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Review article

The efficiency of the regeneration of periodontal intrabony defects in East Asians: A systematic review and pooled analysis

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Abstract This article aimed to assess the efficacy of periodontal regenerative therapy (PRT) for treating periodontal intrabony defects in East Asians. The systematic review was performed according to the PRISMA guidelines. Literature searches on the PubMed and national medical journal databases, and representative clinical journals of the East Asians were performed on July 31, 2018. Randomized controlled trials, prospective case–control studies, retrospective analyses, and case series receiving regenerative procedures, including barrier membrane (BM) and enamel matrix derivative (EMD) applications with or without bone replacement graft (BRG), with follow-up periods of 6 and 12 months were evaluated. The outcome variables were probing depth (PD) reduction and clinical attachment level (CAL) gain. Twenty studies were included, of which eight were assessed for bias risk. Compared to open flap debridement, PD reduction and CAL gain were superior in all PRTs at both follow-up time points. BM or EMD alone showed equivalent outcomes at 6 months, and CAL gain appeared greater with BM alone at 12 months. BM with BRG showed inferior CAL gain relative to BM alone, but EMD with BRG showed superior CAL gain relative to EMD alone at 12 months. In conclusion, PRT showed improved regenerative outcomes compared with OFD in East Asians, while BM application appeared less efficient than in non-East Asians. BRG supplementation provided additional clinical benefits in EMD application.

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Introduction

Bacterial plaque invasion can lead to alveolar bone resorption, and intrabony defects form when the resorption rate on the neighboring tooth surface varies, especially when wide interproximal spaces, open mesiodistal contacts, or traumatic occlusions are present.[1] The intrabony defects create difficulties in nonsurgical/surgical debridement and might also exaggerate plaque-induced inflammation.[2]

Periodontal regenerative therapy (PRT) aims to restore lost periodontal structures and establish new connective tissue (cementum and periodontal ligament [PDL]) and alveolar bone. Therefore, PRT is often recommended for treating teeth with deep intrabony defects.[3] Clinical and histologic evidence shows that PRT can facilitate the healing of intrabony defects.[4] From the clinical perspective, PRT aims to increase periodontal attachment to bone, decrease pocket depth (PD), and minimize gingival recession.[5]

PRT can be divided into two main strategies, guided tissue regeneration (GTR) and enamel matrix derivatives (EMD)-mediated periodontal regeneration, occasionally combined with bone replacement grafts (BRGs). GTR involves placing a barrier membrane (BM) on the defect to prevent the downgrowth of epithelium and maintain space for clot stabilization.[6] EMD contributes to forming acellular cementum to facilitate periodontal attachment apparatus development.[7] BRGs, including autografts, allografts, xenografts, and alloplasts, provide a structural framework to support osseous defects and may show various capabilities (i.e., osteogenicity, osteoinductivity, and osteoconductivity) to coordinate bone formation.[8] While the mechanisms of these strategies differ, they all have shown superior clinical outcomes in PD reduction and clinical attachment level (CAL) gain relative to open flap debridement (OFD). Compared with OFD, GTR was associated with 1.15 mm CAL gain and 1.24 mm PD reduction at 12-month follow-up.[9] A previous systemic review reported that EMD application contributed to an additional 1.2 mm CAL gain and 1.2 mm PD reduction relative to OFD.[10] Meta-analyses have shown that supplementing BRG with GTR or EMD application resulted in additional clinical improvements in CAL and PD compared to GTR or EMD alone.[11,12] Nibali et al. reported that the mean benefit of these PRT strategies was an additional 1.34 mm CAL gain and 1.20 mm PD reduction compared to OFD alone.[9]

There is a generally held view that Asians have a higher prevalence of periodontal diseases due to anatomical variations, including short root trunks or supernumerary distolingual roots (DLRs) on molars and thin gingival tissue. The root length of extracted molars in Taiwanese patients was generally 1–2 mm shorter than in non-Asian populations,[13] potentially leading to unfavorable BM adaptation during regenerative surgery.[14] While the prevalence of DLRs on molars is <5% in Caucasians and Africans, it is 10%–30% in Asians, including Chinese, Japanese, Korean, and Taiwanese populations.[15] The presence of DLRs on mandibular molars may affect bacterial biofilm retention, leading to difficulties when conducting operations to compromise the outcomes of regeneration. A comprehensive cross-sectional survey of gingival tissue thickness in Asian populations found that Asian patients with Chinese, Japanese, Korean, and Vietnamese origins had high percentages of thin gingiva biotype and moderate recession.[16] The gingival tissue thickness in Asian populations was thinner than in non-Asian populations,[17] indicating that Asian populations might be more prone to gingival recession, making periodontal surgery more challenging. Furthermore, thinner palatal masticatory mucosa was also reported in Taiwanese patients.[15] Altogether, these variations might result in higher risks of attachment loss and unexpected prognosis after PRT in Asians.

This article aimed to evaluate the efficacy of regenerative procedures for periodontal intrabony defects in East Asians. The data from included studies were pooled for analysis, which focused on answering the following questions: (1) Does PRT with BM or EMD provide superior clinical improvements than OFD?; (2) Does BM or EMD combined with BRG provide additional improvements over BM or EMD alone?

