Meta-analysis
Orthodontics/
Pediatric Dentistry

Is there a better interceptive treatment for unerupted palatally displaced canines? A network meta-analysis

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Declaration of Interests: The authors certify that they have no commercial or associative interest that represents a conflict of interest in connection with the manuscript.

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https://doi.org/10.1590/1807-3107bor-2022.vol36.0119

Submitted: July 19, 2021
Accepted for publication: May 2, 2022
Last revision: May 23, 2022

Abstract: This systematic review aimed to investigate if there is a better interceptive treatment for palatally displaced canines (PDC) in the mixed dentition stage. The PubMed/MEDLINE, CENTRAL, Scopus, and EMBASE databases were searched for randomized clinical trials related to the research topic. The gray literature and reference lists were also assessed. Network meta-analysis was conducted to analyze the effects of different approaches on PDC eruption. The surface under the cumulative ranking area was calculated to rank the treatments. The certainty of the evidence was evaluated using the GRADE approach. Of the 892 eligible studies, 18 were selected for full-text analysis and 9 for meta-analysis, involving 506 participants and 730 PDC, to compare 9 approaches. The proportion of erupted PDC was significantly higher for all interceptive treatments compared with control (no intervention). Furthermore, the proportion of erupted PDC was higher in patients subjected to rapid maxillary expansion (RME) than those who underwent double extraction of primary canine and primary molar (relative risk (RR) = 2.68 ICr95%: 1.12–9.35). A higher proportion of erupted PDC was found for RME (RR = 3.07 ICr95%: 1.31–10.67), RME *plus* use of transpalatal arch (TA) *plus* extraction of primary canine(s) (EC) (RR = 1.43 ICr95%: 1.09–1.95), EC *plus* use of cervical pull headgear (RR = 1.38 ICr95%: 1.11–1.79), and EC *plus* use of TA (RR = 1.36 ICr95%: 1.00–1.9) than for EC. RME was most likely to be considered as the best interceptive treatment. Overall, the certainty of the evidence was considered low due to imprecision and indirectness. In conclusion, no intervention in the mixed dentition stage is the worst choice for PDC.

Keywords: Tooth, Impacted; Orthodontics, Interceptive; Network Meta-Analysis.

Introduction

Permanent canines are the second most commonly impacted teeth after the third molars.[1] Maxillary canines may fail to erupt due to hard or soft tissue obstruction or an abnormal eruption pathway. Ectopic canines may become displaced in a palatal or buccal direction. It has been demonstrated that about 50% of impacted canines are palatally displaced; the rest are displaced either buccally or in the line of the arch.[2]

Ectopic canines can cause unwanted movement of neighboring teeth, dental crowding and root resorption of adjacent teeth, and cyst formation in rare occasions.[3] Furthermore, patients may undergo surgical management of displaced canines, followed by prolonged and expensive fixed orthodontic treatment.[4,5] To overcome these complications, early diagnosis of palatally displaced canines is crucial to establish interceptive treatments. Several interceptive treatments have been proposed to facilitate eruption of displaced canines, including extraction of primary canines[6-8] that are associated or not with primary molars,[9] use of transpalatal arch,[7] use of cervical pull headgear[8] to distalize the upper posterior segments, and maxillary expansion[7] as methods for gaining space, or even the combination of these treatments.[7]

Scientific literature has been systematically evaluated to determine whether extraction of primary canines is effective in managing the impaction of palatally displaced canines.[10-12] The evidence supporting that extraction of primary canines leads to a successful eruption of palatally displaced canines in comparison with no intervention has a low certainty (50%–69% and 36%–42%, respectively).[11] A recent systematic review[13] suggested that the combination of interceptive treatments facilitates successful eruption of palatally displaced canines. However, only a qualitative evaluation was conducted, and intervention groups ranged considerable in the included studies.[13]

Clinicians wish to offer patients a choice among the most desirable treatment options. However, due to the lack of head-to-head direct comparisons among the interventions, choosing the best one is difficult. The possible solution for this problem is to conduct network meta-analysis of the different treatments; this analysis uses an entire body of evidence with all available direct and indirect comparisons. In addition to providing information on the relative merits of interventions that have never been directly compared, a network meta-analysis may increase the precision of effect estimates by combining both direct and indirect evidence.[14]

Therefore, this systematic review and network meta-analysis aimed to establish a clinically meaningful hierarchy of the different interceptive treatments for palatally displaced canines provided in the mixed dentition stage through the synthesis of available evidence obtained from randomized clinical trials.

Methodology

This study was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[15] and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analysis Statement for Network Meta-analysis.[16] Although the systematic review protocol was planned *a priori*, it was not recorded in the International Prospective Register of Systematic Review because only systematic reviews focusing on COVID-19 were being registered during the start of the study.

Search strategy

The PICOS strategy was employed for the study selection with the following question: Which interceptive treatment has a higher success rate of eruption of palatally displaced canines? (Participants: children with palatally displaced canines in the mixed dentition stage; intervention: treatments available for palatally displaced canines, including no intervention; comparator: treatments available for palatally displaced canines, including no intervention; outcome: success rate of eruption of palatally displaced canines; study design: randomized clinical trials).

The PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, Scopus, and EMBASE databases were searched for literature related to the research topic until April 2022; no publication year or language limits were implemented. The search strategy was established for the PubMed/MEDLINE database and then adapted to the other databases consulted (Table 1). To reduce publication bias, unpublished and ongoing trials were also searched through the clinical trial registries: ClinicalTrials.gov (www.clinicaltrials.gov) and Brazilian Clinical Trials Registry (REBEC) (www.rebec.gov.br). The search results were cross-checked to locate and eliminate duplicates.

Table 1. Search strategies used for all databases consulted.

