Journal of Dentistry 111 (2021) 103733

Contents lists available at ScienceDirect

Journal of Dentistry

journal homepage: www.elsevier.com/locate/jdent

Proximal caries infiltration – Pragmatic RCT with 4 years of follow-up

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ARTICLE INFO

Keywords:
Caries infiltration
Infiltrant
Resin
Caries lesion
RCT
Pragmatic study

ABSTRACT

Objectives: Efficacy of proximal caries infiltration to arrest lesion progression has been shown in university settings, but only once in a practice-based pragmatic design with a follow-up of 18 months. The aim of this randomized split-mouth placebo-controlled study was to follow-up this cohort for 3 years and those with high caries risk for 4 years.

Methods: Originally, in 87 children and young adults pairs of 238 proximal caries lesions, radiographically extending into inner half of enamel (E2) or outer third of dentin (D1), were randomly allocated to two groups: infiltration (Icon; DMG) or mock (control) treatment by five dentists in four private practices. All subjects received risk-related instructions for diet, flossing and fluoridation. The primary outcome was radiographic lesion progression (pairwise comparison) evaluated by two evaluators independently being blinded to treatment allocation.

Results: After 36 months [mean (SD): 1152 (166) days] 165 lesion pairs in 64 patients as well as after 48 months [mean (SD): 1496 (121) days] 71 lesion pairs in 20 high caries risk patients could be re-evaluated clinically as well as radiographically using individualized bitewing holders as at baseline. No adverse events could be observed. After 36 months, progression was recorded in 23/165 test (14%) and 64/165 control lesions (39%) [McNemar/Obuchowski test; $p<0.001$; relative risk reduction (CI95%): 64 (45–77%)]. After 48 months lesion progression was recorded in 13/71 test (18%) and 34/71 control lesions (48%) [$p = 0.003$; relative risk reduction (CI95%): 62 (34–78%)] of high caries risk patients.

Conclusions: It can be concluded that also in a practice-setting proximal caries infiltration is more efficacious in reducing lesion progression compared with individualized non-invasive measures alone over a period of four years.

1. Introduction

For non-cavitated proximal lesions extending radiographically from inner enamel to the outer third of dentin, noninvasive (preventive) interventions, such as fluoridation or flossing alone, have been reported to be less efficacious and cost-effective compared with resin infiltration [1]. By infiltrated resin diffusion of acids from biofilms seems considerably be hampered [2, 3]. However, apart from the first short-term evaluation of the cohort presented previously [4], where patients were recruited and treated in a private practice setting, efficacy data mainly derive from University studies.

These randomized clinical studies have either been conducted in the primary or permanent dentition. For the latter, relative risk reductions (RRR) of 65–90% in favor for the infiltration technique compared with varying self-applied noninvasive interventions alone after a maximum period of three years have been reported [5-10]. Overall efficacy of proximal infiltration has been corroborated by a meta-analysis, which underlined that long-term results are missing [11]. In a recent smaller efficacy study in 17 patients followed for 84 months, 2/22 infiltrated lesions (9%) compared with 10/22 control lesions (45%) progressed ($p = 0.018$). RRR for proximal infiltration in relation to mock treatment was 80% (CI 95%= 19–95%) [12].

For the study sample presented here, a significantly higher proportion of control lesions (58/186; 31%) compared with infiltrated ones (10/186; 5%) progressed (RRR: 83%) after 18 months follow-up. A subset analysis revealed similar progression rates for both groups of individuals either with lower or higher caries risk [4]. The aim of the current evaluation was to assess the clinical efficacy of resin infiltration

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https://doi.org/10.1016/j.jdent.2021.103733
Received 8 May 2021; Received in revised form 11 June 2021; Accepted 14 June 2021
Available online 24 June 2021

of proximal caries lesions after a mean follow-up period of three years and for those individuals with higher caries risk also after four years. The new aspects were the larger sample size compared to previous studies with 3 years' observation time, the pragmatic (practice-based) design as well as the discrimination between lower and higher caries risk patients. It was hypothesized that the radiographic lesion progression of infiltrated proximal lesions is significantly reduced compared with those of non-infiltrated control lesions (mock treatment).

