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Is there a temporal trend in the reported treatment efficacy of periodontal regeneration? A meta-analysis of randomized-controlled trials

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Abstract

Background/Aim: The aim of study was to conduct a meta-analysis to investigate whether or not there was a temporal trend in the treatment efficacy reported in the randomized-controlled trials (RCTs) on guided tissue regeneration (GTR) or enamel matrix protein derivatives (EMD) in the treatment of infrabony defects.

Material and Methods: The treatment outcomes were changes in probing pocket depth (PPD) and clinical attachment level (CAL). Weighted multilevel and ordinary regression analyses were performed to test the temporal relationship between treatment effect difference or treatment effectiveness and publication years.

Results: For PPD reduction, non-significant positive relationships were found in the treatment effect difference or treatment effect of both GTR and flap operation. For CAL gain, a small positive relationship was found in the treatment effect difference, but a significant positive trend in the treatment effect of flap operation was found. No significant temporal trend was found in the treatment effect difference for EMD.

Conclusions: There was no evidence to support or refute a temporal trend in the treatment effect of regenerative procedures, but a positive trend was observed in the control group. These results suggest that only RCTs should be included in the meta-analysis, as the treatment effect of the control group may not be constant.

Key words: enamel matrix protein derivatives; guided tissue regeneration; meta-analysis; randomized-controlled trials

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In the last two decades, barrier membranes to promote periodontal regeneration have been widely used to treat periodontal lesions such as furcation involvement (Jepsen et al. 2002) and infrabony defects (Needleman et al. 2006). Various non-resorbable and resorbable membranes have become available in the market, and their efficacy has been tested in many clinical studies (Cortellini & Tonetti 2000, Murphy & Gunsolley 2003, Needleman et al. 2006). In the last decade, the introduction of enamel matrix protein derivatives (EMD) into the treatment of periodontal lesions has led periodontal regeneration into a new era of tissue engineering (Esposito et al. 2005). These techniques and products have been received with great enthusiasm, and this has been manifested in the numerous publications in the literature (Cortellini & Tonetti 2000, Kalpitis & Ruben 2002, Esposito et al. 2005, Needleman et al. 2006).

Although guided tissue regeneration (GTR) and EMD initially gave rise to a great hope and expectation in achieving regeneration of lost periodontal tissue due to encouraging results from several case reports, recently published

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systematic reviews of randomized-controlled trials (RCTs) (Esposito et al. 2005, Needleman et al. 2006), however, showed that in general GTR and EMD achieved only modestly better results compared with traditional flap operations. Furthermore, they raised the issue of whether these expensive treatments are actually cost-effective (Baelum & Lopez 2003, Lopez & Baelum 2003, Esposito et al. 2005, Needleman et al. 2006).

In medical research on the treatment of human immunodeficiency infection, it has been shown that there is a time lag in the publication of negative findings (Ioannidis et al. 1998). Other studies have shown that the effectiveness of medical therapies reported in the RCTs and meta-analyses seems to decrease over time (Jennions & Moller 2002, Gehr et al. 2006), and this phenomenon has been termed ''fading of reported effectiveness'' (Gehr et al. 2006), i.e. a negative temporal trend. In contrast, it has been suggested in the periodontal literature that the results from GTR on the treatment of infrabony defects seemed to be improving with the increasing experience of clinicians (Cortellini & Tonetti 2000), i.e. a positive temporal trend.

New medical interventions start to become widely adopted after greater efficacy is shown in the clinical studies first published in the academic journals. If there is a negative trend, the biases that give rise to the observed negative trend need to be carefully investigated. This also raises a critical issue regarding when there is enough evidence to justify the use of these new interventions (Gehr et al. 2006). On the other hand, if there is a positive trend as suggested by some literature (Cortellini & Tonetti 2000), perhaps researchers should not be discouraged by the initially small, non-significant benefits of new interventions. Rather, they should be aware of the learning curve with some new interventions and should be encouraged to undertake more RCTs to further evaluate the treatment outcomes and appreciate whether treatment effectiveness may improve over time, as the practical knowledge of implementing these new interventions accumulates (Polanyi 1958, Kidwell et al. 2001). The aim of this study was therefore to conduct a meta-analysis to investigate whether or not there was a temporal trend in the treatment efficacy reported in the RCTs on GTR or EMD in the treatment of infrabony defects.

