博 士 論 文

A Three-Center Study of Dental Arch Relationship Outcomes Following Two-Stage Palatoplasty for Japanese Patients with Complete Unilateral Cleft Lip and Palate

(異なる2段階口蓋形成手術法を行う3施設間の歯槽弓関係・咬合関係の成績比較)

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ABSTRACT

Objective: To compare dental arch relationship outcomes following three centers two-stage palatal repair that the timing and the surgical techniques were different.

Design: Retrospective, cross-sectional study.

Setting: Three cleft palate centers in Japan, Department of Oral and Maxillofacial Surgery of Hokkaido University Hospital, Department of Oral and Maxillofacial Surgery of Niigata University Hospital, and Department of Oral and Maxillofacial Surgery of Osaka Women's and Children's Hospital

Patients: Ninety consecutively treated Japanese patients with complete unilateral cleft lip and palate, consisting of 39 patients In Hokkaido University Hospital born from 1997 to 2011, 26 in Niigata University Hospital born from 1995 to 2004 and 25 in Osaka Women's and Children's Hospital born from 2007 to 2010. The inclusion criteria were complete UCLP, patients without Simonart's band, normal birth weight infants and no associated congenital anomalies.

Interventions: In Hokkaido University Hospital(HU), Cheiloplasty was performed by modified Millard method at the mean age 5.0 months. Soft palate and the posterior half of hard palate closure was done using Perko method or modified Furlow method at the mean age of 1 year 7 months. In Niigata University Hospital(NU), Cheiloplasty was performed by Cronin method at the mean age 6.1 months. Soft palate was repaired using modified Furlow method at the mean age of 1 year 6 months. Hard palate was closed using Pichler method at the mean age of 5year 8months. In Osaka Women's and Children's Hospital(OW), Cheiloplasty was performed by modified Millard method at the mean age 3.0 months. Soft palate was repaired using modified Furlow method at the mean age of 1 year. Hard palate was closed using the Veau method or bridge flap at the mean age of 1 year 5 months.

Main outcome measures: Thirty nine dental casts in H.U. were taken at a mean age of 5.1 years (range 4.9 to 6.3 years), and 26 casts in N.U. were at a mean age of 6.4 years (range 4.3 to 8.0 years) and 25 casts in OW group were at a mean age of 5.1 years (range 4.3 to 6.5 years). The casts were randomly numbered, and dental arch relationships were assessed using the 5-Year-Olds' Index (5-Y) by 4 raters and the Huddart/Bodenham Index (HB) by 2 raters.

Results: Intrarater and interrater reliabilities evacuated using weighted kappa statistics were good or very good for the 5Y and HB rating. The mean 5Y score was 3.0 in H.U.,3.1 in O.W.,2.5 in N.U. (P= ns). There was a significant difference in distributions among three groups ($P < .05$). The mean HB scores of molars on minor segment in OW were significantly smaller than in HU and NU ($P < .05$) and those of canine on minor segment in OW was significantly smaller than in NU ($P < .05$).

Conclusions: We compared dental arch relationship and occlusal relationship outcomes of the patients with UCLP treated in three hospitals with two stage palatoplasty that the timing and the surgical techniques were different. There was no difference in dental arch relationships at around 5 years of age regardless of the time of hard palate closure. Earlier hard palate closure might lead to constriction tendency of minor segmental occlusion.

KEY WORDS: unilateral cleft lip and palate, two-stage palatoplasty, dental arch relationships, 5-Year-Olds' Index, Huddart/Bodenham Index, Japanese infants.

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INTRODUCTION

The primary goal of cleft palate surgery is to provide adequate palatal function for the development of normal speech but also subsequent favorable maxillofacial growth (Rohrich 2000). However, the timing and technique of the surgical intervention have a great influence on both the speech development and the maxillofacial growth. Much attention has been focused on the adverse effects of surgical intervention in patients with cleft lip and palate (CLP) so far (Ross, 1987; Mars and Houston, 1990; Mars et al., 1992). Iatrogenic changes induced by the palatal surgery at the timing of developing phase are regarded as the main cause for maxillary growth disorder (Kremenak 1970). It has been thus thought that the early palatal closure performed to avoid the development of compensatory speech (Dorf and Curtin, 1982) would rise to impairment of midfacial growth (Rohrich et al., 1996).

As a protocol designed to minimize surgical interference with maxillary growth, there is a two-stage palatal surgical protocol that the soft and the hard palate are closed by two separate procedures at different times. With the intention of facilitation of favorable midfacial growth, the surgical invasion to the hard palate is delayed until a late age when less maxillary growth remains (Schmid et al., 1974; Schweckendiek, 1978; Hotz and Gnoinski, 1979; Friede 2001, Lilija et al., 2006). It has been accepted that delayed hard palate closure definitely results in better growth when the operation was postponed until after the age of the maxillary growth spurt that a significant proportion of the final length of maxilla is gained (Schweckendiek 1978, Bardach 1984). According to cephalometric analysis of the general population, the increase in maxillary growth velocity takes place at the age of 6-10 years in girls and 8-14 years in boys (Thilander 2005).

