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REVIEW

USE OF ENAMEL MATRIX- DERIVED PROTEINS COMBINED WITH BONE GRAFT FOR THE TREATMENT OF INTRABONY DEFECTS: OVERVIEW OF REVIEWS (FRISBEE REVIEW)

Uso de proteínas derivadas de la matriz del esmalte combinado con injerto óseo para el tratamiento de defectos intraóseos: Resumen estructurado de revisiones sistemáticas (revisión FRISBEE)

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ABSTRACT

Introduction: The use of enamel matrix-derived proteins (EMD) has increased in recent years due to their tissue-inducing properties that support periodontal regeneration. This study is an overview of systematic reviews with FRISBEE methodology on the use of EMD alone or combined with autologous bone graft materials (BGM) in the treatment of intrabony defects.

Materials and Methods: A systematic search in the Epistemonikos database was performed. RevMan 5.3 and GRADEpro were used for data analysis and presentation

Results: Four systematic reviews and two clinical trials were identified. All studies analysed change in probing depth, clinical attachment level, gingival margin level and bone defect depth (all changes in favour of EMD+BGM groups: mean difference (MD): 0.37 mm more, MD: 0.7 mm more, MD: 0.3 mm less, MD: 0.75 more, respectively).

Conclusions: Adding autologous bone graft to EMD to treat intrabony defects showed better results, but not a relevant clinical difference compared to the use of EMD alone.

Keywords: *Dental enamel proteins; Bone transplantation; Autologous transplantation; Alveolar bone loss; Periodontal diseases; Bone regeneration.*

RESUMEN

Introducción: El uso de proteínas derivadas de la matriz del esmalte (EMD) ha aumentado en los últimos años debido a sus propiedades inductoras de tejidos que apoyan la regeneración periodontal. Este estudio es una revisión sistemática de revisiones sistemáticas utilizando metodología FRISBEE sobre el uso de EMD solo o combinado con materiales injerto óseo autólogo (BGM) en el tratamiento de defectos intraóseos.

Materiales y Métodos: Se realizó una búsqueda sistemática en la base de datos Epistemonikos. Se utilizaron RevMan 5.3 y GRADEpro para el análisis y la presentación de los datos.

Resultados: Se identificaron cuatro revisiones sistemáticas y dos ensayos clínicos. Todos los estudios analizaron el cambio en la profundidad de sondaje, el nivel de inserción clínica, el nivel del margen gingival y la profundidad del defecto óseo (todos los cambios a favor de los grupos EMD+BGM: MD: 0,37 mm más, media de diferencia (MD): 0,7 mm más, MD: 0,3 mm menos, MD: 0,75 más, respectivamente).

Conclusión: La adición de injerto óseo autólogo a la EMD para tratar defectos intraóseos mostró mejores resultados, pero no una diferencia clínica relevante en comparación con el uso de la EMD sola.

Palabras Clave: *Proteínas del esmalte dental; Trasplante óseo; Trasplante autólogo; Pérdida de hueso alveolar; Enfermedades periodontales; Regeneración ósea*

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INTRODUCTION

Periodontitis is a multifactorial chronic infectious disease that begins with bacterial growth and advances to the loss of periodontal tissues.[1] It is the sixth most prevalent disease in the world, and it is estimated to affect 20 to 50% of adolescents and adults.[2,3] Among the consequences of periodontitis is alveolar bone resorption that can lead to intrabony defects, and even tooth loss.[4]

Depending on the direction and extent of the apical spread of the periodontal lesion, bone defects are classified as horizontal or vertical bone defects. Vertical bone defects, also known as intrabony defects, are associated with a higher risk of severity and progression of periodontal disease.[5]

Treatment includes non-surgical and surgical approaches for mechanical debridement of the contaminated root surface (deep scaling and root planing) or periodontal regenerative procedures,[6] together with an appropriate oral hygiene technique that motivates the patient to perform it.[7]

Currently, among regenerative treatments for intrabony defects, there are several alternatives that include bone graft materials (BGM), guided tissue regeneration, and the use of enamel matrix-derived proteins (EMD) and their combinations.[8] The purpose of these procedures is to generate an osteogenic effect that promotes the proliferation and differentiation of osteoprogenitor cells and, in some cases, to be a scaffold for osteoblasts to produce new bone and bone healing.[9,10]

The continuous scientific advances in periodontics and the large number of publications on treatments for periodontal intrabony defects, make it difficult for clinicians to be updated on the most effective treatment they can apply. Thus, the present study aims to evaluate the effectiveness of the use of enamel matrix-derived proteins combined with bone graft compared to the use of enamel-derived proteins alone for the treatment of periodontal intrabony defects through a synthesis of the available evidence that can be more accessible for clinicians.