Material and Methods

Literature search

We adopted similar selection criteria for inclusion of RCTs in this meta-analysis as reported by two recently updated Cochrane reviews on the efficacy of EMD or GTR in the treatment of periodontal infrabony lesions (Esposito et al. 2005, Needleman et al. 2006). In the studies included, the test treatment was always compared with flap operation as the control group. In short, for studies to be included, the patients/defects needed to be randomly allocated to either the test or control group, and treatment outcomes were measured at baseline and at least 12 months after the treatments. Studies that included treatment of shallow infrabony defects <4 mm were excluded. Also, studies that used barrier membranes or EMD in conjunction with bone grafting or other growth factors were excluded. As the literature search in those systematic reviews was conducted on the databases up to April 2004 and May 2005, respectively, an electronic search of the database MEDLINE and EMBASE from the year 2004 to 2006 was undertaken to identify studies that compared the treatment effects of GTR or EMD with the flap operation. Electronic searches of the journal websites of four major periodontal journals, *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Journal of Periodontal Research* and *International Journal of Periodontics and Restorative Dentistry*, were also undertaken. The key words used for electronic search were ''guided tissue regeneration'', ''GTR'', ''emdogain'' and ''enamel matrix proteins''.

Meta-analyses

The treatment outcomes used in the meta-analysis were changes in probing pocket depth (PPD) and clinical attachment level (CAL) recorded at least 12 months after the lesions were treated by periodontal regeneration. Changes in the bone level were not measured clinically or radiographically in this study due to few studies reporting these findings. Where a trial reported both results at the 12-month follow-up and longer than that, the results with the longest follow-up time were used in our meta-analysis. In making our decision of which follow-up interval to use, we took the view that what really matters to patients and clinicians are the long-term results, and we therefore opted to use the longest follow-up in our meta-analysis. When a study had more than one treatment group, which were each treated with different types of resorbable or non-resorbable barrier membranes, the study was considered as a separate study in the data entry according to the membrane types. Further analyses were also undertaken by including the types of membranes as a covariate. The relevant data were then extracted into a spreadsheet for further statistical analyses.

To account for the multiple study entries from one publication (due to more than one treatment group) and multiple studies from one research group, a weighted two-level multilevel regression analysis was performed to test the temporal relationship between treatment effect difference or treatment effectiveness and publication years by taking into consideration the sample sizes of each study. When analysing the temporal trend for the control group, studies with more than one treatment group but with only one control group were still treated as one study. For any study with multiple treatments where each treatment group had its own control group, the control groups were treated as multiple studies at the lower level in the multilevel analysis. The treatment effect difference was defined as the difference in PPD reduction (or CAL gain) between periodontal regeneration (GTR or EMD) and the control (traditional flap operation). The treatment effect was defined as the change in PPD (or CAL) from baseline values before and after the surgical interventions of periodontal regeneration (GTR or EMD) or flap operation. The research hypothesis of this study was that there was no temporal trend in the relationship between treatment effect difference or treatment effect, and publication years, i.e. the true treatment effect difference between regenerative surgery and flap operation or treatment effect of these interventions remained constant over the years. The alternative hypothesis was that because the introduction of GTR and EMD, the reported treatment effect difference or treatment effect decreased significantly as suggested by the previous studies in medical research (i.e. negative temporal trend) or increased significantly as suggested by the periodontal literature (i.e. positive temporal trend). The multilevel regression analyses were performed using statistical software MLwiN 2.02

