UiT
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Ectopic and normal maxillary canine eruption: maxillary incisor root resorption and interceptive treatment

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A dissertation for the degree of Philosophiae Doctor

“When meditating over a disease, I never think of finding a remedy for it, but, instead, a means of preventing it”.

Louis Pasteur (1822–1895)

1 Contents

2 Acknowledgements

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3 List of papers

This thesis is based on the following papers, which are referred to by their corresponding Roman numerals in the text:

I. **Root resorptions related to ectopic and normal eruption of maxillary canine teeth: A 3D study.**

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II. **Does headgear treatment in young children affect the maxillary canine eruption path?**

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Hadler-Olsen S, Pirttiniemi P, Kerosuo H, Sjögren A, Pesonen P, Julku J, Lähdesmäki R.

III. **Double versus single primary tooth extraction in interceptive treatment of palatally displaced canines: A randomized controlled trial.**

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4 Abbreviations and terms

BDC	Buccally displaced canines
CBCT	Cone beam computed tomography
CI	Confidence interval
CG	Control group
DEG	Double extraction group
FOV	Field of view
ICC	Intraclass correlation coefficient
N	Number
HG	Headgear
HGG	Headgear group
P	Level of significance
PDC	Palatally displaced canine
RCT	Randomized controlled trial
SD	Standard deviation
SEG	Single extraction group

5 Summary

Ectopic eruption of maxillary canines is not very common (0.8–5.2 per cent prevalence), but can create problems if left untreated. Such problems may be the malpositioning and retention of the ectopic tooth, external root resorption, migration of neighbouring teeth, dentigerous cyst formation, and referred pain. Treatment is often time consuming and imposes a substantial cost on the affected patient/family and on society. The scientific evidence concerning the adverse effects as well as interceptive treatment of ectopic maxillary canine eruption is scarce. The overall objectives of this study were therefore to provide new knowledge of the most common adverse effect, i.e., root resorption of maxillary incisors, as well as new insight into the interceptive treatment of ectopic maxillary canine eruption.

Cone beam computed tomography (CBCT) was used to assess the prevalence and severity of root resorption of maxillary incisors. Root resorption of maxillary incisors was commonly found in relation to maxillary canine eruption. Although root resorption was significantly more frequent in patients with ectopically erupting canines, lateral incisor resorption was found in association with approximately 1/3 of normally erupting canines. The best predictor of root resorption was found to be location of the maxillary canine mesial to the lateral incisor midline.

Headgear (HG) treatment was studied to see whether it affected the maxillary canine eruption path in young children. We also studied whether space conditions in the maxillary arch affected the maxillary canine eruption path. The study showed that HG treatment in young children with Angle Class II occlusion shifts the eruption path of maxillary canines to a more vertical direction. The change in eruption path seemed to be related to space conditions in the

maxillary arch, especially in the intercanine region, with the most significant effect in the HG group with spaced dental arches rather than crowded dental arches.

The impact of primary canine extraction versus that of primary canine and primary first molar extraction on the emergence rate of palatally displaced canines (PDCs) was investigated in a randomized clinical trial. Positional changes of PDCs and factors influencing the emergence of PDCs after extractions were analysed. The study showed that there was no statistically significant difference between the two procedures in the emergence rate of PDCs or emergence in a favourable position in the dental arch. The initial canine angulation and space conditions in the maxillary arch seemed to be the best predictors of the successful eruption of PDCs.

In conclusion, the present work showed that root resorption is a common finding for maxillary incisors in association with normally and ectopically erupting maxillary canines. HG treatment in children shifts the eruption path of maxillary canines in a more vertical direction and there was no difference in the emergence rate of PDCs depending on whether the primary canine or both primary canine and primary first molar were extracted.

6 Introduction

The treatment of ectopic maxillary canines can be challenging. The treatment takes longer than the average orthodontic treatment (1), is technically difficult, and may involve a painful surgical procedure (2). The treatment involves several dental specialists (i.e., a radiologist, oral surgeon, paediatric dentist, and orthodontist) and is expensive for the patient as well as the funding government (3). There are also reported serious side effects of ectopic eruption, such as root resorption (4).

6.1 Normal maxillary canine eruption

Calcification of the maxillary canine starts at approximately 12 months of age between the roots of the first deciduous molar at the lower border of the orbit (5). The canine is then left behind as the deciduous molar erupts, allowing development of the first premolar between the deciduous molar roots. At this stage, the permanent canine is located immediately above both the first premolar and the first deciduous molar. As the deciduous teeth erupt towards the occlusal plane, the permanent incisor and canine crypts migrate forward in the jaws at a greater rate than the forward movement of the deciduous teeth themselves. At the age of 7 years, the canine crown is medial to the root of its deciduous predecessor (6). From 8 years of age, buccal movement is expected in normally erupting canines (7). At this stage of development, the canine is located lingual to the root apex of the deciduous canine. From there it normally moves downward, forward, and laterally away from the root of the lateral incisor if there is sufficient space. In cases of insufficient space in the apical base, the “ugly duckling” stage is often seen between 8 and 12 years of age (5), in which the lateral incisors are spread out in a fan shape. As the canines in the final phase of eruption drive their way between the lateral incisors and first premolars, the lateral incisors and first premolars move into a more erect upright alignment (6).

6.2 Ectopic maxillary canine eruption

6.2.1 Definition

The definition of an ectopic canine varies in the literature (8-16). Common names of ectopic canine eruption are: impacted canine, displaced canine, included canine, and retained canine. Some authors use one of these terms to describe a very specific condition, while others use the same term with much more general connotations. There are also language differences that may alter the meaning of a term, so an author's geographical location may determine the word used in a journal report (16). Consequently, in this study, different names may be used to refer to the same condition depending on the cited literature source.

Most studies use generalized definitions of canine displacement, such as: "unerupted canine after complete root development, or if the contralateral tooth was erupted for at least 6 months with complete root formation" (15), or "developmental dislocation to a palatal site often resulting in tooth impaction requiring surgical and orthodontic treatments" (17). A few studies have been based on numerical values for the canine position. Bonetti et al. (9) defined a palatally displaced canine as having an alpha angle ≥25° (Angle C, Figure 1) and as located in sectors 2–5 (Figure 2), according to methods developed by Ericson and Kurol (10). Sigler et al. (11) defined a PDC as having an alpha angle ≥15° and as located in sectors 2–5.

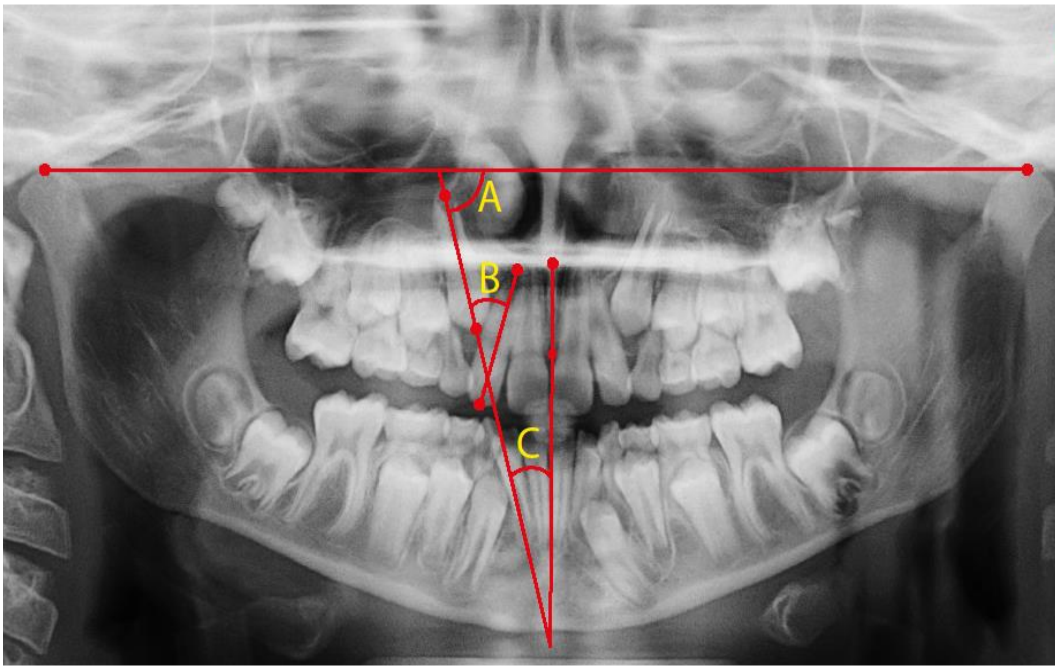

Figure 1. Angular measurements of the maxillary canine.

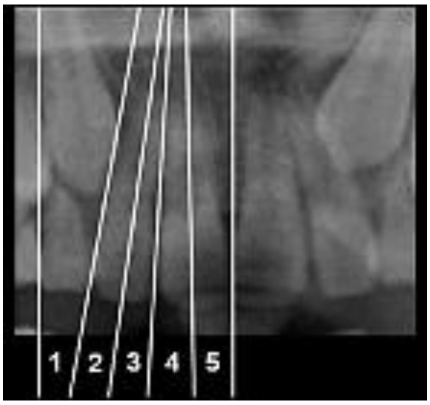

Figure 2. Sector location of the maxillary canine.

6.2.2 Prevalence

The maxillary canine is the most frequently impacted tooth except for the third molar (18-20). The reported prevalence of canine impaction ranges from 0.8 to 5.2 per cent (19-25). Bilateral impaction is seen in 17–45 per cent of cases (25), and impacted canines are more common in females than males (8, 19, 25). More canines are reported to be displaced palatally (85%) in contrast to labially (15%) (25-28).

The ectopic eruption of maxillary canines is 10–20 times more common than the ectopic eruption of mandibular canines (29), and dental age estimation using Demirjian's method has been found to be lower than expected in subjects with maxillary canine impaction (30, 31). In a Caucasian population, maxillary canine displacement is five times more common than in an Asian population, and most canines in Caucasians are palatally displaced, while buccal displacement is more common among Asians (32).

6.2.3 Aetiology

The aetiology of the ectopic eruption of maxillary canines is not fully understood. Historically, the most common explanation for palatal ectopic eruption is based on the longer and more difficult eruption path of the maxillary canine than those of other teeth. It was hypothesized that due to this tortuous eruption path, the maxillary canine was more likely to be retained than were other teeth (33). Later, the aetiology was divided into general and local factors: general factors include endocrine diseases, febrile diseases, radiation, and vitamin D deficiency (7); local factors, generally considered the most important causes of maxillary canine retention, include space deficiency, blocked eruption pathway, a small or missing lateral incisor, and morphological characteristics (34).

There is also discussion of the extent to which genetic factors influence ectopic canine eruption (7, 31, 35-39).

Space deficiency:

For the labial canines, space deficiency is considered the primary etiologic factor, whereas for palatally erupting canines, space deficiency is usually not present (28). Jacoby found that 85% of palatally impacted canines had sufficient space for eruption, compared with 17% of labially impacted canines (7).

When labial ectopia are observed in dentitions with sufficient space, possible etiologic factors affecting impaction were reported to be lack of guidance from a lateral incisor and genetic factors (40).

Blocked eruption pathway:

Retention of maxillary canines may happen due to the retention of primary teeth, odontomas, or rotation of premolars that blocks the eruption pathway of the maxillary canine (36). Follicular cyst development in the dental follicle covering the maxillary canine crown may also block the eruption, as the hydrostatic pressure within the cyst can counteract the eruption force, causing displacement of the maxillary canine (36). Also, chronic apical periodontitis from deciduous canines may lead to retention of the permanent canine (36). Retention of the maxillary canine may also happen secondary to the retention of other teeth, such as the maxillary incisors. Chaushu et al. showed that the incidence of retained maxillary canines was 41.3% on the side with retained incisors as opposed to 4.7% on the contralateral side (41).

Small or missing lateral incisors:

The guidance theory suggests that palatal displacement is a result of lack of guidance along the root of the lateral incisor due to a congenitally missing lateral or an abnormally shaped lateral (42). In an Israeli study, 93% of the general population had normal lateral incisors as opposed to 53% of the population with palatally displaced canines (43). Interestingly, the association with PDCs was strongest for small laterals followed by peg-shaped and missing laterals.

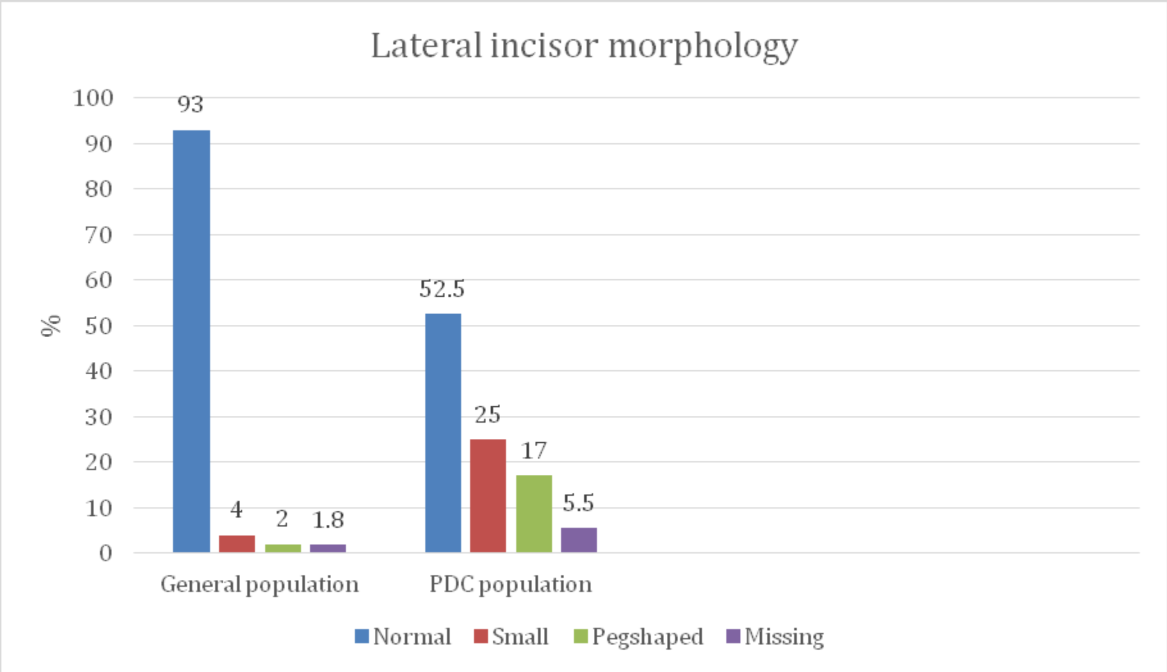

Figure 3. Lateral incisor morphology in the general population and PDC population. Based on data from Brin et al. (43).

The findings of Brin et al. (43) suggest that local factors may be more important than genetic factors in the aetiology of PDC, as the stronger genetic disturbance (missing laterals) seems to be less correlated with PDC than is the minor genetic disturbance (small laterals). Becker (29) presented a theory as to why small laterals and peg-shaped laterals are more correlated with PDC than are missing laterals. He described several stages and outcomes of the impaction process. The first step is that both late-developing and missing laterals will lead to a lack of guidance for the permanent canine, as there are no lateral roots present at the critical time for the developing canine. As the eruption process proceeds, the maxillary canine erupts farther, often spontaneously into the oral cavity when the lateral is missing, but with small or late-developing laterals the eruption path may be blocked. Thus, subjects with small or peg-shaped laterals have more impacted canines than do those with missing laterals.

As missing, small, and peg-shaped teeth are more commonly found in females, this may be a reason why females experience ectopic eruption more often than do males (29, 44).

Genetic factors:

The theories that stress genetic influences on maxillary canine retention refer to the fact that this abnormality is often present along with other genetically controlled dental abnormalities such as: discrepancy in tooth shape, number, and structure; hypoplastic enamel; infra-occluded primary molars; and aplastic second bicuspids (22, 31, 39, 45). With regard to tooth size, it is generally agreed that children with PDC have smaller mesiodistal crown widths than do non-PDC children (46-49). Ely et al. reported that some cases of impacted canines have “primary tooth germ displacement” that, for example, may lead to canine/first premolar transposition (50); according to Becker, such cases are “under genetic control” (51). Other cases of canine impaction may have both genetic and local environmental etiologic factors; for example, the parity of prevalence of ectopic canines between monozygous and dizygous twins is difficult to explain if the aetiology of PDC is exclusively genetic (36).

Morphological characteristics:

Whether morphological characteristics in the maxillary jaw play a role as an etiologic factor affecting PDCs is disputed. Studies have found smaller (52), larger (53), and equal (46, 47) palatal widths in patients with PDC compared with non-PDC controls. These contradictory reports could be due to the use of different methods (i.e. CBCT, plaster models, and cephalograms) to measure the size of the maxilla (54). Another reason could be differences in study samples. The number of uni- or bilateral PDCs and age of children in the studied samples could influence the results, as the absence of permanent canines causes a narrower dental arch (55). One study excluded patients with space deficiency, which could mean that it was not representative of the average population (54).

6.2.4 Root resorption of incisors

The most common adverse effect of ectopic canine eruption is external root resorption of neighbouring teeth. Root resorption is defined as "a condition of dental complication associated with either a physiological or pathological activity of the tooth resorbing cells, which results in loss of cementum and/or dentine" (56). Most studies have found root resorption to be more common in females, with the female/male ratio being 2:1–4:1 (4, 26, 57), though an equal male/female ratio has been reported for "ordinary" resorption and for the severity and location of root resorption (58, 59). When patients with "severe" root resorption (affecting more than a third of the root length) were studied, a 5:1 female to male ratio was found (60). Possible reasons for the gender difference in susceptibility to root resorption could be genetic or hormonal factors, or differences in skeletal and dental development (60).

The incidence of root resorption found in different studies is also dependent on the imaging technique used to detect resorption, with new 3D techniques detecting approximately 50% more resorption cases than conventional 2D radiographs (26, 61). The lateral incisor is most prone to external root resorption, with reported frequencies of 27–67% versus 9–23% for roots of central incisors (57, 61, 62). Ectopic canines may also cause root resorption in first premolars, with an incidence rate of 10% reported in a Chinese population (63). External root resorption leads to loss of tooth substance, which can cause some weakening. However, a long-term study of resorbed incisor roots showed that the overall prognosis for these teeth was good (64).

The exact etiologic factors causing root resorption by neighbouring teeth are still unknown. Physical pressure from the erupting teeth is one theory (65-67), while others claim that the dental follicle and not the tooth itself is the causative agent (68). Others point towards a multifactorial explanation in which both systemic factors within the patient as well as local factors around the ectopic canine (e.g., dental follicle, tooth shape, and physical contact between teeth) work together (60). When severe root resorption was studied in a multifactorial analysis, sex (female), enlarged dental follicle, and normal size of the lateral incisor were found to significantly increase the risk of severe root resorption (60).

Other less common complications of ectopically erupting canines are loss of vitality of adjacent incisors, shortening of the dental arch, formation of follicular cysts, canine ankylosis, recurrent infections, recurrent pain, internal resorption, or a combination of these (69).

6.2.5 Diagnostics

There are three main methods for localizing the permanent canine: visual inspection, palpation, and radiographic examination (70).

<u>Visual inspection and palpation:</u>

A bulge at the alveolar crest in the buccal sulcus is usually present 1–1.5 years before the eruption of the canine (71). This bulge is a sign of a normally erupting canine and may already be present at the age of 8 years and should generally be palpable in the buccal by the age of 10 (8, 72). If the permanent canine cannot be palpated at that time, it may be a sign of a developing eruption disturbance (72). The axial position of the adjacent lateral incisor may be influenced by the eruption of the canine (72). This may be a normal physiological process ("ugly duckling"), but it can also be an indication of the ectopic eruption of the canine. The absence of a distal inclination or the proclination of the lateral incisor crown are reportedly predictive signs of eruptive disorders of the canines (72, 73). If the deciduous canine is mobile, it is a sign that the permanent canine is erupting normally, although some exceptions may occur (8). However, the permanent canine may erupt ectopically even in cases displaying varying degrees of deciduous canine root resorption, and ectopic eruption of permanent maxillary canines has been reported in cases in which less than 1/3 of the root of the deciduous canine remained (10). Based on findings from visual inspection and palpation, Ericsson and Kurol suggested the following indications for radiographic examination when eruption disturbances are suspected: 1. asymmetry on palpation; 2. the canine cannot be palpated in a normal position at the expected time; and 3. the lateral incisor is late in eruption or shows a pronounced buccal displacement or proclination (72). According to these criteria, further radiographic examination was indicated in 12.8% of 10 year olds (72).

Radiographic examination:

In cases of ectopic teeth, radiographic examination is vital in order to visualize the tooth's position relative to neighbouring teeth and other skeletal structures. Radiograms also show the severity of root resorption in teeth (61) and may indicate their long-term prognosis (74), information which is vital for treatment planning (4).

In orthodontics today, the most commonly used radiographic methods are:

a) Periapical radiography	Intraoral technique	2D
b) Lateral cephalogram	Extraoral technique	2D
c) Orthopantomogram	Extraoral technique	2D
d) Conebeam CT	Extraoral technique	3D

Periapical radiography is an intraoral technique using standard intraoral radiographic sensors or films (75). This method is inexpensive and the x-ray exposure is low. To determine the position of an ectopic tooth, "Clark's rule" or the "buccal object rule" is utilized (76) (Figure 4). In brief, two periapical images are taken, for example, of a canine and lateral, with different projections. The object that is positioned more buccally will move more relative to the object positioned more palatally and vice versa.

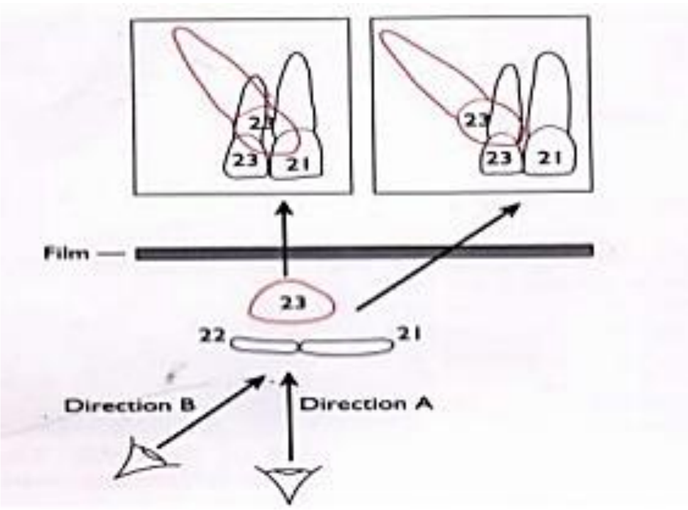

Figure 4. Clark's rule (reprinted with permission from John Wiley & Sons Limited).

The lateral cephalogram is a radiographic imaging technique commonly used in orthodontics for diagnosing anomalies, treatment planning, and evaluating growth and treatment results. The images obtained can also be used to evaluate the anterior–posterior and vertical position and inclination of the canine, though it is usually not the primary reason for using this imaging technique (77).

The orthopantomogram is an extraoral technique that is routinely used in orthodontic treatment (77). It is an excellent imaging technique if used with the understanding that it has greater value for screening than diagnostic purposes. Orthopantomograms provide useful information about: mandibular symmetry; present, missing, or supernumerary teeth; root positions; dental age; eruption sequence and gross periodontal health; sinuses; and TMJ`s (78). However, the orthopantomogram has shortcomings related to the reliability and accuracy of the size, location, and form of the image obtained. These discrepancies arise because the image is made by creating a focal trough or region of focus within a generic jaw form and size (79). Any deviation from this generic jaw will result in structures that are not centred within the focal trough. The resulting image will show differences in size, location, and form when compared with the actual object. Generally, structures that are close to the x-ray beam will appear magnified on the image relative to structures far from the x-ray beam. This can give an indication of the position of an ectopic tooth, for example, as palatal canines will appear larger on the image relative to laterals that are in “normal” positions (79).

The first 3D images were CT images used for medical applications. The effective radiation dose from acquiring these images was much higher than from conventional 2D images. In addition, these images were relatively expensive. Therefore, using CT for the routine analysis of impacted canines seemed to be unjustified (80, 81).

A new 3D imaging technique, cone beam computer tomography (CBCT) (Figure 5), was developed in the 1990s.

