angle classification or overjet).[40] An evaluation of the occlusion in more than one direction is rare. Because the introduction of the Goslon Yardstick, a clinical tool is available to categorize late mixed and permanent dentitions in a sensitive way.[38] Noverraz et al.[41] showed that the original Goslon Yardstick was a reproducible method to score the dental arch relationship in other stages of dental development, too.

Nevertheless, a separate index, the 5-year-old index, was later developed to assess treatment outcome in the deciduous and mixed dentition.[36,37] Because the 5-year-old index is the most commonly used method for the deciduous dentition, this method was used for Dutchcleft. Although many studies used indices,[14,28,42-45] only one mentioned problems with the categorization. Friede et al.[42] used a modification of the Goslon yardstick. In their yardstick, Class 1 represents no crossbite or minor lateral or minor anterior crossbite; class 2 is a lateral crossbite with or without a minor anterior crossbite; class 3 means an anterior and lateral crossbite; class 4 represents patients with an anterior and lateral crossbite and a slight malrelation between the maxilla and mandible, whereas in class 5 there is an definite malrelation between the arches. In Dutchcleft, all examiners tended to score many casts as 1.5 or 2.5, although the 5-year-old index has only five categories. Some rules of the original index (Table 1) were adjusted to be able to score such a cast as a 1 or 2, instead of 1.5. The results show that most patients were categorized in groups 1 to 3 (Figure 3). Only two patients were graded as 4 (one at the age of 4 years and one 6 years of age). None of the patients was graded as 5.

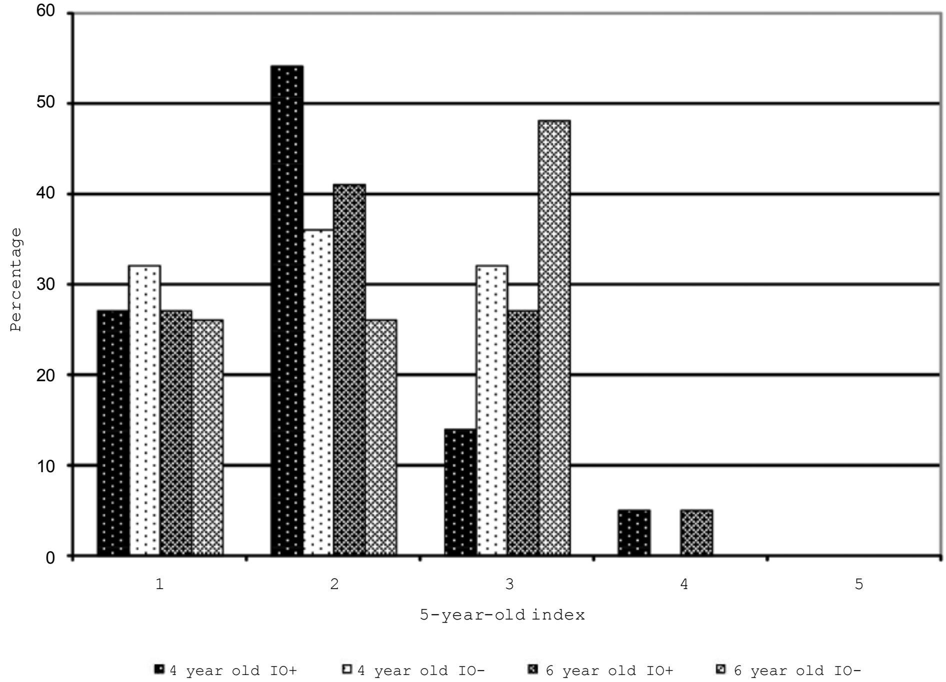

Figure 3 *Graphic representation of the percentages of the total sample in each 5-year-old index group; at the age of 4 and of 6 years for IO+ and IO- (1=excellent, 2=good, 3=fair, 4=poor, and 5=very poor). The actual number of subjects in each group, given in the same sequence as the bars of this figure (from left to right), is: group 1: =6, 7, 6, 6; group 2: n=12, 8, 9, 6; group 3: n=3, 7, 6, 11; group 4: n=1, 0, 1, 0;group5:n=0, 0, 0, 0.*

This is in contrast with the results of the Clinical Standards Advisory Group (CSAG) study,[45,46] for which the 5-year-old index was developed and 37% of the cases were classified in groups 4 and 5. To classify samples with good treatment results more precisely, future studies might consider modifying the original index in such a way that a better discrimination in the lower categories is achieved.

In addition to this index, the overjet, overbite, sagittal, and transverse occlusion were also measured to show whether positive differences between the IO+ and IO- groups for the 5-year-old index were due to deviations in the sagittal, vertical, or transverse dimension.

Few studies have been published regarding occlusion in the deciduous dentition, and even fewer studies have been written about the effect of IO on the deciduous dentition in patients with UCLP. Nordén et al.[47] evaluated the deciduous dentition in children treated without IO, using the overbite, the overjet, the sagittal occlusion, and a crossbite score that was described by Pruzansky and Aduss,[20] but no conclusions on these variables can be drawn because the study included patients with all kinds of clefts.

Huddart[25] completed a retrospective non-randomized study into the effect of IO with a passive plate. By using his numerical crossbite score, he showed that at 5 years of age, there was no significant difference between the IO+ group (-6.32 SD 4.55) and the IO- group (-6.31 SD 3.97). These findings are in accordance with our findings, but the crossbite scores in our study show fewer teeth in crossbite and less severe crossbites (4-year-olds: IO+: -1.44 SD 3.28; IO-: -2.46 SD 4.22; 6-year-olds: IO+: -3.02 SD 3.34; IO-: -3.52 SD 3.77). This might be explained by differences in treatment protocols. Part of the Huddart sample had lip surgery and palate closure in one operation, and part of the sample underwent two separate operations. The type of surgery used and the timing was not mentioned. In the Dutchcleft study, lip surgery was performed at the age of 18 weeks and the soft palate was closed at the age of 52 weeks. The differences in crossbite scores might also reflect an improvement in CLP treatment between the 1970s and today.

Table 6 *Comparative studies, using the 5-y-old index, including the 4-y-old group and the 6-y-old group of dutchcleft.*

					Dutchcleft	
Index Category	*CSAG %* (n=223)*	*Bristol % (n=46)*	*Oslo % (n=54)*	*Perth % (n=54)*	*4 y. % (n=44)*	*6 y. % (n=45)*
1	*5*	*} 35*	*} 57*	*4*	*30*	*27*
2	*24*			*24*	*45*	*33*
3	*34*	*19*	*28*	*49*	*23*	*38*
4	*18*	*} 46*	*} 15*	*19*	*2*	*2*
5	*19*			*4*	*0*	*0*

** CSAG = clinical standard advisory group (United Kingdom).*
† Because there were no significant differences between the IO+ and IO- groups, both groups were taken together.

More recently studies mainly use the Goslon Yardstick or the 5-year-old index to evaluate occlusion. Table 6 shows the case distribution of several studies, including Dutchcleft, over the five categories of the 5-

year-old index groups. Atack et al.[14] evaluated samples from Bristol, United Kingdom (n=46) and Oslo, Norway (n=54). In the CSAG study, dental arch relationships of 5-year-olds (n=223) from 50 National Health Service cleft teams in the United Kingdom were evaluated.[45,46] Five percent of the sample was found to have an excellent dental arch relationship, 24% had a good occlusion, and 34% a fair occlusion. The percentages for poor and very poor dental arch relationships were 18% and 19% respectively. Johnson et al.[44] found that 4% of the patients at the Princess Margaret Hospital in Perth had excellent results, 24% good results, 49% fair, 19% poor, and 4% very poor results. Table 6 shows that the results of the Dutchcleft sample compare favorably with the other studies, especially because there are only two patients in group 4 and none in group 5. Part of the different results among mentioned centers may be explained by the difference in treatment protocols. However, the Eurocleft study has shown that acceptable results can be achieved with different treatment schedules.[27-29] Only standardization and centralization of care and the participation of high volume operators seem to be associated with good treatment outcome.[27-29,45,46] These criteria were all fulfilled in Dutchcleft.

The results of this part of the Dutchcleft study are in agreement with the other findings of this trial determined to date. Except for a small but significant improvement in speech development, no positive or negative influence of IO was found in the Dutchcleft study.[16-19,24,34,35,48]

2.5 Conclusion

Infant orthopedics did not influence the occlusion of the deciduous dentition at the age of 4 and 6 years. Therefore, from the orthodontic point of view, there is no need to perform IO in children with UCLP.

2.6 Acknowledgment.

The authors thank Professor Bill Shaw, Dr. Gunvor Semb, and Phil Eyres of the University of Manchester (United Kingdom) for their help in scoring all casts with the 5-year-old index. We also appreciate the help of Karolien Windels and Charlotte Prahl.

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Chapter 3

Infant orthopedics has no effect on maxillary arch dimensions in the deciduous dentition of children with complete unilateral cleft lip and palate

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Summary

Objective: Evaluation of the effect of infant orthopedics on maxillary arch dimensions in the deciduous dentition in patients with unilateral cleft lip and palate.

Design: Prospective two-arm randomized controlled clinical trial with three participating cleft palate centers.

Setting: Cleft palate centers of the Radboud University Nijmegen Medical Center, Academic Center of Dentistry Amsterdam, and University Medical Center Rotterdam, the Netherlands.

Patients: Children with complete unilateral cleft lip and palate (n=54) were included.

Interventions: Patients were randomly divided into two groups. Half of the patients (IO+) had a presurgical orthopedic plate until surgical closure of the soft palate at the age of 52 weeks; the other half (IO-) did not undergo presurgical orthopedics.

Mean outcome measures: Maxillary arch dimensions were assessed on dental casts at 4 and 6 years of age with measurements for arch width, arch depth, arch length, arch form, and the vertical position of the lesser segment. Contact and collapse were assessed also.

Results: There were no clinically significant differences found between IO+ and IO- for any of the variables.

Conclusions: Infant orthopedics had no observable effect on the maxillary arch dimensions or on the contact and collapse scores in the deciduous dentition at the ages of 4 and 6 years. Considering the Dutchcleft results to date, there is no need to perform infant orthopedics for unilateral cleft lip and palate patients.

3.1 Introduction

The effect of infant orthopedics (IO) on maxillary arch dimensions in unilateral cleft lip and palate (UCLP) has been studied for decades, but controversy regarding the effect of IO on the maxillary arch still exists. Advocates of IO claim that the presurgical orthopedic plate molds the alveolar segments into a better arch form and prevents the tongue from positioning in the cleft. In this way, the dentomaxillary development would improve.[1-13] Opponents of this therapy claim that lip surgery alone has the same effect and that the presurgical orthopedic plate is only an expensive appliance used to comfort the parents by starting treatment at the earliest moment possible.[14-23]

Several studies describe the effect of IO on maxillary arch dimensions, but most are cohort studies in which UCLP patients treated with IO are compared with a control group of non-cleft children, or case series that study changes in maxillary arch dimensions after IO treatment without comparison to a control group.[6,24-30] Kuijpers-Jagtman[27] and Kozelj[30] described that during IO the cleft narrowed in the anterior part, and the anterior arch depth increased less than in non-cleft controls. Although the appliance was maintained after lip surgery, the cleft width decreased a considerable amount during the first 6 weeks after the operation. Later, a segmental displacement with the center of rotation at the tuberosities was found. At the age of 8 years the posterior arch width was not significantly different from the control group, but the anterior arch was narrower than in the control group.

As illustrated by the publications mentioned above, it can not be concluded whether or not IO is an effective treatment approach. Therefore, a prospective randomized clinical trial was performed in three cleft palate centers in the Netherlands (i.e., the cleft palate centers of Nijmegen, Amsterdam, and Rotterdam) to investigate the effect of infant orthopedics with a passive plate in children with complete UCLP.[31] The first results, up to 1.5 years of age, showed that IO had a temporary effect on maxillary arch dimensions that did not last beyond surgical soft palate closure.[23] Also, IO could not prevent collapse of the maxillary arch.[32] No differences between IO+ and IO- could be shown in the occlusion at the ages of 4 and 6 years.[33] Data published by Konst et al.[34] show the cost-effectiveness of the speech outcome at the age of 2.5 years. Speech therapists were asked to rate the speech quality of 10 IO+ children and 10 IO- children on a 10-point scale. The IO+ group had a significantly better rating for speech. The resulting cost-effectiveness ratio was 1041 euros for 1.34 points of speech improvement.[34,35] An evaluation of the speech data at the age of 6 has to be done to see whether the cost-effectiveness will change due to speech therapy from the ages of 3 to 6. More detailed findings on speech have been published elsewhere.[36-39]

The purpose of the part of the trial presented here was to evaluate the effect of IO on maxillary arch dimensions in deciduous dentition in UCLP children, ages 4 and 6 years. The hypothesis tested was that the maxillary arch dimensions in the IO+ group were larger than in the IO- group and that less collapse occurred in the IO+ group compared with the IO- group.

3.2 Methods

In a previous publication, a detailed description was given with respect to the experimental design, treatment assignment, treatment protocol, and operators.[23] A summary of the most important issues is given below.

The study was designed as a prospective two-arm randomized controlled clinical trial in the cleft palate centers in Nijmegen, Amsterdam, and Rotterdam, the Netherlands. The local ethical committees approved the study protocol. The inclusion criteria were complete UCLP, infants born at term, both parents Caucasian and fluent in the Dutch language, and trial entrance within 2 weeks after birth. Exclusion criteria included soft tissue bands and other congenital malformations. Figure 1 shows the sample until the age of 6 with the reasons for exclusion from evaluation. When the parents agreed to participate in the study, they were asked to sign an informed consent. Between 3 and 6 months of age, all included children were assessed by the geneticist of their own cleft lip and palate team as being non-syndromic.

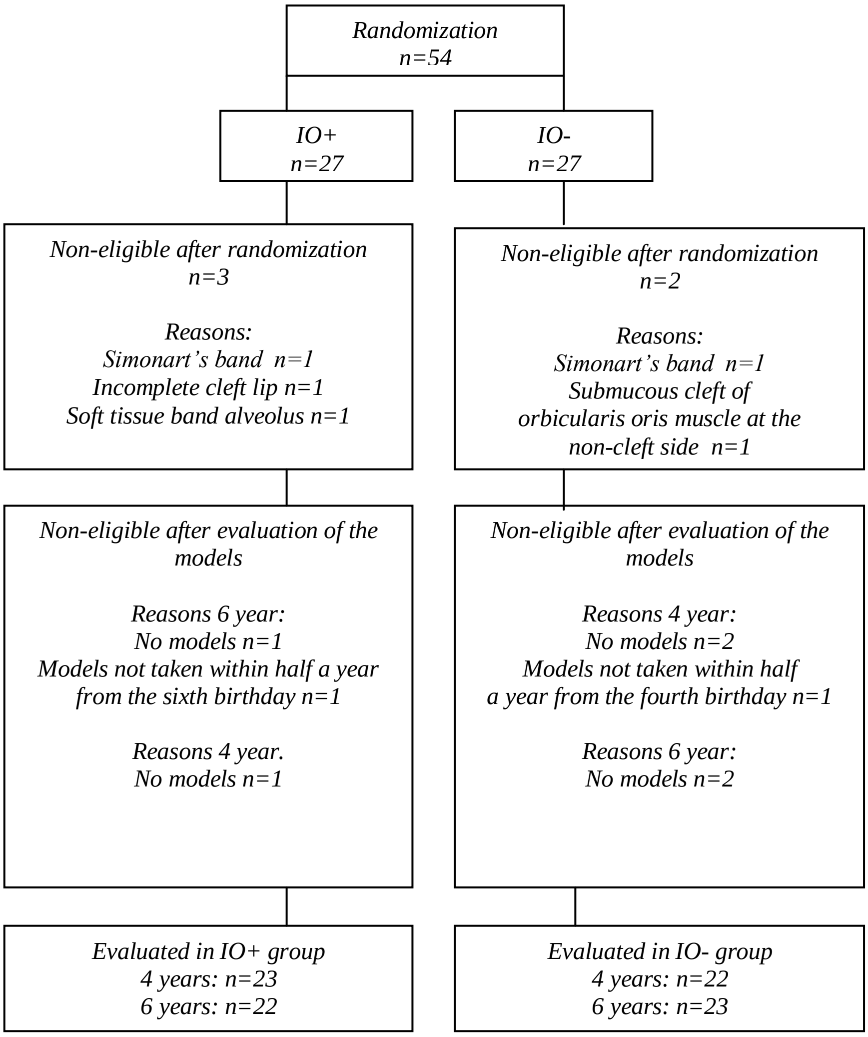


Figure 1 *Flow diagram of trial children with the reasons for exclusion of evaluation.*

3.2.1 Treatment

Half of the patients were treated with IO by means of passive plates until surgical soft palate closure (n=27), and half did not receive a plate (n=27). The plates were made on a plaster cast using compound soft and hard acrylic. The IO+ children had their plates adjusted every 3 weeks to guide the maxillary segments, by grinding at the cleft margins; maxillary growth and emergence of upper deciduous teeth indicated the necessity for a new plate. After surgical lip closure, the plate was replaced the same day. Check-ups were planned every 4 to 6 weeks following lip surgery. The plate was maintained until soft palate closure. The IO group visited the clinic at 6 weeks, as well as before and after lip surgery and soft palate closure. In both groups, lip surgery was performed at the age of 18 weeks using the Millard technique. Soft palate surgery was performed at the age of about 52 weeks according to a modified Von Langenbeck method. Hard palate repair was scheduled together with bone grafting. In the studied age period (until 6 years of age), other interventions were performed if indicated, including pharyngoplasty (n=22), lip revision (n=13), facial mask treatment (n=1), plate to facilitate speech (n=15), and closure of the anterior palate (n=6). These interventions were equally distributed over the IO+ and the IO- group.

3.2.2 Data acquisition

In order to evaluate arch dimensions, impressions were taken at ages 4 and 6. Plaster casts were fabricated. To eliminate bias, all models were duplicated and trimmed in the same way. In this way the examiners were not able to identify a patient or a cleft palate center.

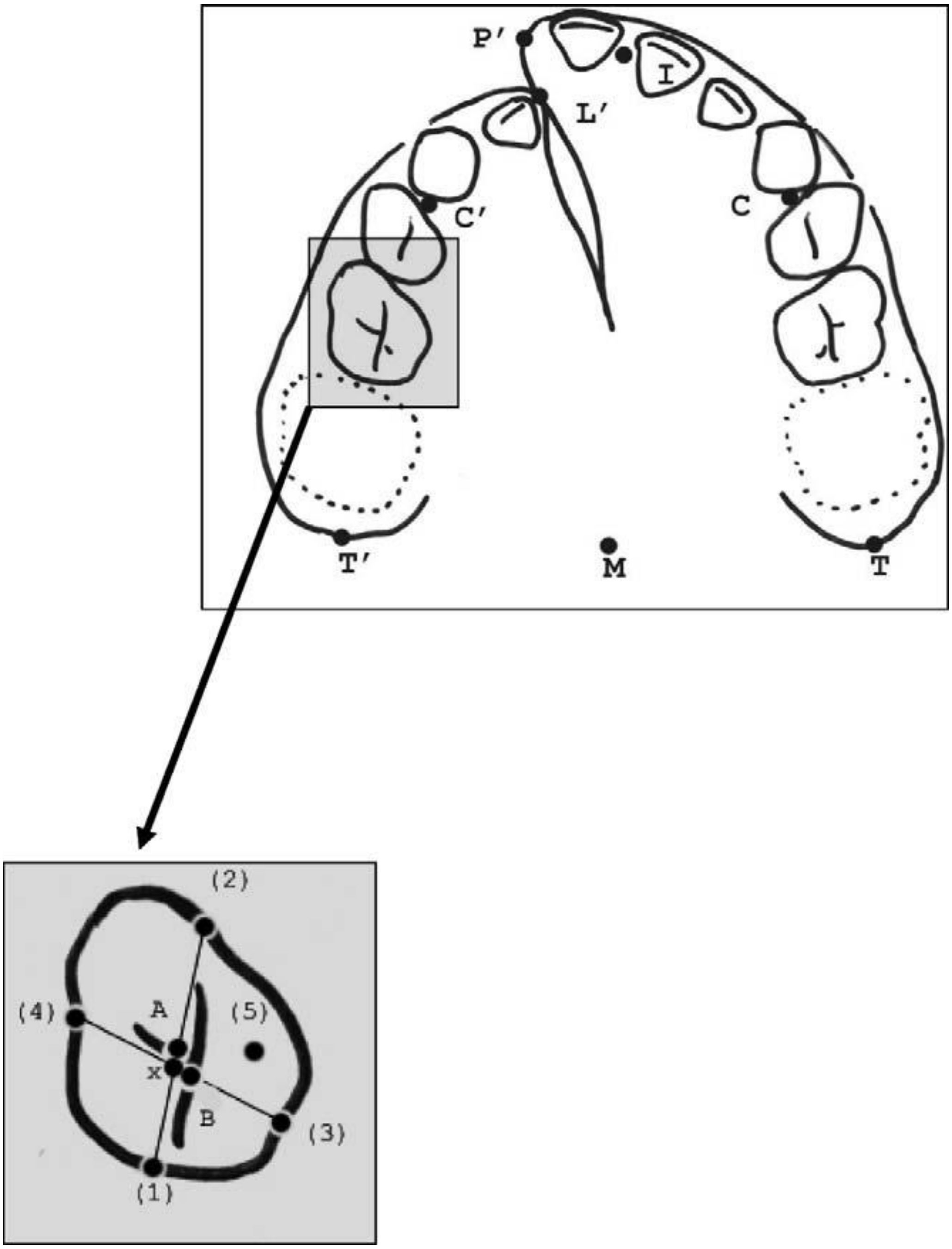
Table 1 *Distances and angles as measured on the maxillary casts (See figure 2 for definitions).*

	Measurements	*Points*
Arch width	*Centroid-Centroid*	*Ce-Ce'*
		P1-P1'
		P2-P2'
	Mesiopalatal cusp-mesiopalatal Cusp	*C(5)-(5)'*
		P1(5)-(5)'
		P2(5)-(5)'
	Tuberosity-tuberosity	*T-T'*
	Canine-canine	*C-C'*
Arch depth		*I-CC'*
		I-TT'
Arch length	*Line through centroids*	*L'-T'*
		P'-T
	Total arch length	*L'-T' + P'-T*
Arch form		*angle M-T-C(5)*
		angle M-T'-C(5)'
		angle P'-C(5)-T
Vertical position of lesser segment		*C(5)-occl*
		P1(5)-occl
		P2(5)-occl
Collapse		*0-1-2-3*
Contact		*0-1*

The maxillary casts were analyzed three-dimensionally using the Reflex Microscope (Reflex Measurement, Somerset, UK).[40-42] First, reference points were marked on the casts (Figure 2). To calculate interexaminer error in marking casts, two observers marked the reference points. To be able to mark the casts blindly, both original models and duplicated casts were used. Points L', P', T, T', I, C, and C' correspond with the points used by Prahl et al.,[23] who evaluated the maxillary arch dimensions of the Dutchcleft children up to the age of 78 weeks. The other points were used as proposed by Moyers et al.,[43] Derijcke et al.,[44] and Heidbüchel and Kuijpers-Jagtman.[45] Second, the reference points were digitized by the two observers. With the digital coordinates, the distances and angles shown in Table 1 could be calculated.