(©Multilevel Models Project Institute of Education, London, UK, 2005) with the estimation procedure of restricted iterative generalized least squares (equivalent to restricted maximum likelihood). The estimation of multilevel analysis was an iterative process of maximizing the likelihood function. When changes in the estimates between the consecutive steps were very small, the statistical package would then consider that the estimation procedure had converged and the iteration process had finished. However, due to small sample sizes, the estimation procedure sometimes might not converge (Hox 2002). When multilevel regression failed to achieve convergence, ordinary regression analyses were performed using function lm for linear regression with the argument ''weights'' in the statistical software R 2.5.1 (R foundation for statistical computing 2007).

Results

Four RCTs that were additional to those in the Cochrane review by Needleman et al. (2006) comparing GTR with flap operation were identified (Tonetti et al. 2004, Vouros et al. 2004, Aimetti et al. 2005, Camargo et al. 2005), and two more RCTs comparing EMD with flap operation were identified since 2004 (Francetti et al. 2005, Bokan et al. 2006). However, two of the studies (Tonetti et al. 2004, Camargo et al. 2005) were then excluded, because bone grafts were also used in conjunction with GTR. Another study was also excluded, because the treated defects were wide and shallow (Aimetti et al. 2005). A summary of the studies included is given in Tables 1 and 2. As treatment groups with uses of different barrier membranes within one RCT were considered as separate studies, in

Table 1. Summary of studies included in the meta-analysis for the comparison between guided tissue regeneration (GTR) and periodontal flap operation

Study	Tx effect difference	Tx effect of GTR	Tx effect of flap operation	Year	Membrane type	Number of test group	Number of control group	Total number
PPD								
Blumenthal & Steinberg (1990)	0.48	1.99	1.51	1990	R	10	10	20
Pritlove-Carson et al. (1995)	1.23	2.67	1.44	1995	NR	20	20	40
Cortellini et al. (1995)	1.7	6.3	4.6	1995	NR	15	15	30
Cortellini et al. (1995)	0.9	5.5	4.6	1995	NR	15	15	30
Mora et al. (1996)	1.8	5.35	3.55	1996	NR	10	10	20
Cortellini et al. (1996)	1.6	5.9	4.3	1996	NR	12	12	24
Cortellini et al. (1996)	1.2	5.5	4.3	1996	R	12	12	24
Mayfield et al. (1998)	0.1	2.9	2.8	1998	R	20	18	38
Cortellini et al. (1998)	1.3	4.3	3	1998	R	23	23	46
Pontoriero et al. (1999)	1.1	4.8	3.7	1999	R	10	10	20
Pontoriero et al. (1999)	0.9	4.1	3.2	1999	R	10	10	20
Pontoriero et al. (1999)	1.4	4.7	3.3	1999	NR	10	10	20
Silvestri et al. (2000)	4.5	5.7	1.2	2000	NR	10	10	20
Ratka-Kruger et al. (2000)	0.23	3.71	3.48	2000	R	11	11	22
Cortellini et al. (2001)	0.8	4.4	3.6	2001	R	55	54	109
Sculean et al. (2001)	0.5	4.2	3.7	2001	R	14	14	28
Zucchelli et al. (2002)	2	6.5	4.5	2002	NR	30	30	60
Loos et al. (2002)	0.14	2.41	2.27	2002	R	25	25	50
Vouros et al. (2004)	2.58	5.09	2.51	2004	R	14	12	26
Vouros et al. (2004)	2.22	4.72	2.5	2004	R	14	12	26
CAL								
Blumenthal & Steinberg (1990)	0.42	1.17	0.75	1990	R	10	10	20
Chung et al. (1990)	1.27	0.56	−0.71	1990	R	10	10	20
Cortellini et al. (1995)	2.9	5.3	2.4	1995	NR	15	15	30
Pritlove-Carson et al. (1995)	0.02	0.55	0.53	1995	NR	20	20	40
Cortellini et al. (1995)	2.6	5	2.4	1995	NR	15	15	30
Cortellini et al. (1996)	2.9	5.2	2.3	1996	NR	12	12	24
Mora et al. (1996)	1.3	3.85	2.55	1996	NR	10	10	20
Cortellini et al. (1996)	2.3	4.6	2.3	1996	R	12	12	24
Mayfield et al. (1998)	0.2	1.5	1.3	1998	R	20	18	38
Tonetti et al. (1998)	0.86	3.04	2.18	1998	R	69	67	136
Cortellini et al. (1998)	1.4	3	1.6	1998	R	23	23	46
Pontoriero et al. (1999)	1.6	3.4	1.8	1999	R	10	10	20
Pontoriero et al. (1999)	1.4	3	1.6	1999	R	10	10	20
Pontoriero et al. (1999)	1.1	2.9	1.8	1999	NR	10	10	20
Silvestri et al. (2000)	3.6	4.8	1.2	2000	NR	10	10	20
Ratka-Kruger et al. (2000)	0.18	3.13	2.95	2000	R	11	11	22
Cortellini et al. (2001)	0.9	3.5	2.6	2001	R	55	54	109
Sculean et al. (2001)	1.4	3.1	1.7	2001	R	14	14	28
Zucchelli et al. (2002)	2.3	4.8	2.5	2002	NR	30	30	60
Loos et al. (2002)	0.11	1.4	1.29	2002	R	25	25	50
Vouros et al. (2004)	1.86	4.4	2.54	2004	R	14	12	26
Vouros et al. (2004)	1.28	3.72	2.44	2004	R	14	12	26