MATERIALS AND METHODS

An overview was performed applying FRISBEE (Friendly Summaries of Body of Evidence using Epistemonikos) methodology[11] to summarize the best available evidence on the use of EMD combined with autologous bone graft when performing periodontal regeneration for the treatment of intrabony defects.

The research question was based on the PICO strategy as follows:

Population (P): Patients with chronic periodontitis presenting one or more intrabony defects;

Intervention (I): Enamel matrix-derived proteins combined with autologous bone graft;

Comparison (C): Enamel matrix-derived proteins (alone);

Out-comes (O): probing depth, clinical attachment level; gingival margin level; and bone defect depth.

To answer the research question, a systematic search was conducted in the Epistemonikos database of systematic reviews, which includes

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multiple information sources (MEDLINE, EMBASE, Cochrane Library and LILACS).[12]

The search did not include any language restriction and it was filtered for systematic reviews only. Articles were included up to February 25th, 2022.

The terms used for the search were *"intra-bony defects", "intrabony", "enamel matrix derivatives", "emdogain", "bone graft", and "autogenous bone"* (Appendix 1). Duplicate articles were manually removed through Mendeley v1.19.8 software.

To identify relevant articles, the inclusion criteria was applied. Systematic reviews that answered the clinical question were selected and the primary studies included in the systematic reviews were analysed for data extraction.

Two authors (JMPV, AGS) independently evaluated the titles and abstracts of each identified study and the relevant information for data extraction; any disagreement between the two authors was resolved by discussion and consensus, in case of disagreements a third author (CMG) was involved. A matrix in XLSX format (from Microsoft EXCEL) was used for data collection including:

The search strategy, description of systematic reviews and primary studies, assessment of the risk of bias and relevant dichotomous or continuous outcomes. RevMan 5.3 software was used for data analysis.

Regarding measures of treatment effect, we combined the results by performing a meta-analysis for the continuous outcome with a random-effects model, using inverse variance weighting. The result was reported by mean difference (MD), calculated with their 95% CI.

We assessed statistical heterogeneity in each meta analysis using the Tau^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if the I^2 is greater than 75% and either the Tau^2 is greater than zero, or if there is a low *p*-value (less than 0.50) in the Chi^2 test for heterogeneity (Appendix 2).

GRADEpro software was used to evaluate the certainty of the evidence. A summary of findings table was included following the GRADE approach (SoF Table). The research protocol is available upon request from the corresponding author.

RESULTS

Twelve studies were found from the systematic search, four of which were duplicates. Eight studies were screened by title and abstract for inclusion and six articles were included for full-text screening. Four systematic reviews.[9,13-15] were finally included in this study and two primary studies corresponding to randomized clinical trials that met the eligibility criteria (Figure 1).[16,17] Table 1 shows the overall overlap of the included studies.

All studies included systemically healthy adult patients with at least one bone defect larger than 3 mm. Neither of the two trials specified whether they analysed vital or nonvital teeth.In the Yilmaz *et al.*,[16] trial treated teeth were premolars and molars,while in the Guida *et al.*,[17] trial, treated teeth were incisors, canines, premolars and molars. All trials compared enamel matrix proteins combined with autologous bone graft com-pared to enamel matrix proteins alone when performing bone regeneration for the treat-ment of intrabony defects (Table 2). The clinical trials measured multiple out-comes, which were pooled by systematic reviews as follows: Change in probing depth (baseline - 12 months follow-up).

Table 1: Overall overlap of the included studies.