Materials and methods

Protocol

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18] A direct online search was performed in the PubMed database on July 31, 2018, without language restriction, using the following search terms and filters: ((((enamel matrix derivative OR membrane OR Emdogain))) AND ((intrabony defects OR periodontal defects OR vertical defects))) AND ((periodontal OR periodontitis)) AND ((randomized controlled trials OR randomized clinical trials OR prospective study OR comparative study)) AND ((East Asia OR Taiwan OR China OR Japan OR Korea OR Hong Kong OR Singapore)). In addition, electronic searches were also performed on the following national medical journal databases: CiNii (Japan), CNKI (China), and KoreaMed (Korea). The search criteria were identical to those used with PubMed except for the country filters. Furthermore, a manual search of representative East Asian clinical journals was performed: Journal of Investigate and Clinical Dentistry (Hong Kong), Singapore Medical Journal (Singapore), Singapore Dental Journal (Singapore), Journal of Formosan Medical Associations (Taiwan), Journal of Dental Sciences (Taiwan), and Journal of Taiwan Academy of Periodontology (Taiwan).

Eligibility criteria

The titles and abstracts of articles in the search results were searched by TS and screened by PCC. Only studies fulfilling the following PICOST questions were considered eligible for inclusion: (i) populations are patients with periodontal intrabony defects; (ii) interventions are periodontal regeneration procedures, including EMD alone, EMD with BRG, BM alone, BM with BRG, and BRG alone; (iii) for

comparison, no comparison was required; (iv) outcomes are CAL or PD measurements; (v) study types are randomized clinical trials, prospective case–control studies, retrospective analyses, and case series with >10 patients receiving the same treatment; (vi) timing is a follow-up period of 6–12 months.

Studies were excluded if they met any of the following criteria: (i) duplication with other studies; (ii) Materials or treatment procedures are not clearly reported, (iii) follow-up period shorter than six months after regeneration procedures; (iv) fewer than 10 patients.

Disagreements on inclusion or exclusion of the retrieved studies were resolved by discussions among authors until a consensus was reached.

Quality assessment

Studies involving the direct comparison of two treatment groups were assessed for their risk of bias (RoB) by examining six main criteria: (i) random sequence generation (adequate, inadequate, or unclear); (ii) allocation concealment (adequate, inadequate, or unclear); (iii) blinding of outcome assessment (yes, no, or unclear); (iv) blinding of outcome assessment (yes, no, or unclear); (v) incomplete outcome data (yes, no, or unclear); (vi) selective reporting (yes, no, or unclear). The results were illustrated using a meta-analysis managing software (Review Manager v.5.3; Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark), and the studies were grouped into three RoB categories: (i) low risk: the study met all criteria; (ii) moderate risk: the study met ≥3 criteria; (iii) high risk: the study met <3 criteria.

Statistical analysis

Due to the diversity of reported data, the data were grouped into two categories and analyzed independently: (i) the clinical parameters at baseline and evaluation time point; (ii) the change of clinical parameters during the evaluation period. In each category, the clinical parameters, including PD and CAL, in the same treatment group at the same evaluation time point/period, were pooled from the included studies. The data of each included study are presented as mean ± standard deviation (SD), and the pooled data in each treatment group (OFD, BM, BM with BRG, EMD, EMD with BRG) are presented as pooled mean ± pooled SD. Differences between treatment groups were evaluated using the unpaired t-test. Results with $P < 0.05$ were considered statistically significant.

Results

Selected studies

Eighty-two articles were identified through our electronic database searches. FiftySixty-two articles were excluded as they met at least one of the exclusion criteria. Therefore, 20 articles were included in our analyses: 17 from Japan, two from Korea, and one from Taiwan.

Risk of bias

Twelve of the 20 included studies only involved a single treatment group. Therefore, eight studies were assessed for RoB, and the results are shown in Fig. 1. Only the study by Kitamura et al. was considered to have a low RoB, and most included studies had a moderate RoB. The study by Mitani et al. was considered to have a high RoB because the patients chose the treatment procedures based on information provided by the researchers.

Probing depth reduction and clinical attachment level gain at 6 months

9 clinical studies reported PD and CAL at the preoperative and 6-month postoperative time points, and the results are summarized in Table 1. Preoperative PD and CAL were