CAL, clinical attachment level; PPD, probing pocket depth; Tx, treatment; membrane type – R, resorbable; NR, non-resorbable.

total, there were 20 studies reporting PPD and 22 reporting CAL as the outcomes for GTR at the lower level. At the upper level, the three treatment groups from one study (Pontoriero et al. 1999) were treated as one group, and the studies by the same first author (Cortellini) were treated as one group in the multilevel analysis. Ten studies reporting PPD and CAL for EMD were analysed using weighted ordinary regression, although two studies were from the same research group. This is because the convergence could not be achieved in multilevel analysis probably due to the small sample size.

GTR

Table 3 and Fig. 1 summarized the results from the weighted two-level multilevel analysis. In terms of PPD reduction, a small non-significant positive relationship was observed between treatment difference and publication years (0.067 mm per year, 95% confidence interval = [− 0.125, 0.259]; $p = 0.454$). A slightly greater positive temporal relationship was observed in treatment effectiveness for the GTR group (0.122 mm per year [− 0.094, 0.338]; $p = 0.237$), and a small non-significant positive temporal relationship was found for the control group who had the conventional flap surgery (0.029 mm per year [− 0.134, 0.192]; $p = 0.7$). When membrane type was included as a covariate, RCTs using non-resorbable membranes achieved a

Table 2. Summary of studies included in the meta-analysis for the comparison between enamel matrix proteins derivatives (EMD) and periodontal flap operation