Primary Studies		Systematic Reviews	
Study ID	**Reference**	**Reference**	**Year**
1	Guida *et al.*,[17] 2007	Annunziata *et al.*,[9]	2019
		Matarasso *et al.*,[13]	2015
		Li *et al.*,[14]	2012
		Kao *et al.*,[15]	2015
2	Yilmaz *et al.*,[16] 2010	Annunziata *et al.*,[9]	2019
		Matarasso *et al.*,[13]	2015
		Li *et al.*,[14]	2012

Table 2: Characteristics of the included primary studies.

Author, and year of publication	Population study	Age (years)	Inclusion criteria	Exclusion criteria	Intervention	Comparison	Outcomes Statement and Conflicts of Interest	Funding
Yilmaz et al., 2010[16]	Adult patients with advanced chronic periodontitis.	30 – 50 years.	No systemic diseases Non smokers. Agood level of oral hygiene. Compliance with the maintenance programme. Presence of one intrabony defect with a probing depth of at least 6 mm and an intrabony component of at least 3 mm as detected on the radiographs.	Not specified	Enamel matrix protein derivative and autogenous bone.	Autogenous bone	Probing pocket depth. Gingival recession. Clinical attachment level. Probing bone level.	It is not reported in the article whether there was any funding or conflict of interest in the development of the study.
Guida et al., 2007[17]	Adult patients with advanced chronic or aggressive periodontitis.	46.3 (SD: 8.7)	At least one intraosseous defect in need of surgical treatment after initial periodontal treatment and reevaluation. Probing Depth ≥ 6 mm; and radiographic intraosseous defect ≥4 mm.	Systemic diseases that contraindicate periodontal surgery. Medications affecting periodontal status. Pregnancy or lactation and full mouth plaque score and full-mouth bleeding score >20% at the time of surgical procedure. Furthermore, third molars, teeth with Class III mobility, furcation involvement, inadequate endodontic treatment, or restoration.	Enamel matrix protein derivative and autogenous bone.		Autogenous bone.	Radiographic depth of the defect. Radiographic defect fill. Bleeding score. Clinical attachment level. Probing pocket depth. Marginal gingival recession.

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Table 3: Summary of findings table using the GRADE approach.

Outcome	Absolute effect* WITH EMD alone	WITH EMD + Bone graft	Relative effect (95% CI)	Certainty of evidence (GRADE)
Change in probing depth	5.1 mm	5.47 mm	---	⨁◯◯◯ Very low[a,b,c]
	MD 0.37 mm more			
	(Margin of error: 1.08 a 1.82 more)			
Change in clinical attachment level	4.00 mm	4.70 mm	---	⨁◯◯◯ Very low[a,c]
	MD 0.7 more			
	(Margin of error: 0.17 a 1.23 more)			
Change in gingival margin level (gingival recession)	1.15 mm	0.85 mm	---	⨁◯◯◯ Very low[a,c,d,e]
	MD 0.3 less			
	(Margin of error: 1.28 a 0.68 less)			
Change in bone defect depth	3.55 mm	4.30 mm	---	⨁◯◯◯ Very low[a,c,e]
	MD 0.75 more			
	(Margin of error: 0.25 a 1.76 more)			

* The risk in the intervention group (and its 95% confidence interval) is based on the risk assumed in the comparison group and the relative effect of the intervention (and its 95% confidence interval).
CI: Confidence interval; MD: Mean difference

Certainty of the evidence GRADE Working Group

High certainty: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different is low.

Moderate certainty: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different is moderate.

Low certainty: This research provides some indication of the likely effect. The likelihood that the effect will be substantially different is high.

Very low certainty: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different is very high.

EXPLANATIONS

a. The certainty of the evidence was downgraded in two levels for risk of bias, because the study by Yilmaz et al., (2010) has a high risk of bias for not having an adequate sequence and concealment of randomization16

b. The certainty of the evidence was downgraded for inconsistency, due to the meta-analysis being heterogeneity (I2: 79%).

c. The certainty of the evidence was downgraded for indirect evidence, as it corresponds to a surrogate outcome.

d. The certainty of the evidence was downgraded inconsistency because the meta-analysis has heterogeneity (I2: 85%).

e. The certainty of the evidence was downgraded for imprecision, as the studies together have a small sample size.