In addition, the casts were examined for presence of contact or collapse of the alveolar segments, as was done by Prahl et al.[32], a method comparable to Pruzansky and Aduss.[46] The method[32] is an ordinal scoring system. Contact was scored as absent (score 0) or present (score 1), and collapse was scored as absent (score 0), slight (score 1), moderate (score 2), or severe (score 3). From these scores, four groups were formed: NC-NO = no contact and no overlap; NC-O = no contact and overlap; C-NO = contact and no overlap; C-O = contact and overlap. Four observers scored all models for contact and for collapse.

Figure 2 *Explanation of the reference points used: I—The top of the interdental papilla between the (deciduous or permanent) central incisors; L'—Lesser segment margin, where the continuation of a line marking the crest of the ridge turns from the oral side to the nasal side at the anterior end of the segment; P'—The larger segment margin, where the continuation of a line marking the crest of the ridge turns from the oral side to the nasal side at the anterior end of the segment (P' = L' when the segments touch each other); I1/I1'—Centroid of the central incisor; I2/I2'—Centroid of the lateral incisor; Ce/Ce'—Centroid of the canine; P1/P1'—Centroid of the first deciduous molar or first premolar; P2/P2'—Centroid of the second deciduous molar or second premolar; C(5)/C(5)'—The most occlusal point of the cusp of the canine; P1(5)/P1(5)'—The most occlusal point of the palatal cusp of the first deciduous molar or first premolar; P2(5)/ P2(5)'—The most occlusal point of the palatal cusp of the second deciduous molar or second premolar; C/C'—The top of the interdental papilla between the (deciduous or permanent) canine and first premolar / first deciduous molar; T, T'—Tuberosity points, at the junction of the crest of the ridge with the outline of the tuberosity; M—Midpoint between T and T'; Occl—Plane formed by the palatal cusp of the M1 on both sides and the cusp of the canine on the non-cleft side. Centroid is the intersection of four points (X). The middle of (1) and (2) is A, and the middle of (3) and (4) is B; the centroid is the midpoint of A and B. (1) distal midpoint: the point on the distal point of the tooth, midway between the buccal and lingual surfaces; (2) mesial midpoint: the point on the mesial point of the tooth, midway* *between the buccal and lingual surfaces; (3) most lingual point: at the lingual fissure location for the permanent molars and the second deciduous molars; for the premolars, first deciduous molars, canines and incisors, it is the most lingual point on the lingual surface; (4) most buccal point: at the buccal fissure location for the permanent molars and the second deciduous molars; for the premolars, first deciduous molars, canines, and incisors, it is the most buccal point on the buccal labial surface.*



3.2.3 Statistical analyses

The interexaminer errors were calculated for each arch dimension at 4 and 6 years of age, for both the marking of the reference points as well as digitization only. Further, the corresponding reliability coefficients were calculated at ages 4 and 6 as Pearson correlation coefficients.

For the interexaminer errors of the contact and collapse scores, weighted kappas were calculated. To test the differences in maxillary arch dimensions between IO+ and IO- for the ages of 4 and 6 and for the increment, two-tailed t-tests were performed.

For the difference in collapse between IO+ and IO-, at 4 and 6 years of age, a two-tailed t-test was used. For the contact-score differences, a chi-square test was done. A difference was considered to be significant at $p < .05$.

3.3 Results

At intake 54 patients participated in the study. An overview of the sample characteristics is given in Table 2. Two IO+ children hardly used the plate; in one case, the plate was mistakenly worn until 78 weeks.

Table 2 *Sample Characteristics*.*

Variable	*IO + (n=27)*			*IO- (n=27)*		
Gender: male/female (n)	*20/7*			*21/6*		
Side of cleft: left/right (n)	*17/10*			*18/9*		
Patients per centre: 1/2/3 (n)	*7/11/9*			*7/10/10*		
Age 4-year casts (years.months)	*mean: 4.0 range:3.8-4.4*			*mean: 4.0 range:3.10-4.6*		
Age 6-year' casts (years.months)	*mean: 6.0 range:5.9-6.2*			*mean: 6.0 range:5.11-6.5*		
	IO +			*IO -*		
	P10	*P50*	*P90*	*P10*	*P50*	*P90*
Age at trial entrance (days)	*0*	*3*	*7*	*1*	*6*	*13*
Birth weight (gram)	*2660*	*3350*	*4020*	*2920*	*3600*	*4280*
Cleft width at birth (mm)	*9.5*	*12.5*	*14.4*	*8.6*	*12.4*	*16.4*
Age lip repair (days)	*117*	*127*	*142*	*117*	*125*	*138*
Age soft palate closure (days)	*355*	*375*	*438*	*301*	*367*	*389*

** Some variables are presented in percentiles because of skewness (P10, P50, and P90). IO+ = patients treated with infant orthopedics; IO- = patients not treated with infant orthopedics; P10 = 10th percentile; P50 = 50th percentile; P90 = 90th percentile.*

These children remained in the IO+ group according to the intention-to-treat principle. The mean duration of IO was 50 (± 16 weeks SD). The flow diagram in Figure 1 shows the reasons for non-evaluation.

3.3.1 Measurement reliability

The interexaminer errors and the reliability coefficients for the interexaminer agreement for the maxillary measurements are shown in Table 3. The kappas for interexaminer agreement of the contact and the collapse scores also are shown in Table 3. A kappa value between .81 and 1.00 indicates a very good agreement, whereas a kappa between .61 and .80 indicates good agreement. The measurements in the vertical direction have low reliability. Therefore, C(5)-occl, P1(5)-occl, P2(5)-occl were excluded from further analysis. Two other measurements with low reliability were maintained to make comparisons possible with the other measurements and research done by Prahl et al.[23]

Table 3 *Interexaminer measurement errors (in mm or degrees) and reliability in person correlation coefficients (r) and kappas for the measured variables (see figure 2 for definitions).*

	Interexaminer	
Variable	*Marking points and digitization Error (r)*	*Digitization Error (r)*
Ce-Ce'	*0.52 (.934)*	*0.59 (.949)*
P1-P1'	*0.64 (.920)*	*0.50 (.960)*
P2-P2'	*0.55 (.948)*	*0.42 (.974)*
C (5)-(5)'	*0.85 (.896)*	*0.58 (.962)*
P1 (5)-(5)'	*0.72 (.909)*	*0.55 (.955)*
P2 (5)-(5)'	*0.67 (.938)*	*0.43 (.974)*
T-T'	*1.85 (.838)*	*1.40 (.864)*
C-C'	*0.89 (.879)*	*0.59 (.951)*
I-CC'	*1.14 (.727)*	*0.75 (.891)*
I-TT'	*1.26 (.691)*	*0.59 (.952)*
L'-T'	*3.77 (.500)*	*1.90 (.869)*
P'-T	*3.27 (.709)*	*1.78 (.874)*
Angle M-T-C(5)	*2.17 (.767)*	*3.01 (.677)*
Angle M-T'-C(5)'	*3.01 (.849)*	*1.07 (.947)*
Angle P'-C(5)-T	*10.50 (.884)*	*3.44 (.989)*
C(5)-occl	*1.38 (.546)*	*0.58 (.784)*
P1(5)-occl	*0.52 (.569)*	*0.29 (.713)*
P2(5)-occl	*0.05 (1.000)*	*0.12 (.544)*
Variable	*Interexaminer weighted kappa*	*SE*
Contact	*.741*	*.029*
Collapse	*.877*	*.012*

Table 4 *Number (n†), means, standard deviations, and confidence intervals (CI) of the measured variables (in mm or degrees) for IO+ (bold) and IO- (normal) at the age of 0 to 2 weeks, 78 weeks, and 4 and 6 years;* variables of the ages 0 to 2 weeks and 78 weeks are copied from Prahl et al. (2001); See figure 2 for definitions.*

Variable	*0-2 wk n Mean (SD)*	*78 wk n Mean (SD)*	*4 y n Mean (SD) [95% CI]*	*6 y n Mean (SD) [95% CI]*
Ce-Ce'			*22 25.99 (2.14)*	*21 25.85 (2.63)*
			23 26.37 (3.13)	***22 26.12 (3.10)***
			[-1.99–1.24]	*[-2.05–1.50]*
P1-P1'			*22 32.48 (2.10)*	*22 32.54 (2.46)*
			23 32.36 (2.74)	***22 32.15 (2.67)***
			[-1.34–1.60]	*[-1.17–1.95]*
P2-P2'			*22 39.28 (2.10)*	*22 39.85 (2.57)*
			23 38.82 (2.88)	***22 38.87 (2.88)***
			[-1.06–1.98]	*[-0.68–2.64]*
C (5)-(5)'			*22 26.26 (2.21)*	*22 6.60 (2.82)*
			23 26.76 (3.54)	***22 27.12 (3.54)***
			[-2.28–1.29]	*[-2.47–1.43]*
P1 (5)-(5)'			*22 28.81 (2.15)*	*22 28.94 (2.55)*
			23 28.80 (2.88)	***22 28.58 (2.76)***
			[-1.54–1.54]	*[-1.26–1.97]*
P2 (5)-(5)'			*22 34.51 (2.04)*	*22 34.84 (2.40)*
			23 34.31 (2.96)	***22 34.14 (2.94)***
			[-1.34–1.73]	*[-0.93–2.33]*
T-T'	*22 33.4 (2.0)*	*18 36.0 (3.0)*	*19 39.91 (2.27)*	*18 42.63 (2.99)*
	23 33.3 (1.9)	***14 34.5 (2.7)***	***21 38.64 (2.91)***	***19 40.27 (4.52)***
			[-0.41–2.96]	*[-0.22–4.93]*
C-C'	*24 32.7 (2.3)*	*20 29.8 (3.0)*	*22 27.58 (2.28)*	*22 27.16 (2.70)*
	24 33.9 (1.9)	***19 30.3 (3.9)***	***23 27.27 (2.94)***	***22 26.76 (2.73)***
			[-1.28–1.90]	*[-1.25–2.06]*
I-CC'	*24 9.3 (2.2)*	*20 9.8 (1.6)*	*22 11.75 (2.27)*	*20 12.02 (2.16)*
	24 8.4 (1.4)	***19 10.0 (1.7)***	***23 12.55 (2.11)***	***21 12.49 (1.93)***
			[-2.12–0.51]	*[-1.77–0.81]*
I-TT'	*22 25.9 (2.8)*	*18 32.0 (2.4)*	*19 30.14 (2.62)***	*18 33.36 (2.34)*
	23 25.0 (1.9)	***14 32.0 (2.8)***	***21 32.81 (1.98)***	***18 33.47 (3.37)***
			[-4.14–1.18]	*[-2.07–1.86]*
L'-T'			*22 37.38 (3.65)*	*22 39.31 (4.58)*
			23 38.37 (4.88)	***22 39.65 (4.89)***
			[-3.59–1.61]	*[-3.22–2.54]*
P'-T			*22 54.46 (4.87)*	*22 55.35 (3.89)*
			23 53.37 (3.33)	***22 56.24 (4.97)***
			[-1.40–3.59]	*[-3.61–1.83]*
Total arch length	*22 65.5 (5.6)*	*12 82.0 (4.4)*	*22 91.85 (7.41)*	*22 94.66 (7.49)*
	23 64.5 (3.4)	***7 82.9 (6.6)***	***23 91.73 (6.27)***	***22 95.88 (7.83)***
			[-4.01–4.22]	*[-5.90–3.44]*
Angle M-T-C(5)	*22 82.5 (3.9)***	*18 77.4 (5.1)*	*19 40.55 (3.05)**	*18 43.17 (3.98)*
	23 86.0 (3.8)	***14 80.1 (5.7)***	***21 43.37 (3.85)***	***19 43.46 (6.98)***
			[-5.05–0.57]	*[-4.11–3.52]*
Angle M-T'-C(5)'	*22 95.0 (5.4)*	*18 86.2 (3.8)*	*19 72.58 (4.61)*	*18 69.96 (4.39)*
	23 95.9 (3.7)	***14 87.6 (4.9)***	***21 74.52 (4.39)***	***19 73.11 (5.04)***
			[-4.82–0.94]	*[-6.31–0.17]*
Angle P'-C(5)-T			*19 95.36 (25.91)*	*19 105.16 (32.62)*
			22 93.07 (28.16)	***18 102.88 (28.01)***
			[-14.9–19.5]	*[-18.1–22.6]*

† n may vary because of incidental missing values (e.g., maxillary tuberosities not visible on the model, shedding teeth).
** 0.5 ≥ p > .01; ** 01 ≥ p > .001. Differences between IO+ and IO- were tested with t tests. The level of significance is indicated with p values.*

3.3.2 Treatment effect

Mean values and standard deviations for all variables for both ages are given in Table 4. Measurements at 0 to 2 weeks and at 78 weeks of age from an earlier publication on the same sample[23] also are shown in Table 4. No significant differences were found between the IO- and IO+ groups at age 4 and at age 6, except for I-TT', and angle MT-C(5) at the age of 4 years and angle M-T-C(5) at 0 to 2 weeks.

The arch depth (I-TT') at the age of 4 years was larger in the IO+ group; at 0 to 2 weeks of age and at 4 years of age, the angle M-T-C(5) was larger in the IO+ group than in the IO- group.

Table 5 *Number (n*) and percentage of children with collapse (overlap) and/or contact between the alveolar segments, for IO+ (n=45; bold) and IO- (n=45; normal)† at the age of 0 to 2 weeks, 78 weeks, and 4 and 6 years; 95% confidence intervals (CI) are given also; variables for ages 0 to 2 weeks and 78 weeks are copied from Prahl et al. (2003); see figure 2 for definitions.*

Variable	*0-2 wk n %*	*78 wk n %*	*4 y n % 95 % CI*	*6 y n % 95 % CI*
NC-NO	*25 100.0*	*6 25.0*	*3 13.6*	*1 4.3*
	24 100.0	***7 30.4***	***3 13.0***	***0 0.0***
			-19. 3–20.5	*-4.0–12.7*
C-NO	*0 0.0*	*4 16.7*	*4 18.2*	*3 13.0*
	0 0.0	***5 21.7***	***7 30.4***	***6 27.3***
			-37.0–12.5	*-37.4–8.9*
NC-O	*0 0.0*	*4 16.7*	*3 13.6*	*4 17.4*
	0 0.0	***1 4.3***	***2 8.7***	***2 9.1***
			-13.5–23.3	*-11.3–27.9*
C-O	*0 0.0*	*10 41.7*	*12 54.5*	*15 65.2*
	0 0.0	***10 43.5***	***11 47.8***	***14 63.6***
			-22.4–35.9	*-26.4–29.6*
NC-NO and C-NO			*7 31.8*	*4 17.4*
			10 43.5	***6 27.3***
			-39. 8–16.4	*-34.1–14.3*
NC-O and C-O			*15 68.2*	*19 82.6*
			13 62.2	***16 72.7***
			-16.4–39.8	*-14.3–34.1*

** n may vary because of incidental missing values (e.g., maxillary tuberosities not visible on the model, shedding teeth).*
† Differences between IO+ and IO- were tested with chi-square tests. No significant differences were found between IO+ and IO-.
NC-NO = no contact, no overlap; C-NO = contact, no overlap; NC-O = no contact, overlap; C-O = contact, overlap.

Table 5 presents the contact and collapse results. Included are the results at age 0 to 2 weeks and at 78 weeks.[32] The mean severity score for collapse at the age of 4 years was 1.32 (± 1.04 SD) for the IO- group and 1.05 (± 0.95 SD) for the IO+ group. The severity scores for the age of 6 years were 1.72 (± 0.98 SD) for IO- and 1.39 (± 1.06 SD) for IO+. The mean score for contact at 4 years of age was 0.73 for IO- and 0.78 for IO+. At the age of 6 years IO+ scored a mean of 0.78 and IO- 0.90.

There were no significant differences found for collapse and contact between IO+ and IO- at the ages of 4 and 6 years. Further, looking at IO+ and IO- for the combined groups of no overlap (NC-NO and C-NO) compared with the combined overlap groups (NC-O and C-O), no significant differences were found.

3.4 Discussion

To compensate for shortcomings of earlier studies, the design of the present study was a prospective two-arm randomized controlled clinical trial[23]. The number of patients involved in the study decreased from 54 to 45 in the age groups of 4 and 6 years, but the number remained larger than in most published studies. Sarnäs et al.[26] and Mishima et al.[13] both compared IO+ with IO- patients. Mishima et al.[13] sampled 12 IO+ children and 8 IO- children. Sarnäs et al.[26] compared 24 IO+ patients with 18 IO- patients. However, neither study was designed as a randomized clinical trial.

The dental casts were digitized by means of a Reflex Microscope (Reflex Measurement). As is known from Drage et al.[41], a Reflex Microscope (Reflex Measurement) is best used by trained observers. However, untrained observers can use the microscope well after some practice. As was also found in this study, errors were found to be greatest in the z-axis, along the axis of the eye. Errors were also rather high at the margins of the segments. The study of Speculand et al.[40] shows that it is possible to generate reproducible results for redigitization with an intraexaminer error of less than .15 mm for linear measurements. This was not found for all measurements in this study. The measurement errors found in this study for landmark positioning (marking points) are comparable to those reported by Seckel et al.[42] The errors for the measurements of contact and collapse done in this study are comparable to those reported by Prahl et al.[23]

A few significant differences between IO+ and IO- are shown in Table 4, but they do not show a consistent pattern over the different periods. All significant differences faded away at the age of 6 years. Therefore, the few inconsistent significant influences at the age of 4 years may be either temporary or falsely significant, probably due to the large number of tests. The confidence intervals mentioned in Tables 4 and 5 are not extremely large. Only the angle P'-C(5)-T and the contact-collapse variables show a large interval, which could point to a type II error. These variables should be interpreted with caution.

Many studies have been published about the effect of IO on maxillary arch dimensions or on collapse or contact of the alveolar segments, but most studies are nonrandomized. The two studies with the best research design were published by Mishima et al.[13,47] and Sarnäs et al.[26] Mishima et al.[47] reported that in a quasi-randomized trial at the age of 18 months, the Hotz plate seemed to stimulate growth of the segments, could prevent collapse of the segments after lip closure, and resulted in less steepness of the segments, combined with more forward migration of the lesser segment toward the larger segment. In 2000, Mishima et al.[13] reported that at the age of 4 years, the width of the palate was larger in the group treated with Hotz plates than in the group treated without plates. Sarnäs et al.[26] followed a group of 24 IO+ children and 18 IO- children in a retrospective two group cohort study and evaluated them at the ages of 3 and 19 months. All patients had lip surgery at the age of 3 months and palatal surgery at the age of 19 months. In the IO+ group the plate was worn until the moment of palatal surgery. The IO+ group had larger transverse dimensions and less rotation of the greater segment. Although the first results in Dutchcleft showed that IO had a temporary effect on the maxillary arch dimensions, this did not last beyond surgical soft palate closure.[23] Also, no significant differences were found in Dutchcleft in width measurements at the ages of 4 and 6 years. In addition, the results of Dutchcleft are not really comparable to the Mishima and Sarnäs studies because those studies did not use a randomized study design.

