

Early and late studies of EMD use in periodontal intrabony defects

Mueller VT, Welch K, Bratu DC, Wang H-L. Early and late studies of EMD use in periodontal intrabony defects. *J Periodont Res* 2013; 48: 117–125. © 2012 John Wiley & Sons A/S

Background and Objective: The clinical efficacy of EMDs for the treatment of periodontal intrabony defects has been reported. However, recent publications have questioned the validity of results from early findings. Hence, the purpose of this study was to compare the results obtained from early and late studies when EMD was used as an adjunct in treating human intrabony defects during flap surgery. The aim of this meta-analysis was to evaluate the validity of results published from early studies compared with those published from later studies.

Material and Methods: PubMed and MEDLINE searches were performed. The evaluation period was 1997–2010 and it was divided into two groups of equal periods of time: early studies (1997–2003) and late studies (2004–2010). The clinical parameters assessed were clinical attachment level (CAL), probing pocket depth and bone gain (BG; measured as a percentage or in mm).

Results: No statistically significant difference was found between the results obtained from early studies (1997–2003) and late studies (2004–2010) with regards to CAL gain, probing pocket depth reduction and BG. Nonetheless, both study periods showed a benefit for using EMD to treat periodontal intrabony defects when compared with the groups without EMD during open flap surgery.

Conclusions: The results obtained from this study failed to show any potential differences between the results published from early studies and late studies with regards to the clinical effectiveness of EMD in treating periodontal intrabony defects.

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One Sentence Summary: Additional application of enamel matrix derivatives was shown to be more effective in managing periodontal intrabony defects when compared to traditional flap surgery regardless when the papers were published.

Key words: biological agents; Emdogain; enamel matrix derivatives; periodontal intrabony defects

Accepted for publication June 8, 2012

The ultimate goal of periodontal therapy has always been the regeneration of the lost periodontal supporting structures. Several methods have been employed over time to achieve this goal. Guided tissue regeneration (GTR) using bone grafts, barrier membranes or a combination of both has been the most commonly used approach. The results obtained from these treatments have been shown to be superior to open flap debridement (1–4). However, GTR has been proven

to be very technique sensitive and the results achieved were often unpredictable (4). This can be attributed by frequent exposure (4) of the implanted materials to the oral cavity and many other factors such as interproximal bone level, defect morphology, wound control, smoking habit and poor oral hygiene (5–10). Consequently, a search began for second-generation regenerative agents. Among these agents, EMDs have become the first bioactive agent to be used in periodontal clinical

practice. The commercially available product is called Emdogain (Strauman international, Basel, Switzerland). EMD is obtained from developing teeth germs of 6-mo-old piglets (11) and is believed to participate in the development of periodontal supporting structures during tooth-formation processes (12) such as amelogenesis (13). Furthermore, EMD can also exert effects on cell attachment, spreading, chemotaxis, proliferation and cell survival (14). Moreover, EMD has the

capacity to express growth factors, cytokines and extracellular matrix components, as well as molecules pertinent to osteogenesis and osteoclastogenesis (14). Lastly, EMD possesses antibacterial function which is largely attributed to its vehicle, propylene glycol alginate (14,15). EMD has also been shown to enhance periodontal regeneration after surgery (11), to improve treatment results in intrabony and mandibular Class II furcation defects (2), to minimize postsurgical complications when used as an alternative to GTR barrier membrane (16) and to aid soft tissue root-coverage procedures (17).

Generally, studies published around the time that a product is launched often report favorable clinical outcomes (18–20). However, a recent publication documented inferior results of EMD in noncontained defects when compared with GTR (21). Hence, the aim of this meta-analysis was to determine any differences between the results of early studies and late studies results when EMD was used as an adjunct to treat human intrabony defects during flap surgery.