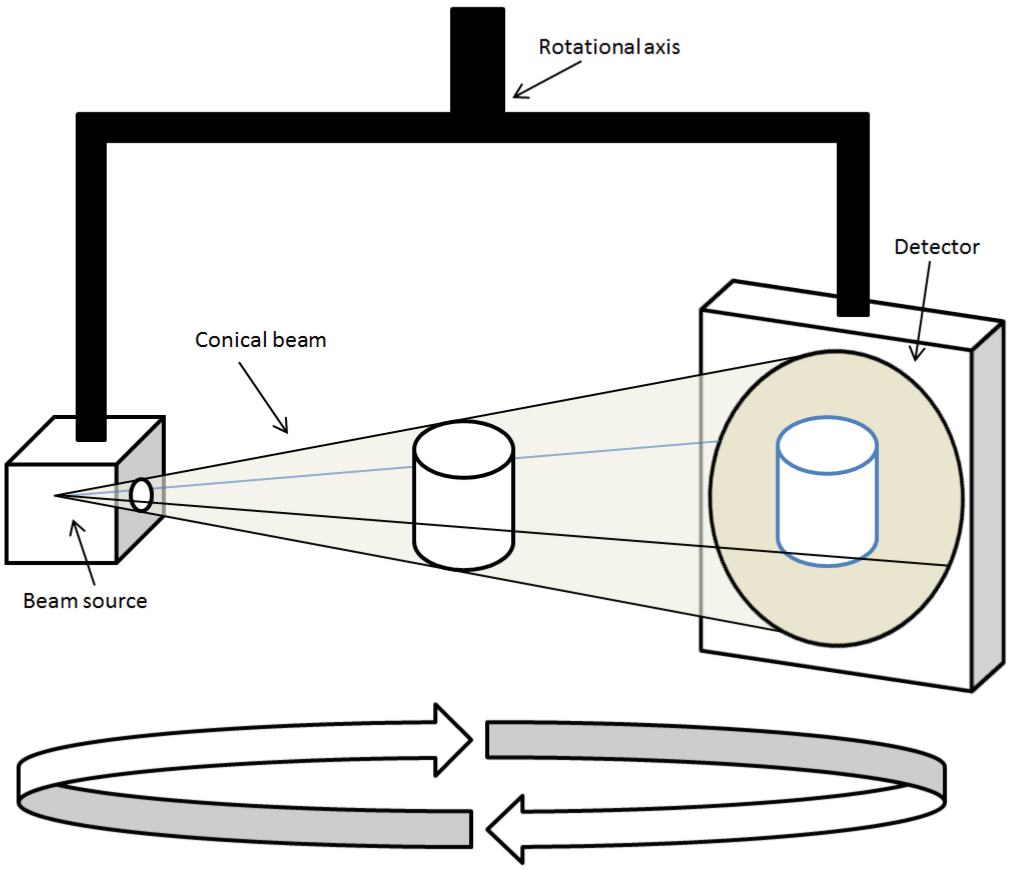

Figure 5. Principle of CBCT.

By Aron Saar - Own work, CC BY-SA 3.0

According to Scarfe et al., CBCT imaging is the most significant technological advance in maxillofacial imaging since the introduction of panoramic radiography (82). This method has been shown to reduce the patient's x-ray exposure by up to 98% compared with CT, and the machines are much cheaper than conventional medical CT devices (80). CBCT imaging uses a conically shaped x-ray beam that is exposed to an object for one lap around the object.

Using computer software, a 3D image is then reconstructed from the acquired data. In many studies, CBCT has proven to be superior to 2D methods used in the craniofacial area (83, 84), and its diagnostic accuracy and validity for the localization of ectopic teeth have been shown to be better for 3D than 2D images (84). When evaluating changes in root surface morphology, such as root resorption, CT images have been shown to increase the root resorption detection rate by 50% (66). In particular, mild and early resorptions are detected more accurately with 3D than 2D images (85). The sensitivity and specificity for detection of root resorption using CBCT with a 0.3-mm voxel size are reportedly 97% and 94%, respectively (86), versus 48% and 85% for 2D radiographs (87).

Although 3D imaging requires higher radiation doses (88), the difference in dosage between CBCT and panoramic radiographs varies between studies. One study showed that CBCT had a radiation dose 2–4 times higher than that of panoramic radiographs (84). Another study of impacted canines using both panoramic radiographs and CBCT found that CBCT had a 15–30-fold higher radiation dose (89). Comparing CBCT with standard periapical radiograph imaging of a single impacted canine showed that the estimated effective dose would be 70–140-fold higher for CBCT depending on the choice of CBCT device (89). The radiation dose of CBCT may differ 15-fold between low- and high- dose resolution protocols for the same field of view (90). Therefore, adhering to the as low as reasonably achievable (ALARA) principle, 3D techniques should only be used on proper indications (75).

<u>Radiographic prediction of root resorption:</u>

Several studies have used CBCT to investigate radiographic predictors of incisor root resorption in conjunction with an ectopic canine. Correlations between root resorption and 1) canine position, 2) mesial overlap with adjacent teeth, 3) available space for the ectopic canine, 4) closed canine apex, 5) contact relationship, and 6) dental follicle have been shown (58, 60, 91, 92). However, other studies contradict these results (65, 67, 93, 94).

As panoramic radiography is more commonly used in orthodontics, and has a lower cost and radiation dosage than does CBCT, Alqerban et al. investigated a possible prediction model for root resorption based on panoramic radiographs (95). In the prediction model, patient gender (female), canine apex (open apex), vertical canine crown position (above middle third of incisor root), and canine magnification (magnified: yes, i.e., palatal) were the strongest predictors of root resorption with an area under the curve (AUC) of 0.74 (i.e., fair accuracy). This indicated that panoramic radiographs may be used to predict root resorption, particularly as a helpful tool to justify the need for an additional CBCT (95).

6.2.6 Interceptive treatment

Interceptive orthodontic treatment can be defined as:

- any procedure that eliminates or reduces the severity of malocclusion in the developing dentition (96); and
- all simple measures that eliminate the developing malocclusion (97).

Previous studies have mainly focused on the palatal ectopic canines (3, 8, 11-14, 49, 98-103). The reason for this is not known, but is probably related to the fact that palatal ectopic canines occur much more frequently than do buccal ectopic canines.

The most common orthodontic interceptive treatment for PDCs is to extract the deciduous canine on the same side as the ectopic permanent canine. A prospective study by Ericson and Kurol (103) in 1988 showed that this procedure was successful in improving the eruption path of the permanent canine. The lack of a control group in this study raised questions about the conclusions reached, though a similar study by Power and Short (8) confirmed the findings of Ericson and Kurol and further concluded that crowding adversely affected the favourable eruption of the canine.

Newer studies with a randomized controlled design (RCT) show that the success rate of extraction of the primary canine is 67–69% as opposed to 39–42% in the control group (13, 14). Bazargani et al. (13) stated that the treatment effect is significantly better in younger age groups (10–11 years old) than older age groups (12–14 years old), which they proposed was due to the longer eruption time and greater deviation in the older subjects. Also, they recommended maintaining the arch perimeter of the maxilla by means of a palatal arch in order not to lose space after the extraction procedure.

Some studies have shown that the addition of headgear (HG) or a rapid maxillary expander increases the effectiveness of the extraction procedure. Baccetti et al. found that the addition of HG treatment increased the success rate from 65.2% to 87.5% (98). However, this study was criticized for methodological weaknesses by Naoumova et al. (101). Silvola et al. (104) investigated the effects of early HG treatment in 7-year-old children with Angle Class II tendency and moderate crowding. They concluded that the eruption pattern of the maxillary permanent canines was more vertical after 2 years of HG treatment than in the control group. This finding may be related to the fact that HG treatment can expand the dental arch and distalize first molars (105). Transseptal fibres (106) may apply a distal force on the posterior dentition, increasing space for the erupting maxillary canine.

Sigler et al. (11) studied the effect of concomitant extraction of the deciduous canine and use of a rapid maxillary expander followed by a transpalatal arch on the eruption of ectopic canines. They found an 80% success rate in the treatment group as opposed to 28% in the control group. This study included mild forms of displaced canines (alpha angle ≥15°) and a heterogeneous sample (i.e., Angle Class II, Angle Class III, and mild space deficiency).

Bonetti et al. (9) compared the effect of extraction of both the primary canine and primary first molar with extraction of the primary canine only on the emergence rate of PDCs as well as angular changes in the canines. Their findings indicated that the double extraction procedure was significantly more effective than the extraction of the primary canine only. However, the study was criticized by Peck (107) for having a problematic sample, since the prevalence of the bilateralism of ectopic canines was 2–3-fold higher than in other studies, and also for including relatively young children (8 and 9 year olds).

Naoumova et al. analysed which PDC patients would benefit from the extraction of primary canines (99) based on panorama radiographs. They concluded that canines located in sector 4 with an alpha angle exceeding 30° need immediate surgical exposure, and that canines located in sector 2 with an alpha angle under 20° could be observed without extraction of the primary canine. Patients with PDCs located in sectors 2 and 3 and an alpha angle of 20–30° would likely benefit from primary canine extraction, according to their study. Power and Short (8) reported that canines angulated 31° or more to the midline had a decreased chance of successful eruption after primary canine extraction, whereas Ericson and Kurol (103) reported that a more mesial location of the crown as well as a more horizontal position of the PDCs reduced the chance of canine emergence. On the other hand, Alqerban et al. (108) found that the prediction of maxillary canine impaction based on panorama radiographs was weak, and that the best predictors to discriminate canine impaction for early intervention were the canine–first premolar angle, canine cusp tip to midline distance, and canine cusp tip to maxillary occlusal plane distance. Based on a CBCT study, Naoumova et al. (102) found that a small mesio–angular angle, a long distance from the canine cusp tip to the midline, and a short distance from the canine cusp tip to the midline were the best predictors of the successful eruption of PDCs after primary canine extraction.

The definition of “success” varies between interceptive studies concerning displaced maxillary canines. Most studies use “full eruption of the maxillary canine into the mouth allowing bracket placement” as the criterion for success (9, 11, 12, 109). Other studies have used: “canine emerged through the gingiva” (14), “eruption above the gingival margin in an aesthetically acceptable location in the dental arch” (13), and “normalization of the path of eruption and later clinically correct position” (103).

7 Objectives

The objectives of this thesis were to provide new knowledge of the root resorption of maxillary incisors in conjunction with maxillary canine eruption and to determine the influence of different interceptive treatment modalities in relation to the normal and ectopic eruption of maxillary canines.

Specific aims:

1. Measure the prevalence and severity of the root resorption of maxillary incisors caused by ectopically and normally erupting maxillary canines, and determine predictors of root resorption of incisors using CBCT imaging
2. Assess whether HG treatment in young children affects the maxillary canine eruption path, and determine whether the potential effect on the eruption pattern is related to space conditions in the dental arch
3. Assess whether extraction of the primary canine and primary first molar is more effective than extraction of the primary canine alone in improving the emergence rate of PDCs, measure the positional changes of PDCs and find predictors of the emergence of PDCs into the oral cavity.

8 Subjects and methods

8.1 Subjects

<u>Paper I:</u>

The inclusion criteria in this study were patients with eruption disturbances in the maxillary canine region and subject to CBCT imaging in the period from January 2008 to December 2011 at the University Hospital of Oulu, Finland. All patients had been referred by their general dentist or orthodontist after clinical and radiographic examination. The main reasons for referral were suspicion of maxillary incisor root resorption and abnormal eruption pattern of the maxillary canine. Ninety-seven patients were enrolled (Figure 6), 38 of whom were excluded for the following reasons: insufficient image quality (n = 10), presence of orthodontic appliances (n = 15), and other reasons (e.g., mesiodens and too early eruption stage, n = 13). In total, 59 patients with 80 canines were entered into the study. The study group was divided into the “Ectopic canine group” (46 canines, mean age 11.9 years, range 8.9–16.7 years) and “Normal canine group” (34 canines, mean age 10.7 years, range 8.8–16.7 years). An ectopic canine was defined as located in sectors 3–5, or located in sector 2 with an alpha angle ≥25° (Figures 1 and 2). Canines with less severe displacements, erupting in sectors 1 and 2 with an alpha angle <25°, and that, vertically, had reached the middle of the lateral incisor root were defined as normal. No canines were located in transposition or horizontally above the apex of the incisors.

The data were collected after approval from the Ethics Committee of Oulu University Hospital, Finland, on 12 December 2011.

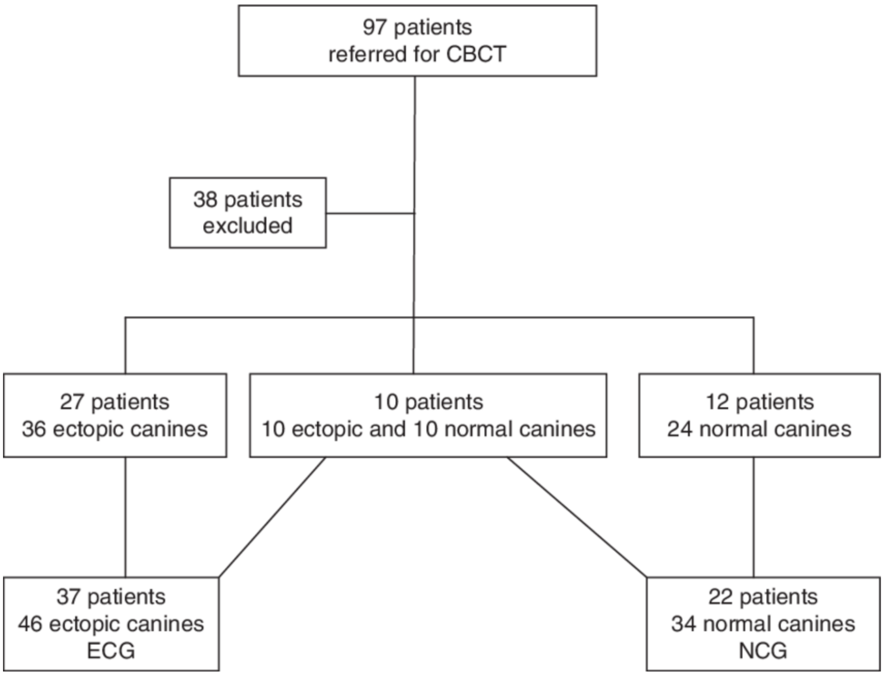

Figure 6. Grouping of patients and teeth. CBCT, Cone beam computed tomography; ECG, Ectopic canine group; NCG, Normal canine group.

<u>Paper II:</u>

The data in this study were pooled from two RCTs performed in northern Finland studying the outcomes of early HG treatment. The inclusion criteria were need for orthodontic treatment due to moderate crowding and Angle Class II occlusion or tendency to Angle Class II occlusion (cusp to cusp). Children with known syndromes and a cleft lip and palate diagnosis were excluded. The first RCT (4, 11) included 71 seven-year-old children (mean age 7.2 years, SD 0.6 years), and the second RCT included 67 seven-year-old children (mean age 7.6 years, SD 0.3 years) (Figure 7). In both RCTs, the children were randomly divided into two groups of equal size: the HG treatment group (HGG) and the control group (CG). Thirty-nine individuals were excluded from the pooled sample for the following reasons:

interceptive extraction of primary teeth (*n* = 17), missing images (*n* = 15), poor image quality (*n* = 2), full eruption of maxillary canines at T1 (*n* = 2), agenesis of lateral incisors (*n* = 2), and transposition (canines and first premolars) (*n* = 1). The final study sample therefore consisted of 99 subjects: 51 in the treatment group (HGG) and 48 in the CG. The HGG comprised 39 per cent females and 61 per cent males, and the corresponding numbers for the CG were 38 per cent females and 62 per cent males. The mean age of the pooled sample at T_0 was 7.7 years (SD 0.4 years) in the HGG and 7.5 years (SD 0.4 years) in the CG. Interceptive slicing of the mesial surface of the primary canines was performed in two children in the HGG and three children in the CG; these cases were not excluded. No further interceptive treatment was done in either group.

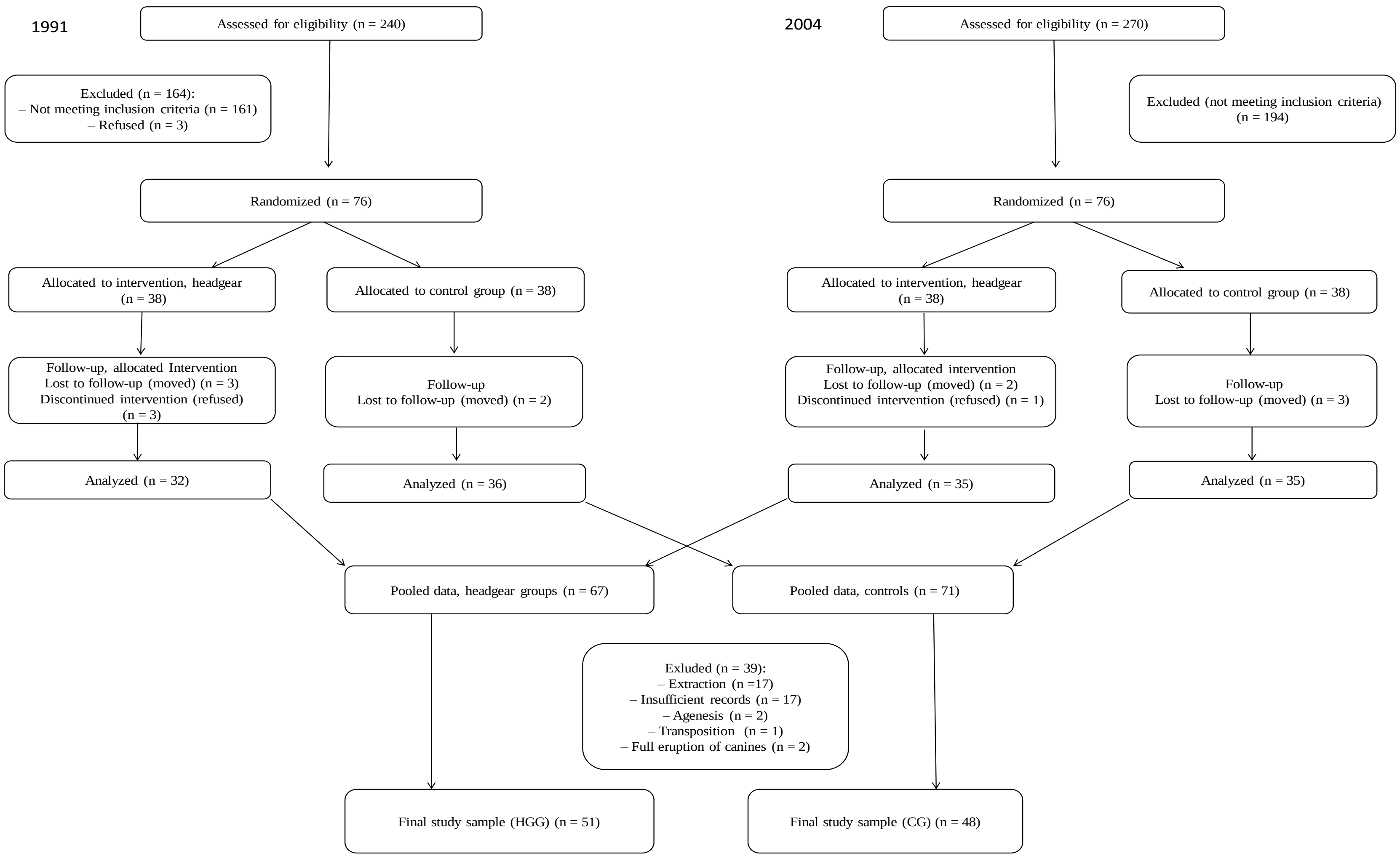

Figure 7. Patient flow chart, Paper II.

Parental informed consent was obtained before randomization. The second RCT was approved by the Ethics Committee of Oulu University Hospital, Finland (EETTMK: 46/2003), and registered at Clinicaltrials.gov, number NTC02010346.

Paper III:

This study took place at the Public Dental Health Competence Centre of Northern Norway and one private clinic in Bryne, Norway, between 1 January 2013 and 31 December 2018. Inclusion criteria were: children with dental age of at least 9.5 years (110) and the presence of both primary maxillary canine and primary maxillary first molars and a palatally displaced permanent maxillary canine (PDC). PDC was defined as eruption of the maxillary canine in sectors III and IV according to Lindauer et al. (15) or eruption of the maxillary canine in sector II with an angle between the long axis of the canine and the facial midline (Angle C) of at least 25° (Figure 1).

Exclusion criteria were: previous orthodontic treatment, any disease not allowing local anaesthesia or extraction, craniofacial syndromes, cleft lip palate, odontomas, cysts, and agenesis of the maxillary lateral incisor.

Thirty-two children, 18 girls and 14 boys with mean ages (SD) of 10.7 (0.7) and 11.2 (1.0), respectively, were invited to participate in the study, and all accepted. Sixteen children had bilateral PDCs and each single canine served as a separate unit in the study; in total, 48 PDCs were included in the study.

The data were collected after approval by the regional ethics committee (REC North) in June 2012 (2012/623/REK nord). Informed consent was obtained from the child and a parent or from an adult with parental responsibilities and rights.

8.2 Methods

Paper I:

The study was designed as a retrospective study. CBCT images acquired in small (*n* = 56) and medium (*n* = 3) field of view (FOV) were analysed.

The following measurements were performed for every subject on the CBCT images:

1. grading of root resorption severity according to Ericson and Kurol (61)
2. localization of the resorptions (i.e., apical, middle, or cervical third of the root)
3. position measurements of the canines:
    a. palatal, labial, or in line with the arch (Figure 8)
    b. distance from the most inferior point of the canine crown to the occlusal plane (Figure 9)
    c. canine angulation to the lateral (Figure 10)
    d. canine angulation to the midline (Figure 10)
    e. canine location in sectors (Figure 2) (panorama reconstruction view)

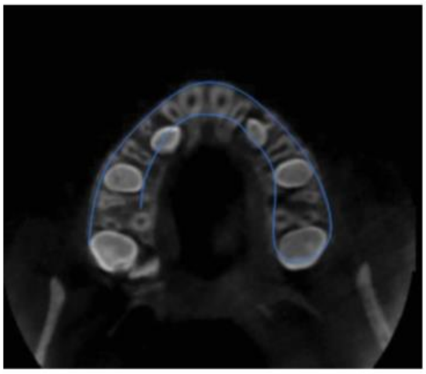

Figure 8. Maxillary canine location relative to the dental arch.

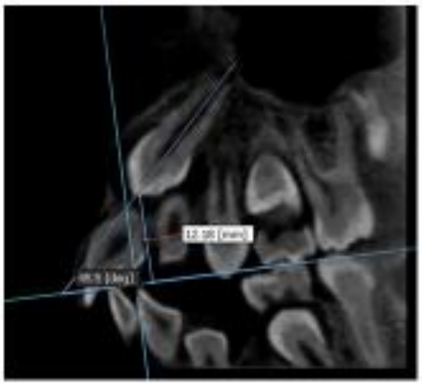

Figure 9. Maxillary canine angulation and distance to the occlusal plane.

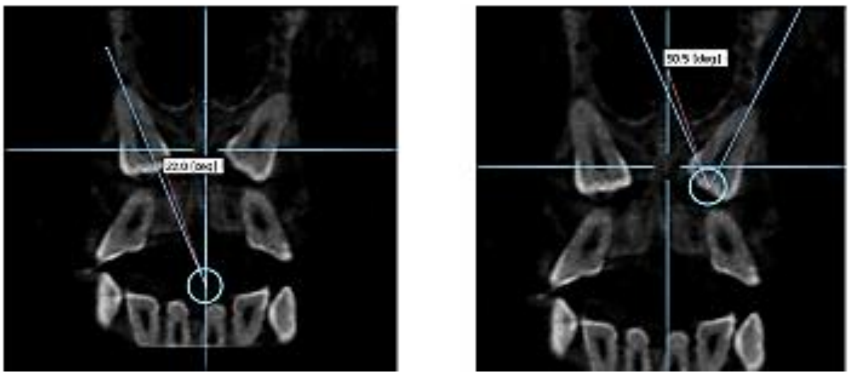

Figure 10. Maxillary canine angulation to the midline and lateral incisor.

Paper II:

The data in this study were pooled from two RCTs studying the outcomes of early HG treatment.

Children in the HGG were treated with cervical HG using 400–700-g force for 1 year or until Angle Class I was achieved. The mean treatment time was 23.8 months (SD 5.6).

Panoramic radiographs and dental casts were taken before (T_0) and after (T_1) the study. The radiographs were imported into the Facad® tracing programme (Ilexis, Linkoping, Sweden) and angular measurements of the maxillary canine were performed (angles A–C, Figure 1)

Dental casts were digitized and analysed using Ortho Analyzer™ computer software (3Shape, Copenhagen, Denmark). Digital model measurements were performed along a constructed occlusal plane, using the mesiobuccal cusp tips of the maxillary right and left first molars and the incisal edges of the right or left central incisor. In cases with a deviating incisor position, the incisor considered to be in the most “correct” position was used. Dental arch distances were measured between the most buccal aspects of the contact points. For transpalatal measurements, distances were measured between cusp tips (Figure 11).