IO could not prevent collapse of the maxillary arch.[32] Table 5 shows that, over time, the number of children with contacting and overlapping segments increases for both groups, IO+ and IO-. At birth all children have no contact and no overlap between the alveolar segments, and at the age of 6 years the majority (97.8%) has contact, collapse, or both. This means that the impact of lip surgery and palatal surgery is much greater than the effect of IO.

The results of this part of the Dutchcleft study are in agreement with the other findings of this trial to date. Except for a small but significant improvement in speech development, no positive or negative influence of IO was found in the Dutchcleft study.[23,31-34,36-39,48,49]

3.5 Conclusion

IO did not influence the maxillary arch dimensions, the collapse, or the contact between the alveolar segments at the ages of 4 and 6 years. Therefore, from the orthodontic point of view, there is no need to perform IO in children with UCLP.

3.6 References

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Chapter 4

Effect of infant orthopedics on facial appearance of toddlers with complete unilateral cleft lip and palate

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Summary

Objective: To evaluate the effect of infant orthopedics (IO) on facial appearance of UCLP patients, aged 4 and 6 years.

Design: Prospective two-arm randomized controlled clinical trial in three Cleft Palate Centers in the Netherlands (Dutchcleft-trial).

Interventions: Patients were divided randomly into two groups. Half of the patients (IO+) had a plate till surgical closure of the soft palate at the age of ± 52 weeks; the other half (IO-) received no intervention.

Mean outcome measures: Facial appearance at 4 and 6 years of age assessed on full face photographs and photographs showing only nose and mouth. Ratings were performed on a VAS-scale by professionals and laymen.

Results: At 4 years of age the full face pictures of IO+ children were scored to be more attractive than full face pictures of IO- children. However, this difference had faded away at 6 years of age. At the age of 6, only professionals saw a significant difference on nasolabial photographs between IO+ and IO-. Regression analysis showed a minor effect of occlusion, liprevision, or type of nose reconstruction on the esthetic results.

Conclusions: IO had a positive effect on full facial appearance of UCLP children at the age of 4 years, but at the age of 6, only professionals saw a positive effect of IO on the nasolabial photographs. This is irrelevant for UCLP patients since they deal with laymen in their daily life.

4.1 Introduction

The effect of infant orthopedics (IO) in unilateral cleft lip and palate (UCLP) would seem to be well known by now. The contrary is true, however. The subject has been studied for decades, but the controversy about the effect of IO still exists. Besides other claimed advantages, IO is said to improve facial appearance of the children, because lip surgery should be easier, and maxillary growth might be stimulated or adjusted positively.[1-4] However, this view is not supported by everyone[4-6]; probably lip surgery alone will have the same effect. Because of the uncertainty of the effect of IO, a prospective randomized clinical trial was performed in three cleft palate centers in the Netherlands (the cleft palate centers of Nijmegen, Amsterdam and Rotterdam) to investigate the effect of IO with a passive plate in children with complete unilateral cleft lip and palate.[7] The first results, showed that IO had a temporary effect on maxillary arch dimensions, which did not last beyond surgical soft palate closure.[8,9] Also, IO could not prevent collapse of the maxillary arch.[9,10] In the occlusion at the age of 4 and 6 years no differences between patients with infant orthopedics (IO+) and those without (IO-) could be shown.[11] Feeding and the nutritional status of the infants were not improved by IO.[12] Data published in 2004 show the cost-effectiveness of the speech outcome at the age of 2.5 years: listeners (speech therapists) were asked to rate the speech quality on a 10-point scale of 10 IO+ children and 10 IO- children. The IO+ group had a significant better rating for speech. The resulting cost-effectiveness ratio was 1041 euro for 1.34 point of speech improvement.[13,14] An evaluation of the speech data at the age of 6 still has to be performed. More detailed speech findings have been published elsewhere.[15-18] Finally, the results of the esthetic scores at age 1,5 showed no effect of IO on facial appearance.[19]

The purpose of this paper is to report on with UCLP the effect of IO on the facial appearance in children, aged 4 and 6 years. The hypothesis tested was that the facial appearance of the IO+ group would be better than that of the IO- group.

4.2 Patients and methods

This study was designed as a prospective two-arm randomized controlled clinical trial in the Cleft palate Centers in Nijmegen, Amsterdam, and Rotterdam, in the Netherlands. The local ethical committees approved the study protocol and informed consent was obtained from all participants. The inclusion criteria were: complete UCLP, infants born at term, both parents white and fluent in the Dutch language, and trial entrance within two weeks after birth. The exclusion criteria were soft tissue bands, and other congenital malformations. Figure 1 shows the sample till the age of 6 with the reasons for exclusion of evaluation.

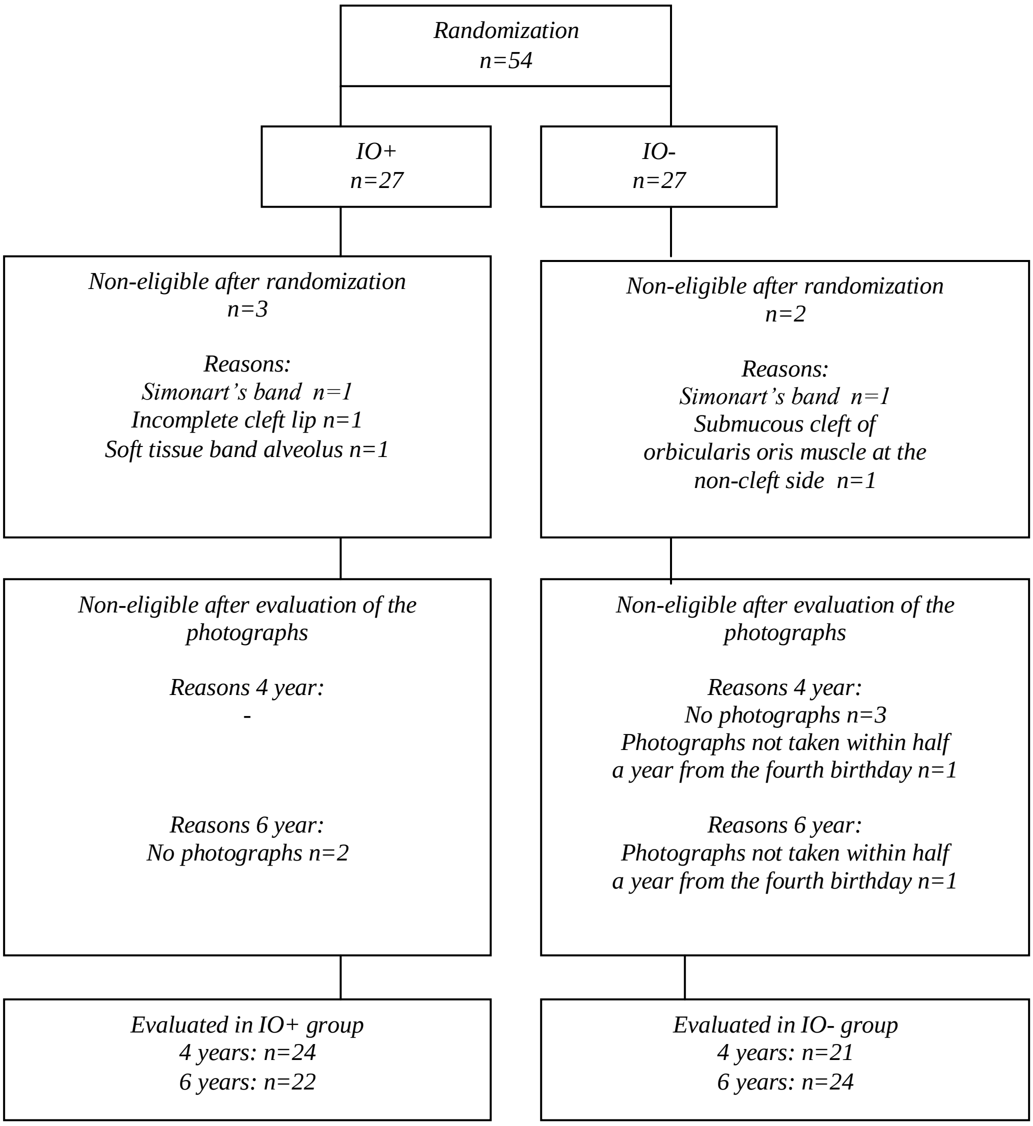


Figure 1 *Flow diagram of trial children with the reasons for exclusion of evaluation.*

Between 3 and 6 months of age all included children were assessed by the geneticist of their own CLP team as being non-syndromic.

In a previous publication, a detailed description is given with respect to the experimental design, treatment assignment, treatment protocol and operators.[8] A summary of the most important issues is given.

4.2.1 Treatment

Half of the patients were treated with infant orthopedics by means of passive plates till surgical soft palate closure (n=27), and half did not recieve a plate (n=27). The plates were made on a plaster cast using compound soft and hard acrylic. The IO+ children had their plates adjusted every three weeks to guide the maxillary segments, by grinding at the cleft margins; maxillary growth and emergence of deciduous teeth indicated the necessity for a new plate. After surgical lip closure the plate was replaced the same day. Check-ups were planned every 4-6 weeks following lip surgery. The plate was maintained untill soft palate closure. The IO- group visited the clinic at 6 weeks, and before and after lip surgery and soft palate closure. In both groups, lip surgery was performed at the age of 18 weeks by the Millard technique. At lipsurgery, the cleft teams of Amsterdam and Nijmegen used the McComb's technique for the nose, while the Rotterdam cleft team preferred their own method that combined the McComb and Pigott techniques. Soft palate surgery was performed at the age of about 52 weeks according to a modified Von Langenbeck method including levator muscle repositioning. In the studied age period (until 6 years of age), other interventions were performed if indicated, and included: pharyngoplasty (n=22), lip revision (n=13; in all cases performed before the age of 4 years), facial mask treatment (n=1), plate to facilitate speech (n=15), closure of the anterior palate (n=6). These interventions were equally distributed over the IO+ and the IO- group.

4.2.2 Data acquisition

In order to evaluate esthetics, facial photographs were made of all children at the age of 4 and 6. The slides were scanned and saved in two ways: one photograph was saved without changes except for changing all right-sided clefts into left-sided clefts, and one was cropped to a view of the nasolabial area. With these photographs two PowerPoint presentations were made of the full face frontal photographs and two of the nasolabial area photographs (figure 2). The sequence of the photographs was randomized in every presentation. On every PowerPoint (Microsoft, Inc., Redmond, WA) slide in the presentation a photograph of one of the trial children was shown, next to a reference picture. There was one reference picture for the boys and one for the girls.

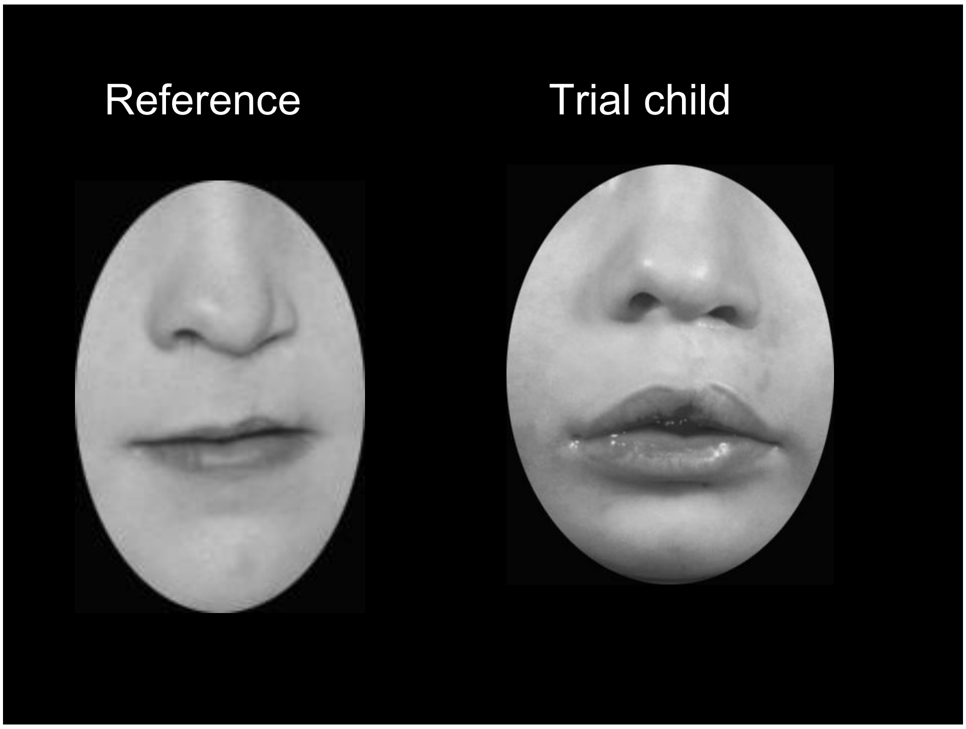


Figure 2 *Example of presentation slide with the reference picture on the left and a nasolabial area photograph on the right.*

Twenty-six observers, 16 professionals and 10 laymen, were asked to evaluate the photographs in the presentations. To be a member of the professional-group, the observer had to be a doctor in attendance in a cleft palate team (e.g. otorhinolaryngologist, surgeon, orthodontist); the laymen were the remaining observers. Each slide was shown 15 seconds. Facial esthetics was scored using a magnitude estimation method.[19,20] The reference picture (average cleft lip and palate appearance) was given a value expressed as a line of defined length (visual analogue scale (VAS)). The observers were asked to compare the experimental picture with the reference picture and to rate the attractiveness of the face in relation to the line length of the reference picture. A shorter line meant less attractive than the reference picture, while a longer line meant more attractive. No limits were given. Secondly, the observers had to express their judgment in a number. The reference photograph was given 100. To calculate reliability, two presentations were scored with the VAS-method and two with number- scorings. Since most authors of articles concerning esthetics use a VAS- scoring method, these scores were used for further evaluation.

The dental arch relationship was assessed in an earlier study on dental casts using the 5-year-olds' index.[11]

4.2.3 Statistical analysis

Reliabilities over the four series of scores were calculated for all observers as Cronbach's alpha. A differentiation was made between professionals and laymen and between full face and nasolabial photographs. By deleting one observer at a time and using the Cronbach's alpha calculation again, the validity of the scores of each observer was checked.

Mean VAS-scores and standard deviations were computed for professionals, and laymen, for full face photographs and nasolabial photographs. Since all observers had their own scoring range, the scores were normalized. The higher the score the more attractive the photograph was scored. Pearson correlation was calculated between the full face photographs and the nasolabial photographs at the age of 4 and 6 years and between professionals and laymen at 4 and 6 years of age.

Finally, the effect of IO was tested for the full face photographs, and the nasolabial photographs for professionals and laymen, at 4 and 6 years of age with two tailed t-tests.

Also, regression analysis was done to test the influence of IO, occlusion at 4 or 6 years of age, liprevision or the type of nose reconstruction done at initial lip closure on the esthetic result.

4.3 Results

4.3.1 General

At intake 54 patients participated in the study. An overview of the sample characteristics is given in table 1. Two IO+ children hardly used the plate; in one case the plate was worn by mistake till 78 weeks. These children remained in the IO+ group according to the intention to treat principle. The mean duration of IO was 50 weeks; SD was 16 weeks. The flow diagram in figure 1 shows the reasons for non-evaluation.

Table 1 *Sample characteristics*.*

Variable	*IO + (n=27)*			*IO- (n=27)*		
Gender: male/female (n)	*20/7*			*21/6*		
Side of cleft: left/right (n)	*17/10*			*18/9*		
Patients per centre: 1/2/3 (n)	*7/11/9*			*7/10/10*		
Age 4-year casts (years.months)	*mean: 4.0 range:3.8-4.4*			*mean: 4.0 range:3.10-4.6*		
Age 6-year' casts (years.months)	*mean: 6.0 range:5.9-6.2*			*mean: 6.0 range:5.11-6.5*		
	IO +			*IO -*		
	P10	*P50*	*P90*	*P10*	*P50*	*P90*
Age at trial entrance (days)	*0*	*3*	*7*	*1*	*6*	*13*
Birth weight (gram)	*2660*	*3350*	*4020*	*2920*	*3600*	*4280*
Cleft width at birth (mm)	*9.5*	*12.5*	*14.4*	*8.6*	*12.4*	*16.4*
Age lip repair (days)	*117*	*127*	*142*	*117*	*125*	*138*
Age soft palate closure (days)	*355*	*375*	*438*	*301*	*367*	*389*

** Some variables are presented in percentiles because of skewness (P10, P50, and P90). IO+ = patients treated with infant orthopedics; IO- = patients not treated with infant orthopedics; P10 = 10th percentile; P50 = 50th percentile; P90 = 90th percentile.*

4.3.2 Reliability of measurements

Table 2 shows the reliability of professionals and laymen for full faces and for nasolabial photographs. When deleting one observer at a time, the reliability values did not change significantly, meaning that all observers were reliable.

Table 2 *Reliability of professionals and laymen for full faces and nasolabial photographs (Cronbach's alpha).*

	full face photographs	*nasolabial photographs*	*all photographs*
All observers	*0.94*	*0.96*	*0.96*
Professionals	*0.91*	*0.94*	*0.95*
Laymen	*0.87*	*0.89*	*0.91*

4.3.3 Treatment effect

Table 3 shows the correlation coefficients between full face and nasolabial photographs and between professionals and laymen. A moderate correlation between full face and nasolabial photographs was found. Table 3 also shows that the correlation between professionals and laymen was high.

Table 3 *Pearson's correlation coefficients between ratings of full face and nasolabial photographs, for professionals and laymen, are given.*

		full face and nasolabial photographs			*professionals and laymen*
professionals	*4 y*	*0.739*	*full face*	*4 y*	*0.856*
	6 y	*0.767*		*6 y*	*0.859*
laymen	*4 y*	*0.679*	*nasolabial*	*4 y*	*0.896*
	6 y	*0.566*		*6 y*	*0.921*

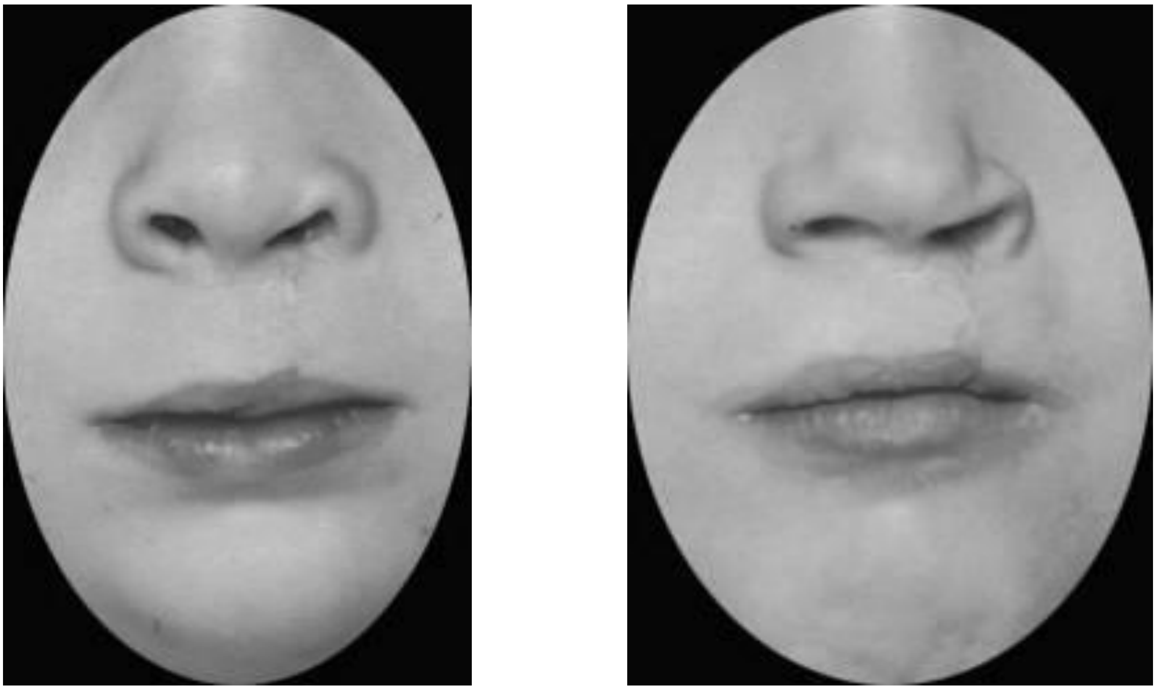
In Table 4 the effect of IO is shown for full face photographs, and nasolabial photographs. A comparison was made between the esthetic scores at different ages (4 and 6 years) for professionals and laymen.