Material and methods

PubMed and MEDLINE searches were performed for the period January 1997 to July 2010. Articles included were clinical trials in which EMD was used for the treatment of intrabony defects. The search used the medical subject heading (MeSH) terms Emdo-gain, enamel matrix derivatives, enamel matrix proteins, dental enamel proteins, periodontal intrabony defects and biologic agents. Inclusion criteria included English language publications of human clinical trials (randomized clinical trials, case-control studies and case series). Clinical outcomes such as clinical attachment level (CAL) gains, probing pocket depth reductions and bone gain (BG) were documented. Studies were then divided into two evaluation time-periods: 1997–2003 and 2004–2010. Moreover, studies limited to the use of EMD alone or in which at least one arm of the study evaluated EMD alone for regeneration of intrabony defects were included in

this meta-analysis. Furthermore, each evaluation period was divided according to the available outcome measures: probing pocket depth reduction (in mm), CAL gain (in mm) and BG (in mm, or as a percentage if available). Lastly, the standard deviation of each individual parameter had to be reported, in order to facilitate statistical analysis. In total, 76 studies were screened and, of these, 39 met the inclusion criteria. Studies were excluded if they did not report the clinical parameters listed above, if no standard deviations were present, if no full-text reports were retrievable or if no treatment with EMD alone was evaluated.

Twenty early studies (carried out in the time-period from 1997 to 2003) met the inclusion criteria (18–20,22–38). A total of 11 studies reported BG after treatment with EMD: four reported BG in both mm and as a percentage (14,18,19,24,37); five studies reported BG in mm (22,27,28,31,36); and only two reported BG as a percentage (25,26). Eighteen late studies (carried out in the time-period 2004–2010) met the inclusion criteria (16,21,27,39–53). A total of nine studies evaluated BG: three reported BG in both mm and as a percentage (41–43,53); five reported BG in mm only (44,46,50,52,53); and one study reported bone gain only as a percentage (48) (Tables 1A,B).

The statistical analysis was performed by the Center for Statistical Consultation and Research at the University of Michigan. We used a random-effects meta-analysis to combine information from the 39 studies included in this meta-analysis, stratified by group (early studies vs. late studies). A random-effects meta-regression was used to compare the effect of each outcome variable for early studies vs. late studies. All statistical analyses were carried out using STATA SE version 11.2 ϕ (StataCorp LP, 4905 Lakeway Drive, College Station, TX 77845, USA).

Results

A total of 39 studies were available, 20 in the early time-period (1997–2003) (18–20,22–38) and 18 in the late time-

period (2004–2010) (16,21,27,39–53). The results were analyzed according to the evaluated clinical parameters, namely CAL gain, probing pocket depth reduction, BG as a percentage and BG in mm.

Clinical attachment level

In general, there was a significant overall increase in CAL [overall mean increase in attachment level = 3.048 mm, 95% confidence interval (95% CI) = 2.658–3.437; $p < 0.001$]. This effect was not significantly different for early studies vs. late studies ($p = 0.526$). The mean increase in CAL for the early studies group was 3.150 mm (95% CI = 2.585–3.715 mm; $p < 0.001$) whereas for the late studies group, the mean increase in CAL was 2.937 mm (95% CI = 2.423–3.450 mm; $p < 0.001$) (Fig. 1).

Probing pocket depth reduction

Similarly to the gains in CAL, there was a significant overall reduction of probing pocket depth; the overall mean reduction of probing pocket depth was 4.049 (95% CI = 3.659–4.440; $p < 0.001$). This effect was not significantly different between early studies and late studies ($p = 0.231$). The mean probing pocket depth reduction for early studies was 4.223 mm (95% CI = 3.606–4.841 mm; $p < 0.001$), whereas it was 3.845 mm (95% CI = 3.516–4.175 mm; $p < 0.001$) for late studies (Fig. 2).

Bone gain (%)

When BG was examined as a percentage, a statistically significant increase of 43.024% (95% CI = 30.486–55.563%; $p < 0.001$) was found. However, this was not statistically significantly different between early studies and late studies ($p < 0.023$). Mean BG was 36.212% (95% CI = 21.030–51.395%; $p < 0.001$) for the early studies and 59.292% (95% CI = 54.109–64.474%, $p < 0.001$) for the late studies. Nonetheless, these results should be regarded with great care because data were available from only two studies in the early studies group (Fig. 3).

