Success of secondary alveolar bone grafting and canine eruption in cleft subjects

Nahul Patel

BDS, MFDS (RCPSG)

A thesis submitted to the University of Birmingham for the degree of Masters of Philosophy

Department of Orthodontics

School of Dentistry

St Chad's Queensway

Birmingham

B4 6NN

Abstract

Aims

A retrospective observational cohort study to:

1. Determine the success of secondary alveolar bone grafting (SABG) defined by spontaneous canine eruption.
2. Investigate the influence of the following factors on canine eruption;

- Post-Operative Bone Fill Index
- Age at SABG
- Presence of lateral incisor
- Horizontal position and angulation of the canine
- Expansion prior to SABG
- Unilateral or bilateral cleft

Method

Records of 66 subjects amounting to 86 clefts were examined to determine the height of bone post-SABG using the Post-Operative Bone Fill Index as well as the eruptive status of the canine. Study models, radiographs and clinical entries were used to determine the presence and morphology of the lateral incisor, position of the unerupted canine and presence of expansion.

Results

74.4% of 86 canines erupted spontaneously. Using the Post-Operative Bone Fill Index, 54.4% scored 1, 26.7% scored 2, 10.5% scored 3 and 8.1% scored 4. 52.3%

of clefts were associated with missing lateral incisors and 30.2% were expanded pre-SABG. There was no statistical significant correlation (P>0.05) between spontaneous eruption and any of the variables.

Conclusion

There was a good success rate of SABG, however, the height of bone post-SABG was not statistically correlated with spontaneous canine eruption.

Acknowledgements

I would like to thank the following people:

Mr Lars Enocson and Professor Thomas Dietrich for their continuous guidance and support.

Mr Lars Enocson and Mr Ian Sharp for supporting the study with clinical data.

Dr Jay Kindelan and Dr Gunvor Semb for their help on using the Post-Operative Bone Fill Index.

Dr Paul Davies and Professor Thomas Dietrich for statistical support.

Mr David Spary, Mr John Turner, Mr Rognvald Linklater, Mr Lars Enocson and Mr James Dickson for allowing me to visit their departments in order to collect data.

I would like to dedicate this thesis to my uncle, aunt, parents, Hitendra, Ruth, Jayendra and Meena for their support and inspiration.

Contents

Chapter 1 Literature review **Page**

Chapter 2 Participants and methods **Page**

Chapter 3	Results	Page

List of figures

Chapter 1

Literature review

Chapter 1 Literature review **Page**

1.1.1 Prenatal development of the lip and palate

The embryological development of the maxilla is well described in books written by Mitchell, (2007) and Cobourne and Dibiase, (2010). The maxilla, palate and the lateral portion of the upper lip is formed from the maxillary process of the first pharyngeal arch. The development of the face is a complicated process involving neural crest cell migration, proliferation and fusion of the swelling surrounding the stomodeum. At approximately four weeks *in utero*, five processes appear; the frontonasal process, two maxillary processes and two mandibular processes. At approximately five weeks *in utero*, the medial and lateral nasal processes form within the frontonasal process where olfactory cells are developed. The two nasal passages are formed by the enlargement of the frontonasal and maxillary processes resulting in the formation of the nasal septum. Maxillary swellings enlarge by growing medially and ventrally and fuse to create the philtrum and the growth pushes the nasal process inferiorly to form the primary palate. The upper lip is formed from the lateral aspects of the maxillary process and the medial nasal process. The palate is formed by the medial extensions of maxillary swellings which are formed approximately seven weeks *in utero* and grow inferiorly lateral to the tongue. At approximately eight weeks *in utero*, the tongue moves in a downward direction and the palatine shelves rotate upwards and continues to enlarge horizontally. The palatine shelves fuse at approximately 9 weeks *in utero* in a direction from the ventral aspect to the dorsal aspect and following fusion, an epithelial seam is formed. A fibroblastic morphology is developed by apoptosis of the epithelial cells as well as epithelial- mesenchymal transformation which again differentiates into keratinocytes.

1.1.2 Post-natal development of the maxilla

This is well described by Cobourne and Dibiase, (2010). Maxillary growth occurs though surface remodelling and growth at the circum maxillary sutures including the frontomaxillary, zygomaticomaxillary, pterygomaxillary, zygomaticofrontal and zygomaticotemporal sutures. The height of the maxilla increases by deposition at the infrazygomatic crest, hard palate and alveolar process with resorption at the orbital and nasal floor. The maxilla widens by growth at the mid palatal suture, deposition posteriorly and laterally with resorption below the zygomatic buttress.

1.1.3 Tooth formation

Tooth formation can be classified into three basic stages (Cobourne and Dibiase, 2010).

<u>Bud stage</u>

There is localised proliferation of the oral epithelium which invaginates into the underlying bone. This is regulated by Sonic Hedgehog and is antagonised by WNT7. MSX1 and PAX9 also play a key role at this stage.

<u>Cap stage</u>

The tooth bud begins to resemble the early morphology of the crown. The signalling originates from the enamel knot by the release of various mediators such as FGF4 which mediate proliferation of the epithelium. FGF10 mediates cell division the epithelium and BMP induces MSX1 and PAX9.

Bell stage

At this stage, there is formation of the enamel, dentine and cement in the crown and root. The inner enamel epithelium activates the cells in the dental papilla to differentiate into odontobalsts which lay predentine. The predentine induces the cells of the inner enamel epithelium to differentiate into ameloblasts which lays down enamel. The root morphology is induced by growth of cells at the cervical loop in an apical direction with differentiation of root odontoblasts. The dental follicle is then exposed to the root dentine inducing the differentiation of cementoblasts which lay cementum. The dental follicle cells also produce the alveolar bone and collagen fibres of the periodontium

1.1.4 Theories of tooth eruption

Sandy, (1992) summarises the various theories of tooth eruption which are described below.

Pulp theory

Extrusion of the pulp creates propulsive forces by;

- Growth of dentine
- Interstitial pulp growth
- Vasculature hydraulic effect

Vascular Theory

The pressure in the blood vessels creates the propulsive force, however, there are many authors that have found that eruption was unaffected by the use of hypotensive drugs.

Root elongation Theory

The root of the tooth by elongation is pushed against the alveolar bone.

PDL Theory

The fibroblasts vibrate and contract creating a force that lifts the root against gravity. Administration of Lathyritic compounds which inhibit cross-linking of collagen should prevent the fibroblasts from vibrating and contracting have not been shown to inhibit eruption.

Alveolar Bone growth

Bone is laid down beneath the crypts of erupting teeth. Kurihara *et al*, (1980) examined dried skull of humans from birth to fourteen years of age in order to examine the pattern of resorption and deposition in relation to developing teeth. The authors reported that at the perinatal stage, there was no remodelling of the maxilla of the mandible. During the early deciduous dentition stage, there was remodelling of the premaxilla which involved little cortical bone. In the late deciduous dentition stage, the resorption had spread superiorly, laterally and inferiorly whilst in the mandible, the resorptive field were positioned irregularly. There were localised remodelling of cortical bone in relation to tooth movements occurring during eruption and drift. They reported that bone grew more rapidly when teeth erupted and there were small thin deposits of periosteal lamellar bone covering localised bulges of crowns and roots of erupting teeth. The growth in bone from erupting teeth was not differentiated between cause and effect.

Follicular Theory

Factors such as cytokines, eicosanoids and growth factors are released by the dental follicle which are responsible for bone remodelling and hence eruption.

Tooth eruption dates

Helm and Seidler, (1974) carried out a cross sectional observational study on Danish school children in order to determine the timing of permanent tooth eruption. Their results are shown below

Male			**Female**		
Maxilla					
Tooth	Mean age of emergence	SD	Tooth	Mean age of emergence	SD
I1	7.18	0.74	I1	6.90	0.70
I2	8.21	0.87	I2	7.82	0.90
C	11.45	1.21	C	10.84	1.25
P1	10.59	1.46	P1	10.10	1.28
P2	11.43	1.47	P2	11.03	1.42
M1	6.25	0.71	M1	6.08	0.67
M2	12.39	1.26	M2	11.89	1.22
Mandible					
I1	6.19	0.66	I1	6.02	0.67
I2	7.38	0.90	I2	7.05	0.79
C	10.54	1.13	C	9.64	1.05
P1	10..68	1.48	P1	10.04	1.30
P2	11.53	1.44	P2	10.99	1.43
M1	6.21	0.68	M1	6.02	0.61
M2	11.90	1.30	M2	11.36	1.21

The mean age of eruption of the maxillary lateral incisors are 8.21and 7.82 in males and females respectively. The mean age of eruption of the maxillary canines are 11.45 and 10.84 in males and females respectively. These teeth are commonly situated adjacent to the alveolar cleft and the consequence of the timing of their eruption described below in chapter 1.8.

1.2 Incidence of cleft lip and palate

Cleft lip and palate is the most common craniofacial abnormality. The incidence of it varies among racial groups, however, the non-syndromic form is approximately 1:700 live births in the UK (Gorlin *et al,* 1971*).* Coupland and Coupland*,* (1988) examined 930 children born in the Trent region between 1973 and 1982. The incidence of cleft palate varied by a small degree each year with an incidence of 1.47 per 1000 live births in 1974 to 0.91 per 1000 live births in 1982. The lowest incidence was found in 1977 with an incidence of 0.91/1000 live births. They found a distribution of types of clefts amongst genders. 39% had isolated cleft palates and 61% had a cleft lip with or without a cleft palate. In the isolated cleft palate group, females accounted for 55% and males 45%. In the group of cleft lips, a higher proportion was seen in males which accounted for 62%. Jensen *et al*, (1988) studied the incidence of clefts in a Danish population between 1986 and 1981. They found that 678 live births were registered with cleft lip, palate or both resulting in a incidence of 1.89 per 1000 live births, however, they excluded isolated submucous clefts. The unilateral cleft group accounted for 55.8% of males and 33.5% of females. The bilateral cleft group accounted for 6.3% of males and 1.4 % of females. The unilateral cleft group consisted of cleft lip in (33.5%) almost twice as prevalent in males. The cleft lip and palate (39.1%) was again almost twice as prevalent in males, however, the cleft palate only (27.4%) was 1.5 times common in females. The authors also found that a small proportion of the cleft palate group were associated with Pierre Robin syndrome. Seventy percent of the cleft cases were non-syndromic occurring in isolation whereas the remaining 30% were syndromic. Cobourne, (2004), Carmichael *et al,* (2007) and Botto *et al*, (2002) found that the greatest incident of orofacial clefts were amongst Caucasian or Hispanic patients with the least incidence in afro-Caribbean and Asian ethnicity.

Nagese *et al*, (2010) carried out a cross sectional study in Japan to investigate the gender differences in cleft pattern. The authors analysed 782 subjects and the following results were documented. They reported that the most frequent type was the cleft lip and palate which was more common in males whereas the cleft palate was more common in females. A possible explanation for the gender difference was mentioned including a relationship between female sex hormones and the palatine process with the slight differences in the timing of embryological development. The cleft lip/cleft lip and palate was also more common on the left and they theorised that a possible reason for this was that the facial artery development is slower on the left.

1.3.1 Aetiology- Genetic

Losee and Kirschner, (2009) discuss the embryology of cleft palate. The clefting of the palate is due to lack of fusion of the 3 elements that form the palate which are median frontonasal prominence, the primary palate and the two lateral palatal shelves. The V-shaped clefts are a result of lack of tissue in the shelves to complete closure whereas the U-shaped clefts are a result of micrognathia and glossoptosis. The greater the posterior involvement of the palate, the greater the severity of the cleft. A cleft of the secondary palate is due to deficient fusion posterior to the incisive foramen whereas a cleft of the primary palate is due to deficient fusion anterior to the incisive foramen of the medial, lateral nasal processes and the maxillary process. The palatal shelves elevation and fusion is discussed in greater detail below.

It is believed that the aetiology of cleft lip and palate may be due to a genetic predisposition, an environmental cause or combination of both. Syndromic disorders are caused by single gene mutations with varied levels of penetrance and expressivity. There are a broad range of variations in structure and number that can cause gene malformations and therefore altered gene function. Deletions and duplications can both have an aetiological impact in the development of cleft lip and palate (Cobourne, 2004).

Developmental disturbances can broadly be categorised into one of the following

- Alteration in the force to elevate the palatal shelves
- Failure of tongue to drop
- Non-fusion of shelves
- Failure of mesodermal migration
- Rupture of a cyst formed at the site of fusion

Sonic Hedgehog is a protein that is secreted in the oral epithelium that induces growth of the palatine shelves. Rice *et al,* (2004) found that signalling from Sonic Hedgehog protein induced palatal shelves proliferation and growth with lack of this protein resulting in a reduced development of the mesenchymal cells. The authors also showed that mice lacking fibroblast growth factor 10 or its receptor, fibroblast growth factor 2b developed a cleft palate due to the lack of outward growth of the palatine shelves. Bush and Jiang*, (2012)* suggest that Sonic Hedgehog and

Fibroblast Growth Factor function as a positive feedback loop. Bone morphogenic proteins are also required for palatogenesis. Liu *et al, (2005)* knocked out Bone Morphogenic Protein 4 in mice and found that they developed a cleft lip but not a cleft palate as it affected the function of the maxillary mesenchyme. Bone morphogenic proteins are cytokines which play a significant role in embryonic development by stimulating gene expression via phosphorylation. In particular BMPs play a specific role in the epithelial- mesenchymal interaction during the formation of organs. Li *et al*, (2011) investigated the effects of Bmprla and Bmprlb which are encoders for BMP receptors and BMP signalling. The authors found that inactivation of Bmprla led to the development of a cleft palate as well as lack of tooth development and a hypoplastic mandible.

1.3.1 Palatal shelves elevation

Several theories have been proposed for the elevation and rotation of the palatal shelves. The following were discussed by Bush and Jiang, (2012).

- There could be regression of the distal portion of the shelves and outgrowth in the horizontal direction.
- A mechanism exists whereby the anterior portion of the shelves swing upwards and the posterior flow down.

Stanier and Moore, (2004) describes the following theories

- Elevation could be due to an intrinsic force due to increased turgidity by recruitment of water resulting in an increased level of glycosaminoglycans such as hyaluronan.

- The author discusses the involvement of Pax9 and a mutation in the gene resulting in an abnormal morphology of the palatal shelves in which they are shorter and broader. This experiment was carried out in mice and the palatal shelves had a mechanical inhibition of elevation.

1.3.2 Palatal shelves fusion

As discussed above the fusion and elevation of the palatal shelves can be influenced a number of specific gene mutation. Fusion of the palate occurs by interaction of desmosomes and cell adhesion molecules. They contact in a midposition horizontally and close in a direction from the primary palate to the uvula. Experiments on mice have shown that halpoinsufficiency of Interferon Regulatory Factor 6 has lead to failure of palatal shelves fusion (Coubourne, 2004). Polovirus receptor 1 gene encodes a cell adhesion molecule called nectin 1 and a nonsense mutation of this gene has resulted in the failure of fusion of the palatal shelves. Suzuki *et al*, (2000) and Stanier and Moore, (2004) discussed a number of genes in which the mutations have contributed to the development of cleft palate by inhibiting mesenchymal proliferation and therefore fusion in the horizontal plane including MSX1 and Lhr8.

Linde, (2007*)* presents a table in the review article which lists the gene involved with failure of palatine shelves proliferation, elevation or fusion.

- Bmprl1a- the positioning of the shelves are altered and positioned more anteriorly
- Fgf10- apoptosis is increased of the shelves and there is adhesion of the shelves to other epithelia
- Tgfbr2- Proliferation defects of the palatal mesenchyme

- Alpha v integrins- the shelves elevate but fail to make contact
- Ephb2- results in hypoplastic shelves
- Pdgfc- There is delayed elevation and well as hypolasia and failure of the fusion

Lateif *et al*, (2012) carried out a study to compare the widths and angulation of the palatal shelves in unilateral and bilateral cleft patients using study casts. They examined the casts of unoperated patients aged 13 consisting of 68 unilateral, 13 bilateral cleft lip and palate and 24 in the non-cleft control group. In the unilateral cleft group, the palatine shelves width was significantly smaller on the cleft and non cleft side compared to control group. They were also positioned more vertically and rotated towards the cranium. In the bilateral group, the shelves were rotated by 10° compared to the control group. This study confirms the work of others mentioned above. The fact that the shelves were smaller suggests hypoplasia or failure of proliferation.

Bush and Jiang, (2012) present a table in which all the gene mutations have been identified to cause syndromic and non syndromic cleft lip+/- palate. They have presented the following:

Non-syndromic cleft lip and palate

- BMP4, FGF8, FGFR2, FOXE1, IRF6, MSX1, PDGFC and SUM01

Non-syndromic cleft palate only

- FOXE, IRF6, MSX1, SATB2 and TBX22

There are a host of syndromic genes and an example of a few are demonstrated below.

- TCOF1- Treacher Collins syndrome
- TBX1- DiGeorge
- GLI3 – Oro- facial- digital syndrome
- FGFR2- Crouzon’s and Apert’s syndrome
- IRF6- Van de Woude

1.4 Aetiology- Environmental

1.4.1 Teratogens

A teratogen is any agent that can cause a birth defect by disturbing the development of the embryo or foetus. Teratogens linked to cleft lip and palate include Phenytoin, Thalidomide, Valproic acid, maternal alcohol, tobacco smoking, altitude and herbicides such as Digoxin. Murray, (2002) and Little *et al,* (2004) carried out a meta-analysis to determine a correlation between maternal smoking and cleft lip and palate. They included 22 case control publications and 10 cohort studies and reported that there was a significant association between maternal smoking and cleft lip and palate.

1.4.2 Seasonal

Coupland and Coupland, (1988) found a seasonal variation between the years of 1973 and 1982. In the group consisting of cleft palate only, the greatest incidence occurred in August with approximately 36 births and the lowest incidence was in April with approximately 26. This was different to the incidence of cleft lip with or without palate. In this group, the greatest incidence was found in December with 54 births and the lowest in May with 41 births. The authors acknowledge that that season variability is a well recognised phenomenon and has been reported in neural tube defects.

1.4.3 Maternal and paternal age

Jensen *et al*, (1988) in their retrospective study found that maternal age group was increased in the bilateral complete cleft lip and palate group and increased paternal age was associated with left side complete cleft lip. Paternal age was however normal for the cleft palate group. Botto *et al*, (2002), however, found that the greatest incidence was in a maternal age between 25 and 29.

1.4.5 Stress

There are many studies that have reported an increased in maternal stress and neural tube defects. Carmichael *et al*, (2000) and Suarez *et al*, (2003) have suggested that stress may lead to an increase in the levels of corticosteroids which act as teratogens as well as elevated corticotrophin releasing hormones. Carmichael *et al*, (2007) carried out a telephone based interview study with 1335 mothers with affected children and 700 control mothers. The mothers were asked about stressful events such as a lost or new job, financial or legal problems, serious illnesses, drugs, alcohol, violence or crime, losing a loved one or relationship troubles. The results showed that an increase in the number of stressful life events was associated with birth defects especially cleft lip with or without a cleft palate.

