EFFECTIVENESS OF ORTHODONTIC PROCEDURES, ALTERNATIVE OR ADJUNCTIVE TO EXTRACTION OF THE PRIMARY CANINES, FOR INTERCEPTIVE MANAGEMENT OF PALATALLY DISPLACED PERMANENT CANINES: A SYSTEMATIC REVIEW

Ibrahim Ahmed Al Naqbi
DDS, Ajman University of Science and Technology, 2010

Presented to the Hamdan Bin Mohammed College of Dental Medicine
of the Mohammed Bin Rashid University of Medicine and Health Sciences
in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Orthodontics
2018

ABSTRACT

Effectiveness of orthodontic procedures, alternative or adjunctive to extraction of the primary canines, for interceptive management of palatally displaced permanent canines: A systematic review

Ibrahim Ahmed Al Naqbi

Principal supervisor: Professor Athanasios E. Athanasiou

Co-supervisor: Assistant Professor Eleftherios G. Kaklamanos

Aim: Although Rapid Maxillary Expansion (RME), Trans-Palatal Arch (TPA) and Cervical-pull Headgear (HG) have been suggested as interventions in the mixed dentition to increase the rate of normal eruption of the palatally displaced permanent canines (PDCs), existing knowledge on the subject has been inconclusive. The aim of this study was to investigate their effectiveness in an evidence-based manner.

Materials and method: Search without restrictions for published and unpublished literature and hand searching took place. Data on the prevalence of physiologic PDCs eruption from randomized controlled trials (RCTs) that investigated the use of RME, TPA and HG alternatively or adjunctively to extraction of the primary canines were reviewed. The individual study risk of bias was assessed using the Cochrane Risk of Bias Tool.

Results: From the initially identified records, finally, data from 5 RCTs (at high risk of bias) were included, involving the analysis of 480 PDCs in total with a follow up period of 5 years. RME, TPA and HG, used alternatively or adjunctively to extraction of primary canines, can significantly increase the rate of normal eruption of PDCs in the long term compared to no intervention, while no difference was observed in comparison to extraction. Only when HG was used after the

extraction of the primary canine, was a statistically significant benefit shown compared to the extraction of the primary canine only group.

Conclusions: RME, TPA and HG used alternatively or adjunctively to extraction of primary canines can significantly increase the rate of normal eruption of PDCs compared to no intervention. However, when compared to extraction, no differences were noted overall. Further research and better study standardization are warranted.

DEDICATION

To start with, most of all thanks to Allah (God) without whom I would not have what I am thankful for now. I would also like to dedicate my Master Thesis to my parents, wife and children for their understanding, continuous prayers and support. Without them being around me and bearing the circumstances, I might not have been able to write it.

DECLARATION

I declare that all the content of the thesis is my own work. There is no conflict of interest with any other entity or organization.

Name: Ibrahim Ahmed Al Naqbi

Signature:

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude and sincere appreciation to Professor Athanasios E. Athanasiou, Dean, Hamdan Bin Mohammed College of Dental Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences and my thesis principal supervisor for what he offered me throughout my journey to successfully finish the Master of Science in Orthodontics program. Without his continuous academic support and his fatherly presence, I would not be able to stand proudly to be granted my degree in orthodontics.

I would like also to express my deep gratitude and appreciation to my thesis co-supervisor Assistant Professor Eleftherios G. Kaklamanos who guided me with positive motivation, endless support and through whose open door policy I was able to benefit from the professional guidelines which built my self-confidence about my research thesis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. INTRODUCTION

Maxillary permanent canines are the second most common impacted teeth after the third molars, with a prevalence rate ranging from less than 1% to about 9 % (Takahama and Aiyama, 1982; Grover and Lorton, 1985; Ericson and Kurol, 1986a; Peck et al., 1994; Hou et al., 2010; Fardi et al., 2011; Mercuri et al., 2013; Herrera-Atoche et al., 2017). Maxillary canine impaction occurs more frequently on the palatal aspect of the dental arch (Hitchin, 1956; Rayne, 1969; Jacoby, 1983; Ericson and Kurol, 1986b; 1987a; Peck et al., 1994; Mercuri et al., 2013) and affects females more than males in a 2:1 ratio (Bishara, 1992; Mercuri et al., 2013). Bilateral impaction of the maxillary canine has been found to form from 8% to 10% of the impaction cases (Bishara, 1992; Quirynen et al., 2000; Herrera-Atoche, et al., 2017).

Prevention of impaction of the maxillary permanent canines is of paramount importance for avoiding subsequent complications such as root resorption of the adjacent teeth, especially the incisors and the first premolars. Other side effects include cyst formation (Rafflenbeul et al., 2018; Guarnieri et al., 2016; Husain et al., 2016; Becker and Chaushu, 2005; Zuccati et al., 2006; Barlow et al., 2009), increased treatment time and cost (Mavreas and Athanasiou, 2008), as well as complicated orthodontic mechanics (Manne et al., 2012). Since crown resorption of the impacted canine can also occur, especially in adult patients (Azaz and Shteyer, 1978), early identification and prompt intervention is required (Manne et al., 2012).

Intervention may vary from interceptive extraction of the primary canine, which is the most popular preventive intervention, surgical exposure and orthodontic traction, surgical removal, auto-transplantation, to regular monitoring with no active treatment (Counihan et al., 2013; Husain et al., 2016). Interceptive management may also refer to procedures alternative or adjunctive to the extraction of the primary canines (Hadler-Olsen et al., 2018; Leonardi et al., 2004; Baccetti et al., 2008; 2009; 2011; Armi et al., 2011) including Rapid Maxillary Expansion (RME), Trans-

Palatal arch (TPA), or cervical-pull Headgear (HG), aiming to maintain, or provide additional, space to accommodate the palatally displaced permanent canines (PDCs); however, the relevant data have not been summarized in an evidence base manner.

The aim of this study was to investigate the available data on the effectiveness of orthodontic procedures alternative or adjunctive to the extraction of primary canines as interceptive measures for the management of PDCs.

2. REVIEW OF THE LITERATURE

Canine impaction is the most frequent consequence of PDCs (Baccetti et al., 2008). PDCs are characterized as developmental dislocation of the maxillary permanent canines to the palatal side leading to tooth impaction, which requires surgical exposure and orthodontic traction (Peck et al., 1996). Tooth impaction is defined as the inability of a tooth to erupt at its appropriate site in the dental arch, within its normal period of eruption, and with the presence of clinical and/or radiographic evidence that further eruption is not anticipated (Kokich and Mathews, 1993; Thilander and Jakobsson, 1968).

According to Dewel (1949), the maxillary permanent canine is the most interesting tooth from a developmental point of view, as it develops in the deepest area of the maxilla, has the longest period of development and most tortuous path of eruption. The bud of this tooth is located between the nasal cavity, the orbit, and the anterior wall of the maxillary sinus (Jacoby, 1983). At 4-5 months after birth, the maxillary permanent canine starts to calcify and by the age of 6-7 years the enamel formation is completed (Counihan et al., 2013). Although the eruption time differs significantly between genders, it is around the age of 11-12 years that maxillary canines usually erupt while the root completion occurs between 13 -15 years of age (Wedl et al., 2004). During its long period of development, this tooth moves in all three planes of space namely: horizontal, vertical and lateral (Coulter and Richardson, 1997). From age 5 years to age 15 years, it travels on average 22 mm, which make its path of eruption the longest and most sinuous among the permanent teeth (Coulter and Richardson, 1997).

The crown of the maxillary permanent canine is in intimate relation to the root of the adjacent lateral incisor during the course of development (Bishara, 1992). As a result, root resorption of the maxillary lateral incisors or impaction of the maxillary permanent canines, or both, may occur if early correction of flared and distally tipped lateral incisors is attempted (Broadbent, 1941).

2.1. Epidemiology of palatally displaced permanent maxillary canines

The presence of palatally impacted canines has been observed in ancient human skulls from the 6th century BCE (Iseri and Uzel, 1993; Baccetti et al., 1995). Several studies have shown that impaction of the maxillary permanent canines in the Caucasian population occurs more frequently in the palatal direction than the buccal (Walker et al., 2005; Ericson and Kurol, 1988; Oliver et al., 1989), while the reverse is true in Oriental populations (Oliver et al., 1989). In general, the prevalence of palatally impacted canines is low, but it varies between populations depending on their ethnic origin (Becker, 2012). PDCs occur five times more frequently in European populations than in Asians (Peck et al., 1994). The lowest prevalence of palatally impacted canines was found among the Japanese with less than 0.3% (Takahama and Aiyama, 1982). Four and a half percent of the Portuguese population presents with PDCs (Moreira, et al., 2015) whereas the highest rate was reported in Italians with 6.8% (Mercuri, et al., 2013).

The use of Cone Beam Computed Tomography (CBCT) in Chinese and European populations to localize the impacted canines in the three planes of space has demonstrated that around 45% of the cases showed labial impaction , 40% palatal and 15% were in the middle of the alveolar process (Liu et al., 2008; Alqerban et al., 2011; 2014).

2.2. Associated anomalies

PDCs do not constitute an isolated phenomenon, since often they commonly occur in conjunction with multiple related dental anomalies (Naoumova and Kjellberg, 2018; Mercuri, et al., 2013; Garn and Lewis, 1970; Peck et al., 1994). These anomalies involve congenital missing or malformed teeth, such as the maxillary permanent lateral incisors, peg shaped crowns, tooth transposition and a generalized underdevelopment of the dentition (Naoumova and Kjellberg, 2018; Mercuri, et al., 2013; Bass, 1967; Peck et al., 1993; 1994; Garn and Lewis, 1970). PDCs have been also associated

with aplasia of at least one tooth, especially the third molars (Naoumova and Kjellberg, 2018; Peck et al., 1996; 2002; Bulter, 1939). Unilateral PDCs are commonly associated with aplasia of the maxillary lateral incisors, while bilateral PDCs are associated with missing third molars (Sacerdoti and Baccetti, 2004). Family members of patients with PDCs are also likely to be affected by the same condition, in addition to other dental anomalies such as peg-shaped or missing maxillary lateral incisors and delayed development of the dentitions (Ziberman et al., 1990). A generalized reduction in the crown size is also a common finding in patients with PDCs and is reflected by the infrequency of dental crowding (Peck et al., 1994). Low angle vertical relationships and occlusal deep bite have also been associated with PDCs (Sacerdoti and Baccetti, 2004; Leifert and Jonas, 2003).

2.3. Etiology of palatally displaced permanent maxillary canines

In general, impaction as a result of tooth displacement is a multifactorial condition and has no specific causes; however, local factors are the most common causes while general factors can play role as well (Bishara, 1992).

2.3.1. General factors

Although evidence supporting the genetic theory of the etiology of PDCs is available from multiple studies (Peck et al., 1994), the current trend of attributing the cause of canine impaction to genetics appears to be unwarranted (Becker and Chaushu, 2015).

The following observations can be considered as evidence that supports the genetic etiology of canine impactions (Peck et al., 1994; Baccetti, 1998):

a) Presence of other dental anomalies that have a genetic origin associated with PDCs (missing or anomalous maxillary lateral incisors, aplasia of second premolars, infra-occlusion of

primary molars, transposition and enamel hypoplasia).

b) Bilateral incidence.

c) Sexual dimorphism.

d) Familial trends.

e) Variation among populations.

On the other hand, genetic science and logical explanations supported by evidence gathered from different studies contradict the genetic theory (Becker and Chaushu, 2015). These explanations suggest that if the canine impaction is genetically determined therefore:

a) Bilateral impaction should be more frequent than unilateral, as in genetics, bilateralism is the rule rather than the exception (Power and Short, 1993; Ericson and Kurol, 1987).

b) Identical (monozygotic) twins should be affected by impacted canine more than dizygotic twins (Camilleri et al., 2008).

c) Impacted canines in one side should be associated with missing lateral incisors (stronger genetic trait) in the other side, more than anomalous laterals (weaker genetic trait) (Becker et al., 1999).

However, in the examples described above the reverse is true which refutes and contradicts the genetic theory (Becker and Chaushu, 2015).

One example can be considered as an exclusive genetic cause of canine impaction. This condition is a bilateral mislocation of the root apices of the maxillary canines, where the apices of both canines are displaced distally and palatally to the premolars (Becker and Chaushu, 2015).

With regards to general factors, multiple diseases and conditions that might be associated with tooth impaction have been reported, including endocrine deficiencies, febrile diseases and

irradiation (Bishara, 1992). Familial adenomatous polyposis (FAP), or Gardner syndrome are commonly associated with multiple impacted permanent teeth. In FAP, the incidence rate of tooth impaction ranges between 4% and 38%, approximately 10 times higher than the incidence in the normal population (de Oliveira-Ribas et al., 2009; Wijn et al., 2007). Cleidocranial dysplasia, Yunis-Varon syndrome and Down syndrome are also associated with impacted teeth (Gorlin et al., 2001; Lapeer and Fransman, 1992; Yildirim et al., 2004).

2.3.2. Local factors

According to Becker and Chaushu (2015), together with the genetic or hereditary factors, the etiology of canine impaction can be attributed to three local factors:

a) Soft tissue lesions or obstructions.

b) Hard tissue obstruction.

c) Developmental disturbance of the maxillary incisors.

Deflection or impeding the eruption of the permanent maxillary canine could result from soft tissue lesions such as a tumor, radicular cyst, dentigerous cyst or periapical granuloma (Bishara, 1992; Becker and Chaushu, 2015). These lesions may develop in the presence of over-retained non-vital primary canines (Becker and Chaushu, 2015).

Hard tissue lesions such as odontomata, supernumerary teeth or prolonged retention of the primary canine can be considered as an obstacle to the normal development and eruption of the permanent maxillary canine (Becker and Chaushu, 2015; Bishara, 1992).

Thick palatal mucosa or dense overlying bone could also deflect the canine to the palatal side causing difficulties in eruption and therefore impaction (Alkadhimi et al., 2017).

Normal development of the dentition adjacent to the maxillary permanent canines is a very

important factor to ensure normal eruption and alignment of these teeth (Becker and Chaushu, 2015). The presence of a maxillary lateral incisor with normal crown morphology and adequate root size in addition to a normal time of development are crucial factors to guide the mesially erupting maxillary canine and redirect it into a normal and more favorable position (Becker et al., 1981; Jacoby, 1983; Miller, 1963; Bishara, 1992) according to the guidance theory (Broadbent, 1941).