Database	Search strategy
PubMed/MEDLINE	((((((((((((((Cuspid[MeSH Terms]) OR Cuspid*) OR Canine teeth) OR Canine tooth) OR Canine*) AND Tooth, Impacted[MeSH Terms]) OR Impacted tooth) OR Impacted teeth) OR Displaced tooth) OR Displaced teeth) OR Unerupted tooth) OR Unerupted teeth) AND Dentition, Mixed[MeSH Terms]) OR Dentition*, Mixed) OR Mixed Dentition) OR Transitional Dentition*) AND (((((((((((((((Palatal Expansion Technique[MeSH Terms]) OR Palatal Expansion Technique*) OR Expansion Technique*, Palatal) OR Technique, Palatal Expansion) OR Palatal Expansion Technic*) OR Maxillary Expansion) OR Tooth Extraction[MeSH Terms]) OR Tooth Extraction) OR cervical pull headgear) OR crossbar) OR nance button) OR transpalatal arch) OR non extraction)) OR Teeth extraction))
EMBASE	(((mixed AND dentition OR (transitional AND dentition)) AND cuspid OR canine) AND displaced AND tooth OR (impacted AND tooth) OR (unerupted AND tooth)) AND interceptive AND orthodontics
Scopus	(TITLE-ABS-KEY (*transitional* AND *dentition*) OR TITLE-ABS-KEY (*mixed* AND *dentition*) AND TITLE-ABS-KEY (*cuspid*) OR TITLE-ABS-KEY (*canine*) OR TITLE-ABS-KEY (*impacted* AND *t??th*) OR TITLE-ABS-KEY (*displaced* AND *t??th*) OR TITLE-ABS-KEY (*unerupted* AND *t??th*) AND TITLE-ABS-KEY (*palatal* AND *expansion* AND *technique*) OR TITLE-ABS-KEY (*maxillary* AND *expansion*) OR TITLE-ABS-KEY (*cervical* AND *pull* AND *headgear*) OR TITLE-ABS-KEY (*extraction*) OR TITLE-ABS-KEY (*crossbar*) OR TITLE-ABS-KEY (*nance* AND *button*) OR TITLE-ABS-KEY (*transpalatal* AND *arch*) OR TITLE-ABS-KEY (*non* AND *extraction*))
CENTRAL	mixed dentition in All Text AND canine in All Text AND interceptive treatment in All Text
Clinical Trials	impacted canine AND interceptive treatment
Brazilian Clinical Trials Registry (REBEC)	mixed dentition AND canine AND interceptive treatment

Eligibility criteria and selection process

The titles and abstracts were reviewed independently and in duplicate by two authors (S.H. and V.Z.A.), who were previously trained and calibrated for study selection (Kappa = 0.91). The studies were considered eligible if they were clinical trials that evaluated any interceptive treatment for palatally displaced canines in the mixed dentition stage. When only a relevant title without a listed abstract was available, a full copy of the article was evaluated. The references of all the selected studies were manually searched for additional relevant studies that met the inclusion criteria.

A final decision about the inclusion of potentially relevant studies was made based on the full-text evaluation. Studies that had non-random allocation of subjects or less than two arms, had a follow-up period shorter than 12 months after the intervention, had a dropout rate higher than 30%, had no similar follow-up for subjects in both groups evaluated in the same manner, did not report computable data for both groups, included participants with craniofacial syndromes or anomalies, and did not consider the eruption of permanent canines without surgery and fixed braces as outcome were excluded. To avoid overlapping data, when there were multiple reports of the same study, only the study with more complete data was considered. Disagreements between the reviewers were resolved through discussion. If agreement could not be reached, a third reviewer (T.L.L.) was consulted.

Data extraction

A protocol for data extraction was established. Both reviewers collected the data of the eligible studies independently and in duplicate using a standardized sheet in Microsoft Office Excel 2013 (Microsoft Corporation, Redmond, USA). For each study, the following data were systematically extracted: publication details (authors, year, and country), sample characteristics (number and age of the subjects pre-treatment and number of the participants and the palatally displaced canines), methodology (method used for the diagnosis of palatally displaced canines, treatment measures, follow-up, and dropout rate), outcome (success rate of eruption of permanent canines), and funding sources. The authors of the included studies were contacted twice *via* e-mail if data were missing or more information was needed.

Risk of bias assessment

Two reviewers (S.H. and V.Z.A.) assessed the risk of bias independently and in duplicate using the RoB 2 tool.[17] The criteria were divided into five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the outcome measurement, and bias in the selection of the reported result. The studies were evaluated by rating each domain as low risk of bias, some concerns, or high risk of bias. For the final classification of the risk of bias, disagreements between the reviewers were solved by reaching a consensus.

Certainty of the evidence assessment

The GRADE approach was employed to appraise the confidence in the estimates derived from the network meta-analysis according to the method described by Puhan et al.[18] Direct evidence from randomized clinical trials starts at high confidence and can be rated based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity), and/or publication bias to levels of moderate, low, and very low confidence. The rating of indirect estimates starts at the lowest rating of the pairwise estimates that contribute as first-order loops to the indirect estimate but can be rated further for imprecision or intransitivity (dissimilarity between studies in terms of clinical or methodological characteristics). If only direct or indirect evidence was available for a given comparison, the network quality rating was based on that estimate.

Statistical analysis

A per-protocol analysis (analysis of participants based on the intervention they received and their availability for follow-up) was conducted in this study. The effect of the different interceptive treatments on the eruption of palatally displaced maxillary canines was investigated using traditional pairwise meta-analysis, followed by Bayesian network meta-analysis.[19] A successful outcome was tooth eruption, which allows bracket positioning for the final arch alignment when needed.

The network meta-analysis was based on a binomial model with a log link function.[20] Therefore, the effect-size measure was relative risk (RR) and credibility interval (ICr 95%). The model allows the inclusion of multi-arm studies. Both fixed-effects and homogeneous variance random-effects models were considered. The model and goodness of fit were selected based on the deviance information criterion. The models were adjusted using Markov chain Monte Carlo methods with non-informative priors. Convergence was assessed using trace plots.[21] However, inconsistency was not evaluated because the network results for each pair of comparisons came only from either direct or indirect evidence.

The surface under the cumulative ranking curve (SUCRA) was used to evaluate the expected ranking of efficacy for all treatments. The higher the SUCRA value and the closer it is to 100%, the higher the likelihood that a therapy is in the top rank or one of those in the top ranks; the closer the SUCRA value to 0, the higher the likelihood that a therapy is in the bottom rank or one of those in the bottom ranks.[14] Statistical analysis was conducted using the R software with the Meta- and GeMTC-packages, version 3.4.4. Publication bias was not assessed due to the small number of included studies.[15]