1.4.6 Multivitamins and Folic acid

Folic acid is also known as foliate, vitamin B9, vitamin Bc or vitamin M is a vitamin of the B complex which is found naturally in leafy green vegetables, kidney or liver. It is necessary for DNA synthesis, cell production and prevention of gene mutations. There are many studies which have reported an association between deficiency in folic acid and a greater incidence of cleft lip and palate. Badovinac *et al*, (2007) found in the meta-analysis of 5 prospective and 12 case control studies that there was a positive correlation between the two, but also acknowledge the potential for bias and uncontrolled confounding factors. Matok *et al,* (2009) examined an association between folic acid antagonists and congenital malformations during the first trimester of pregnancy in a retrospective cohort study. The folic acid antagonists are commonly found in medication such as Phenytion, Valproic acid, Carbamazepine, Lamotrigine, Primidone and Cholesyramine. The workers found that folic acid antagonists were significantly associated with neural tube and cardiovascular defects. Johnson and little, (2008) found in their meta-analysis study that there was weak evidence for associations between orofacial clefts and folic acid intake. The researchers did, however, conclude that multivitamin use may protect against orofacial clefts but there are many confounding factors not accounted for. Mosey *et al,* (2009) discusses the role of nutrition and mentioned that a deficiency in zinc leads to an increase risk of cleft lip and palate development and vitamin B6 reduces the serum concentration of homocysteine which is thought to be a risk factor. Botto *et al*, (2002) found in their case control study that febrile risk with no multivitamin intake around time of conception was associated with increased risk with neural tube defects and cleft lip and palate. An explanation for these results is that multivitamins and febrile illnesses affect vascular disruption and apoptosis antagonistically. The authors mention the possibility of recall bias in their discussion and also that the results could have occurred by chance, however, that could be unlikely as it is agreement with other workers.

Little *et al*, (2004*)* in their meta-analysis mention that the smoking could interact with a number of genes involved in the aetiology of cleft lip and palate as mentioned below.

- Smoking or alcohol or vitamins alter TGFA expression
- Smoking and alcohol can also alter MSX1 and TGFB gene

1.5 Classification

Veau, (1931) classified his 4 categories by morphology.

1. Cleft of the soft palate only

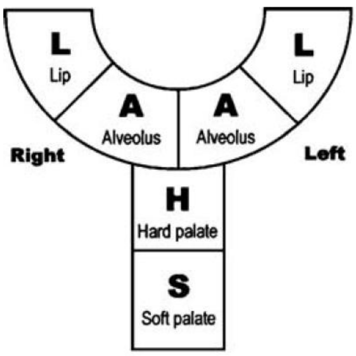
2. Cleft of the hard and soft palate up to the incisive foramen

3. Complete unilateral cleft of the soft and hard palate as well as the alveolar ridge and the lip on that side
4. Complete bilateral cleft of the soft and hard palate as well as the alveolar ridge and the lip on both sides

Kernahan and Stark, (1958*)* based the categories according to the embryology and designates the incisive foramen as the dividing structure. Group 1 involves clefts of the primary palate up to the incisive foramen. This is subgrouped as unilateral, bilateral or median. Group 2 involves clefts of the soft and hard palate up to the incisive foramen which can be subgrouped as unilateral or bilateral. Group 3 involves the soft or hard palate but not up to the incisive foramen and therefore can be complete or incomplete as well as unilateral or bilateral.

Hodgkinson *et al*, (2005) cited the LAHSAL code for classifying the type of cleft.

Figure 1.5.1 The LAHSAL code



The LAHSAL code is a modification of the classification of the Kernahan and Stark index. The Y diagram is divided first into halves which are the left and right. It is then divided into 6 parts which consist of the right lip, right alveolus, hard palate, soft palate, left alveolus and left lip. The code is written as if the clinician facing the patient with the first character being the right lip and the last character being the left lip.

1.6 Anomalies

1.6.1 Growth

Jensen *et al*, (1988) examined the general condition of cleft children. They found that body length in females with cleft palate was significantly reduced at age 9 weeks. The height at 22 weeks of boys and girls with cleft lip+/- palate was significantly less than children with cleft lip only and the weight for both was significantly reduced compared non-cleft controls. Head circumference was not greatly impacted except for the boys with cleft palate only at 22 months. Semb, (1991.a) carried out cephalometric analysis of 257 patients in Oslo with unilateral cleft lip and palate. The researcher found that patients had increased anterior vertical facial proportions, reduced posterior face height, short retrusive maxilla, retrusive mandible and a flatter nose. The nose showed a more downward and backward growth. These subjects had their hard palate repaired with Von Lagnenbeck procedure and the lip was closed with Le Mesurier’s procedure before 1961 and Millards procedure after 1961. They also had their secondary alveolar bone grafts between ages 9 and 11. Semb, (1991b*)* examined the growth and facial characteristics of 90 patients with bilateral cleft lip and palate using cephalometric measurements. The pattern was similar to that of the unilateral cleft lip and palate group with increased anterior facial height, shorted posterior face height and reduced length of the maxilla as well as the mandible when compared to controls. The maxilla was prominent until aged 5, however, receded from aged 7 to 18. It was also reported that the influence of the vomer flap during palate closure on facial growth was insignificant. The facial characteristics are attributed to the primary surgery resulting in scar tissue hindering maxillary and concomitant mandibular growth. Heidbuchel, (1997) reports that in unoperated adults of bilateral cleft lip and palate, the columella and prolabium is underdeveloped, however, there is no difference in the sagittal dimension with the exception of the cleft when compared to non-cleft controls. The mandibular plane is steep in unoperated cleft subjects. Heidbuchel *et al*, (1998) examined study casts to investigate the development of maxillary arch dimensions of operated cleft subjects compared to non-cleft subjects. The results showed that following lip closure, the anterior arch width and depth reduced and following palatoplasty, the posterior arch width reduced. Semb and Shaw, (1990), reported that subjects with pharyngeal flaps had reduced maxillary length, reduced upper and lower face height and a more retrusive mandible.

1.6.2 Associated anomalies

Andersson *et al*, (2010) studied 994 patients born with a cleft palate to describe associated anomalies. They found miscellaneous facial anomalies as the most common anomaly in 132 subjects, skeletal system anomalies in 51 subjects, cardiovascular system anomalies in 47 subjects, mental disabilities in 43 subjects and central nervous system anomalies in 40 subjects. Other organ anomalies included the ear, eye, urogenital, skin, gastro-intestinal, endocrine, respiratory system and the brain

1.6.3 Cognitive Functioning

Lack of cognitive functioning could be due to smaller frontal lobe, smaller brain volumes, psychological effects, speech deficits and the effect of living with a facial disfigurement. Roberts *et al*, (2012) studied the effects of cognitive function of cleft patients in a meta-analysis study. They reported that cleft patients can present with deficits of immediate memory, attention and language abilities, processing speed, sensory-motor function and academic ability.

1.6.4 Hypodontia

Andersson *et al*, (2009) found in their sample of 994 cleft subjects that 88 individuals had hypodontia. One hundred and fifty one teeth were missing with the second premolars in the maxilla or mandible being the most frequently missing. 39 subjects showed hypodontia of two or more teeth. There was an increased trend for hypodontia with a greater severity of cleft. Many other authors have reported a similar prevalence of hypodontia between 35 and 45 percent. Ranta *et al*, (1983) examined orthopantograms of children aged between 6 and 12 and found that there was an increased risk of hypodontia with an increasing extension of cleft with a prevalence ranging from 45% to 56% with 3rd molars being excluded. Larson *et al*, (1998) examined orthopantograms and found a prevalence of 30% with the most common missing tooth being the mandibular second premolar followed by maxillary lateral incisor and maxillary second premolar. Tortora *et al*, (2008) evaluated panoramic radiographs of 29 subjects with bilateral cleft lip and palate and 87 subjects with unilateral cleft lip and palate. They reported a 48.8% prevalence of hypodontia involving the upper lateral incisors and 7.3% with supernumerary lateral incisors. The second most common missing tooth was the maxillary second premolar on the cleft side in 4.9% of the subjects.

1.6.5 Size and form of teeth

McCance *et al*, (1993) examined the study models of 23 cleft subjects and 100 control subjects to determine any associations in tooth size, chord length and arch width. The author reported significantly smaller tooth size in cleft patients, especially with incisors and canines. The cleft group also had smaller incisor to canine chord length but not from canines to first molars. The mean arch widths were also smaller in the cleft group indicating a narrow arch and the possibility of crossbite development. Ranta, (1986) reports that the lateral incisor on the cleft side is almost always smaller in size and different in shape. There is an extremely high incidence of hypoplasia in the incisor region, which may be due to the lip repair.

1.6.6 Caries

Bokhout *et al*, (1997) investigated the prevalence of caries in the primary dentition in subject with cleft palate compared to controls. The study included 158 subjects, 81 subjects with oral clefts and 77 control subjects. The subjects were examined at months three, six, nine and twelve followed by six monthly intervals until aged 4. The parents were given a questionnaire asking about the subject's dietary habits, fluoride exposure and socio-economic status of the parents. The results showed that the subjects with orofacial clefts had significantly poorer oral hygiene and greater gingival inflammation. 101 carious teeth were registered with 91% belonging to the group with orofacial clefts. The teeth most affected were the maxillary incisors followed by maxillary molars, mandibular molars and maxillary canines. 62% of the cleft subjects came from a low socio-economic class compared to 29% in the control group. The authors discuss the possibility that parents from a higher socio-economic class are more likely to comply with nutritional recommendations and restrict cariogenic foods. The incidence of caries was 3.5 times greater in subject with oral clefts. This is in agreement with Britton and Welbury, (2010) who reported a greater prevalence of caries in children with oral clefts aged between 0.5 years and 6 years of age compared to non cleft subjects. Both anterior and posterior teeth were involved with more carious anterior teeth in the younger age group. Hasslöf and Twetman, (2007) in their systematic review of case studies did not find that children with cleft lip and palate had a greater prevalence of caries.

1.6.7 Tooth formation and eruption

Ranta, (1986) discusses that tooth formation and eruption is delayed by 0.3 to 0.7 years with an increase in delay which is proportional to the severity of the cleft extension. This delay occurs throughout the permanent dentition and in both upper and lower arches. The delay in tooth formation increases with an increase in the number of missing units and the delay can be significantly longer with increasing age (1.1 years for subjects aged between 9 and 12, and 0.6 years for subjects aged 6 to 9). The canines and incisors on the cleft side can erupt later than the corresponding teeth on the non-cleft side. Bjerklin *et al*, (1993) examined the prevalence of maxillary first permanent molar ectopia in 225 children using radiographs. They reported a significantly greater prevalence in the cleft patients of 21.8% compared to 4.3% in the control group with 94 ectopic molars in the cleft lip and palate group, 65 in the cleft lip and 66 in the cleft palate group. The authors believe that the surgical treatment is a major local factor as well as a genetic tendency. Borodkin *et al*, (2008) found a delay of 0.52 years with boys accounting for all the delay and no significant difference between unilateral and bilateral clefts. This is in agreement with Pioto *et al*, (2005), who found delayed root development of the lateral incisor on the cleft side compared to the non-cleft side. Heidbuchel *et al*, (2002) discussed that delay in tooth formation could be due to factors that are associated with the aetiology of the oral cleft such as risk factors during gestation, unfavourable postnatal environments such as recurrent chest and ear infections, operations, feeding problems, inadequate bone support or scar tissue created from surgical procedures.

1.6.8 Speech and hearing (velopharyngeal insufficiency)

The aetiology of speech defects are complex and multifactorial. This can be due to velopharyngeal insufficiency, hearing problems, oronasal fistulas, occlusal and dental problems (Habel *et al*, 1996). Velopharyngeal insufficiency occurs when the lateral pharyngeal walls and the soft palate ineffectively separate the nasal cavity from the oral cavity resulting in hypernasality or an abnormal tone. The aetiology can be due to structural deficits, faulty learning, neurological deficits or a combination of them. Treatment can include surgery, speech therapy or prosthetics (Sell and Ma, 1996). There is an increased risk of middle ear infections due to abnormal attachments of the Levator Palati muscle to the eustacian tube which in turn leads to poor drainage (Habel *et al*, 1996).

1.6.9 Psychological

Turner *et al*, (1998) highlight particular important psychological issues that cleft subjects can encounter. The environment that the family creates is an important factor as it can impact on the attitude and self esteem of the child. Facially disfigured children can have a negative reaction from the parents at an early age. Surgery for the disfigurement can result in an increase in self confidence, self esteem and satisfaction with appearance. Cleft patients may experience an increase frequency with learning problems and speech in addition to verbal and language deficiency. Snyder *et al*, (2005) examined medical records of 64 adolescents with craniofacial anomalies that contained the self-report psychosocial adjustment scales and the parent-report psychosocial adjustment scales. The craniofacial syndromes included

Crouzons, Treacher Collins syndrome, hemifacial microsomia, cleft lip and many others involving a facial asymmetry. They showed that parents reported a social deficit and a withdrawn feeling. Common psychological disturbances by the cleft subjects included activity and social incompetence, anxiety, depression, identity problems and aggressive behaviour.

1.7 Management

The clinical standards advisory group is an independent source of expert advice to the U.K. Health Ministers on standards of clinical care and to advise on access to and availability of selected NHS specialised services in order to prevent the standard of care from deteriorating to an unacceptable level (Sandy *et al*, 2001).

Sandy *et al*, (1998) carried out a questionnaire survey which was sent to each cleft team in the United Kingdom in order to ascertain the outcome of care. They identified 57 active cleft teams in the UK of which 48 replied with the questionnaire. The results from their study showed that there were 75 cleft surgeons with few cases each year with poor outcomes in bone grafting demonstrated by a failure or defective rate of 42%. A high need of treatment for caries was required for 40% of 5 year olds and 20% of 12 year olds. 19% of the parents of 5 year olds and 28% of the parents of 12 year olds reported that their child's self confidence was affected mainly by teasing with 9% dissatisfied with overall outcome of care.

Bearn *et al,* (2001) listed many recommendations that were made by the CSAG to the UK government in 1998 of which a few are listed below.

- Concentration of the 57 cleft units to 18-5 centres in the UK.
- The services should be reviewed by each trust ensuring that the range of clinical skill are available.
- A database should be created detailing information of when and what information should be available for audit and research purposes.
- The cleft centres should provide the cleft clinicians with training programmes where a high volume of clinical experience is available.

As discussed in the previous section, there are many anomalies associated with cleft lip and palate and therefore the management involves a multidisciplinary approach. The multidisciplinary team would involve the plastic surgeons, orthodontists, speech therapists, oral and maxillofacial surgeons, psychologists, specialist nurses, ear, nose and throat surgeons, audiologists, paediatricians and geneticists. Diagnosis can be made upon an ultrasound scan and an immediate referral should be made to the regional cleft lip and palate team (Habel *et al,* 1996).

1.7.1 Parental management

Hodgkinson *et al*, (2005) describes their experience in Newcastle. Parents are often shocked and therefore need time, reassurance and support. All parents would need help understanding their emotions with counselling. During pregnancy, the families are allowed to meet the cleft team as well as other parents who have children with oral clefts.

1.7.2 Respiratory management

Children born with a cleft may have respiratory problems, for example, in Pierre Robin syndrome, the mandible is micrognathic and therefore, the tongue may occlude the airway because it is posteriorly attached. This may be managed by inserting a nasopharyngeal airway tube above the epiglottis until the surrounding structures have grown sufficiently enough. The worst case scenario would involve a tracheostomy (Habel *et al*, 1996).

Kirschner *et al*, (2003) advocated the use of lip adhesion to manage the airway obstruction. The authors report that in all their cases that had a tongue- lip adhesion, a flap was sutured from the ventral surface of the tongue to a superiorly based mucosal flap from the posterior lower lip and this was successful in 25 out of the 29 cases. The main causal factor for failure was due to the mucosal dehiscence. Hong and Bezuhyl, (2013) report that the tongue can tether leading to swallowing difficulties requiring a nasogastric tube. They also describe the use of mandibular distraction osteogenesis in order to relieve upper airway obstruction by lengthening the mandible resulting in a more forward position of the genioglossus and other muscular attachments. Following the osteotomy, the distractor is usually activated by 1-2mm per day which causes the soft tissues to gradually stretch. The authors report good outcomes with distraction osteogenesis overall but poorer outcomes in patients with Pierre Robin Syndrome due to other medical problems such as neurological dysfunction.

1.7.3 Feeding

Feeding difficulties are common and children often have poor weight gain. Feeding can also be prolonged due to ulceration of the nasal mucosa and a high metabolic rate due to other associated conditions such as congenital heart disease. Negative intraoral pressure is required for successful breast feeding, however, this would not be possible with a cleft palate. Habel *et al,* (1996) and Hodgkinson *et al*, (2005) describe the mechanism for successful feeding. The baby has to lift the soft palate to separate the nasal cavity from the oral cavity and the tongue has to move forward over the lower gum in order to cup the nipple or teat. The negative intra-oral pressure with a rhythmic jaw and tongue movement enables the nipple to be help in position. Martin and Bannister, (2004) describe various feeding techniques and variety of bottles and teats available. Most mothers are able to breastfeed if they have been taught to exaggerate the attachment technique. Other methods include the use of various bottles which should be soft and easy to squeeze with a simple design. The Haberman feeding system is a bottle with a one way valve, however, the teat can result in ulceration of the nasal turbulence. The Mead Johnston bottle is useful for parents who have reduced manual dexterity, however, it can sometimes be too soft. They mention that a dummy at feeding times will enhance the development of the oral skills and hence the cognitive link between sucking and feeling of hunger. Counselling, support and advice is usually available from a specialist nurse to help reduce anxiety about weight gain and promote adequate intake. They highlight the importance of specialist nurses for successful feeding immediately after birth. If the mother chooses a formula feed, then the specialist nurse would demonstrate feeding techniques and provide the soft bottles and if the mother prefers to breastfeed, equipment is used to help the expression of breast milk (Habel *et al,* 1996; Hodgkinson *et al*, 2005)

1.7.4 Presurgical orthopaedics

Presurgical orthopaedics was first advocated by a McNiel who was a prosthodontist from Scotland. The process would reduce the size of the alveolar gap and the distance between the medial and lateral aspects of the alar cartilages as well as increasing nasal tip projection (Losee and Kirschner, 2009).The aim was to approximate and align the alveolar segments whilst to some degree correct the nasal cartilage and soft tissue deformity which would allow symmetric growth of the mandible (Grayson and Cutting, 2001). Advocates claim that the benefits include facilitation with lip and palate repair, help with feeding as well as enhance speech and facial growth, however, the benefits and the use remain a controversy.

There are broadly two types of appliances.

Passive appliances

A passive appliance as suggested by its name is an appliance without an active component. An example of such appliance is the Hotz plate (Hotz, 1969). The author describes an appliance made from hard and soft acrylic that obturates the hard palate and as much of the soft palate that the child tolerates. Normal growth cause the maxillary segment to grow, however, the desired direction of growth can be controlled by selectively grinding the plate. The author also mentions that the plate allows the tongue to adapt to a more normal position resulting in a more normal swallowing pattern. The plate is normally worn after the lip closure in order to prevent collapse of the maxillary segments.