Table 4 *Number (n), means and SDs of the esthetic scores are given for full face photographs, nasolabial photographs for IO+ and IO- at the age 4 and 6 years. Differences between IO+ and IO- were tested with t-tests.*

			4 years				*6 years*			
Variable			*n*	*mean*	*(SD)*	*p*	*n*	*mean*	*(SD)*	*p*
Full face	*Professional*	*IO-*	*21*	*94.18*	*(12.0)*	*.006***	*24*	*95.21*	*(11.04)*	*.08*
		IO+	*24*	*105.27*	*(13.94)*		*22*	*100.63*	*(9.47)*	
	Laymen	*IO-*	*21*	*89.75*	*(11.65)*	*.02**	*24*	*96.19*	*(9.86)*	*.15*
		IO+	*24*	*99.10*	*(14.22)*		*22*	*100.71*	*(11.19)*	
Nasolabial	*Professional*	*IO-*	*21*	*93.06*	*(13.50)*	*.47*	*24*	*96.85*	*(11.78)*	*.04**
		IO+	*24*	*95.98*	*(13.09)*		*22*	*105.41*	*(14.57)*	
	Laymen	*IO-*	*21*	*91.20*	*(12.50)*	*.27*	*24*	*96.13*	*(13.35)*	*.10*
		IO+	*24*	*95.16*	*(10.98)*		*22*	*103.05*	*(14.25)*	

*The level of significance is indicated with p values: * $0.05 \geq p > 0.01$; ** $0.01 \geq p > 0.001$; *** $p \geq 0.001$*
n may vary because of incidental missing values

Children in the IO+ group were found to have a significantly more attractive appearance than children in the IO- group, at the age of 4, looking at full face photographs. For the nasolabial photographs no significant differences were found. At 6 years of age the only significant difference was found for the nasolabial photographs scored by professionals. In figure 3 two examples are shown of esthetic scores (score 96 and 104).



A ***B***

Figure 3 *Example of a nasolabial picture with esthetic score 96 (B) and 104 (A).*

In Table 5 the results of the regression analysis are shown. Besides the effect of IO shown in table 4, only the 5-year-olds' index influences the esthetic result at 6 years of age in full face photographs, but only to a minimal extent, since the total adjusted R square is 7% or lower.

Table 5 *P-values from regression analysi to test whether IO, occlusion at 4 or 6 years of age, lip revision or the type of nose reconstruction at initial lip closure, influence the esthetic result.*
Adjusted R2 is given to show how much of the esthetic result can be explained by each of these items.

	Full face				*Nasolabial*			
	4 years		*6 years*		*4 years*		*6 years*	
	laymen	*prof.*	*laymen*	*prof.*	*laymen*	*prof.*	*laymen*	*prof.*
IO	*.03**	*.01**	*.24*	*.15*	*.39*	*.53*	*.11*	*.04**
5/year-index	*.69*	*.88*	*.03**	*.06*	*.43*	*.21*	*.72*	*.15*
liprevision	*.71*	*.30*	*.96*	*.58*	*.56*	*.79*	*.11*	*.08*
nose correction	*.79*	*.84*	*.40*	*.24*	*.55*	*.47*	*.06*	*.07*
adjusted R^2	*.03*	*.10*	***.07***	*.06*	*-.06*	*-.43*	*.10*	*.15*

*p values: * p > .05*

4.4 Discussion

The aim of this part of the Dutchcleft study was to evaluate the effect of IO on facial appearance at a young age. The method chosen to test this, was comparable to the methods used by Prahl et al.[19] and Peerlings et al.[20] In the literature several methods to score photographs can be found the lite. Here, VAS-scorings were chosen. Peerlings et al.[20] demonstrated that both line and number scorings show reliable results. Scales like the one made by Tobiasen et al.[21] or Asher-McDade et al.[6] were not used because they were employed on children of other ages than in the present study. However, cropped photographs of the nasolabial part of the face were used, as was done by Asher-McDade et al.,[6] to blind for other facial factors. Characteristics of a face, and variation in facial expression were found to blur the judgment of full faces in a positive way.[22,23] This was also found by Prahl et al.[19] for the Dutchcleft children in the present study at the age of 1.5 years. The same was found in the present study. The nasolabial photographs do not have this problem, and can be interpreted with less caution.

Because some studies[24-26] found differences between the opinion of laymen and the appreciation of the facial appearance of professional observers, it was decided to ask observers with different backgrounds. Furthermore, Tobiasen[27] and Okkerse et al.[28] found a difference between the ratings for boys and girls in appreciation of facial appearance. Therefore, the boys and girls had their own reference pictures.

Although it has been claimed that infant orthopedics benefits the esthetic outcome of cleft surgery, this has never been tested. Therefore, the results from the present randomized clinical trial cannot be compared to other studies. Reviewing the changes in facial esthetics in Dutchcleft during the first 6 years of life and the differences between IO+ and IO-, it can be noticed that infant orthopedics has no direct major influence on facial esthetics as measured as early as 18 months of age.[19] When growing up some significant differences between the groups were found but these showed no consistent pattern over the different age periods. At 4 years of age full face pictures of children, who were treated with infant orthopedics during the first year of life were scored to be more attractive than full face pictures of children without infant orthopedics. However, this difference had disappeared at 6 years of age. The nasolabial photographs showed significance only at 6 years of age for professionals: IO+ was better than IO-. As a child functions in his own social context, mainly consisting of laymen, this result can be considered to be unimportant.

Regression analysis was done to test whether the small difference found between IO+ and IO-, could be partly caused by the jaw relationship as expressed by the 5-year-olds’ index at 4 or 6 years of age, lip-revision or the type of nose reconstruction at initial lip closure. None of these items could explain the differences between in IO+ and IO-. As is shown in table 5, only the 5-year-olds’ index at the age of 6 had a minor influence on the esthetic scores for full face photographs. A low p-value was found for liprevision and nose correction at 6 years evaluation of the nasolabial photographs. This can explain at most 15% of the significant differences found between the IO-groups. In the literature no articles were found regarding these relationships.

4.5 Conclusion

IO had a positive effect on full facial appearance of UCLP children at the age of 4 years, but at the age of 6, only professionals saw a positive effect of IO on the nasolabial photographs. This difference is irrelevant for patients with UCLP, since they deal with laymen in their daily life.

Considering all results of Dutchcleft studies to date, there is no indication for the use of IO for patients with UCLP. Those who are promoting different methods of IO including nasoalveolar molding should consider the long-term benefits of their interventions using the same rigorous methodology as applied in Dutchcleft.

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Chapter 5

Identification of cephalometric landmarks in unilateral cleft lip and palate patients: are there alternatives for point A, ANS, and PNS?

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Summary

Objective: To test the reliability of some cephalometric measurements in unilateral cleft lip and palate patients. Measurements with A, ANS, and PNS, were compared to measurements performed with alternatives for point A, ANS, and PNS: A1, A2, ANS1, ANS2, and PNS1.

Patients: 164 children with complete unilateral cleft lip and palate (UCLP), with a lateral head film taken at age 4 to 6 years.

Mean outcome measures: Intraobserver and interobserver reliability for cephalometric measurements including A, ANS, PNS or their alternatives: Dahlberg errors, systematic errors, and Pearson correlation coefficients were calculated.

Results: The measurements using ANS and PNS or their alternatives, were comparable. The systematic error between observers for measurements using A2 was less than for measurements using A or A1. The scatterplot of point A showed a slightly better distribution of the points than the plots of A1 and A2.

Conclusions: Although the landmarks A, ANS, and PNS are hard to trace in UCLP patients with tooth germs in the anterior maxilla, no better landmarks were found in this study. Cephalometric studies using A, ANS, and PNS in UCLP patients should be interpreted with caution.

5.1 Introduction

Cephalometric analysis is the classic tool used to describe facial growth and development in cleft lip and palate patients. However, cephalometric measurements have an inherent method error that varies depending on the radiographic projection, measuring system, type of landmark, and observer. Radiographic projection errors may occur due to magnification and distortion of the object during the procedure of taking the radiograph. A general magnification factor can be used to correct the magnification, but the distortion, due to a difference in magnification of one structure compared to the other, is not easy to correct. Errors in the measuring system itself are minimal because of the current use of digital recording devices. This leaves the error in landmark identification the major source of cephalometric error. The type of landmark, the precision of the landmark definition, and the observer are important factors in the uncertainty within landmark-positioning.[1] In a study on cleft and control patients (ages 18 to 33 years) in which 92 different cephalometric measurements were used,[2] seven measurements had an error greater than 1.5 mm or 1.5 degrees, while all other measurements showed a smaller error. Differences in the magnitude of the measurement error are caused by the precision of the landmark definition and the amount of noise of adjacent structures. Several studies have pointed out that the observer also has an effect on the magnitude of the error.[3,4] Errors can be reduced if measurements are done twice and their average value is used in the further analysis, and by tracing all radiographs on the same day.[4]

In young cleft lip and palate patients, identification of cephalometric landmarks is even more difficult due to the abnormal anatomy. This especially holds true for localization of the landmarks point A, anterior nasal spine (ANS), and posterior nasal spine (PNS). As was described by Hotz and Gnoinski,[5] point A is difficult to locate in young individuals because of the tooth germs molding the anterior contour of the maxilla. Furthermore, point A, ANS, and PNS can be hard to locate because of reduced radiopacity due to the cleft. And, point ANS is not positioned in the midline in a patient with unilateral cleft lip and palate (UCLP) due to outward rotation of the larger segment of the maxilla. The most difficult age to examine radiographs in cleft patients is the period before shedding of the incisors, since all above mentioned problems occur in this period of time.

Although many cephalometric studies on facial growth in unilateral cleft lip and palate patients have been published (for example Mølsted et al. and Brattström et al.[6,7]) only a few discuss in detail the reliability of cephalometric measurements in which point A, ANS, and PNS are involved or describe the use of alternative landmarks for the maxilla.[5,8-10] These studies were the basis for the current research project.

Krogman et al.[8] described an alternative for point PNS. In the absence of PNS due to clefting, PNS can be approximated by extending Ptm until it intersects the palatal plane (PNS alternative 1). Tindlund et al.[10] constructed additional points for point A and ANS, because of difficulties in their study in determining these points in young patients with cleft lip and palate (CLP). They used the line N-Gn. The intersection of this line with the palatal plane, forms sp'', an alternative for ANS (ANS alternative 1). In their study, Maxp was the alternative for point A: a construction point formed by the intersection of a line parallel to the palatal plane, 7 mm below, and the anterior contour of the maxilla (A alternative 1). Hotz and Gnoinski[5] did not propose other landmarks, but tried to offer a very clear definition of point A and interpreted the results of measurements involving PNS, with caution. The same description was later used by Rygh and Sirinavin.[9]

There are no studies available on the reliability of these alternative descriptions and points, and it is not clear whether their use is meaningful in cephalometric analysis of young CLP patients. Therefore, the aim of the present study was to test the reliability of cephalometric measurements using Point A, ANS, and PNS and three alternatives in unilateral cleft lip and palate patients.

5.2 Methods

5.2.1 Data acquisition

Table 1 *Descriptions of landmarks and measurements*

Landmark	*Name*	*Description*
N	*Nasion*	*The most anterior limit of the frontonasal suture*
S	*Sella*	*The geometric center of the sella turcica*
Ar	*Articulare*	*The point of intersection of the projection of the dorsal contours of the processus articularis mandibulae and the pharyngeal part of the clivus*
Ptm	*Pterygomaxillary fissure*	*Lowest point on the pterygomaxillary fissure between the anterior margin of the pterygoid process and the posterior margin of the maxillary tuberosity*
Pg	*Pogonion*	*The most anterior point on the chin of the mandible*
Me	*Menton*	*The most inferior point on the symphysis of the mandible, relative to the mandibular border*
Gn	*Gnathion*	*A point midway between Pg and Me on the outline of the symphysis*
Pr	*Prosthion*	*The point of the maxillary alveolar process in the midline that projects most anteriorly*
A	*Point A*	*The deepest point on the anterior contour of the upper alveolar process above the tooth germs of the permanent incisors (Hotz and Gnoinski, 1976)*[5]
A1	*Point A alternative 1*	*Intersection between a line parallel to the palatal plane, 7 mm below, and the anterior contour of the maxilla (Tindlund et al., 1993)*[10]
A2	*Point A alternative 2*	*The projection of point Pr on a line parallel to the palatal plane, 7 mm below the palatal plane*
ANS	*Anterior nasal spine*	*The tip of the bony anterior nasal spine*
ANS1	*Anterior nasal spine alternative 1*	*Intersection between the line N-Gn and the palatal plane (Tindlund et al., 1993)*[10]
ANS2	*Anterior nasal spine alternative 2*	*The projection of Pr on the palatal plane*
PNS	*Posterior nasal spine*	*The posterior end of the hard palate, if visible. Otherwise at the point of intersection of the dorsal maxillary contour and the soft palate contour (Hotz and Gnoinski, 1976)*[5]
PNS1	*Posterior nasal spine alternative 1*	*The intersection of the palatal plane and the apex of the pterygomaxillary fissure (Krogman et al., 1975)*[8]

*Variables**	*Description*
< ANS-PNS / SN	*Measures the inclination of the maxilla relative to the cranial base*
< S-N-A	*Measures the anteroposterior position of point A in relation to the anterior cranial base*
Ratio ANS-Me / N-Me	*Measures the ratio of the lower face height relative to the total face height*
< N-ANS-Pg	*Angle of convexity according to Harvold*
Length A-Ar (mm)	*Measures the anteroposterior position of point A relative to Ar*
Ratio ANS-PNS / MP	*Measures the ratio of the maxillary length relative to the mandibular length*

** Where A, ANS, or PNS is written, A1, A2, ANS1, ANS2, and PNS1 were also used.*

Lateral head films of 164 patients with a complete unilateral cleft lip and palate were selected at random from the patient archive of the cleft palate craniofacial Unit of the Radboud University Nijmegen Medical Center (the Netherlands). The age at which the radiograph was taken had to be between 4 and 6 years.

The lateral head films were obtained with the patient positioned in a cephalostat and oriented to the Frankfort horizontal plane. All lateral head films were traced by hand by one observer, and 16 lateral head films were traced twice with a time interval of approximately 2 months. A second observer traced 28 lateral head films that were also traced by the first observer. Both observers marked the landmarks on their own tracings, independently of each other.

The landmarks used and their definitions are listed in Table 1. Two alternative cephalometric landmarks were defined for both Point A and PNS: A1, A2, ANS1, and ANS2, respectively. For PNS, one alternative (PNS1), was defined. Figure 1 shows a tracing with the locations of these points.

The tracings were scanned on a flat-bed scanner (Linotype-Hell AG, type H391, Eschborn, Germany). The landmarks on the scans were digitized on the scanned images by two observers using Viewbox software (version 3.1.0.5; dHal Orthodontic Software, Athens, Greece) and the angular, linear and ratio variables, as listed in Table 1, were calculated. To determine the error of the digitizing procedure, observer one digitized 28 scans twice and observer two did the same for 15 scans. A magnification correction (3.93%) was applied to the scans to yield life size measurements.

5.2.2 Statistical analysis

Intraobserver duplicate measurement errors were calculated for both the tracing and the digitization of the landmarks (Figure 1 and Table 2) according to Dahlberg’s formula, and reliability coefficients between the first and second tracing or digitization were calculated as Pearson correlation coefficients. The presence of systematic differences between the first and the second tracing or digitization was investigated using paired t-tests. The same calculations were performed for the interobserver errors between observer one and two.

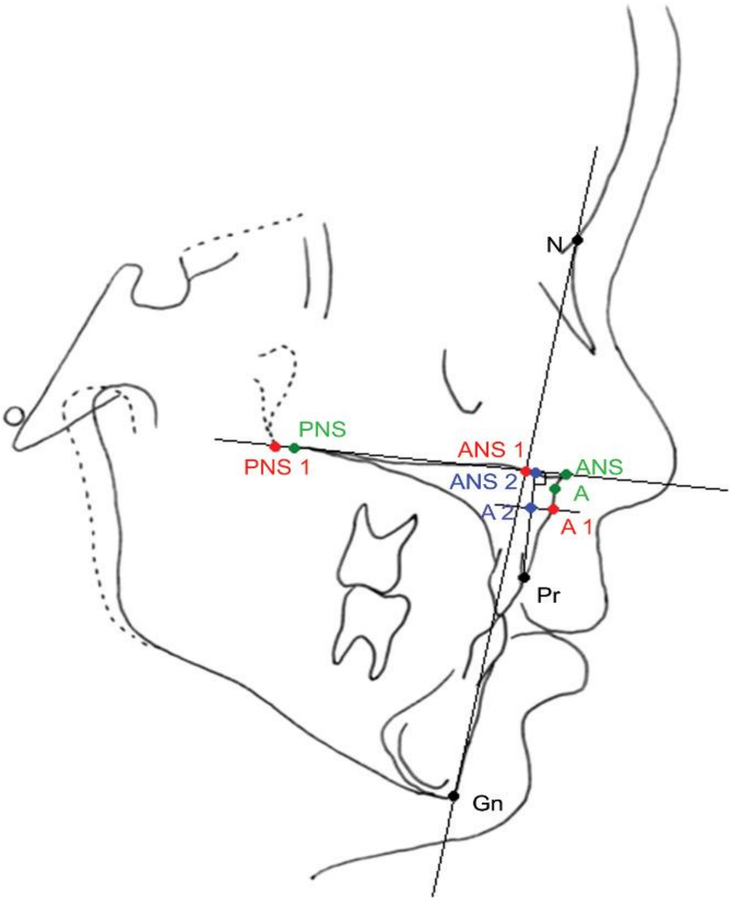

Figure 1 *Tracing showing the different landmarks: A, ANS, PNS, and the alternative landmarks: A1, A2, ANS1, ANS2, and PNS1.*

To compare the same variables, using A, A1, or A2, and ANS, ANS1, or ANS2, and PNS or PNS1 the systematic error, Dahlberg's error and Pearson correlation coefficients were evaluated for the intraobserver and interobserver calculations. A measurement was considered to be more useful in UCLP cephalometric analysis when it had a smaller systematic and/or duplicate error and a higher correlation coefficient compared to the same measurement with an alternative for A, ANS, or PNS.

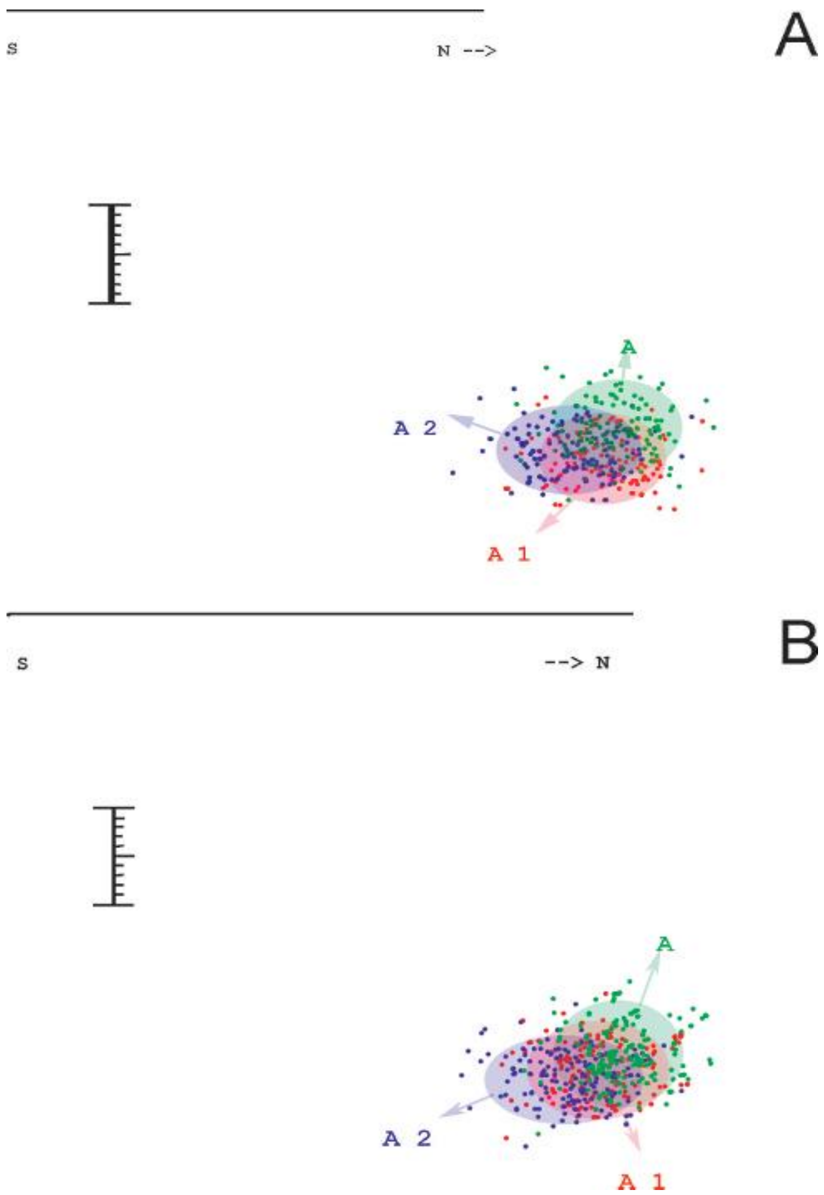

Figure 2 *Scatterplot of A and its alternative points, measured on x-rays of 4-year-old (A) and 6-year-old (B) children.*

5.3 Results

In Table 2, intraobserver and interobserver errors are presented for all cephalometric variables. The intraobserver reliability was better or comparable to the interobserver reliability. As expected, duplicate measurement errors were larger for the tracing procedure than for the digitization.