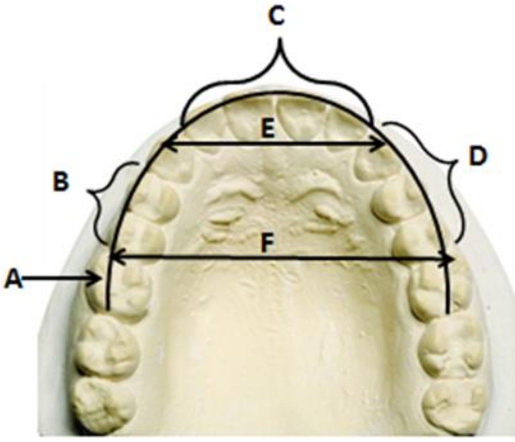

Figure 11. Digital model analysis: (A) arch perimeter, (B) premolar space, (C) incisor space, (D) premolar and canine space, (E) intercanine distance, and (F) intermolar space.

Paper III:

The study was designed as a randomized controlled clinical trial. The randomization was performed using the block randomization method and the children were assigned in an allocation ratio of 1:1 to either the double extraction group (DEG, *n* = 25) or single extraction group (SEG, *n* = 23). The children were examined clinically, and by panoramic radiographic imaging before extraction (T_0) and every 6 months until the canine erupted into the mouth (T_1–T_x). If the canine position worsened or improvement was undetectable after 12 months, alternative treatment was administered (i.e., surgical exposure, fixed orthodontic appliances, and extractions). Clinical photos were taken of each participant before and at the end of the study.

The panoramic radiographic images were imported into the Facad® tracing program (Ilexis, Linkoping, Sweden) and angles A, B, and C (Figure 1) and sectors (Figure 2) were measured.

The clinical photos were visually inspected by one orthodontist (SHO) and each patient was categorized according to the space conditions in the maxillary arch:

- crowding: one or more teeth are overlapping and displaced
- no crowding: all teeth are well aligned
- minor spacing: small open spaces between teeth (total ≤2 mm)
- major spacing: larger spaces between teeth (total >2 mm)

<u>The following outcomes were assessed:</u>

Primary outcome:

- emergence of the maxillary canine into the oral cavity:
  - “successful”: maxillary canine emerged through the gingiva
  - “unsuccessful”: no eruption of the maxillary canine into the oral cavity
- emergence of the maxillary canine in a “favourable position”:
  - maxillary canine emerged in sector I in normal bucco–palatal relationship with occluding teeth in the mandible (i.e., no crossbite)

Secondary outcome:

- maxillary canine positional changes (angles A–C and sectors)
- changes in maxillary arch space conditions

8.3 Reliability of measurements

<u>Paper I:</u>

Eighteen consecutive cases were evaluated by two observers to assess inter-rater agreement, and 21 consecutive cases were evaluated with a time lapse of 1 month to assess intra-rater agreement. Intraclass correlation was used for continuous variables and Kappa statistics (Cohen's kappa) for categorical variables. Both the inter- and intra-rater reliability showed substantial agreement for the categorical variables (kappa = 0.64 – 0.88) and good–excellent agreement for the continuous variables (ICC = 0.81 – 0.96).

Paper II:

Thirty panoramic radiographs and 20 digital models were measured and scored twice within 2 weeks by one investigator (SHO). The reliability analysis of the measurements of panoramic radiographs indicated "acceptable" agreement for the measurement "canine to the maxillary midline" (ICC = 0.745), and "excellent" and "almost perfect" agreement for all other variables (ICC = 0.905–0.984, kappa = 0.92–1.00). For the 3D model analysis, the reliability of all the variables was rated as "excellent" (ICC: 0.904–0.997).

Paper III:

The reliability of panoramic radiograph measurements was reported in Paper II.

The reliability of the space condition analysis was tested by measuring 20 randomly selected plaster models (measured with sliding callipers) and 20 digital photos (measured visually). The ICC was calculated to be 0.889, indicating excellent agreement.

8.4 Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software for Windows, version 19, 24 and 25 (IBM, Armonk, NY, USA), and G**p*ower, version 3.1.9.2 (copyright 2010–2013, Heinrich-Heine Universität, Düsseldorf, Germany) were used for all calculations. Descriptive statistics were calculated and presented as mean values and standard deviations. The differences between various variables were tested using the Chi-square test, *t*-tests (independent and paired), and the Mann–Whitney U test. To test the association between various variables and root resorption, binary multiple logistic regression was used (Paper I). To search for the best predictors of change in canine angulation (Paper II) and the emergence of the maxillary canine (Paper III), the statistically significant variables from a univariate calculation were entered into a stepwise regression model, and variables were excluded one by one on the grounds of the *P*-value or the effect of beta. The level of significance was set at $p < .05$.

<u>Sample size calculation:</u>

<u>Paper II:</u>

Based on an earlier published study, which used part of the present sample (104), 44 canines each were needed in the HG and control groups. This calculation was based on the non-significant changes observed in the alpha angle for the left maxillary canine after 2 years of HG treatment, with alpha = 0.05, beta = 0.2, and power = 0.8.

<u>Paper III:</u>

Based on a comparable study by Bonetti et al. (109), 22 canines each were required in the single and double extraction groups. This sample size is based on the differences in Angle C (i.e., alpha angle) between the single and double extraction groups, with alpha = 0.05, beta = 0.2, and power = 0.8.

9 Results

Prevalence and severity of root resorption (Paper I):

When the maxillary canine was located ectopically, root resorption was found in 11% of central incisors and 67 per cent of lateral incisors, versus 0% and 36%, respectively, when the canine erupted normally. The difference in root resorption prevalence between the ectopic and normal canine groups was statistically significant ($p = .002$). Most cases of resorption were defined as “slight” and located in the middle third of the root. The best predictor of resorption was the maxillary canine located mesial to the midline of the lateral incisor.

The impact of HG treatment on the eruption path of maxillary canines (Paper II):

The dental arch size increased in both the headgear group (HGG) and control group (CG) from start (T_0) to end (T_1) of the study. HG treatment led to significantly greater increases in arch perimeter ($p = .002$), intermolar distance ($p < .001$), and intercanine distance ($p < .001$) than found in the CG.

The mean angular change of the permanent maxillary canine (Angle A) was significant in the HGG (left: $p = .012$, right: $p = .051$), but not in the CG (left: $p = .332$, right: $p = .295$).

The space conditions in the dental arch affected the change in canine angulation in the HGG but not in the CG. In the HGG, the maxillary canine angulation changed significantly more in spaced than in crowded arches (left: $p = .020$, right: $p = .031$). A significant difference between the HGG and CG was seen on the left side (i.e., a more vertical eruption pattern in spaced than in crowded dental arches) ($p = .025$). In crowded arches, there was no difference in canine angulation between the HGG and CG.

The best predictor of change in canine angulation (“Angle A, T1–T0”) was “incisor space” at T_0 (Figure 11).

The impact of double versus single extraction on the emergence of PDCs (Paper III):

Primary outcome:

No significant difference in the emergence rate of the maxillary canine was observed between the DEG and SEG, i.e., 16/25 (64%) versus 18/23 (78%) ($p = .283$), and no significant difference was found in emergence in a “favourable position”, i.e., 16/25 (64%) versus 13/23 (57%) ($p = .600$).

Of the PDCs that emerged into the oral cavity (34/48), significantly more canines emerged in a “favourable position” in the DEG than in the SEG: 100 per cent versus 72 per cent ($p = .025$).

Secondary outcome:

The angular and sector measurements indicated significant distal movement of the canines in both groups ($p < .001$). However, no significant difference was found between the two groups in changes in canine angle (A–C) or sector.

A significant reduction in estimated space was seen in both groups from T_0 to T_{end} ($p < .001$), but no significant difference was recorded between the groups ($p = .727$).

Predictive factors for the emergence of the maxillary canine into the oral cavity:

Emergence of the maxillary canine was significantly associated with its angulation and space conditions at T_0. Canines that emerged into the oral cavity exhibited a significantly greater Angle A at T_0 than did non-emerged canines (p = .003). More PDCs emerged into the oral cavity the more space was available at T_0 (p = .029) (major spacing > minor spacing > no crowding > crowding) (Figure 12). No canines emerged into the oral cavity in the crowded group.

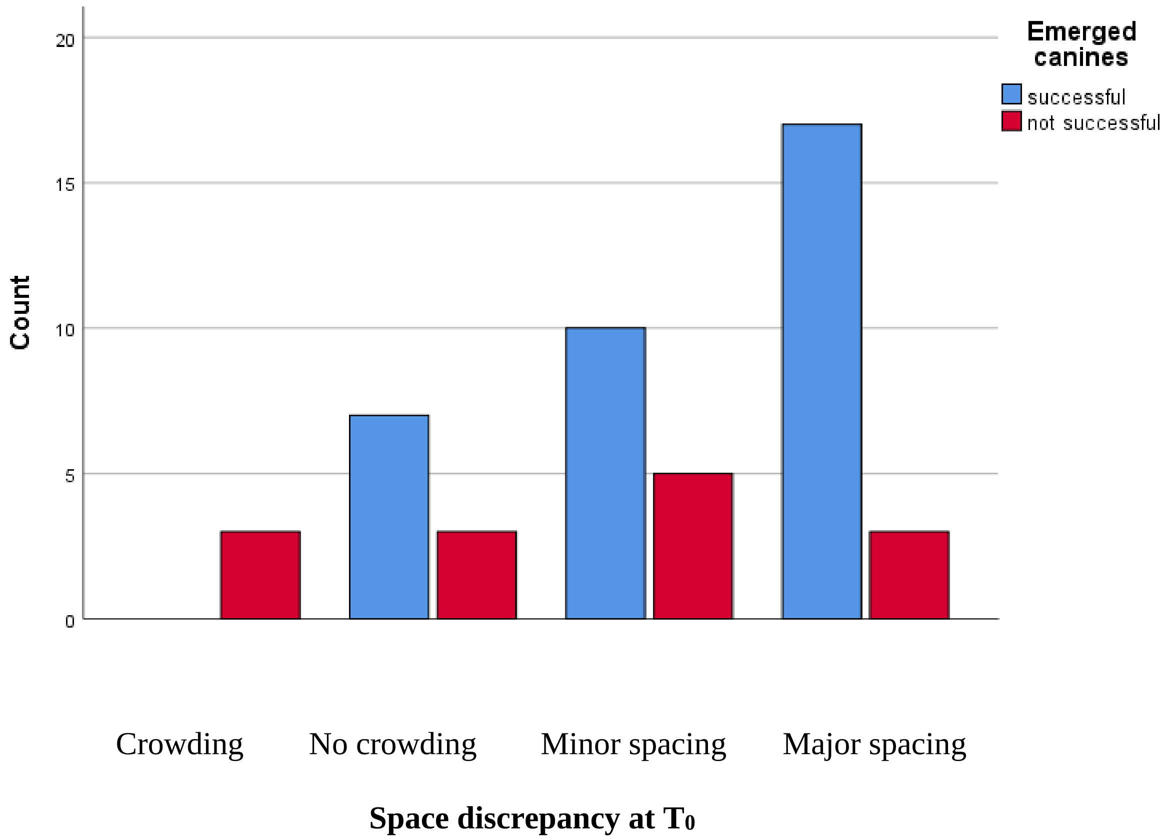

Figure 12. Relationship between space discrepancy at T_0 and emergence of PDCs.

10 Discussion

10.1 Methodological considerations: strengths and weaknesses

<u>Paper I:</u>

This study was designed as an observational study with a cross-sectional, retrospective design. The advantage of such studies is that subjects are not deliberately exposed, treated, or not treated, so there are seldom ethical difficulties. They are also relatively cheap to perform and it is possible to study multiple outcomes (111). A general problem with cross-sectional studies is that they do not provide an explanation of the results, so only association and not causation can be inferred. This is because it is impossible to control for confounding factors that may affect the outcome in a retrospective study.

In this study, only patients with suspicion of or actual eruption disturbance in the maxillary canine region were included. These patients were selected and referred by their general dentist or orthodontist for CBCT imaging. Sampling bias may therefore be present, as the selection was dependent on the doctor's decision.

Ninety-seven children were included in the study, but x-ray images from 38 patients had to be excluded for various reasons (e.g., patient movement, noise, syndromes, too early eruption stage, and presence of orthodontic appliances). Observer selection may therefore have occurred, as exclusion was dependent on the researcher's opinion concerning which patients to exclude (112).

When measuring the canine position in sagittal view, the occlusal plane was used as the reference line (Figure 9). This is in accordance with several previous studies (9, 12, 103, 109), but as the occlusal plane is an unstable structure, this may be inaccurate. A more reliable reference line would be the “spina nasalis anterior to spina nasalis posterior”, which was used by Naoumova et al. (14).

This study did not assess the validity of the CBCT measurements. However, previous studies have found the linear and angular CBCT measurements of PDCs to be good (100), with a mean difference between physical and 3D measurements of 0.5 ± 0.39 mm for the sagittal angle and 0.22 ± 0.19 mm for the mesio–angular angle (100). These angles are comparable to those used in this study (Figure 10). The reliability of the measurements was good in the present study, as the intra- and inter-rater calculations indicated good to excellent agreement for the localization of canines and substantial agreement for the assessment of root resorption.

The different voxel sizes of different CBCT devices can influence the detection of slight root resorption (65). In this study, 56 images were taken with a 0.2-mm voxel size and three images were taken with a 0.3-mm voxel size. According to Liedke et al. (86), the difference between voxel sizes of 0.2, 0.3, and 0.4 mm in the detection of external root resorption using CBCT imaging is not statistically significant. Therefore, different voxel sizes should not represent a significant bias in this study.

In clinical practice, it is important to note that angles and sectors are displayed differently between CBCT and panorama radiographs (84). Generally, the PDC position is exaggerated on panorama radiographs relative to CBCT images (113). Therefore, there is a chance of overestimating the root resorption risk, as clinicians mainly use panorama radiographs and studies of root resorption generally use CBCT images.

<u>Paper II:</u>

The data were pooled from two randomized controlled trials concerning the outcomes of early HG treatment. When pooling data from different studies, the combined results may contradict the results of the individual studies. This effect, also known as “Simpson’s paradox”, may arise when important subgroup characteristics in the different studies are not considered or weighted (114). As these two studies were similar in design, weighting of the subgroups was not considered necessary and therefore was not performed.

Lack of patient compliance records is a weakness of this study, but the endpoint of full Angle Class I occlusion implies proper use of HG. However, large individual variation in how much the HG was used and how the patients reported their compliance has been reported (115). The treatment effect may therefore be underestimated for compliant patients and overestimated for non-compliant patients. For future studies, objective monitoring of HG use is recommended.

Exclusion of patients from RCTs may induce selection bias (112). In the present study, 39 children were excluded from the study for the following reasons: extraction of primary teeth, ($n = 17$), incomplete records ($n = 17$), and inappropriate sampling (i.e., agenesis, $n = 2$; transposition, $n = 1$; full eruption, $n = 2$).

Exclusion of patients due to primary tooth extraction was necessary, as the extraction of primary teeth affects the eruption path of permanent teeth (11, 14, 103). Incomplete records were mainly due to insufficient radiographic image quality. Generally, panorama image quality is operator dependent, and these images may not always correctly capture the patient’s condition (116). Angular measurements were performed, as distortion and overlapping make horizontal measurements unreliable in panorama radiographs (79). Blurring may accentuate the upper incisor region due to ghost shadows of the cervical spine (117). This may be the reason for the reduced reliability (ICC = 0.745) of the angle between the canine and facial midline (alpha angle or Angle C, Figure 1). On the other hand, the angle between the canine and the bicondylar line (Angle A, Figure 1) proved to be a more reliable variable, and was therefore used as the dependent variable in the regression analysis. Parenti et al. also reported Angle A to be the most reliable angle to measure for erupting maxillary canines (118). However, Angle A may be unstable on a long-term basis as it is prone to changes in the condyles, so caution should be taken in follow-up studies in this field.

In the present study, plaster models were digitized and analysed using Ortho Analyzer™ computer software (3Shape, Copenhagen, Denmark). Digital model measurements have been found to be reliable, valid, and accurate in comparison to conventional impressions (119-121).

The digital model measurements (Figure 11) were performed along a constructed occlusal plane, using the mesiobuccal cusp tips of the maxillary right and left first molars and the incisal edges of the right or left central incisor. In cases with a deviating incisor, the incisor considered to be in the "correct position" was used. As "correct position" may be a somewhat subjective assessment, the construction of the occlusal plane may be inaccurate. Furthermore, in cases of severe crowding, the arch perimeter (A, Figure 8) may be difficult to place, and may be assessed differently between raters. The intra-rater reliability indicated excellent agreement (ICC: 0.904-0.997) for the model analysis, but inter-rater agreement could have been determined to ensure sufficient reliability.

<u>Paper III:</u>

This study was designed as a randomized controlled trial with a two-arm parallel group design. This design is considered the gold standard for primary studies (112). In the randomization process, each canine was used as one unit in this study. Each person could also have been used as a unit, in view of the genetic aetiology theory of PDCs (25), as children with bilateral ectopic canines may react similarly to treatment on both sides of the maxilla.

However, if each child was used as a unit, the study would have been more difficult to perform as more children would have had to be included. Also, it would be impossible to see whether changes in treatment outcome were dependent on the person or the treatment method. According to our sample size calculations, 22 canines were needed in each of the two arms; to compensate for possible dropouts, 48 canines were included in the study. During recruitment, it was originally planned that information about the study would be given by an independent person without a relationship to the patient (i.e., not a nurse or doctor treating the patient). This proved difficult in practice, as questions regarding treatment were difficult for persons not involved with the patient to answer. However, caution was taken not to persuade patients to take part in the study, so that participation would be freely chosen.

Randomization was performed using the block randomization method (122). Block sizes varied randomly among 2, 4, 6, and 8, as two closely balanced groups were needed at all times in case the study had to be terminated. The study was unblinded, as the treatment was impossible to hide for the patient and the doctor. In studies with an objective outcome, such as this one, unblinded studies do not tend to be more biased than blinded ones (123). To reduce bias, an independent person, not knowing the purpose of the study, measured the radiographs.

Allocation was concealed by enclosing assignments in sequentially numbered sealed envelopes. After randomization, children were assigned in an allocation ratio of 1:1 to either the double extraction group (DEG) or single extraction group (SEG). None of the children refused to take part in the study and there were no drop-outs, which is a great strength. A control group was not included, as withholding treatment was considered unethical in this patient group (9, 13, 14).

10.2 Statistical analysis

In statistical analysis there are many potential sources of bias. One essential factor is the sample size used in the studies (124). Non-significant results may turn out to be statistically significant with larger group sizes. Also, the division of samples into smaller subgroups may weaken the chance of achieving statistically significant results. As a rule, multivariate analysis needs a minimum of ten events per variable to ensure reliable modelling (125). In Paper III, the variable “space discrepancy at T_0” was not included as it contained groups of fewer than 10 cases. The multivariate analysis in Paper III could therefore have had a different outcome with a larger sample size.

When calculating the required sample size, it is important to evaluate which variable to use as a basis for the power calculation. This is especially important in studies in which multiple outcomes are studied. It may be that the sample size calculation is appropriate for one outcome and not for another. In Paper III, observed change in the alpha angle was used (Angle C) for the sample size calculation, in accordance with several previous studies of PDCs (9, 13, 14). That means that our study had a sufficiently large sample to investigate changes in alpha angle, but may have had too low a power to actually detect any difference in some of the other outcome variables. Low power is unfortunately a common problem in science. A meta-analysis of studies in neuroscience showed that the average study had a power of approximately 21% (126). The problem with low power is that the likelihood of detecting a difference, if there is one, is low (i.e., type II error). In retrospect, the sample size in Paper III could have been larger to more reliably address some of the outcomes studied. To achieve sufficient sample size for conditions with low prevalence, such as ectopic canines, a multicentre study would have been preferable.

10.3 Ethical considerations

Children are considered a vulnerable group, so research involving children is strictly regulated. Clinical studies of children should be performed in such a way that new useful knowledge is generated. The aims of our studies were to improve our understanding of oral health in children and to reinforce the scientific foundation for the treatment of ectopic maxillary canines. These aims are in accordance with the United Nations Convention on the Rights of the Child (Article 24):

1. States Parties recognize the right of the child to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health. States Parties shall strive to ensure that no child is deprived of his or her right of access to such health care services.

As the children in these studies were young, they had reduced autonomy and were dependent on their parents or an adult with parental responsibilities and rights. Therefore, informed written consent was obtained from the child by his or her caregiver, but if situations had arisen in which the child did not want to participate, he or she would not have been included in the study in order to respect the ethical principle of autonomy. Age-adapted written information about the study was given as well as information about, for example, the study's purpose, benefits, potential negative effects, data handling, and examination method, as well as the principle of voluntary participation.

Radiographs were taken during the studies, but no *extra* images were taken for the purpose of the studies. If caries or other signs of oral disease were found, the children's regular dental clinics were informed.

The studies were performed according to the Declaration of Helsinki, which represents one of the key ethical guidelines for research with human subjects (127).

No financial support influenced the studies and their results.

10.4 Discussion of main findings

Paper I:

The aims of this study were to measure the prevalence and severity of the root resorption of maxillary incisors caused by ectopically and normally erupting maxillary canines, and to determine predictors of the root resorption of incisors using CBCT imaging.

The prevalence of the root resorption of maxillary incisors varies with the population studied (128). To the best of our knowledge, this is the first study of root resorption in Finnish children, so we do not have exactly comparable data. However, comparing the results from the ectopic canine group with the results of studies from other parts of the world reveals both similar (57, 61) and lower (62) prevalences of incisor resorption. These differences likely reflect variance in the malposition of the maxillary canine, female to male ratio, and age group of the samples. In addition, recent studies have found that genetic background plays an important role, as individual susceptibility to root resorption is considered a major factor, both in orthodontic treatment and in other contexts (129, 130). One study claimed that genetic influence accounted for approximately 50% of the observed variation in external root resorption after orthodontic treatment, with variation in the gene for the inflammatory cytokine Interleukin 1B determining 15% of the observed variation (129). Differences in the definition of “ectopic canine” between studies, or even the lack of a definition, also make comparison difficult. Some use numerical values in their definitions (9, 11), whereas others are limited to a qualitative description of the canine position on radiographs and in clinical examinations (14). These differences may cause bias when comparing studies of root resorption.

Interestingly, approximately 1/3 of the patients with canines erupting normally exhibited resorption, a significantly higher prevalence than the 5% previously reported (61). However, studies of root resorption in normally erupting canines are scarce. Our finding suggests that small root resorptions may be more common than previously assumed, but future studies are needed to verify this finding, preferably in a less selective population.

The mesio–distal position of the canine (sectors 3–5, Figure 2) was found to be the best predictor of root resorption in the present sample. As opposed to previous studies, we did not find any significant association between canine angulation relative to the facial midline (Angle C > 25°, Figure 1) (26) or between canine angulation relative to the lateral incisor (Angle B > 54 º, Figure 1) and root resorption (131).

Paper II:

The aims of this study were to assess whether HG treatment in young children affects the maxillary canine eruption path and to determine whether the potential effect on the eruption pattern is related to space conditions in the dental arch.

This study showed that HG treatment in young children influences the eruption pattern of maxillary canines. In a previous study, the same relationship was found, but only for the right maxillary canine (104). Our study has a larger sample size and therefore a higher chance of detecting a difference in canine angulation. Our study does not reveal the mechanisms by which HG treatment influences the canine eruption pattern, but it may be related to transseptal fibres (106) applying a distally directed force to the maxillary teeth as the first molars are pulled distally. In addition, both papers II and III in our study indicate that increased space in the maxillary arch promotes maxillary canine eruption. The HG treatment may increase the space in the canine region by distalization, the lip bumper effect, and an increased transversal dimension. Of special interest is the correlation between available space in the anterior part of the maxilla and the vertical eruption of the maxillary canine. In spaced dental arches, the maxillary canine changes its eruption pathway to become significantly more vertical than in crowded arches. This is consistent with the findings of Paper III, showing that the amount of space available in the maxillary arch is related to maxillary canine emergence. Other studies have found that the emergence rate of PDCs increases when HG, rapid maxillary expanders, or transpalatal arches are used in addition to primary canine extraction (11, 12), but they did not quantify the association between the space discrepancy in the maxilla and canine angular change.

The children in the present study sample were approximately 7.5 years old at T_0. Canine displacement cannot be diagnosed at such a young age (132), so we cannot conclude that HG treatment influences displaced canines. To verify the influence of HG on ectopic canines, studies of an older patient cohort with verified displaced canines are needed.