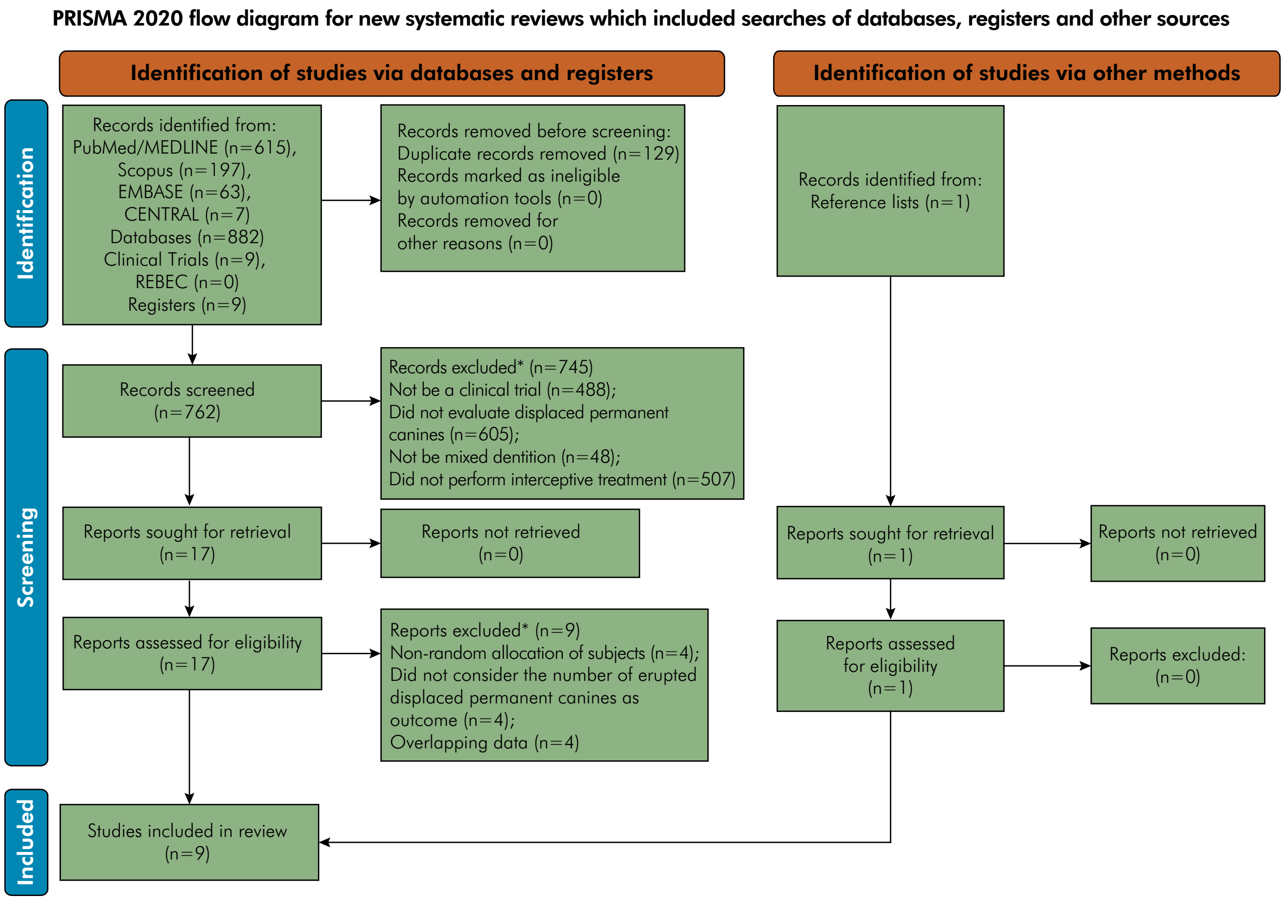
Results

Study selection

The search strategy identified 892 potentially relevant studies, of which 762 remained after the exclusion of duplicates. After screening the titles and abstracts, 18 studies were selected for further analysis. In addition, another study was identified in the reference lists of related reviews. Finally, nine randomized controlled trials that met the eligibility criteria were included in the systematic review. The process of the study selection and the reasons for exclusions are summarized in the flow chart presented in Figure 1. The characteristics of the excluded studies are listed in Table 2.

Characteristics of the included studies

The main characteristics of the included studies are listed in Table 3. The studies were conducted in Italy,[8,9,22-25] Sweden,[6,26] and Norway[27] and published



*One study could be excluded for more than one reason.

Figure 1. Flow diagram of the study selection according to the PRISMA statement.

between 2004 and 2020. The following interceptive treatments for palatally displaced canines during the mixed dentition stage were evaluated: extraction of canine(s),[6,8,9,22,26,27] double extraction–primary canine and primary molar,[9,27] use of cervical pull headgear,[25] extraction of canine(s) *plus* use of transpalatal arch,[24] extraction of canine(s) *plus* use of cervical pull headgear,[8,22] use of cervical pull headgear *plus* rapid maxillary expansion,[25] rapid maxillary expansion *plus* use of transpalatal arch *plus* extraction of canine(s),[24] and rapid maxillary expansion.[23] Most of the studies had a control group. The follow-up period ranged from 18 to 52 months, with a dropout rate of 0%–10%.

Risk of bias assessment

The final assessment of the risk of bias for the included studies is summarized in Table 4. Five studies[8,22-25] were classified as being at a high risk of bias, and four studies[6,9,26,27] were judged to raise some concerns in at least one domain but were not at a high risk of bias for any domain.

Network meta-analysis

A network plot of treatment comparisons for network meta-analysis is presented in Figure 2. There were nine approaches for palatally displaced canines during the mixed dentition stage, including 506 participants and 730 displaced maxillary canines. The size of the nodes (blue circles) corresponds to the sample size for the interventions. The comparisons are connected by a straight line, of which the thickness corresponds to the number of trials that assessed the comparison. As can be seen from the network plot, the number of interventions varied in different subjects.

Table 2. Characteristics of excluded studies.

Study	Reason(s) for exclusion
Barros SE, Hoffelder L, Araújo F, Janson G, Chiqueto K, Ferreira E. Short-term impact of rapid maxillary expansion on ectopically and normally erupting canines. Am J Orthod Dentofacial Orthop. 2018 Oct;154(4):524-534.	Non-random allocation of subjects Did not consider the eruption of permanent canines without surgery and fixed braces as outcome
Naoumova J, Kiellberg 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 Nov 30;40(6):565-574.	Did not consider the eruption of permanent canines without surgery and fixed braces as outcome Overlapping data
Naoumova J, Kürol J, Kiellberg H. Extraction of the deciduous canine as an interceptive treatment in children with palatally displaced canines - part II: possible predictors of success and cut-off points for a spontaneous eruption. J Orthod. 2015 Apr;37(2):219-29.	Did not consider the eruption of permanent canines without surgery and fixed braces as outcome Overlapping data
Naoumova J. Interceptive treatment of palatally displaced canines. Swed Dent J Suppl. 2014;(234):7-118.	Overlapping data
Sigler LM, Baccetti T, McNamara Jr JA. Effect of rapid maxillary expansion and transpalatal arch treatment associated with deciduous canine extraction on the eruption of palatally displaced canines: A 2-center prospective study. Am J Orthod Dentofacial Orthop. 2011 Mar;139(3):e235-44.	Non-random allocation of subjects
Silvola A, Arvonen P, Julku J, Lähdesmäki, R, Kantomaa T, Pirttiniemi P. Early headgear effects on the eruption pattern of the maxillary canines. Angle Orthod. 2009 May;79(3):540-5.	Did not consider the eruption of permanent canines without surgery and fixed braces as outcome
Bonetti GA, Parenti SI, Zanarini M, Marini I. Double vs single primary teeth extraction approach as prevention of permanent maxillary canines ectopic eruption. Pediatr Dent. Sep-Oct 2010;32(5):407-12.	Overlapping data
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 Aug;20(3):215-23.	Non-random allocation of subjects
Ericson S, Kurol J. Early treatment of palatally erupting maxillary canines by extraction of the primary canines. Eur J Orthod. 1988. Nov;10(4):283-95.	Non-random allocation of subjects or less than 2 arms