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- Change in clinical attachment level (baseline - 12 months follow-up).
- Change in gingival margin level (baseline - 12 months follow-up).
- Change in bone defect depth in millimeters (baseline - 12 months follow-up).

The information on the effects of the use of EMD combined with autologous bone grafting for the treatment of intrabony defects is based on two randomized trials involving 68 periodontal sites of therapeutic intervention in 67 patients. All study trials measured the proposed relevant outcomes (Table 3).

The summary of the results is as follows: The use of EMD combined with BGM com-pared to the use of EMD alone could:
- Increase the change in probing depth,
- Increase the attachment level change
- Decrease the change of gingival margin level,
- Increase the change in the level of bone defect depth, which means that EMD combined with BGM could help in bone regeneration after 12 months of follow-up compared to the use of EMD alone. However, all these changes are not clinically relevant (very low certainty of the evidence).

DISCUSSION

The results of this study are widely applicable to all adult patients with bone defects greater than 3 mm around permanent teeth, in either incisors, canines, premolars, or molars. Our study evaluated four outcomes considered important for assessing the use of enamel matrix-derived proteins combined with autologous bone grafting for the treatment of intrabony defects.

All outcomes showed a very low certainty of the evidence. It was also found that there is an agreement between two out of the four identified systematic reviews in terms of the assessed outcomes[9,15] as there were no significant differences in favour of EMD combined with autologous bone grafting compared to EMD alone. However, in the Yilmaz *et al.*,[16] trial, the direction of the effect was slight in favour of the combined therapy, and the conclusion of the review by Matarasso *et al.*,[13] describes that the combination of EMD and bone grafting may result in clinical improvement in terms of insertion level gain and reduction of probing depth. However, it is important to consider that different bone grafts were analysed in Matarasso's review such as autologous, demineralized bovine, silicate, and demineralized freeze-dried allograft bone grafts.[13]

In addition, the review by Li *et al.*,[14] indicates that combination therapies have better clinical outcomes after short-term follow-up; whereas results are not significantly different after long-term follow-up. In terms of the limitations of this study, when using the GRADE approach criteria, there were problems with the domains of risk of bias, indirect evidence, inconsistency, and imprecision because one of the two included studies presented a high risk of bias due to inadequate sequencing and allocation

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concealment.[16] This study also presented indirect evidence because the study out-comes were surrogate and did not directly measure the main clinical benefit of the intervention.[18-21] In addition, the magnitude of the effect reported a high heterogeneity in two of the four outcomes, and a small sample size was reported in all outcomes, with total of 68 periodontal sites of therapeutic intervention included in the analysis of each outcome.[9,13,15]

One of the strengths of this study was that the applied methodology allows that all evidence available in systematic reviews on this topic together with their included primary studies were synthesized and presented in this overview. Another strength of this study was that there was no language restriction on the inclusion of clinical trials and systematic reviews. Despite this, we found only a small number of systematic reviews and clinical trials on this topic, which was also limited by a high overlap in the primary studies included in the systematic reviews.

Using the keywords described in the methods section, we did not identify any ongo-ing randomized trials on this topic in the In-ternational Clinical Trials Registry Platform of the World Health Organization, nor in *clinicaltrials.gov*. However, we identified two ongoing systematic reviews in the International Prospective Register of Systematic Reviews (PROSPERO) of the National Institute for Health Research on biomaterials to improve bone regeneration.[22,23]

Therefore, it could be possible that in the future, new research could provide better certainty of evidence regarding the effectiveness of the use of EMD combined with BGM; with the likelihood that the conclusions reported in this study could change due to the uncertainty in the existing evidence on the clinical question raised in this study, and due to the inclusion of more studies that might be developed.

CONCLUSION

In conclusion, although it is not clear whether the combined intervention improves therapeutic effectiveness, it is possible that associating EMD with BGM does not produce a relevant clinical difference compared to using EMD alone.