On the other hand, the presence of adequate space in the canine region and the normal location and development of the unerupted maxillary permanent canines do not guarantee their successful eruption (Becker and Chaushu, 2015; Jacoby, 1983) because eruption disturbances or impactions can occur in many circumstances such as in case of mesiobuccal rotation of the first premolar (Becker and Chaushu, 2015) or more frequently in case of unilateral impaction of the central incisor (Chaushu et al., 2003). In cases of mesiobuccal rotation of the first premolar, the palatal root of this tooth will interfere with the path of eruption of the permanent canine (Becker and Chaushu, 2015) while in cases of impacted central incisors, tipping of the lateral incisor crown mesially and root apex distally will occur leading to disturbance of the path of eruption of the permanent canine (Becker and Chaushu, 2015).

Trauma to the maxilla is also another factor that might contribute to the development of tooth impaction since it can cause dilaceration to the developing root and crown or displacement of the unerupted tooth and subsequent impaction (de Amorim et al., 2018; do Espírito Santo Jácomo and Campos, 2009; Brin et al., 1993b).

2.4. Consequences of palatally displaced permanent maxillary canines

The maxillary permanent canine is one of the most important teeth in the dental arch since it plays

a very important role in terms of function, esthetics and dental arch continuity as well as in guiding and protecting the occlusion (Pokorny, 2008; Thiruvenkatachari et al., 2017). Therefore, periodic dental examination of the maxillary permanent canines must be performed at the correct time to avoid untoward complications and consequences that might arise due to its displacement or impaction.

The main consequence of maxillary canine impaction is root resorption of the adjacent teeth, especially the lateral incisors (Ericson and Kurol, 2000; Walker et al., 2005) with the peak frequency occurring between 11 and 12 years old (Ericson and Kurol, 1988; 2000). The prevalence of root resorption is higher in females than in males, with the ratio between genders ranging from 2:1 to 10:1 (Ericson and Kurol, 1987b; 1988; Arens, 1995; Bjerklin and Ericson, 2006; Brin et al., 1993a). Walker et al. (2005) found that the lateral incisors adjacent to the impacted canines are affected by root resorption in 66.7% of the cases, whereas the equivalent figure was only 11.1% for the central incisors. The cause of root resorption of the adjacent incisors is due to the pressure exerted by the impacted canine during eruption and the frequency of this resorption increased with the proximity of the impacted canines to these teeth (Ericson and Kurol, 2000; Walker et al., 2005). First premolars might also be affected but in a lower prevalence (Walker et al., 2005).

The loss of vitality in the adjacent permanent incisors due to root resorption is also another potential consequence of impacted PDCs (Kettle, 1957).

The major consequences of root resorption are the need for extractions of the affected teeth, prolonged orthodontic treatment and expensive and complicated orthodontic mechanics (Ericson and Kurol, 1987b; Manne et al., 2012). Resorption can also affect the crown of the impacted tooth, especially in adult patients (Azaz and Shteyer, 1978). Although the frequency of occurrence is low, impacted teeth are susceptible to coronal crown resorption, mainly on the enamel surface, which is caused by inflammatory processes that destroy the enamel epithelium. One study revealed

that 14% of the impacted maxillary canine cases are affected by crown resorption (Azaz and Shteyer, 1978).

The migration of the adjacent teeth to close the space of an unerupted maxillary canine is another possible consequence of impaction and results in a loss of dental arch length (Manne et al., 2012; Shafer et al., 1963).

Cystic changes in the follicular sac of the unerupted maxillary canine comprise another complication leading to the possible development of a dentigerous cyst (Shafer et al., 1963; Manne et al., 2012 Becker and Chaushu, 2015).

Combinations of the above events may also be encountered (Manne et al., 2012; Shafer et al., 1963).

2.5. Diagnosis and localization of palatally displaced permanent maxillary canines

A bulge in the palate, slight displacement of lateral incisors or over retained primary canines do not usually cause discomfort to patients or encourage them to seek professional help. Therefore, during the periodic checkup, which should be routinely performed by pediatric or general dentists, the accurate diagnosis of canine impaction by careful clinical observation, examination and radiographic inspection at the correct time is mandatory to facilitate successful treatment planning and judicious management of any displacement or impaction.

This practice allows the problem to be diagnosed at an early age and is very important, not only from the etiologic point of view but also as an indication of the need to investigate the possibility of other dental abnormalities since there is a significant reciprocal association between PDCs and various other dental anomalies (Sacerdoti and Baccetti, 2004). In order to achieve an optimal diagnosis and to avoid any side-effects, several steps must be followed sequentially. These steps

involve clinical inspection, palpation and radiographic examination, all aimed at the three dimensional (3D) localization of the position of the impacted tooth, and the verification of its status as well as that of the surrounding structures.

2.5.1. Inspection and palpation

There are many signs, symptoms and clinical features that might suggest displaced or impacted maxillary permanent canines during clinical inspection. Prolonged retention of the primary canine beyond its normal age of shedding, with no significant mobility or delayed eruption of the permanent canine beyond the normal age of eruption can be considered as signs of canine displacement or impaction (Bishara, 1992; Power and Short, 1993; Hurme, 1949).

Although it is not a definitive indication, the absence of a normal labial canine bulge between the ages of 10 and 12 years must be taken as a possible indication and supplemented by a radiographic examination to confirm the normal path of eruption (Bishara, 1992; Ericson and Kurol, 1986a). In addition to the presence or absence of a palatal bulge, asymmetric features of labial canines bulge, exfoliation of the primary canines and eruption of the permanent canines should not be overlooked (Bishara, 1992; Shapira and Kuftinec 1998).

The periodontal health of the adjacent teeth should also be inspected, especially the presence of tooth mobility, amount of keratinized gingiva and signs of attachment loss (Chapokas et al., 2012).

The inclination of the adjacent lateral incisor can give an indication of the most probable position of the unerupted permanent canine (Chapokas et al., 2012, Counihan et al., 2013). When the adjacent lateral incisor is mesially inclined or labially tipped, the most probable position of the unerupted canine is labially, whereas, if it is distally inclined, palatally tipped, or if the root of the lateral incisor is labially palpable; then, the expected position of the impacted canine is palatally (Counihan et al., 2013; Chapokas et al., 2012; Becker, 2012).

A persistence of “ugly duckling” stage beyond the age of 11 is an indicative feature that the natural dynamics of canine eruption have been disturbed (Becker and Chaushu, 2015, Becker, 2012).

Clinical examination of the PDCs and canine impaction also includes assessment of the mobility of the corresponding primary canine, if present, and digital palpation of the alveolar process, buccal sulcus and palatal mucosa (Ericson and Kurol, 1987a; Husain et al., 2016; Counihan et al., 2013). This process should be started at early age, between 8 and 9 years (Power and Short, 1993). The majority of canines undergoing normal eruption should be palpable in the buccal sulcus by 10 to 11 years of age (Husain et al., 2016).

The presence of significant mobility of the primary canine is an indication for root resorption and may relate to a normal eruptive movement of the permanent successor while digital palpation of the gingival tissues around the permanent canine can provide an indication of the potential site of the tooth and the periodontal anatomy (Chapokas et al., 2012; Maverna and Gracco, 2007; Jacobs, 1999).

2.5.2. Radiography

Along with clinical examination, radiographic evaluation is mandatory to confirm the clinical findings of the inspection and palpation, identify any disturbance in the path of eruption and to avoid further complications (Ericson and Kurol, 1986a; 1986b).

Radiographic examination for the canine is dependent on the somatic development of the individual child and should not be performed prior to the age of 10 years since it does not give any reliable baseline evidence for the definitive future prognosis of the path of eruption (Ericson and Kurol, 1986b; 1987a). Another reason that prohibits exposing the patient to x-ray radiation at this age is the absence of real complications caused by ectopic eruption (Olow-Nordenram and Anneroth, 1982; Thilander and Jakobsson, 1968).

In dental practice, several types of X-rays can be used for the maxillary canine examination. Extraoral radiographs such as panoramic and lateral cephalographs are very important part of pretreatment records in orthodontic practice, but they are, along with frontal cephalogram, unreliable in determining the exact position of the canine in relation to the other structures or even in detecting any root resorption of adjacent teeth (Ericson and Kurol, 1987a; Bishara, 1992). The overlap of these structures is the major problem in evaluating the impacted canine by means of panoramic and cephalometric radiography (Chapokas et al., 2012).

Intraoral periapical radiographs (IOPA'Rs) can be considered as a reliable form of X-rays examination in localizing the position of the canines (Bishara, 1992). The position of the canine in the mesiodistal and superioinferior directions can be confirmed by a single (IOPA'R). Since this type of X-ray represents the dentition in only two-dimensions, a second (IOPA'R) should be taken but at a different angulation to the first, so as to determine the position of the canine in a faciolingual direction (Bishara, 1992). This radiographic technique is called the parallax technique. Parallax can be defined as an apparent movement or displacement of an object because of a change in position by the examiner (Husain et al., 2016).

Depending on the direction of the tube head movement, two types of parallax technique can be used to determine the position of the impacted maxillary canine, vertical and horizontal parallax (Southall and Gravely, 1989). The vertical parallax technique results from the tube head being moved in a vertical plane, while the horizontal parallax technique, which is more reliable in localizing impacted canines, is the result of moving the tube head in a horizontal plane (Armstrong et al., 2003).

Vertical parallax can be accomplished by combining the panoramic radiograph with either a standard upper occlusal radiograph or an IOPA'R, while horizontal parallax can be achieved by taking double IOPA'Rs with different horizontal tube head angulation or by combining an IOPA'R

with a standard upper occlusal radiograph (Husain et al., 2016).

Cone Beam Computer Tomography (CBCT) has been introduced as a new imaging technique for the maxillofacial region and has become exceedingly popular among dental practitioners across the world. This technique is considered the most accurate radiographic method for the 3-D localization of impacted maxillary canines and for detecting root resorption (Walker et al., 2005; Naoumova et al., 2014; Doğramaci et al., 2015). However, the routine use of CBCT in the dental practice is not recommended (Halazonetis, 2012; Isaacson et al., 2015) because it involves a higher effective dose of ionizing radiation compared to more traditional techniques. To overcome this problem, a small field of view (FOV) of CBCT can be used to examine the impacted canine in selected cases (SEDENTEXCT, 2012).

2.6. Interventions for the management of impacted permanent maxillary canines

When PDCs become impacted, a multidisciplinary team of specialists is the best approach for the assessment and treatment. This team is comprised by the orthodontists, oral surgeons, periodontists, pediatric dentists and general dental practitioners (Alkadhimi et al., 2017). Some cases do not require immediate intervention but only observation and follow-up (Husain et al., 2016). The indications for observation with regular radiographic follow-ups of impacted canines are: severely displaced teeth away from the dentition, intact roots of adjacent teeth, no associated pathologies, and a good prognosis for the primary canine (Husain et al., 2016).

Different procedures are available to accommodate the impacted maxillary canines in the dental arch, varying from removal of any impediments followed by surgical exposure and orthodontic traction to extraction or auto-transplantation of the impacted tooth in rare cases (Alkadhimi et al., 2017).

2.6.1. Surgical interventions

A surgical procedure with orthodontic intervention is sometimes required to guide the canine into its correct position in the dental arch (Jacoby, 1983; Bishara, 1992; Johnston, 1969). Although there are no clinical guidelines for choosing a preferred surgical technique to manage palatally impacted canines, the surgical decision depends on several factors. These may include factors relating to the individual patient, clinical factors, radiographic factors and the skill and experience of both the surgeon and the orthodontist (Alkadhimi et al, 2017; Fleming et al., 2010). Surgical exposure is indicated if the impacted canine is not severely displaced, adjacent teeth reveal mild or no root resorption, and if patient's age is beyond the time of interceptive treatment (Husain et al., 2012).

Space availability in the dental arch is a prerequisite for surgical exposure. Therefore, in most cases, surgical exposure is performed after 6-9 months of alignment of the maxillary teeth (Fleming et al., 2010).

Root resorption, defects in periodontal health, canine ankylosis, and poor esthetic outcomes are potential complications that could be encountered during surgical exposure and orthodontic traction (Chapokas et al., 2012).

The main two techniques to expose the palatally impacted canines are the closed and the open (Alkadhimi et al, 2017). Although it is very important to be aware of the main advantages and disadvantages associated with both techniques, there is lack of high quality of evidence to indicate any preference of one technique over the other, and further studies are recommended (Parkin et al., 2008; Alkadhimi et al., 2017).

In closed exposure, a full thickness palatal mucoperiosteal flap is raised, the canine crown is exposed by removing the overlying tissues (Hunt, 1977) and a bracket with attached "gold" chain

or metallic ligature is bonded to the palatal surface or to the most accessible tooth surface. Then the flap is repositioned with the "gold" chain or metallic ligature passing through the incision into the gingival margin (Alkadhimi et al., 2017).

In the open exposure method, there are two techniques, either excising the oral mucosa overlying the impacted tooth or raising a full thickness mucoperiosteal flap with enough bone removal to facilitate placing the orthodontic attachment followed by flap repositioning with a hole which can be filled with a surgical dressing, depending on the vertical position of the impacted tooth (Alkadhimi et al., 2017). Open exposure could be accompanied by, or without orthodontic traction depending on the axial inclination of the impacted tooth and root completion (Alkadhimi et al., 2017).

In case of correct axial inclination and incomplete root formation, spontaneous eruption by open exposure without traction is expected although it will take longer time than active traction (Kokich, 2004; Bishara, 1992; 1998). This method will reduce the active treatment time but in case gingival overgrowth occurs, there will be a need for re-exposure (Kokich, 2004; Alkadhimi et al., 2017).

On the other hand, open exposure with traction must be used to guide the impacted tooth into the correct position in the dental arch, especially if the root is completed and the tooth has an incorrect axial inclination (Kokich, 2004; Bishara, 1992; 1998). This method has two approaches regarding the timing of the attachment bonding and force application (Bishara, 1998). In the one-step approach, placement of the attachment takes place on the same day as the surgery and, therefore, any delay in force application is avoided. On the other hand, in the two-step approach, if the attachment bonding procedure is compromised due to bleeding, it might be delayed until the wound has initially healed (Lewis, 1971). Both types of surgical exposure can be carried out for the palatal impacted canine since the palatal gingiva is attached, thick and keratinized (Alkadhimi et al., 2017).

