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The timing of extraction of non-restorable first permanent molars: a systematic review

ABSTRACT

Aim To identify the ideal timing of first permanent molar extraction to reduce the future need for orthodontic treatment.

Materials and methods A computerised database and subsequent manual search was performed using Medline database, Embase and Ovid, covering the period from January 1946 to February 2013. Two reviewers (JE and ME) extracted the data independently and evaluated if the studies matched the inclusion criteria. Inclusion criteria were specification of the follow-up with clinical examination or analysis of models, specification of the chronological age or dental developmental stage at the time of extraction, no treatment in between, classification of the treatment result into perfect, good, average and poor. The search was limited to human studies and no language limitations were set.

Results The search strategy resulted in 18 full-text articles, of which 6 met the inclusion criteria. By pooling the data from maxillary sites, good to perfect clinical outcome was estimated in 72% (95% confidence interval 63%-82%). Extractions at the age of 8-10.5 years tended to show better spontaneous clinical outcomes compared to the other age groups. By pooling the data from mandibular sites, extractions performed at the age of 8-10.5 and 10.5-11.5 years showed significantly superior spontaneous clinical outcome with a probability of 50% and 59% likelihood, respectively, to achieve good to perfect clinical result

($p < 0.05$) compared to the other age groups (<8 years of age: 34%, >11.5 years of age: 44%).

Conclusion Prevention of complications after first permanent molars extractions is an important issue. The overall success rate of spontaneous clinical outcome for maxillary extraction of first permanent molars was superior to mandibular extraction. Extractions of mandibular first permanent molars should be performed between 8 and 11.5 years of age in order to achieve a good spontaneous clinical outcome. For the extraction in the maxilla, no firm conclusions concerning the ideal extraction timing could be drawn.

Keywords Extraction; First permanent molar; Systematic review; Timing.

Introduction

There are various clinical situations in which extraction of first permanent molars might be considered as the therapy of choice: extensive caries or restorations, endodontic and periodontal problems, periapical pathologies, hypomineralisation or hypoplasia [Sandler et al., 2000]. The first permanent molar is the tooth most prone to caries in the permanent dentition [Skeie et al., 2006] and more than 30% of the children over the age of 11 experience caries activity in these teeth [Lader et al., 2003]. Additionally, there is a relatively high incidence of hypomineralised first permanent molars (3.6-19.3%), often in combination with hypomineralised incisors [Koch et al., 1987; Alaluusua et al., 1996; Weerheijm et al., 2001; Leppäniemi et al., 2001; Jälevik et al., 2001]. Molars affected by molar-incisor hypomineralisation often show a disintegration of the enamel in their occlusal parts that might favour subsequent caries development [Jälevik and Norén, 2000]. Therefore, these teeth might need to be extensively restored soon after eruption [Leppäniemi et al., 2001; Alaluusua et al., 1996]. The treatment of these teeth is challenging both for the patient and for the dentist due to difficulties in achieving a sufficient anaesthesia [Jälevik and Möller, 2007]. Additionally, the retreatment rate, due to defective fillings and unpredictable behaviour of apparently intact opacities, is reportedly very high [Jälevik and Klingberg, 2002; Weerheijm, 2004]. Even breathing cold air and dental hygiene often provoke shooting pain of the affected teeth which lead to more dental fear and anxiety [Jälevik and Klingberg, 2002]. From this point of view and as a result of behaviour management problems, for children with severe molar-incisor hypomineralisation the extraction of compromised first permanent molars would probably be beneficial [Jälevik and Klingberg, 2002; Ong and Bleakley, 2010].