Study	Tx effect difference	Tx effect of EMD	Tx effect of flap operation	Year	Number of test group	Number of control group	Total number
PPD							
Heijl et al. (1997)	0.7	3.1	2.4	1997	31	31	62
Pontoriero et al. (1999)	0.7	4.4	3.7	1999	10	10	20
Okuda et al. (2000)	0.78	3	2.22	2000	16	16	32
Silvestri et al. (2000)	3.5	4.8	1.3	2000	10	10	20
Tonetti et al. (2002)	0.6	3.9	3.3	2002	83	83	166
Zucchelli et al. (2002)	0.6	5.1	4.5	2002	30	30	60
Francetti et al. (2004)	1.86	4.86	3	2004	12	12	24
Francetti et al. (2005)	0.51	4.02	3.51	2004	64	46	110
Rösing et al. (2005)	− 0.22	4.17	4.39	2005	14	14	28
Bokan et al. (2006)	0.1	3.9	3.8	2006	19	18	37
CAL							
Heijl et al. (1997)	0.60	2.20	1.60	1997	31	31	62
Pontoriero et al. (1999)	1.10	3.00	1.90	1999	10	10	20
Silvestri et al. (2000)	3.30	4.50	1.20	2000	10	10	20
Okuda et al. (2000)	0.89	1.72	0.83	2000	16	16	32
Zucchelli et al. (2002)	1.60	4.20	2.60	2002	30	30	60
Tonetti et al. (2002)	0.60	3.10	2.50	2002	83	83	166
Francetti et al. (2004)	1.58	4.29	2.71	2004	12	12	24
Rösing et al. (2005)	− 0.15	2.01	2.16	2005	14	14	28
Francetti et al. (2005)	1.00	3.51	2.51	2005	64	46	110
Bokan et al. (2006)	1.60	3.70	2.10	2006	19	18	37

CAL, clinical attachment level; PPD, probing pocket depth; Tx, treatment.

Table 3. Results of weighted multilevel regression analysis for the temporal trend in the treatment effect difference between guided tissue regeneration (GTR) and flap operation or the treatment effect of GTR and flap operation

	Tx effect difference			Tx effect			Control effect		
	value	SE	*p*-value	value	SE	*p*-value	value	SE	*p*-value
PPD									
Fixed effects									
Intercept	− 133.614	171.364	0.454	− 239.265	193.146	0.244	− 54.205	145.579	0.717
Year	0.067	0.086	0.454	0.122	0.097	0.237	0.029	0.073	0.700
Random effects									
Level-2 variance	1.133	0.453	0.031	1.547	0.615	0.031	1.074	0.400	0.023
Level-1 variance	3.462	2.182	0.144	1.957	1.242	0.146	0.269	0.222	0.253
− 2log likelihood	50.76			55.862			41.325		
CAL									
Fixed effects									
Intercept	− 25.172	126.919	0.846	− 259.226	170.341	0.154	− 249.65	86.407	0.014
Year	0.013	0.064	0.842	0.131	0.085	0.149	0.126	0.043	0.013
Random effects									
Level-2 variance	1.005	0.35	0.014	1.948	0.660	0.012	0.517	0.181	0.014
Level-1 variance	1.826	1.482	0.242	1.222	1.000	0.245	0.209	0.172	0.248
− 2log likelihood	55.883			69.039			34.023		

CAL, clinical attachment level; PPD, probing pocket depth.

significantly greater treatment effect difference in PPD reduction (0.868 mm [0.099, 1.637]; $p = 0.031$) but the positive temporal relationship remained non-significant (0.093 mm per year [− 0.059, 0.245]; $p = 0.201$). The number of studies using resorbable membranes was slightly greater than the number using non-resorbable membranes (Table 1). When membrane type was included as a covariate, RCTs with use of non-resorbable membranes achieved a significantly greater treatment effectiveness in PPD reduction (0.799 mm [0.131, 1.467]; $p = 0.024$) but a non-significant positive relationship was observed (0.172 mm per year [− 0.020, 0.364]; $p = 0.073$).

In terms of CAL gain, a non-significant positive relationship was observed between treatment difference and publication years (0.013 mm per year [− 0.126, 0.152], $p = 0.842$) (Fig. 1). A greater positive temporal relationship was observed in treatment effectiveness for GTR (0.131 mm per year [− 0.054, 0.316]; $p = 0.149$), and a similar positive trend was found for the control group (flap operation) (0.126 mm per year [0.032, 0.220]; $p = 0.013$). When membrane type was included as a covariate, RCTs with use of non-resorbable membranes achieved a greater but non-significant treatment effect difference in CAL gain (0.791 mm [− 0.072, 1.654]; $p = 0.069$), and the positive relationship remained non-significant (0.022 mm per year [− 0.104, 0.148]; $p = 0.711$). When membrane type was included as a covariate, RCTs with use of non-resorbable membranes achieved a greater but non-significant treatment effectiveness in CAL gain (0.773 mm [− 0.303, 1.849]; $p = 0.144$), and no significant positive relationship was observed (0.148 mm per year [− 0.028, 0.324]; $p = 0.093$).