2. Materials & methods

The study design was a split-mouth placebo-controlled (mock treatment) randomized clinical trial. Ethical approval was given by the local institutional board at Christian-Albrechts-Universität zu Kiel (A 122/10). Due to the start of enrolment in 2009, registration in a clinical trial register was not mandatory and also not considered as necessary retrospectively. The methodology was set-up according to our previous university study [10] and reported largely for the first follow-up period of the present cohort [4]. However, for better intelligibility we repeat important methodological aspects.

2.1. Screening and baseline evaluation

Eight presumably preventively oriented dentists one of the authors knew from either continuing education ($n = 4$) or personally ($n = 4$) were approached. Five of these working in four practices located in Bad Bramstedt, Hamburg, Heiligenhaus and Norden in Germany agreed to participate. After screening (visual-tactile caries assessment) their patients for general eligibility (suspicion of proximal caries lesions), a pair of standardized digital bitewing radiographs was taken using individualized holders in order to avoid overlapping depiction of proximal surfaces. Inclusion criteria were: two or more non-cavitated proximal caries lesions with radiolucencies involving the inner half of enamel (E2) up to the outer third of dentin (D1), age: 13–40 years, given informed consent. Exclusion criteria were pregnancy, current participation in another study, incapability of contracting, and institutionalized patients. Radiographs were sent anonymously to the principal investigator (HML) and scored accordingly: (E1) radiolucency confined to the outer half of enamel, (E2) radiolucency involving the inner half of enamel, (D1) radiolucency in the outer third of dentin, (D2) radiolucency in the middle third of dentin, (D3) radiolucency in the inner third of dentin (modified from [13]).

From 100 screened subjects 87 patients with 238 lesion pairs met the inclusion criteria, of whose 79 gave their informed consent. Additionally, two patients were excluded due to cavitated lesions, resulting in 39 patients with lower and 38 higher caries risk, who had 1–2 and ≥3 lesion pairs, respectively, that were included in the study (details see participant and lesion pair flow charts, Fig. 1). If deeper lesions (D2/D3) were detected advice for invasive treatment was given. Pairs of lesions were created, if possible, firstly with the same stage and secondly being located at contralateral tooth sites. One caries lesion of each pair was allocated to the infiltration and another one to the mock treatment using randomly permuted blocks generated by a third person and sealed in envelopes. If a control lesion was situated adjacent to a test lesion this pair dropped out. Papilla bleeding was recorded after probing with a blunt probe and cavitations were checked by using a thin probe after placing the separating wedge (Icon; DMG, Hamburg, Germany). Caries risk of treated patients was assessed at baseline and at follow-ups

