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TECHNOLOGY REVIEW (MINI-HTA)

Platelet Rich Plasma (PRP), Platelet-Rich Fibrin (PRF) and Concentrated Growth Factor (CGF) for Treatment of Periodontal Disease

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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EXECUTIVE SUMMARY

Background
Periodontal diseases are chronic disease which is largely preventable. It is a condition whereby tooth-supporting tissues (gingiva, alveolar bone, periodontal ligament, and cementum) are affected by bacterial infection. Direct two-way communication between oral and soft tissue through junctional epithelium providing a pathway for bacterial ingression, thus giving potential for adverse effects on oral health. Conventional treatment of periodontal disease (scaling and root debridement, open flap surgery for access of debridement procedure) may arrest bone destruction but usually does not restore the lost alveolar bone or periodontal connective tissue. The bone deformities resulted from periodontitis can be reconstructed or regenerated in regenerative procedures which involves multiple techniques and accurate selection of autogenous grafts or using bone substitutes available in the market. Bone substitutes derived from another human, synthetic or animal are considered as foreign bodies, thus will create an immune reaction during healing process post operatively. Autologous platelet concentrates (APC) which contains platelet rich plasma (PRP), platelet-rich fibrin (PRF) and concentrated growth factor (CGF) has gained interest as an adjunctive to all procedures described in the treatment of periodontal diseases.

Objective/ aim
To assess the effectiveness, safety and cost-effectiveness of platelet rich plasma (PRP), platelet – rich fibrin (PRF) and concentrated growth factor (CGF) for periodontal therapy.

Results and conclusion
A total of 306 records were identified through the Ovid Medline and PubMed interfaces, and five were identified from other sources. The review included seven systematic reviews with meta-analysis. The included articles were published between 2016 and 2019. Most of the studies were from multi-country.

Effectiveness
Based on the above review, there was fair level of retrievable evidence on the use of platelet rich plasma (PRP), platelet-rich fibrin (PRF) and concentrated growth factor (CGF) for periodontal therapy. Evidence demonstrated that (PRP), (PRF) and (CGF) as adjunctive use for treatment of infrabony defects especially in open flap debridement and open flap debridement with bone graft were effective in reducing the pocket depth (PD) and improving the clinical attachment level (CAL) gain. Summary of included studies listed in **Table 1**.

Table 1. Summary of included studies

Study, Year	Study Design	Sample Size, Setting	Interventions	Gold Standard	Reported Outcome(s)
Del FM et., 2018	MA	38 RCTs total patients =1016	OFD+APC	OFD alone	**PD reduction**: MD 1.29; 95% CI: 1.00 to 1.58 **CAL gain**: MD 1.47, 95% CI 1.11 to 1.82
			OFD+BG+APC	OFG+BG alone	**PD reduction** MD 0.54; 95% CI: 0.33 to 0.75 **CAL gain:** MD 0.72; 95% CI: 0.43, 1.00
Zhou S et al.,2018	MA	9 RCTs total patients =259	DFDBA+PRP	DFDBA alone	**PD reduction:** MD 0.47; 95% CI: 0.14 to 0.80 **CAL gain:** MD 0.80; 95% CI: 0.27 to 1.32
			DFDBA+PRF	DFDBA alone	**PD reduction:** MD 0.88; 95% CI: 0.41 to 1.34 **CAL gain:** MD 1.61; 95% CI: 1.10 to 2.12
			Subgroup analysis between PRF and PRP		**PD reduction:** better in PRF **CAL gain:** better in PRF
Li A et al., 2018	MA	12 RCTs total patients =538	OFD+PRF	OFD alone	**PD reduction**: WMD 1.14; 95% CI: 0.94 to 1.33 **CAL gain**: WMD 1.29; 95% CI: 0.96 to 1.61
Hou X et al., 2016	MA	12 RCTs total patients =353	PRP+ graft material	graft material alone	**PD reduction:** WMD 0.53; 95% CI: 0.21 to 0.85 **CAL gain**: WMD 0.76 mm; 95 % CI: 0.34 to 1.18 mm
Franchini M et al., 2019	MA	11 RCTs total patients =566	PRP	control	**PD reduction:** MD -0.39; 95% CI: -0.80 to 0.02 **CAL gain**: MD -0.57; 95% CI: -0.93 to -0.20
Li F et al., 2017	MA	12 RCTs total patients =444	recombinant human FGF-2	control/placebo	**PD reduction:** MD=1.12; 95% CI 0.28 to 1.96 **CAL gain**: MD=0.76; 95% CI 0.28 to 1.24
Cãlin C et al., 2017	MA	5 RCTs total patients =287	rhPDGF-BB+βTCP	β -TCP alone	**PD reduction:** p=0.0004 **CAL gain**: p= 4.748^{-8}