Paper III:

In Paper III, we tested two different interceptive treatment protocols (i.e., double vs. single extractions) for PDCs, as previous studies have presented conflicting results about the outcome (9, 109) and have been criticized for their methodology (107).

The two protocols did not identify any statistically significant difference in the emergence rate of PDCs depending on whether the primary canine only was extracted or both the primary canine and primary first molar were extracted. This is similar to the results of Bonetti et al.'s first study (109) and in contrast to those of their second study (9). These two studies also found that the angle of the maxillary canine (Angle C, Figure 1) changed significantly more when double rather than single extractions were performed, which was not verified in the present study. The discrepancy between the two studies by Bonetti et al. (9, 109) and the present one is likely related to differences in the samples studied. Compared with previous studies, the present study included older patients with more severe malpositioning of the maxillary canine.

In the present study, significantly more of the emerged canines in the DEG erupted in a "favourable position" versus in the SEG. The reason for this observation is unknown, but may be related to a change in the first premolar eruption path (109) that secondarily affects the canine eruption path. It may also be a random finding. To investigate this finding further, a larger study cohort is needed.

We found an interesting significant association between canine emergence and space conditions in the maxillary arch. No canines emerged in the "crowded" group but more canines gradually emerged as the available space increased (Figure 12). A similar finding was reported by Power and Short (8). This information could be valuable for clinicians, who should be sure to facilitate canine emergence by increasing the maxillary dental arch space when needed.

Bonetti et al. claimed that the extraction of two teeth is no more traumatic for the patient or technically difficult than the extraction of one tooth (9). Based on experience from the present study, I disagree with this statement. Compared with extracting just the single-rooted primary canine, extracting both the primary canine and the multi-rooted first primary molar takes longer, requires more anaesthesia, and entails more patient discomfort.

Papers I–III:

Overall, this study shows that it is important to monitor the ectopic maxillary canine eruption in children, as root resorption is commonly found on maxillary incisors. HG treatment affects the eruption path of normally erupting maxillary canines in such a way that it may be beneficial for ectopically erupting maxillary canines, but this matter should be studied further. Space conditions in the maxillary arch affect both the normal and ectopic eruption of maxillary canines. The present study supports the currently most common interceptive treatment method, primary canine extraction, as the best interceptive treatment modality for PDCs.

11 Conclusions

In line with the objectives specified for the thesis, the following main conclusions were drawn:

1. Lateral incisor root resorption was found in association with approximately 2/3 of ectopically erupting canines and 1/3 of normally erupting canines in patients referred for CBCT imaging due to maxillary canine eruption disturbances.
2. The best predictor of root resorption in our cohort was location of the canine mesial to the midline of the lateral incisor root in the panoramic reconstruction view of a CBCT image.
3. HG treatment in young children with Angle Class II occlusion may shift the eruption path of maxillary canines to a more vertical direction, and the effect is related to space conditions in the maxillary arch.
4. Double or single primary tooth extraction procedures are similar in supporting the eruption of PDCs into the oral cavity and into a “favourable position” in the dental arch.
5. Initial canine angulation and space conditions may be used as predictors of the successful eruption of PDCs.

12 Future perspectives

Even though ectopic eruption of the maxillary canines affects many children each year, there is still limited scientific evidence for interceptive treatment of this condition. An interesting avenue for future research would be to further investigate the impact of single versus double primary tooth extraction on PDC emergence in a larger sample. It would also be interesting to investigate the effects of double extractions concomitant with orthodontic appliances such as HG, the quad helix, or transpalatal arches on PDC emergence and on space conditions in the maxillary arch. Cost/benefit analyses of different treatment approaches are needed, as are investigations of the patient perspective on treatment. In addition, more basic research employing genetic tests for predicting ectopic eruption as well as susceptibility to root resorption would be interesting to pursue.

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14 Appendix

REC application (paper III)

REC approval (paper III)

Papers I-III

Prosjektsøknad Skjema for søknad om godkjenning av forskningsprosjekt i de regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK)

2012/623-1
Dokument-id: 259434 Dokument mottatt 27.03.2012

Forebyggende behandling av overkjevens permanente hjørnetenner med frembruddsproblemer

1. Generelle opplysninger

a. Prosjekttittel
Forebyggende behandling av overkjevens permanente hjørnetenner med frembruddsproblemer
Interceptive study of ectopic eruption of permanent maxillary teeth

b. Prosjektleder	
Navn:	Sigurd Hadler-Olsen
Akademisk grad:	Cand.Odont
Klinisk kompetanse:	Spesialist i Kjeveortopedi
Stilling:	Kjeveortoped
Hovedarbeidssted:	Tannhelsetjenestens kompetansesenter for Nord-Norge
Arbeidsadresse:	Postboks 2406
Postnummer:	9271
Sted:	Tromsø
Telefon:	99532166
E-post adresse:	sigurd.hadler-olsen@tromsfylke.no

c. Forskningsansvarlig

1. Forskningsansvarlig

Institusjon:	Institutt for klinisk odontologi, Universitetet i Tromsø
Kontaktperson:	Heidi Kerosuo
Stilling:	Professor
Telefon:	77649124
Mobiltelefon:	45271959
E-post adresse:	heidi.kerosuo@uit.no

d. Andre prosjektopplysninger

Initiativtaker til prosjektet er prosjektleder eller forskningsansvarlig (bidragsforskning)

Utdanningsprosjekt/doktorgradsprosjekt PHD programmet ved Universitet i Tromsø, PHD

e. Prosjektmedarbeidere

1. Prosjektmedarbeider

Navn:	Pertti Pirttiniemi
Stilling:	Professord
Institusjon:	University of Oulu
Akademisk rolle:	PHD, DDS
Prosjektrolle:	Veileder

2. Prosjektmedarbeider

Navn:	Raija Lahdesmaki
Stilling:	Førsteamanuensis
Institusjon:	Universitetet i Oulu, Finland
Akademisk rolle:	PHD,DDS
Prosjektrolle:	Veileder

2. Prosjektopplysninger

a. Formål

Prosjektleders prosjektbeskrivelse

I 1-3% av befolkningen bryter hjørnetennene i overkjeven frem på feil plass. Dette kan føre til en rekke problemer for pasienten f.eks manglende frembrudd av hjørnetannen, skade på nabotenner, utvikling av cyster, smerter og et dårligere estetisk tannsett. Behandlingen er kostbar og omfattende og krever behandling av flere typer tannlegespesialister. Forebyggende behandling skjer i dag først og fremst ved tidlig diagnostisering og ekstraksjon av melkehjørnetannen som står i relasjon til den displasserte hjørnetannen. En nylig studie hvor man ekstraherte både melkehjørnetannen og første melkejeksel har vist høyere suksessrate. Vi ønsker å gjøre en prospektive randomisert klinisk studie hvor vi tester denne prosedyren på et større materiale i Norge. Videre vil vi teste om denne nye behandlingsmetoden er assosiert med mer eller mindre smerte for pasienten.

b. Forskningsdata

Nye helseopplysninger

Funn på røntgenbilder samt spørsmål om pasientens tidligere erfaring med tannbehandling og erfaringer med den behandling som blir utført i studien.

c. Forskningsmetode

Både statistiske og fortolkende analysemetoder

Klinisk undersøkelse

Undersøkelse av røntgenbilder. Ingen ekstra røntgen vil bli tatt som følge av studien

Spørreskjema

Begrunnelse for valg av data og metode

Ekstraksjon av melkehjørnetann er internasjonalt en standard prosedyre å utføre i tilfeller med displassering av den permanente hjørnetannen. Ekstraksjon av både første melkejeksel og melkehjørnetann er ikke en vanlig prosedyre å utføre i Norge, mens det i Sverige er tradisjon for dette. Det har vært utført få studier som har sammenlignet ekstraksjon av melkehjørnetann med ekstraksjon av melkehjørnetann+ første melkejeksel i tilfeller med displassering av den permanente hjørnetannen. En nylig studie fra Italis har vist at det er mer effektivt å ekstrahere både melkehjørnetannen og første melkejeksel i slike tilfeller. Samtidig ekstraksjon av melkehjørnetann og første melkejeksel antas å ikke være noe mer teknisk vanskelig eller traumatisk for pasienten sammenlignet med ekstraksjon av bare melkehjørnetannen. Tannekstraksjonen utføres i lokal anestesi og samme mengde anestesi vil være krevet i begge studiegruppene. Behovet for røntgenbilder vil være det samme i begge studiegruppene . Det vil ikke være noen kontrollgruppe da det regnes som uetisk å ikke behandle denne tilstanden. For å sammenligne pasientens opplevelse av av de to forskjellige behandlingsprosedyrene vil pasientene få 3 spørreskjema. 1. skjema før behandlingen starter som sier noe om tidligere erfaring med tannbehandling og angst for tannbehandling. 2. Et skjema som fylles ut samme dag som ekstraksjon foretaes som omhandler smerte, ubehag og bruk av smertestillende samme dag som ekstraksjonen(e) ble foretann 3. Et skjema som fylles ut 1 uke etter tannekstraksjonen(e) ble utført som omhandler smerte, ubehag og bruk av smertestillende den første uken etter tannekstraksjonen(e). Disse tre skjemaer har vært brukt i tidligere internasjonale forskningsprosjekt og reliabilitet og validitet er vurdert som akseptabel.

d. Utvalg

Mindreårige med mangelfull samtykkekompetanse - under 12 år

Den aktuelle aldersgruppen i denne studien er barn i alderen 10-13 år. Dette er på grunn av at det er i denne alderen at hjørnetenner bryter frem i munnhulen, og dersom det skjer avvik i tannfrembruddet er det i denne alderen der er aktuelt å gjøre forebyggende tiltak

e. Antall forskningsdeltakere

Antall forskningsdeltakere i Norge 80

Avvik i frembrudd av hjørnetenner skjer i ca 2 % av befolkningen. Om vi inkluderer 3 årskull i Tromsø første år, deretter to årskull de neste to årene, vil antall deltagere maksimalt bli 100. Styrkeberegning viser at vi bør ha minst 26 individer i hver av de to test gruppene. Med tanke på eventuelt frafall i gruppene planlegges antall forskningsdeltagere til 80.

Styrkeberegning

Ut i fra tidligere studier har vi funnet at vi må ha minimum 26 deltagere i hver gruppe når forskjellen i alpha vinkel mellom gr 1 og gr 2 er 10 grader, ved en alfa nivå på 0,05 og med en styrke på 80%

3. Informasjon, samtykke og personvern

Samtykke innhentes for alle data

Spesifikt informert aktivt skriftlig samtykke

Beskrivelse av rekrutteringsprosedyre

Alle pasienter ved Tannhelsetjenestens kompetansesenter for Nord Norge i Tromsø med den aktuelle problemstillingen vil bli spurt om deltagelse i forskningsprosjektet. Informasjon vil bli gitt skriftlig og muntlig og pasienten vil få betenkningstid slik at de kan rådføre seg med andre.

For deltakere med mangelfull samtykkekompetanse innhentes samtykke:

Fra pårørende/foreldre alene

For barn under 12 år er det pårørende/foreldre som har samtykkekompetanse
Dersom noe av barna i studien er mellom 12 og 16 år, og av grunner som bør respekteres, ikke ønsker at foreldrene, andre med foreldreansvar eller barnevernstjenesten gjøres kjent med opplysninger om barnet, skal dette ivaretas

4. Forskningsetiske utfordringer ved prosjektet

a. Fordeler

Grupper av personer

Barn som i fremtiden vil ha avvik i frembrudd av permanente hjørnetenner

Studien vil gi økt kunnskap om forebyggelse av avvik i frembrudd av permanente hjørnetenner. Fremtidige pasienter vil få den mest effektive tilnærming til problemet og potesielt unngå mye omfattende behandling

Vitenskapen

Vitenskapen vil få økt kunnskap om forebygging av og tiltak mot frembruddsavvik av permanente hjørnetenner.

b. Ulemper

Den enkelte prosjektdeltaker

Individene i gruppen som skal trekke to melketenner (i forhold til gruppen som skal trekke en melketann) vil potensielt oppleve noe mer ubehag. Siden melketennene sitter løst mener at den ekstra belastningen vil bli liten.

c. Tiltak

Det vil ikke være nødvendig med særlige tiltak for å beskytte deltagerne i forskningsprosjektet

d. Forsvarlighet

Forskningsprosjektet medfører ingen risiko eller ulempe for deltageren, samfunn eller miljø. Metodene i prosjektet er kjente og har ikke vist å gi bivirkninger.

5. Sikkerhet, interesser og publisering

a. Personidentifiserbare opplysninger

Opplysninger som registreres i prosjektet er direkte personidentifserbare - Navn, adresse og/eller fødselsdato

b. Internkontroll og sikkerhet

Personidentifiserbare opplysninger oppbevares:

På institusjonens server

c. Forsikringsdekning for deltakere

Pasientskadeerstatningsloven

d. Vurdering av andre instanser

Egen institusjon

Instanser i utlandet

Universitet i Oulu, Finland, hvor to av medarbeiderene i prosjektet er tilknyttet

e. Interesser

Finansieringskilder

Vertsinstitusjonen (tannhelsetjenestens kompetansesenter for nord-norge) finansierer lønn til forsker samt driftsmidler til prosjektet.

Godtgjøring til institusjon

Ingen

Honorar prosjektleder/-medarbeidere

Ingen

Kompensasjon for forskningsdeltakere

Det vil bli søkt om eksterne midler for frikjøp av forsker i fra klinisk virksomhet i perioder med økt forskningsaktivitet

Eventuelle interessekonflikter for prosjektleder/-medarbeidere

Ingen

f. Publisering

Det er ikke restriksjoner med hensyn til offentliggjøring og publisering av resultantene fra prosjektet

Publisering i internasjonale fagtidskrifter, samt formidling på internasjonale kongresser/møter

h. Tidsramme

Prosjektstart 01.06.2012

Prosjektslutt 01.06.2017

Etter prosjektslutt skal datamaterialet anonymiseres

Rådata vil bli oppbevart slik at resultatene kan etterprøves dersom det skulle bli behov for det.

6. Vedlegg

#	Type	Filnavn	Lagt inn dato
1.	spørreskjema 2	Spørreskjema 2 smerte, ubehag, medisin første kveld etter tanntrekking.docx	15.03.12
2.	spørreskjema 3	Spørreskjema 3 smerte,ubehag, fritid, medisin en uke etter tanntrekking.docx	15.03.12
3.	Spørreskjema	spørreskjema 1 MDAS oversatt til Norsk.doc	15.03.12
4.	CV for prosjektleder	CV sigurd.docx	14.03.12
5.	Forespørsel om deltakelse	innhenting samtykke.doc	14.03.12
6.	Forskningsprotokoll	Interceptive treatment of palatally displaced caninens.ppt.docx	14.03.12

7. Ansvarserklæring

Jeg erklærer at prosjektet vil bli gjennomført i henhold til gjeldende lover, forskrifter og retningslinjer

Jeg erklærer at prosjektet vil bli gjennomført i samsvar med opplysninger gitt i denne søknaden

Jeg erklærer at prosjektet vil bli gjennomført i samsvar med eventuelle vilkår for godkjenning gitt av REK eller andre instanser

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord	Veronica Sørensen	77620758	15.06.2012	2012/623/REK nord
			Deres dato:	**Deres referanse:**
			11.06.2012	

Vår referanse må oppgis ved alle henvendelser

Sigurd Hadler-Olsen
Postboks 2406

2012/623 Forebyggende behandling av overkjevens permanente hjørnetenner med frembruddsproblemer

Forskningsansvarlig institusjon: Heidi Kerosuo
Prosjektleder: Sigurd Hadler-Olsen

Prosjektleders prosjektbeskrivelse

I 1-3% av befolkningen bryter hjørnetennene i overkjeven frem på feil plass. Dette kan føre til en rekke problemer for pasienten f.eks manglende frembrudd av hjørnetannen, skade på nabotenner, utvikling av cyster, smerter og et dårligere estetisk tannsett. Behandlingen er kostbar og omfattende og krever behandling av flere typer tannlegespesialister. Forebyggende behandling skjer i dag først og fremst ved tidlig diagnostisering og ekstraksjon av melkehjørnetannen som står i relasjon til den displasserte hjørnetannen. En nylig studie hvor man ekstraherte både melkehjørnetannen og første melkejeksel har vist høyere suksessrate.
Vi ønsker å gjøre en prospektive randomisert klinisk studie hvor vi tester denne prosedyren på et større materiale i Norge. Videre vil vi teste om denne nye behandlingsmetoden er assosiert med mer eller mindre smerte for pasienten.

Vurdering

Vi viser til prosjektendring av 11.06.2012.Endringen går ut på bytte av prosjektleder fra Sigurd Hadler-Olsen til Heidi Kerosuo.
Rek har vurdert cv til Kerosuo og anser at ny prosjektleder har den nødvendige kompetanse for stå som prosjektleder.

Etter fullmakt er det fattet slikt:

Vedtak
Med hjemmel i helseforskningsloven § 10 og forskningsetikkloven § 4 godkjennes prosjektendringen og prosjektet.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding på eget skjema senest et halvt år etter prosjektslutt,jf.helseforskningslovens § 12.

Prosjektleder skal sende søknad om prosjektendring til REK dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. helseforskningslovens § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. helseforskningslovens §10,3 ledd og forvaltningslovens § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette e- brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Vi ber om at tilbakemeldinger til komiteen og prosjektendringer sendes inn på skjema via vår saksportal:

http://helseforskning.etikkom.no.

Øvrige henvendelser sendes på e-post til post@helseforskning.etikkom.no.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Veronica Sørensen
rådgiver

Kopi til: *heidi.kerosuo@uit.no*

Paper I

Acta Odontologica Scandinavica. 2015; Early Online, 1–7

informa healthcare

ORIGINAL ARTICLE

Root resorptions related to ectopic and normal eruption of maxillary canine teeth – A 3D study

SIGURD HADLER-OLSEN[1], PERTTI PIRTTINIEMI[2,3], HEIDI KEROSUO[4], NAPAT BOLSTAD LIMCHAICHANA[4], PAULA PESONEN[2,3], SOILI KALLIO-PULKKINEN[3] & RAIJA LÄHDESMÄKI[2,3]

[1]*Public Dental Service Competence Centre of Northern Norway, Tromso, Norway,* [2]*Research Center for Oral Health Sciences, Medical Faculty, University of Oulu, Oulu, Finland,* [3]*Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland, and* [4]*University of Tromso, Institute of Clinical Dentistry, Tromso, Norway*

Abstract

Objective. To assess the incidence and severity of root resorption of maxillary incisors caused by ectopically and normally erupting maxillary canines and to analyse factors influencing root resorption of incisors using cone beam computed tomography. ***Subjects and methods.*** The study sample comprised 59 patients with a total of 80 canines. Forty-six of the canines, in 37 patients, were defined as ectopic and 34 canines, in 22 patients, were defined as normal. The severity of root resorptions were analysed according to studies by Ericson and Kurol. Multiple logistics regression was used to evaluate the association between various factors and root resorptions. ***Results.*** The prevalence of root resorptions was significantly higher in the ectopic canine group, 11.0% of the central incisors and 67.6% of the lateral incisors in comparison to 0% and 36.2% in the normal erupting group. Most resorptions were defined as 'slight' and were located in the middle third of the root. There was a statistically significant relationship between canines located mesial to the midline of the lateral incisor and root resorption on the maxillary incisors. ***Conclusion.*** The present results show that root resorption of maxillary lateral incisors was common in patients referred to CBCT imaging due to maxillary canine eruption disturbances. Although significantly more frequent in patients with ectopically erupting canines, lateral incisor resorption was also found in association with approximately every third of the normally erupting canines. The best predictor for root resorption seemed to be location of the canine mesial in relation to the midline of the lateral incisor root.

Key Words: *Cone-beam computed tomography, tooth diseases, tooth eruption*

Introduction

Root resorption is the breakdown or destruction and subsequent loss of root structure of a tooth [1]. When the primary tooth exfoliates, root resorption, caused by odontoclasts, is a natural process making way for the permanent dentition. However, pathological root resorptions may also occur in the permanent dentition due to trauma, excessive occlusal loading, tooth mobility caused by periodontal breakdown, cysts, tumours, inflammation, orthodontic treatment and ectopic eruption of adjacent teeth [2–6].

Ectopic tooth eruption or tooth displacement is defined as an abnormal tooth position, often leading to tooth impaction [7,8]. Depending on the population examined, the prevalence of ectopically erupting maxillary canines is 0.8–5.2% [9–11] and a higher prevalence is reported among females than males [12,13]. When maxillary canines erupt ectopically, root resorptions of maxillary lateral and central incisors are reported in up to 50% of the cases [14–17].

When maxillary canines erupt normally, a 5% incidence of root resorption of the lateral incisors has been reported [17]. The number of studies of root resorptions related to normal eruption is, however, very limited.

The diagnosis of ectopic eruption of permanent canines is based on both clinical and radiographic examinations. Clinically, palpation of the buccal

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surface of the maxillary alveolar process, distal to the lateral incisor tooth, may reveal the position of the maxillary canine and has been recommended as a diagnostic tool [18]. Radiographically, ectopic teeth have traditionally been located using a two-dimensional technique with periapical radiographs known as Clark's rule [19]. For diagnosis of routine cases in orthodontics, panoramic radiography with collimation and limited field to reduce radiation dose can be used [14]. Recently, cone beam computed tomography (CBCT) has been introduced with 3D imaging capability for dental structures. As assessment of root resorption and localization of ectopic teeth are more accurate in CBCT compared to 2D, several authors have recommended CBCT imaging of patients with ectopic teeth [14,20].

The aim of the present study was to assess the incidence and severity of root resorption of maxillary incisors caused by ectopically and normally erupting maxillary canines, and to analyse factors influencing root resorption of incisors using CBCT imaging.

Subjects and methods

The data in this retrospective study were collected after approval from the ethical committee of the University Hospital of Oulu on 12 December 2011. The inclusion criterion was patients with eruption disturbances in the maxillary canine region and that had taken a CBCT image in the period January 2008 to December 2011 at the University Hospital of Oulu. All patients in the study had been referred for CBCT imaging by a general dentist or an orthodontist after clinical and radiographic (panorama radiograph) examination. The main reasons for referral were suspicion of maxillary incisor root resorption and abnormal eruption pattern of the maxillary canine. A total of 97 patients, born between 1992–2003, were enrolled in the study (Figure 1). Out of these 97, 38 patients were excluded due to the following reasons: insufficient image quality (six patients due to patient movement, four patients due to noise), presence of orthodontic appliances (15 patients) or other reasons such as mesiodens, too early eruption stage and syndromes (13 patients). Thus, 59 patients were entered into the study. Not all CBCT images showed both maxillary canines. Therefore, the total number of canines entered into the study was 80. Canines were used as the unit in the study. Forty-six of the canines, in 37 patients, were defined as ectopic. This ectopic canine group (ECG) comprised 22 (59.5%) girls and 15 (40.5%) boys, with a mean age of 11.9 years, range = 8.9–16.9 years. The total number of normal canines was 34. Ten of these 34 were contra-laterals of ectopic canines. This normal canine group (NCG) consisted of 22 patients with a mean age of 10.7 years, range = 8.8–16.7 years and an equal gender distribution. In 12 patients normally erupting canines were found bilaterally. In these patients, the reasons for CBCT images were: suspicion of resorption of the permanent lateral incisor root (six patients), abnormal eruption of the canine (two patients) and lack of space where extractions of an adjacent tooth (lateral incisor or 1st premolar) were considered (four patients). The lateral incisor was missing in four (8.7%) of the patients in ECG, but not in any of the patients of the NCG. In the ECG, 23.9% had peg-shaped lateral incisors, compared to

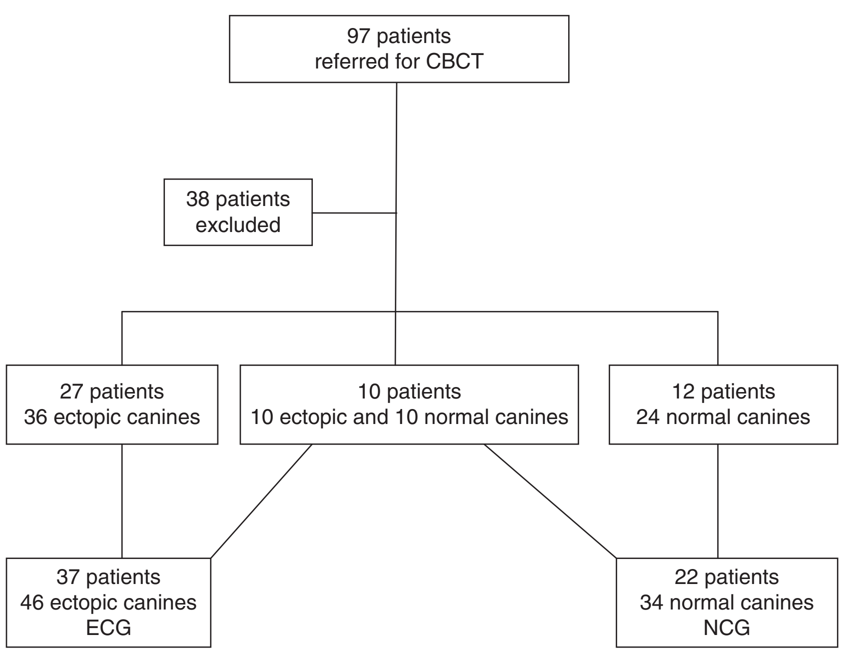

Figure 1. Grouping of patients and teeth. CBCT, Cone beam computed tomography; ECG, Ectopic canine group; NCG, Normal canine group.