The results from the traditional pairwise meta-analysis (Figure 3) and network meta-analysis are summarized in Table 5. The network meta-analysis revealed that the proportion of erupted permanent canines was significantly higher for all interceptive treatments than for control (no interceptive treatments). Furthermore, the proportion of erupted palatally displaced canines was higher for patients subjected to rapid maxillary expansion than those who underwent double extraction of primary canine and primary molar (RR = 2.68 ICr95%: 1.12–9.35). In addition, a higher proportion of erupted permanent canines was observed for rapid maxillary expansion (RR = 3.07 ICr95%: 1.31–10.67), rapid maxillary expansion *plus* use of transpalatal arch *plus* extraction of primary canine(s) (RR = 1.43 ICr95%: 1.09–1.95), extraction of primary canine(s) *plus* use of cervical pull headgear (RR = 1.38 ICr95%: 1.11–1.79), and extraction of primary canine(s) *plus* use of transpalatal arch (RR = 1.36 ICr95%: 1.00–1.9) than for extraction of primary canine(s) alone. According to the SUCRA (Figure 4), rapid maxillary expansion followed by use of cervical pull headgear *plus* rapid maxillary expansion was most likely to be considered as the best interceptive treatment for palatally displaced canines. On the other hand, no intervention and extraction of primary canine(s) were ranked as the first and second least-effective treatments, respectively.

Table 3. Detailed chart related to studies included in the systematic review.

Publication details	Diagnostic method of displaced canine	Treatments	Sample	Follow-up (months)	Dropout (%)	Number of erupted permanent canines/total of canines per group	Funding sources
Leonardi et al. (2004),[8] Italy	Panoramic and periapical radiographs	Extraction of primary canine(s) Extraction of primary canine(s) *plus* cervical pull headgear No intervention	50 subjects with either unilateral or bilateral impacted canines 8-13 years	48	8	Extraction of primary canine(s): 7/14 Extraction of primary canine(s) *plus* cervical pull headgear: 26/32 No intervention: 8/16	Not reported
Baccetti et al. (2008),[22] Italy	Panoramic radiographs and lateral cephalograms	Extraction of primary canine(s) Extraction of primary canine(s) *plus* cervical pull headgear No intervention	75 subjects and 92 maxillary canines 8-13 years	18	6.7	Extraction of primary canine(s): 16/25 Extraction of primary canine(s) *plus* cervical pull headgear: 31/35 No intervention: 9/26	Not reported
Bacetti et al. (2009),[23] Italy	Posteroanterior cephalograms and panoramic radiographs	Rapid maxillary expansion No intervention	60 subjects with either unilateral or bilateral impacted canines 7.6-9.6 years	52	10	Rapid maxillary expansion: 27/42 No intervention: 4/31	Not reported
Baccetti et al. (2011),[24] Italy	Panoramic radiographs and lateral cephalograms	Rapid maxillary expansion *plus* transpalatal arch *plus* extraction of primary canine(s) Transpalatal arch *plus* extraction of primary canine(s) Extraction of primary canine(s) No intervention	120 subjects with either unilateral or bilateral impacted canines 9.5-13 years	36-52	2.5	Rapid maxillary expansion *plus* transpalatal arch *plus* extraction of primary canine(s): 53/66 Transpalatal arch *plus* extraction of primary canine(s): 26/36 Extraction of primary canine(s): 21/34 No intervention: 11/42	Not reported

Continue

Continuation

Armi et al. (2011),[25] Italy	Panoramic and periapical radiographs	Cervical pull headgear	64 subjects and 81 maxillary canines			Cervical pull headgear: 20/25	
		Rapid maxillary expansion *plus* cervical pull headgear	8-13 years	18	6.2	Rapid maxillary expansion *plus* cervical pull headgear: 26/30	Not reported
		No intervention				No intervention: 9/26	
Bonetti et al. (2011),[9] Italy	Panoramic radiographs	Extraction of primary canine(s)					
		Extraction of primary canine *plus* first molar (Double extraction)				Extraction of primary canine: 22/28	
			71 subjects and 123 maxillary canines	18	4.3	Extraction of primary canine *plus* first molar (Double extraction): 36/37	Not reported
			8-13 years				
		Extraction of primary canine	24 subjects and 48 maxillary canines			Extraction of primary canine: 16/24	
Bazargani et al. (2014),[6] Sweden	Panoramic and intraoral occlusal radiographs	No intervention	10-14 years	18	0	No intervention: 10/24	Supported by the Uppsala-örebro Regional Research Council; however, the authors' work was independent of the funders
	Cone beam computed tomography	Extraction of primary canine(s)	Sixty-seven subjects with either unilateral or bilateral impacted canines	24	0	Extraction of primary canine(s): 31/45	The Local Research and Development Board for Gothenburg and Södra Bohuslän and from the Health & Medical Care Committee of the Regional Executive Board, Västra Götaland Region
Naoumova et al. (2015)[26] Sweden		No intervention	10-13 years			No intervention: 17/44	The Local Research and Development Board for Gothenburg and Södra Bohuslän and from the Health & Medical Care Committee of the Regional Executive Board, Västra Götaland Region
		Extraction of primary canine(s)	Thirty-two subjects and 48 maxillary canines			Extraction of primary canine(s): 18/23	
	Periapical radiographs	Extraction of primary canine *plus* first molar (Double extraction)	9.5-13.5 years	24	0	Extraction of primary canine *plus* first molar (Double extraction): 16/25	
							No funding

Certainty of evidence

The ratings of the certainty of the direct, indirect, and network evidence are listed in Table 6. Overall, the certainty of the evidence of the network meta-analysis was graded as low due to imprecision and indirectness.

Table 4. Summary of the risk of bias assessment of the included studies.

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Leonardi et al. (2004)[8]	-	+	?	?	?	-
Baccetti et al. (2008)[22]	-	+	?	?	?	-
Bacetti et al. (2009)[23]	-	+	?	?	?	-
Baccetti et al. (2011)[24]	-	+	+	?	?	-
Armi et al. (2011)[25]	-	+	?	?	?	-
Bonetti et al. (2011)[9]	+	+	?	?	?	?
Bazargani et al. (2014)[6]	?	+	+	?	?	?
Naoumova et al. (2015)[26]	+	+	+	?	+	?
Hadler-Olsen et al., (2020)[27]	?	+	+	?	?	?