Safety
There was no retrievable evidence on safety of platelet rich plasma (PRP), platelet-rich fibrin (PRF) and concentrated growth factor (CGF) for periodontal therapy.

Economic evaluation/cost-effectiveness analysis
There was no retrievable evidence on cost-effectiveness analysis of platelet rich plasma (PRP), platelet-rich fibrin (PRF) and concentrated growth factor (CGF) for periodontal therapy.

Cost analysis conducted
Cost analysis showed the estimated additional cost associated with PRF or CGF treatment ranged from RM62 to RM 68 per patient per year. A decrease by at least one outpatient visit would yield an estimate of MYR293 of cost saving per patient.

Methods
Literature search was done to search for published articles to assess the effectiveness, safety and cost-effectiveness of platelet rich plasma (PRP), platelet-rich fibrin (PRF) and concentrated growth factor (CGF) for periodontal therapy. The following electronic databases were searched via, OVID: MEDLINE (1946 to 03 March 2021), EBM Reviews-Cochrane Database of Systematic Reviews (2005 to September 29, 2021), EBM Reviews–Cochrane Clinical Answers (September 2021), EBM Reviews–Database of Abstracts of Review of Effects (1st Quarter 2016), EBM Reviews–Health Technology Assessment (4th Quarter 2016), NHS economic evaluation database (1st Quarter 2016), PubMed and INAHTA database. The last search was run on 03 March 2021.

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ABBREVIATION

APC(s)	Autologous platelet concentrate(s)
BG	bone grafting
CAL	clinical attachment level
CASP	Critical Appraisal Skills Programme
CGF	Concentrated Growth Factor
CI	Confidence interval
HTA	Health Technology Assessment
GR	gingival recession
GTR	guided tissue regeneration
IGF	insulin like growth factor
MaHTAS	Malaysian Health Technology Assessment Section
MA	Meta-analysis
MOH	Ministry of Health
PD	probing depths
PDGF	platelet derived growth factor
PRF	Platelet-Rich Fibrin
PRP	Platelet Rich Plasma
RCT	Randomised controlled trial
RecRed	recession reduction
SR	systematic review
VEGF	vascular endothelial growth factor
WMD	weighted mean difference

1.0 BACKGROUND

Periodontal diseases including gingival diseases and periodontitis are chronic diseases which are largely preventable. Its prevalence has been reported as high as 90%, while its severe form, periodontitis has been reported to affect up to 15% of the global population.[1] It is a condition whereby tooth-supporting tissues (gingiva, alveolar bone, periodontal ligament, and cementum) affected, thus giving potential for severe adverse effects on oral health.[2] Untreated periodontitis results in progressive attachment loss that eventually lead to lost of supporting bone and early extraction of the affected teeth.[3; 1; 4] Main cause of tooth loss in adults, due to bacterially induced inflammation and breakdown of periodontal supporting tissue, which leads to infrabony defects.[5] Infrabony defects are one of the morphological types of alveolar bone defects that can be observed during periodontitis.[2]

In 2010, National Oral Health Survey for Adults (NOHSA) had found that the prevalence of Malaysians adults (aged 15 years old and above) with periodontal diseases (both gingivitis and periodontitis) was 94%. From this population, the prevalence of moderate and severe periodontitis were 30.3% and 18.2%, respectively.[6] Assuming current prevalence in 2021 is similar to the 2010 findings, it is estimated about 4.3 million Malaysians are at risk for severe periodontitis[7] and in need of Periodontal Specialists care.