2.9% in the NCG. Bilateralism of ectopic canines was present in 24.3%.

Methods

The CBCT images were taken with a Scanora 3D CBCT (Soredex, Tuusula, Finland). Fifty-six images were taken in small field of view (FOV = 6 × 6 cm; resolution = 0.2 × 0.2 mm, spacing = 0.2 mm, matrix = 300 × 300, exposure = 45 mAs, 85 kv, 15 mAs) and three images were taken in medium field of view (FOV = 7.5 × 10 cm; resolution = 0.3 × 0.3 mm, spacing = 0.3 mm, matrix = 333 × 333, exposure = 38 mAs, 85 kv, 15 mAs). Small FOV was used for locating of the canines in the upper jaw, whereas medium FOV were used to locate ectopic canines in both jaws. The images were evaluated in a dimmed light room which was designed to avoid daylight. The computer monitor was a 24-inch Samsung Syncmaster, 1920 × 1200 pixels.

The following measurements were performed for every subject:

Canine positions:

CBCT axial view:

- Permanent canine location in relation to the dental arch was defined as: palatal, labial or in line with the arch. If more than half of the canine crown was located outside the line intersecting the labial or palatal surfaces of adjacent teeth (Figure 2), the canine was regarded as in either labial or palatal position.

CBCT sagittal view:

- The distance from the most inferior point of the canine crown to the occlusal plane was measured. The occlusal plane was formed by a line from the incisal edge of the mandibular central incisor and the most superior occlusal edge of the mandibular first permanent molar.

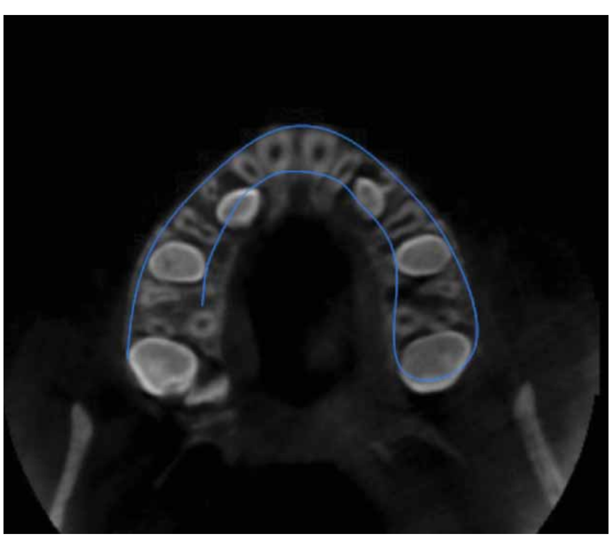

Figure 2. Maxillary canine location relative to the dental arch.

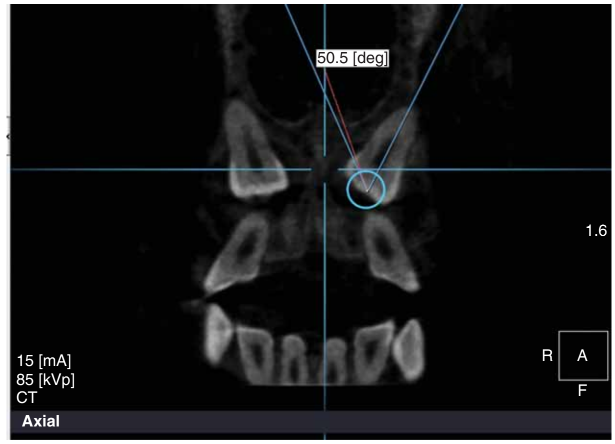

Figure 3. Angle between the maxillary canine and lateral incisor.

CBCT coronal view:

- Canine angulation to the lateral incisor: The angle between a line from the canine cusp and the canine apex bisecting a line from the mid-crown of the lateral and the apex of the lateral (Figure 3).
- Canine angulation to the midline: The angle between a line through the midline suture of the maxilla and a line through the canine cusp and the canine apex.

Panorama reconstruction view of CBCT image:

- Permanent canine location in sectors according to Ericson and Kurol [17] (Figure 4).
- An ectopic canine was defined using a panorama reconstruction view of the CBCT images with 20 mm thickness. The canine was defined as ectopic when it was located in sector 3–5, or located in sector 2 with an alpha angle of at least 25°. Canines with less severe displacements, erupting in sectors 1–2 with an alpha angle <25° and that vertically had reached the middle of the lateral incisor root were defined as normal canines. No canines were located in transpositions or horizontally above the apex of the incisors.

Root resorptions:

In order to evaluate the severity and localization of root resorption, a CBCT view perpendicular to the long axis of the root was used. The view varied depending on the inclination of the incisor.

- Severity of the root resorption in the incisors were graded as follows based on the system suggested by Ericson and Kurol [17].

  1 = no resorption: intact root surface
  2 = slight resorption: resorption of less than half of the dentine thickness

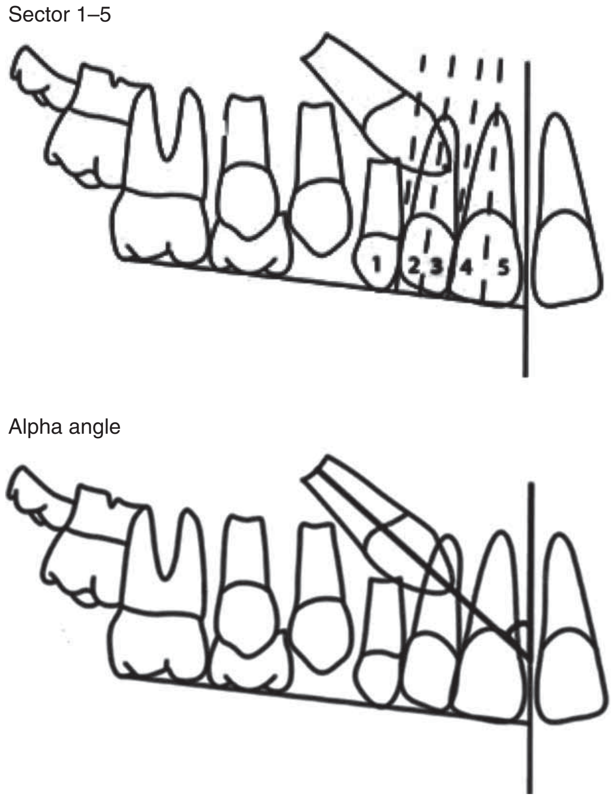

Figure 4. **Sector and alpha angle.**

3 = moderate resorption: resorption of the dentine midway to the pulp or more, the pulp lining being unbroken

4 = severe resorption: resorption reaches the pulp.

- Location of the resorption. The location of the diagnosed resorption defect was recorded as being in the apical, middle or cervical third of the root.
- Reliability of measurements.

For calculation of inter-rater and intra-rater agreement, intra-class correlation (ICC) was used for continuous variables and Kappa statistics (Cohen's kappa) was used for categorical variables. To assess inter-rater agreement, 18 consecutive cases were evaluated by two observers (SHO and NLB), and for intra-rater agreement 21 consecutive cases were evaluated with a time lapse of 1 month.

Statistical methods

The statistical analysis was performed using version 19.0 of the SPSS software package (SPSS inc, Chicago, IL). Descriptive statistics (mean, SD) were used to report the data. The difference in prevalence of root resorptions on maxillary incisors in the ectopic and normal canine group, as well as the difference in prevalence of peg-shape of the lateral incisors in the ectopic and normal canine group was tested with Chi-square test. In order to evaluate the association between various factors (age, gender, shape of the lateral incisor, labio-palatal position of the canine, the angle between the canine and the maxillary midline, the angle between the canine and the lateral incisor and sector location of the canine) and root resorptions on incisors, multiple logistic regression was used to calculate odds ratios and two-sided 95% confidence intervals. The level of significance was set at $p < 0.05$.

Statistical power analyses were performed for the comparison between root resorption on the incisors in the ectopic and normal canine group (statistical power calculator, DSS research.com, © 2014 Decision Support Systems, LP, Fort Worth, TX 76109). For the multivariate logistic regression, power analysis was made with the two significant findings (sectors 1 and 3, sectors 1 and 4 + 5) (G*power, version 3.1.9.2, © Copyright 2010–2013 Heinrich-Heine-Universität Düsseldorf, Germany) [21].

Results

Both the inter- and intra-rater reliability showed substantial agreement for the categorical variables and good-to-excellent agreement for the continuous variables (Table I). This gave acceptance to the measurement methods. All further measurements were, therefore, done by one investigator (SHO).

Table I. Inter- and intra-rater agreement.

	Kappa values		Intra-class correlation (Chronbach's alpha)	
Variable	Inter-rater agreement	Intra-rater agreement	Inter-rater agreement	Intra-rater agreement
Severeness of root resorption (slight, moderate, severe)	0.69	0.69		
Sector location	0.64	0.88		
Angle Canine/lateral			0.96	0.81
Angle Canine/midline			0.94	0.92
Distance Canine/occlusal plane			0.84	0.96

Kappa values: no agreement, < 0; slight, 0–0.2; fair, 0.21–0.40; moderate, 0.41–0.60; substantial, 0.61–0.80; almost perfect, 0.81–1 [30]. ICC Values: unacceptable, < 0.50; poor, 0.51–0.60, questionable, 0.61–0.70, acceptable, 0.71–0.80; good, 0.81–0.9; excellent 0.91–1 [31].

Table II. Prevalence and location of root resorptions on maxillary incisors.

	Ectopic canine group		Normal canine group	
	Central incisor n = 46	Lateral incisor n = 42	Central incisor n = 34	Lateral incisor n = 34
Resorptions				
No	41 (89.0%)	14 (33.4%)	34 (100%)	22 (64.7%)
Slight	5 (11.0%)	19 (45.2%)	0	8 (23.5%)
Moderate	0	4 (9.5%)	0	4 (11.8%)
Severe	0	5 (11.9%)	0	0
Location of resorption				
Apical third	3 (60.0%)	7 (25.0%)	0	5 (41.7%)
Middle third	2 (40.0%)	19 (67.9%)	0	7 (58.3%)
Cervical third	0	2 (7.1%)	0	0

In the ECG 11.0% of the central incisors and 67.6% of the lateral incisors exhibited resorption, whereas in the NCG the corresponding numbers were 0% and 36.3%. The difference in prevalence of root resorptions on maxillary incisors between the ectopic and normal canine eruption groups was statistically significant (p = 0.002, 1-β = 0.83). Most of the resorptions in both groups were 'slight resorptions' and were located in the middle third of the root (Table II).

Most of the canines in the ECG were located palatally (54.5%) to the dental arch, whereas most of the canines in NCG were located in line with the dental arch (88.2%). The mean angle between the canine and the lateral incisors was 30° in the ECG and 25° in the NCG, and the mean angle between the canine and the maxillary midline was 23° in the ECG and 14° in the NCG. Most of the canines in the ECG were located in sector 4 (52.2%), whereas most of those in the NCG were located in sector 2 (55.9%) (Table III). Peg-shape of the lateral incisors was seen in 23.9% of the cases in the ECG and 2.9% in the NCG. The difference was statistically significant (p = 0.009).

Table III. Descriptive data regarding the location of canines.

	Ectopic canine group	Normal canine group
Canine localization relative to dental arch		
Labial	2 (4.3%)	2 (5.9%)
In line with	19 (41.3%)	30 (88.2%)
Palatal	25 (54.4)	2 (5.9%)
Angle canine/lateral[a]		
Mean	30°	25°
SD	11.4	7.5
Angle canine/midline[a]		
Mean	23°	14°
SD	13.2	8.3
Distance canine/occlusal plane[b]		
Mean	9 mm	9 mm
SD	3.6	2.3
Sector[c]		
Sector 1	0	15 (44.1%)
Sector 2	6 (13.0%)	19 (55.9%)
Sector 3	13 (28.3%)	0
Sector 4	24 (52.2%)	0
Sector 5	3 (6.5%)	0

[a]CBCT coronal view, [b]CBCT sagittal view, [c]According to measurements developed by Ericson and Kurol [23].

The multivariate logistic regression revealed a significant association between maxillary incisor root resorptions and canines located in sectors 3 (OR = 7.4, CI = 1.1–48.7) and 4 + 5 (OR = 11.5, CI = 1.8–74.1). Sectors 4 and 5 were combined due to low numbers of canines located in sector 5. None of the other measured variables showed a significant association with maxillary incisor root resorption (Table IV). The statistical power of the multivariate logistic regression for the statistically significant variables were 0.91 (sectors 1 and 3) and 0.98 (sectors 1 and 4 + 5).

Discussion

In this retrospective study CBCT images of 59 patients with 80 canines were evaluated. The prevalence of root resorptions and the position of canines were compared between an ectopic canine group (ECG) and a normal canine group (NCG). As expected, the prevalence of root resorptions was significantly higher in the ECG compared to the NCG. However, the prevalence of root resorptions on the lateral incisors in the NCG was surprisingly high (36.3%). To our knowledge, there are very few other studies to compare these findings with, as most studies focus on ectopic eruption rather than normal eruption. Ericson et al. [17] found 5% root resorption on the lateral incisor in normal eruption cases, when using CT as a method of diagnosing. A problem when comparing studies of maxillary canine eruption is that there seems to be no consensus in the literature

Table IV. Odds ratios and upper and lower boundaries of 95% Confidence Interval for (independent) variables related to maxillary incisor root resorption. Gender, peg-shape of lateral incisors and sector are categorical variables, whereas the others are continuous variables.

	Maxillary incisor root resorption			
Independent variables	OR	CI Lower	CI Upper	Significance
Age	1.094	0.777	1.540	0.608
Female gender	2.057	0.601	7.040	0.251
Peg-shape of lateral incisor	0.905	0.198	4.137	0.897
Angle: Canine to maxillary	1.006	0.947	1.068	0.850
Midline	0.990	0.932	1.052	0.751
Angle: Canine to lateral incisor	1.008	0.835	1.218	0.931
Distance Canine to Occlusal plane				
Sector 1 : Reference				
Sector 2	3.019	0.597	15.262	0.181
Sector 3	7.355	1.111	48.709	0.039*
Sector 4 + 5	11.521	1.792	74.079	0.010*

*$p < 0.05$.
CI, confidence interval; OR, odds ratio.

regarding the precise definition of normal and ectopic canines. A few studies, however, have been based on exact criteria. Bonetti et al. [22] defined a palatal displaced canine as having an alpha angle ≥25° and being located in sector 2–5, according to methods developed by Ericson and Kurol [23]. The weakness of this definition is that it excludes ectopic canines located in sector 3–5 with an alpha angle <25°. Sigler et al. [24], on the other hand, defined a palatally displaced canine as having an alpha angle ≥15° and being located in sector 2–5 [24]. A study by Warford et al. [25], who used a modification of the Ericson and Kurol's sector method [26], showed that most teeth in sector 3 and 4 will become impacted, and that an increase in alpha angle only has a potential significance in the prediction of impactions in sector 2. Therefore, when defining ectopic eruption in the present study we used the highest value of the alpha angle (≥25°), as reported in the study by Bonetti et al. [22], as these canines are more likely to become impacted. Furthermore, all canines in sector 3–5 were defined as ectopic, regardless of the value of the alpha angle. It is, therefore, possible that the definition of normal erupting canines in this study is more permissive than in previous studies, and including cases in the NCG that in other studies would be considered as ectopic. On the other hand it is also possible that slight root resorption is a common phenomenon in the normal eruption of teeth. More studies with larger sample sizes are needed in order to verify this finding.

In the current study, neither age, gender, lateral incisor shape, labio-palatal position of the canine, angle between the canine and the maxillary midline nor angle between the canine and the lateral incisor significantly affect the prevalence of root resorptions. However, canines located in sector 3–5 inter-related significantly with root resorptions. This is in line with previous studies by Ericson and Kurol [17,23]. Ericson and Kurol have also reported a correlation between ectopic canines with the alpha angle ≥25° and root resorptions [6], which we could not verify in the present study.

We found that root resorptions appeared with similar frequencies in association with buccal and palatal canines. This is in line with a study of Ericson and Kurol [17], whereas Cernochova et al. [27] found that buccal canines were more frequently related to root resorptions of incisors than palatal canines.

Measurements of canine angulations showed that our ECG had comparable mean canine-to-lateral angle, and larger canine-to-maxillary midline angle compared to a previous study of Alqerban et al. [14] (30.0° vs 31.6° and 23.0° vs 14.5°, respectively). This may reflect that the present study sample included more advanced cases of ectopic canine eruption. The present study also shows higher numbers of slight root resorptions than other analogous studies [14,17,28]. The differences may reflect the fact that the populations studied are different with regard to genetic background, age distribution and number of complicated cases. Different voxel sizes of different CBCT or CT devices could also influence the detection of slight root resorptions [28]. In the present study, 56 images were taken with 0.2 mm voxel size and three images were taken with 0.3 mm voxel size. According to Liedke et al. [29], the difference between voxel size 0.2 mm and 0.3 mm in the detection of external root resorptions with CBCT imaging is not statistically significant. Therefore, different voxel sizes should not represent a significant bias in the present study.

The agreement between the orthodontist and the radiologist who performed the analyses of the CBCT images in the present study was good-to-excellent for localization of canines and substantial in the assessment of root resorptions. This is in line with previous studies showing high inter-rater agreement in CBCT studies [28].

Conclusions

The present results show that root resorption of maxillary lateral incisors was common in patients referred to CBCT imaging due to maxillary canine eruption disturbances at the University Hospital of Oulu, Finland. Although significantly more frequent in patients with ectopically erupting canines, lateral incisor resorption was also found in association with approximately every third of the normally erupting canines. The best predictor for root resorption seemed to be location of the canine mesial to the midline of the lateral incisor root in panorama reconstruction view of CBCT image.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Paper II

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OXFORD

Original article

Does headgear treatment in young children affect the maxillary canine eruption path?

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Summary

Objective: To test whether early headgear (HG) treatment and space conditions in the dental arch affect the eruption pathway of the maxillary canines in young children with mixed dentition.
Subjects and methods: Data from two randomized controlled trials studying the effects of early HG treatment were pooled, yielding a study sample comprising 99 children (38 girls and 61 boys, mean age 7.6 years) with Angle Class II occlusion. Fifty-one children were treated with HG and 48 children served as an untreated control group (CG). Digital 3D models and panoramic radiographs were taken before (T0) and after (T1) treatment, and changes in the maxillary canine eruption angle and interdental spaces were measured at T0 and T1. A paired samples *t*-test was used to assess changes in maxillary canine angulation, and an independent samples *t*-test was used to evaluate the effect of HG treatment on spacing in the dental arch. Associations between intra-arch space conditions and changes in maxillary canine angulation were estimated with linear regression models.
Results: The eruption pattern of the permanent canine was significantly more vertical in the HG group than in the CG. The linear regression models showed a statistically significant association among the intercanine distance, crowding in the anterior part of the maxilla, and changes in the maxillary canine eruption angle. The maxillary canine eruption pattern changed significantly more to a vertical direction in spaced dental arches than in crowded dental arches in the HG group.
Conclusion: This study shows that early HG treatment in children with Angle Class II occlusion may change the eruption pattern of permanent maxillary canines to a more vertical direction. This change appears to be related to space conditions in the maxillary arch, especially in the intercanine region, with more effect in children with spaced dental arches than in children with crowded dental arches.

Introduction

During orthodontic treatment, it is common to move the maxillary permanent first molars distally by means of extraoral headgear (HG). This treatment modality has been used in orthodontics since the early 1900s (1), and 62 per cent of orthodontists in Canada and the USA still view HG as a viable treatment method (2, 3). The purpose of this treatment is usually to correct a Class II sagittal molar relationship and a large overjet, to provide space for maxillary teeth, or to provide anchorage for tooth movement, and most previous studies have concentrated on these effects (4–8). However, a few studies have shown that HG treatment may also have an effect on the eruption pattern of the maxillary canines, and therefore could be used as an interceptive treatment modality in cases with ectopic maxillary canine eruption. Armi *et al*. (9) found that the use of a cervical pull HG significantly improved the eruption rate of palatally displaced canines compared with an untreated control group (CG). Baccetti *et al*. (10) studied the outcome of HG treatment together with extraction of primary canines on the eruption of palatally displaced canines, and compared the results with extraction of the primary canines only. This study showed that the addition of HG treatment to the extraction of primary canines significantly improved the successful eruption of the displaced canines (10). Silvola *et al.* (11) investigated the effects of early HG treatment in seven-year-old children with a Class II tendency and moderate crowding on panoramic radiographs. They concluded that the eruption pattern of the maxillary permanent canines was more vertical after 2 years of HG use than in a CG.

These studies (9–11) indicate that HG treatment may influence the eruption pattern of maxillary canine teeth. However, the number of studies in this field is limited, and the research quality and methodological standards in a number of these studies have been criticized (12). The aim of the present study was to investigate whether HG treatment in young children affects the maxillary canine eruption path. Also, we wanted to study whether the potential effect of HG treatment on the eruption pattern of maxillary canines is related to space conditions in the dental arch.

Subjects and methods

The present data were adopted and pooled from two randomized clinical trials (RCTs) studying the outcomes of early HG treatment (Figure 1). The first RCT (4, 11) consisted of 71 seven-year-old children (mean age 7.2 years, SD 0.6 years). The inclusion criteria were Class II occlusion or tendency to Class II occlusion (cusp to cusp). Children with known syndromes and a cleft lip and palate diagnosis were excluded. The second RCT was analogous in design to the first RCT and included 67 seven-year-old children (mean age 7.6 years, SD 0.3 years).

In both RCTs, the children were randomly divided into two groups of equal size: the HG treatment group (HGG) and the CG. HG treatment started immediately after records were taken (T0) and lasted for at least 1 year or until full angle Class I occlusion was achieved on both sides (T1). In the treatment group, no other appliances were used during the follow-up period. The long outer bows of the HG were bent 10 degrees upwards in relation to the inner bow, which was expanded 5–10 mm compared with the maxillary first molars. The mean force on the HG was 400–700 g, and the patients were instructed to use the HG for 8–10 h per night. No records of HG compliance were taken.

Records collected from both groups (HGG and CG) at T0 and T1 included comprehensive clinical examination, dental casts, and panoramic radiographs.

