Effect of flap design for enamel matrix derivative application in intraosseus defects

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SUPPLEMENTAL APPENDIX

(SUPPLEMENTARY MATERIAL FOR ONLINE PUBLICATION)

Appendix Table 1. MEDLINE, SCOPUS and COCHRANE search strategies.

MEDLINE search

1. SEARCH TERMS: (“emd” OR “emdogain” OR “enamel matrix derivative” OR “enamel matrix proteins”) AND (“intraosseous” OR “infrabony” OR “infraosseous” OR “angular”)
2. FILTERS: /

SCOPUS search

1. SEARCH TERMS: (“emd” OR “emdogain” OR “enamel matrix derivative” OR “enamel matrix proteins”) AND (“intraosseous” OR “infrabony” OR “infraosseous” OR “angular”)
2. LIMITS: /

COCHRANE search

1. SEARCH TERMS (each used individually): “emd”, “emdogain”, “enamel matrix derivative”, “enamel matrix proteins”

Appendix Table 2. List of articles excluded after full-text evaluation and reason for exclusion.

Author - Date	Reason for exclusion
Seshima et al. (2019)	Lack of information about flap design/less than 10 patients included
Nemoto et al. (2018)	Lack of information about flap design
Seshima et al. (2017)	Lack of information about flap design
Agrali et al. (2016)	Lack of information about flap design
Ogihara et al. (2014)	Lack of information about flap design
Bhutda et al. (2013)	Lack of information about flap design
Dori et al. (2013)	Lack of information about flap design
Pietruska et al. (2012)	Lack of information about flap design
Parashis et al. (2012)	Lack of information about flap design
Aspriello et al. (2011)	Lack of information about flap design
Yilmaz et al. (2010)	Lack of information about flap design
Chambrone et al. (2010)	Lack of information about flap design
Leknes et al. (2009)	Lack of information about flap design
Fickl et al. (2009)	Lack of information about flap design
Hoidal et al. (2008)	Lack of information about flap design
Dori et al. (2008)	Lack of information about flap design
Sculean et al. (2008)	Lack of information about flap design
Sculean et al. (2007b)	Lack of information about flap design
Sculean et al. (2007a)	Lack of information about flap design
Guida et al. (2007)	Different flap designs were used and were not analyzed separately
Farina et al. (2007)	Different flap designs were used and were not analyzed separately
Chambrone et al. (2007)	Lack of information about flap design
Harris et al. (2007)	Lack of information about flap design
Sculean et al. (2006b)	Lack of information about flap design
Sculean et al. (2006a)	Lack of information about flap design
Parashis et al. (2006)	Lack of information about flap design
Trombelli et al. (2006)	Different flap designs were used and were not analyzed separately
Kuru et al. (2006)	Lack of information about flap design
Heden et al. (2006)	Lack of information about flap design
Sculean et al. (2005)	Lack of information about flap design
Dori et al. (2005)	Lack of information about flap design
Sculean et al. (2004)	Lack of information about flap design
Parodi et al. (2004)	Lack of information about flap design
Parashis et al. (2004)	Lack of information about flap design
Gurinsky et al. (2004)	Lack of information about flap design
Silvestri et al. (2003)	Lack of information about flap design
Sculean et al. (2003b)	Lack of information about flap design
Sculean et al. (2003a)	Lack of information about flap design
Windisch et al. (2002)	Lack of information about flap design
Velasquez-Plata et al. (2002)	Lack of information about flap design

Scheyer et al. (2002)	Lack of information about flap design
Trombelli et al. (2002)	Different flap designs were used and were not analyzed separately
Minabe et al. (2002)	Lack of information about flap design
Cardaropoli et al. (2002)	Less than 10 patients included in the study
Sculean et al. (2002a)	Lack of information about flap design
Sculean et al. (2002b)	Lack of information about flap design
Rosen et al. (2002)	Lack of information about flap design
Sculean et al. (2001c)	Lack of information about flap design
Sculean et al. (2001b)	Lack of information about flap design
Sculean et al. (2001a)	Lack of information about flap design
Pietruska (2001)	Lack of information about flap design
Froum et al. (2001)	Lack of information about flap design
Camargo et al. (2001)	Lack of information about flap design
Lekovic et al. (2001b)	Lack of information about flap design
Lekovic et al. (2001a)	Lack of information about flap design
Parashis et al. (2000)	Lack of information about flap design
Okuda et al. (2000)	Lack of information about flap design
Lekovic et al. (2000)	Lack of information about flap design
Heard et al. (2000)	Lack of information about flap design
Silvestri et al. (2000)	Lack of information about flap design
Pontoriero et al. (1999)	Lack of information about flap design
Sculean et al. (1999)	Lack of information about flap design
Harrel et al. (2016)	The flap design used in this study (V-MIS) is not included in the analysis of the present systematic review
Harrel et al. (2014)	The flap design used in this study (V-MIS) is not included in the analysis of the present systematic review
Aslan et al. (2017)	The flap design used in this study (EPPT) is not included in the analysis of the present systematic review
Silvestri et al. (2011)	Different regenerative strategies were used and were not analyzed separately
Rasperini et al. (2013)	Less than 10 patients included in the study
Pilloni et al. (2014)	Lack of information about flap design
Ragghianti Zangrando et al. (2014)	Lack of information about flap design
Zucchelli et al. (2017)	Less than 10 patients included in the study
Eickholz et al. (2014)	Data already published
Miliauskaite et al. (2008)	Data at 6-12 months not reported
Meyle et al. (2011)	Data already published
Hoffmann et al. (2016)	Data already published
Sculean et al. (2003c)	Data at 6-12 months not reported
Gutierrez et al. (2003)	Data at 6-12 months not reported