-High risk of bias; +Low risk of bias; ?Some concerns

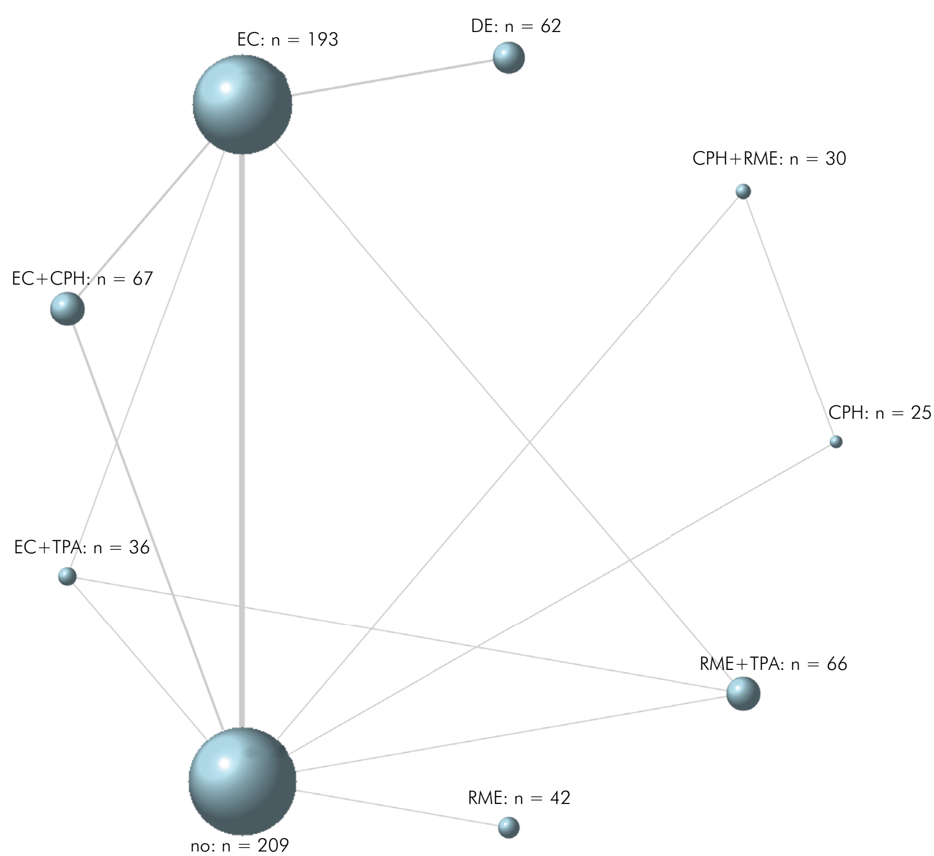
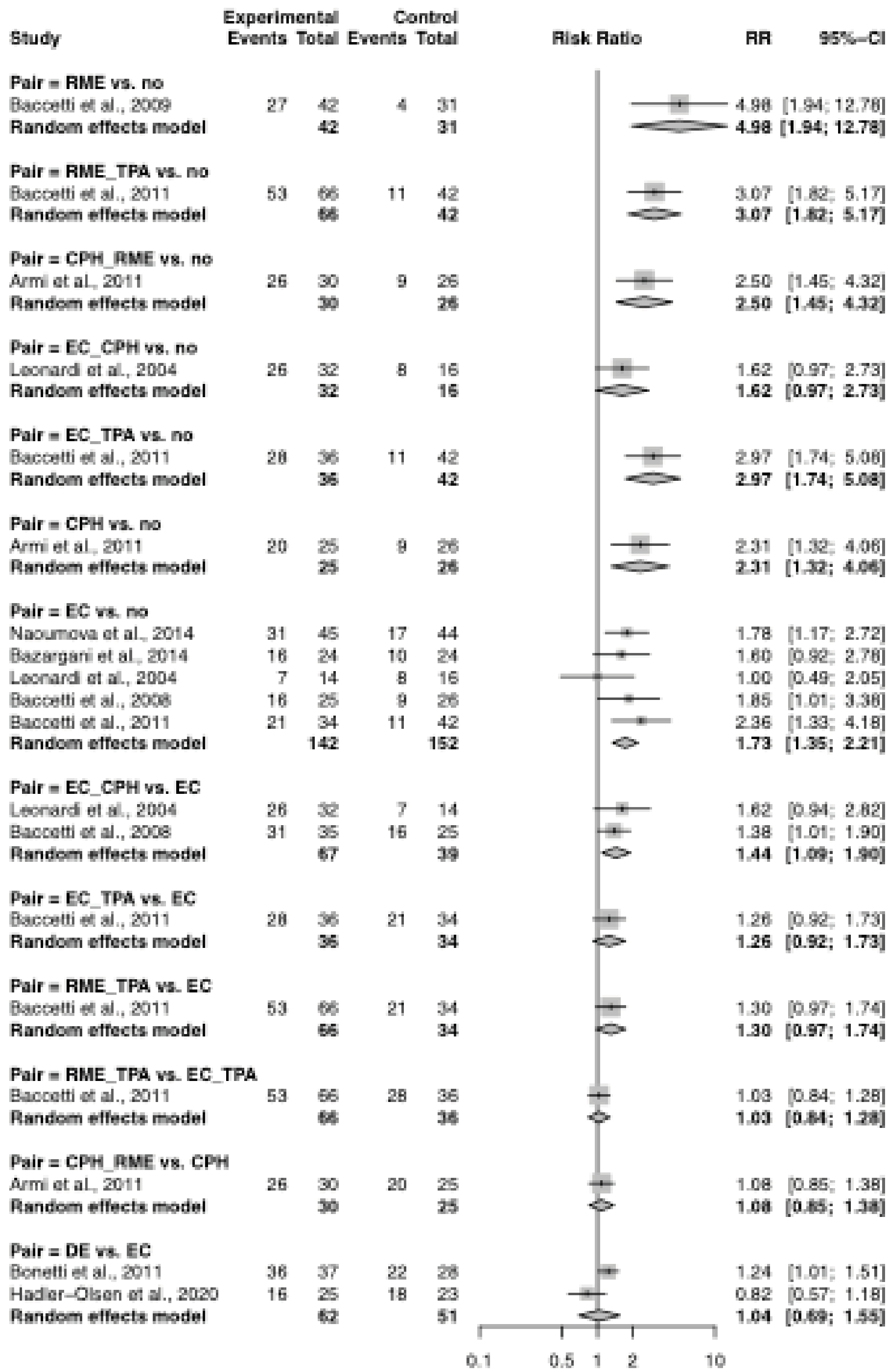


Figure 2. Network plot of treatment comparisons for Bayesian network meta-analysis. The size of the nodes (blue circles) corresponds to the sample size of the interventions. Comparisons are linked with a line, of which the thickness corresponds to the number of trials that assessed the comparison.