Active appliances

Active appliances are secured intraorally and apply a mechanical force with screws, plates and elastic chains. An example of an active appliance is the Latham appliance (Latham, 1980). The author described an intraoral appliance made from acrylic that was used in subjects with a unilateral cleft palate. The appliance was retained by the non-cleft segment with pins and had a split down the midline with the two halves held together by a stainless steel bar posteriorly. A screw measuring 25mm in length was secured onto the appliance in an antero-posterior direction. Activation of the screw once a day moved the cleft segment anteriorly resulting in a reduced discrepancy between the two maxillary segments and better alignment of the dento-alveolar ridge.

Naso-alveolar moulding (NAM)

NAM was a term that followed the term presurgical orthopaedics as is consists of an appliance to mould the alveolus such as the Hotz plate with the addition nasal moulding which occurs independently of alveolar moulding (Loose and Kirschner, 2009)

These appliances also involve the use of an external force which is applied to position the segments posteriorly. The external force may be a head cap with elastic straps, external taping, or surgical adhesion for the lip.

Grabowski *et al*, (2006) followed up 43 subjects with a cleft lip and palate that were managed with pre-surgical orthopaedics until the primary dentition was established. Study models were then examined. Their findings included normal development between ages 3 and 4 compared to non-cleft subjects and advocate the use to guide the growth of the alveolus. Mishima *et al*, (1996) used a Hotz plate which is an active appliance that postures the tongue into its normal position and guides the growth of the maxillary segments. They found that the plate prevents tongue intrusion into the cleft, leading to a larger palate and smaller cleft. Maull *et al,* (1999) reported that nasal moulding with alveolar moulding increased symmetry of the nose, however, the children were not fully grown and the control group was not matched for age. Konst *et al,* (2003) studied the effects of presurgical orthopaedics on speech. They performed a prospective trial in which 27 subjects wore a passive appliance and 27 subjects acted as controls (cleft patients who were not managed with presurgical orthopaedics). The authors reported that between the ages of 2.5 and 3, the group with the intervention did produce longer sentences but this result was diminished by age 6.Other authors have reported no beneficial effects of naso-alveolar moulding (Lee *et al,* 2004). Bongaarts *et al* (2006) and Prahl *et al*, (2003) found no indication in the use of passive plates.

1.7.5 Lip repair

This is normally undertaken at approximately 3 months in the UK. The lip is closed for restoration of a normal appearance, functional restoration to allow drinking and eating as well as speech development. It also allows facial growth, preventing the deformity from worsening (Hodgkinson *et al,* 2005). The two most commonly used techniques are the modification of Tennison and the Millards procedure. The Tennison procedure was described by Tennsion, (1952) which produces a zig zag repair results in a fuller appearance of the lip. The Millard technique devised by Millard, (1957) allows advancement of the lateral aspect of the lip by lengthening and rotation inferiorly. The Tennison procedure is easier to perform and lengthens the upper lip, preserving Cupids Bow, however a prominent horizontal scar is normally visible giving an anaesthetic appearance, whilst with the Millard technique, the horizontal scar is hidden (Cobourne, 2004).

Lip adhesion is a procedure used to approximate the alveolar segments at an early stage approximately at the time of primary bone grafting and was first described by Gustav Simon in 1964. It converted a complete cleft into an incomplete cleft, released the tension in the lip by elongation of the prolabium, thus facilitating the lip repair at a later date (Hamilton *et al*, 1969).

1.7.6 Alveolar repair in infancy

The primary grafting involves grafting of bone in the neonatal cleft at the time of the lip repair thus prior to the eruption of the deciduous incisors. Secondary alveolar bone grafting is carried after the lip repair and can be further classified according to the age (Loose and Kirschner 2009). Primary bone grafting is carried out before the age of 2, early secondary bone grafting is carried out between ages 2 and 5, intermediate secondary bone grafting between ages 6 and 15 and late secondary alveolar bone grafting is performed after the cessation of growth. Rosenstein *et al*

(1982) discuss that poor dental arch relationships following primary bone grafting due to many factors such as tissue hypoplasia, surgical interferences on overlying tissue, undermining of the alveolar ridge in order to accommodate the graft and increased lip pressure. Friede and Johanson, (1974) suggested that advocates of primary bone grafting believed that growth of the maxilla was aided by growth of the nasal septum and there was reduced tendency for crossbite development due to the bone graft bridging the cleft. The researchers found that their sample of patients who had undergone primary bone grafting developed significant anterior and lateral crossbites. The alveolus was repaired via a vomerine flap which is freed from the vomer and sutured to the oral tissue to form the nasal floor resulting in the formation of a mucosal layer. Boyne and Sands, (1972) discuss that early bone grafting would be too time consuming and would result in constriction of the palate causing failure of the maxilla to grow to a normal width. On the other hand, the bone segment could be brought under the control of growth stimulus of the nasal septal cartilage.

Gingivoperioplasty first described by Skoog in 1967 is often used in conjunction with naso-alveolar moulding, involves repair of the gingivoperiosteum at the site of the alveolus to form a bony union and hence eliminate the intention of secondary alveolar bone grafting during the mixed dentition (Santiago *et al,* 1998). They reported that that 12 of the 20 sites that had gingivoperioplasty in their study did not require secondary alveolar bone grafting. The adverse effects include iatrogenic restriction of facial growth resulting in deterioration of facial projection thereby increasing the likelihood for orthognathic treatment. It therefore play a controversial role (Loose and Kirschner, 2009).

1.7.8 Palate repair

The palate consists of the hard and soft palate and the timing and order in which the palate is closed remains a controversy. Some of the combinations include closure of the hard palate followed by the soft palate, closure of the soft palate followed by the hard palate or delayed hard palate closure. The consequences of the combination and timing include effects on growth of the maxilla and speech.

Hard palate repair

The two most common procedures for repair of the hard palate are the Von Langenbeck technique and the modified Veau-Wardill- Kilner pushback technique (Martin and Bannister, 2004). The Von Langenbeck procedure involves the use of mucoperiostal flaps which are moved medially in order to close in the midline. The incisions begin from the alveolus anteriorly and extend posteriorly along the alveolus laterally and then anteriorly along the medial aspect of the cleft segment. The incisions can be extended onto the soft palate, however, the aim of this technique is not to lengthen the soft palate which in turn results in less scar tissue compared to the Veau-Wardill- Kilner pushback technique (Martin and Bannister, 2004; Loose and Kirschner, 2009). The Veau-Wardill- Kilner pushback technique described by Veau, 1931 is named pushback because it aims to lengthen the soft palate using the mucoperiosteum from the hard palate in order to improve speech outcome by facilitating velopharyngeal closure. This technique resulted in formation of excess scar tissue and therefore increased the risk of adverse growth effects. (Howard and Lohmander, 2011; Loose and Kirschner, 2009).

Soft palate repair

One of the major techniques in order to repair the soft palate includes the Furlow double-opposing *Z*-plasty. Incisons are made asymmetrically in order to create a *Z*-shaped flap allowing alignment of the levator sling (consists of the tensor and levator palate to form a sling) and lengthening of the soft palate. Other techniques involve the intravelar veloplasty which again involves dissection of the muscles of the soft palate and reconstruction of the levator sling (Howard and Lohmander, 2011; Loose and Kirschner, 2009).

Delayed hard palate closure

In 1944 Herman Schweckendiek suggested a delayed hard palate closure in which the soft palate was closed at approximately 8 months of age and the hard palate was closed between ages 12 and 15. Advocates of the philosophy report that facial growth was less affected because the clefted palate grows at normal rate due to reduced scarring and interruption to the blood supply (Loose and Kirschner, 2009). Friede *et al,* (2012) performed a retrospective study to investigate the long term effects of the delayed hard palate closure on maxillary growth. The authors reported satisfactory outcomes with only 10% of the 50 subject requiring orthognathic surgery and concluded that a scar as closer to the posterior border of the hard palate would interfere less with maxillary growth than a more anteriorly positioned scar.

1.7.9 Speech therapy

As described in the previous section, many cleft patients have speech deficiencies due to a multifactorial aetiology. Hypernasality is produced when the sound waves enter the oral and nasal cavity of which the main cause is velopharyngeal insufficiency. The oro-nasal fistula may also play a role as air enters the nasal cavity through the fistula in the soft or hard palate. When velopharyngeal insufficiency is suspected, the following investigations may be performed (Habel *et al*, 1996):

Multiview videofluoroscopy involves the child drinking a small amount of Barium and also the Barium is also placed into the nasal cavity via a syringe. A moving x-ray is then taken to which gives a 3 dimensional view of the velopharyngeal port. Nasendoscopy which involves a fibre optic examination allowing visualisation and evaluation of the velopharyngeal structure. Other speech problems may include difficulty in consonant articulation and this needs to be distinguished between other aetiological causes. The speech and language therapists aim to find the aetiology, enhance development, monitor as well as advise other members of the team. Another instrument for investigation is with the use of an electropalatography plate which has a high diagnostic role as it provides visual feedback (Howard and Lohmander, 2011). A custom fitted device with electronic sensors records the position of the tongue and speech sounds to provide a real time visual feedback.

1.7.10 Ear, Nose and Throat input

Middle ear infections and hearing loss is a very common complication of cleft palates with a prevalence of 90% in Caucasians and 69% in Japanese children requiring ENT input at some stage (Sharma and Nanda, 2009). Hearing can be impaired due to the following reasons. Hodgkinson *et al*, (2005) highlights three potential causes

1. The eustacian tube inadequate in length
2. The lumen collapses because the lateral lamina of the tube is deficient
3. The insertion of the tensor veli palatine is inserted into the tube in an abnormal position.

As described in the previous section, cleft subjects are at an increased risk of middle ear infections due to poor drainage. Audiologist monitor hearing and grommets may need to be inserted by an ENT surgeon. A grommet is a Tympanostomy tube which is a small tube inserted into ear drum in order to prevent accumulation of mucus due to velopharyngeal incompetence (Habel *et al*, 1996).

1.7.11 Paediatric and orthodontic considerations

Paediatric dentists would monitor the developing dentition, provide preventative advice such as dietary advice, oral hygiene instruction as well as restoration and extraction of carious teeth. Orthodontists role include the following as described by Hodgkinson *et al*, (2005)

1. Fabrication of intra-oral appliances for the speech and language therapist in order to reduce hypernasality.

2. Presurgical orthopaedics.
3. Preparation for secondary alveolar bone grafting.
4. Alignment of the maxillary dentition if the appearance causes distress or if there is soft tissue trauma.
5. Preparation for orthognatic treatment.

1.8 Secondary Alveolar bone grafting (SABG)

The primary grafting involves grafting of bone in the neonatal cleft at the time of the lip repair thus prior to the eruption of the deciduous incisors Bone grafting in the mixed dentition has been referred to secondary alveolar bone grafting.

Advantages

Secondary alveolar bone grafting is carried out by restoring the osseous defect in the alveolar cleft. The Cochrane review by Gou *et al* (2011) lists the following reasons of performing a SABG. These are

- It gives bony support to the teeth adjacent to the cleft site
- It provides a bone for eruption of the teeth above the cleft and prevents drifting of the teeth adjacent to the cleft into the cleft resulting in their premature loss
- It reunites the maxillary arch and establishes a contour
- It prevents maxillary arch collapse by maintaining the arch width
- It provides stability to the maxillary arch required during mastication
- It reduces the notching in the alveolar ridge

- It eliminates the oro-nasal fistula.
- It provides support to the alar base thereby improving naso labial contour and improving facial appearance

Boyne and Sands, (1972) felt that following the bone graft, the canine eruption could be encouraged maintaining osseous support around the tooth. They describe particular advantages such as complete restoration of the osseous dental arch, improved facial appearance and closure of oro-nasal fistulas. In addition to the advantages mentioned above, Enmark *et al*, (1985) reported absence of hypernasality following elimination of the oro-nasal fistula and better periodontal conditions. They also reported complications involving external root resorption at the cement-enamel junction. This is in agreement with Andlin- Sobocki *et al*, (1995) who found that canine erupting though grafted bone showed periodontal conditions similar to those on the contralateral non-cleft side. Waite and Waite, (1996) report that failure to reconstruct the alveolus may results in reduced maxillary growth, dental crowding and facial asymmetry. Eldeeb *et al*, (1986) compared canines that erupted though grafted bone with canine that erupted in non-cleft patients. The authors reported greater plaque indices in cleft subjects and more gingival inflammation on the palatal surfaces of the canine through the grafted bone and significantly more attachment loss on the mesiolabial, labial and mesiopalatal surface of the canine on the cleft side when compared to the canine on the non-cleft side. Canines that erupted through the grafted cleft defect also had a smaller width of attached labial gingivae compared to non-cleft control group and non-cleft contralateral side.

1.8.1 Timing of secondary alveolar bone grafting

Boyne and Sands, (1972) suggested that the procedure can be undertaken anytime after 8 years of age but the preferred time is between age 9 and 11 just before full eruption of the canine teeth. Bergland *et al,* (1986) advocates the timing of the bone graft between the ages of 9 and 11 when the canine root is a half to two thirds formed. When the graft was performed before the eruption of the canine, 64% of the cleft had greater than 75% bone height compared to 37% after the canine eruption. The authors also discuss that when the bone is grafted before the full eruption of the canine, sufficient bone would be present to allow forward migration allowing erupting tooth to generate further bone. If the lateral incisor is missing, the canine would drift into its space and allow some spontaneous space closure. The researchers also advocate the timing because growth of the maxilla has peaked by age 9 and any further significant retardation of maxillary growth, particularly in the transverse direction is unlikely. Brattstrom and McWilliam, (1989) investigated the effects of timing of SABG with the height of the bone graft and dental anomalies. There described 3 groups

Group 1- had the bone graft before 1 year of age

Group 2- had the bone graft after the eruption of the incisor but before eruption of the canine

Group 3- had the bone graft after the eruption of the canine

Dental anomalies were investigated by a panoramic radiograph and the height of the bone was measured using the Bergland scale. The study showed that group 1 had the fewest supernumerary teeth with the least amount of malformed incisors. Group 2 had the greatest bone height and the least number of abnormal lateral incisors.

Group 3 had the greatest frequency of hypodontia. The authors advocate the timing of SABG after incisor eruption and before canine eruption. Helms *et al*, (1987) found that bone grafting less than a year of age resulted in increased bone height and greater number of tooth retention adjacent to the cleft. The bone graft performed when the canine was a quarter to a half formed or after canine eruption resulted in a reduced bone height and greater prevalence of anterior and posterior crossbites. The researchers did use rib grafts for the early surgery and iliac crest grafts for the latter two which could be a confounding factor. Freihofer *et al*, (1993) found that the greatest success of the bone graft was achieved before the eruption of the canine, however, they defined success as closure of the oro-nasal fistula with at least 50% of the bone graft in situ. Shashua and Omnell, (2000) suggested that an earlier SAGB can be performed before the eruption of the lateral incisor if it is in the cleft in order to provide an osseous support and prevent the risk of its loss. Enmark *et al*, (1987) reported significantly shorter lengths of the maxilla when the SABG was performed after the eruption of the canine and suggest better results are obtained prior to the eruption of the canine. Lilja, (2009) reports that the success of bone grafting is lower following the eruption of the canine and complete space close is more difficult. This is in agreement with Lilja *et al,* (2000) who found that when the bone was grafted to facilitate eruption of the lateral incisors, the cleft space could be closed in all patients. They suggest that the bone graft should take place when the lateral incisor or the canine adjacent to the cleft is covered by a thin shell of bone. Tertiary alveolar bone grafting or late secondary alveolar bone grafting has also been performed in conjunction with a the orthognatic surgery. Browns and Egyegi, (1980) reported having carried out an osteotomy of the premaxilla in conjunction with a maxillary osteotomy in bilateral cleft palate cases. In a few of the cases, a bone graft was required as tilting of the premaxilla was necessary. Satisfactory results were reported with regards to occlusal relationships and stabilisation, however, they mentioned technical difficulties resulting in irregular and scarred gaps adjacent to the premaxilla. In summary, most authors advocate bone grafting prior to the eruption of the teeth adjacent to the cleft to allow their eruption and make complete space closure possible.

1.8.2 Donor sites

Donor sites can include

1. The iliac crest
2. Rib grafts
3. Mandibular symphysis
4. Calvarium
5. Tibial
6. Synthetic bone

Cancellous bone is preferred to cortical bone as it has the ability to revascularise quickly and remodel to alveolar bone. The survival of cortical bone depends heavily on blood flow though the canaliculi and if this is blocked, the bone will die. The iliac crest provides a large reservoir of cancellous bone, however, there are complications of scarring, pain, joint injury and risk to the nerve (Sivarajasingam *et al, 2001).* Newlands, (2000) reported one case involving neuopraxia of the lateral femoral cutaneous nerve as a possible complication of grafting from the iliac crest. This is in agreement with Lilja, (2009), who reports that cancellous bone is superior to cortical bone due to the increased vascularity and greater ability for bone regeneration due to primary healing by osteogeneis. Cortical bone dies after grafting and regenerate following invasion of bone cells from the recipient site resulting in a delay of tooth bearing function.

The most common technique used is the one described by Boyne and Sands, (1972). They describe a procedure where the periosteum from the walls of the cleft is raised and sutured to establish the nasal boundary. The donor site is the cancellous bone taken from the lateral aspect of the iliac crest which is packed into the cleft defect. The labial mucosa is then extended over the grafted area and the arch is stabilised with orthodontic banding and an archwire. Complications of the operation include a shortening of the vestibular sulcus, which may result in tension on the philtrum and a dehiscence of the palatal incision with loss of some of the bone fragments grafted from the iliac crest. Borstlap *et al*, (1990) discuss their technique used for rib and chin grafts. With regards to the rib graft, a 4 cm infra-mammary incision is made, the muscles and tissue of the rib chosen is divided and approximately 8cm of the rib is removed. The chin graft is performed by a marginal incision of the gingivae of the lower incisors with two vertical relieving incisions to expose the anterior surface of the mandibular symphysis. The bone is drilled avoid in the developing mandibular canines. The authors advocated chin bone as opposed to rib graft as it was reported that over 50% of the rib graft was resorbed in 15.7% of the patients. Complications involving the chin graft included a wound dehiscence and dilacerations of the developing mandibular canine. Freihofer *et al*, (1993) reported that when the bone graft was performed before the eruption of the canine, the greatest success was achieved with grafted chin bone followed by the rib graft. Sivarajasingam *et al*, (2001) compared the optical densities of bone grafts from the iliac crest with tibial bone grafts and found no significant difference. Lilja, (2009) reports that the source of the bone graft does not seem to influence the outcome. Losee and Kirschner (2009) mentioned that bone morphogenic protein which is a type of synthetic human protein have been reported in the literature as having good preliminary results, however, currently there is lack of indication for grafting this bone as quoted in the FDA standards.

1.9 Assessment of bone fill

Assessment of the bone fill should ideally be carried out at least 3 months after the bone grafting. This is because the grafted bone transforms into normal trabecular bone by 3 months (Bergland *et al*, 1986).

1.9.1 Bergland Score

Bergland *et al*, (1986) assessed the amount of bone fill using a four point scale measuring the inderdental adjacent to the erupted canine.