Therefore, when analysing the risk-benefit for patients, it is inferred that EMD alone could give the same effectiveness as when using it with an autologous bone graft, avoiding possible risks with another surgical procedure in the patient,[24] and decreasing the total cost of the treatment. The probability that the effect found in this study is substantially different is very high. Future studies and those under development that have an adequate randomization protocol, allocation concealment and blinding (including participants, trial personnel and outcomes evaluators) will be able to answer this question with a higher certainty of the evidence.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

ETHICS APPROVAL

Not applicable.

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None to declare

AUTHORS' CONTRIBUTIONS

Juan Marcos Parise-Vasco: Conceptualization, Methodology, Data collection, Data acquisition and analysis, Data interpretation, Writing – original draft preparation, Writing – review and editing, Final approval.

Andrea Gavilánez-Sánchez: Conceptualization, Data collection, Data acquisition and analysis, Writing – original draft preparation, Final approval.

Camila Montesinos-Guevara: Conceptualization, Methodology, Data acquisition and analysis, Data interpretation, Writing – original draft preparation, Writing – review and editing, Final approval.

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ANNEXES

Supplementary file A.1 – Search Strategy

DATABASE	SEARCH STRATEGY
EPISTEMONIKOS	(title:((title:((title:((intrabony defects) OR ((intrabony) AND (defects))) OR abstract:((intrabony defects) OR ((intrabony) AND (defects)))) AND (title:(((enamel) AND (matrix) AND (deriv*)) OR (emd) OR(emdogain)) OR abstract:(((enamel) AND (matrix) AND (deriv*)) OR (emd) OR (emdogain))) AND (title:(((bone) AND (graft*)) OR (bg) OR ((autogenous) AND (bone) AND (graft)) OR (abg) OR ((osseous) AND (graft))) OR abstract:(((bone) AND (graft*)) OR (bg) OR ((autogenous) AND (bone) AND (graft)) OR (abg) OR ((osseous) AND (graft))))) OR abstract:((title:((intrabony defects) OR ((intrabony) AND} (defects))) OR abstract:((intrabony defects) OR ((intrabony) AND (defects)))) AND (title:(((enamel) AND (matrix) AND (deriv*)) OR (emd) OR (emdogain)) OR abstract:(((enamel) AND (matrix) AND (deriv*)) OR (emd) OR (emdogain))) AND (title:(((bone) AND (graft*)) OR (bg) OR ((autogenous) AND (bone) AND (graft)) OR (abg) OR ((osseous) AND (graft))) OR abstract:(((bone) AND (graft*)) OR (bg) OR ((autogenous) AND (bone) AND (graft)) OR (abg) OR ((osseous) AND (graft))))))) OR abstract:((title:((title:((intrabony defects) OR ((intrabony) AND (defects))) OR abstract:((intrabony defects) OR ((intrabony) AND (defects)))) AND (title:(((enamel) AND (matrix) AND (deriv*)) OR (emd) OR (emdogain)) OR abstract:(((enamel) AND (matrix) AND (deriv*)) OR (emd) OR (emdogain))) AND (title:(((bone) AND (graft*)) OR (bg) OR ((autogenous) AND (bone) AND (graft)) OR (abg) OR ((osseous) AND (graft))) OR abstract:(((bone) AND (graft*)) OR (bg) OR ((autogenous) AND (bone) AND (graft)) OR (abg) OR ((osseous) AND (graft))))) OR abstract:((title:((intrabony defects) OR ((intrabony) AND (defects))) OR abstract:((intrabony defects) OR ((intrabony) AND (defects)))) AND (title:(((enamel) AND (matrix) AND (deriv*)) OR (emd) OR (emdogain)) OR abstract:(((enamel) AND (matrix) AND (deriv*)) OR (emd) OR (emdogain))) AND (title:(((bone) AND (graft*)) OR (bg) OR ((autogenous) AND (bone) AND (graft)) OR (abg) OR ((osseous) AND (graft))) OR abstract:(((bone) AND (graft*)) OR (bg) OR ((autogenous) AND (bone) AND (graft)) OR (abg) OR ((osseous) AND (graft)))))))

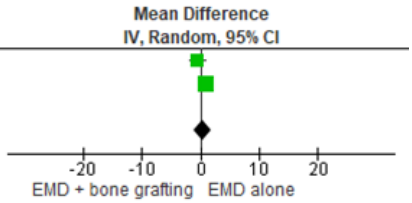
ANNEXES

Supplementary file B.2 – Meta-analysis graph for each outcome.