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Appendix Table 3. Main characteristics of the studies included in the systematic review.

Author (Date)	Study design	Treatment	EMD application	Group size (n patients)	Follow up (months)	Outcome measures
Heijl et al. (1997)	RCT, split mouth	EMD alone	MWF	26	8m	ΔCAL, ΔPD, Rx ΔINFRA, Residual PD
Zetterstrom et al. (1997)	CT	EMD alone	MWF	107	8m	ΔCAL, ΔPD, Rx ΔINFRA
Heden et al. (1999)	Case series	EMD alone	MWF	108	6m	ΔCAL, ΔPD, ΔREC, Rx ΔINFRA, Residual PD
Tonetti et al. (2002)	RCT	EMD alone	MPPT/SPPT	83	12m	ΔCAL, ΔPD, ΔREC
Zucchelli et al. (2002)	RCT	EMD alone	SPPT	30	12m	ΔCAL, ΔPD, Residual PD, ΔREC
Wachtel et al. (2003)	RCT, split mouth	EMD alone	MPPT	11	6m	ΔCAL, ΔPD, ΔREC
Zucchelli et al. (2003)	RCT	EMD alone EMD+DBBM	SPPT SPPT	30 30	12m	ΔCAL, ΔPD, ΔREC, Rx ΔINFRA
Francetti et al. (2004)	RCT	EMD alone	SPPT	11	12m	ΔCAL, ΔPD, Rx ΔINFRA, Residual PD
Sanz et al. (2004)	RCT	EMD alone	SPPT	35	12m	ΔCAL, ΔPD, ΔREC
Francetti et al. (2005)	RCT	EMD alone	SPPT	64	12m	ΔCAL, ΔPD, ΔREC, Rx ΔINFRA, Residual PD
Rosing et al. (2005)	RCT, split mouth	EMD alone	PPT	14	6m	ΔCAL, ΔPD, Residual PD, Rx ΔINFRA
Sipos et al. (2005)	RCT, split mouth	EMD alone	MPPT/SPPT	11	12m	ΔCAL, ΔPD, Residual PD, ΔREC, Rx ΔINFRA
Bokan et al. (2006)	RCT	EMD alone EMD+β-TCP	MPPT/SPPT MPPT/SPPT	19 19	12m	ΔCAL, ΔPD, Residual PD, ΔREC
Cortellini et al. (2007a)	Case series	EMD alone	MIST	40	12m	ΔCAL, ΔPD, Residual PD, ΔREC
Cortellini et al. (2007b)	Case series	EMD alone	MIST	13	12m	ΔCAL, ΔPD, Residual PD, ΔREC
Cortellini et al. (2008)	Case series	EMD alone	MIST	20	12m	ΔCAL, ΔPD, Residual PD, ΔREC
Crea et al. (2008)	RCT	EMD alone	SPPT	19	12m	ΔCAL, ΔPD, Residual PD, ΔREC, Rx ΔINFRA