Conventional treatment of periodontal disease (scaling and root debridement, open flap surgery for better access in root debridement) may halt the bone destruction but usually does not or has limited success in restoring the lost alveolar bone and periodontal connective tissue attachment. Recent approaches for treatment of intrabony defects involve a combination of advanced regenerative or reconstructive surgical techniques with platelet-derived growth factors alone or as an adjunct to bone grafting procedures produced better and more predictable outcome for the treatment of intrabony defects.[2] Depending on the complexity of bone deformities and size of intrabony defects, patients are normally reviewed frequently for the first 4 months following any regenerative surgery. The frequency is highly depending on the post-operative complications. Experience of users indicated that, the additional use of PRF and CGF reduced the post-operative inflammation and morbidity[14] in terms of the pain and frequency of visit. The application seems to speed up the healing as indicated by reduced incidence of wound dehiscence and the need for re-suturing the wound margin.

Autologous platelet concentrates (APCs) are based on their preparation protocol, can be of various types, including platelet-rich plasma (PRP), platelet rich fibrin (PRF) and plasma-rich growth factors (PRGF) or concentrated growth factors (CGF). However, their indication of use has been confusing because each method leads to a different product with different biological properties and possible applications.[2] Platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) are the two generations of platelet concentrates (PCs), respectively, obtained after processing autologous whole blood samples via centrifugation.[5]

Both PRP and PRF contain highly concentrated growth factors (CGF) such as transforming growth factor-β(TGF- β), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), insulin like growth factor (IGF), epithelial growth factor (EGF), and fbroblast growth factor- β (FGF- β), with platelets as the rich source, having potential to enhance wound healing and periodontal regeneration through modulating neo angiogenesis, cell proliferation, migration, differentiation, and other cellular functions.[5] At present, three different forms of PDGFs have been identified: PDGF-AA, PDGF-AB, and PDGF-BB. Among these, the efficacy of PDGF-BB in both soft and hard tissue regeneration has been most clearly demonstrated. It has been approved by the FDA for use in periodontal therapy in cases of infrabony defects, furcation lesions, and gingival recession.[1]

All these hormones are secreted by platelets to initiate wound healing. Some studies have suggested that following coagulation, PRP preparation exhibits a “sticky consistency” that may improve the clinical handling properties of the combination of PRP and the graft material, thereby enhancing wound stability.[4] In Malaysia, as of now PRP, PRF and PR-CGF centrifuge machine is available only in the state of Penang and Melaka. Therefore, this review is requested to support expansion of provision of this procedure nationwide and may justify the asset requirement.

2.0 OBJECTIVE / AIM.

To assess the effectiveness, safety and cost-effectiveness of platelet rich plasma (PRP), platelet-rich fibrin (PRF) and concentrated growth factor (CGF) for periodontal therapy.

3.0 TECHNICAL FEATURES

Several commercial techniques for obtaining platelet concentrates are available.[2] There are currently more than 40 commercial systems that have been developed to concentrate autologous whole blood into a platelet-rich substance.[8]

Although PRP and PRF are both blood extracts in which platelets are enriched and various growth factors are highly concentrated, they have different biological performances and mechanical properties owing to their different preparation approaches.[5]

The preparation of PRP [the first platelet concentrates (PCs) generation] requires anticoagulants at the moment of blood collection; bovine thrombin and calcium chloride have to be added when used in the gel form. In contrast, PRF (the second PCs generation), much more simply prepared, is nothing more than centrifuged blood without any additives. For PRP preparation, whole blood with anticoagulants needs to be centrifuged twice; after the first centrifugation, the platelet-poor plasma in the upper layer, the “yellow” part in the middle, and a few red blood cells are

carefully collected (pipetting) and centrifuged again in order to obtain the intermediate layer, that is, PRP, which is liquid. Compared with PRP, the preparation of PRF is much easier because it does not need additional anticoagulants and chemical activators.[5]