Open exposure of the canine should be avoided in cases of severe resorption of the adjacent incisors, since this method might endanger the vitality of these teeth (Walker et al., 2005). In addition, this method should not be used in cases of deeply impacted maxillary canines to avoid leaving the canine exposed high in the palate which might be uncomfortable for the patient (McSherry, 1996; Alkadhimi et al., 2017).

During canine exposure, it is important to minimize the amount of bone removal and avoid exposing the cementoenamel junction (Alkadhimi et al., 2017). Judicious orthodontic mechanics and precise directional control are required during forced eruption to avoid unwanted tooth movement, root resorption of adjacent teeth or inability to move the displaced tooth (Arriola-Guillén et al., 2018). Therefore, initial tooth movement should be planned carefully and it may require a combination of distal and occlusal directional force before aligning the tooth buccally into correct position in the dental arch (Fleming et al., 2010).

Inability to move an impacted tooth might be the result of inadequate bone removal, use of inappropriate mechanical systems for its traction or ankylosis (Kokich and Mathews, 1993). Poor esthetic outcomes are related to several factors such as poor torque/ tooth inclination, inadequate height of the attached gingiva, variable occlusal wear and gingival recession (Schmidt and Kokich, 2007).

The low-speed bur, the chemical trauma caused by the phosphoric acid used for enamel etching prior to orthodontic attachment placement and the mechanical trauma in the cervical region due to the direction or magnitude of the orthodontic force can cause injury to the periodontal ligament or root cementum of the impacted tooth and lead to ankylosis-related root resorption (Koutzoglou and Kostaki, 2013; Alkadhimi et al., 2017).

Auto-transplantation is a surgical option that can be considered if other management options are not achievable or are inappropriate (Husain et al., 2016). The availability of sufficient space,

adequate alveolar bone to support the transplanted tooth and transplantation with minimal trauma and before apex closure are prerequisites for achieving the best results (Husain et al., 2016).

The surgical removal of the palatally impacted canine is another surgical option for the management of the impacted canine, however, the patient's willingness to accept active orthodontic treatment, if the dental appearance is esthetically acceptable or if there is radiographic evidence for early root resorption of the adjacent incisors, has to be considered (Husain et al., 2016).

2.7 Interceptive management of palatally displaced permanent canines

Interceptive management is very important in overcoming the problems associated with impacted maxillary canines and their management. This kind of intervention was initially presented in the literature by Buchner (1936), who was among the first to suggest placing a maxillary lingual appliance and extract the maxillary deciduous canines.

Initial reports from Ericson and Kurol (1988), showed that extraction of the corresponding primary canines at the appropriate time may enhance the path of eruption of the PDCs in 78 % of the cases. Power and Short (1993) also reported that spontaneous eruption of the PDCs occurred in 62% of the cases and 19% showed definite improvement after extraction of the corresponding primary canines. A recent systematic review revealed that extraction of corresponding deciduous canines as interceptive management of PDCs may increase the probability of subsequent successful eruption of the displaced canines in the long-term (Alyammahi et al., 2018).

Other orthodontic procedures alternative or adjunctive to the extraction of the primary canine have been proposed, such as managing the space in the upper dental arch by combining the extraction of the primary canines with other adjunctive treatment modalities such as HG, TPA or RME (Leonardi et al., 2004; Baccetti et al., 2008; 2009; 2011; Armi et al., 2011). However, the relevant

data have yet to be summarized in an evidence-based manner.

3. AIM OF THE SYSTEMATIC REVIEW

3.1. The aim of the systematic review

To investigate the effectiveness of orthodontic procedures, alternative or adjunctive to the extraction of primary canines, as interceptive approaches for the management of PDCs in the mixed dentition.

3.2. Objectives of the systematic review

To examine the percentage of PDCs erupting in the dental arch after orthodontic procedures alternative or adjunctive to extraction of the primary canines in the mixed dentition.

To examine differences in patient reported outcomes, adverse effects and economic evaluation data between patients treated with orthodontic procedures alternative or adjunctive to extraction of the primary canines in the mixed dentition compared to no intervention or extraction of the primary canines only.

3.3. Null hypotheses

There is no difference in the percentage of PDCs erupting in the dental arch after orthodontic procedures alternative or adjunctive to extraction of the primary canines in the mixed dentition compared to no intervention or extraction of the primary canines only.

There is no difference in patient reported outcomes, adverse effects and economic evaluation data between patients treated with procedures alternative or adjunctive to extraction of the primary canines in the mixed dentition compared to no intervention or extraction of the primary canines only.

4. MATERIALS AND METHODS

4.1 Protocol development

The present review was based on a specific protocol developed following the guidelines outlined in the PRISMA statement (Moher et al., 2001) and the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) (Higgins and Green, 2011).

The present protocol comprised part of a general protocol registered with PROSPERO-International prospective register of systematic reviews (PROSPERO 2015:CRD42015029130).

4.2. Selection criteria applied for the review

The selection criteria, formulated according to the PICOS format, for the domains of study design, participant characteristics, intervention and comparison characteristics and principal outcome measures that were applied for the present review were as follows:

4.2.1. Types of study design

Studies included in the present thesis had to be Randomized Clinical Trials (RCTs) with at least 12 months of observation period after the intervention.

Animal studies, non-comparative studies (case reports and case series), systematic reviews and meta-analyses were excluded from the present review.

The type of study design was assessed using the algorithm available from SIGN (Scottish Intercollegiate Guidelines Network) available from http://www.sign.ac.uk (Appendix II).

4.2.2. Types of participants

The included studies should involve individuals with mixed dentition and unilateral or bilateral palatally displaced permanent canines.

Studies that included subjects with craniofacial anomalies or syndromes of the head and neck region were excluded from the present review.

4.2.3. Types of interventions and comparisons

The included studies should compare the outcome of orthodontic procedures alternative or adjunctive to extraction of the primary canines as interceptive approaches to palatally displaced permanent canines compared to no treatment, or extraction of the primary canines only [or delayed treatment, as for example in cases where initially a patient was randomized to the non-extraction group but at a later observation point, because of lack of improvement, or even worsening of the canine position, the primary tooth was extracted for ethical reasons] or with another adjunctive interventions.

Studies or study groups involving extraction of additional primary or permanent teeth were excluded from the present review.

4.2.4. Types of outcome measures

The studies included in the present review had to primarily provide data on the percentage of successful outcome in each arm of the study, i.e., the prevalence of eruption of permanent maxillary canines in the dental arch.

Secondly, it was aimed at including additional outcome measures, such as, patient reported outcomes (pain, patient satisfaction, etc.), safety assessments and adverse effects, as well as economic evaluation data.

4.3. Search strategy for identification of studies

The principal investigator (IAA) and the thesis co-supervisor (EGK) developed a detailed search strategies for each database searched. The strategy was developed for MEDLINE but revised appropriately for each database to take account of the differences in controlled vocabulary and syntax rules. The following electronic databases were searched (Appendix III): MEDLINE via PubMed (http://www.ncbi.nlm.nih.gov/pubmed), the Cochrane Central Register of Controlled Trials (CENTRAL) (http://onlinelibrary.wiley.com/cochranelibrary), the Cochrane Database of Systematic Reviews (http://0-ovidsp.tx.ovid.com.amclb.iii.com), Scopus (www.scopus.com), Web of Science Core Collection (http://apps.webofknowledge.com/), Latin-American and Caribbean System on Health Sciences Information (LILACS) (http://lilacs.bvsalud.org/en/), National Databases of Indian Medical Journals (IndMed) (http://indmed.nic.in/indmed.html), Scientific Electronic Library Online (Scielo) (http://www.scielo.org/php/index.php?lang=en), Arab World Research Source (http://0-web.a.ebscohost.com.amclb.iii.com) and Deutsche ZentralbibliotekfuerMedizin (https://www.livivo.de). Unpublished literature was accessed electronically using Google Scholar (https://scholar.google.com), ClinicalTrials.gov (http://clinicaltrials.gov), International Standard Randomized Controlled Trial Number (ISRCTN) registry (http://www.isrctn.com) and OpenGrey (http://www.opengrey.eu). In addition, Pro-Quest Dissertation and Theses Global database (http://search.proquest.com) was searched.

No restriction was placed on the language, date or status of publication. In addition, efforts to obtain conference proceedings and abstracts were made where possible and the reference lists of all eligible studies for additional studies were searched.

4.4. Selection of studies and data extraction

The principal investigator (IAA) and the co-supervisor (EGK) assessed the retrieved records for inclusion independently. They were not blinded to the identity of the authors, their institution, or the results of the research. Subsequently, they obtained and assessed, again independently, the full report of records considered by either reviewer to meet the inclusion criteria. Disagreements were resolved by discussion or consultation with the thesis supervisor (AEA). A record of all decisions on study identification was kept.

The same investigators performed data extraction independently and any disagreements were again resolved by discussion. Data collection forms were used to record the desired information.

a. Bibliographic details of the study.

b. Details on study design, duration of the observation period and verification of study eligibility.

c. Participant characteristics (where available number, age, gender) at the beginning and at the point of data analysis (if patient attrition was observed the respective reasons were noted).

d. Intervention characteristics.

e. Prevalence of successful eruption of permanent maxillary canines in the dental arch.Where needed numerical data were transformed into the desired formats and tested statistically using MedCalc(©2016 MedCalc, Ostend, Belgium) and QuickCalcs (©2016 GraphPad Software, Inc., San Diego, California, USA).

f. Data on patient reported outcomes (pain, patient satisfaction, etc.), safety assessments and adverse effects, as well as, economic evaluation data.

g. Additional information (where available): a priori sample size calculation, baseline

comparability of the groups (regarding age, gender, maxillary canine position, space availability in the arch and malocclusion) and the reliability of the method of assessment.

4.5. Estimates of intervention effect, data synthesis and assessment of publication bias

Data on the primary outcome of the successful eruption of the permanent maxillary canine in the dental arch are dichotomous, thus they were expressed as Risk Ratios (RR) together with the relevant 95% Confidence Intervals (CI).

The random effects method for meta-analysis was used to combine data (Borenstein et al., 2007; Der Simonian and Laird, 1986), since they were expected to differ across studies due to diversity in terms of population groups, settings, procedures and follow-up.

To identify the presence and extent of between-study heterogeneity, the overlap of the 95% CI for the results of individual studies was inspected graphically, and Cochrane's test for homogeneity and the I^2 statistic were calculated (Higgins and Green, 2011). The results of the I^2 statistic were interpreted as follows (Higgins and Greene, 2011):

- I^2 from 0% to 40%: heterogeneity might not be important;
- I^2 from 30% to 60%: may represent moderate heterogeneity;
- I^2 from 50% to 90%: may represent substantial heterogeneity;
- I^2 from 75% to 100%: considerable heterogeneity.

If deemed possible, exploratory subgroup analyses were planned according to participant characteristics, such as gender, or the position of the displaced canine. In addition, if a sufficient number of trials were identified, analyses were planned for “small-study effects” and publication bias (Higgins and Green, 2011).

All analyses were done with Comprehensive Meta-analysis software 2.2.046 (©2007 Biostat Inc., Tampa, Florida, USA). Significance (a) was set at 0.05, except for the 0.10 used for the heterogeneity tests (Ioannidis, 2008).

4.6. Risk of bias assessment and determination of the level of certainty in the evidence

The principal investigator (IA) and the thesis co-supervisor (EGK) assessed the risk of bias in the included studies, independently and in duplicate, during the data extraction process, using The Cochrane Collaboration's Risk of Bias assessment tool for RCTs (Higgins and Green, 2011). Any disagreements were resolved by discussion or consultation with the thesis supervisor (AEA). The Risk of Bias assessment tool includes the following domains.

a. Random sequence generation (selection bias).

b. Allocation concealment (selection bias).

c. Blinding of participants and personnel (performance bias).

d. Blinding of outcome assessors (detection bias).

e. Incomplete outcome data (attrition bias).

f. Selective outcome reporting (reporting bias).

g. Other sources of bias.

After entering in the data extraction form the information reported in each study, every domain would receive a judgment of low, high or unclear risk of bias (indicating either lack of sufficient information to make a judgment or uncertainty over the risk of bias) (Higgins and Green, 2011).

Subsequently, studies were to be judged as being of low, unclear or high risk of bias.

a. Low risk of bias (plausible bias unlikely to seriously alter the results)

b. Unclear risk of bias (bias that raises some doubt about the results)

c. High risk of bias (bias that seriously weakens confidence in the results)

The quality of evidence (confidence in the observed estimate) at longest follow up available was ultimately to be assessed based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (Guyatt et al., 2011). The GRADE profiler (GRADEpro) software (available www.gradepro.org; © 2015, McMaster University and Evidence Prime Inc.) was to be used to facilitate the summary regarding the quality of evidence using the GRADE approach. The principal investigator (IAA) and the thesis co-supervisor (EGK) were to assess the quality of evidence independently and in duplicate. Any disagreements were to be resolved by discussion or consultation with the thesis supervisor (AEA).

During the GRADE assessment and for the purpose of summarizing risk of bias across studies, where possible, relevant information was to be judged as being of low, unclear or high risk of bias.

a. Low risk of bias: most information is from studies at low risk of bias.

b. Unclear risk of bias: most information is from studies at low or unclear risk of bias.

c. High risk of bias: information from studies at high risk of bias could have an effect on the interpretation of the results (Higgins and Green, 2011).

5. RESULTS

5.1. Results of the search

The flow of records through the reviewing process is shown in Figure 1. Initially 2799 references were identified, and 758 were excluded as duplicates and 2026 more on the basis of their title and abstract, and 10 after reading the full paper. Finally, five full-text trial reports were included in this systematic review (Armi et al., 2011; Baccetti et al., 2008; 2009; 2011; Leonardi et al., 2004).