Table 2 *Intraobserver and interobserver agreement for tracing (tracing and marking the points on paper) and digitization (scanning and digitizing the points) of the cephalometric landmarks*

		Intraobserver reliability n (tracing) = 16 n (digitization) = 28			*Interobserver reliability n (tracing) = 28 n (digitization)= 164*		
Variable (Degrees, mm, %)		*duplicate measurement error*	*correlation coefficient*	*systematic error*	*duplicate measurement error*	*correlation coefficient*	*systematic error*
ANS-PNS1 / SN (°)	*Tracing*	*1.72*	*0.723*	*-0.70*	*2.62*	*0.211*	*-0.39*
	Digitization	*0.22*	*0.996*	*-0.05*	*0.27*	*0.994*	*-0.02*
ANS2-PNS / SN (°)	*Tracing*	*1.69*	*0.727*	*-0.64*	*2.58*	*0.231*	*-0.59*
	Digitization	*0.25*	*0.994*	*0.02*	*0.27*	*0.994*	*0.08**
ANS2-PNS1 / SN (°)	*Tracing*	*1.68*	*0.733*	*-0.70*	*2.61*	*0.207*	*-0.54*
	Digitization	*0.22*	*0.995*	*0.03*	*0.28*	*0.994*	*0.06**
ANS-PNS / SN (°)	*Tracing*	*1.74*	*0.716*	*-0.64*	*2.60*	*0.226*	*-0.44*
	Digitization	*0.26*	*0.994*	*-0.06*	*0.26*	*0.994*	*-0.02*
ANS1-PNS / SN (°)	*Tracing*	*1.66*	*0.731*	*-0.52*	*2.61*	*0.220*	*-0.52*
	Digitization	*0.28*	*0.992*	*0.02*	*0.28*	*0.993*	*0.05*
ANS1-PNS1 / SN (°)	*Tracing*	*1.65*	*0.738*	*-0.61*	*2.62*	*0.205*	*-0.45*
	Digitization	*0.25*	*0.994*	*0.03*	*0.30*	*0.992*	*0.04*
ANS-PNS1 / MP (ratio)	*Tracing*	*2.16*	*0.903*	*0.00*	*3.72*	*0.801*	*-3.41**
	Digitization	*0.44*	*0.996*	*0.11*	*0.60*	*0.992*	*-0.01*
ANS2-PNS / MP (ratio)	*Tracing*	*2.76*	*0.819*	*1.29*	*3.97*	*0.637*	*-1.51*
	Digitization	*0.39*	*0.996*	*-0.03*	*0.89*	*0.980*	*-0.01*
ANS2-PNS1 / MP (ratio)	*Tracing*	*1.81*	*0.936*	*-0.88*	*3.47*	*0.859*	*-3.51**
	Digitization	*0.37*	*0.997*	*0.12*	*0.74*	*0.987*	*-0.04*
ANS1-PNS / MP (ratio)	*Tracing*	*2.67*	*0.683*	*2.08**	*2.84*	*0.663*	*-1.80**
	Digitization	*0.39*	*0.989*	*-0.02*	*0.80*	*0.975*	*-0.11*
ANS-PNS / MP (ratio)	*Tracing*	*3.07*	*0.822*	*2.16**	*3.83*	*0.617*	*-1.39*
	Digitization	*0.46*	*0.994*	*-0.04*	*0.71*	*0.986*	*0.02*
ANS1-PNS1 / MP (ratio)	*Tracing*	*1.53*	*0.912*	*-0.09*	*3.51*	*0.732*	*-3.78**
	Digitization	*0.38*	*0.992*	*0.15*	*0.66*	*0.982*	*-0.13*
ANS1-Me / N-Me (ratio)	*Tracing*	*0.72*	*0.837*	*0.25*	*0.74*	*0.804*	*-0.11*
	Digitization	*0.14*	*0.993*	*-0.05*	*0.28*	*0.974*	*-0.01*
ANS-Me / N-Me (ratio)	*Tracing*	*0.90*	*0.801*	*0.40*	*1.02*	*0.739*	*-0.16*
	Digitization	*0.14*	*0.995*	*0.01*	*0.36*	*0.971*	*0.02*
ANS2-Me / N-Me (ratio)	*Tracing*	*0.80*	*0.803*	*0.36*	*0.80*	*0.768*	*-0.06*
	Digitization	*0.13*	*0.995*	*-0.06*	*0.33*	*0.971*	*-0.05*
N-ANS-Pg (°)	*Tracing*	*0.90*	*0.911*	*0.21*	*1.01*	*0.918*	*0.34*
	Digitization	*0.20*	*0.997*	*0.01*	*0.31*	*0.993*	*0.14**
N-ANS2-Pg (°)	*Tracing*	*0.75*	*0.975*	*-0.58**	*1.33*	*0.916*	*-0.05*
	Digitization	*0.18*	*0.999*	*0.06*	*0.33*	*0.993*	*0.11**
N-ANS1-Pg (°)	*Tracing*	*0.32*	*0.037*	*0.01*	*0.98*	*-0.164*	*-0.27*
	Digitization	*0.12*	*0.866*	*0.07**	*0.37*	*0.633*	*0.03*
A-Ar (mm)	*Tracing*	*0.48*	*0.975*	*-0.02*	*0.59*	*0.976*	*0.46**
	Digitization	*0.51*	*0.973*	*-0.13*	*0.23*	*0.998*	*0.14**
A1-Ar (mm)	*Tracing*	*0.68*	*0.945*	*-0.20*	*0.44*	*0.983*	*0.17*
	Digitization	*0.46*	*0.983*	*-0.13*	*0.23*	*0.998*	*0.08**
A2-Ar (mm)	*Tracing*	*0.65*	*0.967*	*-0.49**	*0.88*	*0.938*	*-0.38*
	Digitization	*0.32*	*0.991*	*-0.08*	*0.23*	*0.997*	*0.08**
S-N-A2 (°)	*Tracing*	*0.71*	*0.967*	*-0.44*	*1.43*	*0.860*	*-0.03*
	Digitization	*0.24*	*0.996*	*0.06*	*0.66*	*0.978*	*-0.03*
S-N-A1 (°)	*Tracing*	*0.84*	*0.942*	*0.05*	*1.42*	*0.910*	*1.31**
	Digitization	*0.20*	*0.997*	*0.07*	*0.43*	*0.990*	*0.10**
S-N-A (°)	*Tracing*	*0.73*	*0.959*	*0.13*	*1.27*	*0.924*	*1.03**
	Digitization	*0.25*	*0.996*	*0.10*	*0.45*	*0.989*	*0.13*

** p < .05.*

The correlation coefficients were rather high, except for measurements concerning the inclination of the maxilla relative to the cranial base, where the correlation coefficients for the interobserver agreement for the tracing procedure were rather weak.

The measurements using ANS and PNS or their alternatives, were comparable. The alternatives did not perform better than the commonly used ANS and PNS. Measurements using A2 performed better than measurements using A or A1 as the systematic error of the tracing procedure for variables using A2 showed less significant interobserver differences.

Figure 2 shows scatterplots of the landmarks A, A1, and A2 for the ages 4 and 6 years. For point A, the distribution of the points showed a round configuration, whereas A1 and A2 were more oval, with the long axis horizontally.

5.4 Discussion

This project focused on the reliability of cephalometric measurements involving A, ANS, and PNS in young children with unilateral cleft lip and palate. As could be expected, tracing errors were larger than digitization errors due to difficulties in identifying landmarks. The largest error for angles was found to be 2.6 degrees, while ratios showed a maximum error of 4%, and the largest error for distances was 0.9 mm. Nearly all studies on the reliability of cephalometric landmarks and measurements have been performed on non-cleft individuals. A meta-analysis on landmark identification and reproducibility in non-cleft individuals concluded that 0.6 mm of total error in the x- or y-coordinate was acceptable. Point A, ANS, and PNS were among the points with a mean error distribution close to zero.[11] Since a cephalometric variable is composed of at least two landmarks, the error for a measurement will be larger than the error for a single landmark alone. The errors for distance-measurements found by Perillo et al.[12] on non-cleft adults were higher than in this study, while the correlations were comparable. Tindlund et al.[10] studied 41 cleft cases at five different ages; 30 cephalograms were traced twice. They reported that measurement errors were generally small, except for variables reflecting not fully developed and erupted incisors, but no supporting numerical data were given. Krogman et al.[8] did not report measurement errors at all. Rygh and Sirinavin[9] performed double measurements and used the mean value. They used a sliding caliper with an accuracy of 0.05 mm and a protractor with an accuracy of 0.5 degrees. Unfortunately, measurement reliability was not calculated in their study. Hotz and Gnoinski[5] advised to be cautious with the interpretation of results involving point PNS and point A. In the Eurocleft studies children ages 8 to 10 years were analyzed cephalometrically, using the commonly used landmarks A, ANS, and PNS.[6] The method error was reportedly less than 1.5 degrees or less than 1.5 mm for the skeletal variables. The mean duplicate measurement errors in this study are about the same. Summarizing the results, it must be concluded that the alternative points produced no improvements, although point A2 showed a smaller error than point A and A1.

Researchers that mention difficulties in landmark identification and measurements describe the non-erupted incisors and the displaced and reduced size of the premaxilla as causes. Especially at a young age, the premaxillary region can show a marked shift away from the centerline.[13] With respect to the anatomy of the palate, it is also possible that the palatal shelf is rotated from the midline and/or the posterior palate might be deficient in size, which influences point PNS and its alternative. The distribution of points in the scatterplots showed a horizontal rather than vertical distribution. This will especially affect measurements in the horizontal direction. Scatterplots of point A in the study of Baumrind and Frantz[14] showed a vertical distribution of points. Landmarks were positioned by five persons on 20 lateral head films of non-cleft patients in the orthodontic-treatment-age. In our study two persons positioned the landmarks on 164 lateral head films of cleft patients. Our plot showed a more round set of points in a greater diameter. This may be caused by the larger number of cephalograms evaluated in this study, and by the difference in cleft versus non-cleft patients. Maybe the most important factor, that causes the more horizontal distribution of the scatterplot, is the non-erupted central incisor in the study, while the sample of Baumrind and Frantz[14] was an older age group.

Given the difficulties mentioned above, caution with the interpretation of cephalometric findings is advised, especially concerning UCLP patients at young ages. The tested alternative points seem to have the same concerns and are no better than the traditional point A, ANS, and PNS.

5.5 Conclusions

Although the traditional landmarks A, ANS, and PNS are difficult to trace in children with UCLP, no better landmarks were found in this study. Since measurements using A, ANS, and PNS are prone to interobserver measurement errors during tracing and digitization, results of cephalometric studies in UCLP should be interpreted with caution.

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Chapter 6

Infant orthopedics and facial growth in complete unilateral cleft lip and palate until 6 years of age

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Summary

Objective: To evaluate longitudinally the effect of infant orthopedics (IO) on dentofacial cephalometric variables in UCLP patients from 4 to 6 years of age.

Design: Prospective two-arm randomized controlled clinical trial in three Cleft Palate Centers in the Netherlands (Dutchcleft-trial).

Patients: Fifty-four children with complete UCLP.

Interventions: Patients were divided randomly into two groups. Half of the patients (IO+) had infant orthopedics (IO) until surgical closure of the soft palate at the age of ± 52 weeks; the other half (IO-) received no intervention.

Mean outcome measures: Cephalometric values representing soft tissue, hard tissue and dental structures, measured on lateral headfilms made at 4 and 6 years of age.

Results: In the IO+ group 21 patients were analyzed, in the IO- group 20 patients at age 4 and 22 at age 6. No differences were found between IO+ and IO- except for two measurements: the interincisal angle was larger and the mentolabial angle was smaller in the IO+ group.

Conclusions: For patients with UCLP whose surgical management included soft palate repair at 12 months and delayed hard palate closure, the cephalometric outcome at age 4 and 6 provides no indication for the type of IO used in this study.

6.1 Introduction

The characteristic face of an individual treated for a complete unilateral cleft lip and palate has been described by Dahl in 1970[1] (age group 18-33 years of age). He found that the upper face height was smaller compared to the control group; the maxilla was short, and this was accentuated in the dentoalveolar area due to retroclined incisors, and there was a greater height development in the lower face. More recently Nollet et al.[2] described the Nijmegen UCLP sample born between 1976 and 1986 (aged 8-18 years). Cephalometrically both the maxilla and the mandible showed a retrusive facial pattern; there was a rather hyperdivergent facial growth pattern. The interincisal angle was obtuse, as was the nasolabial angle.[2]

Beside the intrinsic deficiency, there are many iatrogenic factors, that can influence facial growth. Repair of the lip, alveolar process, the soft palate and the hard palate, but also the surgeon himself, the timing of the repair, patient related factors such as scarring, or treatments as infant orthopedics (IO) might affect facial growth.[3,4]

Many different types of infant orthopedic appliances have been described. Some centers use active appliances, others passive appliances. Active appliances are designed with springs or screws to move the maxillary segments into the desired direction. Passive appliances induce arch alignment during growth by grinding away material of the plate. Also described is a plate made on a reconstructed cast to move the maxillary segments in a predetermined position. Beside these appliances, external strapping across the cleft can be part of the treatment protocol. Also naso-alveolar molding is described. It is said to reshape and reposition anatomic structures to achieve more symmetrical relationships between the nasal cartilages, columella and alveolar segments.[5-7]

Since there are a lot of different techniques for IO described, it is hard to compare treatment results. More importantly, the treatment of a cleft patient consists of more than IO alone; all these steps in treatment may have an influence on facial morphology. It is impossible to separate these steps in treatment when comparing results in retrospective research (for example, Ross[3] or Mølsted[8]). Since these studies, and many others are retrospective and show conflicting results, Dutchcleft was started: a prospective randomized clinical trial performed in three Cleft Palate Centers in the Netherlands.[9] In this project passive appliances were used.

The purpose of the part of the trial presented here, is to evaluate longitudinally the effect of IO on dentofacial cephalometric variables in UCLP patients from 4 to 6 years of age. The hypothesis is that the cephalometric outcome of the IO+ group is better than in the IO- group.

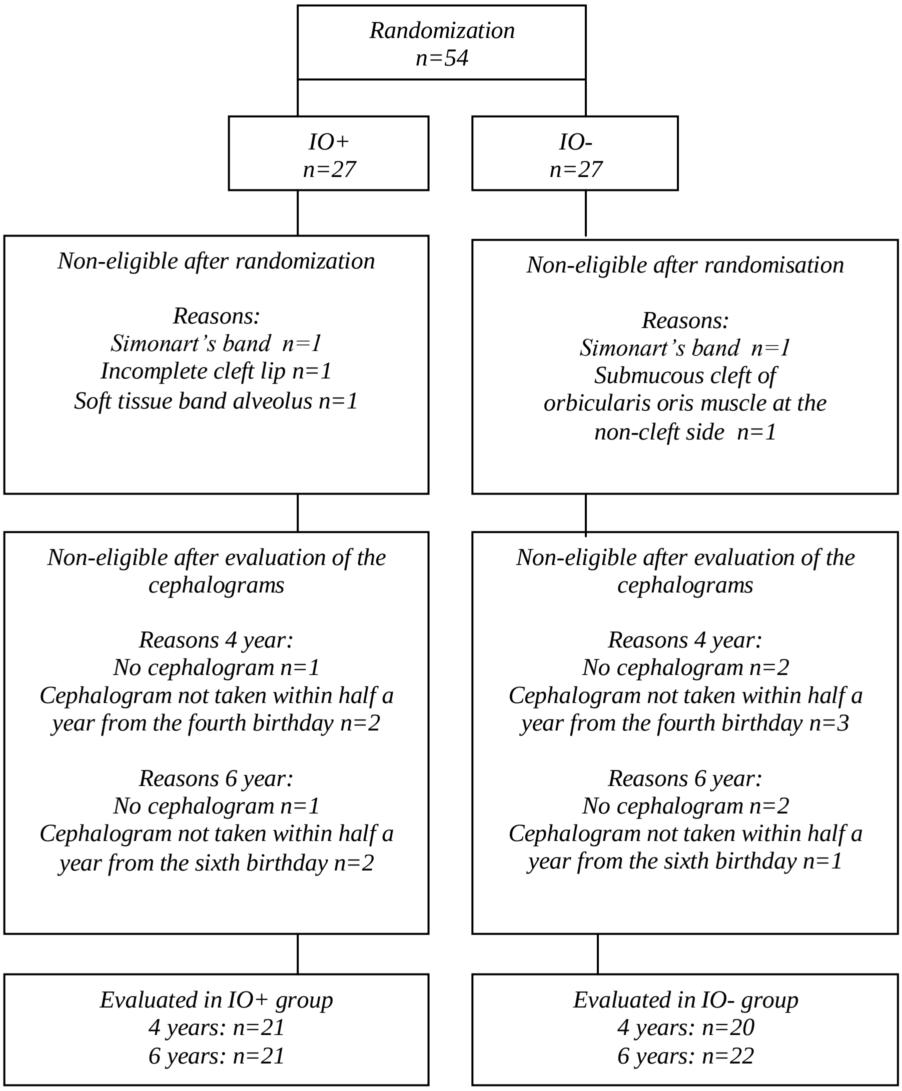

Figure 1 *Flow diagram of trial children with the reasons for exclusion of evaluation.*

6.2 Patients and methods

This study was designed as a prospective two-arm randomized controlled clinical trial in the Cleft Palate Centers in Nijmegen, Amsterdam, and Rotterdam, in the Netherlands. The local ethical committees approved the study protocol. The inclusion criteria were: complete UCLP, infants born at term, both parents Caucasian and fluent in the Dutch language, and trial entrance within two weeks after birth. The exclusion criteria were soft tissue bands, and other congenital malformations. Figure 1 shows the sample until the age of 6 with the reasons for exclusion of evaluation. When the parents agreed to participate in the study, they were asked to sign an informed consent. Between 3 and 6 months of age all included children were checked by the geneticist of their own CLP team as being non-syndromic.

In a previous publication, a detailed description has been given with respect to the experimental design, treatment assignment, treatment protocol and operators.[10] A summary of the most important issues is given.

6.2.1 Treatment

Half of the patients were treated with infant orthopedics by means of passive plates until surgical soft palate closure (n=27), and half did not get a plate (n=27). The plates were made on a plaster cast using compound soft and hard acrylic. The IO+ children had their plates adjusted every three weeks to guide the maxillary segments, by grinding at the cleft margins; maxillary growth and emergence of deciduous teeth indicated the necessity for a new plate. After surgical lip closure the plate was replaced the same day. Checkups were planned every 4-6 weeks following lip surgery. The plate was maintained till soft palate closure. The IO- group visited the clinic at 6 weeks, and before and after lip surgery and soft palate closure. In both groups, lip surgery was performed at the age of 18 weeks by the Millard technique. At lip surgery, the cleft teams of Amsterdam and Nijmegen used the McComb's technique for the nose; the Rotterdam cleft team preferred their own method that combined McComb's with Pigott's technique. Soft palate surgery was performed at the age of about 52 weeks according to a modified Von Langenbeck method including levator muscle repositioning. In the studied age period (until 6 years of age), other interventions were performed if indicated: pharyngoplasty (n=22), lip revision (n=13; in all cases performed before the age of 4 years), facial mask treatment (n=1), plate to facilitate speech (n=15), closure of the anterior palate (n=6). These interventions were equally distributed over the IO+ and the IO- group.

6.2.2 Data acquisition

The lateral head films were obtained with the patient positioned in a cephalostat and oriented to the Frankfort horizontal plane. The patients were instructed to have the lips in a relaxed closed position when taking the X-ray. All lateral head films were traced by hand by one observer; 18 lateral head films were traced twice with a time interval of two months approximately. A second observer traced 18 lateral head films that were also traced by the first observer. The 18 head films were randomly selected from the 4 and 6 year sample. Both observers marked the landmarks on their own tracings, independently of each other.