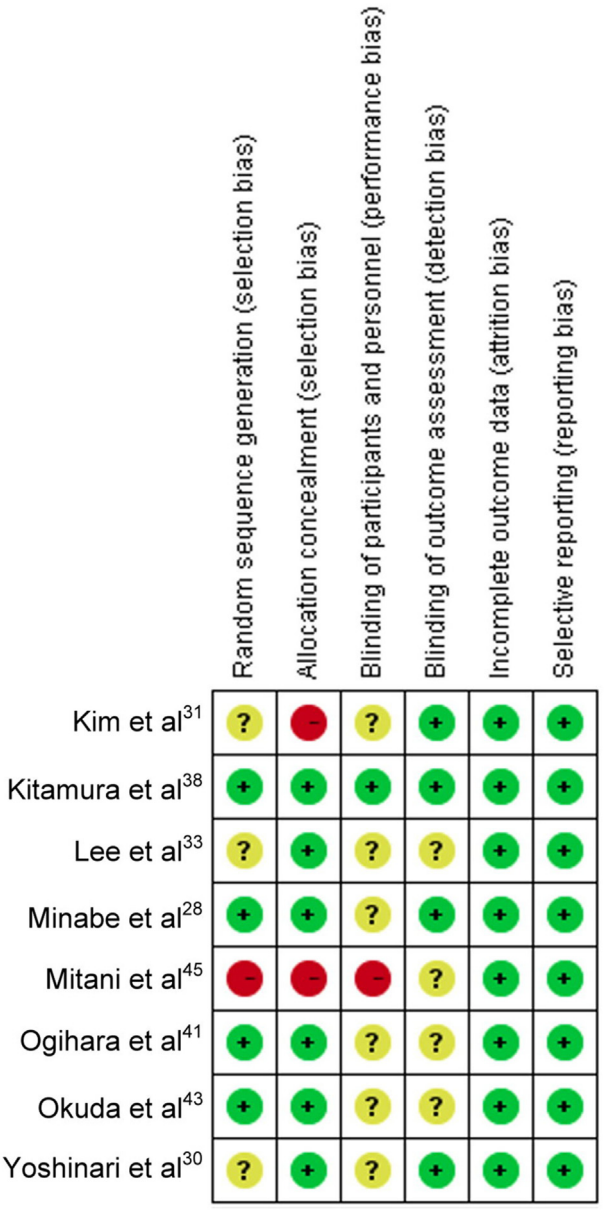

Fig. 1 Risk of bias (RoB) summary of the included studies.

generally at an equivalent level for all treatment groups, except for CAL between BM and EMD ($P = 0.001$). At 6 months postoperatively, PD was significantly higher in the OFD group than in the BM ($P < 0.001$) and EMD ($P < 0.001$) groups; PD was significantly greater in the EMD group than in the BM group ($P < 0.001$). CAL was significantly lower in the EMD group than in the OFD ($P < 0.001$) and BM ($P < 0.001$) groups. 28 patients who received OFD had a 3.1 mm mean PD reduction and 1.7 mm mean CAL gain. 159 patients who received BM had a 4.0 mm mean PD reduction and 3.0 mm mean CAL gain. 13 patients who received BM with BRG had a 4.2 mm mean PD reduction and 2.8 mm mean CAL gain. 105 patients who received EMD had a 3.7 mm mean PD reduction and 3.0 mm CAL gain. There was no clinical data on EMD with BRG at this time point.

12 clinical studies reported the change in PD and CAL from the preoperative to 6-month postoperative time points, including 3 studies investigating sites with combined intrabony and furcation defects. The results are summarized in Table 2. Briefly, 71 patients who received OFD had a 3.1 ± 1.3 mm PD reduction and 1.7 ± 1.1 mm CAL gain. 132 patients who received BM had a 3.6 ± 1.5 mm PD reduction and 2.5 ± 1.6 mm CAL gain. 57 patients who received BM with BRG had a 3.5 ± 1.8 mm PD reduction and 2.8 ± 1.8 mm CAL gain. 266 patients who received EMD had a 3.6 ± 1.6 mm PD reduction and 2.6 ± 1.5 mm CAL gain. There was no clinical data on EMD with BRG in this category. The change in PD was significantly lower in the OFD group than in the BM ($P = 0.003$) and EMD ($P = 0.007$) groups. The change in CAL was significantly lower in the OFD group than in the BM ($P < 0.001$), BM with BRG ($P = 0.008$), and EMD ($P < 0.001$) groups.

Probing depth reduction and clinical attachment level gain at 12 months

7 clinical studies reported PD and CAL at the preoperative and 12-month postoperative time points, and the results are summarized in Table 3. Preoperative PD was significantly lower in the OFD group than in the BM ($P = 0.032$), BM with BRG ($P = 0.009$), EMD ($P < 0.001$), and EMD with BRG ($P = 0.027$) groups. Preoperative CAL was significantly lower in the OFD group than in the EMD group ($P = 0.035$). At 12 months postoperatively, PD was significantly greater in the OFD group than in the BM ($P < 0.001$) and EMD with BRG ($P < 0.001$) groups. In addition, PD was significantly greater in the EMD group than in the BM ($P < 0.001$) and EMD with BRG ($P < 0.001$) groups. Moreover, PD was significantly greater in the BM with BRG group than in the BM group ($P = 0.017$). CAL was significantly greater in the OFD group than in the BM ($P = 0.036$), EMD ($P = 0.004$), and EMD with BG ($P < 0.001$) groups. In addition, CAL was significantly greater in the EMD group than in the EMD with BRG group ($P < 0.001$). 45 patients who received OFD had a 2.9 mm mean PD reduction and 1.4 mm mean CAL gain. 37 patients who received BM had a 4.5 mm mean PD reduction and 3.1 mm mean CAL gain. 13 patients who received BM with BRG had a 4.3 mm mean PD reduction and 2.1 mm

Table 1 The included studies with the data of clinical parameters at the initial and 6-month follow-up examinations.