Conflicting opinions about the extraction of first

permanent molars can be found in the literature. Planned extraction of first permanent molars has the potential to self-correct space-discrepancies and prevent the development of malocclusions [Wilkinson, 1948; Thunold, 1970]. Despite skillful planning of the extractions, unsatisfactory results such as gaps, tipping and rotation of the neighbouring teeth cannot always be avoided and subsequent orthodontic treatment will be needed [Pfyffer, 1951]. Timing of first permanent molar removal is generally more critical in the mandible than in the maxilla [Gill et al., 2001]. Responsible for fewer problems in cases of first permanent molar extractions in the maxilla might be the differences in the eruption paths of second molars in the mandible and maxilla [Crabb and Rock, 1971]. In the maxilla the apex of the second molar is proportionally placed more mesial in relation to the crown. Therefore, the second molar in the maxilla will tilt forward during the eruption process after first permanent molar extraction into a satisfactory position in the arch [Crabb and Rock, 1971]. In the mandible the apex of the second molar is placed more distally and due to that the crown tends to tip further mesially as a bodily drift forward occurs [Crabb and Rock, 1971]. Even though prevention of complications in first permanent molar extraction cases is the most important issue, there is only little scientific evidence about the extraction timing in order to minimise unwanted negative effects. Therefore, the aim of the present systematic review is to identify the ideal timing of first permanent molar extraction to reduce the future need for orthodontic treatment.

Methods

Literature search

In order to identify relevant studies concerning the ideal timing of extraction of first permanent molars, a

computerised database search was conducted using Medline database, Embase and Ovid. The search covered the period from January 1946 to February 2013. The search strategy including the MeSH and text words applied in the Medline database search was “first[All Fields] AND permanent[All Fields] AND (“molar”[MeSH Terms] OR “molar”[All Fields]) AND extraction[All Fields]”. The term used in the Embase and Ovid database search was ‘first permanent molar extraction’.

Manual searches of the bibliographies of all full-text articles, selected from the electronic search, were additionally performed covering the period also before January 1946.

Inclusion and exclusion criteria

The search was limited to human studies and no language limitations were set. Randomised controlled clinical trials, prospective cohort studies, retrospective cohort studies, case series and case reports were included. Further inclusion criteria were specification of the follow-up with clinical examination or analysis of models, specification of the chronological age or dental developmental stage at the time of extraction, no treatment in between, classification of the treatment result into perfect, good, average and poor (Table 1). The exclusion criteria were literature reviews, orthodontic treatment, studies without subsequent clinical examination or analysis of casts in the follow-up and no specification of the chronological age or of the dental development stage at the time of extraction.

Study selection and quality assessment

Titles and abstracts were independently reviewed by two researchers (JE and ME) in a blinded standardised manner using a data-extraction form. Agreement whether the titles and abstracts were relevant to the topic of this review was reached. Any disagreement was resolved by consensus. Full-text articles of the potential studies were obtained and independently evaluated by the two researchers to find eligibility. Manual searches of the reference lists of all potentially eligible full-text articles were additionally performed. These additional relevant publications were added to the list of potential studies to be included in this review. The studies were graded with a score A-C according to pre-determined criteria (Table 2).

Inclusion criteria	Exclusion criteria
RCTs, prospective and retrospective cohort studies, case series, case reports	Animal studies
Follow-up with clinical examination or analysis of models; (after the eruption of all permanent teeth)	No follow-up
Specification of chronological age or dental developmental stage at the time of extraction	No specification of the timing of extraction
Definition of the treatment result: - Perfect: No tipping, no spacing - Good: Slight tipping or slight spacing - Average: Slight tipping and slight spacing - Poor: Severe tipping and severe spacing	Orthodontic treatment after extraction, before follow-up examination
No orthodontic treatment after extraction	Literature reviews

TABLE 1 Inclusion and exclusion criteria.

Grade A: High value of evidence	All inclusion criteria should be met. Randomized controlled clinical trials, prospective studies with a well-defined control group
Grade B: Moderate value of evidence	All inclusion criteria should be met. Retrospective cohort studies, retrospective case series
Grade C: Low value of evidence	Case reports, poorly defined patient material

TABLE 2 Criteria for grading of the assessed studies.