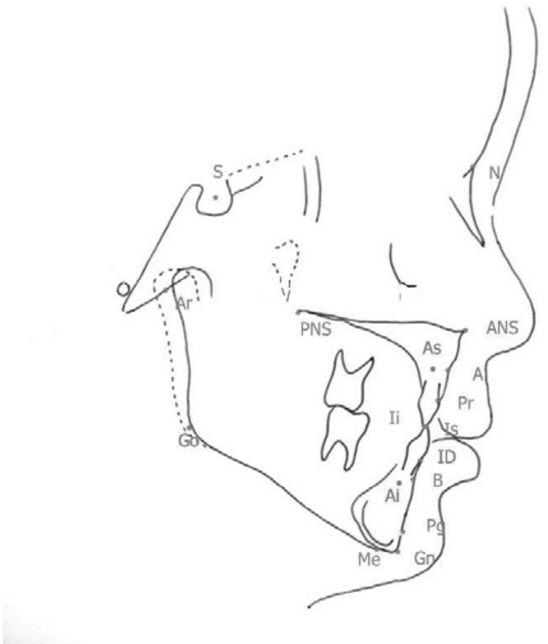

Figure 2A *Tracing of the hard tissue points.*

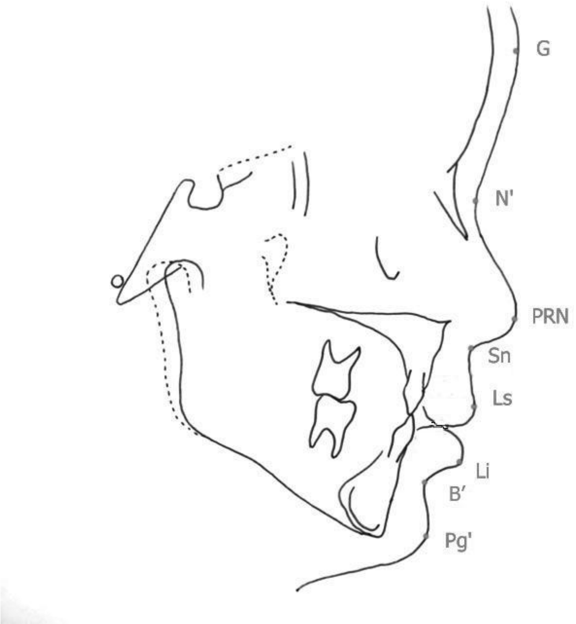

Figure 2B *Tracing of the soft tissue points.*

The used landmarks and definitions are listed in table 1 and figure 2A+B. The tracings were scanned on a flat-bed scanner (Linotype-Hell AG, type H391, Eschborn, Germany). The landmarks were digitized on the scanned images using Viewbox® vs. 3.1.0.5 (dHal Orthodontic Software, Athens, Greece) and angular, linear and ratio variables, as listed in table 1, were calculated. All measurements were recalculated to life size measurements: the magnification factor was 3.93% for Nijmegen and 3.83% for Amsterdam and Rotterdam. Direct scanning of the cephalograms led to more errors, because of the dark area that often occurred near the cleft. Landmarks were better identifiable on the original radiograph and tracing.

In Dutchcleft the occlusion and the esthetic results were also evaluated at age 6. The occlusion was studied on study models by using the 5-year-old index. The index is a five-point scale with 1 for excellent cases (no open bite or crossbite; a positive overjet) and 5 for very poor cases (crossbite on both sides, reversed overjet and poor arch form). The esthetics was scored with a VAS on facial photographs. Both full faces and photographs showing the nasolabial part only, were scored by professionals and laymen.

Table 1 *Descriptions of landmarks and measurements.*

Landmark	Name	Description
N	Nasion	the most anterior limit of the frontonasal suture
S	Sella	the geometric center of the sella turcica
Ar	Articulare	the point of intersection of the projection of the dorsal contours of the processus articularis mandibulae and the pharyngeal part of the clivus
Ptm	Pterygomaxillary fissure	lowest point on the pterygomaxillary fissure between the anterior margin of the pterygoid process and the posterior margin of the maxillary tuberosity
Pg	Pogonion	the most anterior point on the chin of the mandible
Me	Menton	the most inferior point on the symphysis of the mandible, relative to the mandibular border
Gn	Gnathion	A point midway between Pg and Me on the outline of the symphysis
Pr	Prosthion	the point of the maxillary alveolar process in the midline that projects most anteriorly
A	Point A	The deepest point on the anterior contour of the upper alveolar process above the tooth germs of the permanent incisors
ANS	Anterior nasal spine	The tip of the bony anterior nasal spine
PNS	Posterior nasal spine	The posterior end of the hard palate, if visible. Otherwise at the point of intersection of the dorsal maxillary contour and the soft palate
B	Point B	the deepest point on the contour of the mandible between infradentale (ID) and pogonion (Pg)
Go	Gonion	the intersection-point of the outer contour of the mandible with the bisectrice of the angle formed by the mandibular border and the tangent to the ramus from articulare, projected on the mandibular border
As	Apex superior	apex of the root of the most prominent maxillary central incisor
Ai	Apex inferior	apex of the root of the most prominent mandibular incisor
Is	Incision superior	the incisal point of the most prominent maxillary central incisor
Ii	Incision inferior	the incisal point of the most prominent mandibular incisor
ID	Infradentale	the most anterior-superior point on the mandibular alveolar process
m2s	maxillary second deciduous molar	the mesio buccal cusp of the maxillary second deciduous molar
m2i	mandibular second deciduous molar	the mesio buccal cusp of the mandibular second deciduous molar
N’	Soft tissue nasion	The deepest point of the soft tissue contour in the region of the naso-frontal suture
G	Glabella	The most prominent point in the midsagittal plane of the forehead
Sn	Subnasale	The deepest point of the subnasal curvature relative to a line from the nose tip (PRN) to the upper lip (Ls)
B’	Soft tissue point B	The point of the greatest concavity in the midline of the lower lip between Li and Pg’
Ls	Labrale superior	The most prominent point of the vermilion border of the upper lip
Li	Labrale inferior	The most prominent point of the vermilion border of the lower lip
Pg’	soft tissue pogonion	The most anterior point of the soft tissue of the chin in the midsagittal plane
PRN	Pronasale	The most anterior point of the tip of the nose

Variables	Description
SNA angle	Anterior-posterior position of point A in relation to the cranial base
SNB angle	Anterior-posterior position of point B in relation to the cranial base
ANB angle	The relative position of point A and B to each other
Mentolabial angle	Deepness of the mento-labial fold (Pg'-B'-Li)
Upper and lower lip thickness	Thickness in mm (Pr-Ls and ID-Li)
Nose angle	Protrusion of the nose (PRN-N'-Sn)
Facial convexity angle	Soft tissue convexity (G-Sn-Pg')
Nasolabial angle	Upper lip protrusion relative to the collumella line (PRN-Sn-Ls)
Upper and lower lip to E-plane	Soft tissue balance between the lip and the E-line in mm
Upper and lower lip protrusion	Lip protrusion in relation to Sn-Pg' in mm
Interincisal angle	Inclination of upper and lower incisors relative to each other
Lower incisor – Go-Me angle	Inclination of the lower incisor relative to the mandibular plane
Upper and lower incisor to APg	Position of the incisors to A-Pg in mm
Upper incisor - ANS-PNS angle	Inclination of the upper incisor relative to the palatal plane
N-ANS-Pg angle	Convexity of the face according to Harvold
Facial height index	The ratio of the posterior face height relative to the anterior face height (%)
ANS-PNS / Go-Me index	The ratio of the maxillary length relative to the mandibulary length (%)
ANS-PNS	Distance from ANS to PNS in mm
ANS-Me / N-Me index	The ratio of the lower anterior face height relative to the total anterior face height (%)
ANS-Me	Distance from ANS to Me
SN – Go-Me angle	Inclination of the mandibular plane relative to the cranial base
Occlusal Plane - SN angle	Inclination of the occlusal plane relative to the cranial base
ANS-PNS – SN angle	Inclination of the palatal plane relative to the cranial base

The findings are described in Bongaarts et al.[11] and Bongaarts et al.[12] Occlusal scores and facial esthetic scores were used in the present study in combination with the cephalometric measurements to explain possible effects.

6.2.3 Statistical analysis

Intra- and interobserver duplicate measurement errors were calculated for all cephalometric measurements. Paired T-tests showed the systematic errors. The reliability coefficients were calculated as Pearson correlation coefficients and duplicate measurement errors were calculated by $\frac{St.Dev.}{\sqrt{2}}$ meaning "standard deviation / √ 2" (in mm, degrees and %).

Also, the effect of IO was tested at 4 and 6 years of age with two tailed t-tests. The significance is given with the p-value. The increment shows the longitudinal results.

Finally, regression analyses were done to test the influence of cephalometric values, gender and occlusion at 6 years of age, on the overall esthetic result at age 6. P-values and the effect are given to demonstrate any influence and, the R square is given to show how much variance in the esthetic result can be explained by each of these items.

6.3 Results

6.3.1 General

Table 2 *Sample characteristics**

Variable	*IO + (n=27)*			*IO- (n=27)*		
Gender: male/female (n)	*20/7*			*21/6*		
Side of cleft: left/right (n)	*17/10*			*18/9*		
Patients per centre: 1/2/3 (n)	*7/11/9*			*7/10/10*		
Age 4-year casts (years.months)	*mean: 4.0 range:3.8-4.4*			*mean: 4.0 range:3.10-4.6*		
Age 6-year' casts (years.months)	*mean: 6.0 range:5.9-6.2*			*mean: 6.0 range:5.11-6.5*		
	IO +			*IO -*		
	P10	*P50*	*P90*	*P10*	*P50*	*P90*
Age at trial entrance (days)	*0*	*3*	*7*	*1*	*6*	*13*
Birth weight (gram)	*2660*	*3350*	*4020*	*2920*	*3600*	*4280*
Cleft width at birth (mm)	*9.5*	*12.5*	*14.4*	*8.6*	*12.4*	*16.4*
Age lip repair (days)	*117*	*127*	*142*	*117*	*125*	*138*
Age soft palate closure (days)	*355*	*375*	*438*	*301*	*367*	*389*

** Some variables are presented in percentiles because of skewness (P10, P50, and P90). IO+ = patients treated with infant orthopedics; IO- = patients not treated with infant orthopedics; P10 = 10th percentile; P50 = 50th percentile; P90 = 90th percentile.*

At intake 54 patients participated in the study. An overview of the sample characteristics is given in table 2. Two IO+ children hardly used the plate; in one case the plate was worn by mistake till 78 weeks. These children remained in the IO+ group according to the intention to treat principle: the patients are analyzed according to the treatment group to which they were randomized whether they received the treatment or not. The mean duration of IO was 50 weeks; SD was 16 weeks. The flow diagram in figure 1 shows the reasons for non-evaluation.

Table 3 *Intra- and interobserver duplicate measurement errors were calculated for all cephalometric measurements. Paired T-tests showed the systematic errors. The reliability coefficients were calculated as Pearson correlation coefficients and duplicate measurement errors were calculated by* $\frac{St.Dev.}{\sqrt{2}}$ *(in mm, degrees and %).*

Variable	*Inter-examiner*				*Intra-examiner*			
	P	*(mean)*	*error*	*r*	*P*	*(mean)*	*error*	*r*
SNA angle	*.002***	*(1.43)*	*1.15*	*.913*	*.982*	*(-.01)*	*0.70*	*.965*
SNB angle	*.087*	*(0.41)*	*0.62*	*.958*	*.604*	*(0.07)*	*0.43*	*.986*
ANB angle	*.005***	*(0.72)*	*0.58*	*.955*	*.625*	*(-.10)*	*0.62*	*.963*
Mentolabial angle	*.512*	*(1.36)*	*6.09*	*.804*	*.200*	*(2.13)*	*4.92*	*.855*
Upper lip thickness	*.758*	*(-.07)*	*0.64*	*.880*	*.549*	*(0.11)*	*0.56*	*.952*
Lower lip thickness	*.406*	*(-.12)*	*0.41*	*.974*	*.777*	*(0.04)*	*0.45*	*.974*
Nose angle	*.301*	*(-.48)*	*1.36*	*.734*	*.452*	*(0.24)*	*0.95*	*.862*
Facial convexity angle	*.559*	*(-.17)*	*0.84*	*.979*	*.851*	*(.053)*	*0.85*	*.978*
Nasolabial angle	*.094*	*(3.04)*	*5.14*	*.830*	*.007***	*(4.03)*	*4.12*	*.940*
Upper lip to E-plane	*.061*	*(-.26)*	*0.38*	*.983*	*.547*	*(-.07)*	*0.37*	*.984*
Upper lip protrusion	*.384*	*(-.13)*	*0.45*	*.963*	*.191*	*(-.19)*	*0.44*	*.971*
Lower lip to E-plane	*.293*	*(-.13)*	*0.37*	*.984*	*.920*	*(-.01)*	*0.32*	*.989*
Lower lip protrusion	*.965*	*(0.01)*	*0.37*	*.977*	*.736*	*(-.04)*	*0.33*	*.985*
Interincisal angle	*.180*	*(-2.53)*	*4.90*	*.799*	*.293*	*(-2.73)*	*7.75*	*.683*
Lower inc.- GoMe angle	*.070*	*(-1.31)*	*2.03*	*.887*	*.441*	*(0.51)*	*2.00*	*.914*
Lower inc. to APg	*.003***	*(-.59)*	*0.44*	*.892*	*.107*	*(-.19)*	*0.34*	*.947*
Upper inc. to APg	*.005***	*(-.61)*	*0.51*	*.954*	*.733*	*(-.08)*	*0.70*	*.932*
Upper inc.-ANS-PNS angle	*.151*	*(2.65)*	*5.28*	*.653*	*.534*	*(1.49)*	*7.26*	*.497*
N-ANS-Pg angle	*.124*	*(0.62)*	*1.04*	*.888*	*.219*	*(0.33)*	*0.81*	*.943*
Facial height index	*.003***	*(-1.07)*	*0.81*	*.908*	*.158*	*(-.37)*	*0.78*	*.930*
ANS-PNS / GoMe index	*.462*	*(-.97)*	*3.53*	*.665*	*.021**	*(2.02)*	*2.46*	*.840*
ANS-PNS	*.078*	*(0.86)*	*1.38*	*.609*	*.000****	*(1.41)*	*0.98*	*.804*
ANS-Me / N-Me index	*.171*	*(-.63)*	*1.20*	*.655*	*.558*	*(0.17)*	*0.87*	*.815*
ANS-Me	*.284*	*(-.42)*	*1.03*	*.900*	*.792*	*(0.07)*	*0.84*	*.925*
SN - GoMe angle	*.044**	*(0.55)*	*0.68*	*.972*	*.441*	*(0.14)*	*0.56*	*.987*
Occl. Plane - SN angle	*.024**	*(1.89)*	*2.05*	*.827*	*.701*	*(-.19)*	*1.54*	*.888*
ANS-PNS - SN angle	*.694*	*(0.33)*	*2.50*	*.403*	*.271*	*(-.57)*	*1.56*	*.789*

*p values: * 0.05 ≥ p > 0.01; ** 0.01 ≥ p > 0.001; *** p ≥ 0.001*

6.3.2 Reliability of measurements

Table 3 shows the reliability coefficients and the measurement errors in mm, degrees or percentage. The largest errors are found in measurements involving point A or ANS, or the soft tissues. The reliabilities were good to acceptable, except for two measurements: upper incisor to ANS-PNS angle (r=.497 for intra-observer agreement and r=.653 for inter-observer agreement) and ANS-PNS – SN angle (r=.789 for intra-observer agreement and r=.403 for inter-observer agreement). These two measurements were excluded from further analysis.

Table 4 *Number (n), means and SDs of the measurements are given for IO+, IO- at the age 4 and 6 years; also, the increment (inc) is given. Differences between IO+ and IO- were tested with t tests. The level of significance is indicated with the p values.*

Variable		*IO+*			*IO-*			*P-value*
		N	*Mean*	*SD*	*N*	*Mean*	*SD*	
SNA angle	*4 y*	*21*	*84.33*	*4.16*	*20*	*83.31*	*3.40*	*.397*
	6 y	*21*	*82.14*	*4.14*	*20*	*83.43*	*3.98*	*.306*
	inc	*19*	*-1.42*	*1.61*	*18*	*-.86*	*2.53*	*.421*
SNB angle	*4 y*	*15*	*75.61*	*3.46*	*17*	*74.05*	*2.46*	*.149*
	6 y	*15*	*75.22*	*3.68*	*16*	*74.43*	*3.64*	*.550*
	inc	*9*	*0.12*	*1.83*	*12*	*-.13*	*1.60*	*.745*
ANB angle	*4 y*	*15*	*9.27*	*2.27*	*17*	*8.88*	*3.83*	*.733*
	6 y	*15*	*7.65*	*2.25*	*16*	*8.65*	*3.55*	*.362*
	inc	*9*	*-1.64*	*1.47*	*12*	*-1.18*	*2.06*	*.576*
Mentolabial angle	*4 y*	*21*	*55.39*	*14.27*	*19*	*62.47*	*17.51*	*.168*
	6 y	*21*	*49.42*	*16.54*	*22*	*58.27*	*11.59*	*.048**
	inc	*19*	*-6.63*	*21.81*	*17*	*-6.35*	*14.85*	*.964*
Upper lip thickness	*4 y*	*19*	*-11.03*	*1.94*	*18*	*-10.61*	*1.97*	*.513*
	6 y	*18*	*-10.69*	*2.07*	*21*	*-10.85*	*1.56*	*.780*
	inc	*16*	*-.13*	*1.63*	*17*	*-.47*	*1.76*	*.563*
Lower lip thickness	*4 y*	*19*	*-13.15*	*2.13*	*18*	*-12.42*	*2.68*	*.367*
	6 y	*18*	*-12.59*	*2.92*	*21*	*-13.11*	*2.12*	*.524*
	inc	*16*	*.08*	*2.38*	*17*	*-.66*	*2.20*	*.353*
Nose angle	*4 y*	*21*	*19.72*	*2.52*	*19*	*18.42*	*2.44*	*.108*
	6 y	*21*	*19.87*	*2.39*	*22*	*19.42*	*2.54*	*.554*
	inc	*19*	*.68*	*2.07*	*17*	*1.03*	*2.68*	*.666*
Facial convexity angle	*4 y*	*21*	*11.03*	*4.91*	*19*	*9.85*	*5.39*	*.473*
	6 y	*21*	*10.33*	*5.86*	*22*	*10.10*	*5.72*	*.898*
	inc	*19*	*-1.30*	*2.07*	*17*	*.05*	*2.49*	*.086*
Nasolabial angle	*4 y*	*21*	*109.99*	*9.25*	*19*	*115.10*	*10.45*	*.110*
	6 y	*21*	*114.38*	*12.42*	*22*	*116.77*	*10.76*	*.503*
	inc	*19*	*3.11*	*11.27*	*17*	*.77*	*7.57*	*.474*
Upper lip to E-plane	*4 y*	*21*	*-0.15*	*1.53*	*19*	*-0.34*	*2.69*	*.777*
	6 y	*21*	*-1.66*	*2.58*	*22*	*-1.33*	*2.68*	*.683*
	inc	*19*	*-1.67*	*1.66*	*17*	*-1.01*	*1.46*	*.219*
Upper lip protrusion	*4 y*	*21*	*4.07*	*1.29*	*19*	*3.50*	*1.93*	*.278*
	6 y	*21*	*3.06*	*2.13*	*22*	*3.19*	*1.99*	*.833*
	inc	*19*	*-1.00*	*1.54*	*17*	*-.20*	*1.27*	*.104*
Lower lip to E-plane	*4 y*	*21*	*1.45*	*2.21*	*19*	*1.85*	*2.02*	*.550*
	6 y	*21*	*0.43*	*3.16*	*22*	*1.06*	*2.43*	*.463*

	inc	*19*	*-.95*	*2.36*	*17*	*-.77*	*2.24*	*.814*
Lower lip protrusion	*4 y*	*21*	*3.82*	*2.18*	*19*	*3.91*	*1.85*	*.894*
	6 y	*21*	*3.17*	*2.86*	*22*	*3.59*	*2.03*	*.585*
	inc	*19*	*-.43*	*2.04*	*17*	*-.16*	*1.85*	*.685*
Interincisal angle	*4 y*	*15*	*170.42*	*9.97*	*18*	*161.48*	*12.33*	*.012**
	6 y	*15*	*164.50*	*11.10*	*16*	*163.09*	*11.71*	*.432*
	inc	*9*	*-5.16*	*14.28*	*12*	*-.02*	*16.41*	*.462*
Lower inc.- GoMe angle	*4 y*	*21*	*81.96*	*4.99*	*20*	*85.03*	*6.27*	*.090*
	6 y	*21*	*81.71*	*5.64*	*22*	*83.86*	*5.01*	*.196*
	inc	*19*	*.43*	*3.63*	*18*	*-1.17*	*5.47*	*.298*
Lower inc. to APg	*4 y*	*15*	*-2.35*	*1.72*	*17*	*-1.34*	*2.04*	*.144*
	6 y	*15*	*-2.07*	*1.94*	*16*	*-2.47*	*2.05*	*.597*
	inc	*9*	*-.21*	*1.07*	*12*	*-.53*	*.78*	*.438*
Upper inc. to APg	*4 y*	*15*	*-0.72*	*1.71*	*17*	*0.13*	*1.65*	*.163*
	6 y	*15*	*-0.93*	*1.58*	*16*	*-0.41*	*2.05*	*.438*
	inc	*9*	*-.08*	*.75*	*12*	*-.83*	*1.60*	*.208*
N-ANS-Pg angle	*4 y*	*15*	*11.24*	*3.13*	*17*	*10.68*	*3.98*	*.663*
	6 y	*15*	*10.28*	*2.80*	*16*	*10.43*	*3.34*	*.893*
	inc	*9*	*-1.36*	*1.93*	*12*	*-1.46*	*2.67*	*.923*
Facial height index	*4 y*	*15*	*61.61*	*3.42*	*17*	*61.60*	*1.41*	*.994*
	6 y	*15*	*60.44*	*2.92*	*16*	*62.35*	*2.71*	*.070*
	inc	*9*	*-.08*	*3.15*	*12*	*.30*	*1.88*	*.736*
ANS-PNS / GoMe index	*4 y*	*15*	*82.93*	*5.44*	*17*	*84.89*	*7.75*	*.420*
	6 y	*15*	*82.03*	*6.49*	*16*	*86.33*	*7.32*	*.095*
	inc	*9*	*-1.53*	*6.07*	*12*	*.76*	*6.25*	*.411*
ANS-PNS	*4 y*	*21*	*41.38*	*1.78*	*20*	*40.26*	*2.63*	*.118*
	6 y	*21*	*44.43*	*2.00*	*21*	*44.41*	*2.94*	*.976*
	inc	*19*	*2.62*	*2.59*	*17*	*4.03*	*1.94*	*.075*
ANS-Me / N-Me index	*4 y*	*14*	*56.43*	*2.55*	*17*	*56.27*	*1.74*	*.839*
	6 y	*12*	*56.42*	*3.13*	*15*	*56.67*	*2.91*	*.827*
	inc	*8*	*-.06*	*2.02*	*12*	*-.21*	*2.21*	*.883*
ANS-Me	*4 y*	*14*	*48.77*	*3.52*	*17*	*47.69*	*2.42*	*.320*
	6 y	*12*	*53.34*	*4,78*	*15*	*52.26*	*4.33*	*.543*
	inc	*8*	*3.85*	*1.94*	*12*	*4.04*	*2.80*	*.869*
SN - GoMe angle	*4 y*	*15*	*37.82*	*3.40*	*17*	*38.53*	*2.22*	*.565*
	6 y	*15*	*39.29*	*3.71*	*16*	*37.65*	*3.44*	*.211*
	inc	*9*	*-.13*	*2.31*	*12*	*-.25*	*1.78*	*.897*
Occl. Plane - SN angle	*4 y*	*15*	*-159.41*	*4.57*	*17*	*-161.04*	*5.04*	*.350*
	6 y	*15*	*-161.07*	*5.21*	*16*	*-163.18*	*5.85*	*.299*
	inc	*9*	*-.72*	*3.31*	*12*	*-.10*	*4.01*	*.709*

*P values: *0.05 ≥ p > 0.01*

6.3.3 Treatment effect

In Table 4 the effect of IO is shown. Only two significant differences were found between IO+ and IO-: at the age of 4 years the interincisal angle was about 9 degrees larger in the IO+ group. At the age of six years no significant difference could be measured anymore. The other significant difference occurred at the age of 6: the mentolabial angle was almost 9 degrees smaller in the IO+ group.