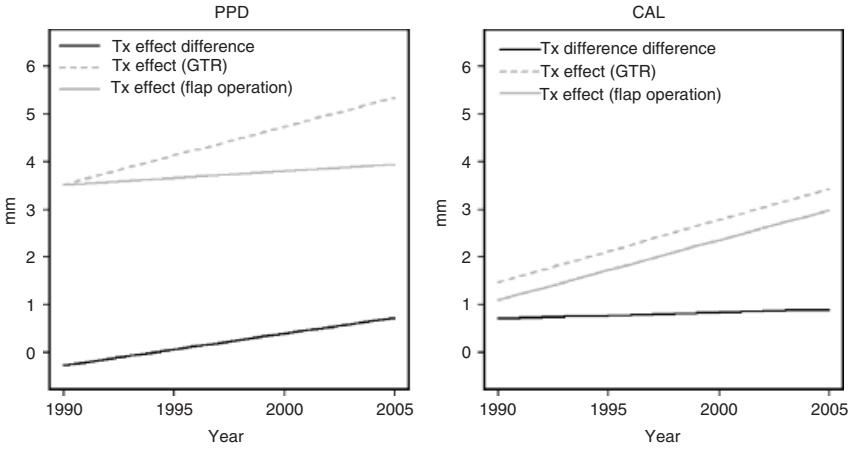

Fig. 1. Plots of the results from regression analysis for randomized-controlled trials on the comparison of guided tissue regeneration (GTR) and flap operation.

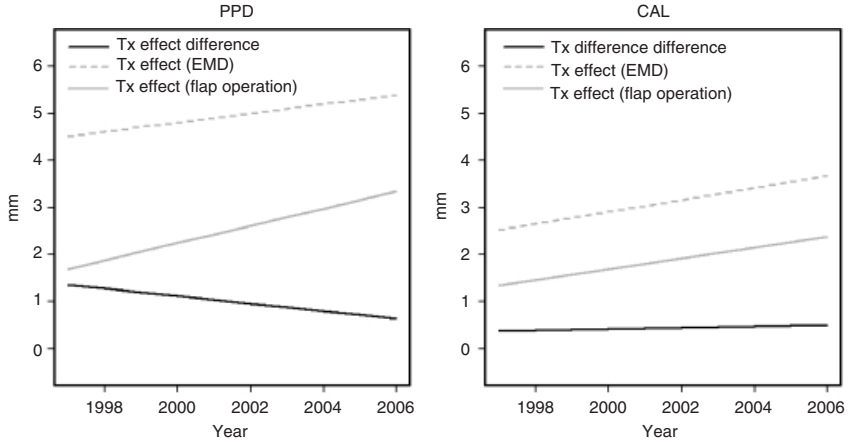

Fig. 2. Plots of the results from regression analysis for randomized-controlled trials on the comparison of enamel matrix protein derivatives (EMD) and flap operation.

EMD

In terms of PPD reduction, a small non-significant negative temporal relationship was observed between treatment difference and publication years (− 0.075 mm per year [− 0.266, 0.116]; $p = 0.390$) (Fig. 2). However, positive but non-significant temporal relationships were observed in treatment effectiveness for the EMD and control groups (0.083 mm per year [− 0.082, 0.249] and 0.166 mm per year [− 0.026, 0.358]; $p = 0.279$ and 0.082, respectively) (Fig. 2).