Nevertheless, delayed hard palate closure may in turn lead to less favorable speech results, as patients treated using such a procedure have shown difficulty in learning normal articulation (Cosman 1980, Witzel 1984, Noordhoff 1987, Lohmander-Agerskov, 1998). Liao (2006) described that delaying hard palate repair until pubertal peak velocity age for patients with CLP is not recommended clinically because previous studies have consistently demonstrated significant speech impairment associated with hard palate closure delayed past the age of 4 (Bardach 1984, Witzel 1984, Noordhoff 1987, Rolich 1996, Lohmander 1998).

The 2-stage procedures with various timing of delayed hard palate closure until the age before pubertal spurt have been thus proposed. However, there are reports to result in good occlusion and maxillary development (Perko 1979 , Nollet 2005, Lilja 2006, Sinko 2008), but conflicting reports also exist (Noverraz 1993). Investigations of the potential mid-facial growth benefit of delayed hard palate closure have shown contradictory results (Rorich 1996, Liao 2006).

The logic that the two-stage palatal repair with delayed hard palate closure is effective for the prevention of maxillary developmental disorders may not be simple. Berkowitz (2005) stated from the analysis using the palatal casts of 242 individuals from eight institutions in the United States and Western Europe that followed a variety of treatment protocols, delaying all cleft closure surgery until 5 years of age and older is unnecessary to maximize palatal growth. It might be considered that the timing of the cleft palate repair did not affect the major deterrent to facial growth interference, instead,

the surgery itself might cause the deformity (Rohrich 2000).

The purpose of this study was to compare the outcomes of dental arch relationships at 5 years of age following three different 2-step palatal repair of primary surgery that vary in time and technique for the patients with complete unilateral cleft lip and palate.

The dental arch relationship can be used as an indicator of the surgical outcome of CLP, as poorly performed primary surgery is likely to compromise dental development and facial growth (Mars 1992, Atack, Jones 2016). The dental arch relationship outcomes were assessed using two assessment methods in this study. The 5-Year-Olds' Index is widely accepted as a simple and sensitive indicator of the early surgical outcome. Huddart Bodenham index detects both frequency and severity of cross-bite in the dentition. Since the 5-year Olds' index has some ambiguous criteria, providing more detailed information regarding maxillary arch constriction was made up for by the Huddart/Bodenham Index.

MATERIALS & METHODS

Treatment protocols in 3 centers

The treatment protocols and the surgical techniques in 3 centers are showed in Table 1 and Fig1, respectively. All patients in each center are carried out the presurgical orthopedic treatment advocated by Hotz and Goninski .

In Hokkaido University Hospital (HU center), cleft lip is repaired by modified Millard method at 5 months of age. As the first palatal repair, the soft palate and the posterior half of the hard palate is closed at 1 year and a half using modified Furlow method. Relieving incision is carried out to close soft palate, but fracture of the hamular process is not made. The posterior half of the hard palate is closed with two layers using an anterior-based vomerine mucoperiosteal flap (Kobus, 1984), in which the cleft margin incision anteriorly is extended onto the vomer to raise it, evading bone exposure. Considering the negative influence on speech development, the posterior half of hard palate closure is done with soft palate closure to reduce as possible the oronasal communication on the hard palate. A palatal plate to cover the residual hard palate cleft is wore if needed to prevent a nasal air escape after the first operation. Residual hard palate repair as second operation of 2-stage palatal repair is performed by two layered closure with alveolar bone grafting at 6 to 8 years old.

In Niigata University Hospital (NU center), cleft lip is repaired by Cronin method at 6 months. As the first palatal repair, the soft palate closure is performed by the modified Furlow method at 1 and a half years old. The first palatal repair is limited to only soft palate to avoid invasion of the hard palate. Relieving incision is not carried out to avoid boney exposure and the hamular processes are fractured to achieve mobility of the flaps. A palatal plate to cover the residual hard palate cleft is wore all patients until hard palate closure. The second palate repair involved the hard palate by a Pichler vomer mucoperiosteal flap is done at from 5 to 6 years old.

In Osaka Women’s and Children’s Hospital (OW center), cleft lip is repaired by modified Millard

Table 1 Treatment Protocols

	HU	*NU*	*OW*
Birth		Presurgical orthopedics by Hotz plate	
3-6 months	Lip repair by modified Millard	Lip repair by Cronin	Lip repair by modified Millard
12 months			Soft palate repair by modified Furlow
18 months	Soft palate repair by modified Furlow	Soft palate repair by modified Furlow	Hard palate repair by Veau or Bridge flap
5-6years		Hard palate repair by Pichler	
6-8 Years	Alveolar bone grafting & Hard palate repair		
8-10 Years		Alveolar bone grafting	Alveolar bone grafting

method at 5 months. As the first palatal repair the soft palate closure is performed at 1 year old using modified Furlow method. Relieving incision is carried out to close soft palate, but fracture of the hamular process is not made. And then as second surgery, the hard palate is closed with two layers using the mucoperiosteum of cleft margins or bridge flap technique at 1 year and a half of age. As the residual cleft in the hard palate usually shrinks after soft palate closure, the residual cleft in the hard palate is basically closed by two layered closure with the mucoperiosteum of cleft margins. When a cleft is relatively wide, hard palate cleft is closed using bridge flap which raised by a relaxing incision inside the greater palatine artery on the major segment (bridge flap technique) (Nisio 2010). In all three centers, the alveolar cleft is kept intact until when alveolar bone grafting is to be done later.