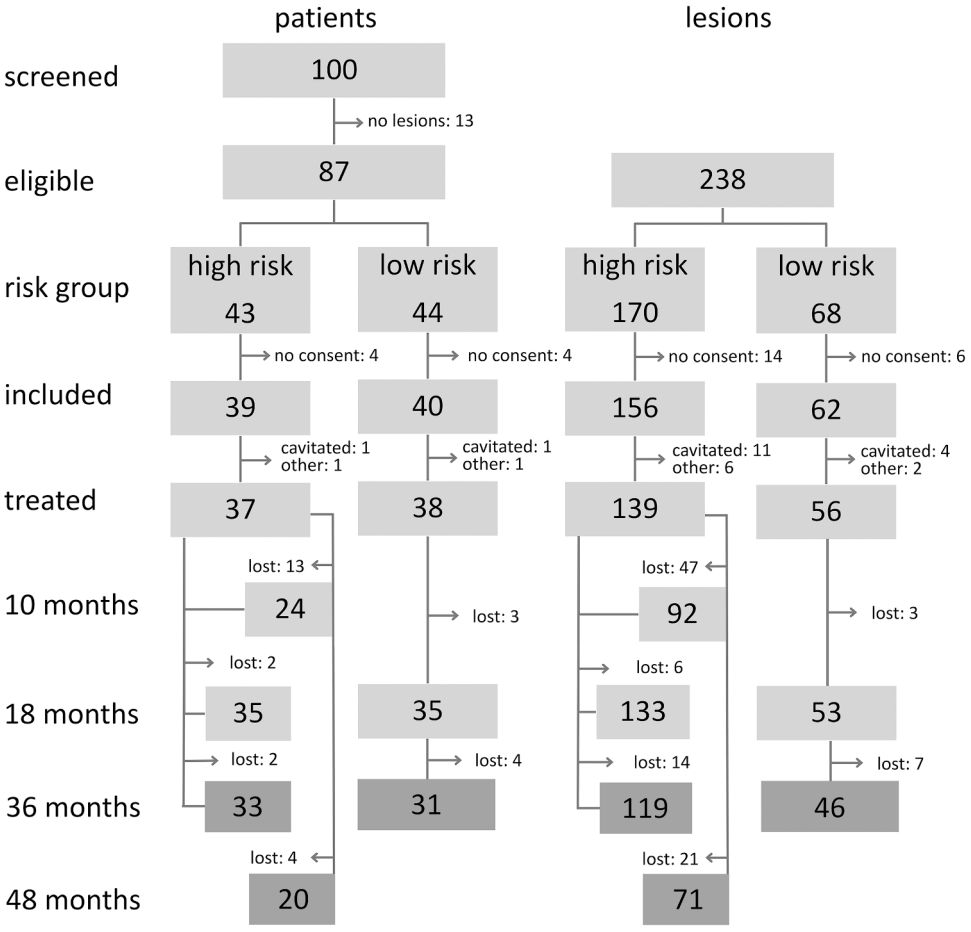

Fig. 1. Flow diagram for patients (left) and lesion pairs (right) for high-risk and low-risk patients. Other: treatment >300 days after the x-ray (2P/7LP) or no lesion at baseline (1P/1LP) (false inclusion).

according to modified Cariogram [14] with no salivary tests being performed (i.e. mutans streptococci count, buffer capacity and stimulated flow rate).

2.2. Treatment

Infiltration (test) and mock treatment (control) were both performed using rubber dam as described previously [10], with the exception to our previous University-based single operator study that the commercialized product for caries infiltration (Icon) and not a pre-product was used. Patients were blinded to lesion allocation throughout the whole study, since a mock treatment was performed on the control lesions. Dentists were trained in a one-day course including treatments on simulation units. Nonetheless, we did not check adhesion of the dentists to the protocol. Patients were instructed for risk-related, self-applied non-invasive interventions (i.e. flossing, fluoride application) for all teeth. General oral hygiene education and dietary advice was given as well as individualized fluoride varnish applications as decided by the respective dentist on a basis of a 6-month recall. A booklet was handed to the patients to inform potential other dentists about the participation in the study and identification of selected teeth for the study.

2.3. Follow-up examinations

After approximately 36 (all; Oct 2013 until Aug 2015) [mean (SD): 1152 (166) days] as well as after 48 months (only participants ≥3 lesion pairs in the study = higher caries risk; Nov 2014 until Nov 2015) [mean (SD): 1496 (121) days] clinical follow-up examinations were performed by the respective dentist, who was not blinded with regard to treatment allocation of teeth at baseline, but most probably unaware of the treatment he performed years before. Patients were interviewed again for possible adverse events. Standardized bitewing radiographs were obtained using the same individualized holders for each patient again. The endpoint was lesion progression as assessed in pairwise reading of radiographs by two independent, calibrated (by HML each time) evaluators (KB and SP at 36 months as well as RJW and CM at 48 months) blinded to treatment allocation (the infiltrant is not radiopaque). The stage of the baseline lesion stage was taken from the previous blind consensus evaluation at 18 months (performed by KB and SP). At each follow-up period firstly, the respective radiographic score (secondary endpoint) was documented, secondly, any progression including those within a stage (primary endpoint) was evaluated by pair-wise comparison of radiographs, both without knowing any previous results. In case of differing interpretation between both examiners at each evaluation period, a consensus score was agreed by looking at the pairs of x-rays again. If a lesion had progressed radiographically up to D2 or D3 restorative treatment was suggested to the respective dentist.

2.4. Statistical analysis

Sample size was calculated on the basis of data from a previous split-mouth study on infiltrating proximal caries lesions [10]. We expected a 2.5. times higher progression rate for the infiltrated lesions as before due to the different population and the pragmatic study design. Assuming a difference of proportions of 17.6% between both groups and a proportion of discordant pairs of 60% with $\alpha = 0.05$ and $1\text{-}\beta = 0.9$ a total of 162 lesion pairs was calculated to be needed to find significant differences using McNemar test. With an estimated drop-out of 30%, at least 231 lesion pairs had to be included in the study. Inter-rater reliability (kappa values) had been reported as being fair (0.4) for pair-wise comparison for the 36-month evaluation [15] and moderate (0.66) for the 48 months evaluation. In numbers, at 36 and 48 months 292/330 and 118/142 lesions, respectively, were judged with agreement. Analysis of the data was performed using an extension of the McNemar test for clustered matched-pair data [16]. The primary outcome variable was also compared between high and low risk patients (only 36 months) and E2/D1 lesions (only pairs of the same stage included) as well as between dentists (Fisher test). Statistical analysis was conducted using Python 3.7.6 (www.python.org) and R 4.0.3 (www.R-project.org).