EC: extraction of canine(s); DE: double extraction – primary canine and first molar extraction; CPH: cervical pull headgear; EC+TPA: extraction of canine(s) *plus* transpalatal arch; EC+CPH: extraction of canine(s) *plus* cervical pull headgear; CPH+RME: cervical pull headgear *plus* rapid maxillary expansion; RME+TPA: rapid maxillary expansion *plus* transpalatal arch *plus* extraction of canine(s); RME: rapid maxillary expansion; NO: no intervention.

Figure 3. Forest plot of the traditional pairwise meta-analysis.

Table 5. Summary of results from network meta-analysis (on the lower triangle) and traditional pairwise meta-analysis (on the upper triangle) on clinical outcome.

RME								**4.98 (1.94, 12.78)**
2.15 (0.87, 7.37)	RME_TPA			1.03 (0.84, 1.28)			1.30 (0.97, 1.74)	**3.07 (1.82, 5.17)**
2.08 (0.72, 7.49)	0.97 (0.47, 1.77)	CPH_RME			1.08 (0.85, 1.38)			**2.50 (1.45, 4.32)**
2.22 (0.93, 7.69)	1.03 (0.72, 1.49)	1.07 (0.59, 2.16)	EC_CPH				**1.44 (1.09,1.90)**	**1.62 (0.97, 2.73)**
2.27 (0.91, 7.91)	1.04 (0.86, 1.33)	1.09 (0.58, 2.29)	1.01 (0.69, 1.5)	EC_TPA			1.26 (0.92, 1.73)	**2.97 (1.74, 5.08)**
2.27 (0.78, 8.48)	1.06 (0.51, 2.00)	1.09 (0.86, 1.46)	1.02 (0.5, 1.89)	1.01 (0.48, 1.93)	CPH			**2.31 (1.32, 4.06)**
2.68 (1.12, 9.35)	1.25 (0.9, 1.76)	1.30 (0.72, 2.63)	1.21 (0.91, 1.63)	1.19 (0.83, 1.73)	1.18 (0.64, 2.41)	DE	1.04 (0.69, 1.55)	
3.07 (1.31, 10.67)	**1.43 (1.09, 1.95)**	1.49 (0.84, 2.97)	**1.38 (1.11, 1.79)**	**1.36 (1.00, 1.90)**	1.35 (0.75, 2.7)	1.14 (0.98, 1.37)	EC	**1.73 (1.35, 2.21)**
5.36 (2.37, 18.12)	**2.51 (1.85, 3.55)**	**2.58 (1.59, 4.98)**	**2.42 (1.82, 3.3)**	**2.39 (1.7, 3.44)**	**2.35 (1.41, 4.6)**	**2 (1.50, 2.71)**	**1.75 (1.38, 2.24)**	NO

On the lower triangle, the column-defining treatment is compared with the row-defining treatment, and risk relatives (RRs) of < 1 favor the column-defining treatment. On the upper triangle, the row-defining treatment is compared with the column-defining treatment, and RRs of < 1 favor the row-defining treatment. To obtain RRs for comparisons in the opposite direction, reciprocals should be taken. Significant results are shown in boldface type. EC: extraction of primary canine; DE: double extraction – primary canine and first molar extraction; CPH: cervical pull headgear; EC_TPA: extraction of canine *plus* transpalatal arch; EC_CPH: extraction of canine *plus* cervical pull headgear; CPH_RME: cervical pull headgear *plus* rapid maxillary expansion; RME_TPA: rapid maxillary expansion *plus* transpalatal arch plus extraction of canines; RME: rapid maxillary expansion; NO: no intervention.

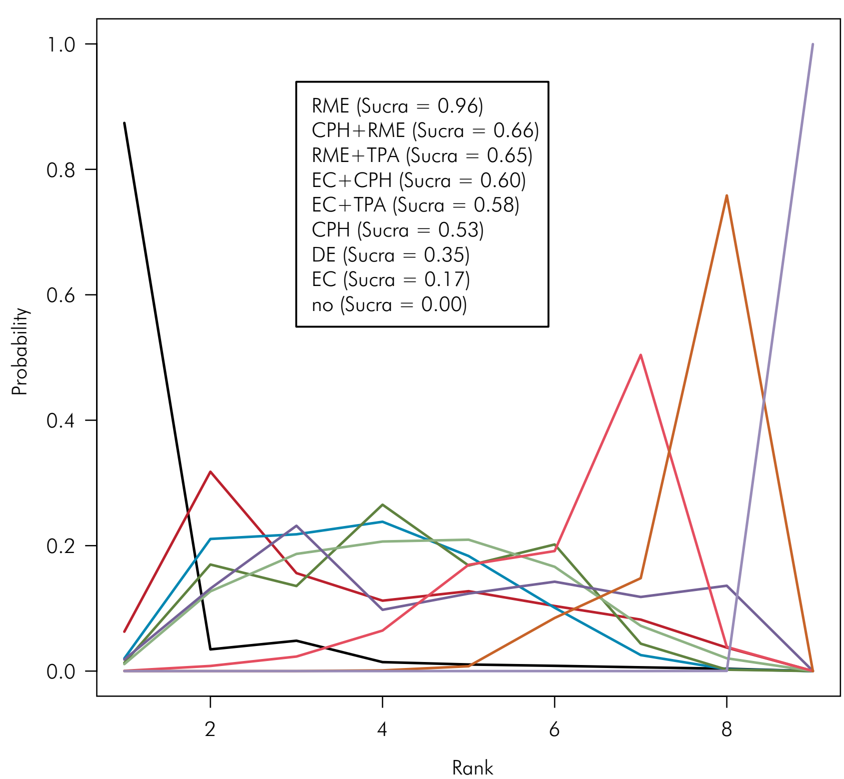


Figure 4. Rankogram and SUCRA for success rate of eruption of displaced permanent canines.

Table 6. Assessment of the certainty of evidence.