Table 1. Summary of early studies

Study	Year	Clinical attachment level gain (mm)	Probing pocket depth reduction (mm)	Bone gain (%)	Bone gain (mm)	Defect morphology	<i>n</i>
Heijl (18)	1997	2	3.2	36	2.6	Predominantly one to two wall defects each, <i>n</i> = 17	34
Zetterstrom (37)	1997	2.9	3.7	31	2.4	Intraosseous defects N/A about wall morphology	45
Sculean (20)	1999	3.2	5.7		0.9	Teeth scheduled for extraction N/A	7
Heden (19)	1999	4.6	5.2	69	2.9	Intrabony component ≥ 3 mm 1-wall = 18 1 + 2-wall = 31 2-wall = 87 2 + 3-wall = 7 3-wall = 2	145
Heden (24)	2000	4.2	4.7	58	3.1	Intrabony component ≥ 3 mm 1-wall = 22 2-wall = 50	72
Okuda (26)	2000	1.72	3	20.2		Intrabony component ≥ 4 mm 1-wall = 5 2-wall = 5 3-wall = 8	18
Parodi (27)	2000	3.43	4.9		2.54	Angular bony defect width ≥ 2 mm and depth ≥ 3 mm	21
Bratthall (22)	2001	2.9	3.7		1	Intrabony defect width ≥ 2 mm and depth ≥ 3 mm	88
Pietruska (28)	2001	2.9	4.24		2.84	Defect depth ≥ 3 mm Nine, 2-wall and three, 3-wall defects	25
Minabe (25)	2002	2.6	3.8	35.3		Eleven 3-wall, seven 2-wall, four 3-wall defects	17
Windisch (36)	2002	2.67	5		1.05	1-wall = 1 2-wall = 5	6
Pontoriero (29)	1999	2.9	4.4			Intrabony component ≥ 3 mm	10
Sculean (31)	1999	3	4.4			Intrabony defect ≥ 6 mm	32
Silvestri (32)	2000	4.5	4.8			Predominant 1- or 2-wall component	10
Sculean (62)	2001	3.4	4.1			1-2-wall = 4 2-wall = 6 3-wall = 4	14
Tonetti (34)	2002	3.1	3.9			Intrabony defect ≥ 3 mm	83
Zuchelli (38)	2003	4.2	5.1			Angular bony defect ≥ 3 mm	30
Gutierrez (23)	2003	1.4	2			N/A	20
Wachtel (35)	2003	3.6	3.9			Intrabony component ≥ 3 mm 1-, 2-, 3-wall defects included	13
Silvestri (33)	2003	4.1	5.3			Intrabony component ≥ 4 mm 1-, 2-, 3-wall defects included	6

Table 1. (Continued)

Study	Year	Clinical attachment level gain (mm)	Probing pocket depth reduction (mm)	Bone gain (%)	Bone gain (mm)	Defect morphology	<i>n</i>
Vandana (53)	2004	3.13	4.5		1.4	Vertical bone loss on X-ray	8
Parashis (48)	2004	3.6	4.3	60		Intrabony component ≥ 4 mm	15
Francetti (42)	2004	4.29	4.86	57.4	3.44	2+3-wall defects Intrabony defect ≥ 4 mm	12
Sculean (50)	2004	2.9	4.3		3.9	1-, 2-, 3-wall defects 1-2-wall = 3 2-wall = 7 3-wall = 1	10
Sipos (52)	2005	1.28	2.86		1.63	Radiographic depth ≥ 4 mm	12
Francetti (43)	2005	3.51	4.02	55	3.18	Intrabony defect ≥ 4 mm	83
Kuru (46)	2006	4.06	5.03		2.15	Intrabony defect ≥ 4 mm 1-2-wall = 4 2-wall = 7 3-wall = 9	10
Crea (41)	2008	2.5	3.5	58.8	2.4	Intrabony defect ≥ 4 mm	19
Grusovin & Esposito (44)	2009	3.3	3.9		2.5	Defect depth ≥ 4 mm Defect width ≥ 2 mm	15
Sanz (16)	2004	3.1	3.8			Intrabony defect ≥ 3 mm	35
Parodi (27)	2004	4.2	4.93			Angular osseous defects ≥ 3 mm	16
Rosing (49)	2005	2.01	4.17			Defect depth ≥ 3 mm Defect width ≥ 2 mm	14
Sculean (51)	2005	3.9	4.5			Intrabony component ≥ 3 mm on X-ray 1-2-wall = 6 2-wall = 7 3-wall = 2	15
Bokan (39)	2006	3.7	3.9			Intraosseous component ≥ 3 mm	19
Chambrone (40)	2007	2.67	3.75			2+3-wall defects	13
Leknes (47)	2009	0.5	2.5			Intrabony component ≥ 3 mm 1-3-wall defects	13
Siciliano (21)	2010	2.4	2.9			Intrabony component ≥ 3 mm 80% 1-wall 2-3-wall in apical portion	20
Harrell (45)	2010	3.42	3.54			Sites with X-ray bone loss N/A	13
Jepsen (63)	2008	1.38	2.55		2.07	Defect morphology: 1-wall 2-wall Combined 1-2 wall Circumferential	35

N/A, Not Applicable.