3. Results

As reported before, recruitment of 100 patients was performed from July 2010 - August 2011. Eighty-seven patients (P) [238 lesion pairs (LP)] were eligible (≥2 proximal lesions E2/D1), but only 79 (218 LP) gave their written informed consent and were treated. Of those, two patients (4 LP) plus 11 LP in another 9 patients showed cavitations at the initial treatment in either one of the allocated lesions and had to be excluded from the analysis. Two other patients were either treated >300 days after the baseline-x-ray (2P/7LP) had been taken or had no lesion at baseline (1P/1LP) as analysed by the independent evaluators. Thus, 75 patients with 195 LP were included as correctly treated patients. For subgroup analysis caries risk was defined for those patients (P) having only 1 or 2 as well as those with ≥3 lesion pairs (LP) included in the study as low (LR; $n = 38$ P/56 LP = 1.4 LP/P) and high (HR; $n = 37$ P/139 LP = 3.8 LP/P) caries risk patients, respectively (Fig. 1& Table 1). After 36 months [mean (SD): 1152 (166) days] 89% HR-patients and 79% LR-patients, having 119/139 LP and 46/56 LP, respectively, could be re-evaluated clinically as well as radiographically using individualized bitewing holders as at baseline. After 48 months [mean (SD): 1496 (121) days], 57% of high-risk (HR) patients with 71/139 LP could be followed (Fig. 1).

Patients did not report any complaints or adverse events. For those 63 patients evaluated after 36 months mean age was 23±6 years with 58% female subjects at baseline. Mean DMFT was 6.0 ± 4.3 and according to modified Cariogram the chance to avoid new caries lesions (CAC = 1-caries risk) was 54%±16%. Those not included but with baseline data ($n = 7$ of 17 available) showed similar data [age: 26±5 years; 50% female; DMFT 5.6 ± 2.9, CAC 69%±11%]. All characteristics are given in Table 1 showing a higher DMFT for HR- compared with LR-patients at baseline that was even more increased for HR at 36 and 48 months.

After 36 months for the primary outcome [pair-wise comparison of radiographs (PW)] progression rates of 64/165 (39%) and 23/165 (14%) [RRR (CI95%): 64 (45–77)%] could be observed for control and test lesions, respectively ($p<0.001$). Slight, but not significant differences in RRR were calculated between HR- [56 (29–73)%] and LR-patients [81 (49–93)%]. The differences in progression rates between control and test lesions were significant in both risk groups [HR: 43/119 (36%) and 19/119 (16%), $p = 0.002$; LR: 21/46 (46%) and 4/46 (9%), $p<0.001$], respectively.

Progression rates for E2 (only pairs with the same stages were included) were 38% and 5% ($p<0.001$) for control and test lesions, respectively (Fig. 2). For D1 respective rates were 40% and 21%

Table 1
General data of the patients.

	36 months all	high-risk #	low-risk #	48 months high-risk #
$N_{(followed)}$	64	33	31	20
age_{BL}	23 ± 6	22 ± 6	23 ± 6	22 ± 5
female	58%	45%	63%	56%
$DMFT_{BL}$	6.0 ± 4.3	6.6 ± 4.4	5.0 ± 4.3	5.7 ± 3.1
$DMFT^{1}_{10m/18m}$	6.6 ± 4.4[2]	7.7 ± 4.3[2]	5.4 ± 4.4[2]	6.3 ± 4.5[1]
$DMFT_{36m/48m}$	10.0 ± 5.3	11.4 ± 5.2	8.3 ± 5.1	11.7 ± 5.5
CAC_{BL}	54% ±16%	51% ±13%	56% ±18%	52% ±13%
$CAC_{36m/48m}$	53% ±12%	49% ±12%	58% ±10%	55% ±11%
lesions in study	330	238	92	142

When applicable SD is given. Abbreviations: BL = Baseline; CAC = chance to avoid new caries lesions. [1 + 2] DMFT values at the respective earlier follow-up of those individuals who were followed-up later.