Thirty-nine individuals were excluded from the pooled sample for the following reasons: (a) interceptive extraction of primary teeth: 17 subjects, (b) missing images: 15 subjects, (c) bad image quality: 2 subjects, (d) full eruption of maxillary canines at T1: 2 subjects, (e) agenesis of lateral incisors: 2 subjects, and (f) transposition (canines and first premolars): 1 subject. The final study sample therefore consisted of 99 subjects: 51 subjects in the treatment group (HGG) and 48 subjects in the CG. The HGG comprised 39 per cent

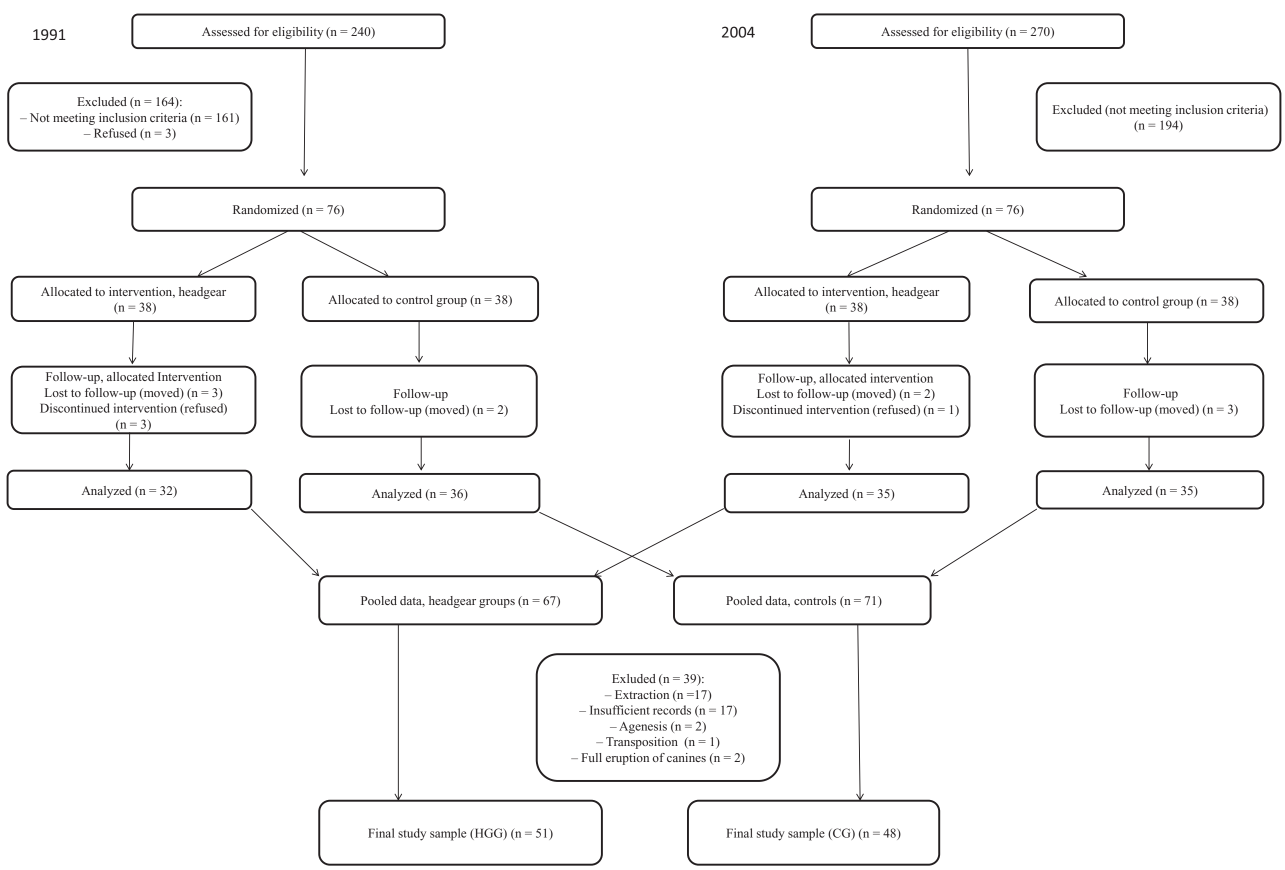

Figure 1. Patient flow chart.

females and 61 per cent males, and the corresponding numbers for the CG were 38 per cent females and 62 per cent males. The mean age in the pooled sample at T0 was 7.7 years (SD 0.4 years) in the HGG and 7.5 years (SD 0.4 years) in the CG. The mean treatment time with the HG was 23.8 months, SD 5.6 months. Interceptive slicing of the mesial surface of the primary canines was performed in two children in the HGG and three children in the CG. These cases were not excluded. No further interceptive treatment was done in either group.

Parental informed consent was obtained before the randomization. The study protocol was approved before the start of the second series of the study by the Ethics Committee of the Oulu University Hospital, Finland (EETTMK: 46/2003). The trial is registered at ClinicalTrials.gov, number NCT02010346.

Digital model measurements

Dental casts were digitized and analyzed using OrthoAnalyzer™ computer software (3Shape, Copenhagen, Denmark). Digital model measurements (Figure 2) were performed along a constructed occlusal plane, using the mesiobuccal cusp tips of the maxillary right and left first molars and the incisal edges of the right or left central incisor. In those cases with a deviating incisor position, the incisor considered to be in the 'correct' position was used. Dental arch distances were measured between the most buccal aspects of the contact points. For trans-palatal measurements, distances were measured between cusp tips.

The following distances were measured (Figure 2):

1. 'Arch perimeter'—formed by a curve from the distal contact points of teeth #16 and #26 through the contact points and incisal edges of the incisors
2. 'Premolar space'—from the mesial contact points of the first molar to the distal contact points of the primary canine in the maxilla (measured on both right and left sides)
3. 'Incisor space'—between the mesial contact points of the right and left maxillary primary canines
4. 'Premolar and canine space'—from the mesial contact point of the first molar to the distal contact point of the lateral incisor in the maxilla (measured on both the right and left sides)
5. 'Intercanine distance'—transversally between the left and right maxillary primary canine cusp tips
6. 'Intermolar distance'—transversally between the left and right maxillary first molar mesiobuccal cusp tips.

In addition, the mesiodistal width of each upper and lower incisor was measured.

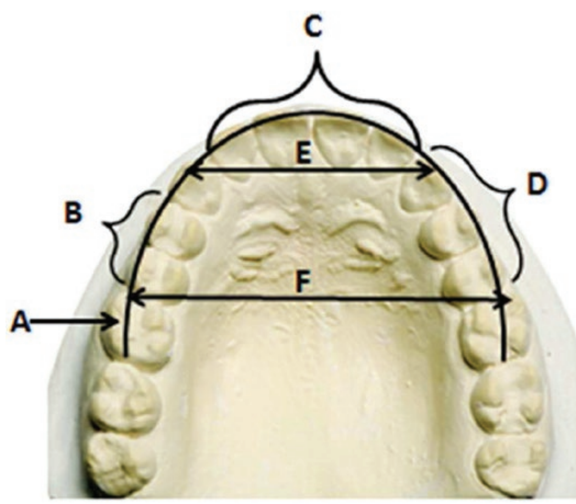

Figure 2. Digital model analysis. (A) arch perimeter, (B) premolar space, (C) incisor space, (D) premolar and canine space, (E) intercanine distance, and (F) intermolar distance.

Space analysis

Space discrepancy in the maxillary arch was estimated as follows: 'estimated arch length/tooth size discrepancy' = the sum of the measured space for the incisors and premolars at T0 minus the sum of the estimated widths of the upper permanent incisors and premolars. The width of the permanent canine and premolars was estimated using Moyers mixed dentition analysis (13) using the lower incisor width: 'estimated anterior arch length/tooth size discrepancy' = the sum of the measured space for the incisors at T0 minus the mesiodistal width of the maxillary permanent incisors.

Panoramic radiograph measurements

The panoramic radiographs and patient positioning were done according to the manufacturer's protocol. The panoramic images were imported into the Facad® tracing programme (Ilexis, Linkoping, Sweden) and analyzed in a dark room using a Lenovo ThinkPad® (Lenovo, Morrisville, North Carolina, USA) with a 15.6-inch screen with 1,366 × 768 resolution.

The following angles were measured (Figure 3):

- Angle A: the long axis of the maxillary canine to a line drawn between the superior edges of the condyles (14)
- Angle B: the long axis of the maxillary canine to the long axis of the maxillary lateral incisor (15)
- Angle C: the long axis of the maxillary canine to the maxillary midline formed by a line drawn though the intermaxillary suture (16)
- Sector location for canines according to Lindauer *et al.* (17).

All measurements were done for both right and left canines by one investigator (SHO).

Reliability of measurements

Thirty panoramic radiographs and 20 digital models were measured and scored twice with a timespan of 2 weeks by one investigator (SHO). Intraclass correlation (ICC) was calculated for continuous variables and kappa statistics for categorical variables.

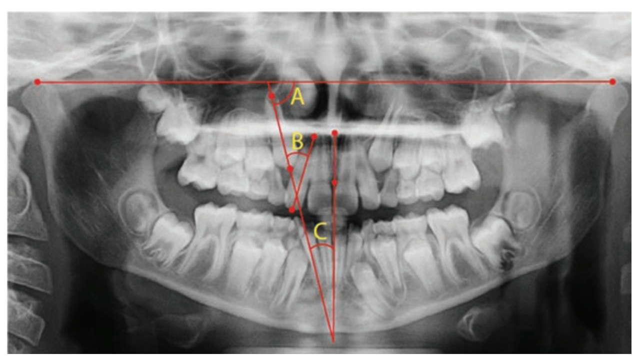

Figure 3. Angular measurements of maxillary canines. Angle A: canine to bicondylar line, Angle B: canine to lateral incisor, Angle C: canine to maxillary midline.

The reliability analysis for the measurements of panoramic radiographs showed 'acceptable' agreement for the measurement 'canine to the maxillary midline' (ICC = 0.745), and 'excellent', and 'almost perfect' agreement for all the other variables (ICC = 0.905–0.984, kappa = 0.92–1.00). For the 3D model analysis, the reliability for all the variables was rated as 'excellent' (ICC: 0.904–0.997).

Statistical methods

Statistical analysis was performed using version 24.0 of the SPSS software package (SPSS Inc, Chicago, Illinois, USA).

An independent sample *t*-test was used to evaluate the difference between the HGG and the CG on distances (Figure 2) measured on digital models. A paired sample *t*-test was used to analyze the mean changes between T0 and T1 in maxillary canine angulation (Angles A, B, and C) within the HGG and the CG. Marginal homogenity test was used to analyze changes between T0 and T1 in sector location for canines. Changes in canine eruption angle (Angle A, T1–T0) in crowed compared to spaced dental arches was analyzed with an independent samples *t*-test.

Crude linear regression models were used to evaluate the relationships between the digital model measurements (independent variables; Figure 2) and a change in the maxillary canine angulation (dependent variable; Angle A, T1–T0). To search for the best predictor of the change in Angle A, the statistically significant variables from this calculation and HGG/CG were then entered into a stepwise regression model, and variables were excluded one by one on the grounds of the *P*-value or the effect of beta.

Scatter plots and regression lines were used to analyze and demonstrate the correlation between the change in Angle A (T1–T0) and the incisor space at T0. The differences between the regressions slopes were calculated using analysis of covariance. *P*-values of less than 0.05 were considered to be statistically significant.

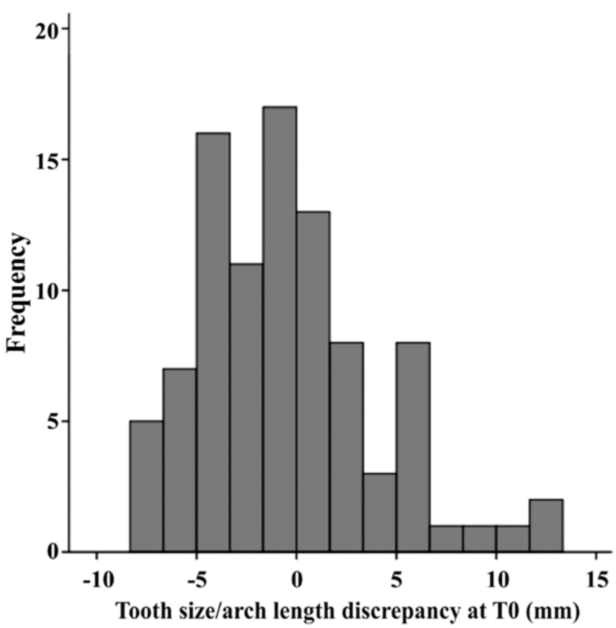

Figure 4. Distribution of tooth size/arch length discrepancy in the study sample.

Results

At T0, the estimated tooth size/arch length discrepancy for the whole study sample was normally distributed, with a mean value of −0.4 mm (min −7.7 mm, max 12.9 mm). The distribution of crowding and spacing in the study sample is shown in Figure 4. There were no statistically significant differences in arch length/tooth size discrepancy between the HGG and the CG ($P = 0.29$).

From T0 until T1, there was an increase in distance for most dental arch parameters in both the HGG and the CG, but with a larger increase in the HGG. Especially for the arch perimeter, the intermolar and intercanine distances increased to a greater statistically significant degree in the HGG than in the CG (Table 1).

The angular measurements of the maxillary permanent canines from T0 and T1 (Table 2) showed that the mean changes for Angle A and Angle C in the HGG were larger (i.e. a more vertical eruption pattern for the maxillary canine) than in the CG. The changes in the HGG were statistically significant on the left side of the maxilla ($P = 0.012$) and almost significant on the right side ($P = 0.051$). The changes in canine Angle A and Angle C were not statistically significant in the CG. For Angle B, the mean changes were larger (i.e. a larger angle between the canine and the lateral incisor) in the CG than in the HGG, and the changes in the CG were statistically significant, in contrast to the HGG. Sector location for canines showed significant distal movement (i.e. into lower-numbered sectors) of the canines from T0 to T1 in both the HGG and the CG (Table 2).

The maxillary canine angulation changed significantly more within the HGG in spaced arches than in crowded arches for both the left side ($P = 0.020$) and the right side ($P = 0.031$). There was also a statistically significant difference between the HGG and the CG in the spaced arches ($P = 0.025$) on the left side (i.e. a more vertical eruption pattern in spaced dental arches than in crowded dental arches)—see Figure 5. In the crowded dental arches, there was no difference between the HGG and the CG in canine angulation.

In the regression analysis, a statistically significant relationship was found among 'incisor space', 'intercanine distance', 'estimated anterior tooth size/arch length discrepancy', and change in canine angulation ('Angle A, T1–T0'). In the CG, a statistically significant relationship was seen on the left side of the maxilla among 'arch perimeter', 'incisor space', 'intercanine distance', and change in canine angulation ('Angle A', T1–T0)—see Table 3.

A stepwise regression model of the statistically significant variables showed that the best predictor for change in canine angulation ('Angle A, T1–T0') was 'incisor space' at T0. In Figure 6, this association is shown by means of scatter plots and regression curves. The curves show generally a larger increase in Angle A (hence a more vertical eruption pattern for the maxillary canine) in the HGG than in the CG. The difference between the regression slopes in the HGG and those in the CG was statistically significant on the left side ($P = 0.043$).

Discussion

One of the most interesting findings in this study was that HG treatment appears to influence the eruption pattern of the maxillary canines, especially in patients with space excess in the dental arch. Previous studies have shown that the maxillary canines are affected by HG treatment (9–11), but the importance of the space discrepancy and the size of the dental arch are unclear. The reason for the maxillary canine erupting more vertically in the HGG is unclear. It may be related to more space being created distally to the canine,

Table 1. Maxillary dental arch space changes, T1–T0.

	HGG mean T1–T0	SD	CG mean T1–T0	SD	Mean difference T1–T0[1]	Sig. (two-tailed)	95% confidence interval of the difference	
							Lower	Upper
Arch perimeter	5.79	4.32	2.78	4.53	3.01	0.002**	1.13	4.89
Premolar and canine space—right side	−0.02	1.69	−0.59	1.71	0.57	0.103	−0.12	1.25
Premolar and canine space—left side	0.12	1.39	−0.65	1.94	0.77	0.027*	0.09	1.45
Intermolar distance	3.81	3.13	1.75	2.59	2.06	<0.001***	0.87	3.24
Intercanine distance	3.07	1.98	1.27	2.27	1.80	<0.001***	0.88	2.72
Incisor space	4.80	2.78	3.39	3.79	1.41	0.053	−0.02	2.84
Premolar space—right side	−0.18	1.11	−0.20	0.61	0.02	0.907	−0.34	0.39
Premolar space—left side	−0.48	1.22	−0.45	1.42	−0.03	0.916	−0.56	0.51
Estimated tz/ald*	5.03	4.14	2.98	4.23	2.05	0.030*	0.21	3.89
Estimated anterior tz/ald*	4.73	2.73	3.24	3.75	1.49	0.041*	0.063	2.91

CG: control group; HGG: headgear group.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, tz/ald = tooth size/arch length discrepancy, measurements in mm.
[1]Mean difference between HGG and CG groups evaluated with independent samples *t*-test.

Table 2. Differences in maxillary canine angulation measured from panoramic radiographs (T1–T0)

	Side	Group	Mean diff.[1]	SD	95% confidence interval of the difference[1]		Sig. two-tailed[2]
					Lower	Upper	
Angle A	Right	CG	1.26	8.16	−1.12	3.61	0.295
		HGG	2.57	9.19	−0.016	5.15	0.051
	Left	CG	0.97	6.85	−1.02	2.96	0.332
		HGG	3.65	10.02	0.83	6.46	0.012*
Angle B	Right	CG	4.88	10.94	1.70	8.06	0.003**
		HGG	1.17	12.63	−2.38	4.72	0.511
	Left	CG	4.55	10.62	1.47	7.64	0.005**
		HGG	−0.43	13.06	−4.10	3.24	0.815
Angle C	Right	CG	−1.32	8.50	−3.79	1.15	0.289
		HGG	−2.24	9.57	−4.93	0.45	0.101
	Left	CG	−0.65	6.96	−2.68	1.37	0.518
		HGG	−3.88	9.92	−6.67	−1.09	0.007**
	Side	Group	Mean diff.	Sector decreased (*N*)	Sector unchanged (*N*)	Sector increased (*N*)	Sig. two-tailed[3]
	Right	CG	0.29	18	25	5	0.006**
Sector	Left	HGG	0.37	21	27	3	<0.001***
	Right	CG	0.19	15	25	8	0.095
	Left	HGG	0.33	20	28	3	<0.001***

CG: control group; HGG: headgear group.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
[1]Mean difference for Angles A, B, and C in degrees, [2]Paired samples *t*-test, [3]Marginal Homogenity test.

since HG treatment has the ability to expand the dental arch and distalize first molars (18). Trans-septal fibers (19) may apply a distal force on the posterior dentition increasing space for the erupting maxillary canine. Increased space created transversally in the dental arch may be another reason for the changed canine angulation. According to previous studies, increased intercanine space created with fixed appliances (20) or rapid maxillary expanders (21) has increased the eruption rate of ectopic maxillary canines. Also, maxillary incisors with signs of eruption disorders appear to improve their vertical and angular position after the use of rapid maxillary expanders (22). The reason for HG treatment seeming to have a greater effect on the canine angulation in spaced arches cannot be explained yet. Our study showed that the expanding effect of HG treatment on the maxilla was actually significantly larger ($P < 0.05$) in narrow arches than in broad dental arches, so less expansion in the crowded cases cannot explain the finding. It is more likely that the maxillary canines are more restricted to move in crowded cases owing to space deficiency than in spaced arches, even though the arches were more expanded in crowded cases than in spaced cases.

Another very interesting finding from the stepwise regression analysis was that space conditions in the anterior part of the maxilla appear to be the most important factor in how much the

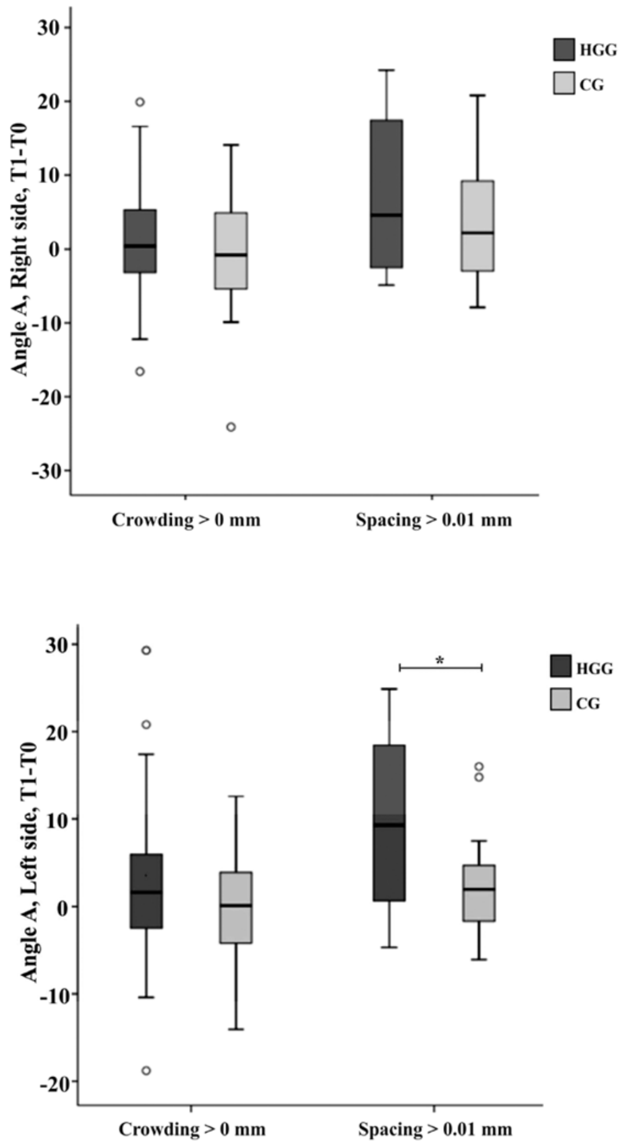

Figure 5. Effect of headgear treatment on change in canine eruption angle (Angle A) in crowed and spaced dental arches.

maxillary canine erupts vertically. The intercanine distance and especially the incisor space at T0 correlated significantly with a change in canine angulation (Angle A, T1–T0). In our study, we found a significantly larger increase in intercanine distance in the HGG than in the CG. This increase is consistent with previous studies (5, 6) in which an expanded inner HG bow was used. This effect may be due not only to the force applied, but also to the inner HG bow relieving the pressure of the lip musculature, and thereby creating a 'lip bumper effect'. The clinical relevance of more vertical and distal movement of the maxillary canines observed in the HG group compared to the CG could have several implications. In patients with crowding in the anterior part of the maxilla, more vertical or distal movement of the canines than normal will relieve crowding and is therefore beneficial. In angle Class II patients, distal movement of the maxillary dentition is usually wanted and the HG-effect seen in this study may therefore be positive. In cases with lateral incisor root resorptions or risk for root resorptions triggered by maxillary canines, distal movement of the maxillary canines away from the lateral is required. At times, fixed appliances are contraindicated and therefore the distal movement of the maxillary canine by a simple appliance like a HG could be advantageous.

During normal tooth eruption, children in the 7–8-year age range are often experience the 'ugly duckling stage' (23). In this period, the maxillary canine crown pushes onto the lateral incisor roots, causing them to flare and leading to an increase in Angle B. In the present study, we saw an increase in Angle B in the CG but no change in Angle B in the HGG. The reason for our seeing no change in the HGG is probably that the maxillary canines moved away distally from the lateral incisor when an HG is used. The fact that Angle B did not change in the HGG may also be because the upper incisors tend to move labially when using a HG, which has been shown earlier (5). Labial tilting of the incisors may change the lateral incisors' position relative to the canines, as well as increase the interdental spaces. Together, these two effects may reduce the flaring of the lateral incisors. Patients in this study started HG treatment around 7.5 years of age. At this age, it is too early to detect palatal or buccal displacement of the canines (24). It is therefore not possible to conclude whether early HG treatment has an effect on ectopically erupting canines. Also, it is important to note that patients with other malocclusions may respond differently than the angle Class II sample selected.

For this study, data from two previous RCTs were pooled. When pooling data from different studies, the combined results may contradict the results of the individual studies. This effect, also known as 'Simpson's paradox', may arise when important subgroup characteristics in the different studies are not considered or weighted (25). In the present study, weighting of the subgroups was not performed, since the two RCTs were similar in design in five ways: (1) the RCTs were conducted in the same region in Finland, (2) they were carried out by the same research team, (3) the research team used the same treatment technique in both studies, (4) the age and gender of the participants were similar for both studies, and (5) the angle classifications were similar.

Seventeen children were excluded from the study because their primary canines had been extracted owing to space discrepancy or ectopic positioning of the maxillary canine. Primary canine extraction may influence both the eruption path and the rate of maxillary canines, as well as reduce the dental arch length (10, 26–28), and thereby create bias. Two children in the HGG and three children in the CG had the mesial surface of their primary maxillary canines slightly sliced in order to facilitate the alignment of their maxillary lateral incisors. It is possible that this procedure might reduce the intercanine width, but it is doubtful that it would affect the maxillary canine eruption pattern, and so we decided not to exclude these patients.

The reliability measurements were 'excellent' and 'almost perfect' for all measurements except the angular measurement of the maxillary canine relative to the maxillary midline (Angle C). The reliability of this measurement was rated as 'acceptable' in this study (ICC = 0.745), and some caution should therefore be taken when interpreting this variable. The lowered reliability of Angle C may be related to difficulty in assessing the maxillary midline in some panoramic radiographs, as blurring of panoramic images may happen in the maxillary midline owing to incorrect patient positioning in the X-ray machine (29). Overall, the most reliable variable was 'Angle A', and it was therefore chosen as the dependent variable in the linear

Table 3. Regression analysis showing the relationship between digital model space analysis (T0) and "Angle A", T1-T0.