Bone gain (mm)

The last parameter evaluated was BG expressed in mm. Once again, there was an overall statistically significant BG of 2.35 mm (95% CI = 1.96–2.75 mm; $p < 0.001$). Yet again, this was not sta-

tistically significant between early studies and late studies ($p = 0.449$). Generally, the early studies group had 2.191 mm (95% CI = 1.530–2.851 mm; $p < 0.001$) of BG and the late studies group had 2.49 mm (95% CI = 2.070–2.91 mm; $p < 0.001$) of BG. (Fig. 4).

Discussion

EMD has been a subject of extensive research, ranging from early investigations to prove its efficacy (18,26,30) to late investigations in combination with other regenerative therapy

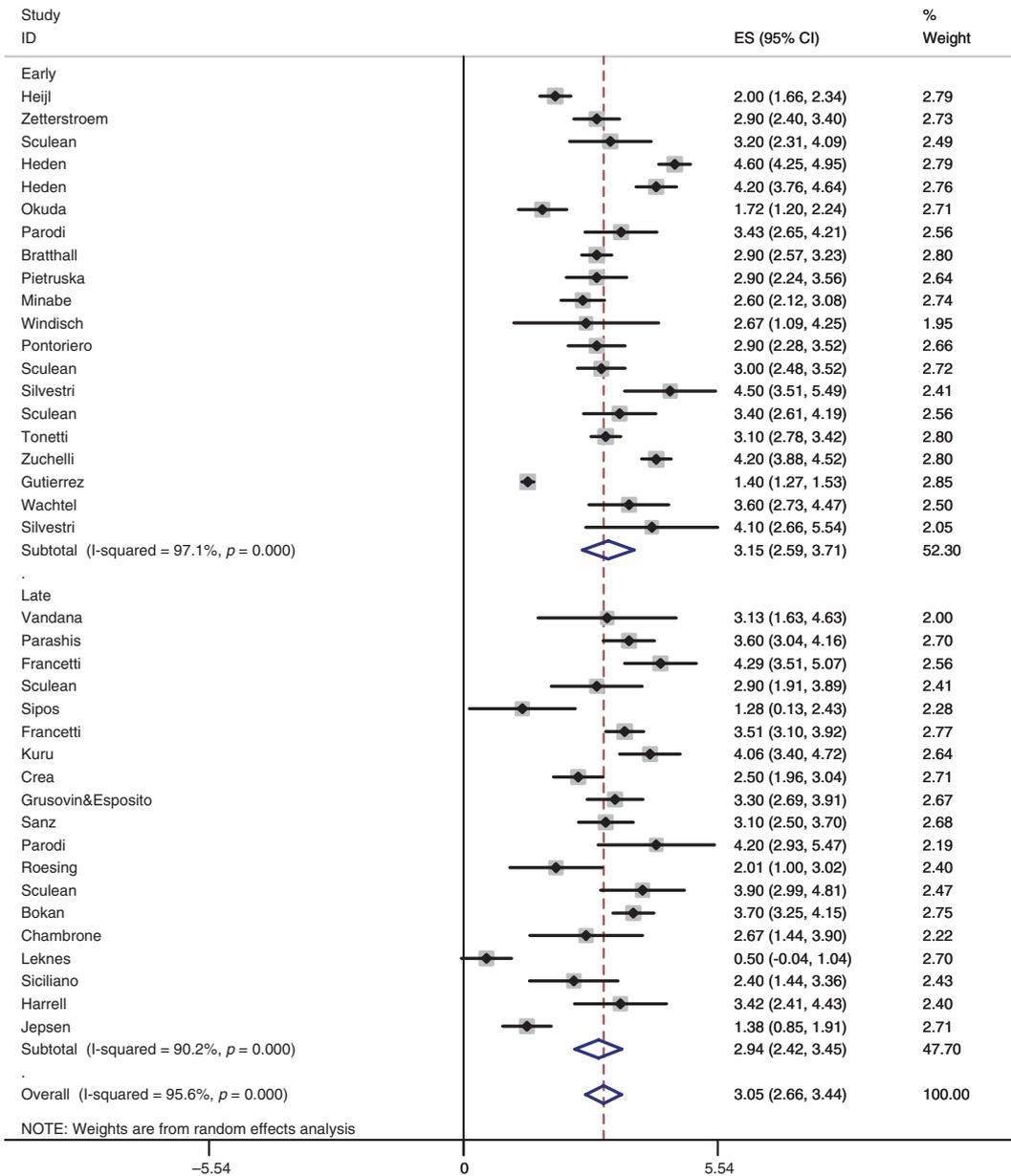


Fig. 1. Random effects analysis of clinical attachment level (CAL) gain.