Subjects

The inclusion criteria were as follows: complete unilateral cleft lip and palate (CUCLP), Japanese ethnic background and normal birth weight infants, but patients with Simonart's bands and associated congenital anomalies were excluded. The characteristics are summarized in Table 2.

In HU center, 43 patients with CUCLP who were born from 1997 to 2011 visited HU before any intervention. Then, of these patients, 4 who underwent soft palate repair by using Perko method was not available for the outcome study. Thus, out of 43 patients, a consecutive series of 39 were investigated as subjects in HU. Cheiloplasty was performed at the mean age 5.0 months (range, 3.5-6.9months). Soft palate and the posterior half of hard palate closure was done at the mean age of 1 year 7 months (range, 1.5-2.1years old).

In NU center, 26 patients with CUCLP who were born from 1995 to 2004 visited NU before any intervention. Then, 26 were investigated as cases in NU without drop-out. Cheiloplasty was performed at the mean age 6.1 months (range, 5.4-7.7months). Soft palate was repaired at the mean age of 1 year 6 months (range, 1.5-2.0 years old). Hard palate was closed at the mean age of 5 year 8 months (range, 5.1-6.8).

In OW center, 26 patients with CUCLP who were born from 2007 to 2010 visited OW before any intervention. One patient was not available because the hard palate was almost closed spontaneously after soft palate repair. Thus, out of 26 consecutive patients, 25 were investigated as cases in OW. Cheiloplasty was performed at the mean age 3.0 months (range, 2.3-3.8months). Soft palate was repaired using modified Furlow method at the mean age of 1 year (range, 0.9-1.0). Hard palate was closed at the mean age of 1year 6 months (range, 1.4-1.8years old). All participants in OW in this study could be completed hard palate closure with the mucoperiosteum of cleft margins without use of bridge flap.

One surgeon in HU, 3 surgeons in NU and 2 surgeons in OW carried out the surgical repair

respectively. They all have experienced cleft lip and palate surgery for over 10 years.

Total subjects in this study were 90 CUCLP patients consisting 39 in HU, 26 in NU and 25 in OW. Of the 95 consecutive patients who initially fulfilled inclusion criteria, 5 patients were not available during treatment. Thus, 90 patients remained as evaluation subjects, for a follow-up rate of 94.7 %. The sex ratio shown in Table 2 was almost the same among 3 centers, and there is no significant difference ($P < .05$).

No patient underwent orthodontic treatment, secondary surgery such as alveolar bone grafting or pharyngeal flap operation prior to dental cast taking.