Study (Ref no.)	Defect pattern	Treatment group	Sample size (n)	Initial PD (mm)	Initial CAL (mm)	6-month PD (mm)	6-month CAL (mm)
Fujinami et al.[26]	1 to 3-wall Intrabony defects (osseous defects at least 4 mm deep and 2 mm wide)	EMD	25	7.1 ± 2.8	8.1 ± 2.4	N/A	4.7 ± 2.0
Narita et al.[27]	Vertical and Horizontal Defect	EMD	90	6.3 ± 2.0	7.5 ± 2.4	3.2 ± 1.1	4.7 ± 1.8
Minabe et al.[28]	2-wall Intrabony defect and class II furcation defect	BM	12	6.5 ± 2.2	7.7 ± 2.2	2.7 ± 0.7	4.6 ± 1.2
Yamanouchi et al.[29]	Intrabony defects	BM	44	6.0 ± 1.8	9.3 ± 2.8	3.0 ± 1.3	6.9 ± 2.8
Yoshinari et al.[30]	Intrabony defects	BM	20	6.0 ± 0.5	7.9 ± 0.6	2.2 ± 0.2	5.9 ± 0.7
		BM	20	5.3 ± 0.5	7.7 ± 0.6	1.8 ± 0.3	4.7 ± 0.7
Kim et al.[31]	Intrabony defects	OFD	13	6.9 ± 1.2	7.5 ± 1.3	3.8 ± 0.9	5.7 ± 1.8
		BM with BRG	13	7.6 ± 1.7	8.5 ± 2.2	3.4 ± 1.3	5.7 ± 1.7
Hou et al.[32]	2 to 3 wall defects (with or without degree II furcation defect)	BM	18	8.1 ± 1.2	9.5 ± 1.8	2.8 ± 0.5	5.6 ± 1.4
		BM	22	8.4 ± 1.4	10.2 ± 2.1	3.0 ± 0.8	5.8 ± 2.5
Minabe et al.[28]	Intrabony defects	BM	23	7.0 ± 1.4	7.7 ± 1.5	2.7 ± 0.8	4.4 ± 1.2
Lee et al.[33]	Intrabony defects	OFD	15	7.47 ± 1.56	8.67 ± 1.72	4.33 ± 1.40	7.0 ± 1.60
		EMD	14	7.57 ± 1.4	8.93 ± 2.23	3.71 ± 1.27	6.00 ± 1.92
	OFD		28	7.2 ± 1.4	8.1 ± 1.5	4.1 ± 1.2	6.4 ± 1.7
	BM		159	6.7 ± 1.4	8.7 ± 2.0	2.7 ± 0.9	5.7 ± 1.9
	BM with BRG		13	7.6 ± 1.7	8.5 ± 2.2	3.4 ± 1.3	5.7 ± 1.7
	EMD		151	6.8 ± 2.0	7.9 ± 2.3	3.1 ± 1.1	4.9 ± 1.8
	EMD with BRG		0	N/A	N/A	N/A	N/A

Abbreviations: PD, probing depth. CAL, clinical attachment level. EMD, enamel matrix derivatives. BM, barrier membrane. OFD, open flap debridement. BRG, bone replacement graft. N/A, not available.

Table 2 The included studies with the data of PD reduction or CAL gain at the 6-month follow-up examination.

Study (Ref no.)	Defect pattern	Treatment group	Sample size (n)	PD reduction (mm)	CAL gain (mm)
Fujinami et al.[26]	1 to 3-wall bony defects (osseous defects at least 4 mm deep and 2 mm wide)	EMD	25	4.4 ± 1.4	3.4 ± 1.4
Narita et al.[27]	1 to 3-wall bony defects and horizontal defects	EMD	90	3.1 ± 1.7	2.8 ± 1.6
Saito et al.[34]	1 to 3-wall Intrabony defects (osseous defects at least 4 mm deep and 2 mm wide)	EMD	25	4.2 ± 1.2	3.2 ± 1.5
Sakata et al.[35]	2-wall intrabony defects and Class II furcation defects	BM	12	3.8 ± 1.9	3.1 ± 1.8
Setoguchi et al.[36]	Intrabony defects	BM	39	3.45 ± 1.43	1.77 ± 1.77
Kobayashi et al.[37]	3-wall Intrabony defects	BM	21	3.1 ± 1.7	2.2 ± 1.4
Yamanouchi et al.[29]	Intrabony defects	BM with BRG	44	3.0 ± 1.9	2.4 ± 2.0
Kitamura et al.[38]	Intrabony defects	OFD	43	N/A	1.7 ± 1.19
		EMD	112	N/A	2.1 ± 1.39
Yoshinari et al.[30]	Intrabony defects	BM	20	3.8 ± 0.5	2.0 ± 0.5
Kim et al.[31]	Intrabony defects	OFD	13	3.1 ± 1.3	1.8 ± 1.1
		BM with BRG	13	4.2 ± 1.9	2.8 ± 2.0
Hou et al.[32]	2 to 3-wall intrabony defects	BM	18	4.4 ± 1.4	3.6 ± 2.2
	(with or without degree II furcation defect)	BM	22	3.9 ± 1.8	3.5 ± 1.6
Lee et al.[33]	Intrabony defects	OFD	15	3.13 ± 1.3	1.67 ± 0.72
	OFD		71	3.1 ± 1.3	1.7 ± 1.1
	BM		132	3.7 ± 1.5	2.5 ± 1.6
	BM with BRG		57	3.3 ± 1.9	2.5 ± 2.0
	EMD		266	3.6 ± 1.6	2.6 ± 1.5
	EMD with BRG		0	N/A	N/A

Abbreviations: PD, probing depth. CAL, clinical attachment level. EMD, enamel matrix derivatives. BM, barrier membrane. OFD, open flap debridement. BRG, bone replacement graft. N/A, not available.