I. Analysis of change in probing depth (baseline - 12 months follow-up)

Study or Subgroup	EMD + bone grafting Mean [mm]	SD [mm]	Total	EMD alone Mean [mm]	SD [mm]	Total	Weight	Mean Difference IV, Random, 95% CI
Guida et al., 2007	5.1	1.7	14	5.6	1.7	14	41.9%	-0.50 [-1.76, 0.76]
Yilmaz et al., 2010	5.6	0.9	20	4.6	0.4	20	58.1%	1.00 [0.57, 1.43]
Total (95% CI)			**34**			**34**	**100.0%**	**0.37 [-1.08, 1.82]**

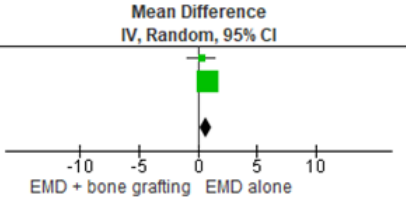
Heterogeneity: Tau² = 0.89; Chi² = 4.88, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 0.50 (P = 0.62)



II. Analysis of change in clinical attachment level (baseline - 12 months follow-up)

Study or Subgroup	EMD + bone grafting Mean [mm]	SD [mm]	Total	EMD alone Mean [mm]	SD [mm]	Total	Weight	Mean Difference IV, Random, 95% CI
Guida et al., 2007	4.9	1.8	14	4.6	1.3	14	20.8%	0.30 [-0.86, 1.46]
Yilmaz et al., 2010	4.2	1.1	20	3.4	0.8	20	79.2%	0.80 [0.20, 1.40]
Total (95% CI)			**34**			**34**	**100.0%**	**0.70 [0.17, 1.23]**

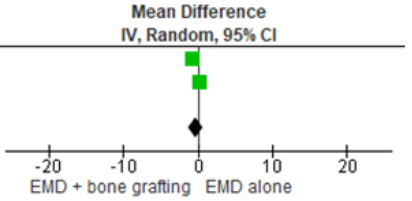
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)



III. Analysis of change in gingival margin level (baseline - 12 months follow-up)

Study or Subgroup	EMD + bone grafting Mean [mm]	SD [mm]	Total	EMD alone Mean [mm]	SD [mm]	Total	Weight	Mean Difference IV, Random, 95% CI
Guida et al., 2007	0.3	0.8	14	1.1	0.7	14	49.6%	-0.80 [-1.36, -0.24]
Yilmaz et al., 2010	1.4	0.9	20	1.2	0.8	20	50.4%	0.20 [-0.33, 0.73]
Total (95% CI)			**34**			**34**	**100.0%**	**-0.30 [-1.28, 0.68]**

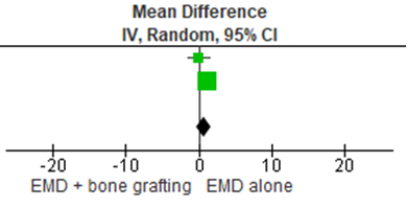
Heterogeneity: Tau² = 0.42; Chi² = 6.53, df = 1 (P = 0.01); I² = 85%
Test for overall effect: Z = 0.59 (P = 0.55)



IV. Analysis of change in bone defect depth (baseline - 12 months follow-up)

Study or Subgroup	EMD + bone grafting Mean [mm]	SD [mm]	Total	EMD alone Mean [mm]	SD [mm]	Total	Weight	Mean Difference IV, Random, 95% CI
Guida et al., 2007	4.3	1.3	14	4.3	2.4	14	31.4%	0.00 [-1.43, 1.43]
Yilmaz et al., 2010	3.9	1	20	2.8	0.8	20	68.6%	1.10 [0.54, 1.66]
Total (95% CI)			**34**			**34**	**100.0%**	**0.75 [-0.25, 1.76]**

Heterogeneity: Tau² = 0.30; Chi² = 1.97, df = 1 (P = 0.16); I² = 49%
Test for overall effect: Z = 1.48 (P = 0.14)



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