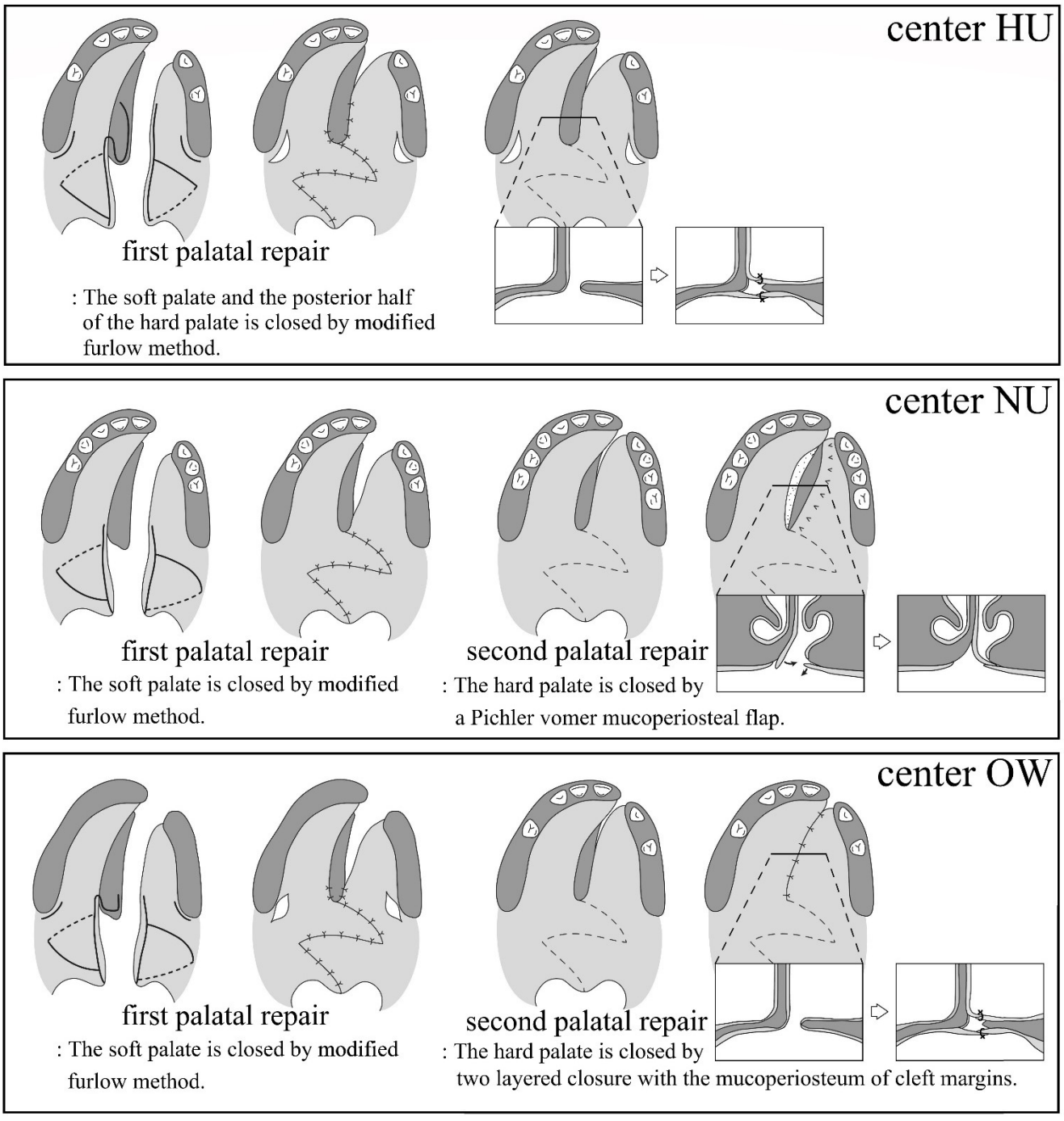

FIGURE 1 Treatment protocol of each centers.

Table 2 Sample Charactaristics

	HU	*NU*	*OW*
Number of patients and sex distribution	39 (19 male 20 female)	26 (17 male 9 female)	25 (17 male 8 female)
Presurgical orthopedics by Hotz Plate	Yes	Yes	Yes
Lip repair	mean 5.0 mo (3.5-6.9 mo)	mean 6.1 mo (5.4-7.7 mo)	mean 3.0 mo (2.3-3.8 mo)
Palate repair	Soft palate to the posterior one half of the hard palate repair : mean 1.7 y (1.5～2.1 y)	Soft palate repair ： mean 1.6 y (1.5～2.0 y) Hard palate repair ： mean 5.8 y (5.1～6.8 y)	Softpalate repair： mean 1.0 y (0.9～1.0 y) Hard palate repair： mean 1.5 y (1.4～1.8 y)
taking	mean 5.1 y (4.9～6.3 y)	mean 6.4 y (4.3～8.0 y)	mean 5.1 y (4.3～6.5 y)

All casts in three centers were duplicated with white stone and trimmed in the same manner. Thirty nine dental casts in HU were taken at the mean age of 5.1 years (range 4.9 to 6.3 years), 26 casts in NU were at the mean age of 6.4 years (range 4.3 to 8.0 years), and 25 casts in OW group were at the mean age of 5.1 years (range 4.3 to 6.5 years). Tukey test showed that age at dental cast taking of NU was significantly later than HU and OW ($P < .05$).

Assessment

The casts were randomly numbered and assessed using the 5-Year-Olds' Index (Atack et al., 1997a, 1997b) and the Huddart/Bodenham Index (Huddart and Bodenham, 1972).

Scoring of the 5-Year-Olds'Index was performed by 5 raters: two orthodontists experienced in cleft care for more than 20 years (T.S., Y.S.) and two oral and maxillofacial surgeons having more than sixteen years of clinical experience (Y.K., Y.I.) and one oral and maxillofacial surgeon having more than two years of clinical experience (J.K.). One orthodontist and two oral and maxillofacial surgeons were involved in cleft care at Hokkaido University hospital, and the remaining two raters were outsiders who participated from the other University Hospital. Five raters scored the casts from 1 to 5 individually with the reference casts provided by Bristol University twice over two days. Two raters attended ''The 5-Year- Olds' Index Calibration Course'' by Dr. Atack and Prof. Sandy held by the Japanese Cleft Palate Association and had completed training in the use of the assessment (Sandy and Atack, 2012) and the remaining three raters acquired the rating skill with them. Before the scoring sessions took place, each rater was calibrated using the test casts of UCLP patients other than the subjects. Each model was given a total of ten individual scores over two sessions.

The Huddart/Bodenham Index was scored independently by two raters: one with more than 15 years of experience as an oral and maxillofacial surgeon (Y.I.) who was engaged in cleft care at Hokkaido University hospital, and one oral and maxillofacial surgeon with more than two years of experience (J.K.) who was engaged in cleft care at Hokkaido University hospital. Both raters carried out the scoring twice with an interval of 3 day. Each model was given a total of four individual scores over two sessions. The total crossbite score, by summing up all the scores for each pair of teeth, and the partial crossbite score, with the dental arch divided into five parts (central deciduous incisors, deciduous canines on the major and minor segments, and first and second deciduous molars on the major and minor segments), were calculated.

None of the patients' operators participated in the rating sessions for both indices.

Statistical analysis

For the evaluation of each case, the mode of the evaluation result is taken as the evaluation result of each case. In the case where there are two modes, the larger one in 5Y and the smaller one in HB are adopted as values so as not to give a bad evaluation.