Table 3 The included studies with the data of clinical parameters at the initial and 12-month follow-up examinations.

Study (Ref no.)	Defect pattern	Treatment group	Sample size (n)	Initial PD (mm)	Initial CAL (mm)	12-month PD (mm)	12-month CAL (mm)
Yoshinari et al.[39]	Intrabony defects	OFD	14	5.1 ± 1.2	6.6 ± 2.3	1.6 ± 0.7	5.0 ± 1.8
		BM	14	6.1 ± 1.3	7.9 ± 2.7	1.9 ± 0.8	4.7 ± 3.1
Seshima et al.[40]	Intrabony defects	EMD	42	6.8 ± 1.2	7.6 ± 1.8	3.3 ± 1.0	4.8 ± 1.3
Ogihara et al.[41]	Intrabony defects	EMD	23	6.56 ± 0.59	7.13 ± 0.87	3.43 ± 0.51	4.09 ± 0.9
		EMD with BRG	23	6.62 ± 0.97	7.28 ± 0.72	2.19 ± 0.40	3.14 ± 0.36
		EMD with BRG	23	6.43 ± 0.79	7.26 ± 0.96	2.74 ± 0.54	2.70 ± 0.47
Ogihara et al.[42]	2-3 wall intrabony defects	EMD with BRG	23	6.43 ± 0.72	7.26 ± 0.94	2.74 ± 0.54	3.74 ± 0.69
Okuda et al.[43]	Intrabony defects	OFD	18	6.22 ± 0.73	6.83 ± 1.2	4.00 ± 1.03	6.00 ± 1.28
		EMD	18	6.33 ± 0.91	6.72 ± 1.13	3.39 ± 0.85	4.94 ± 1.0
Kim et al.[31]	Intrabony defects	OFD	13	6.9 ± 1.2	7.5 ± 1.3	3.9 ± 1.3	5.8 ± 1.9
		BM with BRG	13	7.6 ± 1.7	7.5 ± 1.3	3.3 ± 1.4	5.6 ± 1.9
Minabe et al.[28]	Intrabony defects	BM	23	7.0 ± 1.4	7.7 ± 1.5	2.4 ± 0.7	4.7 ± 1.3
		EMD	22	7.8 ± 1.2	8.6 ± 1.4	2.4 ± 0.9	5.6 ± 1.3
	OFD		45	6.1 ± 1.0	7.0 ± 1.6	3.2 ± 1.0	5.6 ± 1.6
	BM		37	6.7 ± 1.4	7.8 ± 2.0	2.2 ± 0.7	4.7 ± 2.1
	BM with BRG		13	7.6 ± 1.7	7.7 ± 1.3	3.3 ± 1.4	5.6 ± 1.9
	EMD		105	6.9 ± 1.0	7.6 ± 1.5	3.2 ± 0.9	4.8 ± 1.2
	EMD with BRG		69	6.5 ± 0.8	7.3 ± 0.9	2.6 ± 0.5	3.2 ± 0.5

Abbreviations: PD, probing depth. CAL, clinical attachment level. EMD, enamel matrix derivatives. BM, barrier membrane. OFD, open flap debridement. BRG, bone replacement graft. N/A, not available.

mean CAL gain. 105 patients who received EMD had a 3.5 mm mean PD reduction and 3.0 mm CAL gain. and 69 patients who received EMD with BRG had a 3.9 mm mean PD reduction and 4.1 mm CAL gain.

7 clinical studies reported the change of PD and CAL from the preoperative to 12-month postoperative time points, and the results are summarized in Table 4. Briefly, 47 patients who received OFD had a 2.2 ± 0.9 mm PD reduction and 0.9 ± 1.0 mm CAL gain. 12 patients who received BM had a 2.8 ± 0.4 mm PD reduction and 3.7 ± 0.9 mm CAL gain. 13 patients who received BM with BRG had a 4.3 ± 0.5 mm PD reduction and 2.9 ± 0.8 mm CAL gain. 113 patients who received EMD had a 2.8 ± 0.6 mm PD reduction and 2.7 ± 1.1 mm CAL gain. 69 patients who received EMD with BRG had a 3.9 ± 0.5 mm PD reduction and 3.7 ± 0.6 mm CAL gain. The change in PD and CAL were significantly lower in the OFD group than in all other groups ($P \leq 0.001$ for all comparisons). Supplementing BM or EMD with BRG (i.e., BM with BRG or EMD with BRG) significantly improved the change in PD ($P < 0.001$ for both comparisons). The change in CAL was significantly greater in the EMD with BRG group than in the EMD group ($P < 0.001$) but significantly lower in the BM with BRG group than in the BM group ($P = 0.029$). Additionally, the change in CAL was significantly greater in the BM group than in the EMD group ($P = 0.003$).

Discussion

This systematic review analyzed PRT efficacy for treating periodontal intrabony defects in East Asians. The results show that PRT is generally associated with greater PD reductions and CAL gains than OFD. To the authors' knowledge, this is the first review addressing this topic in East Asians.