Grade 1- Height approximately normal

Grade 2- Height at least three quarters of normal height

Grade 3- Less than three quarters of normal height

Grade 4- No continuous bony bridge across the cleft

1.9.2 Modified Bergland score

The modified Bergland scale was devised by Hynes and Earley, (2003). They highlighted that the original Bergland scale does not take into account the basal level of the graft but only the height of the interdental bone. The authors propose using the same scoring system but including the full height extending from the root apices to interdental height. They suggest that scores of 3 may have enough bone for prosthodontic and periodontal support as well as arch stabilisation in the short term but may however be inadequate in subjects who require orthognathic surgery.

1.9.3 Enmark scale

Enmark *et al* (1987) assessed the marginal bone level of teeth adjacent to the cleft using intra oral films on a 4 point scale.

1- Marginal bone level between 100% and 75%

2- Marginal bone level between 75% and 50%

3- Marginal bone level between 50% and 25%

4- Marginal bone level between 25% and 0%

1.9.4 Long *et al* scale

Long *et al (1995)* used periapical radiographs taken 6 months postoperatively to evaluate the contour and bone height relative to root length of the tooth in the proximal segment and root length in the distal segment.

1.9.5 Post-Operative Bone Fill Index

Kindelan *et al*, (1997) produced the Post-Operative Bone Fill Index which assesses the height of the grafted bone in the cleft on an oblique occlusal 6 months post-operatively using a four point scale. The author highlights that this scale can be used prior to eruption of the canine

Grade 1- Greater than 75% bony fill of the cleft
Grade 2- Between 50 and 75% bony fill of the cleft
Grade 3- Less than 50% bony fill of the cleft
Grade 4- No complete bony bridge of the cleft

Dobynn *et al*, (2012) assessed the reliability of the Post-Operative Bone Fill Index. Two examiners examined 84 radiographs independently two weeks apart. The films were scanned and viewed on a computer. The authors reported a very good intra-examiner agreement, moderate to good inter-examiner agreement and both were within acceptable limits. They suggest that more formalised training may result in higher level of agreement.

1.9.6 Chelsea Scale

Witherow *et al*, (2002*)* described the Chelsea scale using intra-oral radiographs and the teeth mesial and distal to the cleft which can be used prior to canine eruption. The scale involves bisecting the cleft vertically and the teeth on either side is divided into 4 equal parts along the root. The bone is measured in relation to the midline of the cleft using the two teeth. Nightingale *et al*, (2003) compared the reproducibility of the Bergland scale, Kindelan score and the Chelsea scale and reported that no scale was more reproducible than the other. Neither occlusal nor periapical radiograph was more reproducible, however, greater reproducibility was found in the mixed dentition as opposed to the permanent dentition.

1.9.8 Cone Beam Computer Topography (CBCT)

Traditionally the bone fill of the cleft has been measured on two dimensional radiographs. Oberoi *et al*, (2009) reports that a two dimensional image of a three dimensional defect allow measurements of the bone height only and not the volumetric infill of the cleft defect. They advocate the use of CBCT as its estimations are more precise and does not overestimate the measurement as with previous studies.

1.10 Outcome of Secondary Alveolar Bone Grafting (SABG)

Numerous studies have been published in which authors have evaluated the success of bone grafts by predominantly measuring the infill of bone using the Bergland scale or the Post-Operative Bone Fill Index. Amanat. and Langdon, (1991) evaluated 47 bone grafts using the Bergland scale and reported 63.3% of subject with score 1 and 19.9% with score 2 with only 2 grafts with total failures. Bayerlein *et al,* (2006) measured success using the Bergland scale and reported that 76% of subject scored

1 or 2 with 13% requiring a repeat bone graft. Collins *et al*, (1998) reported a higher success rate as defined by score 1 or 2 on the Bergland scale with 86.86%. Kalaaji *et al*, (1996) reported that 81% of the subjects in their study had a bone height of 75% or greater, 13% had bone heights between 50 and 75% and 6% had less than 50%. LIlja *et al*, (1998) reported similar results with 94% of subjects achieving more than 75% of bone height, 4% of subjects achieving between 50% and 75% and 2% achieving less than 50%. It appears from most of the reports that the success varies with a range from 70% to 100% of subjects achieving a 75% or greater bony infill of the cleft following bone grafting.

1.11 Factors that may influence outcome of SABG

Factors that may influence the outcome of SABG include age at SABG, root development of teeth in line or adjacent to the cleft, size of cleft, surgical experience and technique, pre-graft orthodontics with emphasis on expansion, type of cleft (unilateral or bilateral) and oral hygiene post-operatively. As described previously numerous studies have reported greater heights of the grafted bone just before eruption of the canine. Van der Meij *et al,* (2003) performed a study to evaluate an association between cleft width and bone height 1 year post-operatively. They reported an average cleft width of 6.4mm in 54 unilateral cleft subjects. The clefts with a width less than 4mm had 67.6% of residual bone left, whereas the clefts wider than 9mm had on average 38.2% bone present. They discuss that revascularisation at the centre of the graft is more unlikely the wider the cleft as well as the amount of bone harvested may be insufficient. Surgical factors may play a role such as good separation of the nasal and oral cavity. Unfavourable loading may result in the collapse of the flaps, exposure of the graft and reduced stability. All these factors would suggest that bilateral clefts would be more likely to fail than unilateral clefts, however, Bergland *et al*, (1986) reported that the bone heights were similar in subjects with unilateral and bilateral clefts following proper immobilisation of the premaxilla postoperatively. Van der Meij *et al,* (2001*)* reported 70% of grafted bone retention after 1 year in unilateral cleft subjects and 45% in the bilateral cleft subjects. Feichtinger *et al,* (2006) reported the absence of correlation between the size of the cleft and success. Revington *et al*, (2010) assessed 235 bone grafts using the Post-Operative Bone Fill Index at 8 different units in England and Wales. They reported 71.7% subjects with grade 1 in unilateral cleft group and 54.8% subjects with grade 1 in the bilateral group. Although the unilateral clefts had more successful bone grafts, the difference was not significantly different. They also reported no significant difference between centres or surgeons. Newlands, (2000) also found no difference in success between unilateral and bilateral cleft however, the success was greater when orthodontic expansion was carried out prior to the SABG. The author suggests that grafting a wide cleft is technically easier and expanding narrow clefts may improve the success of grafting. Kindelan and Roberts-Harry, (1999) reported 63.2% of clefts attaining a grade 1 Post-Operative Bone Fill Index score in expanded subjects and 40% with grade 1 in the non-expanded subjects thus concluding that a greater success when the maxillary arch was expanded.

Losee and Kirschner, (2010) discuss that presurgical arch expansion is not always favourable because more bone is required to restore the defect. They suggest that a greater success of bone grafts is achieved when the bone is stimulated by teeth erupting through the bone graft or by orthodontic movement of adjacent teeth in to the bone graft.

Feichtinger *et al*, (2008) examined CT scans of 20 subjects with unilateral cleft lip and palate. They reported more that more than half of the bone volume was lost in 11 out of 20 subjects and in the 2 subjects who had missing lateral incisors, the bone graft completely failed. The amount of bone resorbed after 1 year correlated positively with the volume and width of cleft. Kalaaji *et al*, (1996) found in their retrospective study that significantly better bone heights were found following SABG when the operation was carried out by the more experienced surgeons. They reported that a surgeon that is most familiar with one procedure is likely to obtain better results and is therefore the most important variable thus recommending that a restricted number of experienced surgeons should perform the alveolar bone grafting. Williams *et al*, (2003) carried out a study to examine factors influencing success of secondary alveolar bone grafting. Their logistic regression showed a significant positive relationship between age at bone grafting and success. They however reported that post-operative complications, grade of surgeon and specialty of surgeon had no effect. Bergland *et al* (1986) reported 2 bone graft failures due to gingivitis.

1.12 Canine eruption

1.12.1 Prevalence of canine impaction in cleft subjects

Canine impaction has been reported as a risk following secondary alveolar bone grafting. Eldeeb *et al*, (1982) examined the behaviour of the canine following SABG.

They reported that at no stage was the canine on the cleft side ahead of the canine on the non-cleft side with regards to root development, however, in bilateral cleft subjects, the canines were at the same stage in root development. Complete root formation occurred for all subjects and in the unilateral cleft subjects, the cleft canine erupted 1.1 years after eruption of the contralateral canine with a mean time of 3.4 years to erupt through the graft. 17% of cleft canines required surgical exposure, 56% required exposure and orthodontic traction and 27% erupted spontaneously. Bergland *et al*, (1986) reported that 95% of canines erupted spontaneously. Turvey *et al*, (1984) reported that 95% of the 33 canines erupted spontaneously with only 1 canine requiring surgical exposure and orthodontic traction. Oberio *et al*, (2005) reported that 12% of the canines required surgical exposure. Matsui *et al*, (2005) reported 78.9% of the 150 canines erupted spontaneously with the remaining requiring surgical exposure. The incidence of canine impaction has been reported to be significant lower in non cleft subjects. Ericson and Kurol, (1987) diagnosed 2.8% potentially ectopic erupting maxillary canines in 3000 non-cleft subjects. Bishara, (1992) discussed the aetiology and sequelae of canine impaction. General causes include febrile diseases, endocrine disorders and irradiation. Local factors include crowding, ectopic position of the developing bud, ankylosis, neoplastic or cystic formation, dilaceration, missing lateral incisor or the presence of an alveolar cleft. The sequelae include ectopic position eruption, migration of adjacent teeth resulting in a reduced arch length, internal resorption, external root resorption of the canine or adjacent tooth, dentigerous cyst formation, referred pain or infection.

1.12.2 Eruption path of canines in cleft subjects

Oberio *et al*, (2005) examined the eruption pathway of 25 canines for up to 1 year following secondary alveolar bone grafting using CBCT. They reported that most of the canines moved mesially, labially and incisally, 5 canines moved palatally and 3 moved distally. Geretzul *et al*, (2005) examined the eruption path of canines in bone grafted clefts, non-bone grafted clefts and non-cleft subjects. They defined the canine angle as the internal angle between the long axis of the canine and a horizontal reference line at the level of the most inferior point of the orbital cavity. The researchers reported that the initial canine angle was not significantly different between the bone grafted and non-bone grafted group in cleft subjects, however, was significantly greater i.e. more vertical in the non-cleft group. The angle of canines in the bone grafted group changed by approximately 0.6°, in the non-bone grafted group changed by 9.3° and in the non-cleft group changed by 9.6°. This study demonstrated that canines erupt without a significant change in angle through the bone graft. They postulate the reason for the angular change in the non-cleft group could be due to the lateral incisor and in the non-bone grafted group due to guidance from the cortical bone.

Factors influencing canine eruption

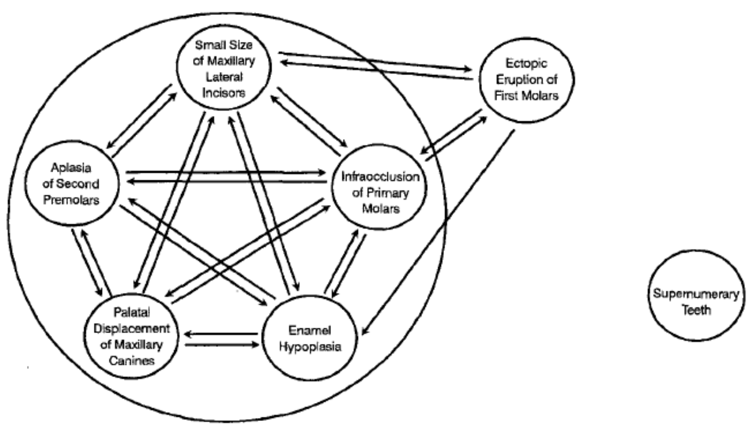
1.13.1 Timing of SABG

As mentioned previously, the timing of the secondary alveolar bone grafting plays a role in allowing forward migration and hence eruption of the canine (Bergland *et al* 1986). See chapter 1.8.1.

1.13.2 Genetic causes

A genetic cause for canine impaction has been suggested because it occurs with other anomalies. Baccetti, (1998) carried out a retrospective study using radiographs on a large sample size of over five thousand subjects. The author presents the following diagram that shows the associated anomalies, however, it is only applicable to palatally displaced canine.

Figure1.12.3: Association of dental anomalies



The diagram shows that there is a statistical reciprocal (represented by two arrows) association between palatally displaced canines and small size of maxillary lateral incisors, infraocclusion of primary molars, enamel hypoplasia and hypodontia of second premolars but no association with supernumerary teeth. Chung *et al*, (2011) also reported that palatal canine impaction was significantly greater in females which again leads to believe that a genetic cause is present.

1.13.4 Presence of lateral incisors and Guidance theory

Enemark *et al*, (2001) reported an increase risk in canine impaction when the lateral incisor was missing. In the subjects who had grafts from the iliac crest, 35.1% of the canines were impacted when the lateral incisor was present as opposed to 50.1% of canine impactions when the lateral incisor was missing. They mention that the reason for this could be that the root of the lateral incisor guides the canine down towards the occlusal plane. This is in agreement with Becker, (1995) who theorised that the root of the lateral incisor guides the eruption the canine. Brin *et al*, (1986) found that 42.6% of palatally impacted canines were associated with peg shaped, small or missing lateral incisors in non-cleft subjects. Oberio *et al,* (2005) and Tortora *et al*, (2008)*,* however, reported a lack of correlation between missing lateral incisor and spontaneous canine eruption in cleft subjects

1.13.5 Canine position in Non-cleft subjects

There are also numerous other factors that influence canine eruption. Erikson and Kurol, (1988) found a success rate of 78% spontaneous canine eruption following extraction of the deciduous canine in non-cleft subjects between 10 and 13 years of age with no crowding. The authors reported that 19 of 24 canines which were distal to the midline of the lateral improved in position whereas 4 of the 22 canines mesial to the midline of the lateral improved. This was similar to the findings reported by Power and Short, (1993). They reported that the prognosis for spontaneous canine eruption was good if the overlap of the adjacent lateral incisor was less than a half and if the angulation to the vertical plane was less than 31°. Vertical height and the eruptive distance was not found to have a significant effect on eruption.

1.13.6 Canine position in cleft subjects

The factors mentioned above in non-cleft subjects are also applicable to the cleft population. Russell and McLeod, (2008) carried out a study examining the vertical and lateral position of the canine following SABG. With respect to the vertical position, the canine was at risk if the long axis of the canine root was greater than 45 degrees to the midsagittal vertical reference line. Laterally the canine was at risk if the canine tip was mesial to the midplane of the lateral incisor root or the midplane to the space distal to the central incisor, if the lateral incisor was missing. The author found that there was a significant reduction in proportion of canines with an abnormal vertical position after SABG, indicating a reduce risk of impactions following SABG. They also found that 61% of cleft sites had abnormal lateral incisor anomaly with more cases of abnormally positioned canines and a lateral incisor anomaly on the cleft side compared to the non-cleft side. There was also a significant greater percentage of canines post-SABG that had abnormal lateral positions when the lateral incisors were missing. Tortora *et al*, (2008) reported that inclination of the canine to the vertical plane had a significant effect on their spontaneous eruption with no canines greater than 45° erupting spontaneously.

1.13.7 Space creation

The provision of space creation appears to be an important factor as shown by Baccetti *et al*, (2008) who found that 87.5% of palatally displaced canines erupted spontaneously when the C was extracted and space was created with the use of headgear compared to 50% success in the control group and 62.5% success in the extraction of the C group. Expansion of the arch in order to create space in non-cleft subject has also been associated with greater likelihood of spontaneous canine eruption Baccetti *et al*, (2009). Enemark *et al,* (2001) found that expansion of the arch had no statistically significant effect on spontaneous canine eruption in cleft subjects.

Chapter 2

Participants and Methods

2.1 Aims

1. To determine the success of secondary alveolar bone grafting (SABG) as determined by spontaneous canine eruption.
2. To investigate the influence of the following factors on canine eruption

- Post-Operative Bone Fill Index (Kindelan et al 1997)
- Age at SABG
- Presence of a lateral incisor
- Horizontal position of canine relative to the midplane of the lateral incisor
- Angulation of canine relative to a 45° vertical reference line
- Presence of expansion prior to SABG
- Type of cleft (unilateral or bilateral)

2.2 Study Design

This was a retrospective observational cohort study using records primarily from the Birmingham Children's Hospital with supplementation from the Birmingham Dental Hospital and several district hospitals in the West Midlands. All subjects had their SABG carried out at the Birmingham Children's Hospital and their orthodontic treatment carried out at the Birmingham Dental Hospital or a district hospital in the West Midlands, hence the reason for the multicentre approach.

2.3 Null Hypothesis

There is no correlation between spontaneous canine eruption and Post-Operative Bone Fill Index , age at SABG, presence of the lateral incisor, horizontal position relative to midplane of lateral incisor, angulation of canine relative to 45° in the vertical plane, presence of expansion prior to SABG and type of cleft.

2.4 Ethical approval

Ethical approval was gained from the University of Birmingham Research and Ethics Committee (ERN_12-1244). Site specific approval at each trust was also gained from the Research and Development or the audit department. An honorary contract was also issued by the Birmingham Children's Hospital.

2.5 Sample size calculation

A sample size calculation based upon an alpha significance level of 0.05 and a power of 80% estimated that subjects with a total of 59 cleft canines would be required to detect a correlation between the Post-Operative Bone Fill Index score and spontaneous canine eruption. This was based upon an assumption that following SABG, 80% of the clefts would have a Post-Operative Bone Fill Index score of 1 and 80% of canines with a Post-Operative Bone Fill Index score of 1 would erupt spontaneously. This was in comparison to 20% of clefts having a Post-Operative Bone Fill Index score of 2, 3 or 4 and 80% of canines with a Post-Operative Bone Fill Index score 2, 3 or 4 not erupting spontaneously.

2.6 Subject selection

Inclusion criteria

- Subjects born with a cleft in the alveolus who have undergone an alveolar bone grafting procedure between October 2004 and December 2006 at the Birmingham Children's Hospital.

Exclusion Criteria

- Subjects with congenitally missing or extracted permanent canines
- Subjects with erupted canines prior to SABG
- Subjects with unusable or missing occlusal radiographs

2.7 Method

Data was collected from five centres which included:

1. Birmingham Children's Hospital
2. Birmingham Dental Hospital
3. Warwick Hospital
4. Burton-Upon-Trent Hospital
5. Gloucester Royal Hospital

Subject records including clinical entries, radiographs which included occlusal radiographs and orthopantograms as well as study models were examined.
The following data was collected;

1. Gender of the subject
2. Type of cleft- unilateral or bilateral
3. The post operative Bone Fill Index score
4. Presence of expansion prior to SABG
5. Age at SABG
6. First or repeat bone graft
7. Presence of lateral incisor
8. Morphology of lateral incisor
9. Time between SABG and post-operative occlusal radiographs
10. Eruption of canine on cleft side- spontaneous or with surgical intervention
11. Eruption of canine on contra-lateral side in subjects with unilateral clefts
12. Angulation of canine relative to a 45° vertical reference line
13. Horizontal position of canine relative to the midplane of the lateral incisor

The gender of the subject and the type of cleft was determined from the subject notes.
The Post-Operative Bone Fill Index score devised by Kindelan *et al*, (1997) *a*ssesses the height of the grafted bone in the cleft using an oblique occlusal radiograph 6 months post-operatively on a four point scale.