5.2. Study characteristics

The characteristics of the studies included in the present systematic review are presented in Tables 1 and 2. The papers were published between 2004 and 2011, and involved, in various groups, 346 analyzed patients with 480 PDCs in total; regarding the comparisons of interest (i.e., RME, TPA, HG, or combination of these treatment modalities with or without extraction of a primary maxillary canine or canines compared to no treatment, or extraction of the primary canines only or with another adjunctive interventions).

Regarding the total post-intervention observation, patients were followed for different periods ranging from 18 months (Armi et al., 2011; Baccetti et al., 2008), 26 months to 42 months (Baccetti et al., 2011), 48 months (Leonardi et al., 2004), and from 52 months to 59 months post-intervention (Baccetti et al., 2009).

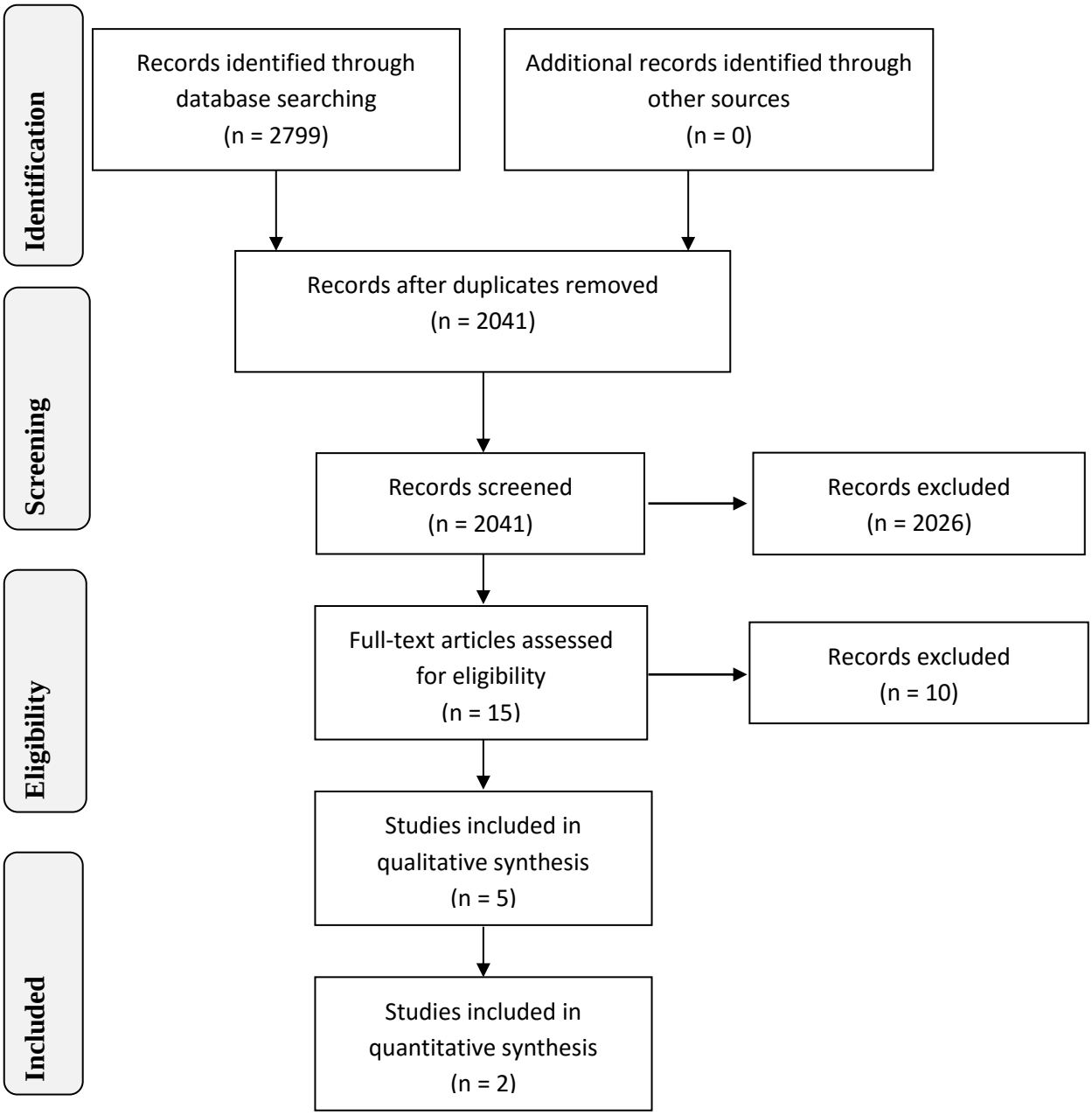


Figure 1. Flow of records through the reviewing process.

One study reported *a priori* calculation of sample size (Baccetti et al., 2011), two studies made reference to the power of the study but it was not specified if the power was calculated *a priori* or *post hoc* (Baccetti et al., 2008; Armi et al., 2011), and another two studies did not report the sample size calculation (Baccetti et al., 2009; Leonardi et al., 2004). In addition, all five included studies considered examining the reliability of the measurements carried out in some way and included reference to baseline comparability.

All five studies provided data on the prevalence of successful canine eruption, but none included additional outcome measures, such as, patient reported outcomes (pain, patient satisfaction etc.), safety assessments and adverse effects, as well as economic evaluation data.

Table 1. General characteristics of the studies included in the systematic review.

Study	Total observation period and Outcomes	Additional information
Leonardi et al., (2004) **RCT [Italy]**	**Total observation period** 48 months for both groups **Definition of successful eruption and assessment** Full eruption of the tooth, permitting bracket positioning for final arch alignment when needed; unsuccessful outcome represented by the lack of eruption of the permanent canine at the completion of the clinical observation period [48 months after the initial observation]	***A priori* sample calculation:** NR **Baseline group comparability:** Yes [age, gender distribution] Reference that […Severity of canine displacement was similar…] **Measurement reliability considered:** Yes
Baccetti et al., (2008) **RCT [Italy]**	**Total observation period** 18 months for all groups **Definition of successful eruption and assessment** Full eruption of the tooth, permitting bracket positioning for final arch alignment when needed; unsuccessful outcome represented by the lack of eruption of the permanent canine at the completion of the clinical observation period [18 months after the initial observation]	***A priori sample calculation:*** Reference that […The power … was greater than 0.85. …] ***Baseline group comparability:*** Yes [age, gender distribution] Reference that […The severity of canine displacement was similar…] ***Measurement reliability considered:*** Yes

Baccetti et al., (2009) **RCT [Italy]**	**Total observation period** Until subjects had an early permanent dentition and a post-pubertal stage of cervical vertebral maturation (CS 4) (Baccetti et al., 2008). RME group 52 months; control group 59 months. **Definition of successful eruption and assessment** Full eruption of the canine, permitting bracket positioning for final arch alignment when needed. Unsuccessful outcome was a lack of eruption of the permanent canine (impaction) at T2.	**A priori sample calculation:** Yes **Baseline group comparability:** Yes [gender; mesioangular angle (o), sagittal angle (o), vertical position (mm), canine cusp tip-dental arch plane (mm), canine root apex-dental arch plane (mm), canine cusp tip-midline (mm); root resorption (Ericson and Kurol, 2000)] **Measurement reliability considered:** Yes
Armi et al., (2011) **RCT [Italy]**	**Total observation period** 18 months for all groups **Definition of successful eruption and assessment** Full eruption of the tooth, thus permitting bracket positioning for final arch alignment when needed. Unsuccessful outcome was defined as the lack of eruption of the permanent canine at the completion of the clinical observation period	**A priori sample calculation:** Yes **Baseline group comparability:** Yes [d (mm), α (o), sector (Ericson and Kurol, 1988); age and gender were controlled within the split mouth design] **Measurement reliability considered:** Yes
Baccetti et al., (2011) **RCT [Italy]**	**Total observation period** Until subjects had an early permanent dentition and a post-pubertal stage of cervical vertebral maturation (CS 5 or CS 6) (Baccetti et al., 2005). RME/TPA/EC group ($\overline{x}$ ±SD): 42 ±16 months; TPA/EC group ($\overline{x}$ ±SD): 33 ±13 months; Extraction Group ($\overline{x}$ ±SD): 26 ±10 months; Control Group ($\overline{x}$ ±SD): 37 ±14 months. **Definition of successful eruption and assessment** Full eruption of the tooth, permitting bracket positioning for final arch alignment when needed; unsuccessful outcome represented by the lack of eruption of the permanent canine at the completion of the clinical observation period [a time point when the subjects had an early permanent dentition and a post-pubertal stage of cervical vertebral maturation (CS 5 or CS 6) (Baccetti et al., 2005)]	**A priori sample calculation:** Yes **Baseline group comparability:** Yes [age; gender ratio; d (mm), α (o), sector (Ericson and Kurol, 1987); CS (Baccetti et al., 2005), Unilateral PDC/Bilateral PDCs, Root development of PDC (Nolla, 1960)] **Measurement reliability considered:** Yes

RCT: Randomized Controlled Trial, PDC: Palatally Displaced Canine, RME: Rapid Maxillary Expansion, TPA: Trans Palatal Arch; EC: Extraction of primary canine, SD: Standard Deviation, CS: Cervical Stage NR: Not Reported.

Table 2. Participant characteristics of the studies included in the systematic review.

Study	Inclusion and exclusion criteria	Number of patients and PDCs included and analyzed
Leonardi et al., 2004	**Inclusion criteria:** Caucasians; unilateral or bilateral PDC; dental age at baseline 8-13 years according (Becker and Chaushu, 2000); skeletal age at baseline showing active phases of skeletal growth (before CS 4) (Baccetti et al., 2002) **Exclusion criteria:** Previous orthodontic treatment; craniofacial syndromes, odontomas; cysts, cleft lip or palate (or both), sequelae of traumatic injuries to the face; or multiple or advanced caries (or both); crowding in the upper arch; aplasia or severe hypoplasia of the crowns of upper lateral incisors **Diagnostic criteria for PDCs:** Intraosseous palatal position of the maxillary permanent canines from panoramic radiographs and periapical radiographs.	**Group 1-** EC **Analyzed:** 11 subjects (5 M, 6 F); 14 PDCs **Age ($\bar{x}$):** 11.6 years. **Group 2-** EC followed by HG **Analyzed:** 21 subjects (7 M, 14 F); 32 PDCs **Age ($\bar{x}$):** 12.2 years **Group 3-**Control, no intervention **Analyzed:** 14 subjects (4 M, 10 F); 16 PDCs **Age ($\bar{x}$):** 11.6 years
Baccitti et al., 2008	**Inclusion criteria:** Caucasians; unilateral or bilateral PDC; dental age at baseline 8-13 years (Becker and Chaushu, 2000); skeletal age at baseline showing active phases of skeletal growth according to the cervical vertebral maturation method (before CS 3) (Baccetti et al. , 2005). **Exclusion criteria:** Previous orthodontic treatment; Craniofacial syndromes, odontomas, cysts, cleft lip and/ or palate, sequelae of traumatic injuries to the face, or multiple and/or advanced caries; Crowding in the upper arch, as evaluated by means of intraoral inspection; Aplasia or severe hypoplasia of the crowns of the upper lateral incisors. **Diagnostic criteria for PDCs:** Intraosseous palatal position of the maxillary permanent canines from panoramic and periapical radiographs. The displacement of the upper canine to the palatal side was checked by means of double determination of the periapical radiographs	**Group 1-** EC. **Analyzed:** 23 subjects (8 M, 15 F); 25 PDCs **Age ($\bar{x}$):** 11.7 years. Group **2-** EC followed by HG. **Analzed:** 24 subjects (10 M, 14 F); 35 PDCs **Age ($\bar{x}$):** 11.9 years **Group 3-** Control, no intervention **Analyzed:** 22 subjects (9 M, 13 F); 26 PDCs **Age ($\bar{x}$):** 11.6 years

Baccitti et al., 2009	**Inclusion criteria: Caucasian** ethnicity; unilateral or bilateral PDC; dental age at baseline 7.6-9.6 years, skeletal age at baseline prepubertal stage of skeletal growth (CS 1 or CS 2) as assessed on lateral cephalograms according to the cervical vertebral maturation method of Baccetti et al., 2005; Class II or Class III tendency, or mild tooth-size/arch-size discrepancy **Exclusion criteria:** Previous orthodontic treatment; and supernumerary teeth, odontomas, cysts, craniofacial malformations, or sequelae of traumatic injuries. **Diagnostic criteria for PDCs:** prediction of canine palatal impaction derived from analysis of PA films according to the method by Sambataro et al., 2005 (score, < -0.565)	**Group 1-** RME. **Analyzed:** 32 subjects; (12M, 20 F) 42 PDCs **Age ($\overline{x}$ ±SD):** 8.8 years ± 9 months **Group 2-** Control, no intervention **Analyzed:** 22 subjects; (8M, 14 F) 31 PDCs **Age ($\overline{x}$ ±SD):** 8.4 years ± 12 months
Armi et al., 2011	**Inclusion criteria: Caucasian** ancestry; unilateral or bilateral PDC, age at baseline 8-13 years (Becker and Chaushu2000); stage; skeletal age at baseline showing active phases of skeletal growth according to the cervical vertebral maturation method (before CS 4) (Baccetti et al., 2005). Presence of mild crowding at the maxillary arch and/ or molar relation showing Class II tendency. **Exclusion criteria:** Previous orthodontic treatment; Craniofacial syndromes, odontomas, cysts, cleft lip and/or palate, sequelae of traumatic injuries to the face, or multiple and/or advanced caries; Aplasia or severe hypoplasia of the crown of upper lateral incisors. **Diagnostic criteria for PDCs:** intraosseous palatal position of the maxillary permanent canines from panoramic radiographs and periapical radiographs. The displacement of the upper canine to the palatal side was checked by means of double determination periapical radiographs.	**Group 1- HG** **Analyzed:** 17 subjects (9 M, 8 F); 25 PDCs **Age ($\overline{x}$):** 11.9 year **Group 2-** RME followed by HG **Analyzed:** 21 subjects (9M,12 F); 30 PDCs **Age ($\overline{x}$):** 11.1 years **Group 3-** Control, no intervention **Analyzed:** 22 subjects (9M,13 F); 26 PDCs **Age ($\overline{x}$):**11.6 years

Baccitti et al., 2011	**Inclusion criteria:** Caucasians; unilateral or bilateral PDCs, age at baseline 9.5 – 13 years; late mixed dentition stage; skeletal age at baseline showing active phases of skeletal growth (before CS 4) (Baccetti et al., 2005); presence of Class II or Class III tendency or mild tooth-size/arch-size discrepancy **Exclusion criteria:** Previous orthodontic treatment; supernumerary teeth, odontomas, cysts, craniofacial malformations, or sequelae of traumatic injuries **Diagnostic criteria for PDCs:** Intraosseous palatal position of the maxillary permanent canines from panoramic radiographs (PDCs showing α angle equal to or greater than 15o according to Ericson and Kurol (1987)); palatal displacement of the canine(s) was confirmed by evaluating the position of the canine on the lateral cephalogram, and, when necessary, by means of Clark's tube shift rule using multiple intraoral radiographs of the canine region (Bishara et al., 1976).	**Group 1-** RME, TPA, and EC **Analyzed:** 40 subjects (15 M, 25 F); 66 PDCs **Age ($\overline{x}$ ±SD):** 10y5m ±10m **Group 2-** TPA and EC **Analyzed:** 25 subjects (10M,15 F); 36 PDCs **Age ($\overline{x}$ ±SD):** 10y9m ±11m **Group 3-** EC **Analyzed:** 25 subjects (11M,14 F); 34 PDCs **Age ($\overline{x}$ ±SD):** 11y1m ±11m **Group 4-** Control, no intervention **Analyzed:** 30 subjects (12M, 18F); 42 PDCs **Age ($\overline{x}$ ±SD):** 10y5m ±10m

PDCs: Palatally Displaced Canines, RME: Rapid Maxillary Expansion, TPA: Trans-Palatal Arch, HG: cervical-pull Headgear, EC: Extraction of the primary canine, CS: Cervical Stage, M: Male, F: Female, $\overline{x}$: Mean, SD, Standard Deviation.