[#] Caries risk groups were defined by the number of included lesion pairs; 1 or 2 (low) and ≥3 lesion pairs (high).

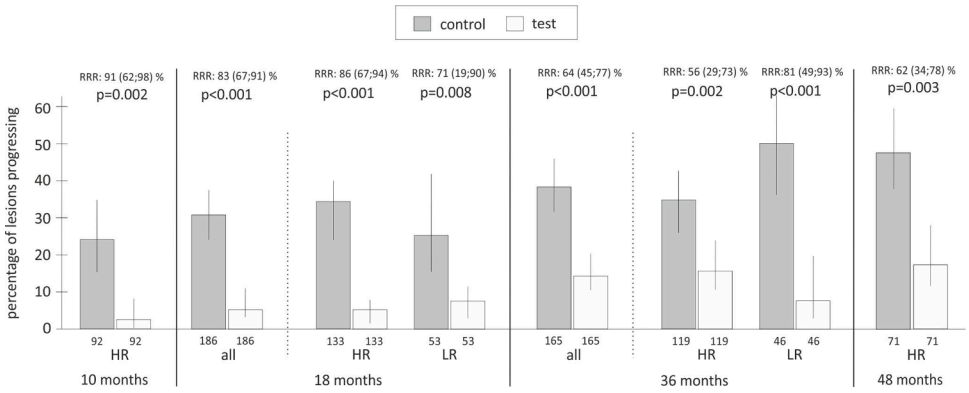

Fig. 2. Percentages of caries lesions progressing after 36 (high-risk, low-risk and all patients) as well 48 months (only high-risk) that were either infiltrated (test) or not (control) evaluated by pairwise comparison (error bars = 95% confidence intervals; p values by McNemar/Obuchowski test for clustered data; RRR= relative risk reduction for the test in relation to the control treatment with 95% confidence intervals). Data after 10 and 18 months are taken from our previous publication for better understanding [4].

(p<0.01). RRR (95% CI) was higher for E2 [87 (64–95)%] compared with D1 lesions [48 (6–71)%].

After 48 months 34/71 (48%) control and 13/71 (18%) test (p = 0.003) lesions progressed [RRR: 62 (34–78)%] (Fig. 2). Here, higher RRR for E2 [81 (24–96)%] compared with D1 lesions [44 (5–68)%] were observed, as well. Progression rates for E2 and D1 were 31% and 6% (p<0.01), and 72% and 40% (p>0.05) for control and test lesions, respectively. Notably, for both follow-up periods the lesion progression rates between dentists/practices were non-significant (p>0.05, Fisher test).

After 36 months secondary analysis with respect to lesion stage revealed rates of lesions staged deeper of 38/165 (23%) and 11/165 (7%) [RRR: 71 (45–85)%] for the control and the test lesions (p<0.001), respectively. The following rates for E2 (control 28% / test 5%; p<0.001) and D1 lesions (19%/9%, p>0.05) as well as for HR- (22%/7%; p = 0.002) and LR-patients (26%/7%; p = 0.014) (Fig. 2) were observed. After 48 months progression rates to a deeper one were 20/71 (28%) for control and 10/71 (14%) for test lesions (p = 0.03). Progression rates for lesion stage for E2 (p = 0.014) and D1 (p>0.05) were 31% and 6%, and 72% and 40% for control and test lesions, respectively (Fig. 3).

4. Discussion

The present study corroborates that resin infiltration of proximal caries lesions confined radiographically around the enamel dentinal junction is highly efficacious also after 4-year follow-up in a private practice-setting using a pragmatic study design. Individuals with higher caries risk showed slightly lower relative risk reductions compared with those at lower risk, but for both caries infiltration decreased the risk of lesion progression significantly compared with individualized non-invasive measures alone.