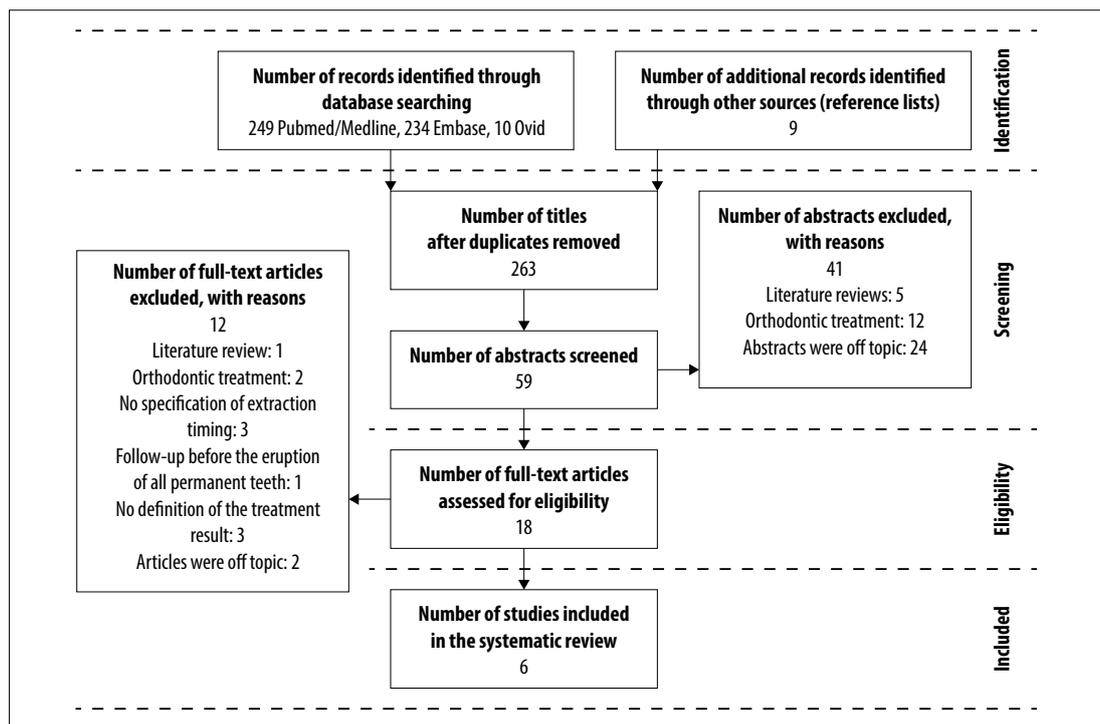


FIG. 1 PRISMA flow diagram of the study selection procedure.

Statistical analysis

Statistical analysis was carried out for the maxilla and the mandible and for each age group. The percentage and exact binomial 95% confidence interval (95% CI) of good or perfect result was calculated. The stratum specific precision (standard error) of the estimate was derived from the lower and upper limits of the 95% CIs, and the midpoint of the 95% CI was used as an estimate for performing the meta-analysis. This allowed including stratum estimates of 0% or 100% for which the approximate standard error formula can no longer be used. Summary estimates from meta-analysis were obtained by using DerSimonian and Laird estimates from random effects models as implemented by the “metan” command in Stata.

We assessed heterogeneity of the results across the studies using the I-squared statistics [Higgins and Thompson, 2002], which estimates the proportion of total variation that is due to heterogeneity, rather than chance. We compared results across the age at extraction using meta-regression [Harbord and Higgins, 2008]. Comparisons were done separately for the maxilla and the mandible.

Results

Figure 1 shows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram illustrating the study selection process [PRISMA, 2013]. Five hundred and two (502) references were retrieved from the database searches, among them 239 duplicate references (Fig. 1). Additional 204 references were

excluded by the two independent reviewers based on the titles as the studies were off the topic (Fig. 1). Forty-one (41) abstracts were excluded for various reasons (Fig. 1). Full-text articles of the remaining 18 papers were obtained. Of the 18 articles retrieved, 12 were excluded from the final analysis. The main reasons for exclusion (Table 3) were: literature reviews [Gill et al., 2001], orthodontic treatment after the extraction of first permanent molars [Seddon, 2004; Bayram et al., 2009], off topic articles [Shargill and Hutton, 2007; Ong and Bleakley, 2010], studies without any clinical examinations or analysis of

