Accepted Manuscript

Maxillofacial growth and speech outcome after one-stage or two-stage palatoplasty in unilateral cleft lip and palate. A systematic review

Rajgopal R. Reddy, MBBS, BDS, FDSRCPS Glasg, Srinivas Gosla Reddy, MBBS, MDS, FDSRCS Eng, FDSRCS Edin, PhD, Anitha Vaidhyanathan, MDS, Stefaan J. Bergé, MD, DDS, PhD, Anne Marie Kuijpers-Jagtman, D.D.S., Ph.D, F.D.S.R.C.S. Eng

PII: S1010-5182(17)30101-4

DOI: 10.1016/j.jcms.2017.03.006

Reference: YJCMS 2630

To appear in: *Journal of Cranio-Maxillo-Facial Surgery*

Received Date: 30 November 2016

Revised Date: 17 February 2017

Accepted Date: 15 March 2017

Please cite this article as: Reddy RR, Reddy SG, Vaidhyanathan A, Bergé SJ, Kuijpers-Jagtman AM, Maxillofacial growth and speech outcome after one-stage or two-stage palatoplasty in unilateral cleft lip and palate. A systematic review, *Journal of Cranio-Maxillofacial Surgery* (2017), doi: 10.1016/j.jcms.2017.03.006.

Maxillofacial growth and speech outcome after one-stage or two-stage palatoplasty in unilateral cleft lip and palate. A systematic review

Authors and Affiliations

Rajgopal R. Reddy[a], MBBS, BDS, FDSRCPS Glasg

Srinivas Gosla Reddy[a], MBBS, MDS, FDSRCS Eng, FDSRCS Edin, PhD

Anitha Vaidhyanathan[a], MDS

Stefaan J. Bergé[b], MD, DDS, PhD

Anne Marie Kuijpers-Jagtman[c], D.D.S., Ph.D, F.D.S.R.C.S. Eng

a: G.S.R. Hospital, Institute of Cranio-Maxillofacial and Facial Plastic Surgery, Vinay Nagar Colony, Saidabad, Hyderabad, India. Head of the Department: Prof. Srinivas Gosla Reddy

b: Department of Cranio-maxillofacial Surgery, Radboud University Medical Center, Nijmegen, The Netherlands. Head of the Department: Prof. Stefaan J. Bergé.

c: Department of Orthodontics, Radboud University Medical Center, Nijmegen, The Netherlands. Professor Emeritus: Anne Marie Kuijpers Jagtman

Corresponding Author:

Rajgopal R. Reddy,

Deputy Director, GSR Institute of Craniofacial Surgery

17-1-383/55, Vinay Nagar Colony,

I.S Sadan, Saidabad, Hyderabad- 500 059

Telephone: +91 40 65764884

Facsimile: +91 40 24530000

Email: raj@craniofacialinstitute.org

Sources of funds supporting the work

This project was supported by institutional funds

Statement of financial interest

No financial interest to declare

List of products used in the manuscript

No products to declare

Background

The number of surgical procedures to repair a cleft palate may play a role in the outcome for maxillofacial growth and speech. The aim of this systematic review was to investigate the relationship between the number of surgical procedures performed to repair the cleft palate and maxillofacial growth, speech and fistula formation in non-syndromic patients with unilateral cleft lip and palate.

Material and methods

An electronic search was performed in PubMed/old MEDLINE, the Cochrane Library, EMBASE, Scopus and CINAHL databases for publications between 1960 and December 2015. Publications before 1950 — journals of plastic and maxillofacial surgery — were hand searched. Additional hand searches were performed on studies mentioned in the reference lists of relevant articles. Search terms included *unilateral*, *cleft lip* and/or *palate* and *palatoplasty*. Two reviewers assessed eligibility for inclusion, extracted data, applied quality indicators and graded level of evidence.

Results

Twenty-six studies met the inclusion criteria. All were retrospective and non-randomized comparisons of one- and two-stage palatoplasty. The methodological quality of most of the studies was graded moderate to low. The outcomes concerned the comparison of one- and two-stage palatoplasty with respect to growth of the mandible, maxilla and cranial base, and speech and fistula formation.

Conclusions

Due to the lack of high-quality studies there is no conclusive evidence of a relationship between one- or two-stage palatoplasty and facial growth, speech and fistula formation in patients with unilateral cleft lip and palate.

Key words

systematic review, cleft palate, surgical procedure, operative, oral fistula, speech, growth

1. Introduction

Despite considerable progress in the treatment of children with non-syndromic cleft lip and palate, there is no agreement as to the optimal timing, sequence and types of surgical procedure that yield the best result. Techniques such as the von Langenbeck (*Wallace, 1987; Lindsay and Witzel, 1990*), the Veau-Wardill-Kilner pushback (*Wallace, 1987*) and the Bardach two-flap (*Bardach and Salyer, 1987; Bardach, 1995*) for single-stage, and the Schweckendiek (*Schweckendiek and Doz, 1978*) and Delaire (*Markus et al., 1993*) for two-stage palatal repair were recommended. Braithwaite (*Braithwaite, 1964*), Kriens (*Kriens, 1969*) and Sommerlad (*Sommerlad, 2003*) advocated intervelar veloplasty in the soft palate by re-orientation of the levator muscle, while the Furlow Z-plasty technique was performed to improve soft palate length (*Furlow, 1986*).

Several earlier systematic reviews have addressed different issues regarding timing and technique of cleft palatoplasty (*Nollet et al., 2005; Liao and Mars, 2006; Yang and Liao, 2010*). In a systematic review on timing of hard palate repair and facial growth in 2006, the authors came to the conclusion that there is no consensus on the effect of timing on facial growth (*Liao and Mars, 2006*). All studies included in this review were retrospective and non-randomized. There was also variation in the timing of hard palate repair and inadequate assessment of outcome variables.

In 2005 a meta-analysis was published on dental arch relationships in complete unilateral cleft lip and palate based on the GOSLON yardstick for assessment of dental arch relationships (*Nollet et al., 2005*). The authors concluded that patients whose hard and soft palates were closed before the age of 3 had poorer GOSLON scores — indicating maxillary growth deficiency — than patients whose palates were closed at a later age.

In 2010 a systematic review was published on the effect of one-stage versus two-stage palatoplasty on maxillofacial growth (*Yang and Liao, 2010*). Nine studies were included, which were all retrospective and non-randomized. Timbang (*Timbang et al., 2014*), in their systematic review, compared speech outcomes between Furlow's Z-plasty and straight-line intravelar veloplasty techniques in isolated cleft palate and unilateral cleft lip and palate. All included studies, except one, were retrospective and non-randomized. There was no statistical difference in fistula rate between Furlow and straight-line repair. The need for secondary procedures to correct velopharyngeal insufficiency in the Furlow group ranged from 0% to 6.7%, as opposed to 6.7% to 19.4% in the straight-line intravelar veloplasty group. Overall, their analyses showed that straight-line repair combined with intravelar veloplasty was associated with an increased risk of a secondary surgery (1.64 times) when compared with the Furlow group.

Until now no systematic review has been published in which the results of one-stage and two-stage palatal repair are compared for different outcome variables. This systematic review was therefore carried out to examine whether one-stage or two-stage palatal repair is more beneficial for maxillofacial growth, speech and fistula rate in patients with non-syndromic unilateral complete cleft lip and palate.

2. Materials and methods

2.1 Information sources and search strategy

The search strategies were developed and databases were selected with the help of a senior librarian who specialized in health sciences. The following databases were searched: PubMed (from 1951 to 31 December 2015), Cochrane (from 1966 to 31 December 2015), EMBASE Excerpta Medica (from 1950 to 31 December 2015), SCOPUS (from 1963 to 31 December 2015), CINAHL (from 1985 to 31 December 2013).

The focus of the search was on two aspects: terms required to search for the surgical intervention of interest; and terms required to search for the congenital deformity of interest. Free text words and MeSH terms were used and individual search strings for each database were formulated, as shown in *Table 1*.

Publications prior to 1950 — journals of plastic and maxillofacial surgery — were hand searched in. Additional hand searches were performed on studies mentioned in the reference lists of relevant articles. There was no language restriction. Grey literature (dissertations, conference abstracts) was not searched.

2.2 Eligibility criteria and study selection

The inclusion criteria for this systematic review were: study on humans; sample size of $n \geq 10$ per group; non-syndromic complete unilateral cleft lip and palate; study that compared one- and two-stage palatoplasty procedures. All reviews, isolated cleft palate studies, letters to editors and case studies and case series were excluded. No language restrictions were imposed.

Eligibility assessment of records was done based on title and abstract in an unblinded manner by two observers (AV, RR) independently. All titles and abstracts were classified as included, excluded or unclear. Inter-observer conflicts were resolved by discussion of each

article to reach a consensus. In the second step, the publications classified under included or unclear were retrieved full text for further review by the two observers.

2.3 Data extraction

Quantitative data extracted from each study included outcomes in relation to craniofacial form, growth of maxilla and mandible, interarch relationship, speech and fistula formation. A data extraction form was developed and piloted and finalized accordingly. Reviewers (AV, RR) independently extracted the following data from the included studies: first author, year of publication, study design, stage (one- or two-stage palatal repair), sample size, cleft type, technique of palatoplasty, timing of surgical repair, type of outcome measure, adequate and reliable measurements at follow ups, and outcomes. Disagreements were resolved by discussion between the two reviewers. If no agreement could be reached a third reviewer decided (AK).

2.4 Quality assessment and level of evidence

Two observers (AV, RR) independently evaluated the methodological quality of the included studies according to a grading system developed by the Swedish Council on Technology Assessment in Health Care, which is based on the criteria for assessing study quality from the Centre for Reviews and Disseminations (CRD) in York, UK (*Deeks et al., 1996; Bondemark et al., 2007*). The grades for methodological quality are listed in *Table 2*. The final level of evidence for each conclusion was graded according to the scale as presented in *Table 3* (*Bondemark et al., 2007; von Böhl et al., 2012*). Conflicts, if any, between the two observers were resolved by discussion of each article.

3. Results

3.1 Study selection

The electronic search revealed a total of 5,159 citations: 2,395 from PubMed/MEDLINE, 293 from the Cochrane Library, 1,376 from EMBASE, 479 from CINAHL and 616 from SCOPUS. No additional publications were identified through hand searches. After exclusion of duplicate records, 2,759 citations remained. Of those, 2,608 were excluded because after reading the abstracts they did not meet the inclusion criteria. The full texts of the remaining 151 publications were reviewed in detail. Of these 151 publications, 125 were excluded for not having met the inclusion criteria. The remaining 26 publications were included in the systematic review. The PRISMA flow diagram (*Figure 1*) provides an overview of the selection process.

3.2 Study characteristics and quality assessment

There was a wide variety of techniques and sequences of surgery. Different methods were used to study the outcome of one- or two-stage palatoplasty, which are included in *Table 4*. We have classified the outcome variables into three categories: skeletal growth (growth of the cranial base, maxilla, palatal morphology, mandible, jaw relation), speech and fistula rates (*Table 5a and 5b*).

Table 4 shows the characteristics of the included studies and the quality grade for each study. All were retrospective and non-randomized comparisons of one- and two-stage palatoplasty. Quality grading of each study was done for growth characteristics studied, speech and fistula rates. Six studies were longitudinal studies (*Vedung, 1995; Corbo et al., 2005; De Mey et al., 2006; Stein et al., 2007; Liao et al., 2010; Nishio et al., 2010*), while the remaining twenty were cross-sectional in design. Seven concerned comparisons of patient groups from multiple centers (*Ross, 1987; Molsted et al., 1992; Zemann et al., 2007; Zemann et al., 2011; Fudalej et al., 2012; Koželj V et al., 2012; Gundlach et al., 2013*). No study received quality

grade A. The other gradings are shown in Table 4 and results from grade-B studies will be described below.

3.2.1 Cranial base

Of the 26 studies that met the inclusion criteria, seven examined the growth of the cranial base (*Ross, 1987; Rohrich et al., 1996; Corbo et al., 2005; Liao et al., 2010; Yamanishi et al., 2011; Alam et al., 2013; Xu X et al., 2015*). There were no high-quality studies (grade A). Two studies were graded of being of moderate quality (grade B) (*Liao et al., 2010; Yamanishi et al., 2011).* Liao *(Liao et al., 2010*) found that a one-stage repair was associated with a longer adult length of the cranial base than a two-stage repair, while Yamanishi (*Yamanishi et al., 2011*) found no difference between the two treatment approaches.

3.2.2 Maxilla

Twenty-four studies included in this review examined the growth and/or morphology of the maxilla. comparing one- and two-stage repair (*Ross, 1987; Molsted et al., 1992; Rohrich et al., 1996; Silva Filho et al., 2001; Kitagawa T et al., 2004; Corbo et al., 2005; De Mey et al., 2006; Holland et al., 2007; Stein et al., 2007; Zemann et al., 2007; Yamanishi et al., 2009; Liao et al., 2010; Nishio et al., 2010; Yamanishi et al., 2011; Zemann et al., 2011; Bakhri et al., 2012; Fudalej et al., 2012; Koželj et al., 2012; Alam et al., 2013; Gundlach et al., 2013; Fudalej et al., 2015; Mikoya et al., 2015; Xu et al., 2015; Tome et al., 2016*). There were no high-quality studies (grade A). Five studies were graded of being of moderate quality (grade B) (*Yamanishi et al., 2009; Liao et al., 2010; Nishio et al., 2010; Yamanishi et al., 2011; Fudalej et al., 2012*).

Two of these studies compared position and length of the maxilla as well as anterior maxillary height after one- and two-stage palatal repair (Table 5a) (*Liao et al., 2010; Yamanishi et al., 2011*). Yamanishi found no difference in the position of the maxilla in relation to the

cranial base at the age of 4 years after one-stage closure at 12 months versus two-stage closure at 12 and 18 months (*Yamanishi et al., 2011*). Liao evaluated two groups of patients at 20 years of age (*Liao et al., 2010*). In the two-stage group, closure of the hard palate was delayed until about 6 years of age while in the other group the palate was closed completely in a single procedure at 1 year of age. Delayed palatal closure was associated with a significantly larger SNA angle at the age of 20. Both studies reported a significantly larger maxillary length in the two-stage group. Only in one study (*Yamanishi et al., 2011*) was maxillary height found to be larger in the two-stage group. The dental cast analyses (*Yamanishi et al., 2009*) for the same group (*Yamanishi et al., 2011*) revealed that transverse arch dimensions were significantly larger at 4 years of age after two-stage palatal closure. Dental cross bite was evaluated in one of the four grade-B studies and it was found that the prevalence of cross bite at 4 years of age was higher after one-stage than after two-stage palatal repair (*Nishio et al., 2010*).

Some additional outcome variables were assessed in studies graded B for quality (not shown in Table 5a). One study found that palatal morphology was better in the one-stage repair when compared with two-stage repair (*Fudalej et al., 2012*). One study found a significant improvement in arch circumference in the two-stage group (*Yamanishi et al., 2009*).

3.2.3 Mandible

Sixteen studies evaluated the effect of one-stage and two-stage palatoplasty on the growth of the mandible (*Ross, 1987; Molsted et al., 1992; Rohrich et al., 1996; Silva Filho et al., 2001; Corbo et al., 2005; De Mey et al., 2006; Holland et al., 2007; Stein et al., 2007; Zemann et al., 2007; Liao et al., 2010; Yamanishi et al., 2011; Zemann et al., 2011, Alam et al., 2013; Fudalej et al., 2015; Xu et al., 2015; Tome et al., 2016*). There were no high-quality studies (grade A). Table 4 shows that two studies were graded as being of moderate quality (grade B) (*Liao et al.,*

2010; Yamanishi et al., 2011). These studies showed no difference between the two groups for the position of the mandible in relation to the cranial base.

Measured as the cephalometric variable Articulare-Menton (Ar-Me) or Articulare-Gnathion (Ar-Gn), one-stage palate repair had a significant influence on the length of the mandible (Ar-Gn, $p = 0.05$) at the age of 20 years (*Liao et al., 2010*), while the other did not show such an effect (Art-Me and ramus length), but this was evaluated at 4 years of age (*Yamanishi et al., 2011*).

3.2.4 Jaw relation

Fifteen studies compared the jaw relation between the two groups (*Ross, 1987; Rohrich et al., 1996; Silva Filho et al., 2001; Kitagawa et al., 2004; Corbo et al., 2005; De Mey et al., 2006; Holland et al., 2007; Stein et al., 2007; Zemann et al., 2007; Liao et al., 2010; Zemann et al., 2011; Fudalej et al., 2012; Fudalej et al., 2015; Xu et al., 2015; Tome et al., 2016*). There were no high-quality studies (grade A) that looked at sagittal jaw relationship and only two studies qualified as grade B (*Liao et al., 2010; Fudalej et al., 2012*). Both studies showed a better sagittal jaw relationship after two-stage palatal repair.

3.2.5 Speech

Seven studies analyzed speech outcomes (Table 5b) (*Vedung, 1995; Rohrich et al., 1996; De Mey et al., 2006; Holland et al., 2007; Liao et al., 2010; Yamanishi et al., 2011; Funayama et al., 2014*). There were no high-quality studies (grade A) that studied speech and only two studies qualified as grade B (*Holland et al., 2007; Yamanishi et al., 2011*). In a retrospective case series study comparing one-stage with two-stage repair, more articulation errors, more hypernasality, more nasal emissions, less favorable values for phonation and more VPI were found at 15 years of age in the two-stage palate repair group (*Holland et al., 2007*). In contrast,

Yamanishi found no significant difference at 4 years of age for incidence of articulation errors and VPI when comparing one-stage and two-stage repair (*Yamanishi et al., 2011*).

3.2.6 Fistulae

Five studies reported on the incidence of fistulae (Table 5b) (*Vedung, 1995; Rohrich et al., 1996; De Mey et al., 2006; Holland et al., 2007; Liao et al., 2010*). All studies were graded as low quality (grade C).

4. Discussion

This systematic review aimed to investigate if one- or two-stage palatoplasty is more beneficial in terms of craniofacial growth, speech and fistula rates. We applied the quality assessment tool as developed by the Centre for Reviews and Disseminations to judge the quality of the individual studies (*Deeks et al., 1996; Bondemark et al., 2007*). We felt that only reporting the quality criteria of each study included in this systematic review would not be adequate. The system we used translates quality scores for individual studies to levels of evidence for the questions we wanted to answer about growth, speech and fistula rate (*Bondemark et al., 2007; von Böhl et al., 2012*). Various scales have been proposed to grade evidence, but at present there is still no agreed gold standard to be used in systematic reviews (*Sanderson et al., 2007; Boutron and Ravaud, 2012*).

4.1 Maxillofacial growth

The translation of quality assessment scores into levels of evidence shows that there is contradictory scientific support for the effect of one- or two-stage palatal surgery on the cranial base (*Liao et al., 2010; Yamanishi et al., 2011*). However, it seems rather unlikely that palate repair affects the growth of the cranial base because of its distance from the field of surgery. Liao and his associates (*Liao et al. 2010*) indeed doubt the importance of this result and give as a possible explanation for this effect that it could be related to differences in body height of the included patients, which is related to length of the cranial base.

There is inconclusive evidence (evidence level 4) for the effect of one- or two-stage palatoplasty on maxillary growth. Though four studies were given quality grade B, the evidence they presented was contradictory (*Yamanishi et al., 2009; Liao et al., 2010; Nishio et al., 2010; Yamanishi et al., 2011*). Besides different surgical protocols, an important reason for the

contradictory results could be the age at which the final assessment was done. Only one study assessed the final outcome after growth had ceased at the age of 20, while the other three studies reported results at 4 years of age (*Liao et al., 2010*).

This systematic review shows that there is limited scientific support (evidence level 3) that two-stage palatal closure leads to a better sagittal jaw relationship in the two studies that qualified as grade B (*Liao et al., 2010; Fudalej et al., 2012*). Mandibular position in relation to the cranial base is not affected by one- or two-stage palatoplasty — two studies graded B for quality showed that mandibular position was comparable after one- or two-stage palatoplasty (*Liao et al., 2010; Yamanishi et al., 2011*).

The two methods that are most commonly used to evaluate maxillofacial growth are cephalometry and dental cast analysis. Though cephalometric studies are widely used they have inherent methodological errors that lead to variation, depending on the radiographic projection (magnification and distortion), type of landmark and the observer (*Bongaarts et al., 2008; Pittayapat et al., 2015*). Aside from the fact that, in multi-center studies, different X-ray devices are used, anatomical landmarks may also be difficult to identify in patients with CLP. For example, in patients with UCLP, A point, and anterior and posterior nasal spine (ANS and PNS) should be considered with caution due to abnormal anatomy brought about by the cleft, which makes it very difficult to locate these cephalometric points properly, especially in children (*Bongaarts et al., 2008*).

Outcome measures to assess the effect of certain treatment protocols on maxillofacial growth often focus on dental arch relationships. Several indices have been developed for this purpose, like the GOSLON index, the EUROCRAN index, the 5-Year-Olds' index, and the modified Huddart-Bodenham cross bite score (*Altalibi et al., 2013; Jones et al., 2014; Haque et*

al., 2015). These indices are reliable and reproducible. However, 3D analysis of longitudinal series of dentals casts is still a problem as it is difficult to determine a stable area that allows for superimposition of serial cast data in three planes of space, especially in growing children (*Chen et al., 2011*).

4.2 Speech

Combining the quality scores of the studies that evaluated speech with levels of evidence, there is inconclusive scientific support (evidence grade 4) for the application of one-stage or two-stage palatal repair regarding phonation, nasal resonance, hypernasality, nasal emission, and speech intelligibility. For articulation errors and prevalence of VPI, two studies were graded B for quality but they show contradictory results and hence no conclusion can be made (*Holland et al., 2007; Yamanishi et al., 2011*).

The approach for speech analyses depends on several factors: whether measurement is taking place for clinical, audit, or research purposes, the perceptual speech assessment in the cleft palate population under study, and the question being asked. For example, approaches to capture the developing sound system of infants are vastly different from phonetic descriptions of consonant production. Overall judgement of speech quality/intelligibility requires a separate set of parameters (*Sell et al., 2005*). In the studies included in this systematic review we found that all seven studies used some form of perceptual speech rating (*Vedung, 1995; Rohrich et al., 1996; De Mey et al., 2006; Holland et al., 2007; Liao et al., 2010; Yamanishi et al., 2011; Funayama et al., 2014.*). In none of these studies were reliability tests performed. Two studies used nasal endoscopy as an adjuvant test, but here, too, the reliability of the method was not tested (*Liao et al., 2010; Funayama et al., 2014*).

4.3 Fistula rate

All five of the studies that compared fistula rates were graded C for quality and therefore there is inconclusive scientific support (evidence level 4) for fistula rates in one- or two-stage palatoplasty. We found no clear description in any of the studies as to how presence of a fistula was tested. When testing the effect of fistula repair on speech and growth, no reliability tests were performed and assessors were not blinded to the type of treatment.

Besides study drawbacks that were related to our research questions, as outlined above, we also encountered methodological problems in the studies that were assessed for this review. Twenty-six studies were included in this review, but all studies were non-randomized, retrospective studies. There was a wide variety of populations examined, sometimes even within studies (*Ross, 1987; Molsted et al., 1992; Corbo et al., 2005; Zemann et al., 2007; Zemann et al., 2011; Koželj et al., 2012; Gundlach et al., 2013; Fudalej et al., 2015). Only six (Corbo et al., 2005; De Mey et al., 2006; Yaminishi et al., 2011; Zemann et al., 2011; Koželj et al., 2012; Xu et al., 2015*) of the 26 included studies used age-matched controls, while some study groups were not perfectly matched with regard to age (*Vedung, 1995; Fudalej et al., 2012; Fudalej et al., 2015*). Most studies had small sample sizes of less than 30 patients (*Molsted et al., 1992; Rohrich et al., 1996; Kitagawa et al., 2004; Corbo et al., 2005; De Mey et al., 2006; Stein et al., 2007; Zemann et al., 2007; Zemann et al., 2011; Koželj et al., 2012; Funayama et al., 2014; Xu et al., 2015*), while in none of the studies was a power analysis reported, which made these studies at risk of being underpowered. The wide age range at assessment of growth and speech variables (from 4 years to 24.8 years) made it very difficult to compare studies as developmental changes may have played a role in the treatment outcome. Only three studies (*SilvaFilho et al., 2001; Nishio et al., 2010; Xu et al., 2015*) included separate measurements for males and females.

Problems such as non-random sampling, wide variations in surgical procedure (including age at surgery), different assessment methods, and no record or mention of secondary revision procedures, have hindered the use of a traditional meta-analysis further and the possibility of drawing evidence-based conclusions. Suggestions to improve the strength of future studies would involve correction of the above-mentioned flaws. Long-term follow-up of one- or two-stage palatoplasty was not performed in most studies included in this systematic review. The studies that had measured long-term effects were not graded sufficiently well to assess the efficacy of one technique over the other.

5. Conclusions

This systematic review shows inconclusive evidence for the relative effects of one-stage or two-stage palate repair on maxillofacial growth, speech and fistula rates in patients with unilateral cleft lip and palate. Further, well-designed, randomized controlled studies, especially targeting long-term results, are required.

References

Alam MK, Iida J, Sato Y, Kajii TS. Postnatal treatment factors affecting craniofacial morphology of unilateral cleft lip and palate (UCLP) patients in a Japanese population. Br J Oral Maxillofac Surg 51: e205-210, 2013

Altalibi M, Saltaji H, Edwards R, Major PW, Flores-Mir C. Indices to assess malocclusions in patients with cleft lip and palate. Eur J Orthod 35: 772-782, 2013

Bakhri S, Rizell S, Saied S, Lilja J, Mark H. Height of the palatal vault after two different surgical procedures: study of the difference in patients with complete unilateral cleft lip and palate. J Plast Surg Hand Surg 46: 155-158, 2012

Bardach J, Salyer K. Surgical techniques in cleft lip and palate. Chicago: Year Books; 1987.

Bardach J. Two flap palatoplasty; Bardach's technique. Op Tech Plast Reconstr Surg 2: 211-214, 1995

Bondemark L, Holm AK, Hansen K, Axelsson S, Mohlin B, Brattstrom V, Paulin G, Pietila T. Long-term stability of orthodontic treatment and patient satisfaction: a systematic review. Angle Orthod 77: 181-191, 2007

Bongaarts CA, Van 't Hof MA, Prahl-Andersen B, Kuijpers-Jagtman AM. Identification of cephalometric landmarks in unilateral cleft lip and palate patients: are there alternatives for point A, ANS and PNS? Cleft Palate Craniofac J 45: 81-86; 2008.

Boutron I, Ravaud P. Classification systems to improve assessment of risk of bias. Clin Epidemiol 65: 236–238, 2012

Braithwaite, F. Cleft palate repair. In T. Gibson (Ed.), Modern Trends in Plastic Surgery. London: Washington, Butterworths, 1964

Chen G, Chen S, Zhang XY, Jiang RP, Liu Y, Shi FH, Xu TM. Stable region for maxillary dental cast superimposition in adults, studied with the aid of stable mini screws. Orthod Craniofac Res 14: 70-79, 2011

Corbo M, Dujardin T, de Maertelaer V, Malevez C, Glineur R. Dentocraniofacial morphology of 21 patients with unilateral cleft lip and palate: a cephalometric study. Cleft Palate Craniofac J 42: 618-624, 2005

Deeks J, Glanville J, Sheldon T. Undertaking systematic reviews of research on effectiveness, CRD Guidance for those carrying out or commissioning reviews. York: NHS Centre for Reviews and Dissemination; CRD Report Number 4, 1996

De Mey A, Swennen G, Malevez C, George M, Mansbach AL. Long-term follow-up of UCLP at the Reine Fabiola Children's Hospital. B-ENT 2(4): 44-50, 2006

Fudalej P, Katsaros C, Dudkiewicz Z, Offert B, Piwowar W, Kuijpers M, Kuijpers-Jagtman AM. Dental arch relationships following palatoplasty for cleft lip and palate repair. J Dent Res 91: 47-51, 2012

Fudalej PS, Wegrodzka E, Semb G, Hortis-Dzierzbicka MJ. One-stage (Warsaw) and two-stage (Oslo) repair of unilateral cleft lip and palate: Craniofacial outcomes. J Cranio-maxillofac Surg 43: 1224-1231, 2015

Funayama E, Yamamoto Y, Nishizawa N, Mikoya T, Okamoto T, Imai S, Murao N, Furukawa H, Hayashi T, Oyama A. Important points for primary cleft palate repair for speech derived from speech outcome after three different types of palatoplasty. Int J Pediatr Otorhinolaryngol 78: 2127-2131, 2014

Furlow LT Jr. Cleft palate repair by double opposing Z-plasty. Plast Reconstr Surg 78: 724-738, 1986

Gundlach KK, Bardach J, Filippow D, Stahl-de Castrillon F, Lenz JH. Two-stage palatoplasty, is it still a valuable treatment protocol for patients with a cleft of lip, alveolus, and palate? J Craniomaxillofac Surg 41: 62-70, 2013

Haque S, Alam MK, Arshad AI. An overview of indices used to measure treatment effectiveness in patients with cleft lip and palate. Malays J Med Sci 22: 4-11, 2015

Holland S, Gabbay JS, Heller JB, O'Hara C, Hurwitz D, Ford MD, Sauder AS, Bradley JP. Delayed closure of the hard palate leads to speech problems and deleterious maxillary growth. Plast Reconstr Surg 119: 1302-1310, 2007

Jones T, Al-Ghatam R, Atack N, Deacon S, Power R, Albery L, Ireland T, Sandy J. A review of outcome measures used in cleft care. J Orthod 41: 128-140, 2014

Kitagawa T, Kohara H, Sohmura T, Takahashi J, Tachimura T, Wada T, Kogo M. Dentoalveolar growth of patients with complete unilateral cleft lip and palate by early two-stage furlow and push-back method: preliminary results. Cleft Palate Craniofac J 41: 519-525, 2004

Koželj V, Vegnuti M, Drevenšek M, Hortis-Dzierzbicka M, Gonzalez-Landa G, Hanstein S, Klimova I, Kobus K, Kobus-Zaleśna K, Semb G, Shaw B. Palate dimensions in six-year-old children with unilateral cleft lip and palate: a six-center study on dental casts. Cleft Palate Craniofac J 49: 672-682, 2012

Kriens, O. B. An anatomical approach to veloplasty. Plast Reconstr Surg 43: 29-32, 1969

Liao YF, Mars M. Hard palate repair timing and facial growth in cleft lip and palate: a systematic review. Cleft Palate Craniofac J 43: 563-570, 2006

Liao YF, Yang IY, Wang R, Yun C, Huang CS. Two-stage palate repair with delayed hard palate closure is related to favorable maxillary growth in unilateral cleft lip and palate. Plast Reconstr Surg 125: 1503-151, 2010

Lindsay WK, Witzel MA. Cleft palate repair: Von Langenbeck Technique. In: Bardach J, Morris HL (ed), Multidisciplinary management of cleft lip and palate. Philadelphia: W.B. Saunders Company; 303-310, 1990

Markus AF, Smith WP, Delaire J. Primary closure of cleft palate: a functional approach. Br J Oral Maxillofac Surg 31: 71-77, 1993

Mikoya T, Shibukawa T, Susami T, Sato Y, Tengan T, Katashima H, Oyama A, Matsuzawa Y, Ito Y, Funayama E. Dental arch relationship outcomes in one- and two-stage palatoplasty for Japanese patients with complete unilateral cleft lip and palate. Cleft Palate Craniofac J 52: 277-286, 2015

Molsted K, Asher-McDade C, Brattstrom V, Dahl E, Mars M, McWilliam J, Plint DA, Prahl-Andersen B, Semb G, Shaw WC. A six-center international study of treatment outcome in patients with clefts of the lip and palate: Part 2. Craniofacial form and soft tissue profile. Cleft Palate Craniofac J 29: 398-404, 1992

Nishio J, Yamanishi T, Kohara H, Hirano Y, Sako M, Adachi T, Mukai T, Miya S. Early two-stage palatoplasty using modified Furlow's veloplasty. Cleft Palate Craniofac J 47: 73-81, 2010

Nollet PJ, Katsaros C, Van 't Hof MA, Kuijpers-Jagtman AM. Treatment outcome in unilateral cleft lip and palate evaluated with the GOSLON yardstick: a meta-analysis of 1236 patients. Plast Reconstr Surg 116: 1255-1262, 2005

Pittayapat P, Bornstein MM, Imada TSN, Coucke W, Lambrichts I, Jacobs R. Accuracy of linear measurements using three imaging modalities: two lateral cephalograms and one 3D model from CBCT data. Eur J Orthod 37: 202-208, 2015

Rohrich RJ, Rowsell AR, Johns DF, Drury MA, Grieg G, Watson DJ, Godfrey AM, Poole MD. Timing of hard palatal closure: a critical long-term analysis. Plast Reconstr Surg 98: 236-246, 1996

Ross RB: Treatment variables affecting growth in cleft lip and palate. Part 6: technique of palate repair. Cleft palate J 24: 64-70, 1987

Sanderson S, Tatt ID, Higgins JPT. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol 36: 666-676, 2007

Schweckendiek W, Doz P. Primary veloplasty; long-term results without maxillary deformity – a 25-year report. Cleft Palate J 15: 268–274, 1978

Sell D. Issues in perceptual speech analysis in cleft palate and related disorders: a review. Int J Lang Commun Disord 40: 103-121, 2005

Silva Filho OG, Calvano F, Assuncao AG, Cavassan AO. Craniofacial morphology in children with complete unilateral cleft lip and palate: a comparison of two surgical protocols. Angle Orthod 71: 274-284, 2001

Sommerlad BC. A technique for cleft palate repair. Plast Reconstr Surg 112: 1542-1548, 2003

Stein S, Dunsche A, Gellrich NC, Harle F, Jonas I. One- or two-stage palate closure in patients with unilateral cleft lip and palate: comparing cephalometric and occlusal outcomes. Cleft Palate Craniofac J 44: 13-22, 2007

Timbang MR, Gharb BB, Rampazzo A, Papay F, Zins J, Doumit G. A systematic review comparing Furlow double-opposing Z-plasty and straight-line intravelar veloplasty methods of cleft palate repair. Plast Reconstr Surg 134: 1014-1022, 2014

Tome W, Yashiro K, Otsuki K, Kogo M, Yamashiro T. Influence of different palatoplasties on the facial morphology of early mixed dentition stage children with unilateral cleft lip and palate. Cleft Palate Craniofac J 53: e28-33, 2016

Vedung S. Pharyngeal flaps after one- and two-stage repair of the cleft palate: a 25-year review of 520 patients. Cleft Palate Craniofac J 32: 206-216, 1995

Von Böhl M, Ren Y, Fudalej PS, Kuijpers-Jagtman AM. Pulpal reactions to orthodontic force application in humans: a systematic review. J Endod 38: 1463-1469, 2012

Wallace AF. A history of the repair of cleft lip and palate in Britain before World War II. Ann Plast Surg 19: 266-275, 1987

Xu X, Kwon HJ, Shi B, Zheng Q, Yin H, Li C. Influence of different palate repair protocols on facial growth in unilateral complete cleft lip and palate. J Craniomaxillofac Surg 43: 43-47, 2015

Yamanishi T, Nishio J, Kohara H, Hirano Y, Sako M, Yamanishi Y, Adachi T, Miya S, Mukai T. Effect on maxillary arch development of early 2-stage palatoplasty by modified Furlow technique and conventional 1-stage palatoplasty in children with complete unilateral cleft lip and palate. J Oral Maxillofac Surg 67: 2210-2216, 2009

Yamanishi T, Nishio J, Sako M, Kohara H, Hirano Y, Yamanishi Y, Adachi T, Miya S, Mukai T. Early two-stage double opposing Z-plasty or one-stage push-back palatoplasty: comparisons in maxillary development and speech outcome at 4 years of age. Ann Plast Surg 66: 148-153, 2011

Yang IY, Liao YF. The effect of 1-stage versus 2-stage palate repair on facial growth in patients with cleft lip and palate: a review. Int J Oral Maxillofac Surg 39: 945-950, 2010

Zemann W, Mossböck R, Kärcher H, Koželj V. Sagittal growth of the facial skeleton of 6-year-old children with a complete unilateral cleft of lip, alveolus and palate treated with two different protocols. J Craniomaxillofac Surg 35: 343-349, 2007

Zemann W, Kärcher H, Drevenšek M, Koželj V. Sagittal maxillary growth in children with unilateral cleft of the lip, alveolus and palate at the age of 10 years: an intercentre comparison. J Craniomaxillofac Surg 39: 469-474, 2011

FIGURE LEGENDS

Figure 1. PRISMA flow diagram of the study

TABLE LEGENDS

Table 1. Databases searched and search strings used

Table 2. Grades for methodological quality

Table 3. Level of evidence based on quality assessment of the included studies

Table 4. Study characteristics with quality grading

Table 5a. Results for cranial base, maxilla and mandible

Table 5b. Results for jaw relationship, speech and fistula rates

Table 1. Databases searched and search strings used

Search engine/ database	Search terms
PubMED	("surgery"[Subheading] OR "palate/surgery"[Mesh] OR palatoplasty) AND (unilateral[tiab] OR bilateral[tiab]) AND ("cleft palate"[MeSH Terms] OR ("cleft"[tiab] AND "palate"[tiab]) OR "cleft lip"[MeSH Terms] OR ("cleft"[tiab] AND "lip"[tiab]))
Cochrane Library	(cleft lip:ti,ab,kw or cleft palate:ti,ab,kw) and (palatoplasty:ti,ab,kw or palat* surgery:ti,ab,kw or palate repair:ti,ab,kw)
EMBASE	(cleft palate/ or cleft palate.mp. or cleft lip/ or cleft lip.mp.) and (palatoplasty/ or palatoplasty.mp.)
Scopus	(TITLE-ABS-KEY (cleft lip) AND TITLE-ABS-KEY (cleft palate) AND TITLE-ABS-KEY (unilateral) OR TITLE-ABS-KEY (bilateral) AND TITLE-ABS-KEY(palatoplasty) OR TITLE-ABS-KEY (palat* surgery) OR TITLE-ABS-KEY(palat* repair) AND TITLE-ABS-KEY (growth) OR TITLE-ABS-KEY (speech) OR TITLE-ABS-KEY (dental arch) OR TITLE-ABS-KEY (fistula))
CINAHL	(AB cleft lip OR AB cleft palate) AND (AB unilateral OR AB bilateral) AND (AB palatoplasty OR AB palat* surgery OR AB palat* repair)

Table 2. Grades for methodological quality

(Deeks J *et al*.,1996; Bondemark L *et al*., 2007)

Quality grade	Methodological criteria
Grade A *high quality*	• Randomized, controlled trial or prospective study with a well-defined control group • Defined diagnosis and end points • Diagnostic reliability tests and reproducibility tests described • Blinded outcome measurements (All criteria should be met; if not, grade B)
Grade B *moderate quality*	• Cohort study or retrospective case series with a defined control or reference group • Defined diagnosis and end points • Diagnostic reliability tests and reproducibility tests described (All criteria should be met; if not, grade C)
Grade C *low quality*	One or more of the following conditions are found: large attrition of the sample; unclear diagnosis and end points; poorly defined patient material

Table 3. Level of evidence based on quality assessment of the included studies

(Bondemark L *et al*., 2007; von Böhl M *et al*., 2012)

Level of evidence	Description of evidence level
Strong scientific support *Evidence grade 1*	• Conclusion based on at least two studies with level A evidence • Studies with opposite conclusions may lower the evidence grade
Moderately strong support *Evidence grade 2*	• Conclusion based on one study with strong evidence (A) and at least two with moderately strong evidence (B) • Studies with opposite conclusions may lower the evidence grade
Limited scientific support *Evidence grade 3*	• Conclusion based on at least two studies with moderately strong evidence (B) • If studies contradicting the conclusion exist, the scientific basis is judged as insufficient or contradictory
Inconclusive scientific support *Evidence grade 4*	• If studies fulfilling the evidence criteria are lacking, the scientific basis for conclusion is considered insufficient

Table 4. Study characteristics with quality grading

Author, year of publication	Design	Stage	Sample size	Palatoplasty Technique		Age		Quality grade	Investigative Analysis
Ross, 1987	Cross-sect Multicenter	one	247	Toronto pushback procedure/other pushback/von Langenbeck		<20M		C (growth)	Latceph
		two	133	Not specified	Not specified	Not specified	11-108M		
Molsted et al., 1992	Cross-sect Multicenter	two	23	vonLangenbeck, PerkoWardill Kriens	Not specified	9-15M	108M (9yrs or 6yrs)	C (growth)	Lat+APceph Dental casts Photograph
		two	26	Wardill	Vomeroplasty	22-24M	2M		
		one	23	Not specified/varied		12M			
		one	26	Not specified/varied		12M			
		two	30	Modified von Langenbeck	Vomeroplasty	18-20M	3M		
		one	23	Veau-Wardill-Kilner		12M			
Vedung S, 1995	Longitud	one	138	Veau-Wardill-Kilner		24M		C (speech) C (fistula)	Speech evaluation
		two	72	Straight line closure for muscle, Z plasty on oral layer		6M/14M/18M	5.2yrs/3yrs/ 2yrs		
Rohrich et al., 1996	Cross-sect	one	15	Modified Veau-Wardill-Kilner		10.8M		C (growth) C (speech) C (fistula)	Speech evaluation Lat +AP ceph Dental casts Photograph Palatal exam ENT evaluation
		two	16	Modified Veau	Vomeroplasty	11.4M	49M		
Silva Filho et al., 2001	Cross-sect	one	53	Not specified		12-44M		C (growth)	Latceph
		two	22	Malek and Psaume	Malek and Psaume	3-11M	10-28M		
		two	10	Widmaier	Not specified	20M	6Y		
Kitagawa et al., 2004	Cross-sect	one	19	Pushback		15.3M		C (growth)	Dental casts Bite registration
		two	15	Furlow	Veau/Bridge flap	15.6M	23M		
Corbo M et al., 2005	Longitud	one	11	Malek		3M		C (growth)	Latceph
		two	10	Not specified	Not specified	3M	6M		
DeMey A et al., 2006	Longitud	one	18	All in one closure		3M		C (growth) C (speech) C (fistula)	Latceph Speech evaluation ENT evaluation
		two	26	Malek	Malek	3M	6M		
Holland S et al., 2007	Cross-sect	one	41	Modified von Langenbeck	Intravelarveloplasty	12M		C (growth) B (speech) C (fistula)	Latceph Speech evaluation
		two	41	Levator muscle approximation	Minimal dissection	12M	7Y		
Stein S et al., 2007	Longitud	one	22	Intravelarveloplasty/Axhausen/von Langenbeck/Modified bridge flap		18-27M		C (growth)	Latceph OPG Dental casts
		two	21	Intravelarveloplasty	von Langenbeck	17-29M	46-126M		
Zemann W et al., 2007**	Cross-sect Multicenter	one	20	Veau		12M		C (growth)	Latceph
		two	20	Intravelarveloplasty	Not specified	12M	30M		
Yamanishi T et al.,2009*	Cross-sect	one	42	Pushback		12M		B (growth)	Dental casts
		two	30	Modified Furlow	Veau	12M	18M		
Liao YF et al., 2010	Longitud	one	31	Two flap		12M		B (growth) C (speech)	Latceph Speech
		two	31	Widmaier	Vomerinemucoperios	18M	72M		

				teal flap					C (fistula)	evaluation
Nishio J et al., 2010*	Longitud	one	42	Pushback		Not specified			B (growth)	Dental casts
		two	30	Modified Furlow	Two/Vomerine flaps	12M		18M		
Yamanishi T et al., 2011*	Cross-sect	one	42	Wardill -Killner		12M			B (growth)	Latceph
		two	30	Furlow	Two/Vomerine flaps	12M		18M	B (Speech)	Speech evaluation
Zemann W et al., 2011**	Cross-sect Multicenter	one	22	Veau		12M			C (growth)	Latceph
		two	32	Intravelarveloplasty	Veau	12M		30M		
Fudalej P et al., 2012	Cross-sect Multicenter	one	61	All in one		9.2M			B (growth)	Dental casts
		two	97	Not specified	Not specified	12-14M		9-11Yrs		
Bakhri S et al., 2012	Cross-sect	one	60	Pushback		16M			C (growth)	Dental casts
		two	116	Not specified	Not specified	6-8M		8-10Yrs		
Kozelj V et al., 2012 EUROCRAN	Cross-sect Multicenter	one	10	Modified von Langenbeck		20-30M			C (growth)	Dental casts Photographs
		one	28	Veau-Wardill-Kilner		7-13M				
		one	20	Veau-Wardill-Kilner		24M				
		one	31	Vomerplasty and soft palate repair		6-12M				
		two	23	Intravelarveloplasty	Wardill-Kilner	12M		2.5Yrs		
		two	17	Not specified	Not specified	12M		3-7Yrs		
Gundlach KK et al., 2013	Cross-sectl Multicenter	one	35	Two flap Veau		12-18M			C (growth)	Dental casts
		two	24	Intravelarveloplasty	Von Langenbeck	15-18M		4-6Yrs		
		two	26	Intravelarveloplasty	Von Langenbeck	3Yrs		5Yrs		
Alam MK et al., 2013	Cross-sect	one	44	Pushback		20M			C (growth)	Latceph
		one	83	Pushback with buccal flap		18M				
		two	13	Furlow/Perko	Not specified	20M		56M		
Funayama E et al., 2014	Cross-sect	one	10	Modified Furlow and intravelarveloplasty		18M			C (Speech)	Speech evaluation
		one	17	Pushback palatoplasty		18M				
		two	11	Modified Furlow	Not specified	18M		5-7Yrs		
Xu X et al.,2015	Cross-sect	one	18	Sommerlad		18-30M			C (growth)	Latceph
		two	22	Sommerlad	Hard palate and lip	18-30M		6-12M		
Mikoya T et al., 2015	Cross-sect	one	37	Pushback palatoplasty- WardillKilner		18M			C (growth)	Dental casts
		two	31	Widmaier-Perko/Furlow	Vomerinemucoperios teal flap	18M		5-7Y		
Fudalej P et al., 2015	Cross-sect	one	61	Extended Vomer flap		9.2M			C (growth)	Latceph
		two	61	Modified von Langenbeck	Vomer flap	17.2M		3.3M		
Tome W et al., 2016	Cross sect	one	38	Push back palatoplasty – Wardill-Kilner		12-18M			C (growth)	Latceph
		two	33	Modified Furlow	Not specified	12M		18M		