Grade 1- Greater than 75% bony fill of the cleft

Grade 2- Between 50 and 75% bony fill of the cleft

Grade 3- Less than 50% bony fill of the cleft

Grade 4- No complete bony bridge of the cleft

Mr Nahul Patel, specialist registrar in Orthodontics contacted the author of the index, Dr Jay Kindelan by telephone and was informed that a calibration course was not available. Upon learning this, the researcher attended the orthodontic specialist interest group meeting on the 20th January 2012 hosted by the Manchester Children's Hospital where Dr Jay Kindelan and Dr Gunvor Semb demonstrated the use of the Post-Operative Bone Fill Index. The session also included a practical session involving scoring and marking of 30 cases followed by answers. The researcher learned the following with regards to accurate application in the use of the index;

1. The pre-operative and the post-operative occlusal radiographs are both required which should be taken at the same angle and same exposure in order to accurately compare the percentage of the cleft filled by bone.
2. The radiographs should be viewed in a dark room over a light background.
3. The assessment is subjective.

Most of the occlusal radiographs were viewed on the AGFA PACS system 6.5.2.657 at the Birmingham Children's Hospital on which the researcher received training on. The pre-operative and post-operative occlusal radiographs on the PACS system were viewed simultaneously and the contrast was adjusted to optimise similarity. The very few remaining occlusal radiographs on a hard copy were viewed on light box and the difference in contrast was accepted.

In order to test the intra-examiner reliability, occlusal radiographs of 20 randomly chosen subjects were assessed for the Post-Operative Bone Fill Index score one month following initial assessment.

The age at secondary alveolar bone grafting was determined to the nearest whole year calculated by using the date of birth and the date of SABG. If the SABG was repeated which was determined from the examination of the operation histories, the age was calculated using the date of the repeated SABG.

The presence of the lateral incisor was determined from the pre-SABG orthopantogram as well as clinical entries. If the lateral incisor was extracted at the time of the SABG, it was classified as missing. The morphology was determined using clinical entries, orthopantograms and study models which was classified as one of the following

1. Normal
2. Peg shaped or small
3. Unerupted or impacted
4. Not known

Unerupted or impacted was also included in this group as it would affect the guidance of the canine. The following criteria was used to assess morphology of the lateral incisor

- Normal - The mesio-distal width was greater than its mandibular counterpart

- Small - The mesio-distal width was smaller than its mandibular counterpart
- Peg – The mesio-distal with was the greatest at the cervical margin

On the study models, mesio-distal widths were measured using a steel ruler with callipers and on the digital orthopantograms, they were measured using a digital ruler.

The lateral incisor was deemed impacted if there was evidence of a physical obstruction preventing it from erupting such as a supernumerary.

The time between SABG and post-operative occlusal radiographs was recorded in months. If the SABG was repeated, the time was recorded following the repeat operation.

Using the method adopted by Russell and McLeod, (2008), the horizontal position of the canine was defined as at ‘risk’ or ‘no risk’ depending on its position relative to the lateral incisor. It was defined as at ‘risk’ if the tip of the canine was mesial to the midplane of the lateral incisor root or mesial to the space that the canine would occupy if the lateral incisor was missing. The width of the canine was measured using a digital ruler and halved to ascertain the midplane of the lateral incisor if it was missing. If the canine was distal to the midplane, it was defined as ‘no risk’. The angulation of the canine was again subcategorised as being ‘at risk’ if the long axis of the canine root was greater than 45° to the midsagittal vertical reference line and at ‘no risk’ if was less than 45°. The vertical reference line was guided by the use the anterior nasal spine. The measurements were made on orthopantograms, which were either taken prior to or after SABG depending on the availability. If both were available, it was measured on the post-SABG orthopantogram.

Spontaneous eruption of the canine was documented if it was charted in the clinical entries as erupted or partially erupted without evidence of surgical intervention. Absence of spontaneous eruption was documented if surgical intervention was required to assist eruption or if it has not erupted.

Data that was not available from the Birmingham Children's Hospital was then supplemented by data collected from the additional hospitals mentioned previously following obtainment of access by the treating consultant orthodontist. The additional data required tended to be the status of canine eruption and presence of expansion.

2.8 Statistical analysis

Statistical advice was given by Dr Paul Davies, statistician at the Birmingham Children's Hospital and by Professor Thomas Dietrich, Professor and Head of Oral Surgery at the Birmingham Dental Hospital. The data was analysed using Minitab Project manager statistical programme for descriptive statistics. The intra- examiner reliability for the assessment of the Post-Operative Bone fill Index score was assessed using the Weighted Cohen's Kappa score for 20 sets of occlusal radiographs. A binary logistic multiple regression analysis was used to investigate an association between the Post-Operative Bone Fill Index Score and spontaneous eruption of the canine as the dependant variable adjusting for presence of expansion, age at SABG, presence of the lateral incisor, type of cleft, horizontal position and angulation risk of the canine. The morphology of the lateral incisor was not included in the logistic regression analysis due to the incomplete sample and because not all clefts were associated with the presence of a lateral incisor.

Chapter 3

Results

Chapter 3	Results	Page

Results

3.1 Characteristic of sample

58 subjects with unilateral clefts of the palate with or without lip involvement were identified of which 12 subjects were excluded amounting to 46 clefts. 22 subjects with bilateral clefts were indentified of which 2 subjects were excluded amounting to 40 clefts. A sum total of 86 clefts therefore satisfied the inclusion criteria. In subjects with unilateral clefts, 26 subjects were male and 20 subjects were female with 33 clefts situated on the left and 13 on the right. Of the 20 subjects with bilateral clefts, 6 were female and 14 were male.

The results are presented in the following tables

Table 3.1.1: Spontaneous eruption of canine

Spontaneous eruption of canine	Number of canines	Number of Canines (%)
Yes	64	74.4
No	22	25.6

Just less than three quarters of the canines erupted spontaneously. Nine canines required surgical intervention and one canine was surgically extracted following SABG. The remaining 12 canines had not erupted when the data was collected between January 2012 to May 2013.

Table 3.1.2: Spontaneous eruption of the canine on the contralateral side in subjects with unilateral clefts

Spontaneous eruption of canine	Number of canines	Number of Canines (%)
Yes	44	95.7
No	2	4.3

Forty four canines of forty six canines (95.7%) erupted spontaneously on the contralateral non-cleft side.

Figure 3.1.3: Post Operative Bone Fill Index Score for all clefts

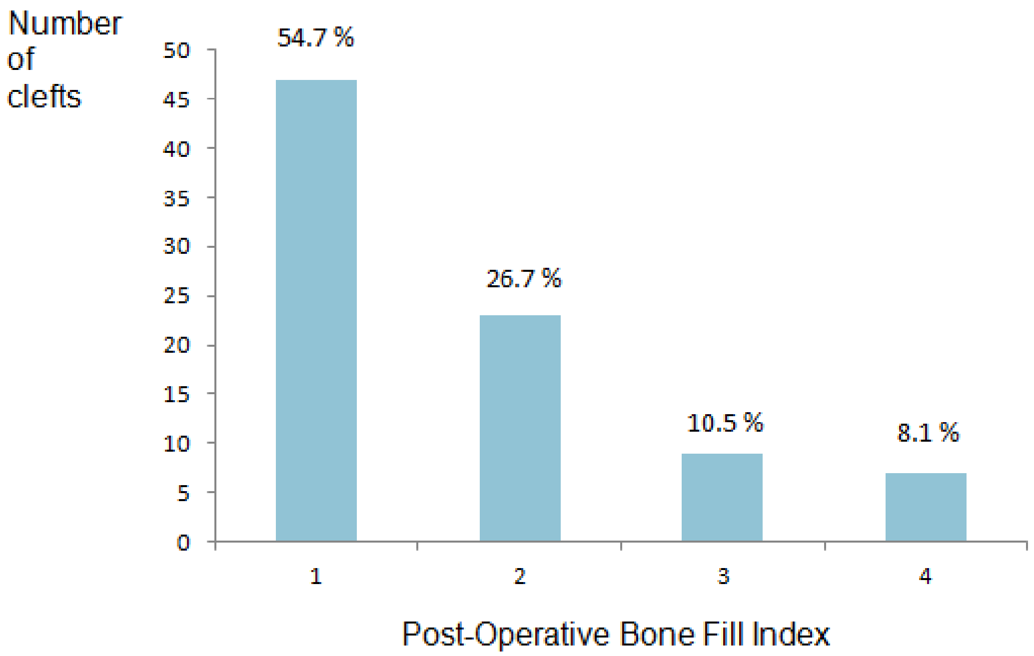


Figure 3.1.4: Post-Operative Bone Fill index score of clefts associated with absence of spontaneous canine eruption

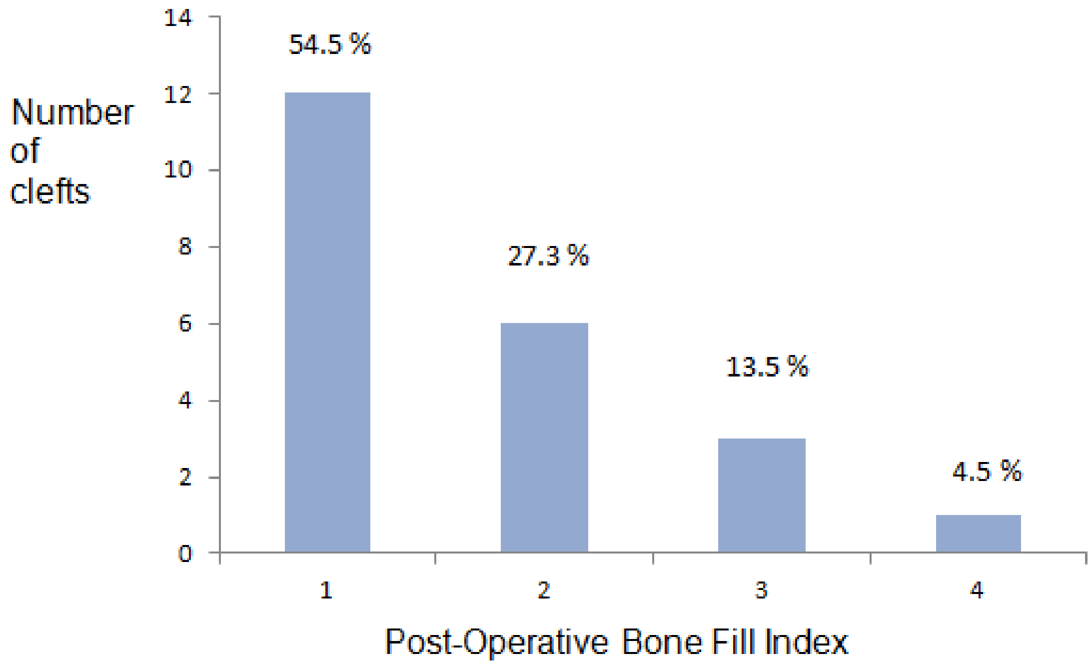


Table 3.1.5: Subjects with expansion

Orthodontic expansion	Number of clefts	Number of clefts (%)
Yes	26	30.2
No	60	60.8

Table 3.1.6: First and repeat bone grafts

Bone graft	Number of clefts	Number of clefts (%)
First	75	87.2
Repeat	11	13.8

Table 3.1.7: Presence of lateral incisor

Presence of lateral incisor	Number of clefts	Number of clefts (%)
Yes	41	47.7
No	45	52.3

Table 3.1.8: Morphology of the lateral incisor

Morphology of lateral incisor	Number of clefts	Number of clefts (% of lateral incisors present)
Normal	11	26.8
Small/Peg	17	41.5
Unerupted/Impacted	5	12.2
Unknown	8	19.5

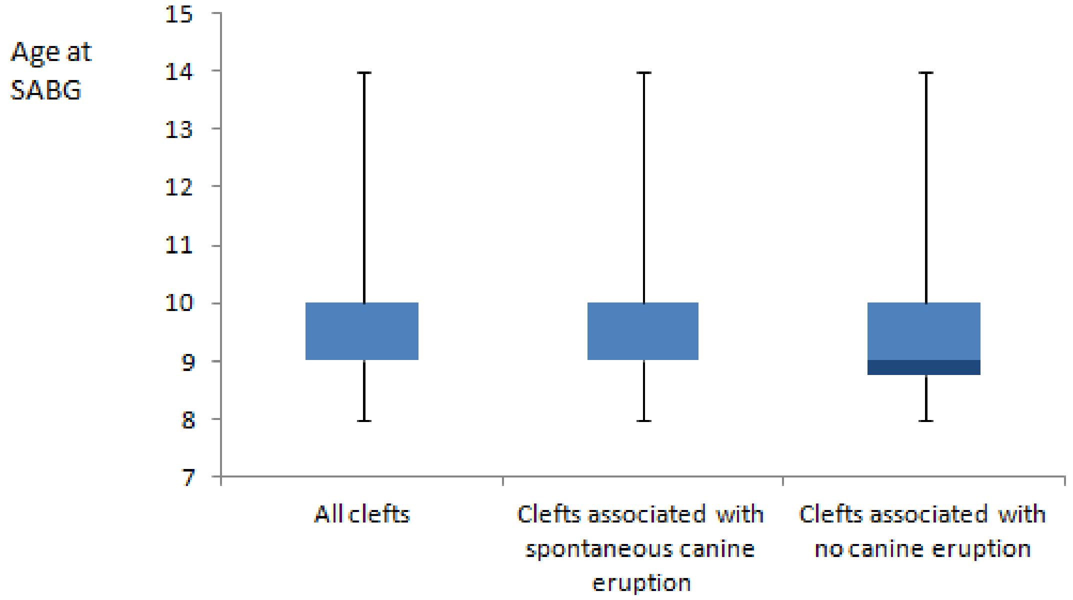
Table 3.1.9: Angulation of canine

Risk	Number of clefts	Number of clefts (%)
Yes	24	27.9
No	62	72.1

Table 3.1.10: Horizontal position of canine

Risk	Number of clefts	Number of clefts (%)
Yes	12	14.0
No	74	86.0

Figure 3.1.11: A box and whisker plot for the age at SABG



The first quartile and the median are the same for ‘all clefts’ and ‘clefts associated with canine eruption’ hence the single box. The median and the lower quartile both indicated 9 years of age.

Figure 3.1.12: Box and Whisker plot for the time between SABG and post-operative occlusal radiograph.

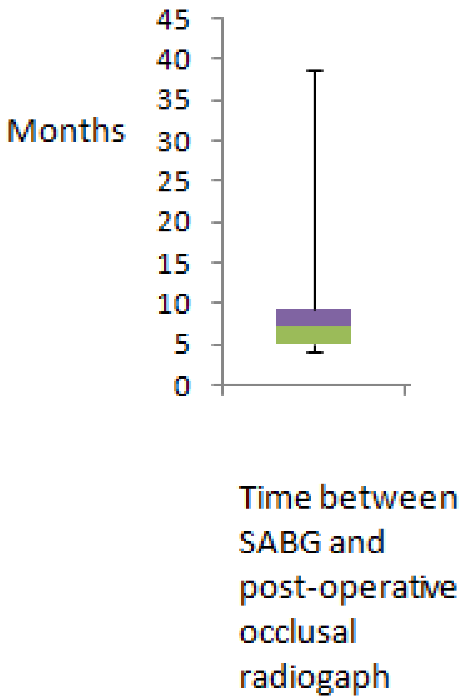


Table 3.1.13: Binary logistic regression analysis of independent variables

Independent variable	P value	Odds ratio	95% Confidence Interval
Post-operative Bone Fill Index Score	0.82	1.07	0.61 - 1.87
Age at SABG	0.35	0.84	0.59 - 1.21
Orthodontic expansion	0.968	0.98	0.30 - 3.18
Lateral position of canine	0.92	0.92	0.20 - 0.43
Angulation of canine	0.221	0.47	0.14 - 1.57
Presence of lateral incisor	0.56	0.75	0.26 - 2.14
Type of cleft (Unilateral/Bilateral)	0.725	0.82	0.27- 2.46

The Binary logistic regression analysis (Table 3.1.13) showed that there was no significant correlation between spontaneous canine eruption and the Post-Operative Bone Fill Index Score (P= 0.82, 95% confidence interval (C.I.) = 0.61, 1.87), age at SABG (P= 0.35, C.I. = 0.59, 1.21), presence of expansion (P= 0.968, C.I. = 0.30, 3.18), presence of lateral incisor (P= 0.56, C.I.= 0.26, 2.14), angulation of the canine to a 45° vertical reference line (P= 0.221, C.I.= 0.14, 1.57), position of canine relative to midplane of the lateral incisor (P= 0.92, C.I.= 0.20, 2.43) and type of cleft-unilateral or bilateral (P= 0.725 C.I.= 0.27, 2.46).

Table 3.1.14. Initial and repeat Post-Operative Bone Fill Index scores used to test intra-examiner reliability.

Initial score	Repeat Score	Agreement
1	1	Yes
2	2	Yes
2	2	Yes
1	1	Yes
4	3	No
1	1	Yes
2	2	Yes
4	3	No
1	1	Yes
3	3	Yes
1	1	Yes
2	2	Yes
3	4	No
2	2	Yes
4	4	Yes
4	3	No
1	1	Yes
3	2	No
1	1	Yes
2	2	Yes

There above table shows that there was agreement in 75% of the scores. The weighted Cohen's Kappa score of 0.78 suggests a good agreement. The majority of the disagreements tended to be distinguishing between scores 3 and 4.

Chapter 4

Discussion

4.1 Discussion

The inclusion criteria of subjects receiving SABG between October 2004 and 2006 would allow ample time for canines to erupt given that the average age of upper permanent canine emergence is 11.45+/- 1.21 years in non-cleft patients (Helm and Seidler, 1974) which is delayed in cleft patients by 0.3 to 0.7 years (Ranta, 1986). The operating surgeon began performing alveolar bone grafts at the Birmingham Children's Hospital in October 2004 and hence confounding factors such as operator specialty and technique would be reduced. Operator experience would however not be eliminated.

Sixty six of the eighty eight canines erupted spontaneously (Table 1), 10 canines required surgical intervention and the remaining 12 had not erupted when the data was collected. Of the 10 canines requiring surgical intervention, 7 canines were exposed and bonded, 1 canine had an apically repositioned flap, 1 canine was extracted and the 1 remaining canine was associated with extraction of the lateral incisor into order to encourage its eruption. The success of spontaneous canine eruption was therefore 74.4%. This is a reasonable level of success as defined by spontaneous canine eruption when compared to other researchers e.g. Eldeeb *et al*, (1982) reported a 27% success rate, Oberio *et al*, (2005) reported a 78.9% success rate, Bergland *et al*, (1986) and Turvey *et al*, (1984) reported that 95% success rate. In subjects with unilateral clefts, spontaneous canine eruption on the contralateral side occurred in 95.7%. (Table 2). The absence of spontaneous eruption on the contralateral side in these subjects of 4.3% is comparable to the general population with a prevalence of 3.58% (Aydin *et al*, 2004). This study found that the failure of spontaneous eruption was 6 times greater when the canine was situated adjacent to a cleft in patients with unilateral oral clefts. Subject with clefts in this study compared to the general population have a 9 fold increase in canine impaction which is much less than the 20 fold increase reported by Russel and Mcleod, (2008).