Authors, y	Reasons for exclusion
Abu Aihajja et al., 2000	No specification of extraction timing
Bayram et al., 2009	Orthodontic treatment
Caglaroglu et al., 2008	No definition of the treatment result
Gill et al., 2001	Literature review
Ong & Bleakley, 2010	Off topic article
Pfyffer, 1951	No specification of extraction timing
Richardson, 1979	No definition of the treatment result
Seddon, 2004	Orthodontic treatment
Shargill & Hutton, 2007	Off topic article
Telli & Aytan, 1989	Follow-up before the eruption of all permanent teeth
Thunold, 1970	No specification of extraction timing
Wilkinson, 1944	No definition of the treatment result

TABLE 3 Twelve full-text articles were excluded because of different reasons.

Authors, y	Quality grade	Number of teeth	Follow up	Age groups at FPM extraction			
				Result (perfect; good; average; poor; not specified)			
				<8 y (n)	8-10.5 y (n)	10.5-11.5 y (n)	>11.5 y (n)
Wilkinson, 1948	B	12	6.6 y	-	8 (5; 3; 0; 0; 0)	2 (2; 0; 0; 0; 0)	2 (2; 0; 0; 0; 0)
Jälevik & Möller, 2007	B	21	5.5 y	9 (7; 0; 0; 0; 2)	9 (9; 0; 0; 0; 0)	2 (2; 0; 0; 0; 0)	1 (1; 0; 0; 0; 0)
Rayman, 1979	C	2	4.5 y	-	2 (2; 0; 0; 0; 0)	-	-
Conway & Petrucci, 2005	C	3	0.7 y	-	-	1 (0; 0; 1; 0; 0)	2 (2; 0; 0; 0; 0)

TABLE 4 Summarised data of the four included studies evaluating the effect of first permanent molar extraction in the maxilla. n, number of extracted teeth; y, year; FPM, first permanent molar.

Reference	Quality grade	Number of teeth	Follow up	Age groups at FPM extraction			
				Result (perfect; good; average; poor; not specified)			
				<8 y (n)	8-10.5 y (n)	10.5-11.5 y (n)	>11.5 y (n)
Wilkinson, 1948	B	12	6.7 y	-	8 (3; 0; 5; 0; 0)	2 (1; 1; 0; 0; 0)	2 (2; 0; 0; 0; 0)
Thilander et al., 1963	B	207	6.6 y	42 (5; 1; 23; 13; 0)	69 (17; 16; 18; 18; 0)	44 (7; 14; 19; 4; 0)	52 (7; 11; 33; 1; 0)
Thilander et al., 1970	B	254	-	3 (0; 1; 0; 1; 1)	61 (17; 14; 11; 15; 4)	93 (48; 17; 12; 5; 11)	97 (23; 18; 16; 21; 19)
Jälevik & Möller, 2007	B	12	5.0 y	2 (2; 0; 0; 0; 0)	6 (5; 0; 1; 0; 0)	-	4 (4; 0; 0; 0; 0)
Rayman, 1979	C	2	4.5 y	-	-	-	2 (0; 2; 0; 0; 0)
Conway & Petrucci, 2005	C	2	1 y	-	-	1 (0; 0; 1; 0; 0)	1 (0; 0; 1; 0; 0)

TABLE 5 Summarised data of the six included studies evaluating the effect of first permanent molar extraction in the mandible. (n), number of extracted teeth; y, year; FPM, first permanent molar.

plaster casts [Richardson, 1979; Caglaroglu et al., 2008; Wilkinson, 1944], follow-up before the eruption of all permanent teeth [Telli and Aytan, 1989], no specifications of chronological age or dental developmental stage at extraction time and publications without relevant information on the entire patient cohort [Thunold, 1970; Abu Aihaija et al., 2000; Pfyffer, 1951]. There were no randomised controlled clinical trials available evaluating the timing of extraction of non-restorable first permanent molars. In the absence of randomised controlled clinical trials and prospective cohort studies, this systematic review was based on four retrospective cohort studies and two case reports (Table 4, 5).