Table 3 Interpretation of Kappa Values (Altman, 1991)

Kappa Value	*Strength of Agreement*
<0.2	Poor
0.2-0.4	Fair
0.4-0.6	Moderate
0.6-0.8	Good
0.8-1.0	Very good

Weighted kappa statistics were used to assess intrarater and interrater reliability scores for the five raters for the 5-Year-Olds' Index and for the two raters for the Huddart/Bodenham Index. The interpretation of the kappa values was based on data according to Altman (1991) (Table 3). The tukey test was used to compare the mean values of the 5-Year-Olds' Index scores and the Huddart/Bodenham Index scores among the three groups. The chi-square test was performed to evaluate the difference in the score distributions of the 5-Year-Olds' Index grades. P values < .05 were considered significant.

Compliance with ethical standards

Ethical approval: This study was conducted in conformity with the Declaration of Helsinki and also approved by the Institutional Review Board and was performed in accordance with the ‘‘Ethical Guidance for Clinical Studies ’’ of the Health, Labor, and, Welfare in Japan.

Disclosure of Conflicts of Interest: There are no conflicts of interest of the authors regarding this subject.

RESULTS

Weighted kappa statistics for double determinations of the 5-Year-Olds' Index for five raters demonstrated values between 0.78 and 0.87 for intrarater agreement (Table 4) and between 0.60 and 0.83 for interrater agreement (Table 5), and weighted kappa statistics for double determinations of the Huddart/Bodenham Index for two raters were 0.82 and 0.83 for intrarater agreement (Table 6) and 0.74 and 0.82 for interrater agreement (Table 7).

Tables 8 and 9 show the score distribution and mean scores of the 5-Year-Olds' Index. In HU, 30.8% were scored 1 and 2, 35.9% were 3, and 33.3% were 4 and 5, with the mean score of 2.95. In OW, 24.0% were scored 1 and 2, 48.0% were 3, and 28.0%were 4 and 5, with the mean score of 3.08. In NU, 46.2% were scored 1 and 2, 26.9% were 3, and 26.9% were 4 and 5, with the mean score of 2.50. The Tukey's test and the chi-square test showed no significant difference in the mean scores among the 3 groups. (P < .05).

Table 10 shows the mean Huddart/Bodenham Index scores. In HU, the total score, the score of the incisors, scores of the canines on the major and minor segments, and the scores of the molars on the major and minor segments were -6.8, -3.6, -0.4, -1.3, -0.3, and -1.1, respectively. In OW, the total score, score of the incisors, scores of the canines on the major and minor segments, and the scores of the

molars on the major and minor segments were -7.6, -3.0, -0.4, -1.8, -0.5, and -2.0, respectively. In NU, the total score, score of the incisors, scores of the canines on the major and minor segments, and the scores of the molars on the major and minor segments were-5.5, -2.8, -0.6, -1.0, -0.4, and -0.7, respectively.

The tukey test showed significant differences in the scores of canine and molars on minor segments ($P < .01$) among the three groups.

In the mean Huddart/Bodenham Index scores, the mean scores of molars on minor segment in OW were significantly smaller than in HU and NU ($P < .05$). The mean scores of canine on minor segment in OW was significantly smaller than in NU ($P < .05$).

Table 4 Intrarater Agreement (Weighted Kappa) for 5-Year-Old's Index Scoring

Raters	*Kappa Value*	*Kappa*	*95% Confidence Intervals*
T.S.	0.86	0.03	0.80 - 0.92
Y.S.	0.87	0.03	0.80 - 0.93
Y.K.	0.83	0.04	0.75 - 0.91
Y.I.	0.82	0.04	0.75 - 0.89
J.K.	0.78	0.04	0.70 - 0.85

Table 5 Interrater Agreement (Weighted Kappa) for 5-Year-Old's Index Scoring

Raters	*Kappa Value*	*Standard Error of Kappa*	*95% Confidence Intervals*
First rating			
T.S.×Y.S.	0.78	0.04	0.70 - 0.85
T.S.×Y.K.	0.71	0.04	0.63 - 0.79
T.S.×Y.I.	0.79	0.04	0.70 - 0.87
T.S.×J.K.	0.80	0.04	0.73 - 0.88
Y.S.×Y.K.	0.76	0.05	0.67 - 0.85
Y.S.×Y.I.	0.67	0.05	0.58 - 0.76
Y.S.×J.K.	0.79	0.04	0.71 - 0.87
Y.K.×Y.I.	0.63	0.05	0.53 - 0.72
Y.K.×J.K.	0.71	0.05	0.63 - 0.80
Y.I.×J.K.	0.73	0.04	0.64 - 0.81
Second rating			
T.S.×Y.S.	0.77	0.04	0.69 - 0.85
T.S.×Y.K.	0.60	0.05	0.50 - 0.71
T.S.×Y.I.	0.76	0.04	0.68 - 0.85
T.S.×J.K.	0.76	0.04	0.68 - 0.84
Y.S.×Y.K.	0.69	0.05	0.58 - 0.79
Y.S.×Y.I.	0.68	0.05	0.59 - 0.77
Y.S.×J.K.	0.69	0.04	0.61 - 0.78
Y.K.×Y.I.	0.63	0.05	0.53 - 0.73
Y.K.×J.K.	0.66	0.05	0.57 - 0.76
Y.I.×J.K.	0.83	0.03	0.76 - 0.90