Author (Date)	Study design	Treatment	EMD application	Group size (n patients)	Follow up (months)	Outcome measures
Jepsen et al. (2008)	RCT	EMD alone EMD+BCP	MPPT/SPPT MPPT/SPPT	35 38	6m	ΔCAL, ΔPD, Residual PD, ΔREC, Clinical ΔINFRA
Cortellini et al. (2009)	CT	EMD alone	M-MIST	15	12m	ΔCAL, ΔPD, Residual PD, ΔREC
Grusovin et al. (2009)	RCT	EMD alone	MPPT/SPPT	15	12m	ΔCAL, ΔPD, Residual PD, ΔREC, ΔINFRA
Harrel et al. (2010)	Case series	EMD alone	MIS	13	11m	ΔCAL, ΔPD, Residual PD, ΔREC
Ribeiro et al. (2010)	Case series	EMD alone	MIST	12	6m	ΔCAL, ΔPD, Residual PD, ΔREC
Saito et al. (2010)	Case series	EMD alone	PPT	16	6m	ΔCAL, ΔPD
Cortellini et al. (2011)	RCT	EMD alone EMD+DBBM	M-MIST M-MIST	15 15	12m	ΔCAL, ΔPD, Residual PD, ΔREC, Rx ΔINFRA
Fujinami et al. (2011)	Case series	EMD alone	PPT	13	6m	ΔCAL, ΔPD
Ribeiro et al. (2011)	RCT	EMD alone	MIST	15	6m	ΔCAL, ΔPD, Residual PD, ΔREC, Rx ΔINFRA
Siciliano et al. (2011)	RCT	EMD alone	MPPT/SPPT	20	12m	ΔCAL, ΔPD, Residual PD, ΔREC
Rollke et al. (2012)	RCT	EMD alone +/- systemic doxycycline	MPPT/SPPT MPPT/SPPT	27 27	6m	ΔCAL, ΔPD, Residual PD, Rx ΔINFRA,
De Leonardis et al. (2013)	RCT, split mouth	EMD alone EMD+BCP	MPPT/SPPT MPPT/SPPT	34 34	12m	ΔCAL, ΔPD, Residual PD, ΔREC, Rx ΔINFRA
Al Machot et al. (2014)	RCT	EMD alone	MPPT	19	6m	ΔCAL, ΔPD, Residual PD, ΔREC, Clinical ΔINFRA
Farina et al. (2014)	Pragmatic trial	EMD alone EMD+DBBM	SFA SFA	12 12	6m	ΔCAL, ΔPD, Residual PD, ΔREC
Mitani et al. (2015)	Retrospective cohort	EMD alone	MIST	12	12m	ΔCAL, ΔPD, ΔREC
Abu-Ta'a (2016)	RCT	EMD+DFDBA + systemic amoxicillin EMD+DFDBA	MPPT MPPT	20 20	12m	ΔCAL, Residual PD, ΔREC
Aydemir Turkal et al. (2016)	RCT	EMD alone	MPPT/SPPT	25	6m	ΔCAL, ΔPD, Residual PD, ΔREC, Rx ΔINFRA
Ghezzi et al. (2016)	RCT	EMD+DBBM	MIST	10	12m	ΔCAL, ΔPD, Residual PD, ΔREC
Aimetti et al. (2017)	RCT	EMD alone EMD alone	SFA/M-MIST Flapless	15 15	12m	ΔCAL, ΔPD, Residual PD, ΔREC, Rx ΔINFRA

Author (Date)	Study design	Treatment	EMD application	Group size (n patients)	Follow up (months)	Outcome measures
Losada et al. (2017)	RCT	EMD alone EMD+ BCP	SPPT SPPT	25 21	6m	ΔCAL, ΔPD, Residual PD, ΔREC, Rx ΔINFRA
Trombelli et al. (2017)	Retrospective cohort	EMD+DBBM	SFA	15	6m	ΔCAL, ΔPD, Residual PD, ΔREC
Ferrarotti et al. (2018)	Case series	EMD+AB	MIST	15	12m	ΔCAL, ΔPD, Residual PD, ΔREC, Rx ΔINFRA
Trombelli et al. (2018)	Retrospective cohort	EMD+DBBM (smokers) EMD+DBBM (non-smokers)	SFA SFA	11 15	6m	ΔCAL, ΔPD, Residual PD, ΔREC
Bertoldi et al. (2019)	Retrospective cohort	EMD alone EMD+DBBM	M-MIST M-MIST	10 10	12m	ΔPD, ΔREC
Moreno Rodriguez et al. (2019)	Retrospective cohort	EMD+DBBM	MIST	15	12m	ΔCAL, ΔPD, Residual PD, ΔREC

Table legend

AB: Autogenous Bone; β-TCP: Beta-TriCalcium Phosphate; BCP: Biphasic Calcium Phosphate; CT: Controlled Trial; DBBM: Demineralized Bovine Bone Mineral; EMD: Enamel Matrix Derivative; MIS: Minimally Invasive Surgical approach; MIST: Minimally Invasive Surgical Technique; M-MIST: Modified Minimally Invasive Surgical Technique; MPPT: Modified Papilla Preservation Technique; MWF: Modified Widman Flap; PPT: Papilla Preservation technique; RCT: Randomized Controlled Trial; SFA: Single Flap Approach; SPPT: Simplified Papilla Preservation Technique; ΔCAL: Clinical Attachment Level change; ΔPD: Probing Depth change; ΔREC: Gingival Recession change; Rx ΔINFRA: Radiographic Infrabony defect change.