Comparison	Inform	Direct evidence		Indirect evidence		Network meta-analysis	
		RR (95%CI)	Certainty of evidence	RR (95%CI)	Certainty of evidence	RR (95%CI)	Certainty of evidence
RME	NO	4.98 (1.94–12.78)	Very low[1,3]	-	-	5.36 (2.37–18.12)	Very low
RME+TPA	NO	3.07 (1.82–5.17)	Low[1,2]	-	-	2.51 (1.85–3.55)	Low
CPH+RME	NO	2.50 (1.45–4.32)	Low[1,2]	-	-	2.58 (1.59–4.98)	Low
EC+CPH	NO	1.62(0.97–2.73)	Moderate[1]	-	-	2.42 (1.82–3.3)	Moderate
EC+TPA	NO	2.97 (1.74–5.08)	Low[1,2]	-	-	2.39 (1.70–3.44)	Low
CPH	NO	2.31(1.32–4.06)	Low[1,2]	-	-	2.35 (1.41–4.60)	Low
DE	NO	-	-	2.00 (1.5–2.71)	Low[2,4]	2.00 (1.5–2.71)	Low
EC	NO	1.73 (1.35–2.21)	Moderate[1]	-	-	1.75 (1.38–2.24)	Moderate
RME	EC	-	-	3.07 (1.31–10.67)	Very low[3,4]	3.07 (1.31–10.67)	Very low
RME+TPA	EC	1.30 (0.97–1.74)	Moderate[1]	-	-	1.43 (1.09–1.95)	Moderate
CPH+RME	EC	-	-	1.49 (0.84–2.97)	Low[2,4]	1.49 (0.84–2.97)	Low
EC+CPH	EC	1.44 (1.09–1.90)	Moderate[1]	-	-	1.38 (1.11–1.79)	Moderate
EC+TPA	EC	1.26 (0.92–1.73)	Moderate[1]	-	-	1.36 (1.00–1.9)	Moderate
CPH	EC	-	-	1.35 (0.75–2.70)	Low[2,4]	1.35 (0.75–2.70)	Low
DE	EC	1.04 (0.69–1.55)	Moderate[1]	-	-	1.14 (0.98–1–37)	Moderate
RME	DE	-	-	2.68 (1.12–9.35)	Very low[3,4]	2.68 (1.12–9.35)	Very low
RME+TPA	DE	-	-	1.25 (0.90–1.76)	Low[2,4]	1.25 (0.90–1.76)	Low
CPH+RME	DE	-	-	1.30 (0.72–2.65)	Low[2,4]	1.30 (0.72–2.65)	Low
EC+CPH	DE	-	-	1.21 (0.91–1.63)	Low[2,4]	1.21 (0.91–1.63)	Low
EC+TPA	DE	-	-	1.19 (0.83–1.73)	Low[2,4]	1.19 (0.83–1.73)	Low
CPH	DE	-	-	1.18 (0.64–2.41)	Low[2,4]	1.18 (0.64–2.41)	Low
RME	CPH	-	-	2.27 (0.78–8.48)	Very low[3,4]	2.27 (0.78–8.48)	Very low
RME+TPA	CPH	-	-	1.06 (0.51–2.00)	Low[2,4]	1.06 (0.51–2.00)	Low
CPH+RME	CPH	1.08 (0.85–1.38)	Moderate[1]	-	-	1.09 (0.86, 1.46)	Moderate
EC+CPH	CPH	-	-	1.02 (0.5–1.89)	Low[2,4]	1.02 (0.5–1.89)	Low
EC+TPA	CPH	-	-	1.01 (0.48–1.93)	Low[2,4]	1.01 (0.48–1.93)	Low
RME	EC+TPA	-	-	2.27 (0.91–7.91)	Very low[3,4]	2.27 (0.91–7.91)	Very low
RME+TPA	EC+TPA	1.03 (0.84–1.28)	Moderate[1]	-	-	1.04 (0.86–1,33)	Moderate
CPH+RME	EC+TPA	-	-	1.09 (0.58–2.29)	Low[2,4]	1.09 (0.58–2.29)	Low
EC+CPH	EC+TPA	-	-	1.01 (0.69–1.5)	Low[2,4]	1.01 (0.69–1.5)	Low
RME	EC+CPH	-	-	2.22 (0.93–7.69)	Very low[3,4]	2.22 (0.93–7.69)	Very low
RME+TPA	EC+CPH	-	-	1.03 (0.72–1.49)	Low[2,4]	1.03 (0.72–1.49)	Low
CPH+RME	EC+CPH	-	-	1.07 (0.59–2.16)	Low[2,4]	1.07 (0.59–2.16)	Low
RME	CPH+RME	-	-	2.08 (0.72–7.49)	Very low[3,4]	2.08 (0.72–7.49)	Very low
RME+TPA	CPH+RME	-	-	0.97 (0.47–1.77)	Low[2,4]	0.97 (0.47–1.77)	Low
RME	RME+TPA	-	-	2.15 (0.87–7.37)	Very low[3,4]	2.15 (0.87–7.37)	Very low

[1]downgraded by risk of bias; [2]downgraded by imprecision; [3]downgraded by severe imprecision; [4]downgraded by intransitivity (indirectness).
EC: extraction of canine(s); DE: double extraction: primary canine and first molar extraction; CPH: cervical pull headgear; EC+TPA: extraction of canine(s) *plus* transpalatal arch; EC+CPH: extraction of canine(s) *plus* cervical pull headgear; CPH+RME: cervical pull headgear *plus* rapid maxillary expansion; RME+TPA: rapid maxillary expansion *plus* transpalatal arch *plus* extraction of canine(s); RME: rapid maxillary expansion; NO: no intervention.

Discussion

Summary of evidence

In the clinical practice of Pediatric Dentistry and Orthodontics, professionals often work with deviations from path of eruption of permanent canines in growing patients. To the best of our knowledge, this is the first network meta-analysis that investigated if there is an effective interceptive treatment in the mixed dentition stage to prevent impaction of palatally displaced canines, considering successful eruption as the outcome. In the traditional pairwise meta-analysis from the present study, the success rate of eruption of palatally displaced canines was higher in subjects who received interceptive treatment than in those with no intervention, except when extraction of canine(s) *plus* use of cervical pull headgear was performed. There was no direct evidence for the comparison of double extraction (primary canine and primary molar) and no intervention. The network meta-analysis revealed that the proportion of erupted permanent canines was significantly higher for all interceptive treatments than for control (no interceptive treatment). The certainty of the evidence ranged from very low to moderate. These findings indicated that interceptive treatment can reduce the need for future surgery and orthodontic treatment of permanent teeth, thereby reducing the time and cost of the treatment and improving patients' self-esteem and satisfaction.[28]

One suggested intervention to prevent ectopic eruption of permanent canine is to extract the primary canine in the mixed dentition based on the assumption that its persistence would obstruct the growth of the permanent tooth. Interceptive extraction at a younger age, mesial canine crown position, and lower alpha angle are important variables that predict the spontaneous eruption of the palatally displaced canines.[29] Unilateral or bilateral extraction of primary canines was the most investigated treatment in the included studies. In the traditional pairwise meta-analysis, extraction of canine(s) could also be compared with double extraction, extraction of canine(s) *plus* use of transpalatal arch, extraction of canine(s) *plus* use of cervical pull headgear, and rapid maxillary expansion *plus* use of transpalatal arch *plus* extraction of canine(s). Extraction of canine(s) *plus* use of cervical pull headgear exhibited better results than extraction of canine(s) alone.