Table 5 *Number (n), means and SDs of the esthetic scores are given for full face photographs, nasolabial photographs for IO+ (bold italics) and IO- at the age 4 and 6 years. Also, the occlusion scored with the 5-year index. Differences between IO+ and IO- were tested with t tests. The level of significance is indicated with the p values (p*). The information given in this table is described in Bongaarts et al. (2004),[11] and Bongaarts et al. (2008).[12]*

		4 y				*6 y*			
Variable		*n*	*mean*	*(SD)*	*p**	*n*	*mean*	*(SD)*	*p**
Full face	*Professional*	*21*	*94.18*	*(12.01)*	*.006***	*24*	*95.21*	*(11.04)*	*.08*
		24	*105.27*	*(13.94)*		*22*	*100.63*	*(9.47)*	
	Laymen	*21*	*89.75*	*(11.65)*	*.02**	*24*	*96.19*	*(9.86)*	*.15*
		24	*99.10*	*(14.22)*		*22*	*100.71*	*(11.19)*	
Nasolabial	*Professional*	*21*	*93.06*	*(13.50)*	*.47*	*24*	*96.85*	*(11.78)*	*.04**
		24	*95.98*	*(13.09)*		*22*	*105.41*	*(14.57)*	
	Laymen	*21*	*91.20*	*(12.50)*	*.27*	*24*	*96.13*	*(13.35)*	*.10*
		24	*95.16*	*(10.98)*		*22*	*103.05*	*(14.25)*	
5-y-index		*22*	*1.98*	*(0.81)*	*.89*	*21*	*2.16*	*(0.85)*	*.80*
		21	*2.01*	*(0.73)*		*20*	*2.23*	*(0.84)*	

** Differences were tested with t tests. The level of significance is indicated with p values:*
** $0.05 \geq p > 0.01$; ** $0.01 \geq p > 0.001$; *** $p \geq 0.001$*
n may vary because of incidental missing values

For all cephalometric variables and the 5-year index, regression analyses were done to assess the relation between these variables and the esthetic score at 6 year. To be able to see the extent of the effect a certain factor has, the esthetic results and the 5-year index scores are given in table 5.[11,12] The regression analyses were repeated with gender as co-variable and also with pharyngoplasty and gender as co-variable. But since a significant influence of gender or pharyngoplasty was never found (all p’s are 0.17 or higher), only the results for the univariate regression analyses are shown in table 6.

Table 6 *Relation between occlusion at 6 years of age and the cephalometric values at age 6 (independent variables) with the overall esthetics of a patient (dependent variable). Results of regression analysis: P-values and the effect (B and the 95% confidence interval) are given. Also, the R square is given to show how much of the esthetic result can be explained by each of these items.*

	Overall esthetics			
	P-value	*B [95% CI]*		*R square*
SNA angle	*.860*	*-0.072*	*[-.898, 0.753]*	*.001*
SNB angle	*.388*	*-.512*	*[-1.708, .684]*	*.026*
ANB angle	*.304*	*.749*	*[-.714, 2.212]*	*.036*
Mentolabial angle	*.718*	*-.042*	*[-.275, .191]*	*.003*
Upper lip thickness	*.692*	*-.371*	*[-2.249, 1.507]*	*.004*
Lower lip thickness	*.171*	*.952*	*[-.429, 2.333]*	*.049*
Nose angle	*.847*	*-.131*	*[-1.488, 1.227]*	*.001*
Facial convexity	*.582*	*-.164*	*[-.761, .433]*	*.007*
Nasolabial angle	*.314*	*-.140*	*[-.417, .137]*	*.024*
Upper lip to E-plane	*.826*	*.141*	*[-1.152, 1.435]*	*.001*
Upper lip protrusion	*.655*	*.361*	*[-1.256, 1.978]*	*.005*
Lower lip to E-plane	*.370*	*-.530*	*[-1.712, .651]*	*.019*
Lower lip protrusion	*.383*	*-.589*	*[-1.935, .758]*	*.018*
Interincisal angle	*.430*	*.151*	*[-.235, .537]*	*.022*
Lower inc.- GoMe angle	*.182*	*-.427*	*[-1.061, .206]*	*.042*
Lower inc. to APg	*.331*	*-1.047*	*[-3.215, 1.121]*	*.033*
Upper inc. to APg	*.379*	*-1.174*	*[-3.861, 1.513]*	*.027*
N-ANS-Pg	*.361*	*.662*	*[-.798, 2.123]*	*.029*
Facial height index	*.117*	*-1.142*	*[-2.587, .304]*	*.083*
ANS-PNS / GoMe index	*.615*	*.148*	*[-.448, .744]*	*.009*
ANS-PNS	*.379*	*.522*	*[-.644, 1.709]*	*.019*
ANS-Me / N-Me index	*.321*	*-.808*	*[-2.451, .834]*	*.039*
ANS-Me	*.881*	*-.082*	*[-1.202, 1.038]*	*.001*
SN-GoMe angle	*.142*	*.889*	*[-.315, 2.093]*	*.073*
Occl. Plane - SN angle	*.510*	*.253*	*[-.523, 1.030]*	*.015*
5-year index	*.178*	*-2.660*	*[-6.575, 1.255]*	*.043*
Gender	*.607*	*1.929*	*[-5.590,9.449]*	*.006*

*p values: * 0.05 ≥ p > 0.01; ** 0.01 ≥ p > 0.001; *** p ≥ 0.001*

Since the highest R square is .083, these measurements explain the esthetic result only to a minimal extent (not more than 8.3%). For the 5-year index for occlusion, the R square is .043, which means that it explains not more than 4.3% of the esthetic result. One point difference in score in the 5-year index means 2.66 points reduction in esthetic result.

The number of children is not big enough to allow for multiple regression using all variables. There is no clear cut rule to decide what variables are most likely to influence the esthetic score. Therefore, from all univariate regression models, seven variables with the highest R square were included in a backward regression to look for combinations of variables with better potential for explaining the value of the esthetic score. This backward regression model eliminated all but one variables, leaving only the Facial Height Index. This indicates that a combination of variables does not improve the potential for explaining the value of the esthetic score at the age of 6.

6.4 Discussion

The error in landmark identification is the major source of cephalometric error. The type of landmark, the precision of the landmark identification and the observer are important factors in the uncertainty within landmark-positioning.[13-16] Differences in the magnitude of the measurement error are caused by the precision of the landmark identification and the amount of noise of adjacent structures. Also, the non-erupted and often rotated incisors and the displaced and reduced size of the premaxilla can be mentioned as causes for measurement errors in young cleft patients. As was described by Atherton[17] in 1967 there is a marked shift of the premaxillary region away from the centerline. The premaxilla of the cleft side is reduced in size and displaced forward. In a recent study[18] alternatives for point A, ANS and PNS in toddlers were evaluated, but the alternatives were not better than the traditional landmarks. Therefore, the traditional landmarks were used in the present study.

The errors in the present study were acceptable, taking into account the age of the investigated group in which shedding of the incisors is taking place, and the difficulties in locating the essential points A and ANS. Although an error was present, this error was never as big as, or larger than the SD of the measurements. By first tracing and identifying the landmarks and than scanning the tracing, an extra error was added.

Direct scanning of the cephalograms led to more errors, because of the dark area that often occurred near the cleft. Landmarks were better identifiable on the original radiograph and tracing. The extra error that was added by scanning and digitalisation of the landmarks is minimal. In the study of Bongaarts et al.[18] the error for digitalisation was 0.25 for SNA compared to a tracing error of 0.73.

Table 7 *New power calculations based on results*

	Measurement	*Age*	*Expected size if effect on IO*	*From results of research: found SD*	*Number of children necessary in each group*
Original analysis	*SNA*	*4*	*3*	*Assumption: 3.5*	*23*
New calculation	*SNA*	*6*	*2*	*2*	*17*
New calculation	*ANB*	*6*	*2*	*1.75*	*13*
New calculation	*5-year index*	*6*	*0.9*	*1*	*14*
New calculation	*Esthetic score*	*6*	*10*	*10*	*17*

In the Dutchcleft study, the sample size calculation was based on a detectable IO effect of 3 degrees for the SNA angle at the age of 4 years. An assumption was made for the SD: 3.5 degrees. The minimum number of children was found to be 23 in each group. The study started with 27 patients in each group. The number of patients involved in the study decreased due to Simonart's bands, and missing records or records not taken within 6 months before or after the birthday of the child (figure 1). With the results we found, the power was recalculated again for a few variables to check whether the patient groups were large enough to find a possible effect of IO (Table 7). Power was set at 80% and the level of significance was 0.05, as was done for the initial calculations. The table shows that the IO+ and IO- groups were large enough to find significant differences, if there were any.

In a prospective trial in which CLP patients are followed over a long period of time you cannot avoid that different people are involved and that additional interventions are performed. None of these subgroups were segregated out, since these extra interventions were equally distributed over the IO+ and IO- groups. Because the interventions were equally spread over the two groups, they did not interfere with the objective of the study, although they are a source of variability. Because of this, one should be cautious when interpreting of the results.

No clinical relevant effect of IO on the facial growth was found. These findings contradict with other studies in which a positive influence of IO was described.[19,20] In Eurocleft[8] and in the studies of Ross[3] no significant effects of IO were found, but all were non-randomized retrospective studies. Also, the results of this randomized clinical trial are only valid for the passive type of appliance; it is impossible to draw conclusions about active plates or appliances with extensions for nasal molding. To be conclusive about these appliances another clinical trial should be set up.

Since the regression analyses in this study and those in the study about the esthetic result of the Dutchcleft trial,[12] show almost no significant findings until 6 years of age, facial esthetics of young patients with CLP is probably influenced by factors other than the treatment or growth variables. Possibly, facial expression, texture of the skin, colour of eyes or hair are of bigger influence than expected. Of course it is possible that at a later age, a relation can be found between esthetics and other measured factors, since the small, insignificant variations found now, might become more pronounced after the pubertal growth.

The first results of Dutchcleft, showed that IO had a temporary effect on maxillary arch dimensions, which did not last beyond surgical soft palate closure.[10,21] Also, IO could not prevent collapse of the maxillary arch.[21,22] In the occlusion, measured with the 5-year-index at the age of 4 and 6 years, no differences between IO+ and IO- could be shown.[10] Feeding and the nutritional status of the infants were not improved by IO.[23] Data published in 2004 show the cost-effectiveness of the speech outcome at the age of 2.5 years: listeners (speech therapists) were asked to rate the speech quality on a 10-point scale of 10 IO+ children and 10 IO- children. The IO+ group had a significant better rating for speech. The resulting cost-effectiveness ratio was 1041 euro for 1.34 point of speech improvement.[24,25] More detailed speech findings have been published elsewhere.[26-29] An evaluation of the speech data at the age of 6 still has to be performed. Finally, the results of the esthetic scores at age 1½ and 4-6 years, showed no relevant effect of IO on facial appearance.[12,30]

6.5 Conclusion

Considering all results of Dutchcleft until now, there is no indication for the type of IO as used in this study for infants with UCLP whose surgical management included soft palate repair at 12 month and delayed hard palate closure. Those who are promoting different methods of IO including nasoalveolar molding should consider the longterm benefits of their interventions using the same rigorous methodology as applied in Dutchcleft.

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Chapter 7

General discussion

7.1 Introduction

Throughout the present thesis the effect of infant orthodopedics (IO) on patients aged 4-6 years, has been evaluated. The effects on the occlusion and the maxillary arch dimensions were measured on casts (chapter 2 and 3). The influence on the facial appearance was studied in chapter 4 and, the cephalometric results were presented in chapter 6. New cephalometric landmarks were tested in cleft lip and palate patients in order to get valid measurements for the description of facial growth. The tested landmarks were not better than the commonly used ones (chapter 5). It was shown that the type of IO as performed in this study had only very limited effects on all measured variables.

In this chapter some methodological issues as well as results are discussed, and subsequently implications for treatment are given. Finally, suggestions for further research are done.

7.2 Strength and weaknesses of the study

7.2.1. Design of the study

The design of the present study was a prospective two-armed randomized controlled clinical trial.[1] In the Cochrane library (www.mrw.interscience.wiley.com/cochrane, access date 24th of September 2008) two other clinical trials can be found on IO in patients with a unilateral cleft lip and palate (UCLP). One study is about the effect of infant orthopedics on feeding in infants with cleft lip and/or palate compared to non-cleft infants.[2,3] Infant orthopedics did not improve feeding efficiency or general body growth within the first year of life in either group of infants. However, the sucking patterns of infants with non-syndromic complete UCLP differed from those of their non-cleft peers.

The other trial addresses the effects of active IO on occlusal relationships in complete UCLP.[4] The mean GOSLON score was 3.30 for the orthopedic group and 3.21 for the non-orthopedic group. There was no significant difference between the two groups.

In general there are 13 clinical trials about unilateral clefts and orthopedics registered in the Cochrane Library since 1993, with only one systematic review. The register of the U.S. National Institutes of Health for ongoing trials shows one registration from the University of Sao Paulo: a comparison of two primary surgical techniques (von Langenbeck and Furlow double z-plasty) performed in children with cleft lip/palate to determine whether one of the techniques results in significantly better velopharyngeal competency for speech.

All other studies reported in literature are retrospective in design and therefore not adequate for drawing evidence based conclusions about an appliance or treatment. In a prospective clinical trial bias and confounding factors are avoided through the processes of randomization and blinding.

7.2.2. Sample size calculations

In the Dutchcleft study, sample size calculation was based on a detectable IO effect of 3 degrees for the SNA angle at the age of 4 years. The minimum number of children was found to be 23 in each group. The study started with 27 patients in each group. The total number of patients involved in the study decreased from 54 to about 45 due to the presence of Simonart's-bands, and missing records or records not taken within 6 months before or after the birthday of the child (figure 1). The power was recalculated for a few variables to check whether the patient groups were large enough to find a possible effect of IO (Table 1).

Table 1 *Power calculations based on results*

	Measurement	*Age*	*Expected size if effect on IO*	*From results of research: found SD*	*Number of children necessary in each group*
Original analysis	*SNA*	*4*	*3*	*Assumption: 3.5*	*23*
New calculation	*SNA*	*6*	*2*	*2*	*17*
New calculation	*ANB*	*6*	*2*	*1.75*	*13*
New calculation	*5-year index*	*6*	*0.9*	*1*	*14*
New calculation	*Esthetic score*	*6*	*10*	*10*	*17*

Power was set on 80% and the level of significance was 0.05, as was done for the initial calculations. The table shows that the IO+ and IO- groups were large enough to identify significant differences, if such should exist. In the original power analysis the expected difference between IO- and IO+ for < SNA was 3 degrees; an assumption was made for the SD of 3.5 degrees. For the new power calculation the findings of the present thesis were used.

Randomization
n=54

IO+
n=27

IO-
n=27

Non-eligible after randomization
n=3

Reasons:
Simonart's band n=1
Incomplete cleft lip n=1
Soft tissue band alveolus n=1

Non-eligible after randomization
n=2

Reasons:
Simonart's band n=1
Submucous cleft of orbicularis oris muscle at the non-cleft side
n=1

Not evaluated (n) (IO+)

	≤1 y	1½ y	2½ y	4 y	6 y
Models				2	2
Upper arch	0-2	5		1	2
Photograph		4		0	2
Cephalogram				3	3
Speech	6	5	14		18
Feeding	4-8				
Satisfaction	1-6				

Not evaluated (n) (IO-)

	≤1 y	1½ y	2½ y	4 y	6 y
Models				3	2
Upper arch	0-1	5		3	2
Photograph		4		4	1
Cephalogram				5	3
Speech	7	6	15		20
Feeding	1-4				
Satisfaction	1-6				

Evaluated in IO+ group (n)

	≤1 y	1½ y	2½ y	4 y	6 y
Models				22	22
Upper arch	22-24	19		23	22
Photograph		20		24	22
Cephalogram				21	21
Speech	18	19	10		6
Feeding	16-20				
Satisfaction	18-23				

Evaluated in IO- group (n)

	≤1 y	1½ y	2½ y	4 y	6 y
Models				22	23
Upper arch	24-25	20		22	23
Photograph		21		21	24
Cephalogram				20	22
Speech	18	19	10		5
Feeding	21-24				
Satisfaction	20-26				

Figure 1 *Flow diagram of the number of patients in Dutchcleft from birth until 6 years of age*

7.2.3. Generalizability

It has to be acknowledged that the results of this trial relate to one technique of IO (passive plates) and one surgical protocol (delayed hard palate closure) and this combination was shown to have no relevant clinical effect so far. The results are only valid for children with a complete UCLP as children with soft tissue bands, and other congenital malformations were excluded. As Smahel and Horak wrote in 1993[5] clefts with soft tissue bridges cannot be pooled with complete clefts due to the favorable effect that a soft tissue bridge has on the shortening and retrusion of the maxilla, and because of that on the maxillo-mandibular relationship and facial configuration. In Dutchcleft these strict criteria were met to avoid confounding due to tissue bands. Also, the Dutch language factor was included as a trial entrance criterion because of the speech evaluation. Since the facial configuration of different racial types is different, Caucasians were evaluated in Dutchcleft and other races were excluded.

7.2.4. Outcome variables

Many methods are proposed for scoring the effects of an appliance: indices for occlusion, facial growth or facial esthetics and the proposed measurements on cephalograms are countless. For dental casts the Goslon Yardstick is a clinical tool to categorize late mixed and permanent dentitions in a sensitive way.[6] Later a comparable index was developed to assess treatment outcome in the deciduous and mixed dentition: the 5-year-old index.[7,8] Since the 5-year-old index is the most commonly used method for the deciduous dentition, this method was used for Dutchcleft. Both indices, the Goslon Yardstick and the 5-year-old index, were developed about 20 years ago. However, over the years the treatment results for clefts have improved. As a result, the existing indices are not sufficient discriminating in the lower -better- end of the scale. Nowadays results are mostly in categories 1 to 3. Therefore studies are undertaken with the aim to develop a new more discriminative yardstick for the Eurocran studies.