Appendix Table 4. Network meta-analysis results related to the change in gingival recession (ΔREC).

Strategy	Flap design	median	95% CrI
EMD alone	Absolute effect		
	SFVs	0.41	(-0.43, 1.30)
	MWF	0.60	(-0.70, 1.90)
	PPVs	0.61	(-0.22, 1.42)
	MIVs	0.36	(-0.51, 1.23)
	Non-surgical (flapless)	0.60	(-0.45, 1.68)
	deviance	-11.33	
	pD	25.21	
	DIC	13.88	
	n° of studies (n° two-arm trials)	29 (1)	
EMD + graft	Absolute effect		
	SFVs	0.69	(0.04, 1.41)
	PPVs	0.55	(-0.11, 1.24)
	MIVs	0.26	(-0.48, 1.08)
	deviance	-4.49	
	pD	11.86	
	DIC	7.36	
	n° of studies [#] (n° two-arm trials)	14 (0)	

Table legend

PPVs: Papilla Preservation variants including Papilla Preservation technique (Takei et al., 1985), Modified Papilla Preservation technique (Cortellini et al., 1995), and Simplified Papilla Preservation technique (Cortellini et al., 1999); MIVs: Minimally Invasive variants including Minimally Invasive Surgical approach (Harrel, 1999) and Minimally Invasive Surgical Technique (Cortellini et al., 2007); MWF: Modified Widman Flap (Ramfjord et al., 1974); SFVs: Single Flap variants including Single Flap Approach (SFA; Trombelli et al., 2007) and Modified MIST (M-MIST; Cortellini et al., 2009).

[#] For the analysis, the two treatment arms of the study by Abu-Ta'a et al. (2016) (i.e., EMD+DFDBA with or without systemic amoxicillin at sites accessed with MPPT) and Trombelli et al. (2018) (i.e., EMD+DBBM at sites accessed with SFA in smokers and non-smokers) were considered as single arms from two different studies.

Appendix Table 5. Consensus results of the risk of bias assessment: RCTs (RoB 2).

	Hejil et al (1997)	Losada et al. (2017)	Aydemir Turkal et al (2016)	Al Machot et al (2014)	De Leonardis et al (2013)	Siciliano et al (2011)	Jepsen et al (2008)	Crea et al (2008)	Bokan et al (2006)	Sipos et al (2005)	Sanz et al (2004)	Francetti et al (2005)	Francetti et al (2004)	Zucchelli et al (2003)	Wachtel et al (2003)	Zucchelli et al (2002)	Tonetti et al (2002)	Rosing et al (2005)	Ribeiro et al (2011)	Aimetti et al (2017)	Cortellini et al (2011)	Abu/Ta'a et al (2016)	Rollke et al (2012)	Ghezzi et al (2016)	Grusovin et al (2009)
Risk of bias arising from the randomisation process	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Some concerns	Low	Some concerns	Low	Low	Low	Low	Low	Low	Low	Low	Low
Risk of bias due to deviations from the intended interventions – effect of assignment to intervention	Low	Low	Low	Low	Low	Low	Low	Low	Some concerns	Low	Low	Some concerns	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Risk of bias due to deviations from the intended interventions – effect of adhering to intervention	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Some concerns	Low	Low
Missing outcome data	Low	Some concerns	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Risk of bias in measurement of the outcome	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Risk of bias in selection of the reported result	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Some concerns	Low	Low
Overall risk of bias	Low	Some concerns	Low	Low	Low	Low	Low	Low	Some concerns	Low	Low	Some concerns	Low	Some concerns	Low	Some concerns	Low	Low	Low	Low	Low	Low	Some concerns	Low	Low

Appendix Table 6. Consensus results of the risk of bias assessment: Non-RCTs (ROBINS-I assessment tool).

	Zetterstrom et al (1997)	Mitani et al (2015)	Cortellini et al (2009)	Farina et al (2014)	Trombelli et al (2017)	Trombelli et al (2018)	Bertoldi et al (2019)	Moreno Rodriguez et al (2019)
Risk of bias due to confounding	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Risk of bias in selection of participants into the study	Moderate	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Risk of bias in classification of interventions	Low	Low	Low	Moderate	Low	Low	Low	Low
Risk of bias due to deviation from intended interventions	Low	Moderate	Low	Low	Low	Low	Low	Low
Risk of bias due to missing data	Moderate	Moderate	Low	Low	Low	Low	Low	Low
Risk of bias in measurement of outcomes	Low	Low	Low	Low	Low	Low	Moderate	Low
Risk of bias in selection of the reported result	Low	Low	Low	Low	Low	Low	Low	Low
Overall risk of bias	Moderate	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate