This item is the archived peer-reviewed author-version of:

Spontaneous bone regeneration after closure of the hard palate cleft : a literature review

Reference:

Scheuermann Maria, Vanreusel Inne, Van de Castele Elke, Nadjmi Nasser.- Spontaneous bone regeneration after closure of the hard palate cleft : a literature review
Journal of oral and maxillofacial surgery - ISSN 0278-2391 - Philadelphia, W b saunders co-elsevier inc, 77:5(2019), 1074.e1
Full text (Publisher's DOI): <https://doi.org/10.1016/J.JOMS.2018.12.018>
To cite this reference: <https://hdl.handle.net/10067/1603740151162165141>

Accepted Manuscript

Spontaneous bone regeneration after closure of the hard palate cleft: *A literature review*

Scheuermann Maria, Vanreusel Inne, Elke Van de Castele, Nadjmi Nasser

PII: S0278-2391(18)31388-0

DOI: <https://doi.org/10.1016/j.joms.2018.12.018>

Reference: YJOMS 58568

To appear in: *Journal of Oral and Maxillofacial Surgery*

Received Date: 7 August 2018

Revised Date: 30 November 2018

Accepted Date: 20 December 2018

Please cite this article as: Maria S, Inne V, Van de Castele E, Nasser N, Spontaneous bone regeneration after closure of the hard palate cleft: *A literature review*, *Journal of Oral and Maxillofacial Surgery* (2019), doi: <https://doi.org/10.1016/j.joms.2018.12.018>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Title: Spontaneous bone regeneration after closure of the hard palate

cleft: *A literature review*

Scheuermann Maria ^{1*}, Vanreusel Inne ^{1*}, Van de Castelele Elke ^{1,2,4}, Nadjmi Nasser ^{1,3,4}

¹ Faculty of Medicine & Health Sciences, University of Antwerp, Campus Drie Eiken, Universiteitsplein 1, 2610 Antwerp, Belgium

² All for Research vzw, Harmoniestraat 68, 2018 Antwerp, Belgium

³ Department of Maxillofacial Surgery, ZMACK, AZ MONICA Antwerp, Harmoniestraat 48, 2018 Antwerp, Belgium

⁴ Department of Cranio-Maxillofacial Surgery, Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Belgium

* Authors with equal contribution

Scheuermann Maria – Medical master student

Vanreusel Inne - Medical master student

Van de Castelele Elke – MSc PhD – Postdoctoral researcher

Nadjmi Nasser - MD DDS PhD – Professor

Corresponding author:

Nasser Nadjmi MD, DDS, PhD, EFOMFS – Professor and coordinating program director for OMFS at the University of Antwerp (UA), Belgium and Director of the team for Cleft & Craniofacial anomalies
Antwerp, Belgium – nasser@nadjmi.com

Title: Spontaneous bone regeneration after closure of the hard palate

cleft: *A literature review*

Scheuermann Maria ^{1*}, Vanreusel Inne ^{1*}, Van de Castelele Elke ^{1,2,4}, Nadjmi Nasser ^{1,3,4}

¹ Faculty of Medicine & Health Sciences, University of Antwerp, Campus Drie Eiken, Universiteitsplein 1, 2610 Antwerp, Belgium

² All for Research vzw, Harmoniestraat 68, 2018 Antwerp, Belgium

³ Department of Maxillofacial Surgery, ZMACK, AZ MONICA Antwerp, Harmoniestraat 48, 2018 Antwerp, Belgium

⁴ Department of Cranio-Maxillofacial Surgery, Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Belgium

* Authors with equal contribution

Scheuermann Maria – Medical master student

Vanreusel Inne - Medical master student

Van de Castelele Elke – MSc PhD – Postdoctoral researcher

Nadjmi Nasser - MD DDS PhD – Professor

Corresponding author:

Nasser Nadjmi MD, DDS, PhD, EFOMFS – Professor and coordinating program director for OMFS at the University of Antwerp (UA), Belgium and Director of the team for Cleft & Craniofacial anomalies
Antwerp, Belgium – nasser@nadjmi.com

Abstract

Background. There is a wide range of surgical techniques for the treatment of palatal clefts. Some of these surgical procedures result in postoperative osteogenesis at the palatal fissure. The aim of this review was to discuss the current approach of cleft palate surgery leading to spontaneous bone regeneration and to compare these different procedures. Moreover, the causes of bone regeneration, effects on maxillary growth and factors affecting bone regeneration on the hard palate are discussed.

Methods. The selected articles were found on Medline and Web of Science. The keywords for the search were “cleft palate”, “bone regeneration”, “palatoplasty”, “reconstructive surgical procedures” and “cleft palate/surgery”. Studies that examined the effect of primary palatoplasty on spontaneous bone regeneration in the hard palate in children were included in this review. Four articles were analyzed in the qualitative synthesis.

Results. Due to differences in patient characteristics and evaluation methods, it has been difficult to compare different surgical procedures. The use of a mucoperiosteal flap in combination with adequate closure of the mucosa is needed to obtain bone formation. The area with the largest amount of regenerated bone was located in the middle of the hard palate. In literature it was found that complete closure is considered unfavorable because of the negative effects on maxillary growth, but more studies are needed to confirm this. Of the factors that have been studied, only age turned out to be borderline significant.

Conclusion. Only a few studies with small sample size have been published on bone regeneration in the hard palate. More research is needed to validate these findings.

KEYWORDS

Bone regeneration, cleft palate, cleft palate surgery, palatoplasty, reconstructive surgical procedures

INTRODUCTION

A wide range of surgical techniques have been described for the treatment of palatal clefts (1, 2). These techniques mostly differ in terms of patient age at operation and in the amount of interventions required to obtain closure of the soft and hard palate, e.g. one or two separate interventions. Many variations on this surgical procedure do exist; however, most surgeons use mucoperiosteal flaps to obtain soft-tissue closure. It has been established previously that palatoplasty can cause spontaneous bone regeneration in the hard palate. As Saijo et al. (3) reported, a number of researchers have already proven that bone regeneration occurs in the alveolar area after gingivoperiosteoplasty in palatal cleft patients. In contrast, only a few researchers observed that the bone defect on the hard palate became narrower or disappeared spontaneously after palatoplasty.

The objective of this systematic review is to gain more insight into the phenomenon of spontaneous bone regeneration and to determine if there is a difference in bone regeneration for different surgical palatoplasty protocols. Also, the effects of spontaneous bone regeneration on the maxillary growth or development were investigated. In addition, factors that can affect the bone regeneration were analyzed.

By searching for causes, benefits and disadvantages of palatal bone regeneration, it was examined if bone regeneration is something the maxillofacial surgeons have to achieve or rather avoid. In addition, if it turns out to be positive, is there a protocol to attain this?

MATERIALS AND METHODS

The focus of this literature review was bone regeneration in the hard palate in cleft palate patients who underwent primary palatoplasty. Patients with unilateral and bilateral palatal clefts, with or without alveolar cleft or cleft lip, were included. Adults were excluded since reconstructive surgery mostly takes place during early childhood. Different surgical techniques were compared, depending on the provided information. As an outcome of palatoplasty the focus was put on spontaneous bone regeneration in the hard palate. For this systematic review no ethical approval was required.

Design

This review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (4).

Search strategy

The search included the following keywords (see Table 1): "Cleft Palate", "Bone Regeneration", "Palatoplasty", "Cleft Palate Surgery" and "Reconstructive Surgical Procedures". Guidelines, systematic reviews and articles were taken from the National Guideline Clearinghouse, SUMSearch 2, the Cochrane Database and Web of Science. An overview is given in table 1.

Article selection

A flowchart depicting the search strategy is shown in Figure 1. Screening of the records was primary done by the two authors, independent of each other, by using filters and secondary by title and abstract. Therefore, the exclusion criteria listed in Table 2 were used, leading to five articles for eligibility assessment.

Data Extraction

Of the remaining articles the full-text was carefully analyzed and was scored on validity, importance and usefulness with checklists as quality assessment tools (<https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools>). One article was excluded because of the presence of selection and measurement bias. Finally, four studies were included in the qualitative synthesis.

RESULTS

Surgical procedures applied

Each author describes his unique pre-surgical, surgical and follow-up protocol. The characteristics of the patient groups are listed in Table 3.

- Choi et al. (5) investigated the combination of a cheiloplasty with Millard's rotation and advancement flap (at an average age of 4.03 months) with Furlow's palatoplasty for the closure of the soft palate and a two-layer closure with an oral and nasal mucoperiosteal flap for the repair of the hard palate (at an average age of 14.32 months). Gingivoperiosteoplasty was performed simultaneously with the palatoplasty.
- Saijo et al. (3) studied push-back palatoplasty (at an average age of 16 months).
- In the study of Yin et al. (6) all patients underwent von Langenbeck's procedure (at an average age of 6.1 years).

- Pryds et al. (7) examined patients whose lip had been closed by a Tennison procedure together with a hard palate repair by a palato-vomer plasty according to Veau at 2 months of age using palatal and vomerine flaps. The remainder of the palatal defect was closed at 22-24 months by a Wardill-Kilner operation with Wardill flaps.

Bone regeneration

Choi et al. (5) reported that bone regeneration could be observed on CT imaging in all patients. The palatal defect was almost completely closed in two patients. In the majority of patients (23 of 30) the largest amount of regenerated bone was located in the anterior half of the hard palate. In eight of these 23 patients, the relative location of the largest bone regeneration was situated in the most posterior section of the anterior half, thus in the middle, of the hard palate. The location where the widest remaining bony cleft could be observed was rarely located in the middle 1/3rd of the palate. There was a significant negative correlation between these two evaluation items. When studying at which location there still is a hard-palatal osseous defect, they observed that the remnant bony cleft is rarely located in the middle 1/3rd but rather at the posterior nasal spine. The same conclusion could be made when they evaluated the locations at which bone regeneration could not be detected: rarely located in the middle 1/3rd and mostly situated at the posterior nasal spine. With these correlations in mind they were able to state that the observed bone regeneration contributed to the narrowing and closure of the clefts after palatoplasty.

In the study of Saijo et al. (3) none of the patients had a complete osseous closure at the hard palate, but bony union could be seen in five patients. This bony union occurred in the posterior region of the hard palate but could not be observed in the anterior half. The mean width measured on CT at the first molar (3.96 mm) was significantly less than the mean widths at the first premolar (5.7 mm) and at the posterior maxillary region (6.63 mm). Therefore, Saijo et al. (3) stated that bone regeneration might primarily take place at the first molar. This could be due to the fact that tension is less likely to be applied to the oral and nasal mucosa than to the border between the hard and soft palates. Another observation from the authors was that the margin of the fissure was irregularly shaped in nearly all patients and that the height of the fissure differed in some. Regeneration of bone from the periosteum may therefore accompany regeneration from the margin of the fissure. (3).

After von Langenbeck's procedure in the study of Yin et al., regenerated bone was found in 37 of 52 patients (71%) analyzing coronal CT data (6). The location with the highest percentage of bone formation was the area between the premolar and the first half of the molar. Almost no bone regeneration could be observed in the region of the central incisor to the canine area nor in the region of the third molar. The authors refer to Freng (8) to explain why there was less regenerating bone in the posterior area because in his choanal atresia therapy process he also came to the conclusion that the posterior area of the hard palate has less ability to regenerate bone.

As per Prydso et al.'s (7) examination of biopsies at the time of the Wardill-Kilner operation, the cleft in the hard palate had closed with morphologically normal bone. A fusion had been developed between the regenerated bone and the nasal septum without sutural connection. The article did not mention at which locations the bone formation occurred and where not.

Etiology of bone regeneration

In all four studied protocols mucoperiosteal flaps have been used. Yet in 1974 Prydso et al. (7) described that morphologically normal bone is formed if mucoperiosteal flaps from the hard palate and vomer are placed in contact with each other. Yin et al. (6) were the first to suggest that the osteoblasts in this mucoperiosteum play an important role in the bone regeneration at the hard palate. Many studies have examined bone regeneration in the alveolar cleft area after gingivoperiosteoplasty (for this Yin et al. (6) and Saijo et al. (3) refer to Hellquist et al. (9), Takahashi et al. (10), Skoog et al. (11) and Meazinni et al. (12)), but until Yin's writing no explanation had been suggested for the same phenomenon in the hard palate. Yin et al. (6) explained this phenomenon in the palatal gap after palatoplasty by means of the same mechanism of endoperiosteal bone formation. After palatoplasty, the bone defect in the hard palate is sandwiched between a layer of nasal mucosa and a layer of oral mucosa, brought by these flaps so that there only remains a narrow space between the layers of the flaps. Blood clots fill up that space and trigger the osteoblasts which in their turn start to form bone and replace this blood clot. Because of this finding it is important to insert the sutures securely to ensure formation of blood clot without infection (3, 6). Such an endoperiosteal bone formation can only take place when there is an adequate bone defect. According to the theory of critical bone self-reconstruction, wherefore Yin refers to Schmitz (13), it would be impossible for bone to regenerate and repair the defect when the bone defect is too large, e.g. when the defect reaches the critical bone

defect size. Choi et al. (5) and Saijo et al. (3) also refer to Yin et al. (6) to give the same explanation for this bone regeneration.

Effect on the maxillary growth

Most of the information could be extracted from Pryds et al. (7). They observed that as bone regenerated, a fusion between the new bone and the nasal septum formed without developing a suture. As a consequence, the suture is now located lateral to the septum instead of in the middle of the hard palate. They mentioned that according to Björk (14) sutural growth is important for the normal development of the upper face. On biopsies they saw that this suture was extremely active, the edges were covered with tall and cuboidal osteoblasts and a large amount of chondroitine-4-or-6-sulphate could be seen (7). Nonetheless, this suture was not able to ensure normal and symmetrical transverse maxillary development. With this suture being located lateral to the septum at the non-cleft side, the segment of the hard palate at the cleft side is 'locked' to the nasal septum. This will inhibit the compensatory transverse maxillary growth, which may result in a significant reduction of the maxillary base width and the higher frequency of crossbites at the cleft side reported by Dahl (15), who studied the same operational technique as Pryds et al. (7). The bone at both sides of the palate contributes to the vertical maxillary growth. As a conclusion Pryds et al. (7) assumed that it does not make a difference if the hard palate is closed by bone grafting or by using mucoperiosteal flaps because they both result in a reduction of total maxillary width and an increased frequency of crossbites on the cleft side. They recommended to avoid osseous closure of the hard palate until the sutural growth of the upper face has terminated, e.g. when the distal epiphysis of the radius has been closed. Nevertheless, we know from Saijo et al. (3) that the suitable age for operation is much earlier, referring to Berkowitz et al. (16) who suggested that cleft palate closure preferentially has to be performed between 18 and 24 months. Saijo et al. (3) did not evaluate the future maxillary growth but they did mention that complete bony union is considered unlikely because of its negative effects on the maxillary development. Their article ends remarking that further studies are needed to find out if bony union is something that has to be achieved. The same remark has been made by Choi et al. (5) who only mentioned the detrimentally affected maxillary growth because of the contracting forces generated by the midline scar band after palatoplasty.

Factors affecting bone regeneration

Several factors which could affect bone formation were also studied in the articles.

- Sex did not turn out to be a significant factor (Choi et al. (5) and Yin et al. (6)).
- Yin et al. (6) were not able to find a significant effect of cleft type.
- The period between the palatoplasty and the CT imaging has been studied by Choi et al. (5) and had a broad range: 60-166 months. No significant differences have been observed.
- In the study of Saijo et al. (3) the maximal cleft width at the time of operation has been measured in eight of 29 patients. They stated that this did not correlate with the width at the first molar neither with the degree of osteogenesis after palatoplasty.

With respect to the age at palatoplasty it is difficult to draw conclusions. Yin et al. (6) were the only authors who studied this variable. According to their statistical analysis using a chi-square test, this is borderline significant. Their article suggests that the younger the age at which the palatoplasty has been performed, the less bone regeneration occurs. It is generally accepted that the periosteum carries great osteogenic capacities at the age of one to three years, but they assume that the low rate of bone formation in this patient group is due to the shape of the palatal arch. In young children the palate is flat. As a consequence, there will be no adequate space between the nasal and oral mucoperiosteal flap, discouraging osteogenesis. The height of the palatal arch gradually increases as the maxillary bone develops in such a way that there will form a gap between the flaps as the patients become older. They do emphasize that no conclusion could be drawn because of the small sample size of their study. The patients in the article of Choi et al. (5) all underwent palatoplasty at less than three years of age and bone regeneration could be observed in all of them. They did mention that this is in contrast with the results of Yin et al. (6) but explained that this difference could be due to the applied surgical technique, ability of the surgeon and other factors.

DISCUSSION

Postoperative osteogenesis at the palatal fissure after hard palate closure has been described in several papers. The etiology of this bone regeneration has been discussed by Choi et al. (5) and Saijo et al. (3), both referring to the article written by Yin et al. (6) for the explanation of bone regeneration.

One can conclude that complete bony union is not favorable. Pryds et al. (7) documented that this was even leading to a higher appearance of crossbites. Saijo et al. (3) also mentioned that complete union is considered unlikely because of the negative effects on the maxillary growth. A similar remark has been made by Choi et al. (5).

The reader should bear in mind that the characteristics of the patient groups, listed in Table 3, are different in all four studies. Furthermore, different evaluation items are used. The patient characteristics in the studies of Choi et al. (5) and Saijo et al. (3) are nearly the same. The main difference is that the coronal CT data are obtained at a slightly different age. Nevertheless, Choi et al. (5) stated that the time window between operation and measurement has no significant difference. Because of these comparable patient groups, it is interesting that both authors formulate similar conclusions about the locations at which the largest bone regeneration and the widest remaining cleft could be observed, respectively the middle 1/3rd of the hard palate and at the posterior nasal spine. None of the articles gives a proper explanation for these findings.

All four different procedures resulted in bone regeneration at the cleft site in the majority of patients. However, inadequate mucosal closure due to the push-back method in the study of Saijo et al. (3) or due to the von Langenbeck's procedure reported by Yin et al. (6), could have affected osteogenesis in the anterior half of the palate, while most of the regenerated bone was seen at this location by Choi et al. (5). This finding may indicate that different surgical procedures could influence bone regeneration. By comparing these different techniques, we can conclude that the use of a mucoperiosteal flap with complete closure of the mucosal layers is needed to obtain bone regeneration.

Moreover, we want to make some critical remarks about the evaluation methods. Pryds et al. (7) included only a small amount of patients and their follow-up period was rather short, 20-22 months. Neither preoperative imaging nor preoperative measurements of the cleft size are mentioned by Yin et al. (6). Also, Saijo et al. (3) did not report any preoperative imaging. The maximal width of the bony fissure at the time of palatoplasty was only recorded in eight of 29 patients. Only postoperative measurements of the remaining cleft size were performed, by which they stated that at the location with the smallest cleft, the greatest amount of bone regeneration had taken place. The reader should be cautious during the interpretation of these results because the cleft widths before and after the

operation have not been measured at the same location. So, we wonder if it is correct to make a correlation between these evaluation items?

Of the factors which might affect the bone regeneration only age at the time of palatoplasty turned out to be borderline significant. In comparison, patient's age at time of surgery has already been studied in detail for different surgical procedures of the mandible (17, 18). It is stated that spontaneous bone regeneration after segmental resection of the mandible occurs significantly earlier in the younger patient (17). Furthermore, it is proven that increased patient age has a negative influence on the spontaneous healing of bone defects in the mandible (18).

Finally, we want to draw attention to the fact that whether the cleft palate surgery is performed by one or by different surgeons, the performance ability of the surgeon and the genetic characteristics of the patient can be of great influence on the study outcome.

CONCLUSION

Due to the many differences between the four studies, it is difficult to conclude whether one technique is better than another in regard to bone regeneration. Additional research is needed to define the best technique.

For this literature review only four papers were included, indicating that there is still substantial opportunities for additional research and to confirm the theorems mentioned above, preferably using studies with a larger sample size.

References

1. Farronato G, Kairyte L, Giannini L, Galbiati G, Maspero C. How various surgical protocols of the unilateral cleft lip and palate influence the facial growth and possible orthodontic problems? Which is the best timing of lip, palate and alveolus repair? literature review. *Stomatologija*. 2014;16(2):53-60. PubMed PMID: 25209227. Epub 2014/09/12. eng.
2. Lee YH, Liao YF. Hard palate-repair technique and facial growth in patients with cleft lip and palate: a systematic review. *The British journal of oral & maxillofacial surgery*. 2013 Dec;51(8):851-7. PubMed PMID: 24045106. Epub 2013/09/21. eng.
3. Saijo H, Mori Y, Fujihara H, Kanno Y, Chikazu D, Ohkubo K, et al. Evaluation and analysis of formation of bone at the palate in patients with cleft lip and palate after palatoplasty based on computed tomograms and three-dimensional data. *Scandinavian journal of plastic and reconstructive surgery and hand surgery*. 2010 Feb;44(1):21-5. PubMed PMID: 20367061. Epub 2010/04/07. Eng.
4. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS medicine*. 2009 Jul 21;6(7):e1000100. PubMed PMID: 19621070. Pubmed Central PMCID: PMC2707010. Epub 2009/07/22. eng.
5. Choi J, Kwon GY, Kim S, Choi TH. The long-term changes of hard palatal bony cleft defects after palatoplasty in unilateral complete cleft lip and palate. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS*. 2012 Nov;65(11):1461-7. PubMed PMID: 22817881. Epub 2012/07/24. Eng.
6. Yin N, Ma L, Zhang Z. Bone regeneration in the hard palate after cleft palate surgery. *Plastic and reconstructive surgery*. 2005 Apr 15;115(5):1239-44. PubMed PMID: 15809580. Epub 2005/04/06. Eng.
7. Pryds U, Holm PC, Dahl E, Fogh-Andersen P. Bone formation in palatal clefts subsequent to palato-vomer plasty. Influence on transverse maxillary growth. *Scandinavian journal of plastic and reconstructive surgery*. 1974;8(1-2):73-8. PubMed PMID: 4450114. Epub 1974/01/01. Eng.
8. Freng A. Subperiosteal early resection of the mid-palatal suture. A morphological study in twelve patients operated for choanal atresia. *Scandinavian journal of plastic and reconstructive surgery*. 1979;13(2):289-93. PubMed PMID: 545671. Epub 1979/01/01. Eng.
9. Hellquist R, Svardstrom K, Ponten B. A longitudinal study of delayed periosteoplasty to the cleft alveolus. *The Cleft palate journal*. 1983 Oct;20(4):277-88. PubMed PMID: 6580968. Epub 1983/10/01. Eng.
10. Takahashi T, Fukuda M, Yamaguchi T, Kochi S, Inai T, Watanabe M, et al. Use of an osseointegrated implant for dental rehabilitation after cleft repair by periosteoplasty: a case report. *The Cleft palate-craniofacial journal : official publication of the American Cleft Palate-Craniofacial Association*. 1997 May;34(3):268-71. PubMed PMID: 9167081. Epub 1997/05/01. Eng.
11. Skoog T. The use of periosteal flaps in the repair of clefts of the primary palate. *The Cleft palate journal*. 1965 Oct;2:332-9. PubMed PMID: 5213337. Epub 1965/10/01. Eng.
12. Meazzini MC, Tortora C, Morabito A, Garattini G, Brusati R. Alveolar bone formation in patients with unilateral and bilateral cleft lip and palate after early secondary gingivoalveoloplasty: long-term results. *Plastic and reconstructive surgery*. 2007 Apr 15;119(5):1527-37. PubMed PMID: 17415247. Epub 2007/04/07. Eng.
13. Schmitz JP, Hollinger JO. The critical size defect as an experimental model for craniomandibulofacial nonunions. *Clinical orthopaedics and related research*. 1986 Apr(205):299-308. PubMed PMID: 3084153. Epub 1986/04/01. Eng.
14. Bjork A. Sutural growth of the upper face studied by the implant method. *Acta odontologica Scandinavica*. 1966 Sep;24(2):109-27. PubMed PMID: 5225742. Epub 1966/09/01. Eng.
15. Dahl E. Craniofacial morphology in congenital clefts of the lip and palate. An x-ray cephalometric study of young adult males. *Acta odontologica Scandinavica*. 1970;28:Suppl 57:11+. PubMed PMID: 5274406. Epub 1970/01/01. Eng.
16. Berkowitz S, Duncan R, Evans C, Friede H, Kuijpers-Jagtman AM, Prah-Anderson B, et al. Timing of cleft palate closure should be based on the ratio of the area of the cleft to that of the palatal segments and not on age alone. *Plastic and reconstructive surgery*. 2005 May;115(6):1483-99. PubMed PMID: 15861051. Epub 2005/04/30. Eng.
17. Anyanechi CE, Saheeb BD, Bassey GO. Spontaneous bone regeneration after segmental mandibular resection: a retrospective study of 13 cases. *International journal of oral and maxillofacial surgery*. 2016 Oct;45(10):1268-72. PubMed PMID: 27138240.

18. Ihan Hren N, Miljavec M. Spontaneous bone healing of the large bone defects in the mandible. International journal of oral and maxillofacial surgery. 2008 Dec;37(12):1111-6. PubMed PMID: 18760900.

TABLES

Table 1: Keywords

Databases	Search terms	Results
National Guideline Clearinghouse SUMSearch 2 Cochrane Database Web Of Science	1) "Cleft Palate" AND "Bone Regeneration" AND "Palatoplasty" 2) "Cleft Palate" AND "Bone Regeneration" AND "Cleft Palate Surgery" 3) "Cleft Palate" AND "Bone Regeneration" AND "Reconstructive Surgical Procedures"	0 guidelines 5 systematic reviews 24 articles
MEDLINE	"Cleft Palate"[MeSH] AND "Bone Regeneration"[MeSH] AND ("Palatoplasty" OR "Reconstructive Surgical Procedures"[MeSH] OR "Cleft Palate/Surgery"[MeSH])	77 articles

Table 2: Exclusion criteria

Topic	Explanation	Filter	No. excluded
Species	Studies performed on animals	'Humans'	15 articles
Language	Studies not written in English	'English'	9 articles
Age	Studies which do not focus on children	'Child: birth – 18 years'	15 articles
Document Type	Letters	'Document Type'	1 article
Title and Abstract	<ul style="list-style-type: none"> • Treatments that focus exclusively on the repair and bone regeneration of alveolar clefts (although those patients may also have palatal clefts) • Studies which do not investigate spontaneous bone regeneration: <ul style="list-style-type: none"> ○ Bone grafting / bone transplantation ○ Stimulated bone regeneration (e.g. due to drugs/growth factors) • Secondary repair after an inadequate primary cleft operation • Studies which focus on syndromal patients 	-	45 articles 5 systematic reviews

Table 3: Patient Characteristics

	Choi et al. (5) (2012)	Saijo et al. (3) (2010)	Yin et al. (6) (2005)	Prydso et al. (7) (1974)
Hospital	Seoul National University Children Hospital	Tokyo Hospital	Cleft Lip and Palate Center of Beijing University School of Stomatology	Cleft Palate Centre in Copenhagen
One- or two-staged procedure	Two-staged	One-staged	One-staged	Two-staged
No. of Patients, Cleft Type	30 complete UCLP	29 complete UCLP	52 patients (43 UCLP, 9 BCLP)	9 complete UCLP
Male/Female Ratio	22/8	22/7	36/16	<i>Not mentioned</i>
Exclusion Criteria	-Syndromic -BCLP -Incomplete cleft palate	Expansion of the maxilla by orthodontic treatments	<i>Not mentioned</i>	<i>Not mentioned</i>
Evaluation Method	CT at an average age of 9.8 years (coronal data)	CT at an average age of 7 years 9 months (coronal data)	CT with an average of 12.6 years after operation (coronal data)	Biopsies at 22-24 months of age (at the time of Wardill-Kilner operation)

FIGURE CAPTIONS

Figure 1: Flowchart of the article selection

ACCEPTED MANUSCRIPT

*Exclusion because of selection and measurement bias