5.3. Results of risk of bias assessment

Table 3 presents a summary of findings regarding the risk of bias assessment for the included studies; more details can be found in Appendix IV.

Table 1. Summary of the risk of bias assessment. [Domains examined: 1: Random sequence generation 2: Allocation concealment, 3: Blinding of participants and personnel, 4: Blinding of outcome assessment, 5: Incomplete outcome data, 6: Selective outcome reporting, 7: Other potential threats to validity]

	Study				
Domain	**Leonardi et al., 2004**	**Baccetti*et al 2008***	**Baccetti et *al.*, 2009**	**Armi et al., 2011**	**Baccetti et al., 2011**
1	Unclear	Unclear	Unclear	Unclear	Unclear
2	High	High	High	High	High
3	Low	Low	High	High	Low
4	Unclear	Unclear	Unclear	Unclear	Unclear
5	Unclear	Unclear	Unclear	Unclear	Unclear
6	High	High	High	High	High
7	Unclear	Unclear	Unclear	Unclear	Unclear
Summary	**High**	**High**	**High**	**High**	**High**

All studies were considered to be at high risk of bias mainly because of problems regarding the domains of random sequence generation and allocation concealment.

Regarding the rest of the considered domains, blinding of the participants and the personnel providing the instructions was not possible. However, in the context of the present research design, there was no reason to believe that bias could be introduced because of absence of blinding in these cases. On the contrary, blinding of the outcome assessment could possibly involve risk of bias because it is not possible to blind the extracted canine and only baseline assessments could be blinded. As the reporting of some of the included studies presented general deficiencies, it is not clear how these could have affected the appraisal of the outcomes included in the present systematic review. Moreover, the risk from incomplete outcome data because of the existence of dropouts was unclear in the studies considered, whereas, regarding the domain selective outcome reporting, most studies were assessed as being of high risk of bias, as significant outcomes were not described adequately. Finally, most studies appeared to be at unclear risk of other sources of bias due to insufficient data.

5.4. Results of individual studies

5.4.1 Effect of interventions alternative to extraction of the primary canines

A. Comparison to no treatment

RME in the early mixed dentition presents a statistically significant benefit in the successful eruption of the PDCs compared to no treatment [RR: 4.813; 95% CI: 1.633-14.187; p= 0.004; n=54 participants] (Baccetti et al., 2009).

Table 4. Quality of available evidence on the effect of RME compared to no treatment in the successful eruption of the PDCs.

Quality assessment						No of PDCs		Effect	Quality
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**RME**	**Control**	**Absolute (95% CI)**	
1	Serious[1]	Not serious	Not serious	Serious[2]	None	42	31	RR **4.813** (1.633 lower to 14.187 higher)***p*=0.004**	⊕⊕◯◯ **Low**

PDCs: Palatal Displaced Canines; RME: Rapid Maxillary Expansion; HG: cervical-pull Headgear; TPA: Tran-Palatal-Arch; CI: Confidence Interval; RR: Risk Ratio.

[1]Results coming from high risk of bias studies.[2]The number of canines analyzed was limited.

Distalization by HG presents a statistically significant benefit in the successful eruption of the PDCs compared to no treatment [RR: 2,265; 95% CI: 1,249-4,106; p=0.007; n=39 participants] (Armi et al., 2011).

Table 5. Quality of available evidence on the effect of HG compared to no treatment in the successful eruption of the PDCs.

Quality assessment						No of PDCs		Effect	Quality
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**HG**	**Control**	**Absolute (95% CI)**	
1	Serious[1]	Not serious	Not serious	Serious[2]	None	25	26	RR **2.265** (1.249 lower to 4.106 higher) ***p*=0.007**	⊕⊕◯◯ **Low**

PDCs: Palatal Displaced Canines; RME: Rapid Maxillary Expansion; HG: cervical-pull Headgear; TPA: Tran-Palatal-Arch; CI: Confidence Interval; RR: Risk Ratio.

[1]Results coming from high risk of bias studies.[2]The number of canines analyzed was limited.

RME followed by the use of HG provides a statistically significant benefit in the successful eruption of the PDCs compared to no treatment [RR: 2.357; 95% CI: 1.320-4.209; p=0.004; n=43 participants] (Armi et al., 2011).

Table 6. Quality of available evidence on the effect of RME followed HG compared to no treatment in the successful eruption of the PDCs.

Quality assessment						No of PDCs		Effect	Quality
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**RME/HG**	**Control**	**Absolute (95% CI)**	
1	Serious[1]	Not serious	Not serious	Serious[2]	None	30	26	RR **2.357** (1.320 lower to 4.209 higher) ***p*=0.004**	⊕⊕◯◯ **Low**

PDCs: Palatal Displaced Canines; RME: Rapid Maxillary Expansion; HG: cervical-pull Headgear; TPA: Tran-Palatal-Arch; CI: Confidence Interval; RR: Risk Ratio.

[1]Results coming from high risk of bias studies.[2]The number of canines analyzed was limited.

5.4.2. Effect of interventions adjunctive to extraction of the primary canines

A. Comparison to no treatment

RME followed by TPA in conjunction with extraction of the primary canines in the late mixed dentition patients presents a statistically significant benefits in the successful eruption of the PDCs compared to no treatment [RR: 2.900; 95% CI: 1.576 – 5.336; p=0.001; n=69 participants] (Baccetti et al., 2011).

Table7. Quality of available evidence on the effect of RME followed by TPA in conjunction with extraction of the primary canines compared to no treatment in the successful eruption of the PDCs.

Quality assessment						No of PDCs		Effect	Quality
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**RPE/TPA/EC**	**Control**	**Absolute (95% CI)**	
1	Serious[1]	Not serious	Not serious	Serious[2]	None	66	42	RR **2.900** (1.576 lower to 5.336 higher) ***p*=0.001**	⊕⊕◯◯ **Low**

PDCs: Palatal Displaced Canines; RME: Rapid Maxillary Expansion; HG: cervical-pull Headgear; TPA: Tran-Palatal-Arch; CI: Confidence Interval; RR: Risk Ratio.

[1]Results coming from high risk of bias studies.[2]The number of canines analyzed was limited.

Extraction of the primary canines followed by the use of HG to maintain the length of the upper arch present statistically significant benefits in the successful eruption of the PDCs compared to no treatment [RR: 2.417; 95% CI: 1.511-3.863; p=0.000; n=81 participants] (Leonardi et al., 2004; Baccetti et al., 2008).

Table 8. Quality of available evidence on the effect of extraction of the primary canines followed by the use of HG compared to no treatment in the successful eruption of the PDCs.

Quality assessment						No of PDCs		Effect	Quality
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**EC/HG**	**Control**	**Absolute (95% CI)**	
2	Serious[1]	Not serious	Not serious	Serious[2]	None	67	42	RR **2.417** (1.511 lower to 3.863 higher) ***p*=0.000**	⊕⊕◯◯ **Low**

PDCs: Palatal Displaced Canines; RME: Rapid Maxillary Expansion; HG: cervical-pull Headgear; TPA: Tran-Palatal-Arch; CI: Confidence Interval; RR: Risk Ratio.

[1]Results coming from high risk of bias studies.[2]The number of canines analyzed was limited.

The use of TPA in conjunction with extraction of the primary canines in the late mixed dentition patients presents statistically significant benefits in the successful eruption of the PDCs compared to no treatment [RR: 2.870; 95% CI: 1.537-5.358; p=0.001; n=53 participants] (Baccetti et al., 2011).

Table 9. Quality of available evidence on the effect of using TPA in conjunction with extraction of the primary canines compared to no treatment in the successful eruption of the PDCs.

Quality assessment						No of PDCs		Effect	Quality
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**TPA/EC**	**Control**	**Absolute (95% CI)**	
1	Serious[1]	Not serious	Not serious	Serious[2]	None	34	42	RR **2.870** (1.537 lower to 5.358 higher)***p*=0.001**	⊕⊕◯◯ **Low**

PDCs: Palatal Displaced Canines; RME: Rapid Maxillary Expansion; HG: cervical-pull Headgear; TPA: Tran-Palatal-Arch; CI: Confidence Interval; RR: Risk Ratio.

[1]Results coming from high risk of bias studies.[2]The number of canines analyzed was limited.

B. Comparison to extraction of the primary canines only

RME followed by the use of TPA in conjunction with extraction of the primary canines in the late mixed dentition patients presents no statistically significant benefits in the successful eruption of the PDCs compared to extraction of primary canine only [RR: 1.280; 95% CI: 0.905–1.810; p=0.163; n=64 participants] (Baccetti et al., 2011).

Table 10. Quality of available evidence on the effect of RME followed by the use of TPA in conjunction with extraction of the primary canines compared to extraction of the primary canines only in the successful eruption of the PDCs.

Quality assessment						No of PDCs		Effect	Quality
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**RME/TPA/EC**	**EC**	**Absolute (95% CI)**	
1	Serious[1]	Not serious	Not serious	Serious[2]	None	66	34	RR **1.280** (0.905 lower to 1.810 higher) ***p*=0.163**	⊕⊕◯◯ **Low**

PDCs: Palatal Displaced Canines; RME: Rapid Maxillary Expansion; HG: cervical-pull Headgear; TPA: Tran-Palatal-Arch; CI: Confidence Interval; RR: Risk Ratio.

[1]Results coming from high risk of bias studies.[2]The number of canines analyzed was limited.

The use of TPA in conjunction with extraction of the primary canines in the late mixed dentition patients presents no statistically significant benefits in the successful eruption of the PDCs compared to extraction of primary canines only. [RR: 1.267; 95% CI: 0.873-1.837; p=0.213; n=48 participants] (Baccetti et al., 2011).

Table 11. Quality of available evidence on the effect of using TPA in conjunction with extraction of the primary canines compared to extraction of the primary canines only in the successful eruption of the PDCs.

Quality assessment						No of PDCs		Effect	Quality
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**TPA/EC**	**EC**	**Absolute (95% CI)**	
1	Serious[1]	Not serious	Not serious	Serious[2]	None	36	34	RR **1.267** (0.873 lower to 1.837 higher) ***p*=0.213**	⊕⊕◯◯ **Low**

PDCs: Palatal Displaced Canines; RME: Rapid Maxillary Expansion; HG: cervical-pull Headgear; TPA: Tran-Palatal-Arch; CI: Confidence Interval; RR: Risk Ratio.

[1]Results coming from high risk of bias studies.[2]The number of canines analyzed was limited.

Extraction of the primary canines followed by the use of HG to maintain the length of the upper arch present statistically significant benefits in the successful eruption of the PDCs compared to extraction of primary canines only [RR: 1.413; 95% CI: 1.062-1.880; p=0.018; n=79 participants] (Leonardi et al., 2004; Baccetti et al., 2008).

Table 12. Quality of available evidence on the effect of extraction of the primary canines followed by the use of HG compared to extraction of the primary canines only in the successful eruption of the PDCs.

Quality assessment						No of PDCs		Effect	Quality
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**EC/HG**	**EC**	**Absolute (95% CI)**	
2	Serious[1]	Not serious	Not serious	Serious[2]	None	67	39	RR **1.413** (1.062 lower to 1.880 higher) ***p*=0.018**	⊕⊕◯◯ **Low**

PDCs: Palatal Displaced Canines; RME: Rapid Maxillary Expansion; HG: cervical-pull Headgear; TPA: Tran-Palatal-Arch; CI: Confidence Interval; RR: Risk Ratio.

[1]Results coming from high risk of bias studies.[2]The number of canines analyzed was limited.

C. Comparison to extraction of the primary canines with another adjunctive interventions

RME followed by the use of TPA in conjunction with extraction of the primary canines in the late mixed dentition patients presents no statistically significant benefits in the successful eruption of the permanent canines compared to extraction of the primary canines and using of TPA [RR: 1.011; 95% CI: 0.781-1.307; p=0.936; n=64 participants] (Baccetti et al., 2011).

Table 13. Quality of available evidence on the effect of RME followed by the use of TPA in conjunction with extraction of the primary canines compared to extraction of primary canines and using of TPA in the successful eruption of the PDCs.

Quality assessment						No of PDCs		Effect	Quality
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**RME/TPA/EC**	**TPA/EC**	**Absolute (95% CI)**	
1	Serious[1]	Not serious	Not serious	Serious[2]	None	40	24	RR **1.011** (0.781 lower to 1.307 higher) ***p*= 0.936**	⊕⊕◯◯ **Low**

PDCs: Palatal Displaced Canines; RME: Rapid Maxillary Expansion; HG: cervical-pull Headgear; TPA: Tran-Palatal-Arch; CI: Confidence Interval; RR: Risk Ratio.

[1]Results coming from high risk of bias studies.[2]The number of canines analyzed was limited.

6. DISCUSSION

6.1. Summary of available evidence

The total number of records originally identified were reduced to five RCTs involving 346 analyzed patients with a total of 480 palatally displaced canines, followed for different periods of time ranging from 18 months to 59 months post-intervention (Armi et al., 2011; Baccetti et al., 2008; 2009; 2011; Leonardi et al., 2004). This outcome reflects the scarcity of relevant research at the top of the widely accepted hierarchy of scientific evidence, although it is widely accepted that well-designed and properly executed RCTs provide the best evidence on the efficacy of health care interventions (Altman et al., 2001; Oxford Centre for Evidence-based Medicine, 2009).

The consequent lack of extensive data with high evidence-based potential is rather surprising bearing in mind not only the prevalence of the problem (Ericson and Kurol, 1986a; Moss, 1972; Thilander and Jakobson, 1968; Bass, 1967), but also the fact that the management of impacted permanent maxillary canines necessitates a comprehensive approach potentially requiring significant commitment and costs for from the patient and healthcare provider (Parkin et al., 2012) and may involve risks and complications, if prognosis, treatment planning and the biomechanics are not thoroughly considered (Becker, 2012). Thus, relevant, evidence-based information on possible interceptive management of the condition would be beneficial in supporting the quality of care provided in these cases.

In general, based on the information provided from the studies eligible for inclusion in the present review, the use of orthodontic procedures alternative or adjunctive to extraction of the primary canines as interceptive approaches to palatally displaced permanent canines resulted in more permanent canines successfully erupting compared to no treatment. Therefore, the null hypothesis regarding this comparison was rejected.

The retrieved RR ranged from approximately 2.5 to 4.5, which greater than the 1.73 {95% CI: 1.226-2.394} reported in a recent meta-analysis comparing extraction of the primary canines to non-extraction. However, these greater RR should be viewed with caution since they were based on statistics with a high risk of bias, and the confidence in the observed estimation was considered to be low.

A statistically significant benefit of HG in conjunction with extraction of the primary canines was noted in comparison to extraction only. Although this adjunctive procedure could potentially be beneficial, one should not forget that also in this case the level of evidence was considered low. Additionally, not all patinet's skeletal pattern allows interventions that include HG use.

6.2. Strengths and limitations of the present review

The strengths of the present review include the methodology that followed well-established guidelines and the fact that it focused exclusively on RCTs. It is widely accepted that well-designed and properly executed RCTs provide the best evidence with reduced risk of bias on the efficacy of health care interventions (Oxford Centre for Evidence-based Medicine, 2009; Altman et al., 2001). The available empirical evidence suggests that intervention effects in orthodontic research seem to differ in non-RCTs compared to RCTs (Papageorgiou et al., 2015). In addition, an attempt was made to summarize the quality of available evidence and thus provide an insight into the strength of the relevant recommendations based on the GRADE approach (Guyatt et al., 2011).

Moreover, the search strategy employed was exhaustive, covering electronic, manual, and gray literature material up to April 2018, and comprehensive, including every available RCTs comparing different interceptive treatment modalities to no treatment or to extraction of the

primary canine only, irrespective of language, date and status of publication. Every effort to reduce bias in the methodology employed was made. Screening, verification of eligibility, abstraction of information, assessment of risk of bias and of the quality of evidence were performed in duplicate, and any disagreement was resolved by discussion until a final consensus was achieved. Finally, the random effects model was employed during exploratory quantitative data synthesis to incorporate any observed heterogeneity (Lau et al., 1997).

There are also some limitations of the present review, mainly arising from the nature and characteristics of the data retrieved during the review process, which resulted in an assessment of the level of available evidence as low. The scarcity of relevant information from low risk of bias RCTs rendered quantitative syntheses exploratory until additional research becomes available. Furthermore, exploratory subgroup analyses and analyses for "small-study effects" and publication bias (Higgins and Green, 2011), could not be carried out even though they were incorporated as possibilities according to the review protocol.

Another limitation of the data retrieved in this study stems from the small number of patients finally analyzed resulting in subsequent problems regarding the precision of the effect estimates. Moreover, it has to be acknowledged that the results of this review relate mostly to patients from the specific ethnic backgrounds of the patients under study. Bearing in mind the reported racial differences in the prevalence of the phenomenon of palatally displaced canines (Peck et al., 1996), the directness and generalizability of the available evidence may be diminished.

6.3. Recommendations for future research

Since canine impaction is a relatively common phenomenon, and its management potentially complex and challenging, the need for well-designed RCTs with better standardization and reporting over long follow-up period could be useful. It would also be beneficial to have future

RCTs examining different groups from ethnic backgrounds other than Caucasian to find if any differences exist. Finally, to fully understand the effect of these strategies, further investigation of the possible predictors of success; inclusion in the analyses of patient-reported outcomes like quality of life; analyses of costs and benefits in the socioeconomic context, as well as investigation of any possible adverse effects should be carried out.

7. CONCLUSIONS

The present systematic review highlights the fact that orthodontic procedures alternative or adjunctive to extraction of the primary canines such as RME, TPA, and HG can significantly increase the rate of normal eruption of PDCs in the long-term compared to no intervention. No difference was observed in comparison to extraction. Only when HG was used after the extraction of the primary canine, was a statistically significant benefit shown compared to the extraction of the primary canine only group. However, more low risk of bias studies, with sufficient sample sizes, are needed in order to enrich the available evidence, increase the precision of the observed effect estimates and unequivocally guide clinical decisions.

8. REFERENCES

1. Alkadhimi AF, Ganesan K, Al-Awadhi E A. Open or closed exposure for palatally impacted maxillary canines? A review. Ortho Update 2017;10:102-110.

2. Alqerban A, Jacobs R, Fieuws S, Willems G. Comparison of two cone beam computed tomographic systems versus panoramic imaging for localization of impacted maxillary canines and detection of root resorption. Eur J Orthod 2011;33:93-102.

3. Alqerban A, Jacobs R, van Keirsbilck PJ, Aly M, Swinnen S, Fieuws S, Willems G. The effect of using CBCT in the diagnosis of canine impaction and its impact on the orthodontic treatment outcome. J Orthod Sci 2014;3:34-40.

4. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gøtzsche PC, Lang T; CONSORT GROUP (Consolidated Standards of Reporting Trials). The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001;134:663-694.

5. Alyammahi AS, Kaklamanos EG, Athanasiou AE. Effectiveness of extraction of primary canines for interceptive management of palatally displaced permanent canines: a systematic review and meta-analysis. Eur J Orthod 2018;40:149-156.

6. Arens DE. An alternative treatment for the severely resorped maxillary lateral incisor: a sequela of ectopic eruption. J Endod 1995;21:95-100.

7. Arriola-Guillén LE, Ruíz-Mora GA, Rodríguez-Cárdenas YA, Aliaga-Del Castillo A, Dias-Da Silveira HL. Root resorption of maxillary incisors after traction of unilateral vs bilateral impacted canines with reinforced anchorage. Am J Orthod Dentofacial Orthop 2018;154:645-656.

8. Armi P, Cozza P, Baccetti T. Effect of RME and headgear treatment on the eruption of

palatally displaced canines: a randomized clinical study. Angle Orthod 2011;81:370-374.

9. Armstrong C, Johnston C, Burden D, Stevenson M. Localizing ectopic maxillary canines--horizontal or vertical parallax? Eur J Orthod 2003;25:585-589.

10. Azaz B, Shteyer A. Resorption of the crown in impacted maxillary canine. A clinical, radiographic and histologic study. Int J Oral Surg 1978;7:167-171.

11. Baccetti T, Franchi L, De Lisa S, Giuntini V. Eruption of the maxillary canines in relation to skeletal maturity. Am J Orthod Dentofacial Orthop 2008a;133:748-751.

12. Baccetti T, Leonardi , Armi P. A randomized clinical study of two interceptive approaches to palatally displaced canines. Eur J Orthod 2008b;30:381-385.

13. Baccetti T, Franchi L, McNamara JA Jr. The cervical vertebral maturation (CVM) method for the assessment of optimal treatment timing in dentofacial orthopedics. Semin Orthod 2005;11:119-129.

14. Baccetti T, Franchi L, McNamara JA Jr. An improved version of the cervical vertebral maturation (CVM) method for the assessment of mandibular growth. Angle Orthod 2002;72:316-323.

15. Baccetti T, Franchi L, MoggiCecchi J, Pacciani E. Associated dental anomalies in an Etruscan adolescent. Angle Orthod 1995;65:75-80.

16. Baccetti T, Mucedero M, Leonardi M, Cozza P. Interceptive treatment of palatal impaction of maxillary canines with rapid maxillary expansion: a randomized clinical trial. Am J Orthod Dentofacial Orthop 2009;136:657–661.

17. Baccetti T, Sigler L, McNamara JA Jr. An RCT on treatment of palatally displaced canines with RME and/or a transpalatal arch. Eur J Orthod 2011;33:601-607.

18. Baccetti T. A controlled study of associated dental anomalies. Angle Orthod 1998;68:267-274.

19. Barlow ST, Moore MB, Sheriff M, Ireland AJ, Sandy JR. Palatally impacted canines and the modified index of orthodontic treatment need. Eur J Orthod 2009;31:362–366.

20. Bass TB. Observations on the misplaced upper canine tooth. Dent Pract Dent Rec 1967;18:25-33.

21. Becker A, Chaushu S. Dental age in maxillary canine ectopia. Am J Orthod Dentofacial Orthop 2000;117:657-662.

22. Becker A, Chaushu S. Etiology of maxillary canine impaction: A review. Am J Orthod Dentofacial Orthop 2015;148:557-567.

23. Becker A, Chaushu S. Long-term follow-up of severely resorbed maxillary incisors after resolution of an etiologically associated impacted canine. Am J Orthod Dentofacial Orthop 2005;127:650-654.

24. Becker A, Gillis I, Shpack N. The etiology of palatal displacement of maxillary canines. Clin Orthod Res 1999;2:62-66.

25. Becker A, Smith P, Behar R. The incidence of anomalous lateral incisors in relation to palatally displaced cuspids. Angle Orthod 1981;51:24-29.

26. Becker A. Orthodontic Treatment of Impacted Teeth. Chichester, West Sussex: John Wiley and Sons, Ltd, 2012.

27. Bishara SE. Impacted maxillary canines: a review. Am J Orthod Dentofacial Orthop 1992;101:159-171.

28. Bishara SE, Kommer DD, McNeil MH, Montagano LN, Oesterle LJ, Youngquist HW.

Management of impacted canines.Am J Orthod 1976;69:371-387.

29. Bishara SE. Clinical management of impacted maxillary canines. Semin Orthod 1998;4:87−98.

30. Bjerklin K, Ericson S. How a computerized tomography examination changed the treatment plans of 80 children with retained and ectopically positioned maxillary canines. Angle Orthod 2006;76:43-51.

31. Brin I, Becker A, Zilberman Y. Resorbed lateral incisors adjacent to impacted canines have normal crown size. Am J Orthod Dentofacial Orthop 1993a;104:60-66.

32. Brin I, Solomon Y, Zilberman Y. Trauma as a possible etiologic factor in maxillary canine impaction. Am J Orthod Dentofacial Orthop 1993b;104:132-137.

33. Broadbent BH. Ontogenic development of occlusion. Angle Orthod 1941;11:223-241.

34. Buchner HJ. Root resorption caused by ectopic eruption of maxillary cuspid. Int J Orthod Oral Surg 1936;22:1236-1238.

35. Butler PM. Studies of the mammalian dentition, differentiation of the post-canine dentition. Proc Zool Soc Lond 1939;109:1-36.

36. Camilleri S, Lewis CM, McDonald F. Ectopic maxillary canines: segregation analysis and a twin study. J Dent Res2008;87:580-583.

37. Chapokas AR, Almas K, Schincaglia GP. The impacted maxillary canine: a proposed classification for surgical exposure. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:222-228.

38. Chaushu S, Zilberman Y, Becker A. Maxillary incisor impaction and its relationship to canine displacement. Am J Orthod Dentofacial Orthop 2003;124:144-150.

39. Coulter J, Richardson A. Normal eruption of the maxillary canine quantified in three-dimensions. Eur J Orthod 1997;18:444-456.

40. Counihan K, Al-Awadhi EA, Butler J. Guidelines for the assessment of the impacted maxillary canine. Dent Update 2013;40:770-772,775-777.

41. de Amorim CS, Americano GCA, Moliterno LFM, de Marsillac MWS, Andrade MRTC, Campos V. Frequency of crown and root dilaceration of permanent incisors after dental trauma to their predecessor teeth. Dent Traumatol 2018;34:401-405.

42. de Oliveira Ribas M, Martins WD, de Sousa MH, de Aguiar Koubik AC, Avila LF, Zanferrari FL, Martins G. Oral and maxillofacial manifestations of familial adenomatous polyposis (Gardner's syndrome): a report of two cases. J Contemp Dent Pract 2009;10:82-90.

43. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-188.

44. Dewel BF. The upper cuspid: its development and impaction. Angle Orthod 1949;19:79-90.

45. do Espírito Santo Jácomo DR, Campos V. Prevalence of sequelae in the permanent anterior teeth after trauma in their predecessors: a longitudinal study of 8 years. Dent Traumatol 2009;25:300-304.

46. Doğramaci EJ, Sherriff M, Rossi-Fedele G, McDonald F. Location and severity of root resorption related to impacted maxillary canines: a cone beam computed tomography (CBCT) evaluation. Aust Orthod J 2015;31:49-58.

47. Ericson S, Kurol J. Longitudinal study and analysis of clinical supervision of maxillary canine eruption. Community Dent Oral Epidemiol 1986a;14:172-176.

48. Ericson S, Kurol J. Radiographic assessment of maxillary canine eruption in children with clinical signs of eruption disturbance. Eur J Orthod 1986b;8:133-140.

49. Ericson S, Kurol J. Radiographic examination of ectopically erupting maxillary canines. Am J Orthod Dentofacial Orthop 1987a;91:483-492.

50. Ericson S, Kurol J. Incisor resorption caused by maxillary cuspids. A radiographic study. Angle Orthod 1987b;57:332-346.

51. Ericson S, Kurol J. Resorption of incisors after ectopic eruption of maxillary canines: a CT study. Angle Orthod 2000;70:415-423.

52. Ericson S, Kurol J. Resorption of maxillary lateral incisors caused by ectopic eruption of the canines. Am J Orthod Dentofacial Orthop 1988;94:503-513.

53. Fardi A, Kondylidou-Sidira A, Bachour Z, Parisis N, Tsirlis A. Incidence of impacted and supernumerary teeth-a radiographic study in a North Greek population. Med Oral Patol Oral Cir Bucal 2011;16:56-61.

54. Fleming PS, Sharma PK, DiBiase AT. How to mechanically erupt a palatal canine. J Orthod 2010;37:262-271.

55. Garn SM, Lewis AB. The gradient and the pattern of crown-size reduction in simple hypodontia. Angle Orthod 1970;40:51-58.

56. Gorlin RJ, Cohen MM, Hennekam RCM. Syndromes of the head and neck. Oxford: Oxford University Press, 2001.

57. Grover PS, Lorton L. The incidence of unerupted permanent teeth and related clinical cases. Oral Surg Oral Med Oral Pathol 1985;59:420-425.

58. Guarnieri R, Cavallini C, Vernucci R, Vichi M, Leonardi R, Barbato E. Impacted maxillary

canines and root resorption of adjacent teeth: A retrospective observational study. Med Oral Patol Oral Cir Bucal 2016;21:e743–e750.

59. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 2011;64:380-382.

60. Hadler-Olsen S, Pirttiniemi P, Kerosuo H, Sjögren A, Pesonen P, Julku J, Lähdesmaki R. Does headgear treatment in young children affect the maxillary canine eruption path? Eur J Orthod 2018;40:583-591.

61. Halazonetis DJ. Cone-beam computed tomography is not the imaging technique of choice for comprehensive orthodontic assessment. Am J Orthod Dentofacial Orthop 2012;141:404,405,407.

62. Herrera-Atoche JR, Agüayo-de-Pau MD, Escoffié-Ramírez M, Aguilar-Ayala FJ, Carrillo-Ávila BA, Rejón-Peraza ME. Impacted maxillary canine prevalence and its association with other dental anomalies in a Mexican population. Int J Dent 2017;2017:7326061. doi: 10.1155/2017/7326061. Epub 2017 Feb 23.

63. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [Updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org (31 October, 2018, date last accessed).

64. Hitchin AD. The impacted maxillary canine. Br Dent J 1956;100:1-14.

65. Hou R, Kong L, Ao J, Liu G, Zhou H, Qin R, Hu K. Investigation of impacted permanent teeth except the third molar in Chinese patients through an X-ray study. J Oral Maxillofac Surg 2010;68:762-767.

66. Hunt NP. Direct traction applied to unerupted teeth using the acid-etch technique. Br J

Orthod 1977;4:211-212.

67. Hurme VO. Ranges of normalcy in the eruption of permanent teeth. J Dent Child 1949;16:11-15.

68. Husain J, Burden D, McSherry P, Morris D, Allen M. National clinical guidelines for management of the palatally ectopic maxillary canine. Br Dent J 2012;213:171-176.

69. Husain J, Burden D, McSherry P. Management of the palatally ectopic maxillary canine. London: Faculty of Dental Surgery, Royal College of Surgeons of England, 2016.

70. https://www.rcseng.ac.uk/-/media/files/rcs/fds/publications/canine-guideline-2016.pdf (Last accessed 21 1 2019)

71. Ioannidis, J.P. Interpretation of tests of heterogeneity and bias in meta-analysis. J Eval Clin Pract 2008;14:951-957.

72. Isaacson KG, Thom AR, Atack NE, Horner K, Whaites E. Orthodontic radiographs guidelines. London: British Orthodontic Society, 2015.

73. Iseri H, Uzel I. Impaction of maxillary canines and congenitally missing third molars. Description of an ancient skull (7250-6700 BC). Eur J Orthod 1993;15:1-5.

74. Jacobs SG. Localization of the unerupted maxillary canine: How to and when to. Am J Orthod Dentofacial Orthop 1999;115:314-322.

75. Jacoby H. The etiology of maxillary canine impactions. Am J Orthod 1983;84:125-132.

76. Johnston WD. Treatment of palatally impacted canine teeth. Am J Orthod 1969;56:589-596.

77. Kettle MA. Treatment of the unerupted maxillary canine. Dent Pract1958;8:245-255.

78. Kokich VG, Mathews DP. Surgical and orthodontic management of impacted teeth. Dent

Clin North Am 1993;37:181-204.

79. Kokich VG. Surgical and orthodontic management of impacted maxillary canines. Am J Orthod Dentofacial Orthop 2004;126:278-283.

80. Koutzoglou SI, Kostaki A. Effect of surgical exposure technique, age, and grade of impaction on ankylosis of an impacted canine, and the effect of rapid palatal expansion on eruption: a prospective clinical study. Am J Orthod Dentofacial Orthop 2013;143:342-352.

81. Kurol J, Ericson S, Andreasen JO. The impacted maxillary canine. In: Andreasen JO, Kølsen-Pedersen J, Laskin DM, eds. Textbook and Color Atlas of Tooth Impactions. Copenhagen: Munksgaard 1997:125-175.

82. Lapeer GL, Fransman SL. Hypodontia, impacted permanent teeth, spinal defects, and cardiomegaly in a previously diagnosed case of the Yunis-Varon syndrome. Oral Surg Oral Med Oral Pathol 1992;73:456-460.

83. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997;127:820-826.

84. Leifert S, Jonas IE. Dental anomalies as a microsymptom of palatal canine displacement. J Orofac Orthop 2003;64:108-120.

85. Leonardi M, Armi P, Franchi L, Baccetti T. Two interceptive approaches to palatally displaced canines: a prospective longitudinal study. Angle Orthod 2004;74:581-586.

86. Lewis PD. Pre-orthodontic surgery in the treatment of impacted canines. Am J Orthod1971;60:382-397.

87. Liu DG, Zhang WL, Zhang ZY, Wu YT, Ma XC. Localization of impacted maxillary canines and observation of adjacent incisor resorption with cone-beam computed

tomography. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:91-98.

88. Manne R, Gandikota C, Juvvadi SR, Rama HR, Anche S. Impacted canines: Etiology, diagnosis, and orthodontic management. J Pharm Bioallied Sci 2012;4:S234-S238.

89. Maverna R, Gracco A. Different diagnostic tools for the localization of impacted maxillary canines: clinical considerations. Prog Orthod 2007;8:28-44.

90. Mavreas D, Athanasiou AE. Factors affecting the duration of orthodontic treatment: a systematic review. Eur J Orthod 2008;30:386-395.

91. McSherry PF. The assessment of and treatment options for the buried maxillary canine. Dent Update 1996;23:7-10.

92. Mercuri E, Cassetta M, Cavallini C, Vicari D, Leonardi R, Barbato E. Dental anomalies and clinical features in patients with maxillary canine impaction A retrospective study. Angle Orthod 2013;83:22-28.

93. Miller BH. Influence of congenitally missing teeth on the eruption of upper canine. Trans Br Soc Stud Orthod 1963;164:17-24.

94. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Open Medicine 2001;3:123-130.

95. Moreira T, Braga A, Ferreira A. Prevalence of palatally impacted canines. Int J Dent Sci Res 2015;3:2-8.

96. Moss JP. The unerupted canine. Dent Pract Dent Rec 1972;22:241-248.

97. Naoumova J, Kjellberg H. The use of panoramic radiographs to decide when interceptive extraction is beneficial in children with palatally displaced canines based on a randomized

clinical trial. Eur J Orthod 2018;40:565-574.

98. Naoumova J, Kjellberg H, Palm R. Cone-beam computed tomography for assessment of palatally displaced canine position: a methodological study. Angle Orthod 2014;84:459-466.

99. Nolla CM. The development of permanent teeth. J Dent Child 1960;27:254-266.

100. Oliver RG, Mannion JE, Robinson JM. Morphology of maxillary lateral incisor in cases of unilateral impaction of maxillary canine. Br J Orthod1989;16:9-16.

101. Olow-Nordenram M, Anneroth G. Eruption of maxillary canines. Scand J Dent Res 1982;90:1-8.

102. Oxford Centre for Evidence-based Medicine – Levels of Evidence. Available from: http://www.cebm.net/index.aspx?o=1025. 2009. Accessed at 31st July 2016.

103. Papageorgiou SN, Xavier GM, Cobourne MT. Basic study design influences the results of orthodontic clinical investigations. J Clin Epidemiol 2015;68:1512-1522.

104. Parkin N, Benson PE, Thind B, Shah A. Open versus closed surgical exposure of canine teeth that are displaced in the roof of the mouth. The Cochrane Library 2008;Issue 4.

105. Parkin N, Furness S, Shah A, Thind B, Marshman Z, Glenroy G, Dyer F, Benson PE. Extraction of primary (baby) teeth for unerupted palatally displaced permanent canine teeth in children. Cochrane Database Syst Rev. 2012 Dec 12;12:CD004621. doi: 10.1002/14651858.CD004621.pub3.

106. Peck S, Peck L, Kataja M. Site-specificity of tooth maxillary agenesis in subjects with canine malpositions. Angle Orthod 1996;66:473-476.

107. Peck S, Peck L, Kataja M. The palatally displaced canine as a dental anomaly of genetic

origin. Angle Orthod 1994;64:249-256.

108. Pokorny PH, Wiens JP, Litvak H. Occlusion for fixed prosthodontics: a historical perspective of the gnathological influence. J Prosthet Dent 2008;99:299-313.

109. Power SM, Short MB. An investigation into the response of palatally displaced canines to the removal of deciduous canines and an assessment of factors contributing to favourable eruption. Br J Orthod 1993;20:215-223.

110. Rafflenbeul F, Gros CI, Lefebvre F, Bahi-Gross S, Maizeray R, Bolender Y. Prevalence and risk factors of root resorption of adjacent teeth in maxillary canine impaction, among untreated children and adolescents.Eur J Orthod 2018,1-7.doi.org/10.1093/ejo/cjy078.

111. Rayne J. The unerupted maxillary canine. Dent Pract 1969;19:194-204.

112. Sacerdoti R, Baccetti T. Dentoskeletal features associated with unilateral or bilateral palatal displacement of maxillary canines. Angle Orthod 2004;74:725-732.

113. Sambataro S, Baccetti T, Franchi L, Antonini F. Early predictive variables for upper canine impaction as derived from posteroanterior cephalograms. Angle Orthod 2005;75:28-34.

114. Schmidt AD, Kokich VG. Periodontal response to early uncovering, autonomous eruption, and orthodontic alignment of palatally impacted maxillary canines. Am J Orthod Dentofacial Orthop 2007;131:449-455.

115. SEDENTEXCT Radiation protection: cone beam CT for dental and maxillofacial radiology. Evidence based guidelines. Luxembourg: European Commission, Directorate-General for Energy; Radiation Protection No. 172. ISSN; 2012. http://www.sedentexct.eu/files/radiation_protection_172.pdf. (last accessed 21 1 2019).

116. Shafer WG, Hine MK, Levy BM. A Textbook of Oral Pathology. 2nd ed. Philadelphia:

WB Saunders, 1963:2-75.

117. Shapira Y, Kuftinec MM. Early diagnosis and interception of potential maxillary canine impaction. J Am Dent Assoc 1998;129:1450-1454.

118. Southall PJ, Gravely JF. Vertical parallax radiology to localize an object in the anterior part of the maxilla. Br J Orthod 1989;16:79-83.

119. Takahama Y, Aiyama Y. Maxillary canine impaction as a possible microform of cleft lip and palate. Eur J Orthod 1982;4:275-277.

120. Thilander B, Jakobsson SO. Local factors in impaction of maxillary canines. Acta Odontol Scand 1968;26:145-168.

121. Thiruvenkatachari B, Javidi H, Griffiths SE, Shah AA, Sandler J. Extraction of maxillary canines: Esthetic perceptions of patient smiles among dental professionals and laypeople. Am J Orthod Dentofacial Orthop 2017;152:509-515.

122. Walker L, Enciso R, Mah J. Three dimensional localization of maxillary canines with cone-beam computed tomography. Am J Orthod Dentofacial Orthop 2005;128:418-423.

123. Wedl JS, Schoder V, Blake FA, Schmelzle R, Friedrich RE. Eruption times of permanent teeth in teenage boys and girls in Izmir (Turkey). J Clin Forensic Med 2004;11:299-302.

124. Wijn MA, Keller JJ, Giardiello FM, Brand HS. Oral and maxillofacial manifestations of familial adenomatous polyposis. Oral Dis 2007;13:360-365.

125. Yildirim D, Yilmaz HH, Aydin U. Multiple impacted permanent and deciduous teeth. Dentomaxillofac Radiol 2004;33:133-135.

126. Ziberman Y, Cohen B, Becker A. Familial trends in palatal canines, anomalous lateral incisors, and related phenomena. Eur J Orthod 1990;12:135-139.

127. Zuccati G, Ghobadlu J, Nieri M, Clauser C. Factors associated with the duration of forced eruption of impacted maxillary canines: a retrospective study. Am J Orthod Dentofacial Orthop 2006;130:349-356.

9. APPENDICES

Appendix I. Systematic review protocol used for registration with international prospective register of systematic reviews (PROSPERO).

Review question(s)

The aim of this study is to compare the effectiveness of alternative or adjunctive treatment modalities with or without extraction of the primary canines used in an interceptive orthodontic manner in mixed dentition for preventing impaction of PDCs.

Searches

Comprehensive electronic database searches will be undertaken (up to April 2018) without language restriction in the following databases:

MEDLINE via PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, Scopus, Web of Science, LILACS, IndMed, Scielo, Arab World Research Source and Deutsche ZentralbibliotekfuerMedizin. Unpublished literature will be accessed electronically using Google Scholar (https://scholar.google.com), ClinicalTrials.gov (http://clinicaltrials.gov), International Standard Randomised Controlled Trial Number (ISRCTN) registry (http://www.isrctn.com) and OpenGrey (http://www.opengrey.eu).