The dental casts were digitized by means of a Reflex Microscope® (chapter 3). As known from Drage et al.,[9] a Reflex Microscope® is best used by trained observers, but also untrained observers can use the microscope after some practice. As was also found in this study, errors were greatest in the z-axis, along the axis of the eye; errors were also rather high at the margins of the maxillary segments. The measurement errors found in this study for landmark positioning (marking points) are comparable with those reported by Seckel et al.[10] The errors for the measurements of contact and collapse of the maxillary dental arch reported in this study are comparable to those reported by Prahl et al.[1] Today three-dimensional digital models are available. Models or impressions can be scanned and measurements done in a three dimensional image. Oosterkamp et al.,[11] produced an intraclass correlation of 0.90 on virtual models of neonatal casts of BCLP patients obtained by laser scanning. Reference points constructed outside the surface of the model could not be validly assessed.

The judgement of facial appearance (chapter 4) is subjective, although most people agree on what they appreciate as beautiful or ugly. This principle is used in VAS scorings. The method chosen in Dutchcleft, was comparable to the method used by Peerlings et al.[12] In the literature several scoring methods of photographs can be found. Scales like the one made by Tobiasen et al.[13] or Asher-McDade et al.[14] were not used because they were used on older children than in the present study. However, cropped photographs of the nasolabial part of the face were used to blind for other facial factors.[14] Because some studies[15-17] found differences between the opinion of laymen and the appreciation of the facial appearance by professional observers, it was decided to ask observers with different backgrounds. Furthermore, Tobiasen[18] and Okkerse et al.[19] found a difference between the ratings for boys and girls in appreciation of facial appearance. Therefore, boys and girls had their own reference pictures. Professionals and laymen had good agreement on facial esthetics, but the correlation between full face photographs and nasolabial photographs was moderate. This can be explained by the absence or presence of surrounding factors besides the nose and mouth, such as hair, eyes, or ears. Both photographic views have their own merits. Evaluating surgical results requires a detailed picture of the region of the former deformity, but in daily life the total facial appearance of a person is important.

Facial growth was analyzed using lateral head films (chapter 6). In the cephalometric analysis errors can occur in landmark positioning and during the digitalization process. As can be expected, tracing errors are bigger than digitalization errors due to difficulties in identifying landmarks. Since a cephalometric variable is composed of at least two landmarks the error for a measurement will be larger than the error for a landmark alone. The errors in Dutchcleft are acceptable, taking into account the age of the investigated group in which shedding of the incisors is taking place, and the difficulties in locating the essential points A and ANS. Although an error was present, this error was never as big as, or larger than the SD of the measurements.

All the outcome variables are two-dimensional, except the casts. In the near future it can be expected that two-dimensional pictures like photographs or cephalograms to be replaced by three-dimensional images, but at the time of this study this technology was not available. Especially in UCLP patients, three-dimensional images can give new insights because asymmetry of the cleft area and the position of the maxillary segments can be evaluated better. But also, the position of the maxilla in the head and the size and form of the cleft can be described more precisely. However, there are no reference values available yet for measurements done on the three-dimensional images.

Finally, comparison of results from present and past to improve the quality of different cleft teams, as was done by Prahl-Andersen and Ju[20] or Shaw et al.,[21] is often difficult due to differences in record taking and the timing of the records. In order to prove that the quality of care is improving, comparisons of results over time, are recommendable. This will become even more difficult in the future because centers may want to change the method of record taking and want to use advanced 3D-equipment. This will hamper standardization of records even more.

7.3 Results

In the studies presented in the chapters 2, 3, 4, and 6 only a few statistically significant differences were found between IO+ and IO-. The only variables showing significant differences were the arch depth (I-TT') at the age of 4 years: larger in the IO+ group, and the angle M-T-C(5): larger in the IO+ group compared to the IO- group at 0-2 weeks of age and at 4 years of age. These few inconsistent significant values at the age of 4 years may be either temporary or by chance significant, probably due to the large number of measurements done on the cephalograms of the Dutchcleft-children. Furthermore, the confidence intervals of the angle P'-C(5)-T and the contact-collapse-variables are large, which may indicate a type II error (difference found, but, there is no difference in reality). These variables should be interpreted with caution.

Children in the IO+ group were found to have a significantly more attractive face than children in the IO- group, at the age of 4, looking at full face photographs. For the nasolabial photographs no significant differences were found. At 6 years of age the only significant difference was found for the nasolabial photographs scored by professionals: IO+ was better than IO-. As a child functions in his own social context, mainly consisting of laymen, this result can be considered of minor importance. On the other hand, it is possible that a small, insignificant variation found now, might become more pronounced after the pubertal growth.

Of all cephalometric measurements, only two showed a significant difference between IO+ and IO-. At the age of 4 years the interincisal angle was about 9 degrees larger in the IO+ group. At the age of six years this difference had faded away. The other significant difference was found at the age of 6: the mentolabial angle was almost 9 degrees smaller in the IO+ group. Since landmark positioning is especially hard in the cleft area and for the soft tissue landmarks, measurements with landmarks in these areas could give false significances. Another possible factor is related to the incisor: the permanent incisors are erupting in the age period 4-6 years and due to the cleft both the deciduous and the permanent incisor can be rotated or dislocated. Because of these difficulties an extra study was done to find an alternative for the landmarks A (point A), ANS (anterior nasal spine) and PNS (posterior nasal spine), all in the cleft region. Measurements using ANS and PNS or their alternatives, were comparable. The alternatives did not perform better than the commonly used ANS and PNS. Hopefully, this problem is less prominent in the future due to the development of three-dimensional cephalometry. The cleft area becomes more visible because of the added third dimension, but the age-related problem of erupting and rotated permanent incisors will not be solved by 3D-cephalometry. When discussing the timing and number of records, these difficulties and the radiation dose should be weighed against the advantages of an insight into skeletal, dental and soft tissue relationships.

7.4 Clinical implications

This clinical trial gives ‘evidence based’ information about the effects of the type of IO used in this study. None of the claimed advantages of IO is proven to be true, only a temporary effect on speech was found in a previous study. Konst et al.[22] showed that IO facilitates speech and language development until 3 years of age. But, at the age of 6 no differences in expressive language skills between the two groups were found.[23] In the decision process whether or not to use IO, all variables should be taken into account. Since there is only one (temporary) positive effect of IO, the treatment has proven to be costly for a small improvement.

In the early 21st century 12 of all centers in the Netherlands used infant orthopedics in their treatment protocol and the type of IO as applied in this study was the most commonly used type.[21] All three centers that participated in Dutchcleft have now abandoned IO. Professionals of the other Dutch CLP-teams are encouraged to discuss the results of this trial within their teams and eventually to adapt their treatment protocols. The Special Interest Groups of the Dutch Cleft Palate Craniofacial Association and the parent organization, BOSK, could be instrumental in disseminating this knowledge to their members and to transform it into a practice guideline.

7.5 Further research

The World Health Organisation has defined areas of limited knowledge in the field of cleft lip and palate and craniofacial anomalies during two meetings (Geneva, 2000 and Park City, 2001). These areas are described in a report of the WHO in the year 2002.[24] There is a pressing need for evaluation of treatment modalities (with the use of proper scientific methodology) of craniofacial anomalies. To mention a few: surgical methods of correction of velopharyngeal insufficiency, different modalities of speech therapy, methods of repair, adjunctive procedures such as presurgical orthopedics and timing of orthodontic treatment. Also, gene-environment interaction, genetics and prevention are areas in need for more research. The testing of treatment modalities should be a continuous activity of all professionals involved in cleft care. There is a pressing need to mobilize a critical mass of clinical research expertise and to accumulate sufficiently large samples of patients for adequate powered clinical trials. In the words of Machiavelli: ‘There is nothing more difficult to carry out, nor more doubtful of success, nor more dangerous to handle than to initiate a new order of things.” These words may explain the frustration felt by many professionals in cleft care.[20]

To facilitate research projects, proper records should be taken from every patient. In the EUROCRAN project (www.eurocran.org), records include dental casts, cephalograms and facial photographs according to a fixed protocol (described in annex 5 of WHO Human genetics Programme, 2002).[24] Techniques for three-dimensional records such as 3D-photographs and 3D-cephalograms are evolving fast. For future research purposes and to improve the quality of care, there should be consensus regarding timing and type of records. Only when standardized records are available can multicenter comparison be executed.

A good patients archive, as proposed by EUROCRAN, makes it possible for a team to compare their treatment outcome to international standards, and for rare cases, case comparison can be helpful to make a treatment plan. Registries such as the COR (Craniofacial Outcome Registry; www.cfregistry.org) of the American Cleft Palate Craniofacial Association in which teams can enter diagnostic and outcome data may also be helpful.

When patients express their interest in treatment outcome in general, this should be appreciated by the professional. Patient organizations and professional organizations should work together to confront uncertainties about the effects of treatments. The James Lind Alliance (www.lindalliance.org) has this statement as a main objective: tackling treatment uncertainties together.

Based on the results of Dutchcleft so far, it is to be recommended to analyze speech for this treatment group at a later stage, since the only temporary positive finding concerned intelligibility at the age of 2.5 years. Since speech is relevant for everyday life, early intervention might be worthwhile, avoiding long speech therapy at a later age. A program for early speech and language therapy should be further developed and tested.

Finally, the results of this trial, so far, only describe the effect of this specific type of IO in combination with delayed hard palate closure, but there are many more existing protocols that have not been tested yet in a rigorous prospective trial design. A remarkable recent (sad) example is the naso-alveolar molding device (developed by Grayson and Cutting[25]) that has gained enormous popularity over the last years. History should not be repeated: the type of IO as performed in Dutchcleft was used for half a century before it was proven to be ineffective.

7.6 References

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Chapter 8

Summary

This thesis describes the effect of infant orthopedics in unilateral cleft lip and palate patients at the age of 4 and 6 years.

Chapter 1 gives a short introduction to the topic of the thesis. The history of infant orthopedics is explained and its shortcomings and benefits. Because there are so many drawbacks of previous studies, no evidence based information was available. This was the reason to start Dutchcleft, a prospective randomized clinical trial in three cleft palate centers (Nijmegen, Amsterdam, and Rotterdam). The study started in 1993 and comprised 4 main subjects: (1) general aspects, (2) surgical and orthodontic aspects, (3) speech and language development, (4) cost-effectiveness. A child entered the study within two weeks after birth, and was randomly assigned to the IO+ (treatment with infant orthopedics) or IO- group (treatment without infant orthopedics). A total of 54 children from three cleft palate centers was included; 27 in each group. In two earlier thesis the short term results of the trial were presented. In the present thesis the midterm results for the orthodontic and surgical variables are presented.

In **chapter 2** the effect of infant orthopedics (IO) on the occlusion of the deciduous dentition is described. Dental arch relationships were assessed at 4 and 6 years of age with the 5-year-old index, the Huddart-score, and with measurements of overjet, overbite, and sagittal occlusion. There were no significant differences found between the IO+ and IO-groups for the 5-year-old index, the Huddart-score, and for overjet, overbite, and sagittal occlusion.

Chapter 3 describes a study into the effect of IO on maxillary arch dimensions in the deciduous dentition. The maxillary arch dimensions were assessed on dental casts at 4 and 6 years of age with measurements for arch width, arch depth, arch length, arch form, and the vertical position of the lesser segment. Contact and collapse were also assessed. IO had no observable effect on the maxillary arch dimensions or on the contact and collapse scores in the deciduous dentition at the age of 4 and 6 years.

Facial appearance at 4 and 6 years of age was assessed and the results are described in **chapter 4**. Full face photographs and photographs showing only nose and mouth were scored. Ratings were performed on a

VAS-scale by professionals and laymen. At 4 years of age the full face pictures of IO+ children were scored to be more attractive than full face pictures of IO- children. However, this difference had faded away at 6 years of age. At the age of 6, only professionals saw a significant difference on nasolabial photographs between IO+ and IO-. Regression analysis showed a minor effect of occlusion, lip revision, or type of nose reconstruction on the esthetic results. IO had a positive effect on full facial appearance of UCLP children at the age of 4 years, but at the age of 6, only professionals saw a positive effect of IO on the nasolabial photographs. This is for UCLP patients irrelevant since they deal with laymen in their daily life.

In **chapter 5** the reliability of some cephalometric measurements in unilateral cleft lip and palate patients was tested. Measurements with A, ANS, and PNS, were compared to measurements performed with alternatives for these points: A1, A2, ANS1, ANS2, and PNS1. Cephalograms of children with complete UCLP (n=164), with a lateral head film taken at age 4 to 6 were used. Intra- and interobserver reliability for cephalometric measurements including A, ANS, PNS or their alternatives were calculated: Dahlberg errors, systematic errors and Pearson correlation coefficients. The measurements using ANS and PNS or their alternatives, were comparable. The systematic error between observers for measurements using A2 was less than for measurements using A or A1. The scatter plot of point A showed a slightly better distribution of the points than the plots of A1 and A2. Although the landmarks A, ANS and PNS are hard to trace in UCLP patients with tooth germs in the anterior maxilla, no better landmarks were found, but cephalometric studies using A, ANS and PNS in UCLP patients should be interpreted with caution.

In **chapter 6** the effect of IO on facial growth of UCLP patients, aged 4 and 6 years was evaluated. Measurements were done on lateral headfilms made at 4 and 6 years of age to get cephalometric values representing soft tissue, hard tissue and dental structures. No differences were found between IO+ and IO-, except for two measurements; the interincisal angle was larger (4 years of age) and the mentolabial angle was smaller (6 years of age) in the IO+ group. It was concluded that facial growth measurements at age 4 and 6 gave no reason to perform IO in UCLP patients.

Finally, in **chapter 7,** the general discussion, some methodological issues regarding the results are discussed. It describes the strength and weaknesses of the studies done, and gives implications for treatment. The general discussion ends with suggestions for further research.

Chapter 9

Samenvatting

Dit proefschrift handelt over het effect van vroege kaakorthopedische behandeling, infant orthopedics (IO), bij kinderen met een complete eenzijdige lip-, kaak-, en gehemeltespleet (schisis), op de leeftijd van 4 en 6 jaar.

In **Hoofdstuk 1** worden de typen schisis beschreven, die kunnen voorkomen, en de multidisciplinaire behandeling die nodig is. De geschiedenis van IO wordt belicht en de voor- en nadelen van eerdere onderzoeken worden besproken. Vanwege de vele nadelen die aan eerdere onderzoeken kleven, kon er nooit een ‘evidence based’ conclusie worden getrokken over het effect van IO. Dat was de reden om Dutchcleft op te zetten, een prospectief gerandomiseerd klinisch onderzoek, waarbij 3 Nederlandse schisiscentra (Nijmegen, Amsterdam, en Rotterdam) waren betrokken. Het onderzoek startte in 1993 en kende 4 hoofdonderwerpen: (1) algemene aspecten, (2) chirurgische en orthodontische aspecten, (3) spraak- en taalontwikkeling en (4) kosteneffectiviteit. Binnen twee weken na de geboorte werd een baby in het onderzoek opgenomen en door de computer toegewezen aan een van de twee groepen: IO+ (infant orthopedics), of IO- (geen infant orthopedics). In totaal deden er 54 kinderen met een eenzijdige lip-, kaak- en gehemeltespleet mee aan Dutchcleft, 27 in elke groep.

Hoofdstuk 2 gaat over het effect van IO op de occlusie van het melkgebit. De kaakrelatie werd bekeken op 4- en 6-jarige leeftijd met behulp van de 5-year-index, de Huddart-score, en de overjet, overbeet en sagittale occlusie volgens Angle. Er werden geen verschillen gevonden tussen de IO+ en de IO- groep.

In **hoofdstuk 3** worden de bovenkaakdimensies in het melkgebit beschreven. Op 4- en 6-jarige leeftijd werden de modellen gemeten op boogdiepte, -breedte en -lengte, de kaakvorm, en de verticale positie van het kleine kaakdeel. Ook de mate van contact of overlapping van de kaakdelen werd gemeten. Ook nu werd er geen verschil tussen beide groepen gevonden.

De esthetiek op 4- en 6-jarige leeftijd komt aan de orde in **hoofdstuk 4**. Volledige gezichtsfoto’s en foto’s die alleen de neus en mond laten zien moesten worden gescoord. Dit is gedaan door zowel leken als professionals met een lijn-score. Op 4-jarige leeftijd vond men de IO+ kinderen mooier dan de IO- kinderen. Dit verschil kwam alleen naar voren op de volledige gezichtsfoto's en niet op de neus-mond-foto's. Op 6-jarige leeftijd zagen leken geen verschil tussen beide groepen. Professionals gaven aan de IO+ groep een hogere score dan aan de IO-groep, en dan alleen voor de neus-mond-foto's. De regressieanalyse toonde aan dat het esthetisch resultaat voor een klein deel verklaard kon worden uit de occlusie, liprevisie en het type neusvleugel reconstructie bij de lipoperatie. Het kleine positieve effect van IO dat werd gevonden op 4-jarige leeftijd, was vrijwel verdwenen op 6-jarige leeftijd, waardoor het klinisch niet relevant is.

In **hoofdstuk 5** werden nieuwe meetpunten voor cephalometrisch onderzoek bij patiënten met een unilaterale schisis getest. Metingen met punt A, ANS en PNS werden vergeleken met metingen met alternatieven voor deze punten: A1, A2, ANS1, ANS2, en PNS1. Er werden 164 laterale röntgenschedelprofielfoto's van kinderen met unilaterale schisis gebruikt (leeftijd 4 tot 6 jaar). Voor ANS en PNS en hun alternatieven werden geen verschillen gevonden. De systematische fout van metingen met A2 was kleiner dan die van metingen met A of A1. Daarom werd een spreidingsdiagram gemaakt van A, A1 en A2. Het spreidingsdiagram van punt A was wat beter dan dat van de twee andere punten. Hoewel A, ANS en PNS moeilijk te zien zijn door de aanwezigheid van de spleet en niet doorgebroken tandkiemen, werden geen betere meetpunten gevonden. Het blijft goed om voorzichtig om te gaan met resultaten van cephalometrisch onderzoek bij jonge kinderen met een enkelzijdige schisis.

Hoofdstuk 6 betreft de gelaatsgroei op 4- en 6-jarige leeftijd. Er werden skelettale, dentale en weke delen metingen gedaan op laterale röntgenschedelprofielfoto's. Er werden geen verschillen gevonden tussen de IO+ en IO- groep, op twee metingen na: de interincisale hoek was groter op 4-jarige leeftijd in de IO+ groep, en de mentolabiale hoek was kleiner in de IO+ groep op 6-jarige leeftijd. Er werd geconcludeerd dat deze resultaten geen aanleiding konden vormen IO te gebruiken bij de behandeling van patiënten met een enkelzijdige schisis.

Tot slot worden in **hoofdstuk 7**, de algemene discussie, de gebruikte methoden bediscussieerd. De sterke en de zwakke punten van het onderzoek worden besproken en de invloed van het onderzoek op de behandeling van patiënten met een enkelzijdige complete schisis wordt besproken. De algemene discussie eindigt met suggesties voor verder onderzoek.

Dit proefschrift is een deel van Dutchcleft, het onderzoek naar infant orthodpedics. Allereerst wil ik iedereen uitdrukkelijk voor zijn, grote of kleine, aandeel binnen dit onderzoek bedanken. Natuurlijk zijn er een aantal mensen, die ik speciaal wil bedanken:
Anne Marie Kuijpers-Jagtman wil ik het eerst noemen, omdat zij mij heeft gemotiveerd tot het doen van onderzoek, zij heeft met Birte Prahl-Andersen het initiatief genomen Dutchcleft op te zetten en te coördineren, en is echt altijd bereid mee te denken, te luisteren, ideeën te ontwikkelen, stukken te lezen en te corrigeren. Haar energie lijkt onuitputtelijk, en ik voel mij vereerd dat ik daarvan heb mogen profiteren.

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Katja Bongaarts werd geboren op 24 december 1973 te Nijmegen. Zij behaalde haar gymnasium diploma in 1992 en ging vervolgens Tandheelkunde studeren aan de Katholieke Universiteit Nijmegen. Na haar afstuderen in 1997 werkte zij in diverse praktijken als waarnemend tandarts. Daarnaast was zij op vrijwillige basis werkzaam aan de afdeling orthodontie. Zij hielp mee aan het onderzoek van dr. Charlotte Prahl en dr. Emmy Konst. Beide onderzoeken horen bij de DUTCHCLEFT clinical trial. Dit motiveerde zodanig, dat in 1999 gestart werd met de specialisatie tot orthodontist. Tijdens de opleiding begon zij aan het vervolgonderzoek voor de evaluatie van de 4- en 6-jarige 'DUTCHCLEFT'-kinderen. Sinds het afronden van de specialisatie in 2003 werd wekelijks doorgewerkt aan het afronden van dit onderzoek. Daarnaast werd in 2004 een specialistisch orthodontische praktijk opgezet: orthodontistenpraktijk Bonoort te Wageningen.

Het artikel: 'Effect of Infant Orthopedics on Facial Appearance of Toddlers With Complete Unilateral Cleft Lip and Palate (Dutchcleft)', is recent uitgeroepen tot het beste artikel van 2008 van het Cleft Palate-Craniofacial Journal met betrekking op lange termijn onderzoek. De Berkowitz Award wordt jaarlijks uitgereikt door de Cleft Palate Foundation en bestaat uit een geldbedrag van 500 dollar.

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