A reduction in the perimeter of the upper arch due to the mesial movement of the primary molars is more pronounced in older patients, which is accentuated by the eruption of the second permanent molars[6]. Hence, maintaining the perimeter of the upper arch or gaining space should be considered as part of the interceptive treatment. Extraction of primary canine(s) followed by the use of cervical pull headgear and then distalization of the buccal segments of the upper arch was the treatment protocol adopted in two studies,[8,22] and the certainty of the evidence for the aforementioned comparison was graded as moderate. The network meta-analysis revealed that the success rate of eruption of palatally displaced canines in subjects that underwent extraction of primary canines was lower than in those who underwent extraction of primary canine(s) along with rapid maxillary expansion *plus* use of transpalatal arch, use of cervical pull headgear or transpalatal arch, and rapid maxillary expansion alone. The certainty of the evidence was graded as moderate, except for the comparison with rapid maxillary expansion that was graded as very low.

The etiology of impacted palatally displaced canines is thought to be multifactorial with a strong genetic component associated with increased presence of other anomalies, such as tooth agenesis, and tooth size reduction, mainly regarding to the upper lateral incisor.[30] Although the maxillary arch width is not a primary contributory factor in the genesis of the palatally displaced canines, rapid maxillary expansion is performed on patients presenting impacted canines with mild tooth size arch length discrepancy.[24] In this case, the possible relationship between the improvement in the position of the palatally displaced canines and rapid maxillary expansion is questionable. It must be considered that a space between the canine crown and the dental follicle is needed and that the space for the canine in the dental arch must be about 1.5 times the canine mesiodistal width.[31] At the beginning of the mixed dentition stage, rapid maxillary expansion increases the transverse width of the basal bone, which would provide a new space scenario in the anterior region. Rapid maxillary expansion is known to cause a redirection of the teeth adjacent to the impacted canines,[32] which may justify the rapid maxillary expansion in cases without maxillary atresia or tooth crowding, considering the limitations of the technique in these cases.

In one included study,[24] rapid maxillary expansion was performed with the main objective of improving the eruption process of palatally displaced canines among other orthodontic indications (*e.g.*, mild-to-moderate crowding of the dental arches, tendency toward Class II malocclusion), being associated with the use of transpalatal arch and extraction of primary canines. The use of transpalatal arch *plus* extraction of primary canines aims to prevent the mesial movement of maxillary primary molars during the transition to permanent dentition[33]. Therefore, the combination of the use of the transpalatal arch and extraction of primary canines may explain the increase in the success rate of eruption of ectopic permanent canines in comparison with the single extraction of primary canines. Some factors are indicative of prognosis of impaction following interceptive treatment, including rapid maxillary expansion/use of transpalatal arch: pubertal cervical vertebral maturation stages *versus* pre-pubertal, more mesial sectors of the intraosseous displacement of the canine, greater alpha angles, and closure of the canine root apex.[24]

Direct comparisons between rapid maxillary expansion *plus* use of transpalatal arch *plus* extraction of canine(s*)* and extraction of canine(s) *plus* use of transpalatal arch, and cervical pull headgear *plus* rapid maxillary expansion and cervical pull headgear also could be made (moderate evidence certainty). No difference was observed between the approaches. Similar results were obtained from the network meta-analysis.

It has been suggested that the removal of the primary molar accelerates eruption and promotes uprighting of the first premolar, thus stimulating correct eruption of the permanent canine by providing more space for the physiologic uprighting of the tooth crown in a distal direction into the alveolar bone.[9] No statistically significant difference was observed between the extraction of primary canine(s) and the double extraction of primary canine and primary molar. In addition, the proportion of erupted permanent canines was higher in patients who underwent rapid maxillary expansion in the early mixed dentition stage than in those who underwent double extraction of primary canine and primary molar. However, the certainty of the evidence was very low.

Strengths, limitations, and future directions

Researchers wish to provide clinicians with the best choice among the available treatment options. Thus, we ranked the treatments using the Bayesian approach by calculating the SUCRA values. The SUCRA value is a single numeric representation of the overall ranking of the interceptive treatments indicating the probability of a treatment to be considered as the best. An overview of the SUCRA values demonstrated that the best interceptive treatment was rapid maxillary expansion. Rapid maxillary expansion combined with other interventions, such as use of cervical pull headgear and use of transpalatal arch *plus* extraction of canine(s), also exhibited high SUCRA values. It is important to highlight that the SUCRA value does not consider the magnitude of the differences in the effects of the treatments (*e.g.*, in a particular simulation, the first ranked treatment may be only slightly, or a great deal better than the second ranked treatment).[14] The use of cervical pull headgear *plus* rapid maxillary expansion ranked as the second best treatment. However, the network meta-analysis revealed that this approach was only better than no intervention. Considering the limited number of the studies and the very low and low risk of bias for most comparisons involving rapid maxillary expansion, the conclusion that this is the better approach seems unwise and impulsive. Moreover, rapid maxillary expansion could be considered in specific clinical situations as interceptive treatment during the early mixed dentition stage for patients with maxillary transverse deficiencies. No intervention and extraction of primary canine(s) were ranked as the first and second least-effective treatments, respectively. Therefore, no intervention is the worst decision adopted by clinicians or public health systems in the mixed dentition stage.

It is important to emphasize that the set of ratings arises from a small body of studies with limitations mainly due to bias arising from the randomization process. The follow-up periods also considerably ranged in the included studies. Because there was only one follow-up in each study, it was impossible to pool the results of the follow-up periods among the clinical trials. It is important to note that most effective treatments had longer follow-up periods (36–52 months). Many of the included studies were conducted by a single research team, which may limit the external validity of the results.

An intention-to-treat analysis is often recommended as the least-biased means to estimate the intervention effects in randomized clinical trials as it always evaluates the worst-case scenario. However, the primary studies only employed per-protocol analysis. Furthermore, some results were imprecise (wide confidence intervals), thus downgrading the certainty of the evidence. We encourage researchers to conduct high-quality, randomized clinical trials to draw more definitive conclusions about the research topic.

Conclusion

Based on the results reported, it is reasonable to conclude that no intervention in the mixed dentition stage is the worst choice for palatally displaced canines. However, we must bear in mind that this conclusion was based mostly on studies with a high risk of bias. Further studies are necessary to determine the better interceptive treatment in these cases.

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