Digital model measurements	Headgear Group: Unstand. Coeff. B[1]	Headgear Group: Sig. (2-tailed)[1]	Headgear Group: 95 % Confidence Interval for B[1] Upper	Headgear Group: 95 % Confidence Interval for B[1] Lower	Control Group: Unstand. Coeff. B[1]	Control Group: Sig. (2-tailed)[1]	Control Group: 95% Confidence Interval for B[1] Upper	Control Group: 95% Confidence Interval for B[1] Lower
RIGHT SIDE:								
Arch perimeter	0.468	0.097	-0.088	1.024	0.670	0.012*	0.159	1.182
Incisor space	1.069	0.001**	0.452	1.686	0.960	0.010*	0.238	1.682
Premolar and canine space	-1.306	0.181	-3.240	0.628	0.572	0.531	-1.251	2.394
Premolar space	-1.984	0.148	-4.699	0.732	0.577	0.657	-2.019	3.172
Intermolar distance	0.756	0.138	-0.252	1.764	0.701	0.182	-0.340	1.742
Intercanine distance	1.310	0.036*	0.092	2.528	1.304	0.031*	0.128	2.479
Estimated tz/ald*	0.291	0.331	-0.305	0.886	0.510	0.076	-0.056	1.076
Est. anterior tz/ald*	0.970	0.007**	0.281	1.660	0.650	0.070	-0.056	1.356
LEFT SIDE:								
Arch perimeter	0.464	0.134	-0.149	1.077	0.359	0.119	-0.096	0.815
Incisor space	1.164	0.001**	0.490	1.837	0.510	0.112	-0.124	1.144
Premolar and canine space	-0.937	0.308	-2.764	0.890	0.461	0.581	-1.209	2.130
Premolar space	-1.490	0.203	-3.812	0.831	1.211	0.312	-1.172	3.594
Intermolar distance	0.845	0.124	-0.242	1.932	0.255	0.573	-0.649	1.159
Intercanine distance	1.457	0.032*	0.132	2.783	0.392	0.449	-0.641	1.424
Estimated tz/ald*	0.540	0.092	-0.091	1.172	0.017	0.943	-0.472	0.507
Est. anterior tz/ald*	1.187	0.002**	0.458	1.915	0.208	0.496	-0.401	0.816

[1]Linear regression, *$p < 0.05$, **$p < 0.01$, tz/ald = tooth size/arch length discrepancy

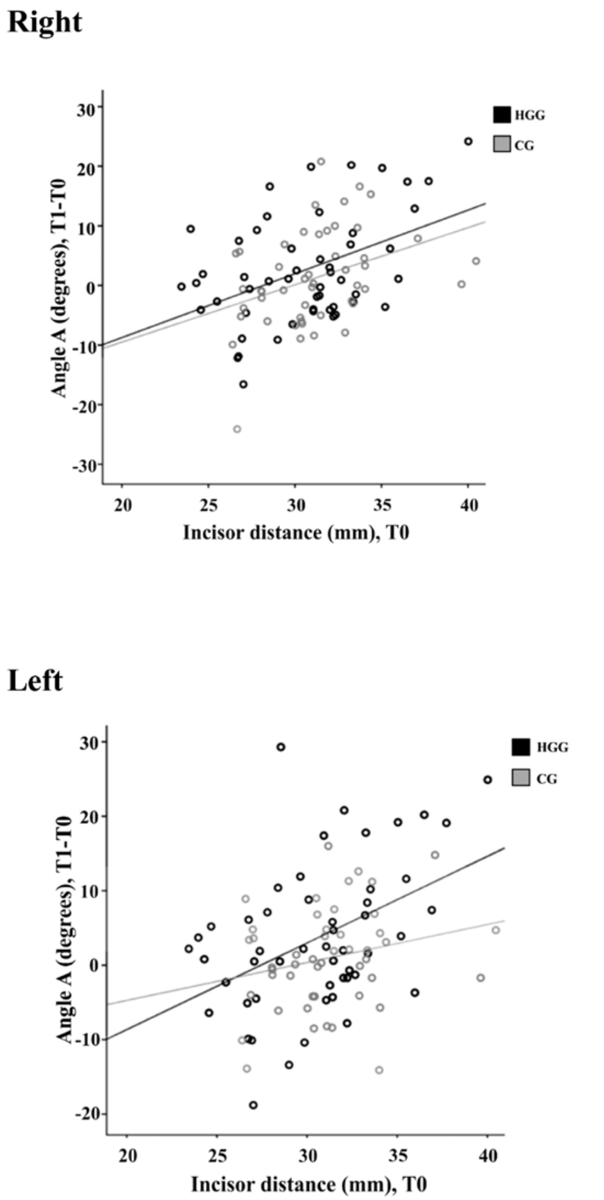

Figure 6. Relationship between 'incisor distance' and 'Angle A' on the right and left side of the maxilla. Linear regression.

regression analysis. HG compliance was not evaluated in the two studies involved. However, full Class I occlusion at the endpoint and a larger increase in most dental arch parameters in the HGG indicated a proper use of the HG.

Estimation of crowding and spacing in mixed dentition is a challenge, since the precise size of the permanent teeth is not possible to measure. In our estimation of tooth size/arch length discrepancy, we used the well-known Moyers mixed dentition analysis (13) to assess the size of the permanent maxillary canines and premolars. The Moyers method may have population variations, and it is suggested that it may be necessary to develop prediction tables for specific populations (30). Certain caution should therefore be taken with regard to our calculations of tooth size/arch length discrepancy. A follow-up study to investigate the final differences in canine position between the HG and CG would be desirable.

Conclusion

This study showed that early HG treatment in children with angle Class II occlusion may change the eruption pattern of maxillary canines to a more vertical direction. The change in the eruption pathway seems to be related to space conditions in the maxillary arch, especially in the intercanine region, with the most significant effect in the HG group with spaced dental arches compared to crowded dental arches.

Conflict of Interest

None to declare.

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Paper III

OXFORD UNIVERSITY PRESS | European Journal of Orthodontics

"Double vs. single primary tooth extraction in interceptive treatment of palatally displaced canines – a randomized controlled trial"

Journal:	*European Journal of Orthodontics*
Manuscript ID	Draft
Manuscript Type:	Randomized Controlled Trial (RCT)
Research Topics:	Clinical trials, RCT (randomized controlled trials), Treatment timing, interceptive orthodontics

Summary:

Objective:

To compare the impact of primary canine and primary first molar extractions with extractions of only the primary canine regarding the correction of palatally displaced canines (PDCs).

Subjects and methods:

A sample of 32 children aged 9.5–13.5 years (18 girls, 14 boys) with 48 PDCs was recruited and randomly allocated to either the double extraction group (DEG) or single extraction group (SEG) using block randomization. No dropouts were recorded during the study. Clinical examinations including panoramic radiographs were performed at baseline (T_0) and at 6-month intervals until the canine emerged into the oral cavity or orthodontic treatment was started. The mean observation time was 14.8 (SD 4.5) months. Outcome measures were: emergence of the maxillary canine into the oral cavity (Y/N), emergence of maxillary canine into a 'favourable position' (Y/N), maxillary canine positional change (angulation and sector), and space conditions in the maxillary arch. Factors influencing PDC emergence were analysed using logistic regression.

Results:

Sixty-four per cent of canines in the DEG emerged into the oral cavity versus 78 per cent in the SEG (P = .283). Favourable PDC position at trial end was seen in 64 per cent of the DEG versus 57 per cent of the SEG (P = .600). Significant distal movement of PDCs and reduction of interdental space were recorded in both the DEG and SEG, though no significant difference was observed between the groups. Significant predictors of canine emergence into the oral cavity were initial canine angulation (Angle A) (P = .008) and space conditions at T_0 (P = .029).

Conclusions:

Double or single primary tooth extraction procedures are equivalent in supporting PDC eruption into the oral cavity and into a favourable position in the dental arch. Initial canine angulation and space assessments may be used as predictors of successful PDC eruption.

Registration:

This trial was registered at http://www.clinicaltrials.gov (NCT02675036).

• Introduction

The maxillary canine is an important tooth from both the aesthetic and functional perspectives. Ectopic eruption and impaction are not very frequent (1–3 per cent prevalence) (1-3), but can create problems if left untreated. Such problems may be malpositioning and retention of the ectopic tooth, external root resorption, migration of neighbouring teeth, dentigerous cyst formation, referred pain, and other complications (4). To avoid complications, interceptive treatment, including extraction of primary teeth, has been suggested, and several studies have evaluated the effects of such treatment (5-12). Considerable variation in diagnostic tools, study design, sample size, and research approach has produced conflicting results, making it difficult to evaluate the conclusions drawn (13). The most widely suggested interceptive treatment approach in cases of palatally displaced maxillary canines (PDCs) is extraction of the deciduous maxillary canine (14). This approach has been presented in several studies as an effective treatment modality that could increase the emergence rate of PDCs from 39–42 per cent without extraction to 67–69 per cent with the primary canine extracted (10, 11). A recent study compared the effects of extracting both the primary canine and primary first molar with extracting the primary canine only. The study reported that the double extraction procedure was significantly more beneficial than extracting the primary canine only (12). The study has been criticized for having a problematic sample, as the occurrence rate of bilateral PDCs was abnormally high and many of the children in the sample were too young to be diagnosed with PDCs (15).

The main objective of this study was to investigate whether extracting the primary canine and primary first molar is more beneficial than extracting only the primary canine in improving the emergence rate of palatally displaced canines. Furthermore, changes in PDC position and space conditions in the maxillary arch were evaluated and predictors of PDC emergence into the oral cavity were analysed.

Our null hypothesis was that there is no significant difference in the emergence rate or positional changes of PDCs depending on whether the primary canine and the primary first molar are extracted at the same time or whether only the primary canine is extracted.

• Subjects and methods

Trial design:

This study was designed as a randomized controlled clinical trial with equal allocation of subjects to either:

1) the double extraction group (DEG): extraction of both the primary canine and the primary first molar; or
2) the single extraction group (SEG): extraction of the primary canine only.

Ethics:

The regional ethical committee approved the study in June 2012 (2012/623/REK nord). Informed consent was obtained from the child and parent or from an adult with parental responsibilities and rights. All procedures were conducted in accordance with the Declaration of Helsinki.

Subjects:

All patients, 9.5–13.5 years of age, examined at the Public Dental Health Competence Center of Northern Norway and one private clinic in Bryne, Norway, between January 1th. 2013 and December 31th. 2017, diagnosed with unilateral or bilateral PDC were invited by the consultant orthodontist to participate in the study. Only patients with a dental age of at least 9.5 years (16) and the presence of both primary maxillary canines and primary maxillary first molars were included in the study. In this study, PDC was defined as the eruption of the maxillary canine in sectors III and IV according to Lindauer et al. (17) (Figure 1) or of the maxillary canine in sector II with an angle between the long axis of the canine and the facial midline (Angle C) of at least 25 degrees (Figure 2) (18). Exclusion criteria were: previous orthodontic treatment, any disease not allowing local anaesthesia or extraction, craniofacial syndromes, cleft lip palate, odontomas, cysts, and agenesis of maxillary incisor.

Thirty-two children, 18 girls and 14 boys with a mean age (SD) of 10.7 (0.7) and 11.2 (1.0), respectively, were invited to participate in the study, and all accepted. Sixteen children had bilateral PDCs and each single canine served as a separate unit in the study; in total, 48 PDCs were included in the study.

Randomization:

Randomization was performed using the block randomization method (19). Block sizes varied randomly between 2, 4, 6, and 8. Blocks were generated using software at http://www.randomization.com. Allocation concealment was done by enclosing assignments in sequentially numbered envelopes. Envelopes that had to be torn open were used, and was opened by a dental nurse after written consent was obtained. After randomization, children were assigned in an allocation ratio of 1:1 to either the double extraction group (DEG) or single extraction group (SEG) (Figure 3).

Due to strong recommendations to treat this patient group (10-12), it was considered unethical to have an untreated control group.

The children were examined clinically, including by taking a panoramic radiograph before the study (T_0) and every 6 months until the canine erupted into the mouth (T_1–T_x). If the canine position worsened or improvement was undetectable after 12 months, alternative treatment was administered (i.e., surgical exposure, fixed orthodontic appliances, and extractions). Clinical photos were taken of each participant before and at the end of the study.

Measurements:

All panoramic radiographs were taken using a Soredex Cranex™ D x-ray system (Soredex, Tuusula, Finland) according to the manufacturer's settings. The following angles were measured on panorama radiographs using the Facad® tracing program (Ilexis, Linkoping, Sweden) (Figure 2) (20):

- Angle A: the long axis of the maxillary canine to a line drawn between the superior edges of the condyles
- Angle B: the long axis of the maxillary canine to the long axis of the maxillary lateral incisor
- Angle C: the long axis of the maxillary canine to the maxillary midline formed by a line drawn through the intermaxillary suture
- Sector (Figure 1) (17)

Measurement reliability has been reported in a previous study (20).

Space conditions:

Clinical photos taken before and after the study were evaluated visually by an experienced orthodontist (SHO). Space conditions mesial to the first maxillary molar were estimated and categorized into the following groups (Figure 4):

1. Crowding: one or more teeth are overlapping and displaced
2. No crowding: all teeth are well aligned
3. Minor spacing: small open spaces between teeth (total ≤ 2 mm)
4. Major spacing: larger spaces between teeth (total > 2 mm)

Reliability was tested by measuring 20 randomly selected plaster models (measured with sliding callipers) and 20 digital photos (measured visually). ICC was calculated to be 0.889, indicating excellent agreement.

Dental age assessment:

Panoramic radiographs of each patient were compared with dental stages at QMUL-Atlas (16), and only patients with crown and root development comparable to or beyond a dental age stage of 9.5 years were included in the study.

<u>Blinding:</u>

Measurements of panoramic radiographs were made by a faculty member (NLB) at the Radiology Department of the University of Tromsø, Norway. The radiographs were not blinded, but to reduce bias, this person was unaware of the purpose of the study.

<u>Primary outcome:</u>

- Emergence of the maxillary canine into the oral cavity:

  - ‘Successful’: maxillary canine emerged through the gingiva (11)
  - ‘Unsuccessful’: no eruption of the maxillary canine into the oral cavity

- Emergence of the maxillary canine in ‘favourable position’:
  - Maxillary canine emerged in sector I (Figure 1) in normal bucco–palatal relationship with occluding teeth in the mandible (i.e., no crossbite)

Secondary outcome:

- Maxillary canine positional changes
  - Angles A, B, and C (Figure 2)
  - Sectors (Figure 1)

- Changes in maxillary arch space conditions

Sample size calculation:

The sample size was based on differences in Angle C (= Alpha angle) between the single and double extraction groups in an earlier comparable study (21). Each of the two groups required 22 canines according to an estimation with alpha = 0.05, beta = 0.2, and a power of 80 per cent. To compensate for possible dropouts, 48 canines were entered into the study.

Statistical analysis:

Descriptive statistics (i.e., mean, SD, min, and max) were used to report the data. The normality of angular and metric data was confirmed using the KS and Shapiro–Wilk tests. An independent sample *t*-test was used to analyse baseline data as well as changes in continuous variables (i.e., angles A–C and space conditions) between the SEG and DEG. The Mann–Whitney U test was used to evaluate the outcome of the variables ‘successful/unsuccessful’ and ‘favourable position’. The marginal homogeneity test was used to test within-group changes in ordinal data (i.e., sector). To evaluate the association between various factors, i.e., group, uni/bilateral canine, dental anomalies (Table 2), gender, angles A–C (T_0), sector (T_0), and emergence of the maxillary canine into the oral cavity, a binary logistic regression was performed to calculate odds ratios and two-sided 95-per cent confidence intervals. The level of significance was set at $p < .05$. Statistical analysis was performed using version 24.0 of the SPSS software package (SPSS Inc., Chicago, IL).

Harms:

No harms were detected during the study.

- **Results**

Participant flow:

Successful cases ($n = 34$) were followed until the tooth had erupted in the mouth. For the unsuccessful cases ($n = 14$), alternative treatment started at 12 months (6 children/7 cases), 18 months (1 child/1 case), and 24 months (3 children/3 cases). Two children (3 cases) were observed for only 6 months because the canine position had worsened severely. The mean observation time for the studied sample was 14.8 months (range 6–24 months). There were no drop-outs in the study (Figure 3).

Baseline findings:

There were no significant differences in gender, age, sector, space conditions, or any of the angular variables between the DEG and SEG (Table 1). Angular and metric data were normally distributed in both groups. The distribution of dental anomalies in the study population is presented in Table 2.

Primary outcome:

Emergence of the maxillary canine into the oral cavity:

Sixteen of 25 canines in the DEG emerged into the oral cavity versus 18 of 23 canines in the SEG (64 per cent vs. 78 per cent; *P* = .283)

In the DEG, 40.0 per cent of canines emerged within 12 months, 53 per cent within 18 months, and 7 per cent within 24 months, versus 32 per cent, 63 per cent, and 5 per cent, respectively, in the SEG. No significant difference was recorded between the groups (*P* = .732).

Among the emerged canines (34/48), all canines in the DEG occurred in sector I, versus 77.8 per cent in sector I, 16.7 per cent in sector II, and 5.6 per cent in sector III in the SEG (*P* = .048). No canines emerged in sector IV.

Uni- and bilateral canines were equally distributed among the PDCs with unsuccessful eruption in the oral cavity (7/14). Two of 16 children with bilateral PDCs had an unsuccessful outcome on both sides.

Emergence of the maxillary canine in ‘favourable position’:

Sixty-four per cent of the canines emerged in the ‘favourable position’ in the DEG versus 57 per cent in the SEG (16/25 vs. 13/23; *P* = .600).

Among the PDCs that emerged into the oral cavity (34/48), significantly more canines emerged in a ‘favourable position’ in the DEG than in the SEG: 100 per cent versus 72 per cent (*P* = .025).

A correct bucco–palatal relationship was present for all canines that emerged in the DEG, whereas 4 of 18 canines emerged in an anterior crossbite position in the SEG.

Secondary outcome:

Maxillary canine positional change:

The angular and sector measurements indicated significant distal movement of the canines in both groups ($P < .001$), with wide individual variation (Figure 5). However, no significant difference was found between the two groups for changes in canine angle (i.e., A, B, or C) or sector (Table 3).

Of the 14 unsuccessful cases, improvement in the eruption path (i.e., reduction in sector and/or Angle A) was seen in 56 per cent (5/9) in the DEG and 60 per cent (3/5) in the SEG. Six of all examined canines (n =48) exhibited a worsened eruption path, 4 in the DEG and 2 in the SEG (P = .449).

Space conditions in the maxillary arch

A significant reduction in estimated space was seen in both groups from T_0 to T_{end} ($P < .001$), but no significant difference was recorded between the groups (P = .727) (Table 3).

Predictive factors for the emergence of the maxillary canine into the oral cavity:

A significant relationship was observed between maxillary canine angulation at baseline (Angle A) and the emergence of PDCs into the oral cavity (OR = 0.882, CI = 0.804–0.968; P = .008).

Canines that emerged into the oral cavity exhibited a significantly greater Angle A at T_0 (i.e., more vertical eruption pattern) than did non-emerged canines (mean 63.7°, SD 6.6 vs. mean 56.2°, SD 9.1; P = .003).

A significant relationship was also seen between space discrepancy at T_0 and the emergence of PDCs (P = .029). More PDCs emerged into the oral cavity the more space was available at T_0 (Major spacing > minor spacing > no crowding > crowding) (Figure 6). No canines emerged into the oral cavity in the crowded group.

- **Discussion**

The main objective of this randomized interceptive study was to compare the emergence rate of PDCs when the primary canine and the primary first molar were extracted compared with extraction of the primary canine only. This study could not find a significant difference in emergence rate between these two procedures. In two previous studies examining double versus single extraction, Bonetti et al. found no difference in emergence rate between the groups in the first study (21), but a significantly higher emergence rate in the double extraction group in the second study (12). In the present study, 64 per cent (DEG) and 78 per cent (SEG) of PDCs emerged into the oral cavity compared with 96 per cent vs. 85 per cent and 85 per cent vs. 79 per cent, respectively, in the two studies by Bonetti et al. (12, 21). One reason for the dissimilarity between these studies could be differences in dental developmental age in the studied samples. In the second study by Bonetti et al. (12), 43 per cent of participants had a dental development age of 8.5 years (16), versus 100 per cent in the 9.5 years and older stage in the present study. McSherry et al. (22) demonstrated that the maxillary canine normally appears radiographically palatal in children younger than 10 years. It has been pointed out that it is too early to define canines as PDCs at 8.5 years of age, and that some of the teeth in Bonetti et al.'s study would have emerged spontaneously without extractions (15).

There were also differences in the initial canine position between the present study and Bonetti's first study (21), which could have influenced the emergence rate. In the present study, no canines were situated in sector I, 1/4 in sector II, 2/3 in sector III, and 7/48 in sector IV. In Bonetti's study (21), 1/4 of canines were located in sector I and 2/3 in sector II. This indicates that the present study had more severe cases. The higher success rate for canine emergence in Bonetti's studies versus the present study could also be related to a longer observation time in the previous studies (i.e., 18 months vs. 14.8 months). Longer observation time may, however, increase the risk of root resorption (11). Therefore, 6 patients (7 canines) with no improvement in canine position after 12 months and 2 patients (3 canines) with severe worsening of the canine position after 6 months were given alternative treatment in the present study. The appropriate length of the observation period is still under debate. Observation intervals of six months (5), 10 months (23), and 12–18 months (12) have been proposed in previous studies. Based on the limited number of canines worsening their position by the 6-month observation in the present study (3 of 48 canines, 6 per cent), radiographic exposure of all children at the 6-month observation seems unjustified according to the 'as low as reasonably achievable' (ALARA) principle (24). Therefore, 12-month intervals seem more appropriate, though more studies including cone beam computed tomography images are needed to determine the proper observation interval.

Bonetti et al. emphasizes that the ultimate criterion for successful outcome may not only be the rate of eruption/non-eruption of PDCs into the dental arch (21). We agree with this statement, as it is also very important *where* in the mouth the canines emerge, as the distance from the emergence point and 'favourable position' in the dental arch affects the orthodontic treatment length and cost (25). In addition, the risk of root resorption is substantially reduced if the canine is localized in sector I (18). Emergence of the maxillary canine in a 'favourable position' was therefore added to the primary outcome, defined as canines erupting in sector I and having a normal bucco–palatal relationship with antagonists in the mandible. No significant difference was seen in this respect between the two extraction groups when all examined canines were analysed. However, for canines that emerged into the oral cavity, significantly more canines emerged in a 'favourable position' in the DEG than the SEG. The reason for this difference is unclear. Previous studies have found that the angle between the first premolar and the facial midline increases more when double rather than single extractions are performed (21), which may lead to a different eruption pattern for canines in the DEG than the SEG.

Canines in both the DEG and SEG changed to a significantly more vertical position from the initial to final observations in both the DEG and SEG, though no significant difference was found between the groups. This is in contrast to two previous studies finding that the double extraction groups experienced greater angular change than did the single extraction groups (12, 21). The angulation of canines in their final position in the dental arch is not only dependent on which interceptive treatment is given, but also dependent on space conditions in the maxillary arch (26) and type of occlusion. Therefore, the angular position of emerged canines may not be the best outcome variable, though it has been used in many PDC studies (5, 6, 11, 12, 21). However, as a selection criterion for decisions regarding primary canine extraction and as a predictive variable during the observation period, canine angulation may be important. In a recent article, Naoumova et al. advocated guidelines for the interceptive extraction of primary canines based on sector location and alpha angle (23). They suggested that interceptive extraction is beneficial when the canine is located in sector II or III with an alpha angle (Angle C) of 20–30 degrees. If the canine is located in sector IV with an alpha angle of greater than 30 degrees, immediate surgical exposure is recommended, and observation is recommended if the canine is located in sector II with an alpha angle of 20 degrees or less. If these guidelines had been applied to the present sample, they would have worked very well for the recommendations to extract (23 of 26 canines emerged successfully), but not as well for the recommendations to implement surgical exposure (3 of 4 canines emerged successfully without surgery). A problem with guidelines is that they have to simplify and sometimes exclude a number of cases – in the present study, 38 per cent of the canines. The definition of success is important when applying a clinical perspective to PDC treatment, and one can argue whether the success definition ('canine emerged through the gingiva') on which these guidelines are based is appropriate. As previously mentioned, the emergence position of PDCs greatly influences the treatment length and cost (25), and should therefore be incorporated into an updated definition of successful eruption.

Anterior dental arch space was significantly reduced from start to endpoint in both extraction groups, though without an intergroup difference, which is in accordance with a previous study (10). Particularly interesting is the finding that cases of successful eruption had significantly more dental arch space before treatment than did unsuccessful cases. This is in line with earlier studies showing that increased maxillary dental arch space positively affects the PDC emergence rate (9, 27, 28). It has also been reported that space conditions in the maxillary dental arch influence the canine eruption path (20, 26). Therefore, there is good reason to use space conditions as an inclusion/exclusion criteria for studies of PDCs, as has previously been done (10, 11).