Several general methodological issues have been discussed in our previous papers [4, 9, 10, 12]; e.g. choice of radiological method (pairwise comparison of original images contra digital subtraction radiography) either with the use of individualizable bitewing holders or

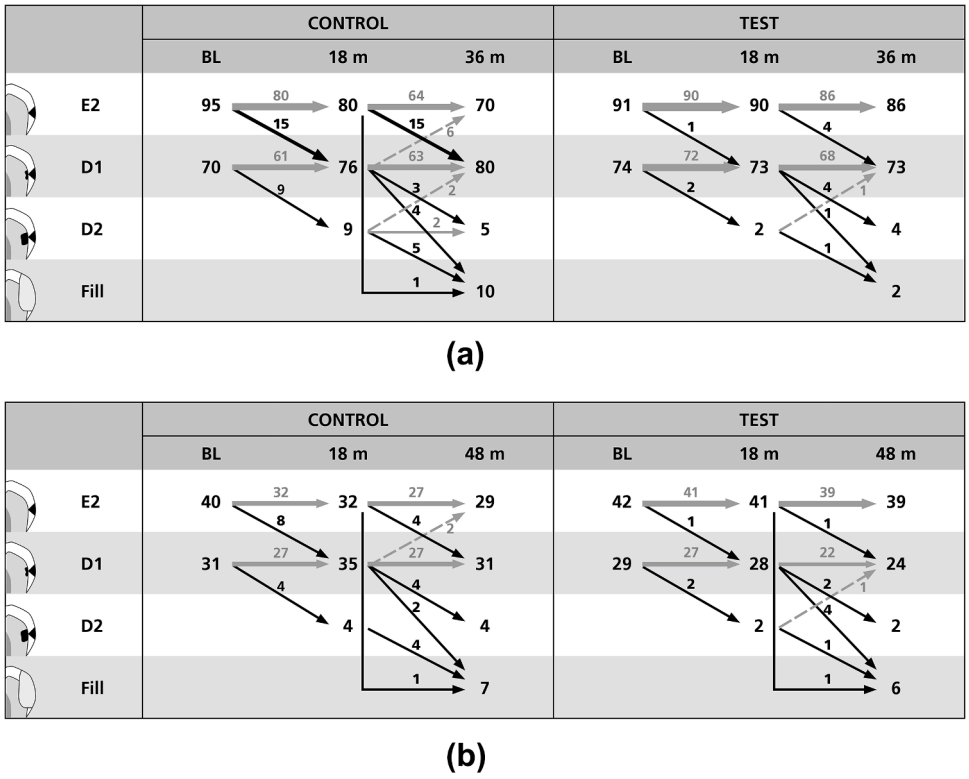

Fig. 3. a&b: Changes in caries stage [modified from [13]] from baseline to 18 and 36 months (A; all patients) and up to 48 months (B; only high risk patients). Control lesions showed significantly higher progression rates than infiltrated ones (36 months: p<0.001; 48 months: p = 0.03; McNemar/Obuchowski).

not. Moreover, representativeness of the population studied, choice and monitoring of preventive (non-invasive) measures, the impact of the preventive philosophies of participating private practitioners, and the interpretation of results in comparison with previous studies with respect to varying application times as well as choice of pre-product or original product have been critically assessed, as well. As it could be expected the drop-out rate was slightly increased compared with the previous evaluation of this cohort after shorter follow-up [4], but still being at an acceptable rate.

In contrast to our University-based study [12], DMFT increased significantly from 18 to 36 months (all individuals) as well as 10 to 48 months (high-risk only). The effect was more pronounced for the high-risk caries individuals showing significantly higher DMFT values than those rated as low-risk caries patients. However, neither increase of DMFT nor change of modified assessment of caries risk [14] were capable to discriminate individuals with high rates from those with very low/none rates of progressing lesions being included in the study. This result corroborates the need to find better predictive models for caries.

Nonetheless, as postulated in the first follow-up of this cohort, efficacy was now higher in low compared with high-risk individuals, which has previously not been the case [4]. Moreover, D1 lesions seem to profit more than E2, but also with a higher risk of failures. Also clustering effects of several progressing lesions in a minority of the studied individuals could again be observed, which supports the observation that caries incidence in younger adults is restricted to a subset of individuals, but does not develop and progress in all who have experienced caries during adolescence [17]. All in all, cost-effectiveness of proximal caries infiltration seems to be given for both risk groups [18], but higher in D1 lesions compared with E2.