Table 6 Intrarater Agreement (Weighted Kappa) for Huddart/Bodenham index Scoring

Raters	*Kappa Value*	*Standard Error of Kappa*	*95% Confidence Intervals*
Y.I.	0.83	0.01	0.80 - 0.86
J.K.	0.82	0.02	0.79 - 0.85

Table 7 Interrater Agreement (Weighted Kappa) for Huddart/Bodenham index Scoring

Raters	*Value*	*Kappa*	*Intervals*
First rating			
Y.I.×J.K.	0.82	0.01	0.79 - 0.85
Second rating			
Y.I.×J.K.	0.74	0.02	0.71 - 0.77

Table 8 Numerical and Percentage Distributions of 5-Year-Old's Index Scores

	HU			*NU*			*OW*		
Scores	*Frequency*	*Percent*		*Frequency*	*Percent*		*Frequency*	*Percent*	
1 (Excellent)	4	10.3%	} 30.8%	8	30.8%	} 46.2%	1	4.0%	} 24.0%
2 (Good)	8	20.5%		4	15.4%		5	20.0%	
3 (Fair)	14	35.9%		7	26.9%		12	48.0%	
4 (Poor)	12	30.8%	} 33.3%	7	26.9%	} 26.9%	5	20.0%	} 28.0%
5 (Very poor)	1	2.6%		0	0.0%		2	8.0%	

Table 9 Comparison of 5-year-Old's Index score among 3 centers

centers	*Sample size*	*Mean*	*SD*	*95% Confidence Intervals*
HU	39	2.95	1.02	2.62 - 3.28
NU	26	2.50	1.21	2.01 - 2.99
OW	25	3.08	0.95	2.69 - 3.47

Table 10 Mean Scores of the Huddart/Bodenham Index of Each Part

	HU			*NU*			*OW*			
	Mean	*SD*	*95% Confidence Intervals*	*Mean*	*SD*	*95% Confidence Intervals*	*Mean*	*SD*	*95% Confidence Intervals*	*Significance*
Total	-6.77	4.31	-8.17 ~ -5.40	-5.46	5.27	-7.59 ~ -3.33	-7.60	4.65	-9.52 ~ -5.68	P>.05
Incisors	-3.59	2.36	-1.55 ~ -0.71	-2.77	3.31	-4.12 ~ -1.43	-2.96	2.44	-4.00 ~ -1.95	P>.05
Canine on major segment	-0.41	0.68	-0.63 ~ -0.19	-0.58	0.70	-0.86 ~ -0.29	-0.40	0.71	-0.69 ~ -0.11	P>.05
Morars on major segment	-0.33	0.84	-0.60 ~ -0.06	-0.38	0.75	-0.69 ~ -0.08	-0.48	1.05	-0.91 ~ 0.05	P>.05
Canine on minor segment	-1.31	0.83	-1.58 ~ -1.04	-1.00	0.80	-1.32 ~ -0.68	-1.76	0.60	-2.01 ~ -1.51	P<.05 (NU/OW)
Morars on minor segment	-1.13	1.30	-1.55 ~ -0.71	-0.73	1.15	-1.20 ~ -0.27	-2.00	1.50	-2.62 ~ -1.38	P<.05 (NU/OW・HU/OW)

DISCUSSION

Analysis of Outcomes

In each of three centers which have the different surgical regimens of 2-step palatal repair with delayed hard palate closure, soft palate closure was completed using the same Furlow method until from 1 to 1 year and a half of age considering to speech development, but hard palate closure was performed by a different closing timing, closing range and closing technique. When soft palate closure that is the first operation in 2-step palatal repair procedure was performed in HU and NU centers, hard palate closure that is the second operation in 2-step procedure had been just finished in OW around 1 year and a half of age. In OW hard palate was closed by using the mucoperiosteum of the cleft margins not to expose bone. In HU, posterior half of the hard palate was closed with soft palate at the same time around 1 year and a half of age. The hard palate cleft was repaired by two layered closure using both extended vomerine flap and mucoperiosteum in the cleft margins without bone exposure. A residual cleft of anterior half of hard palate was left open at the time of assessment of outcomes. In contrast with above 2 centers, in NU, the whole cleft area of hard palate in all cases was left not to be repaired until just around the time of assessment. The dental arch relationship outcomes evaluated by both of the 5-Year-Olds' Index mean scores and the distribution of the scores at the age of 5 years did not significantly differ among three centers. However, the mean Huddart/Bodenham Index scores of molars on the minor segment alone were significantly smaller in the OW than in the HU and the NU, and also the mean scores of a canine on the minor segment alone were significantly smaller in the OW than in the NU. From the findings of the dental arch relationships, it could be thought that the surgical outcomes for the skeletal aspect of maxillary growth would be the same at around 5 years of age even if the hard palate was closed at different time dilations in two-stage palatal repair methods, but that the

earlier closure of a whole area of hard palate in OW protocol tended to bring about a transversal dentoalveolar constriction of minor segment, comparing with in HU and UN.