modalities (20,25,38,51). This meta-analysis found that when EMD was used in combination with flap surgery for the treatment of intrabony defects, a mean CAL gain of 3.04 mm and a mean probing pocket depth reduction of 4.05 mm could be obtained. This is in agreement with the findings of Klapidis & Ruben (54) in their meta-analysis. Esposito *et al.* (55,56), in a meta-analysis, evaluated CAL gains obtained for EMD treatment compared with open flap debridement, but the effect was reduced by almost half (1.1 mm vs. 0.62 mm) when only

studies were used that were at low risk for bias. These findings are in contrast to the results reported on CAL gains in our investigation (3.09 mm) and might be explained by a more stringent exclusion of studies in Esposito's group. Another arm of the meta-analysis of Esposito *et al.* evaluated the clinical outcomes of EMD vs. GTR and reported no significant difference between the two groups. However, more postoperative complications and recession occurred in the GTR-treated sites. The authors acknowledged the difficulty of the attempted comparisons

as a result of the great heterogeneity between the study designs and the outcomes reported (55,56).

Rathe *et al.* conducted a systematic review evaluating the efficacy of EMD for treating intrabony defects; they concluded that EMD can be used predictably for regeneration of intrabony defects, but found that EMD appears to be more effective in well-contained defects. Furthermore, the amount of bone regeneration was less than achieved with GTR (57). Generally our findings, as far as can be compared, also suggest a significant effectiveness of EMD in