The most important predictor of successful emergence into the oral cavity was the angle between the maxillary canine and the bicondylar line (Angle A) at T_0. Naoumova et al. also found canine angulation (alpha angle), apart from primary canine extraction, to be the best predictor of PDC emergence when they compared extraction of the primary canine with an untreated control group (23). Power and Short (6) confirmed this, finding that PDCs angulated more than 31 degrees to the maxillary midline had a reduced chance of successful eruption.

In contrast to the present findings, the sector location of the PDC has been found to be a good predictor of successful emergence into the oral cavity (5, 6, 23). Other predictors of successful canine eruption reported in previous studies are: the distance from the canine cusp tip to the midline, the angle between the canine and first premolar, and the distance from the canine cusp tip to the maxillary occlusal plane (29, 30). However, Alqerban et al. (29) found that the ability to predict maxillary canine impaction based on panorama radiographs is weak, so some caution is warranted regarding these predictive variables.

Dental anomalies such as peg-shaped or small laterals, missing maxillary and mandibular second premolars, generalized small teeth, and localized or generalized delayed eruption have long been seen as major etiologic factors for PDCs (31-33). In the present sample, 56 per cent of the children had one or more of the listed dental anomalies, supporting the genetic theory of PDC occurrence. The regression analysis, however, did not find any association between these dental anomalies and PDC emergence, and PDCs seem to respond similarly to primary tooth extraction whether or not dental anomalies are present.

Limitations:

Though the sample size was based on the best available data when the study was initiated (21), the sample size is limited. The results and conclusions might well have been different if the sample had been larger.

No cone beam computed tomography images were taken since no clinical or radiological signs of root resorption were detected. Therefore, we have no data regarding root resorption or other adverse effects. The observation period and success rates might have been different if such information had been available.

This paper has not taken the patient perspective into account, and the two procedures might differ in terms of pain and discomfort. This matter will be investigated further in a follow-up study.

Generalization:

The present study was conducted using Caucasian children aged 9.5–13.5 years, and cannot be generalized to all populations.

Registration:

The study was registered at ClinicalTrials.gov, number NCT02675036.

Conclusions:

- Double or single primary tooth extraction procedures are equivalent in supporting PDC eruption into the oral cavity and into a favourable position in the dental arch.
- Initial canine angulation and space assessments may be used as predictors of successful PDC eruption.

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No funding or other support was received to conduct this study.

Conflict of interest:

None to declare.

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Figure Legends:

Figure 1 Sector location of the maxillary canine.

Figure 2 Angular measurements of maxillary canines. Angle A: canine to bicondylar line, Angle B: canine to lateral incisor, Angle C: canine to maxillary midline.

Figure 3 Consort flow diagram of participants in the study

Figure 4 Space discrepancy assessment on clinical photos. Crowding: one or more teeth are overlapping and displaced, No crowding: all teeth are well aligned, Minor spacing: small open spaces between teeth (total ≤2 mm), Major spacing: larger spaces between teeth (total >2 mm).

Figure 5 Sector change in palatally displaced canines (PDCs) from start (T_0) to end (T_{end}) of trial in the single and double extraction groups. SEG = single extraction group, DEG = double extraction group.

Figure 6 Relationship between space discrepancy at T_0 and emergence of PDCs.
Crowding: one or more teeth are overlapping and displaced, No crowding: all teeth are well aligned, Minor spacing: small open spaces between teeth (total ≤2 mm), Major spacing: larger spaces between teeth (total >2 mm).

Table 1 Baseline data (T_0) for the single extraction group (SEG) and double extraction group (DEG).

NS: not significant, * *P*-value < .05 is considered statistically significant, [A] Mann–Whitney U test: *P* = .212, [B] Mann–Whitney U test: *P* = .586, [C] Mann–Whitney U test: *P* = .359.

Table 2 Dental anomalies in study population.

[a] Mesiodistal width greatest in cervical margin, [b] Mesiodistal width equal to or smaller than its mandibular counterpart, [c] > 2 SD.

Table 3 Comparison of changes in canine angulation and space discrepancy between initial and end observations; mean observation time, 14.8 months.

NS, not significant, * *P*-value < 0.05 is considered statistically significant, [A] Mann–Whitney U test: *P* = 0.727

Table 1 Baseline data (T_0) for the single extraction group (SEG) and double extraction group (DEG).

Variable	**SEG (*n* = 23)** Mean ± SD	**DEG (*n* = 25)** Mean ± SD	***P*-value ***	
Age	11.0 ± 1.1	10.8 ± 0.7	0.621	NS
Angle A (°)	60.9 ± 7.8	62.1 ± 8.5	0.626	NS
Angle B (°)	36.9 ± 9.5	35.1 ± 6.6	0.485	NS
Angle C (°)	30.4 ± 9.1	27.1 ± 7.7	0.183	NS
	n	***n***		
Crowding	1	2	A	NS
No crowding	5	5	A	NS
Minor spacing	11	4	A	NS
Major spacing	6	14	A	NS
Sector 2	7	4	B	NS
Sector 3	12	18	B	NS
Sector 4	4	3	B	NS
Female	15	13	C	NS
Male	8	12	C	NS

NS: not significant, * *P*-value < .05 is considered statistically significant, [A] Mann–Whitney U test: *P* = .212, [B] Mann–Whitney U test: *P* = .586, [C] Mann–Whitney U test: *P* = .359.

Table 2 Dental anomalies in study population.

Anomalies	**Study sample (*n* = 32)**
Missing maxillary second premolar	3 (9.4%)
Missing mandibular second premolar	2 (6.3%)
Peg-shaped lateral[a]	5 (15.6%)
Small lateral[b]	2 (6.3%)
Generalized small teeth	2 (6.3%)
Localized delayed eruption[c]	1 (3.1%)
Generalized delayed eruption[c]	3 (9.4%)

[a] Mesiodistal width greatest in cervical margin, [b] Mesiodistal width equal to or smaller than its mandibular counterpart, [c] > 2 SD.

Table 3 Comparison of changes in canine angulation and space discrepancy between initial and end observations; mean observation time, 14.8 months.

Variable	**SEG**			**DEG**			***P*-value***	
	Mean	Min	Max	Mean	Min	Max		
Angle A°	–15.3	–29.9	1.7	–14.7	–36.3	6.7	0.846	NS
Angle B°	15.8	–2.5	38.6	14.9	–11.2	44.6	0.818	NS
Angle C°	17.7	–2.7	43.9	13.3	–10.6	33.7	0.203	NS
	T_0 (n)	T_{end} (n)	Change (n)	T_0 (n)	T_{end} (n)	Change (n)		
Crowding	1	5	4	2	7	5	A	NS
No crowding	5	7	3	5	3	–2	A	NS
Minor spacing	11	6	–5	4	7	3	A	NS
Major spacing	6	3	–3	14	8	–6	A	NS

NS, not significant, * *P*-value < 0.05 is considered statistically significant, [A] Mann–Whitney U test: *P* = 0.727

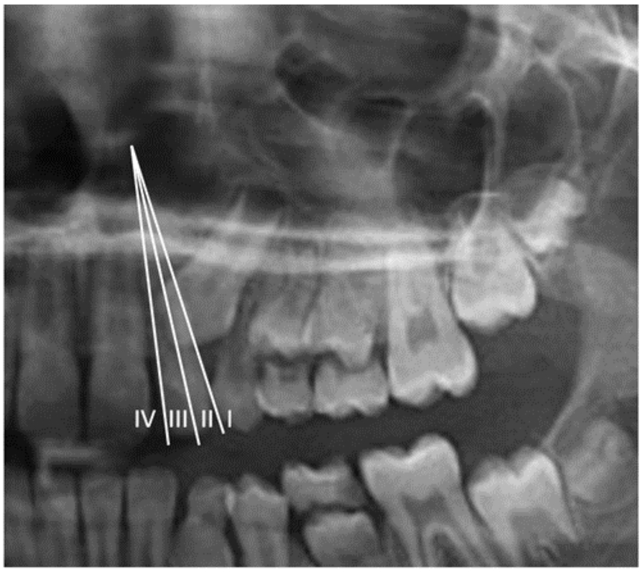


Figure 1. Sector location of the maxillary canine.

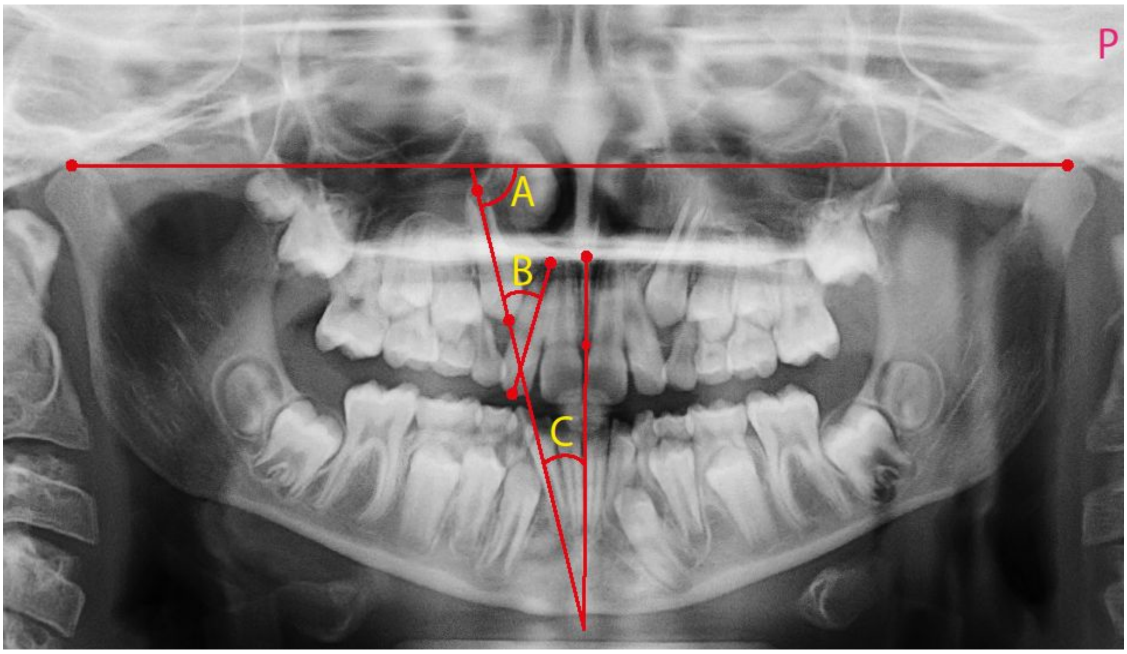


Figure 2. Angular measurements of maxillary canines. Angle A: canine to bicondylar line, Angle B: canine to lateral incisor, Angle C: canine to maxillary midline.

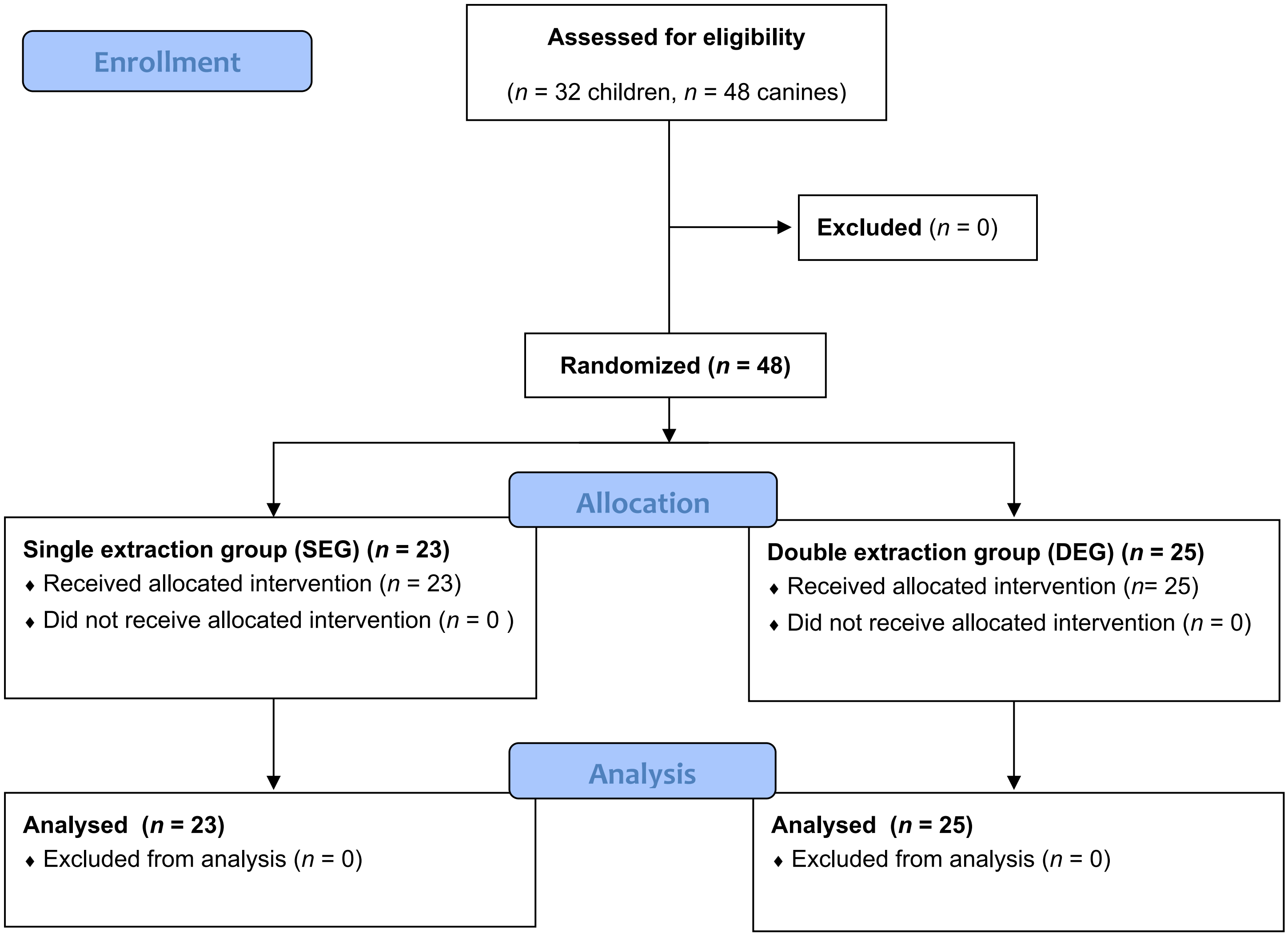


Figure 3. Consort flow diagram of participants in the study

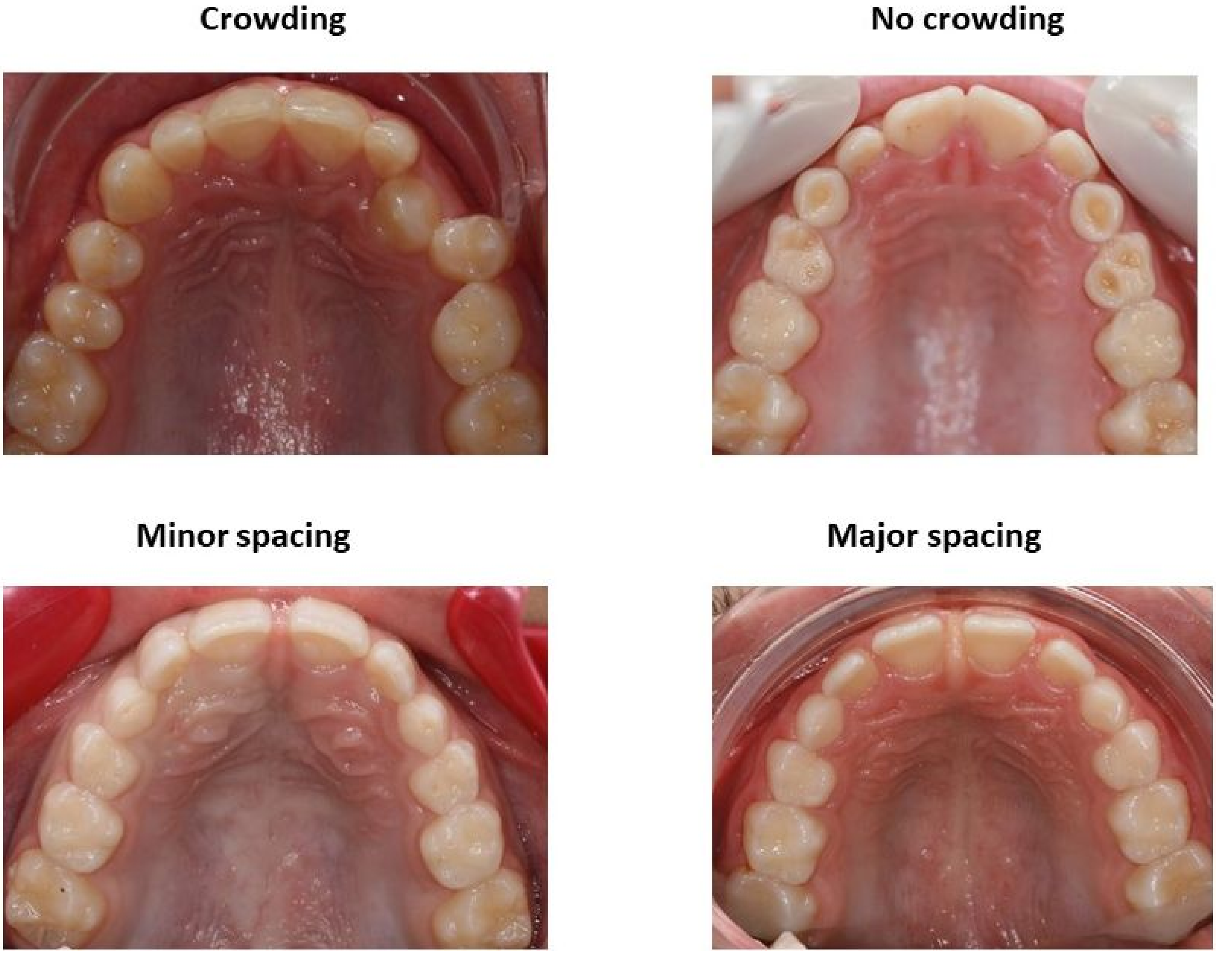
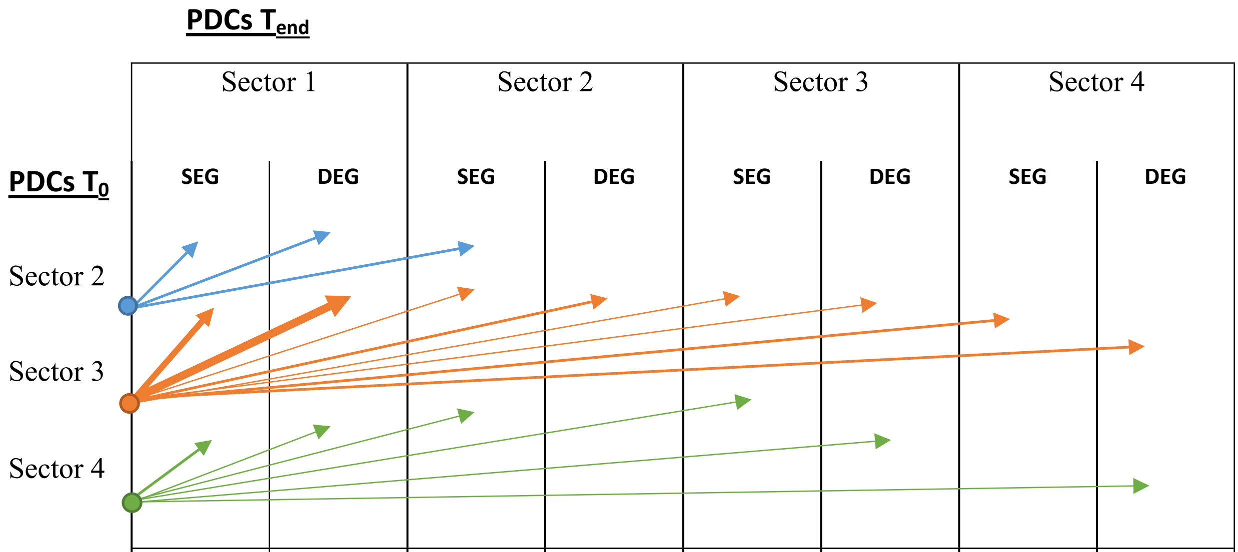


Figure 4 Space discrepancy assessment on clinical photos. Crowding: one or more teeth are overlapping and displaced, No crowding: all teeth are well aligned, Minor spacing: small open spaces between teeth (total ≤2 mm), Major spacing: larger spaces between teeth (total >2 mm).



	Sector 1 SEG	Sector 1 DEG	Sector 2 SEG	Sector 2 DEG	Sector 3 SEG	Sector 3 DEG	Sector 4 SEG	Sector 4 DEG
Sector 2	3	3	3	0	0	0	0	0
Sector 3	9	14	1	2	1	1	2	2
Sector 4	2	1	1	0	1	1	0	1
Total	14	18	5	2	2	2	2	3

Figure 5 Sector change in palatally displaced canines (PDCs) from start (T_0) to end (T_{end}) of trial in the single and double extraction groups. SEG = single extraction group, DEG = double extraction group.

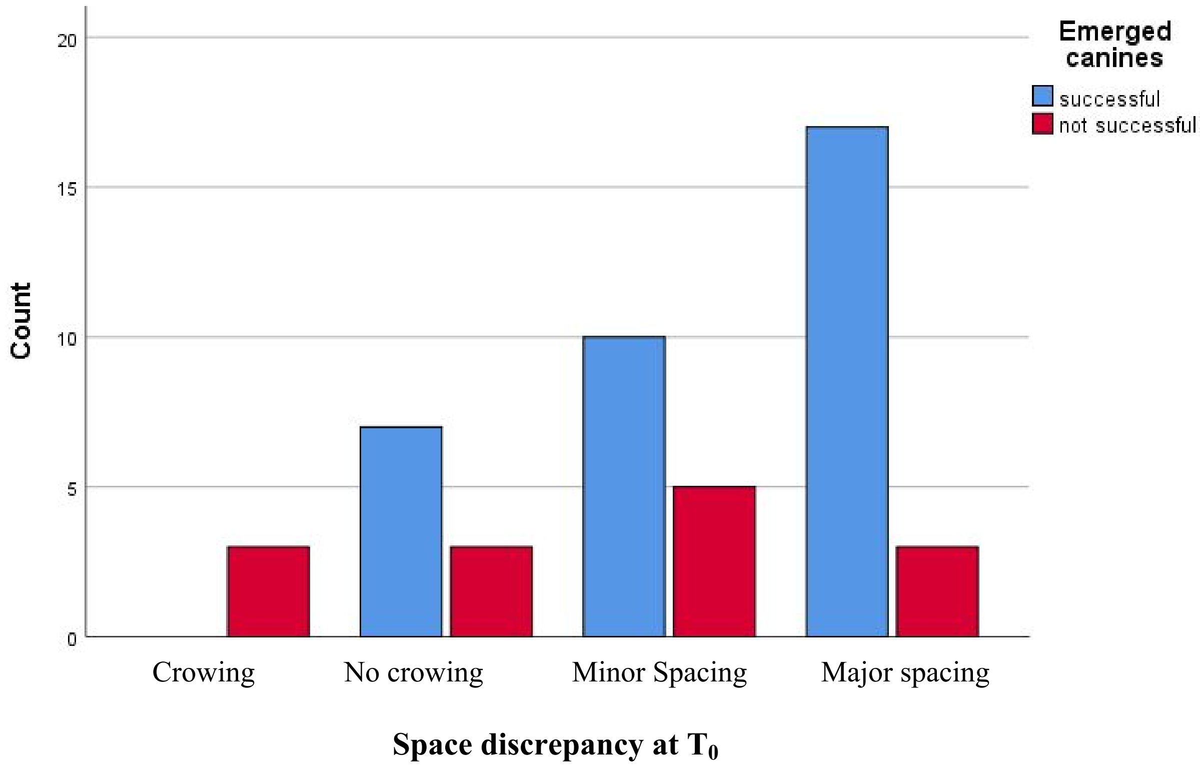


Figure 6 Relationship between space discrepancy at T_0 and emergence of PDCs.
Crowding: one or more teeth are overlapping and displaced, No crowding: all teeth are well aligned, Minor spacing: small open spaces between teeth (total ≤2 mm), Major spacing: larger spaces between teeth (total >2 mm).

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2
	2b	Specific objectives or hypotheses	2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	3
	4b	Settings and locations where the data were collected	3
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	3
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5,6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	3,4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	-

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6,7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	4,5
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	4, figure 3
	13b	For each group, losses and exclusions after randomisation, together with reasons	7
Recruitment	14a	Dates defining the periods of recruitment and follow-up	3
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8,9,10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8,9,10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	7
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	-
Other information			
Registration	23	Registration number and name of trial registry	13
Protocol	24	Where the full trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.