It has been shown that following OFD, the PD reduction and CAL gain were notable at 10 weeks and stable for one year.[19] Cairo et al. showed that a 90% soft tissue rebound occurred within the first 6 months and indicated that a consistent, stable gingival margin could be established at 6 months after OFD.[20] In the present analysis, PD reduction and CAL gain were observed at 6 months after OFD. However, these improvements appeared to be reduced at 12 months (Tables 1–4). This phenomenon might be associated with severe periodontal destruction in the studies included in the 6-month analysis. Compared with a previous systematic review,[9] PD reduction was equivalent at 12 months after OFD, while CAL gain was ~0.5 mm inferior in this analysis, indicating more gingival recession occurred, potentially due to the thin gingival biotype of Asians.[17] On the other hand, the extent of plaque control/gingival inflammation and the level of gingival margin repositioning may also influence the clinical outcome of OFD.[20]

In GTR-treated sites, new cementum, PDL, and alveolar bone regeneration can be observed 6 months after the procedure, with evidence of radiographic bone refilling and CAL gain.[21] This outcome can be maintained for up to 10 years.[22] However, the improvement in CAL gain and PD reduction after 12 months in East Asians was relatively inferior (Tables 3 and 4), presumably due to anatomic variations in Asians, including short root length and DLR presence in molars, causing difficulty in adapting BM and compromised regeneration outcomes.[14] In BM application, primary closure of the surgical wound was required to prevent potential contamination of the wounds. Since Asians are characterized by a thin gingival biotype, primary wound closure could be more difficult, influencing the outcome of BM application. CAL gain increased while PD reduction decreased in sites covered by BM from 6 to 12

Table 4 The included studies with the data of PD reduction or CAL gain at the 12-month follow-up examination.

Study (Ref no.)	Defect pattern	Treatment group	Sample size (n)	PD reduction (mm)	CAL gain (mm)
Saito et al.[44]	1 to 3-wall Intrabony defects (osseous defects at least 4 mm deep and 2 mm wide)	EMD	18	N/A	3.39 ± 1.46
Seshima et al.[40]	Intrabony defects	EMD	42	N/A	2.9 ± 1.2
Mitani et al.[45]	2 to 3-wall intrabony defects	OFD	16	1.0 ± 0.3	0.2 ± 0.3
		BM	12	2.8 ± 0.4	3.7 ± 0.9
		EMD	12	1.7 ± 0.3	2.2 ± 0.9
Ogihara et al.[41]	Intrabony defects	EMD	23	3.26 ± 0.3	3.04 ± 0.53
		EMD with BRG	23	4.38 ± 0.34	4.14 ± 0.36
		EMD with BRG	23	3.7 ± 0.33	3.52 ± 0.5
Ogihara et al.[42]	2 to 3-wall intrabony defects	EMD with BRG	23	3.7 ± 0.76	3.5 ± 0.79
Okuda et al.[43]	Intrabony defects	OFD	18	2.22 ± 0.81	0.83 ± 0.86
		EMD	18	3.0 ± 0.97	1.72 ± 1.07
Kim et al.[31]	Intrabony defects	OFD	13	3.0 ± 1.3	1.7 ± 1.5
		BM with BRG	13	4.3 ± 0.5	2.9 ± 0.8
	OFD		47	2.2 ± 0.9	0.9 ± 1.0
	BM		12	2.8 ± 0.4	3.7 ± 0.9
	BM with BRG		13	4.3 ± 0.5	2.9 ± 0.8
	EMD		113	2.8 ± 0.6	2.7 ± 1.1
	EMD with BRG		69	3.9 ± 0.5	3.7 ± 0.6

Abbreviations: PD, probing depth. CAL, clinical attachment level. EMD, enamel matrix derivatives. BM, barrier membrane. OFD, open flap debridement. BRG, bone replacement graft. N/A, not available.

months in the present analysis, suggesting that creeping attachment occurred during this period.[23]

A systemic review indicated that the EMD application contributed to an additional 1.31 mm CAL gain and 1.04 mm PD reduction relative to OFD at 12 months for periodontal intrabony defects.[9] The dominating EMD constituent, amelogenin, facilitates regeneration by inducing new cementum, PDL, and alveolar bone formation when applied to periodontally affected root surfaces.[24] EMD's flowability overcomes anatomical variations (e.g., supernumerary roots) and allows for the deep penetration into the defects. On the other hand, without placing a BM, primary wound closure can be achieved more easily in the EMD application, even for thin gingival biotypes. Altogether, EMD-treated sites in Asians showed comparable outcomes to non-Asians (Tables 3 and 4).

BRG serves as the defect filler and facilitates osteogenesis.[25] The Bayesian random-effects network meta-analysis by Stavropoulos et al. indicated that combined approaches (i.e., BM with BRG and EMD with BRG) appeared more efficacious for PD reduction and CAL gain compared to monotherapies (i.e., BM or EMD alone).[11] In the present analysis, PD reduction was improved by BRG supplementation at 12 months, regardless of BM or EMD application (Table 4). However, CAL gain was reduced with BM but increased with EMD, suggesting that more gingival recession occurred when BM was supplemented with BRG. The phenomenon could be still associated with the thin gingival biotype of Asians because BRG prevents BM's collapse, and more effort would be required to ensure primary wound closure.