The Post-Operative Bone Fill Index scores (Figure 3.1.3) demonstrate that over half of all clefts (54.7%) had a score of one, 26.7% clefts had a score of two, 10.5% had a score of three and 8.1% had a score of 4. The success rate in this study according the bone fill would translate to 81.4% assuming that scores one and two are defined as a success. This is again comparable to other reports in which the Post-Operative Bone Fill Index has been used. Kindelan *et al,* (1997) reported 50% of grafts achieving grade one, 23% with grade two, 22% with grade three and 5% with grade four. Rawashdeh and Nimri, (2007) reported 90% with grade one, 5% with grade two, 5% with grade three and none with grade four in subjects with unilateral clefts. They however defined success as score one only. Although there are a multitudinous number of studies reporting eruption of canines through unoperated alveolar clefts, to the best of my knowledge, no study in the published literature has reported on the amount of bone in the clefts associated with absence of spontaneous canine eruption (Figure 3.1.4). This study found that out of 22 clefts associated with absence of spontaneous canines eruption, twelve clefts (54.5%) achieved a score of one, six clefts (27.3%) scored two, four clefts (13.5%) scored three and one cleft (4.5%) scored four. The results of the overall scores and scores associated with no canine eruption are very similar with both sets scoring one in just over half the sample of clefts and approximately a quarter scoring two.

Twenty six of eighty six clefts (30.2%) were expanded and sixty of eighty six clefts (60.8%) were not expanded (Table 3.1.5). The low rate of expansion was because a full time orthodontist was not present at the Birmingham Children's Hospital during the period involved in which the SABG was carried out. Examination of the records revealed that the expansion was carried out with a quadhelix or a trihelix.

Eleven of the eighty six clefts (13.8%) had a repeat bone graft (Table 3.1.6). The main reason documented in the records was the inadequate level of bone in the grafted alveolar cleft.

The lateral incisor was present in forty one of the eighty six clefts (47.7%) and therefore missing in greater than half the clefts (52.3%). Of the forty one lateral incisors present, eleven had a normal morphology (26.8%), seventeen were small or peg shaped (41.5%), five were unerupted or impacted (12.2%) and it was not possible to determine the morphology of the remaining due to missing or inadequate records. The prevalence of a peg or diminutive lateral incisor in this study was 19.7% which is approximately three times greater than that reported by Tortora *et al,* (2008) of 6.8%. Agenisis of lateral incisor in this study was 52.3% which is similar to the prevalence reported by Bartzela *et al*, (2013) of 39.1%, Hermus *et al*, (2013) of 49.1% and Dentino *et al,* (2012) of 37.6%. The prevalence of missing maxillary lateral incisors in the non-cleft population is reported as 1.58% to 1.78% (Poulder *et al, 2004*) which translates to approximately a twenty nine fold increase of missing maxillary lateral incisors in cleft subjects.

Hypodontia or malformations of the lateral incisor as mentioned previously is a common feature in subjects with oral clefts. Ranta, (1986) discusses many theories including an increase in length of the oral epithelium due to the cleft resulting in an increase in length of the dental lamina thus creating a supernumerary tooth. The tooth germ develops after the development of the cleft, therefore, the cleft may divide the tooth bud as it lies across the nasopalatal sulcus. There may be inadequate support for the bud due to deficiency in mesenchyme or previous surgery may interfere with the bud formation. This is in agreement with Dentino *et al*, (2012) who suggest that the lack of fusion between the medial nasal process and maxillary process results in lack of blood supply and mesenchyme. Loose and Kirschner, (2009) report that a gingivoperioplasty performed at three months at the time of the lip repair can result in damage to the developing central and lateral incisor. As the calcification of the lateral incisor begins at approximately six to seven months, at the time of the lip repair, the lateral incisor would be in the bud or cap stage and therefore any dissection of the follicle would disturb its formation. A common genetical aetiology may also be involved.

Table 3.1.9 shows that 24 of 68 canines (27.9%) were at greater than 45° to the vertical plane and sixty two of the eighty six canines and (72.1%) were less than 45° to the vertical plane.

Table 3.1.10 shows that twelve of the eighty six canines(14%) were mesial to the midplane of the lateral incisor and seventy four canines were distal to the midplane of the lateral incisor (86%). Oberio *et al* found that twice as many canines moved when compared to the non-cleft side with a minimum of 0.6mm and a maximum of 9.8mm. The reason for the mesial drift could be due to the large number of missing lateral incisors or absence of guidance from the lateral incisor root.

Table 3.1.11 shows that all alveolar bone grafting was carried out at the immediate stage i.e. between the ages of 6 and 15. The minimum age of SABG was 8 and the maximum was 14 for all clefts and therefore that includes clefts associated with spontaneous canine eruption as well as clefts associated with absence of spontaneous canine eruption. The median and the lower interquartile range of SABG for all clefts and clefts associated with spontaneous canine eruption was 9 years of age whereas the median for the clefts associated with no spontaneous eruption was 8.75 years, which was deemed clinically insignificant.

Figure 3.1.12 shows the box and whisker plot for the time between SABG and the post-SABG occlusal radiograph. The minimum time post-SABG was 2.9 months, median was 7.2 months and the maximum was 29.2 months. The interquartile range was 4.4 months. The time at which the post-operative occlusal radiograph used for measurement of bone levels is an important factor. Ozawa *et al*, (2007) showed that the volume of bone varies immediately post-SABG and at 6 months post-SABG. Using Cone Beam CTs, the authors reported a mean volume of 1.37mL immediately post- SABG, which reduced by 46.7% to 0.73mL at 6 months post-SABG due to the volume occupied by the eruption of the teeth, however, they reported a range of 13.11% to 63.79% of bone resorption at 6 months. They also stated that the eruption of the canine and formation of the bony bridge were proportional hence eruption of the canine in itself was associated with increased levels of bone in the cleft, however they did not distinguish between cause and effect. Feichtinger *et al,* (2008) reported an average of 64% bone loss at one year following secondary alveolar bone grafting and stated that the clefts with greater bone levels were associated with eruption of teeth. In this study, the level of eruption of the unerupted canine was not assessed and therefore the amount of bone formed by the eruption would make the assessment of bone fill less accurate. The fact that the occlusal radiographs were all taken at different times would again reduce the accuracy of the Post-Operative Bone Fill Index score as the bone levels may be subject to change.

The Binary logistic regression analysis (Table 3.1.13) showed that there was no significant correlation between spontaneous canine eruption and the Post-Operative Bone Fill Index Score, age at SABG, presence of expansion, presence of lateral incisor, angulation of canine to a 45° vertical reference line, horizontal position of canine relative to midplane of the lateral incisor and type of cleft- unilateral or bilateral.

The odds ratios have not been commented upon with regards to trends as the p values are significantly above 0.05.

It has been reported in the literature that teeth adjacent to the cleft erupt in the absence of bone but with poor long term prognosis and poor periodontal health. Collins *et al*, (1998) in their sample of 115 subjects, aged between eight and eighteen reported that 58.4% of canines erupted prior to bone grafting. Gerutzel *et al*, (2005) reported that in non-bone graft subjects, the canine still erupted, however it was guided by the available cortical bone. No subjects in study were excluded on the basis that the canines had erupted prior to SABG. This study has shown that there is no statistical correlation between the amount of bone the cleft and spontaneous canine eruption. Bergland *et al*, (1986) states that it is not the percentage of bone in the graft that is of significance but the percentage of graft cells that survive. It therefore seems that surgical factors may play a more significant role in canine eruption such as the surgical technique and type of bone grafted which can improve the quality of the bone. Loose and Kirschner, (2009) mention that the bone margins of the cleft are hypoplastic and bone should be grafted over the margins thus there should be adequate bone grafted that is compressed sufficiently with tight secure closure of the mucoperiosteal flaps. Bergland *et al* (1986) and Lilja, (2009) both discuss the impact of the choice of bone grafted. The ischaemic cancellous bone revascularises quickly in comparison to the ischaemic cortical bone because it is more vascular whereas cortical bone requires invasion of bone cells from the recipient site therefore delaying turnover, remodelling and transformation. Bergland *et al* (1986) describes a case where spontaneous migration of teeth adjacent to the cleft was prevented due to the slow transformation of the cortical graft. All the subjects included in this study had cancellous bone grafted from the Iliac crest. When the cleft is grafted prior to eruption of the canine, alveolar bone is generated as it erupts, therefore, perhaps it is not the amount of bone but the quality of the bone which is related to the surgical technique that plays an influence on canine eruption hence operator experience cannot be eliminated as a confounding factor. This is in agreement with Kalaaji *et al*, (1996) who found significantly better bone height following SABG when the operation was carried out by the more experienced surgeons. Boyarski *et al*, (2006), however, found that there was no statistical difference in bone height amongst surgeons.

The dental age which is related to the root length and hence the eruptive potential would also affect whether the canine erupts spontaneously. Bergland *et al*, (1986) reported that the SABG should be carried out when the canine is a half to two-thirds formed in order to maximise canine eruptive potential however Boyarski *et al*, (2006) found that differences in the canine root development had no statistical effect.

Enemark *et al*, (2001) theorised that a greater prevalence of canine impaction in cleft patients is due to the primary surgery. They found that after changing the type of primary surgery to close the anterior hard palate from a double to a single vomerine flap, less lateral crossbites were observed and speculated that the greater the tilt of the maxillary segment in the medial direction, the greater the likelihood of canine retention.

Matsui, *et al* (2005) reported that the cleft width at the piriform aperture was significantly greater in subjects who had surgical exposure of the canines.

In non-cleft subjects, there is a trend in evidence to suggest that expansion, hence creation of space and presence of lateral incisor is associated with canine eruption (Brin *et al*, 1986: Baccetti *et al,* 2009) There is conflict within the literature as to whether expansion and presence of the lateral incisor has an effect on alveolar bone heights and canine eruption in cleft subjects. This study also found that angulation of the canine greater than 45° relative to the vertical plane had no significant effect on the eruption of the canine whereas Tortora *et al*, (2008) found that no canines greater than 45° erupted. This is because 34 of the 36 canines in their study were less than 15° to the vertical plane and only 2 canines were between 15° and 45° which leads to the question of whether an adequate sample size was utilised. The findings from this study also revealed that spontaneous canine eruption was not associated with the horizontal position of the canine relative to the midplane of the lateral incisor. This is because a large proportion of the lateral incisors were missing and if so, it is likely that the canines erupted into the lateral incisor space.

Studies that have reported a correlation between the age of SABG and dental eruption have compared early, intermediate and late SABG (Brattstrom and

McWilliam, 1989: Helms *et al*, 1987: Bergland *et al*, 1986) As all the SABG in this study was carried out prior to canine eruption and in the intermediate stage, a significant correlation would not be expected.

Other factors for canine impaction include a genetic predisposition associated with both cleft formation and dental anomalies, interference with neural crest cell migration which may alter formation, development and differentiation into dental lamina, delayed root development and scar tissue from previous surgery (*Solis et al* 1998). It therefore seems that no one factor has a significant effect on the eruption of canine in cleft patients. There are more variables that effect the eruption of canine in cleft subjects in comparison to non-cleft subjects which explains why there was no statistical correlation between the angulation the canine, lateral position the canine, presence of the lateral incisor and type of cleft (unilateral or bilateral) with canine eruption. All studies mentioned in this thesis that have found a statistical correlation between any of the factors have been retrospective in nature without a power calculation which therefore reduces the external validity.

It appears that spontaneous eruption of the canine is likely to be due to a small additive effect of the factors listed below

Cleft

- Genetic association between presence of cleft and canine impaction
- Width and morphology of cleft

Surgical factors

- Type and timing of primary surgery

- Operator experience of primary surgery
- Insults to developing tooth germs
- Timing of SABG
- Quality and height of bone in cleft
- Operator specialty, operator experience of SABG
- Surgical technique
- Type of bone grafted

Canine factors

- Stage at root development
- Horizontal position of the canine
- Angulation of the canine

Other factors

- Presence and morphology of lateral incisor
- Presence of expansion prior to SABG

4.2 Limitations of the study

This is a retrospective observational cohort study and the data was not designed in a manner to be used for such study. Although the ideal study would be a randomised control trail, it would be unethical not to bone graft subjects and observe the behaviour of the canine due to the multitudinous purpose of alveolar bone grafting. As a consequence, searching for historical data introduces bias resulting in undermining of the external validity. Selection bias cannot be extrapolated to this study as all participants who had alveolar bone grafting in the defined period were allocated to either the inclusion or exclusion criteria. There was however measurement bias as radiographs were not standardised in their exposure and position, analysis bias as some data was missing and the presence of numerous confounding factors as they were not included in the inclusion and exclusion criteria such as oral hygiene post-operatively.

Errors of measuring the amount of bone on occlusal radiographs are not without their disadvantages. Limitations of occlusal radiographs include two dimensional representation of three dimensional images and therefore the anterior-posterior depth of the cleft is unable to be examined. In the horizontal plane, there may be superimpositions of the adjacent structures along the curvature of the arch and in the vertical plane, there is often distortion due to elongation. Other factors include difference is contrast making it difficult to assess the bone margin as well as lack of reliability of landmark identification. As the occlusal radiographs were not taken by the same operator, the exposure and angle also varied. Ozawa *et al*, (2007) in their CT study found that the bone is not evenly distributed with one side being thinner and therefore volume thickness and architecture cannot be detected with two dimensional radiography. Rosenstein *et al* (2007) compared the amount of bone using CT images to periapical and occlusal radiographs in subjects following alveolar bone grafting. They found that there was good agreement between 3-dimensional and 2-dimensional radiography when the bone levels were greater than 90% or less than 50% but up to 25% variability when in between. The researchers concluded that caution must be taken when assessing bone heights from 2-dimensional radiographs and that 3-dimensional radiographs are superior in determining bone heights. Accuracy of bone fill would have been significantly more accurate had CBCTs been used, however, due to the increased exposure and cost, they are not routinely being taken by cleft team post- alveolar bone grafting.

Following a practical session with Dr Jay Kindelan and Dr Gunvor Semb on the use of the Post-Operative Bone Fill Index, it was observed by the author, Mr Nahul Patel that the scores for each cleft varied amongst different raters and was therefore subjective.

The bone heights were scored from occlusal radiographs at varying times post-SABG and therefore different stages of eruption of the canine would be observed amongst the radiographs. This would alter the amount of bone observed in the alveolar cleft as eruption of the canine would in itself bring down bone into the cleft. The most accurate method of measuring the bone would have been with the use of a 3D technique at a defined period following SABG.

The power calculation was only carried out to determine a significant correlation between spontaneous canine eruption and the Post-Operative Bone Fill Index score, therefore, the validity of the binary logistic regression analysis in determining a correlation between the other variables and canine eruption is reduced.

Chapter 5

Conclusion

5.1 Conclusions

1. Success of secondary alveolar bone grafting as defined by spontaneous canine eruption was 74.4%
2. There was no significant association between the height of bone in the alveolar cleft and spontaneous canine.
3. There was no significant association between spontaneous canine eruption and the following variables:

- Presence of lateral incisor
- Presence of expansion
- Angulation of canine relative to a 45° in the vertical reference line
- Horizontal position of canine relative to the midplane of the lateral incisor
- Type of cleft (unilateral or bilateral)

5.2 Null Hypothesis

In the present study, there was no statistical correlation between spontaneous canine eruption and Post-Operative Bone Fill Index, age at SABG, presence of the lateral incisor, horizontal position relative to midplane of lateral incisor, angulation of canine relative to 45° in the vertical plane, presence of expansion prior to SABG and type of cleft.

- Accepted

5.3 Clinical significance

This study does not add any new information, however, it does show that if alveolar bone grafts are performed according to recommendations made by credible authors, satisfactory outcomes can be achieved. It also confirms that canine eruption in cleft subjects is not influenced by the amount of bone present in the cleft but due to the high biological variability of factors that influence canine eruption such as in non-cleft subjects. See chapter 4.1 for list of factors influencing canine eruption in cleft subjects.

5.4 Suggestions for further study

Most of the studies involving cleft subject have been retrospective in nature and there is conflicting evidence of whether expansion prior to SABG would influence the height of bone and facilitate spontaneous canine eruption. Consideration could be given to a prospective randomised control trial in order to ascertain whether expansion (if required) prior to or post SABG would influence the height of bone in the alveolus and influence spontaneous canine eruption.

References

Amanat, N., Langdon, JD. (1991)
Secondary alveolar bone grafting in clefts of the lip and palate. J Craniomaxillofac Surg. 19(1):7-14.

Andersson, EM., Sandvik, L., Abyholm, F., Semb, G. (2010)
Clefts of the secondary palate referred to the Oslo Cleft Team: epidemiology and cleft severity in 994 individuals. Cleft Palate Craniofac J 47(4):335-42.

Andlin-Sobocki, A., Eliasson, LA., Paulin, G. (1995)
Periodontal evaluation of teeth in bone grafted regions in patients with unilateral cleft lip and cleft palate. Am J Orthod Dentofacial Orthop. 107(2):144-52.

Aydin, U., Yilmaz, HH., Yildirim, D. (2004)
Incidence of canine impaction and transmigration in a patient population. Dentomaxillofac Radiol. 33(3):164-9.

Baccetti, T. (1998)
A controlled study of associated dental anomalies. Angle Orthod. 68(3):267-74.

Baccetti, T., Leonardi, M,. Armi, P. (2008)
A randomized clinical study of two interceptive approaches to palatally displaced canines.
Eur J Orthod. 30(4):381-5.

Baccetti, T., Mucedero, M., Leonardi, M., Cozza, P. (2009)
Interceptive treatment of palatal impaction of maxillary canines with rapid maxillary expansion: a randomized clinical trial. Am J Orthod Dentofacial Orthop. 136(5):657-61.

Badovinac, RL., Werler, MM., Williams, PL., Kelsey, KT., Hayes, C. (2007)
Folic acid-containing supplement consumption during pregnancy and risk for oral clefts: a meta-analysis. Birth Defects Res A Clin Mol Teratol. 79(1):8-15

Bartzela, TN., Carels, CE., Bronkhorst, EM., Jagtman, AM. (2013)
Tooth agenesis patterns in unilateral cleft lip and palate in humans. Arch Oral Biol.(6):596-602

Bayerlein, T., Proff. P., Heinrich, A., Kaduk, W., Hosten, N., Gedrange, T. (2006)
Evaluation of bone availability in the cleft area following secondary osteoplasty.J Craniomaxillofac Surg. 34(2):57-61.

Bearn, D., Mildinhall, S., Murphy, T., Murray, JJ., Sell, D., Shaw, WC., Williams, AC., Sandy, JR. (2001)
Cleft lip and palate care in the United Kingdom--the Clinical Standards Advisory Group (CSAG) Study. Part 4: outcome comparisons, training, and conclusions. Cleft Palate Craniofac J. 38(1):38-43.