In terms of CAL gain, a very small non-significant positive relationship was observed between treatment difference and publication years (0.014 mm per year [− 0.182, 0.210]; $p = 0.871$) (Fig. 2). Positive but non-significant temporal relationships were observed in treatment effectiveness for EMD and control groups (0.128 mm per year [− 0.078, 0.334] and 0.115 mm per year [− 0.016, 0.246]; $p = 0.189$ and 0.078, respectively) (Fig. 2).

Discussion

In general, no substantial positive or negative association between treatment effect difference of GTR and publication years was observed in this study, although the interpretation of these results needs to take into consideration the small number of studies in the multi-level regression analyses. As it is not feasible to perform a prospective power calculation for meta-analysis, the statistical power was calculated retrospectively using the Satorra–Saris method (Brown 2006), which showed that the range of statistical power was between 0.1 and 0.76. The reported treatment effect of GTR seemed to show a slightly stronger temporal relationship with publication years in terms of CAL gain, but it is worth noting that a similar relationship was also found in the control group. This partly explains why no strong temporal association with treatment effect difference was found, because while on average CAL gain using GTR increased over the years, a similar improvement in the treatment outcome was also achieved in the control group. These findings are consistent with the suggestion that with greater experience and improved surgical technique such as

modified or simplified papillae preservation procedures, the treatment effect of GTR has become greater (Cortellini & Tonetti 2000). As these techniques in managing periodontal flaps were also used in the treatment of the control group, this may suggest that these factors also contribute to the observed positive trend in CAL gain in the control group.

Non-significant, negative associations between treatment difference and publication years were found in RCTs comparing EMD with flap operation, while the associations between treatment effectiveness and publication years remained positive but non-significant. As the number of RCTs on EMD was quite small, there was probably not enough statistical power to detect any temporal trend if there was any. The statistical power calculated retrospectively showed that the range of statistical power was between 0.14 and 0.54. However, despite the small sample size, the treatment effect of EMD and flap operation in CAL gain showed a positive (0.128 and 0.115 mm per year, respectively) temporal relationship. This is consistent with the findings from RCTs comparing GTR with flap operation, where the GTR and control group showed a positive relationship. The findings on the positive trend in the control group are intriguing, as the treatment effect of flap operation in the treatment of infrabony defects is supposed to be less likely to show any temporal trend. Although in some recent RCTs, the same surgical procedures such as papillae preservation techniques for regenerative surgeries were also used in the control group, these techniques were designed to contain the regenerative material and prevent postoperative complication such as membrane exposures. It would therefore be expected that the impact of these techniques would be demonstrated in the temporal relationship for the treatment group rather than that for the control group. From a biological viewpoint, these surgical techniques only differ in their management of gingival flaps and not in their potential for periodontal regeneration in the control group. However, our findings do suggest that in conducting systematic review and meta-analysis of surgical interventions such as GTR and EMD, including studies without a control group such as case reports or case series can give rise to potentially misleading results and might overestimate the cost-benefit of these interventions (Hartling et al. 2005), as the treatment effect of flap operation may be changing. Therefore, the interpretation of those studies without a control group needs to be cautious, because the real benefits of the tested treatments, such as GTR or EMD, are difficult to ascertain.