The present analysis had several limitations. First, the quantity of included studies was relatively small and might not represent the actual trends in efficiency after regenerative surgery in East Asians. Second, due to the heterogenicity of the reported data, only pooled analyses could be performed. However, this is the first systemic review searching East Asian databases and collecting studies published in non-English languages such that it may bring new insights on PRT in East Asians. The results may be significant and provide a reference for medical workers in East Asia when deciding the treatment protocol for periodontal problems.

In conclusion, BM and EMD applications showed superior treatment outcomes than OFD for regenerating periodontal intrabony defects in East Asians. The supplementation of EMD with BRG provided additional clinical benefits. BM application in East Asians was less efficient than in non-Asians, potentially due to the variations of molar roots and the thin gingival biotype of Asians.

Declaration of competing interest

The authors have stated that there are no conflicts of interest related to this study.

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References

1. Nielsen IM, Glavind L, Karring T. Interproximal periodontal intrabony defects. Prevalence, localization and etiological factors. *J Clin Periodontol* 1980;7:187—98.
2. An YZ, Ko KA, Kim CS, Gruber R, Wang X, Lee JS. Do periodontal defects affect periodontal inflammation and destruction? Histological/microbiological changes and gene expression profiles of a pilot study in beagle dogs. *J Periodontol* 2021;92:1007—17.
3. Sanz M, Herrera D, Kebschull M, et al. Treatment of stage I-III periodontitis-The EFP S3 level clinical practice guideline. *J Clin Periodontol* 2020;47(Suppl 22):4—60.
4. Nyman S, Lindhe J, Karring T, Rylander H. New attachment following surgical treatment of human periodontal disease. *J Clin Periodontol* 1982;9:290—6.
5. Cortellini P, Tonetti MS. Clinical concepts for regenerative therapy in intrabony defects. *Periodontol* 2000 2015;68:282—307.
6. Newman MG, Takei H, Klokkevold PR, Carranza FA. *Periodontal regeneration and reconstructive surgery. Newman and carranza's Clinical periodontology*, 13th ed. Elsevier Health Sciences, 2018:642—52.
7. Hirooka H. The biologic concept for the use of enamel matrix protein: true periodontal regeneration. *Quintessence Int* 1998;29:621—30.
8. Reynolds MA, Aichelmann-Reidy ME, Branch-Mays GL. Regeneration of periodontal tissue: bone replacement grafts. *Dent Clin* 2010;54:55—71.
9. Nibali L, Koidou VP, Nieri M, Barbato L, Pagliaro U, Cairo F. Regenerative surgery versus access flap for the treatment of intra-bony periodontal defects: a systematic review and meta-analysis. *J Clin Periodontol* 2020;47(Suppl 22):320—51.
10. Graziani F, Gennai S, Cei S, et al. Does enamel matrix derivative application provide additional clinical benefits in residual periodontal pockets associated with suprabony defects? A systematic review and meta-analysis of randomized clinical trials. *J Clin Periodontol* 2014;41:377—86.
11. Stavropoulos A, Bertl K, Spineli LM, Sculean A, Cortellini P, Tonetti M. Medium- and long-term clinical benefits of periodontal regenerative/reconstructive procedures in intrabony defects: systematic review and network meta-analysis of randomized controlled clinical studies. *J Clin Periodontol* 2021;48:410—30.
12. Matarasso M, Iorio-Siciliano V, Blasi A, Ramaglia L, Salvi GE, Sculean A. Enamel matrix derivative and bone grafts for periodontal regeneration of intrabony defects. A systematic review and meta-analysis. *Clin Oral Invest* 2015;19:1581—93.
13. Hou GL, Chen SF, Tsai CC, Huang JS. Analysis of divergent angle and length of CEJ to furcation entrance in extracted molars. *Kaohsiung J Med Sci* 1997;13:710—20.
14. Lu HK. Topographical characteristics of root trunk length related to guided tissue regeneration. *J Periodontol* 1992;63:215—9.
15. Chen JT, Wu IT, Huang RY, et al. Recommendations for treating stage I-III periodontitis in the Taiwanese population: a consensus report from the Taiwan Academy of Periodontology. *J Formos Med Assoc* 2021;120:2072—88.
16. Lee SA, Kim AC, Prusa Jr LA, Kao RT. Characterization of dental anatomy and gingival biotype in Asian populations. *J Calif Dent Assoc* 2013;41(31—3):36—9.
17. Kim DM, Bassir SH, Nguyen TT. Effect of gingival phenotype on the maintenance of periodontal health: an American Academy of Periodontology best evidence review. *J Periodontol* 2020;91:311—38.
18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies

that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009;62:e1—34.
19. Kaldahl WB, Kalkwarf KL, Patil KD, Molvar MP, Dyer JK. Long-term evaluation of periodontal therapy: I. response to 4 therapeutic modalities. *J Periodontol* 1996;67:93—102.
20. Cairo F, Carnevale G, Buti J, et al. Soft-tissue re-growth following fibre retention osseous resective surgery or osseous resective surgery: a multilevel analysis. *J Clin Periodontol* 2015;42:373—9.
21. Windisch P, Sculean A, Klein F, et al. Comparison of clinical, radiographic, and histometric measurements following treatment with guided tissue regeneration or enamel matrix proteins in human periodontal defects. *J Periodontol* 2002;73:409—17.
22. Nickles K, Ratka-Kruger P, Neukranz E, Raetzke P, Eickholz P. Open flap debridement and guided tissue regeneration after 10 years in infrabony defects. *J Clin Periodontol* 2009;36:976—83.
23. Bell LA, Valluzzo TA, Garnick JJ, Pennel BM. The presence of "creeping attachment" in human gingiva. *J Periodontol* 1978;49:513—7.
24. Koop R, Merheb J, Quirynen M. Periodontal regeneration with enamel matrix derivative in reconstructive periodontal therapy: a systematic review. *J Periodontol* 2012;83:707—20.
25. Rosenberg E, Rose LF. Biologic and clinical considerations for autografts and allografts in periodontal regeneration therapy. *Dent Clin* 1998;42:467—90.
26. Fujinami K, Hayakawa H, Ota K, et al. Two-year follow-up of treatment of intrabony periodontal defect with enamel matrix derivative. *Bull Tokyo Dent Coll* 2011;52:215—21.
27. Narita M, Namba S, Tatsumi J, et al. Six-month clinical evaluation of periodontal tissue regeneration using enamel matrix derivative (EMD). *Nihon Shishubyo Gakkai Kaishi* 2009;51:316—25.
28. Minabe M, Kodama T, Kogou T, et al. A comparative study of combined treatment with a collagen membrane and enamel matrix proteins for the regeneration of intraosseous defects. *Int J Periodontics Restor Dent* 2002;22:595—605.
29. Yamanouchi K, Nakagawa T, Seida K, et al. Clinical study on the effect of absorbable membrane applied to guided tissue regeneration technique. *Nihon Shishubyo Gakkai Kaishi* 1994;36:884—94.
30. Yoshinari N, Tohya T, Kawase H, et al. Effect of repeated local minocycline administration on periodontal healing following guided tissue regeneration. *J Periodontol* 2001;72:284—95.
31. Kim CK, Chai JK, Cho KS, et al. Periodontal repair in intrabony defects treated with a calcium sulfate implant and calcium sulfate barrier. *J Periodontol* 1998;69:1317—24.
32. Hou LT, Yan JJ, Tsai AY, Lao CS, Lin SJ, Liu CM. Polymer-assisted regeneration therapy with Atrisorb barriers in human periodontal intrabony defects. *J Clin Periodontol* 2004;31:68—74.
33. Lee KJ, Kim MJ, Yun JH, et al. Clinical effect of enamel matrix derivative(EMD) in the treatment of periodontal intrabony defects. *J Korean Acad Periodontol* 2004;34:593—605.
34. Saito A, Hayakawa H, Ota K, Fujinami K, Nikaido M, Makiishi T. Treatment of periodontal defects with enamel matrix derivative: clinical evaluation at early healing stages. *Bull Tokyo Dent Coll* 2010;51:85—93.
35. Sakata J, Ohazama A, Miyazawa Y, Suzuki M, Hasegawa K. The clinical evaluation of guided tissue regeneration using polylactic acid membrane. *Showa Shigakkai Zasshi* 2002;22:345—51.
36. Setoguchi T, Koura N, Matsunaga M, et al. Clinical evaluation of guided tissue regeneration using a expanded polytetrafluoroethylene membrane. *Nihon Shishubyo Gakkai Kaishi* 1991;33:1032—9.
37. Kobayashi T, Sakurai K, Okuda K, Ishihara F, Hara K. Clinical evaluation of guided tissue regeneration using a expanded polytetrafluoroethylene membrane. *Niigata Dent J* 1996;26:21—8.
38. Kitamura M, Akamatsu M, Kawanami M, et al. Randomized placebo-controlled and controlled non-inferiority phase III trials comparing trafermin, a recombinant human fibroblast growth factor 2, and enamel matrix derivative in periodontal regeneration in intrabony defects. *J Bone Miner Res* 2016;31:806—14.
39. Yoshinari N, Tohya T, Inagaki K, et al. Five years of clinical evaluation of nonresorbable membranes in the treatment of intrabony defects following guided tissue regeneration. *Nihon Shishubyo Gakkai Kaishi* 1996;38:211—9.
40. Seshima F, Aoki H, Takeuchi T, et al. Periodontal regenerative therapy with enamel matrix derivative in the treatment of intrabony defects: a prospective 2-year study. *BMC Res Notes* 2017;10:256.
41. Ogihara S, Tarnow DP. Efficacy of enamel matrix derivative with freeze-dried bone allograft or demineralized freeze-dried bone allograft in intrabony defects: a randomized trial. *J Periodontol* 2014;85:1351—60.
42. Ogihara S, Wang HL. Periodontal regeneration with or without limited orthodontics for the treatment of 2- or 3-wall infrabony defects. *J Periodontol* 2010;81:1734—42.
43. Okuda K, Momose M, Miyazaki A, et al. Enamel matrix derivative in the treatment of human intrabony osseous defects. *J Periodontol* 2000;71:1821—8.
44. Saito A, Nanbu Y, Nagahata T, Yamada S. Treatment of intrabony periodontal defects with enamel matrix derivative in private practice: a long-term retrospective study. *Bull Tokyo Dent Coll* 2008;49:89—96.
45. Mitani A, Takasu H, Horibe T, et al. Five-year clinical results for treatment of intrabony defects with EMD, guided tissue regeneration and open-flap debridement: a case series. *J Periodontal Res* 2015;50:123—30.