Becker, A. (1995)
In defense of the guidance theory of palatal canine displacement. Angle Orthod. 65(2):95-8

Bergland, O., Semb, G., Abyholm, FE. (1986)
Elimination of the residual alveolar cleft by secondary bone grafting and subsequent orthodontic treatment. Cleft Palate J. 23(3):175-205.

Bishara ,SE. (1992)
Impacted maxillary canines: a review. Am J Orthod Dentofacial Orthop. 101(2):159-71.

Bjerklin, K., Kurol, J., Paulin, G. (1993)
Ectopic eruption of the maxillary first permanent molars in children with cleft lip and/or palate. Eur J Orthod. 15(6):535-40.

Bokhout, B., Hofman, FX., van Limbeek, J., Kramer, GJ., Prahl-Andersen, B. (1997)
Incidence of dental caries in the primary dentition in children with a cleft lip and/or palate.Caries Res. 31(1):8-12

Bongaarts, CA., Van 't Hof, MA., Prahl-Andersen, B., Dirks, IV., Kuijpers-Jagtman, AM. (2006)
Infant orthopedics has no effect on maxillary arch dimensions in the deciduous dentition of children with complete unilateral cleft lip and palate (Dutchcleft). Cleft Palate Craniofac J. 43(6):665-72.

Borodkin, AF., Feigal, R.J., Beiraghi, S., Moller, K.T., Hodges, JS. (2008)
Permanent tooth development in children with cleft lip and palate. Pediatr Dent. 30(5):408-13.

Borstlap, WA., Heidbuchel, KL., Freihofer, HP., Kuijpers-Jagtman, AM. (1990)
Early secondary bone grafting of alveolar cleft defects. A comparison between chin and rib grafts. J Craniomaxillofac Surg. 18(5):201-5.

Botto, LD., Erickson, JD., Mulinare, J., Lynberg, MC., Liu, Y. (2002)
Maternal fever, multivitamin use, and selected birth defects: evidence of interaction? Epidemiology. 13(4):485-8.

Boyarskiy, S., Choi, HJ., Park K. (2006)
Evaluation of alveolar bone support of the permanent canine in cleft and noncleft patients.
Cleft Palate Craniofac J. 43(6):678-82.

Boyne, PJ., Sands, NR. (1972)
Secondary bone grafting of residual alveolar and palatal clefts. J Oral Surg. 30(2):87-92.

Brattström, V., McWilliam, J. (1989)
The influence of bone grafting age on dental abnormalities and alveolar bone height in patients with unilateral cleft lip and palate. Eur J Orthod . 11(4):351-8.

Brin, I., Becker, A., Shalhav, M. (1986)
Position of the maxillary permanent canine in relation to anomalous or missing lateral incisors: a population study. Eur J Orthod. 8(1):12-6

Britton, KF., Welbury, RR. (2010)
Dental caries prevalence in children with cleft lip/palate aged between 6 months and 6 years in the West of Scotland. Eur Arch Paediatr Dent. 11(5):236-41.

Brouns ,J., Egyedi P. (1980)
Osteotomy of the premaxilla. J Maxillofac Surg. 8(3):182-6.

Bush, J., Jiang, R (2012)
Palatogenesis: morphogenetic and molecular mechanisms of secondary palate development. Development. 139(2):231-43.

Carmichael, SL., Shaw, GM. (2000)
Maternal life event stress and congenital anomalies. Epidemiology. 11(1):30-5.

Carmichael, SL., Shaw, GM., Yang, W., Abrams, B., Lammer, EJ. (2007)
Maternal stressful life events and risks of birth defects. Epidemiology. 18(3):356-61.

Chung, DD., Weisberg, M., Pagala, M. (2011)
Incidence and effects of genetic factors on canine impaction in an isolated Jewish population. Am J Orthod Dentofacial Orthop. 139(4):e331-5

Cobourne, M. (2004)
The complex genetics of cleft lip and palate. Eur J Orthod. 26(1):7-16.

Cobourne, M., Diabiase. T. (2010)
Handbook of Orthodontics. First edition, Elsevier Ltd

Collins, M., James, DR., Mars, M. (1998)
Alveolar bone grafting: a review of 115 patients. Eur J Orthod. 20(2):115-20.

Coupland, MA., Coupland, AL. (1988)
Seasonality, incidence, and sex distribution of cleft lip and palate births in Trent Region, 1973-1982. Cleft Palate J. 25(1):33-7

Dentino, KM., Peck, S., Garib, DG. (2012)
Is missing maxillary lateral incisor in complete cleft lip and palate a product of genetics or local environment? Angle Orthod. 82(6):959-63.

Dobbyn, LM., Gillgrass, TJ., Devlin, MF. (2012)
Reliability of the Kindelan scoring system for alveolar bone grafting with and without a pre-graft occlusal radiograph in patients with cleft lip and palate. Br J Oral Maxillofac Surg. 50(7):617-20

Eldeeb, M., Messer, LB., Lehnert, MW., Hebda, TW., Waite, DE. (1982)
Canine eruption into grafted bone in maxillary alveolar cleft defects. Cleft Palate J. 19(1):9-16.

Eldeeb, ME., Hinrichs, JE., Waite, DE., Bandt, CL., Bevis, R. (1986)
Repair of alveolar cleft defects with autogenous bone grafting: periodontal evaluation. Cleft Palate J. 23(2):126-36.

Enemark, H., Krantz-Simonsen, E., Schramm, JE. (1985)
Secondary bonegrafting in unilateral cleft lip palate patients: indications and treatment procedure. Int J Oral Surg. 14(1):2-10.

Enemark, H., Sindet-Pedersen, S., Bundgaard, M. (1987)
Long-term results after secondary bone grafting of alveolar clefts. J Oral Maxillofac Surg. 45(11):913-9.

Enemark, H., Jensen, J., Bosch, C. (2001)
Mandibular bone graft material for reconstruction of alveolar cleft defects: long-term results. Cleft Palate Craniofac J. 38(2):155-63.

Ericson, S., Kurol, J. (1987)
Radiographic examination of ectopically erupting maxillary canines. Am J Orthod Dentofacial Orthop. 91(6):483-92

Ericson, S., Kurol, J. (1988)
Early treatment of palatally erupting maxillary canines by extraction of the primary canines.
Eur J Orthod 10(4): 283-295.

Feichtinger, M., Mossböck, R., Kärcher, H. (2006)
Evaluation of bone volume following bone grafting in patients with unilateral clefts of lip, alveolus and palate using a CT-guided three-dimensional navigation system.
J Craniomaxillofac Surg. 34(3):144-9

Feichtinger, M., Zemann, W., Mossböck, R., Kärcher, H. (2008)
Three-dimensional evaluation of secondary alveolar bone grafting using a 3D-navigation system based on computed tomography: a two-year follow-up. Br J Oral Maxillofac Surg. 46(4):278-82

Friede, H., Johanson, B. (1974)
A follow-up study of cleft children treated with primary bone grafting. 1. Orthodontic aspects. Scand J Plast Reconstr Surg. 8(1-2):88-103.

Friede, H., Lilja, J., Lohmander, A. (2012)
Long-Term, Longitudinal Follow-Up of Individuals With UCLP After the Gothenburg Primary Early Veloplasty and Delayed Hard Palate Closure Protocol: Maxillofacial Growth Outcome. Cleft Palate Craniofac J. 49(6):649-56

Freihofer, HP., Borstlap, WA., Kuijpers-Jagtman, AM., Voorsmit, RA., Van Damme, PA., Heidbüchel, KL., Borstlap-Engels, VM. (1993)
Timing and transplant materials for closure of alveolar clefts. A clinical comparison of 296 cases. J Craniomaxillofac Surg. 21(4):143-8.

Gereltzul, E., Baba, Y., Ohyama, K. (2005)
Attitude of the canine in secondary bone-grafted and nongrafted patients with cleft lip and palate. Cleft Palate Craniofac J. 42(6):679-86.

Gorlin, RJ., Cervenka, J., Pruzansky, S. (1971)
Facial clefting and its syndromes. Birth effects, 7: 3-49

Grayson, B.H., Cutting, C.B. (2001)
Presurgical nasoalveolar orthopedic molding in primary correction of the nose, lip, and alveolus of infants born with unilateral and bilateral clefts. Cleft Palate Craniofac J. 38(3):193-8.

Grabowski, R., Kopp, H., Stahl. F., Gundlach, KK. (2006)
Presurgical orthopaedic treatment of newborns with clefts--functional treatment with long-term effects. J Craniomaxillofac Surg. (2):34-44

Guo, J., Li. C., Zhang, Q., Wu, G., Deacon, SA., Chen, J., Hu, H., Zou, S., Ye, Q. (2011)
Secondary bone grafting for alveolar cleft in children with cleft lip or cleft lip and palate.
Cochrane Database Syst Rev. Jun 15;(6):CD008050

Habel, A., Sell, D., Mars, M. (1996)
Management of cleft lip and palate. Arch Dis Child. 74(4):360-6.

Hamilton, R., Graham, W., Randall, P (1969)
The role of lip adhesion procedure in cleft repair. Presentation of paper at the 38th annual meeting of the American Society of Plastic and Reconstructive Surgery.

Hasslöf, P., Twetman, S. (2007)
Caries prevalence in children with cleft lip and palate--a systematic review of case-control studies. Int J Paediatr Dent. 17(5):313-9.

Heidbuchel, KL. (1997)
Blateral cleft lip and palate: Maxillofacial growth and dental development. 1st edition, Sweden.

Heidbuchel, KL., Kuijpers-Jagtman, AM., Kramer, GJ., Prahl-Andersen, B. (1998)
Maxillary arch dimensions in bilateral cleft lip and palate from birth until four years of age in boys. Cleft Palate Craniofac J. 35(3):233-9.

Heidbüchel, KL., Kuijpers-Jagtman, AM., Ophof, R., Van Hooft, RJ. (2002)
Dental maturity in children with a complete bilateral cleft lip and palate. Cleft Palate Craniofac J. 39(5):509-12.

Helm, S., Seidler, B. (1974)
Timing of permanent tooth emergence in Danish children. Community Dent Oral Epidemiol. 2(3):122-9.

Helms, JA., Speidel, TM., Denis, KL. (1987)
Effect of timing on long-term clinical success of alveolar cleft bone grafts**.** Am J Orthod Dentofacial Orthop. 92(3):232-40.

Hermus, RR., van Wijk, AJ., Tan, SP., Kramer, GJ., Ongkosuwito, EM. (2013)
Patterns of tooth agenesis in patients with orofacial clefts. Eur J Oral Sci. 121(4):328-32.

Hodgkinson, P., Brown, S., Duncan, D., Grant, C., Mc Naughten, A., Thomas, P., Mattick, CR. (2005)
Management of children with cleft lip and palate: A review describing the application of multidisciplinary team working in this condition based upon the experiences of a regional cleft lip and palate centre in the United Kingdom. Fetal and maternal medicine review. 16:1-27

Hong, P., Bezuhly, M. (2013)
Mandibular distraction osteogenesis in the micrognathic neonate: a review for neonatologists and pediatricians. Pediatr Neonatol. 54(3):153-60

Hotz, MM. (1969)
Pre- and early postoperative growth-guidance in cleft lip and palate cases by maxillary orthopedics (an alternative procedure to primary bone-grafting). Cleft Palate J. 6:368-72.

Howard, s., Lohmander, A. (2011)
Cleft Palate Speech: Assessment And Intervention. 1st edition, John Wiley & Sons, Sussex

Hynes, PJ., Earley, MJ. (2003)
Assessment of secondary alveolar bone grafting using a modification of the Bergland grading system. Br J Plast Surg. 56(7):630-6.

Jensen, BL., Kreiborg, S., Dahl, E., Fogh-Andersen, P. (1988)
Cleft lip and palate in Denmark, 1976-1981: epidemiology, variability, and early somatic development. Cleft Palate J. 25(3):258-69.

Johnson, CY., Little, J. (2008)
Folate intake, markers of folate status and oral clefts: is the evidence converging? Int J Epidemiol. 37(5):1041-58.

Kalaaji, A., Lilja, J., Friede, H., Elander, A. (1996)
Bone grafting in the mixed and permanent dentition in cleft lip and palatepatients: long-term results and the role of the surgeon's experience. J Craniomaxillofac Surg. 24(1):29-35.

Kernahan, DA., Stark, RB. (1958)
A new classification of cleft lip and palate. Plast. & Reconstr. Surg. 22: 435-441

Kindelan, JD., Nashed, RR., Bromige, MR. (1997)
Radiographic assessment of secondary autogenous alveolar bone grafting in cleft lip and palate patients. Cleft Palate Craniofac J. 34(3):195-8.

Kindelan, J., Roberts-Harry, D. (1999)
A 5-year post-operative review of secondary alveolar bone grafting in the Yorkshire region.
Br J Orthod. 26(3):211-7.

Kirschner, RE., Low, DW., Randall, P., Bartlett, SP., McDonald-McGinn, DM., Schultz, PJ., Zackai, EH., LaRossa D. (2003)
Surgical airway management in Pierre Robin sequence: is there a role for tongue-lip adhesion? Cleft Palate Craniofac J. 40(1):13-8.

Konst, EM., Rietveld, T., Peters, HF., Kuijpers-Jagtman, AM. (2003)
Language skills of young children with unilateral cleft lip and palate following infant orthopedics: a randomized clinical trial. Cleft Palate Craniofac J. 40(4):356-62.

Kurihara, S., Enlow, DH., Rangel, RD. (1980)
Remodeling reversals in anterior parts of the human mandible and maxilla. Angle Orthod. 50(2):98-106.

Larson, M., Hellquist, R., Jakobsson, OP. (1998)
Dental abnormalities and ectopic eruption in patients with isolated cleft palate.
Scand J Plast Reconstr Surg Hand Surg.32(2):203-12.

Latham, RA. (1980)
Orthopedic advancement of the cleft maxillary segment: a preliminary report. Cleft Palate J. 17(3):227-33.

Latief, BS., Lekkas, KC., Schols, JG., Fudalej, PS., Kuijpers, MA. (2012)
Width and elevation of the palatal shelves in unoperated unilateral and bilateral cleft lip and palate patients in the permanent dentition. J Anat. 220(3):263-70

Lee, CT., Grayson, BH., Cutting, CB., Brecht, LE., Lin, WY. (2004)
Prepubertal midface growth in unilateral cleft lip and palate following alveolar molding and gingivoperiosteoplasty. Cleft Palate Craniofac J. 41(4):375-80

Li, L., Lin, M., Wang, Y., Cserjesi, P., Chen, Z. and Chen, Y. (2011).
BmprIa isrequired in mesenchymal tissue and has limited redundant function with BmprIb in tooth and palate development. Dev Biol. 349(2):451-61

Lilja, J. (2009)
Alveolar bone grafting. Indian J Plast Surg. 42(3)110–S115.

Lilja, J., Kalaaji, A., Friede, H., Elander, A. (2000)
Combined bone grafting and delayed closure of the hard palate in patients with unilateral cleft lip and palate: facilitation of lateral incisor eruption and evaluation of indicators for timing of the procedure. Cleft Palate Craniofac J. 37(1):98-105.

Linde, A (2007)
Molecular control of secondary palate development. Dev Biol. 301(2):309-26

Little, J., Cardy, A., Munger, RG. (2004)
Tobacco smoking and oral clefts: a meta-analysis. Bull World Health Organ. 82(3):213-8

Liu, W., Sun, X., Braut, A., Mishina, Y., Behringer, R. R., Mina, M, Martin, JF. (2005).
Distinct functions for Bmp signaling in lip and palate fusion in mice. Development. 132(6):1453-61

Long, RE Jr., Spangler, BE., Yow, M. (1995)
Cleft width and secondary alveolar bone graft success. Cleft Palate Craniofac J. 32(5):420-7.

Losee, J., Kirschner, R. (2009)
Comprehensive cleft care. 1st edition, McGraw-Hill company, China.

Martin, V., Bannister, P. (2004)
Cleft care: A practical guide for health professionals on cleft lip and/or palate. 1st Edition, APS, Wiltshire.

Matok, I., Gorodischer, R., Koren, G., Landau, D., Wiznitzer, A., Levy, A. (2009)
Exposure to folic acid antagonists during the first trimester of pregnancy and the risk of major malformations. Br J Clin Pharmacol. 68(6):956-62.

Matsui, K., Echigo, S., Kimizuka, S., Takahashi, M., Chiba. M. (2005)
Clinical study on eruption of permanent canines after secondary alveolar bone grafting.
Cleft Palate Craniofac J. 42(3):309-13.

Maull, D.J., Grayson, BH., Cutting, CB., Brecht, LL., Bookstein, FL., Khorrambadi, D., Webb. JA., Hurwitz. DJ. (1999)
Long-term effects of nasoalveolar molding on three-dimensional nasal shape in unilateral clefts. Cleft Palate Craniofac J. 36(5):391-7.

McCance, A., Roberts-Harry, D., Sherriff, M., Mars, M., Houston, WJ. (1993)
Sri Lankan cleft lip and palate study model analysis: clefts of the secondary palate. Cleft Palate Craniofac J. 30(2):227-30.

Millard, DR. (1957)
A primary camouflage in the unilateral harelip. Transactions of the First International Congress of Plastic Surgery, Stockholm, Sweden; 160 – 72

Mishima, K., Sugahara, T., Mori. Y., Sakuda, M. (1996)
Three-dimensional comparison between the palatal forms in complete unilateral cleft lip and palate with and without Hotz plate from cheiloplasty to palatoplasty. Cleft Palate Craniofac J. 33(4):312-7.

Mitchell, L. (2007)
An introduction to Orthodontics. 3rd edition, Oxford university press, Oxford.

Mossey, PA., Little, J., Munger, RG., Dixon, MJ., Shaw, WC. (2009)
Cleft lip and palate. Lancet. 374(9703):1773-85

Murray, JC. (2002)
Gene/environment causes of cleft lip and/or palate. Clin Genet (61):248–256

Nagase, Y., Natsume, N., Kato, K., Hayakawa, T. (2010)
Epidemiological Analysis of Cleft Lip and/or Palate by Cleft Pattern. J Maxillofac Oral Surg. 9(4): 389–395.

Newlands, LC. (2000)
Secondary alveolar bone grafting in cleft lip and palate patients. Br J Oral Maxillofac Surg. 38(5):488-91.

Nightingale, C., Witherow, H., Reid, FD., Edler, R. (2003)
Comparative reproducibility of three methods of radiographic assessment of alveolar bone grafting. Eur J Orthod. 25(1):35-41.

Oberoi, S., Chigurupati, R., Gill, P., Hoffman, WY., Vargervik, K. (2009)
Volumetric assessment of secondary alveolar bone grafting using cone beam computed tomography. Cleft Palate Craniofac J. 46(5):503-11.

Oberoi, S., Gill, P., Chigurupati, R., Hoffman, WY., Hatcher, DC., Vargervik, K. (2010)
Three-dimensional assessment of the eruption path of the canine in individuals with bone-grafted alveolar clefts using cone beam computed tomography. Cleft Palate Craniofac J. Sep;47(5):507-12.