Legend: M: months, Y: years, Lat: lateral, AP: antero-posterior, Front: frontal, Ceph: cephalogram

- *Same patient pool at the Osaka Medical Center and Research Institute for Maternal and Child health.
- ** Same patient pool at the Medical University Graz, Austria

Table 5a. Results for cranial base, maxilla and mandible

Author, year of publication	Age at assessment		Cranial base	Maxilla						Mandible			Jaw
	One stage	Two stage	length	Position	Length	Height anterior/posterior	Width	Crossbite	Incisor inclination	Position	Length	Ramus	Relation
Ross, 1987	15.3Y	15.4Y	1S^2S (p = 0.008)	1S=2S	1S^2S (p = 0.02)	2S^1S (p = 0.05)/ 2S^1S (p = 0.001)			2S>1S (p = 0.05)	1S=2S	1S=2S	1S=2S	1S^2S (NS)
Molsted et al., 1992	8-10Y	8-10Y		1S=2S	1S=2S	1S=2S/ 2S(E)1S(F)>1S(D) ($p \leq 0.05$)			1S(D)< 2S(A,E) ($p \leq 0.05$)		1S=2S		
Rohrich et al., 1996	17.0Y	18.2Y	1S=2S	1S=2S	1S=2S		1S=2S				1S=2S		1S=2S
Silva Filho et al., 2001	4-7Y	4-7Y		1S=2S		1S=2S				1S=2S	1S=2S	1S=2S	1S=2S
Kitagawa et al., 2004	3Y	3Y			2S>1S (p < 0.01)		2S>1S (p < 0.05)						1S>2S (NS)
Corbo et al., 2005	7,12Y	7,12Y	1S=2S	1S=2S	1S=2S	1S=2S/ 1S=2S				1S=2S	1S=2S	1S=2S	1S=2S
DeMey et al., 2006	18,36M, 6,10Y	18,36M, 6,10Y		1S=2S	1S=2S					1S=2S			1S>2S (NS)
Holland et al., 2007	15-20Y	15-20Y		2S>1S (p < 0.05)						1S=2S			1S^2S (p = 0.05)
Stein et al., 2007	6,10, 15,18Y	6,10, 15,18Y		1S=2S			2S>1S (p < 0.01)	1S=2S		1S=2S			1S=2S
Zemann et al., 2007	6.5Y	6.5Y		1S=2S						1S=2S			1S=2S
Yamanishi et al., 2009	3,12M,4Y	3,12,18M, 2,3,4Y					2S>1S (p < 0.017)						
Liao et al., 2010	20Y	20Y	1S>2S (p = 0.05)	2S>1S (p < 0.05)	2S>1S (p < 0.05)	1S=2S				1S=2S	1S>2S (p = 0.05)		2S>1S (p = 0.01)
Nishio et al., 2010	4Y	4Y						1S>2S (p < 0.05)					
Yamanishi et al., 2011	4Y	4Y	1S=2S	1S=2S	2S>1S (p = 0.003)	2S>1S (p = 0.0003)				1S=2S	1S=2S	1S=2S	
Zemann et al., 2011	9-12Y	8-12Y		1S=2S						1S=2S			1S=2S
Fudalej et al., 2012	11.2Y	8.7Y											2S^1S (p < 0.000)
Kozelj et al., 2012	5-7Y	5-7Y			1S(1,3)=2S(6), 1S(2,4)2S(5)>2S(6) (p < 0.001)		1S=2S						
Gundlach et al., 2013	7-9Y, 15-17Y	7-9Y, 15-17Y			2S>1S ($p \leq 0.05$)		2S>1S ($p \leq 0.05$)	1S>2S ($p \leq 0.05$)					
Alam et al., 2013	7Y	7Y	1S=2S	2S>1S (NS)	1S=2S				2S>1S (NS)	1S=2S			

Xu et al., 2015	5Y	5Y	1S=2S	1S=2S	1S=2S	1S=2S					1S=2S	1S=2S	1S=2S	1S=2S
Mikoya et al., 2015	5.1Y	5.2Y					2S>1S (NS)	2S>1S (p < 0.05)	2S^1S (NS)					
Fudalej et al., 2015	10.9Y	10.9Y		2S>1S (p < 0.001)	1S>2S (p < 001)				1S>2S (p < 0.05)		1S=2S			2S>1S (p < 0.001)
Tome et al., 2015	7.1Y	7.2Y		1S=2S	1S=2S				2S>1S (p = 0.041)		1S=2S		2S>1S (p = 0.035)	1S=2S

Legend: Y: years, M: months, 1S: one stage, 2S: two stage, =: No difference, >: greater than, ^: better than, (NS): not statistically significant, (p value): statistically significant, (x): study number in multi-center study

Table 5b. Results for jaw relationship, speech and fistula rates

Author, year of publication	Age at assessment		Speech								Fistula rate
	One stage	Two stage	Articulation errors	Phonation	Nasal resonance	Hyper nasality	Nasal emission	Speech intelligibility	VPI	VPI surgery	
Vedung S, 1995	24.8Y	12.7Y								1S^2S (NS)	2S^1S (p = 0.05)
Rohrich et al., 1996	17.0Y	18.2Y	2S>1S (NS)	1S=2S	1S^2S (p < 0.001)	2S>1S (p < 0.01)		1S^2S (p < 0.02)			2S>1S (p < 0.05)
DeMey et al., 2006	18,36M, 6,10Y	18,36M, 6,10Y	1S=2S					1S=2S (NS)		2S>1S (NS)	2S>1S (NS)
Holland et al., 2007	15-20Y	15-20Y	2S>1S (p < 0.05)	2S>1S (p < 0.05)		2S>1S (p < 0.05)	2S>1S (p < 0.05)		2S>1S (p < 0.05)		2S>1S (p < 0.05)
Liao et al., 2010	20Y	20Y							1S^2S (p < 0.001)	2S>1S (p = 0.001)	2S>1S (p = 0.0001)
Yamanishi et al., 2011	4Y	4Y	1S=2S						1S=2S		
Funayama et al., 2014	4,8Y	4,8Y	2S>1S (NS)			2S>1S (p < 0.01)	2S>1S (p < 0.01)		2S>1S (NS)		

Legend: Y: years, M: months, 1S: one stage, 2S: two stage, =: no difference, >: greater than, ^: better than, (NS): not statistically significant, (p value): statistically significant, VPI: velopharyngeal incompetence

Figure 1. PRISMA flow diagram of the study