In the six-center European international (Mars 1992) intercenter studies involving the first published randomized clinical trial for primary surgical protocols for patients with UCLP, the most favorable dental arch relationships using Goslon Yardstick outcomes were obtained in centers with the various surgical protocols. These studies concluded that the timing of primary palate repair alone did not have a statistically significant influence on midfacial growth. Lately, the finding of Scandcleft randomized trials of primary surgery that three surgical procedures for palatal repair varied the timing, staging and technique were tested against a common procedure was published. This result also led to a same conclusion that differences in the timing, staging or sequencing of the hard and soft palate repair did not significantly affect the dental arch relationships at 5 years of age (Helivaara 2017).

It is widely accepted that scar tissue developing over the denuded palatal bone remaining after palatoplasty might increase the risk of subsequent maxillary growth impediment (Ross,1970; Kim et al., 2002; Von den Hoff 2006, Meng et al., 2007). In two classic approaches to palate repair, the von Langenbeck method and the Veau and Wardill-Kilner push-back method, mucoperiosteal flaps are elevated and advanced to the midline for closure of the cleft, leaving two large areas of denuded bone for secondary healing. It has been particularly pointed out that scar tissue developing at the denuded bone sites after the V to Y pushback transpositions of the mucoperiosteal palatal flaps redirects contracting forces from a transverse direction to a sagittal direction (Kremenak et al., 1970; Ross, 1970; Wijdeveld et al., 1987, 1991, Sommerlad, 2009). As Friede (2007) stated, it would be reasonable to think that the maxillary growth outcome would be related more closely to the extent and location of the palatal scar tissue than to the actual age at hard palate surgery as well as whether the palate was closed in one or two stages.

While the potential mid-facial growth benefit of two-step palatal repair with delayed hard palate closure has remained contraversial (Rorich 1996, Gaggl 2003, Nollet et al 2005b, Holland 2007, Liao 2006), similar discussion about differences in the scar situation of the palate can be applied to variation of the surgical techniques used in two-step palatal repair regimen (Friede 2012). Kappen (2017) described that the amount and location of scar tissue may have a greater influence on mid-facial growth than the specific age of hard palate closure during the first decade of life even if one- or two-step palatal closure was used. When the hard palate can be repaired using mobilization of the mucoperiosteum close to the cleft margins, only minor areas of exposed bone is left, and thus only a small amount of scarring is formed on the palate. Furthermore, scar tissue in this part of the palate is much less detrimental to maxillary growth than are scars closer to the alveolar process (Markus 1993). Moreover, it was reported that there was a natural and spontaneous reduction in the residual cleft width of hard palate after the initial soft palate closure in two-stage palatoplasty (Owman-Moll 1998, Lohmander-Agerskov 1997). Narrowing of the cleft would allow for repair using flaps close to the midline of the hard palate, avoiding the need for extensive palatal dissection at palate closure (Lilja 2006).

When it is slightly too wide to repair the hard palate by using mobilization of the mucoperiosteum close to cleft margins, there is a choice to adopt vomerplasty to overcome the negative consequences of scar tissue formation by minimizing the area of denuded bone on the hard palate and by reducing the need for lateral releasing incision (Ganesh 2015, Sommerlad 2015). However, a denuded surface of the vomer following vomerplasty has been claimed to have detrimental effects on facial growth (Delaire & Precious 1985, Friede 1987). Friede (1978) and Farronato (2014) described that scar tissue on the sutures, such as the vomero-premaxillary suture, can restrict the forward and downward expansion of the maxilla. On the other hand, in one of the centers in Eurocleft and Scandcleft rondamized trial, the dental arch relationship of the surgical protocol with early hard palate closure with extended vomer flap did not also provide statistical evidence comparing with other protocols which differed from timing and staging without vomer flap (Mars 1992, Heliovaara 2017). In the present study, the dental arch relationship outcome in HU that soft palate closure and posterior half of the hard palate closure using an anterior-based vomerine mucoperiosteal flap were performed simultaneously at the mean age of 1 year 7 months was identical to in NU that the hard palate was left open with being surgically untouched until the mean age of 5 year 8 months. This finding can be thus in agreement with the results of the Eurocleft and the Scandcleft study. Furthermore, in spite of single layered palatal closure with vomer flap, a detrimental effect on maxillary growth could be minimized in these previous studies, the vomeroplasty in HU that posterior half of the hard palate was closed by two layered sutures on both oral and nasal side to evade bony exposure should be still more able to ignore the harmful effect.

In the six-center European international study (Show 1992), in a Cleft Care UK study (Al-Ghatam 2015), and the three-center randomized trial in Scandcleft groups (Arja Heliovaara 2017), it was pointed out that the experience and skills of the surgeon in terms of tissue management may have more effect on craniofacial development than surgical technique or timing of hard palate closure. In other words, the extent of scar tissue formation would be also influenced by factors such as surgical skill and experience. On interpreting our results, it could be thought that there was not such a concern at all because operators with enough ability were in charge of surgery in each center.

About study design and assessment

The study was a retrospective cross-sectional comparative assessment among the three centers' outcomes of the early treatment of UCLP patients. Of the 95 consecutive patients who initially visited before any intervention, 5 patients were not available during treatment. Thus, 90 patients remained as evaluation subjects, for a follow-up rate of more than 90%.

To equalize the background factors of three groups as much as possible, subjects were limited to patients with complete cleft type, Japanese ethnic background and normal birth weight infants, but patients with Simonart's bands and associated congenital anomalies were excluded. Nollet et al.(2005a) reported in a meta-analysis of published GOSLON outcomes that studies that included patients with Simonart's bands would have better outcomes, and they recommended that such patients

be removed from the analysis. Therefore, it could be thought that the three samples were sufficiently similar at the outset. However, it was impossible to examine each outcome by sex in the present study because the power was limited due to the small sample size; fortunately, there was no significant difference in the sex ratio among the three groups. From the basic point of view that both the 5-Year-Olds' Index and the Huddart/Bodenham Index are measures of relative relationships through which the whole or parts of the maxilla and the mandible are evaluated, it is thought that the influence of sex differences could be almost ignored. On the other hand, it has been reported that cleft patients who had a family history of Class III may tend to develop Class III malocclusion not only as an effect of primary surgery but also due to the genetic influence of excessive mandibular growth, which is particularly common in Japanese (Kajii et al., 2013). In the present study, a family history of Class III could not be considered because it was impossible to confirm. However, genetic influences may have little effect because facial growth is not fully expressed until after the pubertal growth spurt (Flinn et al., 2006; Mars et al., 2006).

Two methods were used to assess the dental arch relationship outcomes in this study.

The 5-Year-Olds' Index has been recommended as the gold standard measure for surgical outcomes in UCLP at 5 years of age and can assess an individual's skeletal and dental relationships in terms of anteroposterior, transverse, and vertical discrepancies, with a subsequent general prediction about the surgical outcome of future correction of the malocclusion (Atack 1997a, 1997b) (Jones 2016). The GOSLON scores have previously been shown to correlate well with cephalometric outcomes related to the positions of the maxilla and mandible (Mars and Plint, 1985). This characteristic is applicable to the 5-Year-Olds' Index scoring. It is notable that the extent of maxillary growth impediment could be extrapolated from the state of the dental arch relationships. Moreover, confounding variables such as orthodontics and secondary surgeries are not performed yet, and genetic influences are also less of a factor because facial growth is not fully expressed until after the pubertal growth spurt. Unless the patient has a severe skeletal discrepancy, the outcome measured in 5-year casts could assess the effects of primary surgery (Flinn et al., 2006; Mars et al., 2006). However, the use of the 5-Year-Olds' Index requires professional judgment regarding the potential for orthodontic management of the interarch discrepancy, and reference casts and a calibration course are absolutely necessary for the use of this tool. When the 5-Year-Olds' Index scoring was performed in this study, four raters were trained in this scoring procedure by the rater who attended a 5-Year-Olds' Index calibrating course (Sandy and Atack, 2012), with calibration just before actual scoring to reduce systematic bias. Both intrarater and interrater agreement evaluated by the weighted kappa statistics was ‘‘good,’’ so that the repeatability and reproducibility of the rating were ensured. However, the 5-Year-Olds' Index scoring cannot verify the details of discrepancies because of a general overview measure. On the other hand, the Huddart/Bodenham Index would be effective to make up for the 5-Year-Olds' Index when a more detailed description of treatment outcome, such as absolute measurement of arch constriction, would be required (Bartzela et al., 2011), although it has disadvantages that it does not assess the skeletal component of the malocclusion and cannot differentiate between a generalized mild malocclusion and

a localized severe malocclusion, nor assess the vertical discrepancies of the malocclusion (Karsten 2017).

Though several contrasting variations in the timing and staging of hard and soft palate repair have been devised, any surgical protocol might be preferable if protocols could minimize the amount of scar tissue formed on palatal bone, facilitating normal speech development simultaneously. Unfortunately, we could not arrive at a conclusion with definite grounds from this study as the following limitation. In this study, the statistical power to find a significant difference between the three groups at a 5% predominance level in the 5-Year-Olds' Index scoring was 39%. The Tukey test calculated that 147 cases were required to reach 80% power. It seems that it may be difficult to secure a large number of cases equalized various background factors at multiple centers. However, it is necessary for a rigorous discussion and is a future issue.

CONCLUSION

The purpose of this study was to compare the dental arch relationship outcomes in the patients with complete unilateral cleft lip and palate following three centers two-stage palatal repair that the timing and the surgical techniques were different. Dental arch relationships were judged and categorized using the 5-Year-Olds' Index and the Huddart/Bodenham Index. Intrarater and interrater reliabilities were good or better for cast ratings using both indices.

The mean value and distribution of the 5-Year-Olds' Index scoring did not show a significant difference among three groups ($P < .05$). There was thus no difference in dental arch relationship regardless of the time of hard palate closure. However, the mean HB scores of molars on minor segment in OW were significantly smaller than in HU and in NU ($P < .05$) and those of canine on minor segment in OW was significantly smaller than in NU ($P < .05$). From this findings, it could be thought that the skeletal aspect of maxillary growth would be the same at around 5 years of age even if the hard palate was closed at different time dilations in two-stage palatal repair methods, but earlier hard palate closure might lead to the tendency of dentoalveolar constriction of minor segment.

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