Extractions of first permanent molars in the maxilla

Five studies provided data on the clinical outcome of maxillary first permanent molar extractions. One study [Thilander and Skagius, 1970] had to be excluded due to missing data on the extraction timing. In the remaining

four studies a total of 38 first permanent molars in the maxilla were extracted [Wilkinson, 1948; Jälevik and Möller, 2007; Rayman, 1979; Conway and Petrucci, 2005] (Table 4).

By meta-analysis, the overall spontaneous clinical outcome was estimated to be good to perfect in 72% (95% CI: 63%; 82%) of the cases (Table 6). By analysing the influence of extraction timing, extractions in the youngest age group obtained a good to perfect spontaneous clinical results in 69% of patients (Table 6). Extractions at the age of 8-10.5 years tended to present a better spontaneous clinical outcome with 80% (Table 6). Less satisfactory results were obtained if extractions were performed between 10.5 to 11.5 years of age (55%) and in patients older than 11.5 years (56%) (Table 5). Due to the small extraction site number, none of the age groups differed statistically significantly from each other. No strong heterogeneity of the results across the studies was observed. However, the small number of studies does not allow excluding substantial heterogeneity (upper limit of

Age Group	Maxilla			Mandible		
	Percentage of good or perfect result SE [95% CI] (n studies; n teeth)	I-squared estimates [95% CI]	p-value*	Percentage of good or perfect result [95% CI] SE (n studies; n teeth)	I-squared estimates [95% CI]	p-value*
Younger than 8 years	0.69 [0.40; 0.97] (1; 9)	n.a.**	-	0.34 [0.06; 0.62] (3; 47)	0.56 [0; 0.88]	-
8 to 10.5 years	0.81 [0.69; 0.92] (3; 19)	0 [0; 0.90]	0.481	0.50 [0.42; 0.58] (4; 144)	0 [0; 0.79]	0.031
10.5 to 11.5 years	0.55 [0.30; 0.81] (3; 5)	0 [0; 0.90]	0.525	0.59 [0.45; 0.73] (4; 140)	0.47 [0; 0.82]	0.006
Older than 11.5 years	0.56 [0.31; 0.82] (3; 5)	0 [0; 0.90]	0.546	0.44 [0.34; 0.53] (6; 158)	0.16 [0; 0.83]	0.081
SE over all age groups	0.72 [0.63; 0.82] (4; 38)	0 [0; 0.62]	-	0.48 [0.39; 0.58] (6; 489)	0.71 [0.52; 0.82]	-

n, number. * p-values from meta-regression comparing the respective age-group with the "before 8 years" age group in separate analyses for maxilla and mandible. ** n.a., not available

TABLE 6 Results from random effect meta-analysis: Percentage of good or perfect results. Summary estimates (SE), I-squared estimates and 95% confidence interval (CI) by age group for the maxilla and the mandible. Comparing the different age groups to the age group <8 years, significantly better results were achieved if the extraction in the mandible was performed between 8 and 11.5 years of age. No statistically significant differences could be found for the extraction in the maxilla.

the 95% CI for the I-squared statistics being 62% over all age groups).

Extractions of first permanent molars in the mandible

Six studies provided data fulfilling the inclusion criteria on spontaneous clinical outcome of first permanent molar extractions in the mandible, four retrospective cohort studies and two case reports [Wilkinson, 1948; Thilander et al., 1963; Thilander and Skagius, 1970; Jälevik and Möller, 2007; Rayman, 1979; Conway and Petrucci, 2005] (Table 5). A total of 489 first permanent molars in the mandible were extracted (Table 5).

By meta-analysis, the overall spontaneous clinical good to perfect outcome was estimated at 48% (95% CI: 39%; 58%) (Table 6). Analysing the influence of extraction timing, extractions performed between 8 and 11.5 years of age showed statistically significant better spontaneous clinical outcomes compared to the age group <8 years ($p_{8-10.5}=0.031$, $p_{10.5-11.5}=0.006$) (Table 6). A good to perfect spontaneous clinical outcome with a probability of 50% for extractions performed at the age between 8 and 10.5 years and 59% for those at the age between 10.5 and 11.5 years was shown, respectively (Table 6). Patients younger than 8 years or older than 11.5 years showed with 34% and 44% the lowest probability for a good to perfect spontaneous clinical outcome (Table 6). Results across the studies were moderately heterogeneous in the mandible.