For the permanent dentition three studies with 3-year observation time [6-8, 19] as well as our University-based with 7 years of follow-up [12] have been published so far. In our University-based study, progression rates for control and infiltrated lesions were 42/4% after 3 years [9] and 45/9% after 7 years [12] being considerably lower [70/32%; [8]] and similar [48/14%; [6]] as reported by others. For the study sample presented here, 31/5% control and test lesions, respectively, progressed after 18 months follow-up. The current data revealed slightly higher progression rates of 39/14% after three years; for both groups being in a similar range as reported previoulsy [6, 9]. After 4 years follow-up for the high-risk only, progression rates were considerably higher for both control (48%) and test lesions (18%) compared with the 10-months evaluation (24/2%) but still in the same range as reported in the other studies. As discussed before [4, 12], one reason for differences between study outcomes might have been the higher proportions of D1 in comparison to E2 test lesions (roughly 60% [8] compared to 40% in this as well as in our University-based study). D1 lesions are more likely to be cavitated [13, 17] that might be diagnostically overlooked [20]. Irrespectively of cavitation D1 lesions seem to progress at a higher rate and speed compared with E2 lesions [17], resulting in lower RRR for D1 compared with E2 due to the higher relative progression rate for non-invasively treated control lesions. Other factors in the previous studies for higher and lower progression rates, respectively, were either inclusion of 5% cavitated lesions [8] or of only 10% D1 lesions, but 25% E1 lesions, which seems rather an early stage for micro-invasive intervention [7]. In general, it can be assumed that caries infiltration technique could correctly be applied by various dentists, which is reflected by their similar outcomes, for all caries risk statuses of patients. Proximal sealing has also been proposed and reported to be efficacious [8]. Besides practical challenges as separation for several days and a more sophisticated application procedure, lower efficacy data compared with proximal infiltration derived from less clinical studies have been reported in recent reviews [21, 22].

It can be concluded that the results of this randomized clinical trial in a pragmatic setting corroborate those of several mainly University-based studies most of them with shorter follow-up periods on the efficacy caries infiltration in non-cavitated proximal lesions extending radiographically into inner half of enamel up to outer third of dentin. The rather low failure rates and relative risk reductions of infiltrated lesions compared with lesions treated by individualized non-invasive measures alone should encourage to choose infiltration as the first option prior to a minimal invasive restoration which can still be performed as a second step in case of infiltration failure.

CRediT author statement

HML: Contributed to conception, design, data acquisition and interpretation, and drafted the manuscript

JK: Contributed to data analyses, and critically revised the manuscript

KB, CM, AW: Contributed to data acquisition and interpretation, and critically revised the manuscript

RJW, SP: Contributed to conception, design, data acquisition and interpretation, and critically revised the manuscript

All authors gave their final approval and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

The study was sponsored by DMG, Hamburg the producer of a commercial kit for caries infiltration. The funder had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript, but monitored the study documentation.

HML and SP are appointed as inventors US and European patents for an infiltration technique for dental caries lesions, held by Charité-Universitätsmedizin Berlin, and receive royalties from DMG. All other authors declare no conflicts of interest.

Acknowledgments

The authors thank the participating dentists A. Balbach, Dr. A. Fernandez-Tenllado, Dr. T. Kaiser, Dr. C. Kaiser, Dr. A. Schult.

References

[1] F. Schwendicke, H. Meyer-Lueckel, M. Stolpe, C.E. Dorfer, S. Paris, Costs and effectiveness of treatment alternatives for proximal caries lesions, PLoS ONE 9 (1) (2014) e86992, https://doi.org/10.1371/journal.pone.0086992.

[2] H. Meyer-Lueckel, S. Paris, Improved resin infiltration of natural caries lesions, J. Dent. Res. 87 (12) (2008) 1112–1116.

[3] S. Paris, H. Meyer-Lueckel, Inhibtion of caries progression by resin infiltration in situ, Caries Res. 44 (1) (2010) 47–54.

[4] H. Meyer-Lueckel, A. Balbach, C. Schikowsky, K. Bitter, S. Paris, Pragmatic RCT on the efficacy of proximal caries infiltration, J. Dent. Res. 95 (5) (2016) 531–536, https://doi.org/10.1177/0022034516629116.

[5] S. Arslan, M.H. Kaplan, The effect of resin infiltration on the progression of proximal caries lesions: a randomized clinical trial, Med. Princ. Pract. 29 (3) (2020) 238–243, https://doi.org/10.1159/000503053.

[6] M.C. Peters, A.R. Hopkins Jr., L. Zhu, Q. Yu, Efficacy of proximal resin infiltration on caries inhibition: results from a 3-year randomized controlled clinical trial, J. Dent. Res. 98 (13) (2019) 1497–1502, https://doi.org/10.1177/0022034519876853.