Several explanations have been proposed in the fading treatment effectiveness observed in some medical interventions. For instance, decreasing publication bias due to the increase in the publication of negative results and change in study quality might give rise to a decrease in the reported treatment efficacy (Kidwell et al. 2001). These biases are more likely to occur if non-RCTs such as case series had been included in our analysis. As this study used inclusion criteria similar to those adopted by the two Cochrane reviews, these biases were considered less likely to affect our results. Another explanation is change in sample sizes, as early trials tend to have a smaller sample size. This is why a weighted regression analysis was performed in this study. The quality of RCTs has been suggested to be related to the reported treatment efficacy (Moher et al. 1998). However, whether or not scoring the quality of RCTs is a useful practice for systematic reviews and meta-analysis remains a controversial issue (Greenland 1994, Jüni et al. 1999, 2001), and therefore we did not score the RCTs included in our meta-analysis. The Cochrane review looked into the impact of surgeon and examiner blinding on the reported treatment efficacy of GTR (Needleman et al. 2006), but we did not find that studies with surgeon and examiner blinding reported significantly better or poorer results in our further analysis. Another possible bias is financial conflict. However, further analysis did not show that RCTs sponsored by manufacturers of these regenerative products reported significantly better or poorer results either. As a few studies included in our meta-analyses were large multicentre studies, we also looked into whether the observed relationships or trends were influenced by these large studies. We undertook further analyses with the exclusion of these multicentre studies, and no substantial differences in both the regression coefficient and the associated p-values were found. For instance, there was still a significant positive trend in the CAL gain (0.131, $p = 0.02$) for the control group of GTR. Nevertheless, as limited numbers of RCTs were identified in this study, extensive statistical modelling on these potential biases was not feasible, and the results of these further analyses are generally exploratory.

One possible explanation for the observed positive trend in CAL gain of flap operation in RCTs on GTR is baseline disease status. Patients and infrabony defects were recruited to receive surgical treatments in RCTs due to their larger normal pocket depth and attachment loss, and, therefore, due to measurement errors, even without surgical interventions, these lesions might show some ''improvement'' on the follow-up occasion. This is known as the phenomenon of regression to the mean (Bland & Altman 1994, Tu & Gilthorpe 2007). Clinical measurements such as PPD and CAL are prone to measurement errors, and the magnitude of measurement errors might increase with the severity of periodontal lesions. To explore this possible explanation, a regression analysis was performed to test whether there is a temporal relationship between baseline CAL and publication years. However, in the 20 studies in which baseline CAL was available, a negative association was found for the control group (-0.239 mm per year; $p = 0.072$). Therefore, the significant positive trend in the improved treatment effect of CAL gain in the control group on GTR cannot be explained by the levels of baseline CAL.

A previous meta-analysis on the fading of reported effectiveness found that baseline values were the most important predictors of effect size (Gehr et al. 2006) and up to 80% of effect size variability can be explained by baseline values. However, no such analyses were attempted in this study, because regressing change on baseline values undergoes mathematical coupling and regression to the mean (Blance et al. 2005, Tu et al. 2005, Tu & Gilthorpe 2007), and the results are potentially misleading.

In summary, within the limits of this study, there was no evidence to support or refute a temporal trend between treatment effect difference and publication years for RCTs on GTR or EMD. However, this might be due to an increase in the treatment effect of the control group. Non-resorbable membranes on average achieved greater PPD reduction and CAL gain than resorbable membranes,

but there was a substantial variation in the reported treatment effect across RCTs. The results of this study suggest that only RCTs should be included in the meta-analysis of GTR and EMD, as the treatment effect of the control group cannot be assumed to be constant. Therefore, systematic review/meta-analyses with a surgical control group may need to explore whether the treatment effect of control group improves over time, and this may help to evaluate the efficacy of a surgical test procedure. Further studies are required to explore the factors that gave rise to the positive trend in the treatment effect of a flap operation in RCTs.

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Clinical Relevance

Scientific rationale for the study: Although the initial results seemed to be promising, recent systematic reviews showed that GTR and EMD only achieved modestly better results compared with conventional flap operation. The rationale for this study was to conduct a formal meta-analysis to test whether there was a temporal trend in the treatment effectiveness of GTR and EMD as suggested in the literature.

Principal findings: Our meta-analysis for RCTs showed that there was no temporal trend in the treatment effect difference between GTR/EMD and flap operation in the treatment of infrabony defects. However, there was a significant positive trend in the reported treatment effect of flap operation.

Practical implications: Clinical attachment gain of flap operations in RCTs on GTR seemed to improve over time, but more research is required to explore the factors for this trend. The interpretation of results from studies without control groups needs to be cautious, as the treatment effect of the control group may not be constant.