Discussion

Extraction of first permanent molars might be considered as the therapy of choice in teeth with poor prognosis due to e.g. extensive caries or restorations, periodontal or endodontic problems, apical pathologies or molar-incisor hypomineralisation [Sandler et al.,

2000]. Although the extraction of first permanent molars might be clinically indicated, there is only little scientific evidence about the ideal extraction timing in order to minimise unwanted negative effects such as remaining space, tipping and/or rotation of the second permanent molar. Therefore, the purpose of this systematic review was to identify the ideal timing of first permanent molar extraction to reduce the future need for orthodontic treatment, i.e. the subsequent efforts to close remaining gaps, to derotate or to upright second permanent molars adjacent to the extraction site. No randomised controlled clinical trial concerning the first permanent molar extraction timing was available, neither for the maxilla nor for the mandible. In the absence of randomised controlled clinical trial and prospective cohort studies, only retrospective cohort studies and case reports were included in this systematic review. A substantial proportion of the published literature had to be excluded due to missing data regarding extraction timing or treatment results.

The computerised database search was conducted using Medline database, Embase and Ovid. Manual searches of the bibliographies of all full-text articles, selected from the electronic search, were additionally performed by both researchers (JE and ME). The searched databases showed a considerable overlap. There is a possible limitation as only three databases were included. Additional electronic databases might have retrieved further possibly eligible studies.

Out of the six studies fulfilling the inclusion criteria, only four met the inclusion criteria for the maxilla. Two studies [Thilander et al., 1963; Thilander and Skagius, 1970] had to be excluded due to missing data on the extraction timing. Due to the small number of included studies and the small number of extracted teeth, the present systematic review did not provide any significant evidence on the extraction timing in the maxilla.

Extractions of maxillary first permanent molars in

patients aged between 8 and 10.5 years tended to show a good to perfect clinical outcome in 81% of cases. The other age groups showed less satisfactory, but still good clinical outcomes. These findings corroborate the results of a study by Teo et al. [2013].

Six studies met the inclusion criteria for the mandible. The results of the present study reveal that extractions of mandibular first permanent molars in patients aged between 8 and 11.5 years showed significantly more spontaneous good to perfect clinical outcome in about 50 to 59% of the cases, compared to extractions at a younger or older age (34 to 44%). A study that was published after the database search of the present systematic review showed similar results: It was concluded that even when lower FPMs are extracted at the so-called optimum stage of root development, incomplete space closure, rotations and/or angulation of the second permanent molar or the second premolar will result [Teo et al., 2013].

The overall success rate of spontaneous clinical outcome after extraction of maxillary first permanent molars (72%) was superior compared to mandibular first permanent molar extraction (48%). The different eruption paths might be the respective reason. In the maxilla, the apex of the second molar is usually mesially placed in relation to the crown. During spontaneous space closure the crown will therefore tilt forward into a more satisfactory position in the arch with only little mesial rotation, tilting and/or spacing [Crabb and Rock, 1971]. The initial position of the lower second molar is less favorable. The apex is distally placed and the crown tends to tip further mesially as the second molar bodily drifts forward [Crabb and Rock, 1971]. The combination of crowding and presence of third molars may also have a positive effect on the spontaneous space closure in the mandible, but the tipping of the neighboring teeth might increase [Thilander and Skagius, 1970]. But those aspects have not been evaluated scientifically yet and were not subject of the present systematic review.