[7] R.A. Arthur, J.E. Zenkner, J.C. d'Ornellas Pereira Junior, R.T. Correia, L.S. Alves, M. Maltz, Proximal carious lesions infiltration-a 3-year follow-up study of a randomized controlled clinical trial, Clin. Oral Investig. 22 (1) (2018) 469–474, https://doi.org/10.1007/s00784-017-2135-x.

[8] S. Martignon, K.R. Ekstrand, J. Gomez, J.S. Lara, A. Cortes, Infiltrating/sealing proximal caries lesions: a 3-year randomized clinical trial, J. Dent. Res. 91 (3) (2012) 288–292, https://doi.org/10.1177/0022034511435328.

[9] H. Meyer-Lueckel, K. Bitter, S. Paris, Randomized controlled clinical trial on proximal caries infiltration: three-year follow-up, Caries Res. 46 (6) (2012) 544–548, https://doi.org/10.1159/000341807.

[10] S. Paris, W. Hopfenmuller, H. Meyer-Lueckel, Resin infiltration of caries lesions: an efficacy randomized trial, J. Dent. Res. 89 (8) (2010) 823–826, https://doi.org/10.1177/0022034510369289.

[11] M. Dorri, S.M. Dunne, T. Walsh, F. Schwendicke, Micro-invasive interventions for managing proximal dental decay in primary and permanent teeth, Cochrane Database Syst. Rev. (11) (2015), CD010431, https://doi.org/10.1002/14651858.CD010431.pub2.

[12] S. Paris, K. Bitter, J. Krois, H. Meyer-Lueckel, Seven-year-efficacy of proximal caries infiltration - Randomized clinical trial, J. Dent. 93 (2020), 103277, https://doi.org/10.1016/j.jdent.2020.103277.
[13] H. Hintze, A. Wenzel, B. Danielsen, Behaviour of approximal carious lesions assessed by clinical examination after tooth separation and radiography: a 2.5-year longitudinal study in young adults, Caries Res. 33 (6) (1999) 415–422.
[14] D. Bratthall, G. Hansel Petersson, Cariogram–a multifactorial risk assessment model for a multifactorial disease, Community Dent, Oral Epidemiol. 33 (4) (2005) 256–264, https://doi.org/10.1111/j.1600-0528.2005.00233.x.
[15] J.R. Landis, G.G. Koch, The measurement of observer agreement for categorical data, Biometrics 33 (1) (1977) 159–174.
[16] N.A. Obuchowski, On the comparison of correlated proportions for clustered data, Stat Med 17 (13) (1998) 1495–1507, https://doi.org/10.1002/(Sici)1097-0258(19980715)17:13<1495::Aid-Sim863>3.0.Co;2-I.
[17] I. Mejare, H. Stenlund, C. Zelezny-Holmlund, Caries incidence and lesion progression from adolescence to young adulthood: a prospective 15-year cohort study in Sweden, Caries Res. 38 (2) (2004) 130–141, https://doi.org/10.1159/000075937.
[18] F. Schwendicke, S. Paris, M. Stolpe, Detection and treatment of proximal caries lesions: milieu-specific cost-effectiveness analysis, J. Dent. 43 (6) (2015) 647–655, https://doi.org/10.1016/j.jdent.2015.03.009.
[19] S. Martignon, K.R. Ekstrand, R. Ellwood, Efficacy of sealing proximal early active lesions: an 18-month clinical study evaluated by conventional and subtraction radiography, Caries Res. 40 (4) (2006) 382–388, https://doi.org/10.1159/000094282.
[20] S. Paris, F. Schwendicke, V. Soviero, H. Meyer-Lueckel, Accuracy of tactile assessment in order to detect proximal cavitation of caries lesions in vitro, Clin. Oral Invest. 23 (7) (2019) 2907–2912, https://doi.org/10.1007/s00784-018-02794-9.
[21] Y. Chen, D. Chen, H. Lin, Infiltration and sealing for managing non-cavitated proximal lesions: a systematic review and meta-analysis, BMC Oral Health 21 (1) (2021) 13, https://doi.org/10.1186/s12903-020-01364-4.
[22] J. Krois, G. Gostemeyer, S. Reda, F. Schwendicke, Sealing or infiltrating proximal carious lesions, J. Dent. 74 (2018) 15–22, https://doi.org/10.1016/j.jdent.2018.04.026.