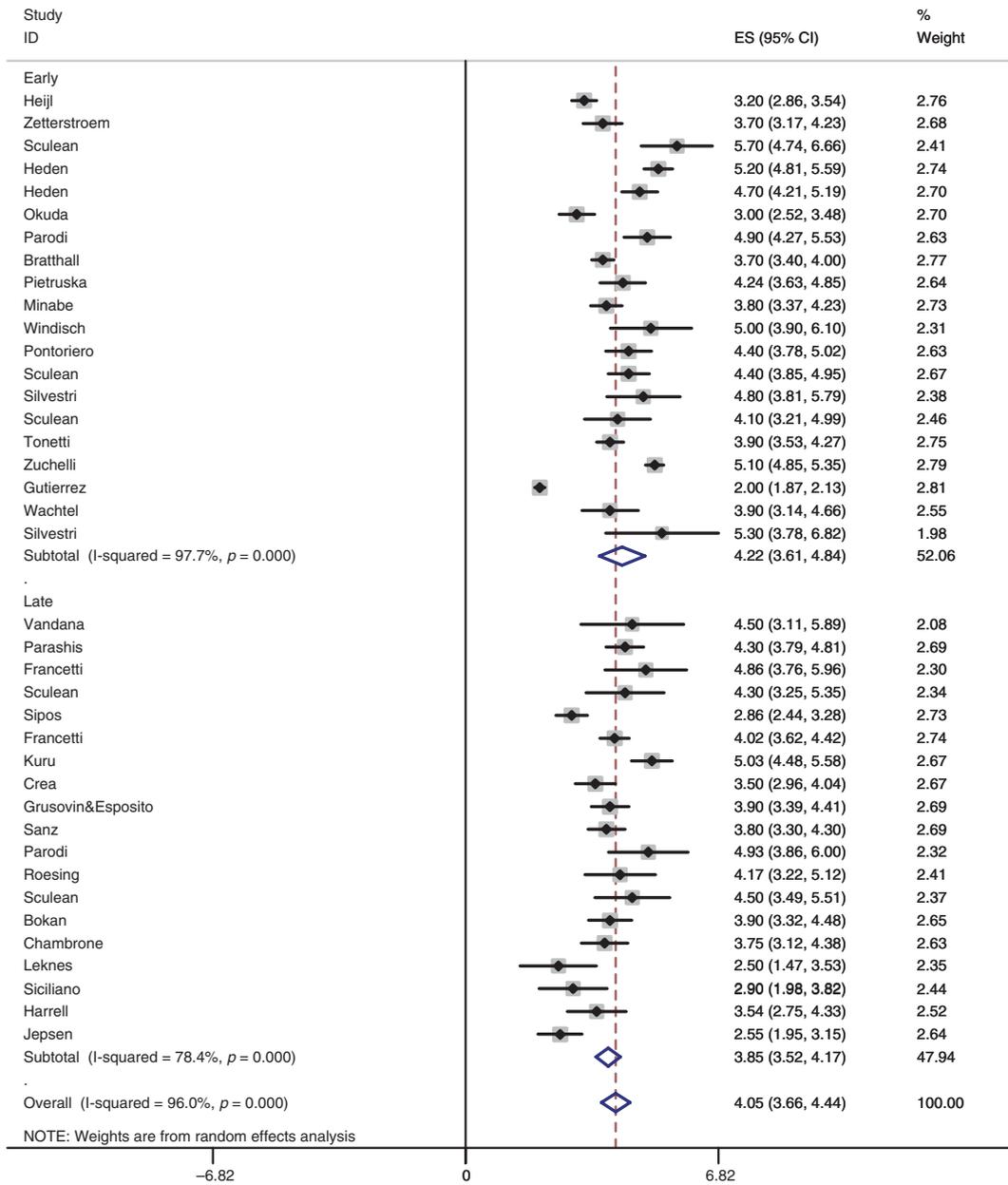


Fig. 2. Random effects analysis of probing pocket depth reduction.

intrabony defects, but the amount of bone regeneration seems to be less pronounced. A comparison between GTR and EMD was not attempted in this meta-analysis and would be valuable for a future comparison.

A benefit associated with the use of EMD can be found when minimally invasive surgical protocols are employed and in esthetic areas (45,58,59). These benefits relate to the ease of application of EMDs. These parameters were not included in the

present study design and would be of great interest in future investigations. Siciliano *et al.* (21) evaluated the performance of EMD vs. GTR in deep, noncontained defects and their results were in favor of the GTR therapy. Clinical application of the above-discussed findings indicates that EMD exhibits potential for regeneration in well-contained periodontal defects, to enhance wound healing and as an adjunct to root coverage procedures combined with Coronally Advanced Flap. This

might be attributed to the effect of EMD in promoting early soft-tissue healing and subsequent enhancement of wound closure (17,60,61).

In addition, data from this meta-analysis demonstrated a radiographic BG of 43.02% and 2.35 mm when EMD plus periodontal flap surgery was used for the treatment of intrabony defects. To the best of our knowledge, no other published meta-analysis has reported BG as a percentage or in mm.