When planning the extraction of first permanent molars with poor prognosis, different variables - such as intramaxillary arch deviations, crowding, intermaxillary relationship, the skeletal pattern, dental age and the presence and condition of the other teeth - must be taken into account [Gill et al., 2001]. The Royal College of Surgeons of England developed guidelines for the extraction of first permanent molars in children in 2009 [Cobourne et al., 2009]:

Dental Class I malocclusion with lack of space: The extraction of a maxillary first permanent molar with a poor prognosis requires the balancing extraction of the contralateral tooth in order to prevent facial midline shifting [Williams and Gowans, 2003, Jälevik and Möller, 2007]. Similarly, the extraction of a mandibular first permanent molar often requires the balancing extraction of the contralateral one to avoid a midline deviation toward the extraction site [Williams and Gowans, 2003].

To prevent the elongation of the upper first permanent molars either extraction of these teeth must be taken into account or a vertical stop with a retainer or a removable appliance must be administered [Williams and Gowans, 2003]. However, uncompensated and unbalanced extractions may also lead to good spontaneous occlusal development [Jälevik and Möller, 2007].

Dental Class II malocclusion with lack of space: The extraction of a maxillary first permanent molar with a poor prognosis should be postponed until the eruption of the second molar, as the created extraction sites might be used in a later orthodontic treatment to camouflage the dental Class II and reduce the overjet [Crabb and Rock, 1971; Williams and Gowans, 2003]. No compensating extractions in the mandible are needed. If a mandibular first permanent molar needs to be extracted, vertical side effects of the opposing tooth are not expected as the upper first permanent molar is in occlusal contact with the lower second deciduous molar [Williams and Gowans, 2003]. To finally correct the dental Class II after mandibular first permanent molar extractions, a Class II growth modification appliance might be needed [Gill et al., 2001].

More evidence-based recommendations might be given in the future. The SIXES dental trial will investigate in a randomised controlled trial whether compensating extraction of upper first permanent molars should be carried out following the loss of lower first permanent molars [Innes et al., 2013]. Up to date, a close cooperation between the pediatric dentist and the orthodontist is recommended in any case, as it is difficult to consider all variables and to make the right decision [Williams and Gowans, 2003].

The limitations of the present systematic review basically result from the only low to moderate level of evidence of the included studies as only retrospective cohort studies and case reports fulfilled the inclusion criteria and the results may have to be regarded with caution. Nevertheless, the effect of extraction timing on the spontaneous space closure is indisputable and documents that it might be detrimental. Another limitation is the lack of information about the variables that might have influenced the migration of teeth after extraction, e.g. crowding or malocclusion. Additionally, the correlation of the dental and chronological age with the amount of tipping and/or rotation of the adjacent molars and premolars must be assessed to achieve a greater degree of conclusiveness.

A favourable effect of first permanent molar extractions is an earlier development and better positioning of the third molar [Jälevik and Möller, 2007; Ay et al., 2006; Yavuz et al., 2006; Livas et al., 2011]. The results of the analysis demonstrate that even when considering an ideal timing for the extraction of first permanent molars, tipping and remaining gaps might not be prevented entirely. Temporary anchorage devices, e.g. miniscrews, miniplates or palatal implants, however, might help to

handle the respective side effects of early first permanent molar extraction. Nevertheless, early extractions are indicated as the subsequent time orthodontic treatment might be significantly reduced by spontaneous space closure. For space closure palatal implants in the maxilla and miniplates in the mandible might be recommended [Schatzle et al., 2009].

Based on these findings and the fact that compensating and balanced extractions have to be considered, we advocate first permanent molar extractions only to be carried out in collaboration between both the paediatric dentist and the orthodontist.

Conclusion

Extractions of maxillary first permanent molars performed between the age of 8 and 10.5 years tended to show more favourable clinical results. The analysed data on mandibular first permanent molar extraction demonstrated that extractions performed in patients aged between 8 and 11.5 years provided significantly better results than in younger or older patients. However, the extraction of first permanent molars should always be planned in collaboration with an orthodontist. Different intramaxillary and intermaxillary variables have to be taken into account and balancing and/or compensating extractions must be considered. It is recommended to extract first permanent molars before the eruption of the second permanent molar to reduce unwanted side effects and to achieve the best clinical outcome.

Conflict of interest

The authors declare that they have no conflict of interest.

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