Ozawa T, Omura S, Fukuyama E, Matsui Y, Torikai K, Fujita K. (2007)
Factors influencing secondary alveolar bone grafting in cleft lip and palate patients: prospective analysis using CT image analyzer. Cleft Palate Craniofac J. 44(3):286-91.

Pioto, N.R., Costa, B., Gomide, M.R. (2005)
Dental development of the permanent lateral incisor in patients with incomplete and complete unilateral cleft lip. Cleft Palate Craniofac J. 42(5):517-20.

Polder, BJ., Van't Hof, MA., Van der Linden, FP., Kuijpers-Jagtman, AM. (2004)
A meta-analysis of the prevalence of dental agenesis of permanent teeth. Community Dent Oral Epidemiol. 32(3):217-26.

Power, S.M., Short, M.B. (1993)
An investigation into the response of palatally displaced canines to the removal of deciduous canines and an assessment of factors contributing to favourable eruption. Br J Orthod. 20(3):215-23.

Prahl, C., Kuijpers-Jagtman, AM., Van 't Hof, MA., Prahl-Andersen, B. (2003)
A randomized prospective clinical trial of the effect of infant orthopedics in unilateral cleft lip and palate: prevention of collapse of the alveolar segments (Dutchcleft). Cleft Palate Craniofac J. 40(4):337-42.

Ranta, R. (1986)
A review of tooth formation in children with cleft lip/palate. Am J Orthod Dentofacial Orthop. 90(1):11-8.

Ranta, R., Stegars, T., Rintala, AE. (1983)
Correlations of hypodontia in children with isolated cleft palate. Cleft Palate J. 20(2):163-5

Rawashdeh, MA., Al Nimri, KS. (2007)
Outcome of secondary alveolar bone grafting before and after eruption of the canine in Jordanian patients with cleft lip and palate. J Craniofac Surg.18(6):1331-7.

Revington, PJ., McNamara, C., Mukarram, S., Perera, E., Shah, HV., Deacon, SA. (2010)
Alveolar bone grafting: results of a national outcome study. Ann R Coll Surg Engl. 92(8):643-6.

Rice, R., Spencer-Dene, B., Connor, E. C., Gritli-Linde, A., McMahon, A. P., Dickson, C., Thesleff, I. and Rice, DP. (2004)
Disruption of Fgf10/Fgfr2b coordinated epithelial-mesenchymal interactions causes cleft palate. J Clin Invest. 113(12):1692-700

Roberts, RM., Mathias, J.L., Wheaton, P. (2012)
Cognitive functioning in children and adults with nonsyndromal cleft lip and/or palate: a meta-analysis. J Pediatr Psychol. 37(7):786-97

Rosenstein, SW., Monroe, CW., Kernahan, DA., Jacobson, BN., Griffith, BH., Bauer, BS. (1982)
The case of early bone grafting in cleft lip and cleft palate. Plast Reconstr Surg. 70(3):297-309

Rosenstein, SW., Long, RE Jr., Dado, DV., Vinson B., Alder ME. (1997)
Comparison of 2-D calculations from periapical and occlusal radiographs versus 3-D calculations from CAT scans in determining bone support for cleft-adjacent teeth following early alveolar bone grafts. Cleft Palate Craniofac J. 34(3):199-205.

Russell, KA., McLeod, CE. (2008)
Canine eruption in patients with complete cleft lip and palate. Cleft Palate Craniofac J. 45(1):73-80.

Sandy, J. (1992)
Tooth eruption and Orthodontic movement. Br Dent J. 172(4):141-9.

Sandy, J., Williams, A., Mildinhall, S., Murphy, T., Bearn, D., Shaw, B., Sell, D., Devlin, B., Murray, J. (1998)
The Clinical Standards Advisory Group (CSAG) Cleft Lip and Palate Study. Br J Orthod. 25(1):21-30.

Sandy, JR., Williams, AC., Bearn, D., Mildinhall, S., Murphy, T., Sell, D., Murray, JJ., Shaw, WC. (2001)
Cleft lip and palate care in the United Kingdom--the Clinical Standards Advisory Group (CSAG) Study. Part 1: background and methodology. Cleft Palate Craniofac J. 38(1):20-3.

Santiago, PE., Grayson, BH., Cutting, CB., Gianoutsos, MP., Brecht, LE., Kwon, SM. (1998)
Reduced need for alveolar bone grafting by presurgical orthopedics and primary gingivoperiosteoplasty. Cleft Palate Craniofac J. 35(1):77-80.

Sell, D., Ma, L. (1996)
A model of practice for the management of velopharyngeal dysfunction. Br J Oral Maxillofac Surg. 34(5):357-63.

Semb, G. (1991.a)
A study of facial growth in patients with unilateral cleft lip and palate treated by the Oslo CLP Team. Cleft Palate Craniofac J. 28(1):1-21

Semb, G. (1991b)
A study of facial growth in patients with bilateral cleft lip and palate treated by the Oslo CLP Team. Cleft Palate Craniofac J. 28(1):22-39

Semb, G., Shaw, WC. (1990)
Pharyngeal flap and facial growth. Cleft Palate J. 217-24.

Sharma, R., Nanda, V. (2009)
Problems of middle ear and hearing in cleft children. Indian J Plast Surg. (42) S144–S148.

Shashua, D., Omnell, ML. (2000)
Radiographic determination of the position of the maxillary lateral incisor in the cleft alveolus and parameters for assessing its habilitation prospects. Cleft Palate Craniofac J. 37(1):21-5.

Sivarajasingam, V., Pell, G., Morse, M., Shepherd, JP. (2001)
Secondary bone grafting of alveolar clefts: a densitometric comparison of iliac crest and tibial bone grafts. Cleft Palate Craniofac J. 38(1):11-4.

Snyder, H.T., Bilboul, M.J., Pope, A.W. (2005)
Psychosocial adjustment in adolescents with craniofacial anomalies: a comparison of parent and self-reports. Cleft Palate Craniofac J. 42(5):548-55.

Solis, A., Figueroa, AA., Cohen, M., Polley, JW., Evans, CA. (1998)
Maxillary dental development in complete unilateral alveolar clefts. Cleft Palate Craniofac J. 35(4):320-8.

Stanier, P., Moore, GE. (2004)
Genetics of cleft lip and palate: syndromic genes contribute to the incidence of non-syndromic clefts. Hum Mol Genet. 13 (1):R73-81

Suarez, L., Cardarelli, K., Hendricks, K., (2003)
Maternal stress, social support, and risk of neural tube defects among Mexican Americans
Epidemiology. 14(5):612-6.

Suzuki, K., Hu, D., Bustos, T., Zlotogora, J., Richieri-Costa, A., Helms, JA., Spritz, RA. (2000)
Mutations of PVRL1, encoding a cell-cell adhesion molecule/herpesvirus receptor, in cleft lip/palate-ectodermal dysplasia. Nat Genet. 25(4):427-3

Tennison, CW. (1952)
The repair of the unilateral cleft lip by the stencil method. Plast Reconstr Surg. 9(2):115-20.

Tessier, P. (1976)
Anatomical Classification of Facial, Cranio-Facial and Latero-Facia Clefts. Journal of Maxillofacial Surgery. 4:69-92

Tortora, C., Meazzini, M.C., Garattini, G., Brusati, R. (2008)
Prevalence of abnormalities in dental structure, position, and eruption pattern in a population of unilateral and bilateral cleft lip and palate patients. Cleft Palate Craniofac J. 45(2):154-62.

Turner, S.R., Rumsey, N., Sandy, JR. (1998)
Psychological aspects of cleft lip and palate. Eur J Orthod. 20(4):407-15.

Turvey, TA., Vig, K., Moriarty, J., Hoke, J. (1984)
Delayed bone grafting in the cleft maxilla and palate: a retrospective multidisciplinary analysis. Am J Orthod. 86(3):244-56

Van der Meij, AW., Baart., JA., Prahl-Andersen, B., Kostense, PJ., van der Sijp, JR., Tuinzing, DB. (2003)
Outcome of bone grafting in relation to cleft width in unilateral cleft lip and palate patients.
Oral Surg Oral Med Oral Pathol Oral Radiol Endod. (1):19-25.

Van der Meij, AJ., Baart, JA., Prahl-Andersen, B., Valk, J., Kostense, PJ., Tuinzing, DB. (2001)
Bone volume after secondary bone grafting in unilateral and bilateral clefts determined by computed tomography scans. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 92(2):136-41.

Veau, V. (1931)
Treatment of the unilateral harelip Birt. J. Surg . 46:311-321

Waite, PD., Waite, DE. (1996)
Bone grafting for the alveolar cleft defect. Semin Orthod. 2(3):192-6.

Williams, A., Semb, G., Bearn, D., Shaw, W., Sandy, J. (2003)
Prediction of outcomes of secondary alveolar bone grafting in children born with unilateral cleft lip and palate. Eur J Orthod. 25(2):205-11.

Witherow, H., Cox, S., Jones, E., Carr, R., Waterhouse, N. (2002)
A new scale to assess radiographic success of secondary alveolar bone grafts.
Cleft Palate Craniofac J. 39(3):255-60.

Appendix 1: Raw data

Subject number	Gender	Unilateral cleft	Cleft number
1	f	R	1
2	m	L	2
3	m	L	3
4	m	L	4
5	m	R	5
6	m	R	6
7	f	L	7
8	f	R	8
9	f	L	9
10	f	L	10
11	m	L	11
12	f	L	12
13	m	R	13
14	m	L	14
15	f	L	15
16	m	L	16
17	m	L	17
18	f	L	18
19	f	L	19
20	f	L	20
21	f	R	21
22	m	L	22
23	m	L	23
24	m	L	24
25	f	L	25
26	f	L	26
27	m	L	27
28	m	R	28
29	m	R	29
30	m	L	30
31	m	L	31
32	m	L	32
33	f	R	33
34	f	L	34
35	m	L	35
36	f	R	36
37	m	R	37
38	f	L	38

39	m	L	39
40	m	R	40
41	m	L	41
42	f	R	42
43	m	L	43
44	f	L	44
45	f	L	45
46	m	L	46
47	m	bilateral	47
47	m	bilateral	48
48	f	bilateral	49
48	f	bilateral	50
49	m	bilateral	51
49	m	bilateral	52
50	m	bilateral	53
50	m	bilateral	54
51	m	bilateral	55
51	m	bilateral	56
52	m	bilateral	57
52	m	bilateral	58
53	m	bilateral	59
53	m	bilateral	60
54	m	bilateral	61
54	m	bilateral	62
55	m	bilateral	63
55	m	bilateral	64
56	m	bilateral	65
56	m	bilateral	66
57	m	bilateral	67
57	m	bilateral	68
58	f	bilateral	69
58	f	bilateral	70
59	f	bilateral	71
59	f	bilateral	72
60	m	bilateral	73
60	m	bilateral	74
61	m	bilateral	75
61	m	bilateral	76
62	f	bilateral	77
62	f	bilateral	78
63	f	bilateral	79
63	f	bilateral	80
64	m	bilateral	81

64	m	bilateral	82
65	m	bilateral	83
65	m	bilateral	84
66	f	bilateral	85
67	f	bilateral	86

Cleft number	Spontaneous eruption of canine	Age at SABG	Orthodontic expansion
1	y	8	n
2	y	14	y
3	n	11	y
4	y	8	n
5	y	9	y
6	n	9	n
7	y	8	n
8	y	11	n
9	y	10	n
10	y	10	n
11	n	8	n
12	n	8	y
13	n	11	y
14	n	8	n
15	y	8	n
16	y	8	n
17	y	8	n
18	y	10	n
19	n	9	n
20	n	9	y
21	n	9	y
22	y	9	y
23	y	10	y
24	y	11	n
25	n	9	n
26	y	9	n
27	y	9	y
28	y	12	y
29	y	9	n
30	y	8	n
31	y	10	n
32	y	8	n

33	y	9	n
34	y	11	y
35	n	9	n
36	y	8	y
37	y	9	n
38	y	10	n
39	y	9	n
40	y	10	n
41	y	9	y
42	y	9	n
43	n	8	n
44	y	9	n
45	y	10	n
46	y	9	n
47	y	9	n
48	y	9	n
49	n	14	n
50	n	14	n
51	y	13	y
52	n	13	y
53	y	9	n
54	y	9	n
55	n	10	n
56	n	10	n
57	n	10	y
58	y	10	y
59	y	9	y
60	y	9	y
61	y	10	n
62	y	10	n
63	n	9	y
64	y	9	y
65	y	8	n
66	y	8	n
67	n	8	n
68	y	8	n
69	y	9	n
70	y	9	n
71	y	8	n
72	y	8	n
73	y	10	y
74	y	10	y
75	y	9	n

76	y	9	n
77	y	10	y
78	y	10	y
79	n	11	n
80	n	11	n
81	y	11	n
82	y	11	n
83	y	12	n
84	y	12	n
85	y	10	n
86	y	10	n

Cleft number	First/repeat bone graft	Presence of lateral incisor	Morphology of lateral incisor normal(1)/small/peg(2))/ impacted/UE(3) missing (4),don't know (6)
1	1	n	4
2	1	y	2
3	1	n	4
4	1	y	2
5	1	n	4
6	1	n	4
7	1	y	1
8	1	n	4
9	1	n	4
10	1	y	2
11	1	y	2
12	1	n	4
13	1	y	6
14	1	n	4
15	1	n	4
16	1	n	4
17	1	n	4
18	2	y	1
19	1	n	4
20	1	n	4
21	1	n	4
22	2	y	2
23	2	y	1
24	1	n	4

25	2	n	4
26	1	y	2
27	1	y	1
28	2	n	4
29	1	n	4
30	1	n	4
31	1	y	2
32	1	y	6
33	1	n	4
34	1	y	2
35	1	y	2
36	1	n	4
37	1	y	2
38	2	n	4
39	1	n	4
40	1	y	6
41	1	y	2
42	1	y	1
43	1	y	1
44	1	n	4
45	1	n	4
46	2	y	2
47	1	y	2
48	1	n	4
49	1	n	4
50	1	n	4
51	1	n	4
52	1	n	4
53	1	n	4
54	1	y	1
55	1	y	3
56	1	y	3
57	2	y	2
58	2	n	4
59	2	n	4
60	2	n	4
61	1	n	4
62	1	n	4
63	1	y	1
64	1	y	1
65	1	y	6
66	1	y	6
67	1	y	2

68	1	y	2
69	1	y	6
70	1	y	6
71	1	n	4
72	1	n	4
73	1	y	1
74	1	y	1
75	1	y	6
76	1	n	4
77	1	n	4
78	1	n	4
79	1	y	3
80	1	y	3
81	1	n	4
82	1	y	3
83	1	n	4
84	1	n	4
85	1	n	4
86	1	y	2

Cleft number	Vertical position of canine, at risk?	Lateral position of canine, at risk?
1	n	n
2	n	n
3	y	y
4	n	y
5	y	n
6	n	n
7	n	n
8	n	n
9	y	y
10	n	n
11	n	n
12	y	y
13	n	n
14	y	n
15	n	n
16	n	n
17	n	n
18	n	n

19	n	n
20	y	n
21	n	n
22	y	y
23	n	n
24	n	y
25	n	n
26	n	n
27	y	n
28	n	n
29	n	n
30	n	y
31	n	n
32	n	n
33	n	n
34	y	n
35	n	n
36	n	n
37	n	n
38	y	y
39	n	y
40	n	n
41	y	n
42	n	n
43	n	n
44	n	n
45	y	n
46	n	y
47	n	n
48	n	n
49	y	y
50	y	y
51	y	n
52	n	n
53	n	n
54	y	n
55	n	n
56	n	n
57	y	n
58	y	n
59	y	n
60	n	n
61	n	n

62	n	n
63	n	n
64	n	n
65	n	n
66	n	n
67	y	n
68	n	n
69	n	n
70	n	n
71	n	n
72	n	n
73	n	n
74	n	n
75	n	n
76	n	n
77	y	n
78	y	n
79	y	n
80	n	n
81	n	n
82	y	n
83	n	n
84	n	n
85	n	n
86	n	n

Cleft number	Post Op bone fill index score	Repeat post Op bone fill index score	Difference Date of SABG and Date of rad
1	2		11.4
2	2		7.5
3	1		3.2
4	1	1	9.4
5	2		6.6
6	2	2	9.4
7	1		7.8
8	2	2	8.4
9	1	1	24.6
10	4		5.0
11	1		3.8
12	4	3	5.7

13	2		5.0
14	1		3.6
15	1	1	6.4
16	3		5.2
17	1		10.1
18	1		5.0
19	1		5.5
20	1		4.1
21	1		4.8
22	2		9.4
23	2		12.6
24	1		9.4
25	2		6.6
26	1		11.7
27	1		8.7
28	1		4.5
29	1		10.1
30	1		9.4
31	1		3.4
32	1		10.3
33	2	2	4.3
34	1		7.1
35	2		5.4
36	1		3.2
37	1		4.1
38	4	3	6.7
39	1	1	5.7
40	1		37.0
41	2		5.2
42	1		2.9
43	3	3	9.8
44	3		8.4
45	1		8.4
46	1	1	7.7
47	1		5.7
48	2	2	5.7
49	1		5.5
50	1		5.5
51	3		8.9
52	3	4	8.9
53	3		6.6
54	3		6.6
55	1		10.8

56	1		10.8
57	2	2	29.5
58	2		29.5
59	4	4	38.6
60	4		38.6
61	4	3	9.1
62	4		9.1
63	1		4.8
64	1		4.8
65	1	1	9.1
66	1		9.1
67	3		5.0
68	1		5.0
69	1		4.1
70	1		4.1
71	3	2	7.3
72	1		7.3
73	2		11.9
74	2		11.9
75	1	1	5.7
76	2		5.7
77	2		8.2
78	1		8.2
79	1		8.5
80	2	2	8.5
81	2		17.5
82	2		17.5
83	2		5.5
84	1		5.5
85	1		3.4
86	1		3.4

Cleft number	Eruption of canine on contralateral side	Other information
1	y	
2	y	
3	y	
4	y	
5	y	

6	y	
7	y	
8	y	
9	y	
10	y	
11	y	Expose+Bond
12	y	Expose+Bond
13	n	Had SR UR1 and UR2 to encourage eruption UR3
14	y	Expose+Bond
15	y	
16	y	
17	y	
18	y	
19	y	Expose+Bond
20	y	Expose+Bond
21	y	Apically repositioned flap
22	y	
23	y	
24	n	
25	y	
26	y	
27	y	
28	y	
29	y	
30	y	
31	y	
32	y	
33	y	
34	y	
35	y	
36	y	
37	y	
38	y	
39	y	
40	y	
41	y	
42	y	
43	y	Expose+Bond
44	y	
45	y	

46	y	
47		
48		
49		
50		
51		
52		
53		
54		
55		
56		
57		
58		
59		
60		
61		
62		
63		
64		
65		
66		
67		
68		
69		
70		
71		
72		
73		
74		
75		
76		
77		
78		
79		UL3 extracted
80		Expose+Bond
81		
82		
83		
84		
85		
86		