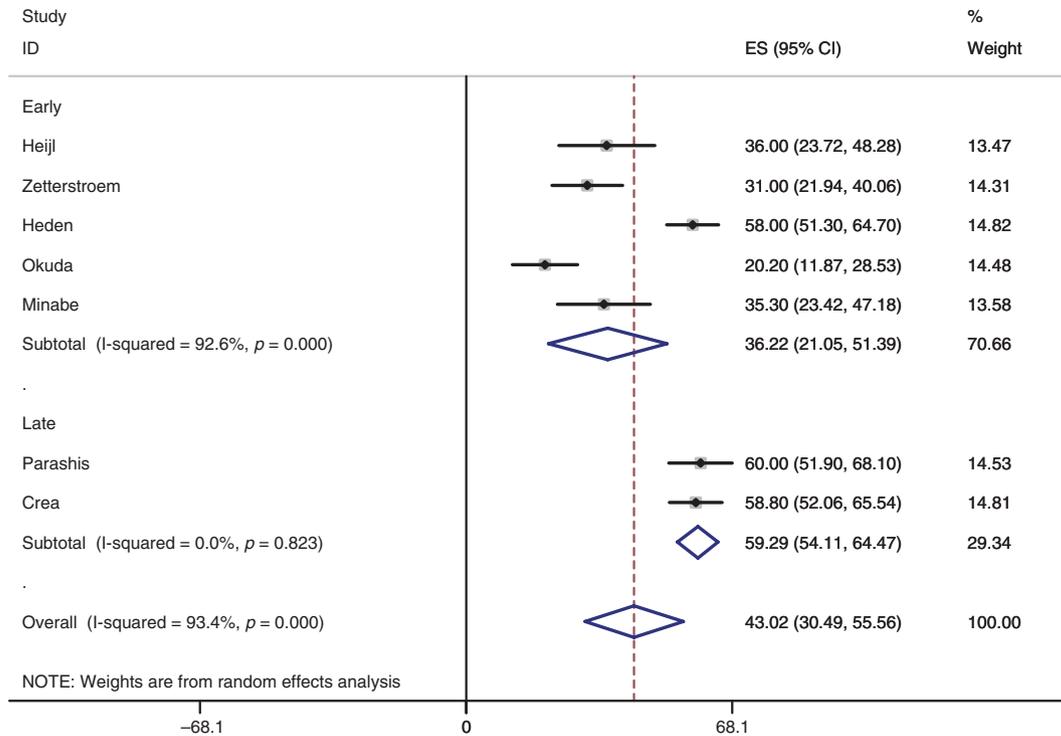


Fig. 3. Random effects analysis of bone gain (BG) expressed as a percentage.

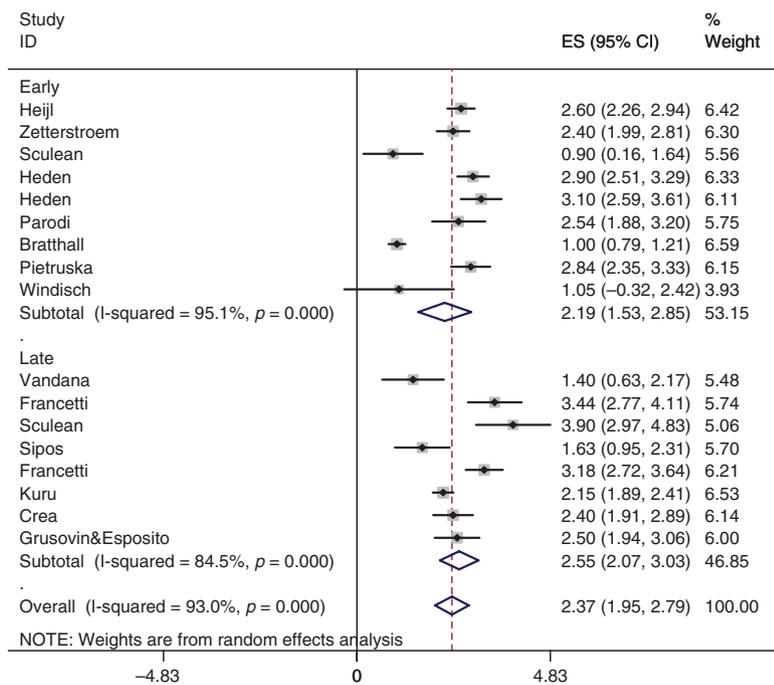


Fig. 4. Random effects analysis of bone gain (BG) expressed in mm.

When these findings were compared with the available data from the *Annals of Periodontology*, the efficacy of EMD appeared uncertain (2,3) as a conventional periodontal flap procedure

can achieve a mean BG of 40–50%, which is comparable with the results reported for EMD in this meta-analysis. One can assume that there was minimal added benefit of EMD as

the percentage of BG was almost identical to that achieved using the conventional flap surgical procedure. Nonetheless, the benefits of biologic agents, such as EMD, cannot simply be disregarded. Postoperative complications after GTR, for example membrane exposure, have been reported to occur in almost 75% of sites; however, in the EMD group only 6% of subjects experienced similar adverse events (16). Lastly, the effect of EMD on BG has been reported to be less marked than with conventional GTR (57).

To our knowledge, a comparison between early studies (1997–2003) vs. late studies (2004–2010) regarding the treatment of periodontal intrabony defects using EMD has not previously been attempted. Comparison of early studies with late studies identified no statistically significant difference in the efficacy of EMD determined using the following clinical parameters: CAL, probing pocket depth or BG (expressed either as a percentage or in mm).

The limitations of this present investigation are the limited sample size, the timelines selected (which could have been further divided into

additional time intervals) and the sole assessment of EMD. More studies are needed to substantiate or refute the reported results.

Conclusions

This meta-analysis failed to show any significant differences between the clinical results published in early or later studies regarding the use of EMD to treat periodontal intrabony defects.

Acknowledgements

This study was partially supported by the University of Michigan Periodontal Graduate Student Research Fund.

Disclaimers

The authors do not have any financial interests, either directly or indirectly, in the products or information listed in the paper.

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