In addition, ProQuest Dissertation and Theses Global database will be searched. Efforts will be made to obtain conference proceedings and abstracts where possible. Authors will be contacted to identify unpublished or ongoing clinical trials and to clarify methodology and data as necessary. Reference lists of included studies will be screened for additional relevant research.

Types of study to be included

The trials to be included should be RCTs.

Condition or domain being studied

Interceptive orthodontic treatment of palatally displaced permanent canines.

Participants/ population

Patients in mixed dentition with unilateral or bilateral PDCs.

Intervention(s), exposure(s)

Various interceptive orthodontic approaches (such as, but not limited to RME, using of TPA, using of HG or any combination of these treatments with or without extraction of primary canines).

Comparator(s)/ control

No treatment or alternative interceptive approaches.

Outcome(s)

Primary outcomes

Percentage of successful outcomes.

Secondary outcomes

Side effects, economic evaluation data, patient reported outcomes (pain, patient satisfaction etc.).

Data extraction, (selection and coding)

All assessments including titles and/or abstract screening, full text evaluation, and extraction of data will be performed independently and in duplicate by two investigators (IA and EGK). The investigators will not be blinded to the authors or the results of the research. Disagreements will be resolved by discussion and consultation with a third author where necessary (AEA).

Risk of bias (quality) assessment

Assessment of risk of bias will be performed independently and in duplicate by two investigators (IA and EGK) using the Cochrane Collaboration risk of bias tool that considers seven domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of assessors; incomplete outcome data; selective reporting of outcomes; and other potential sources of bias.

Each domain will receive a rating of low, high or unclear risk of bias (indicating either lack of sufficient information to make a judgment or uncertainty over the risk of bias). Studies will be finally grouped into the following categories:

• Low risk of bias (plausible bias unlikely to seriously alter the results): if all key domains of the study are at low risk of bias,

• Unclear risk of bias (bias that raises some doubt about the results): if one or more key domains of the study are unclear, and,

• High risk of bias (bias that seriously weakens confidence in the results): if one or more key

domains are at high risk of bias.

Disagreements will be resolved by discussion and consultation with a third author where necessary.

Strategy for data synthesis

Where studies have used the same type of intervention, we will pool the results using a random-effects meta-analysis analysis in view of the likely variation in population groups and settings. Depending on the variation of the indices used to quantify primary or secondary outcomes we will use weighted or standardized mean differences for continuous outcomes and risk ratios for binary outcomes, and calculate 95% confidence intervals and two sided p values for each outcome. Heterogeneity will be assessed using both the Chi-squared test and the I-squared statistic. If an adequate number of trials are identified, we will carry out analyses for "small-study effects" and publication bias.

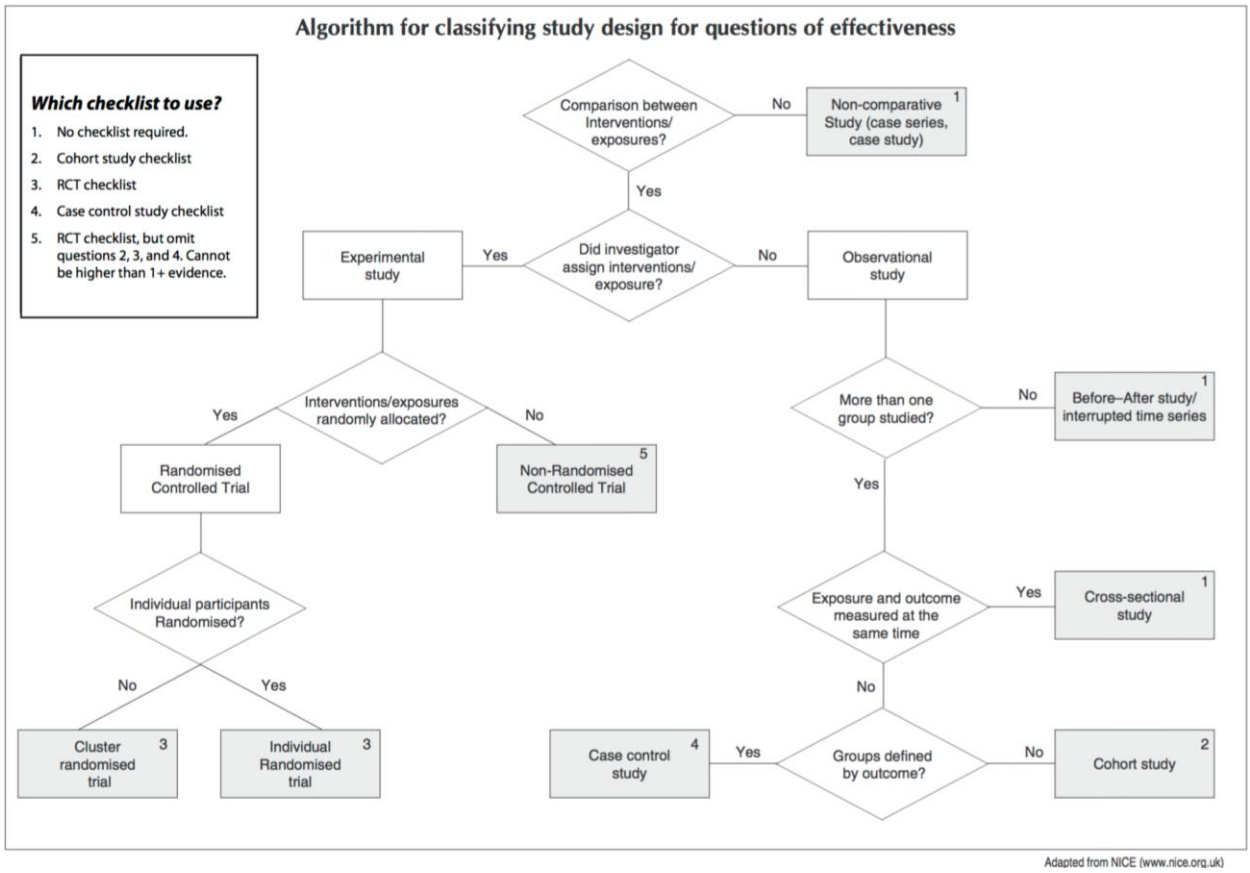
Analysis of subgroups or subsets

If the necessary data are available, subgroup analysis will be performed for gender and displaced canine position.

Dissemination plans

Peer-reviewed orthodontic journal.

Appendix II. Scottish Intercollegiate Guidelines Network (SIGN) algorithm for classifying study design for questions of effectiveness.



Appendix III. Strategy for database search (up to April 4th, 2018).

Database	Search strategy	Hits
PubMed	(((randomized controlled trial) OR (controlled clinical trial) OR randomized[tiab] OR placebo[tiab] OR (drug therapy) OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh])) AND (canine* OR cuspid*) AND (impact* OR unerupt* OR displace* OR ectop* OR malpos*) Filters activated: Human	**368**
Cochrane Central Register of Controlled Trials	(orthodon*) AND (canine* OR cuspid*) AND (impact* OR unerupt* OR displace* OR ectop* OR malpos*) in Title, Abstract, Keywords in Trials	**38**
Cochrane Database of Systematic Reviews	(orthodontic OR orthodontics) AND (canine OR canines OR cuspid OR cuspids) AND (impacted OR impaction OR unerupted OR displaced OR ectopic OR malpositioned OR malposition) {Including Limited Related Terms}	**6**
Scopus	TITLE-ABS-KEY ((orthodon*) AND (canine* OR cuspid*) AND (impact* OR unerupt* OR displace* OR ectop* OR malpos*)) AND (LIMIT-TO (EXACTKEYWORD,"Human"))	**1324**
Web of Science™ Core Collection	TOPIC: ((orthodon*) AND (canine* OR cuspid*) AND (impact* OR unerupt* OR displace* OR ectop* OR malpos*)) Timespan: All years. Search language=Auto	**893**
Arab World Research Source	(orthodon*) AND (canine* OR cuspid*) AND (impact* OR unerupt* OR displace* OR ectop* OR malpos*)	**14**
ClinicalTrials.gov	(orthodontic OR orthodontics) AND (canine OR canines OR cuspid OR cuspids) AND (impacted OR impaction OR unerupted OR displaced OR ectopic OR malpositioned OR malposition)	**4**
ProQuest Dissertations and Theses Global	ti((canine* OR cuspid*) AND (impact* OR unerupt* OR displace* OR ectop* OR malpos*)) OR ab((canine* OR cuspid*) AND (impact* OR unerupt* OR displace* OR ectop* OR malpos*)) Filters activated: Full text; NOT (veterinary services AND animals AND animal sciences AND zoology AND dogs AND wildlife conservation AND livestock AND animal training AND case studies AND food science AND forestry AND parasitology)	**150**

Appendix IV. Details of risk of bias assessment [Domains examined: 1: Random sequence generation; 2: Allocation concealment; 3: Blinding of participants and personnel; 4: Blinding of outcome assessment; 5: Incomplete outcome data; 6: Selective outcome reporting; 7: Other potential threats to validity]

Study	Rating		Reasons for rating
Leonardi et al. (2004)	**1.**	Unclear	Insufficient information about the sequence generation process. ["…they were assigned randomly…]
	2.	High	No information about the allocation concealment process. The review authors believe that probably no measures were taken and that there might possibly be a high risk of bias regarding this domain owing to general deficiency in the reporting and possibly conduct of the study.
	3.	Low	Blinding of the participants and personnel was not possible. However, the review authors believe that the outcome is not likely to be influenced by lack of blinding.
	4.	Unclear	No statement that the investigator was blinded with regards to assessing successful eruption of the permanent canine. However, the review authors believe that the risk of bias regarding is unclear owing to general deficiency in the reporting of the study.
	5.	Unclear	Dropouts are described and explained, but not in adequate extent.
	6.	High	Important outcomes are not adequately reported.
	7.	Unclear	Insufficient information to assess whether an important risk of bias exists
Baccetti *et al.*	**1.**	Unclear	Insufficient information about the sequence generation process. ["…All PDC subjects were assigned randomly…]

Study	Rating		Reasons for rating
(2008)	**2.**	High	No information about the allocation concealment process. The review authors believe that probably no measures were taken and that there might possibly be a high risk of bias regarding this domain owing to general deficiency in the reporting and possibly conduct of the study.
	3.	Low	Blinding of the participants and personnel was not possible. However, the review authors believe that the outcome is not likely to be influenced by lack of blinding.
	4.	Unclear	No statement that the investigator was blinded with regards to assessing successful eruption of the permanent canine. However, the review authors believe that the risk of bias regarding is unclear owing to general deficiency in the reporting of the study.
	5.	Unclear	Dropouts are described and explained, but not to an adequate extent.
	6.	High	Important outcomes are not adequately reported.
	7.	Unclear	Insufficient information to assess whether an important risk of bias exists.

Appendix IV. Details of risk of bias assessment [Domains examined: 1: Random sequence generation; 2: Allocation concealment; 3: Blinding of participants and personnel; 4: Blinding of outcome assessment; 5: Incomplete outcome data; 6: Selective outcome reporting; 7: Other potential threats to validity] [Continued]

Study	Rating		Reasons for rating
Baccetti *et al.* (2009)	**1.**	Unclear	Insufficient information about the sequence generation process. ["…All PDC subjects were assigned randomly…]
	2.	High	No information about the allocation concealment process. The review authors believe that probably no measures were taken and that there might possibly be a high risk of bias regarding this domain owing to general deficiency in the reporting and possibly conduct of the study.
	3.	Low	Blinding of the participants and personnel was not possible. However, the review authors believe that the outcome is not likely to be influenced by lack of blinding.
	4.	Unclear	No statement that the investigator was blinded with regards to assessing successful eruption of the permanent canine. However, the review authors believe that the risk of bias regarding is unclear owing to general deficiency in the reporting of the study.
	5.	Unclear	Dropouts are described and explained, but not to an adequate extent.
	6.	High	Important outcomes are not adequately reported.
	7.	Unclear	Insufficient information to assess whether an important risk of bias exists
Armi et al.	**1.**	Unclear	Insufficient information about the sequence generation process. ["…they were assigned randomly…]

Study	Rating		Reasons for rating
(2011)	**2.**	High	No information about the allocation concealment process. The review authors believe that probably no measures were taken and that there might possibly be a high risk of bias regarding this domain owing to general deficiency in the reporting and possibly conduct of the study.
	3.	Low	Blinding of the participants and personnel was not possible. However, the review authors believe that the outcome is not likely to be influenced by lack of blinding.
	4.	Unclear	No statement that the investigator was blinded with regards to assessing successful eruption of the permanent canine. However, the review authors believe that the risk of bias regarding is unclear owing to general deficiency in the reporting of the study.
	5.	Unclear	Dropouts are described and explained, but not to an adequate extent.
	6.	High	Important outcomes are not adequately reported.
	7.	Unclear	Insufficient information to assess whether an important risk of bias exists.

Appendix IV. Details of risk of bias assessment [Domains examined: 1: Random sequence generation; 2: Allocation concealment; 3: Blinding of participants and personnel; 4: Blinding of outcome assessment; 5: Incomplete outcome data; 6: Selective outcome reporting; 7: Other potential threats to validity] [Continued]

Study	Rating		Reasons for rating
Baccetti *et al.*	**1.**	Unclear	Insufficient information about the sequence generation process. ["…All PDC subjects were assigned randomly…]
(2011)	**2.**	High	No information about the allocation concealment process. The review authors believe that probably no measures were taken and that there might possibly be a high risk of bias regarding this domain owing to general deficiency in the reporting and possibly conduct of the study.
	3.	Low	Blinding of the participants and personnel was not possible. However, the review authors believe that the outcome is not likely to be influenced by lack of blinding.
	4.	Unclear	No statement that the investigator was blinded with regards to assessing successful eruption of the permanent canine. However, the review authors believe that the risk of bias regarding is unclear owing to general deficiency in the reporting of the study.
	5.	Unclear	Dropouts are described and explained, but not in adequate extent.
	6.	High	Important outcomes are not adequately reported.
	7.	Unclear	Insufficient information to assess whether an important risk of bias exists.