In contrast to PRP, PRF contains a higher concentration of growth factors and matrix proteins, which are released more slowly and constantly due to the three-dimensional architecture of the adhesive glycoproteins in the fibrin. Moreover, PRF is endowed antimicrobial and anti-inflammatory properties by the concentrated leucocytes trapped in the fibrin mesh. Another superiority of PRF over PRP lies in the mechanical strength of the condensed and strong fibrin-rich membrane matrix of PRF, which is more suitable for manipulation and space maintenance.[5]

Measures of outcome for the evaluation of periodontal defects were the following:[11]

- probing depths (PD): a measure of the depth of a sulcus or periodontal pocket (pathologically deepened sulcus) determined by measuring the distance from a gingival margin to the base of the sulcus or pocket with a calibrated periodontal probe
- clinical attachment level (CAL): a measure of the position of the base of the pocket in relation to the cemento-enamel junction
- gingival recession (GR): the distance of the gingival margin from the cemento-enamel junction
- radiographic bony defect (RBD): measured in various ways, implying procedural and numerical heterogeneity.

4.0 METHODS

4.1 SEARCHING

Number of hits from the available databases: Via OVID Medline (306), HTA database (0), Systematic Review (89), RCT (39), NHS economic evaluation (0), PubMED (27), FDA (0), Horizon scanning (0), INAHTA database (0).
Electronic databases searched through the Ovid interface:

- MEDLINE (R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to 03 March 2021
- EBM Reviews – Cochrane Central Register of Clinical Answer – September 2021
- EBM Reviews – Database of Abstracts of Review of Effects – 1st Quarter 2016
- EBM Reviews – Cochrane Database of Systematic Reviews – 2005 to September 29, 2021
- EBM Reviews – Health Technology Assessment – 4th Quarter 2016
- EBM Reviews – NHS Economic Evaluation Database – 1st Quarter 2016

Other databases:

- Pubmed
- INAHTA

Other website:

- USFDA

Additional articles were identified from reviewing the references of retrieved articles. General search engine was used to get additional web-based information. The search was limited to English articles on humans. Appendix 1 showed the detailed search strategies. The last search was conducted on 03 March 2021.

4.2 SELECTION

Abstracts/titles identified from the search were screened by two reviewers (P.T) and (A.S) Disagreements about study inclusion or exclusion were initially resolved by consensus, and when such resolution was not possible, they were arbitrarily resolved by a third reviewer. The inclusion and exclusion criteria were:

Inclusion criteria

Population	periodontitis, periodontal disease
Interventions	platelet rich plasma (PRP), platelet rich fibrin (PRF) and concentrated growth factor (CGF)
Comparators	placebo, treatment as usual/ usual care, control and conventional management of periodontal treatment e.g. scaling, debridement and open flap surgery
Outcomes	i. Clinical effectiveness in pocket depth (PD), clinical attachment loss (CAL) gain, recession reduction (RecRed)

	and bone defect filling (RBF) ii. Adverse effects iii. Cost, cost-effectiveness, cost utility, cost-analysis and economic evaluation iv. Organizational – guidelines, training
Study design	Health Technology Assessment (HTA) reports, Systematic Review (SR) and Meta-analyses, Randomised Controlled Trials (RCT), Non-randomised controlled trials, cohort studies, cross-sectional studies

Exclusion criteria

i. Animal / laboratory / case reports / case series / cohort studies / cross-sectional studies
ii. Narrative review
iii. Non-English full text articles

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) checklist and evidence were graded according to the US/Canadian Preventive Services Task Force (See Appendix 2).

5.0 RESULTS

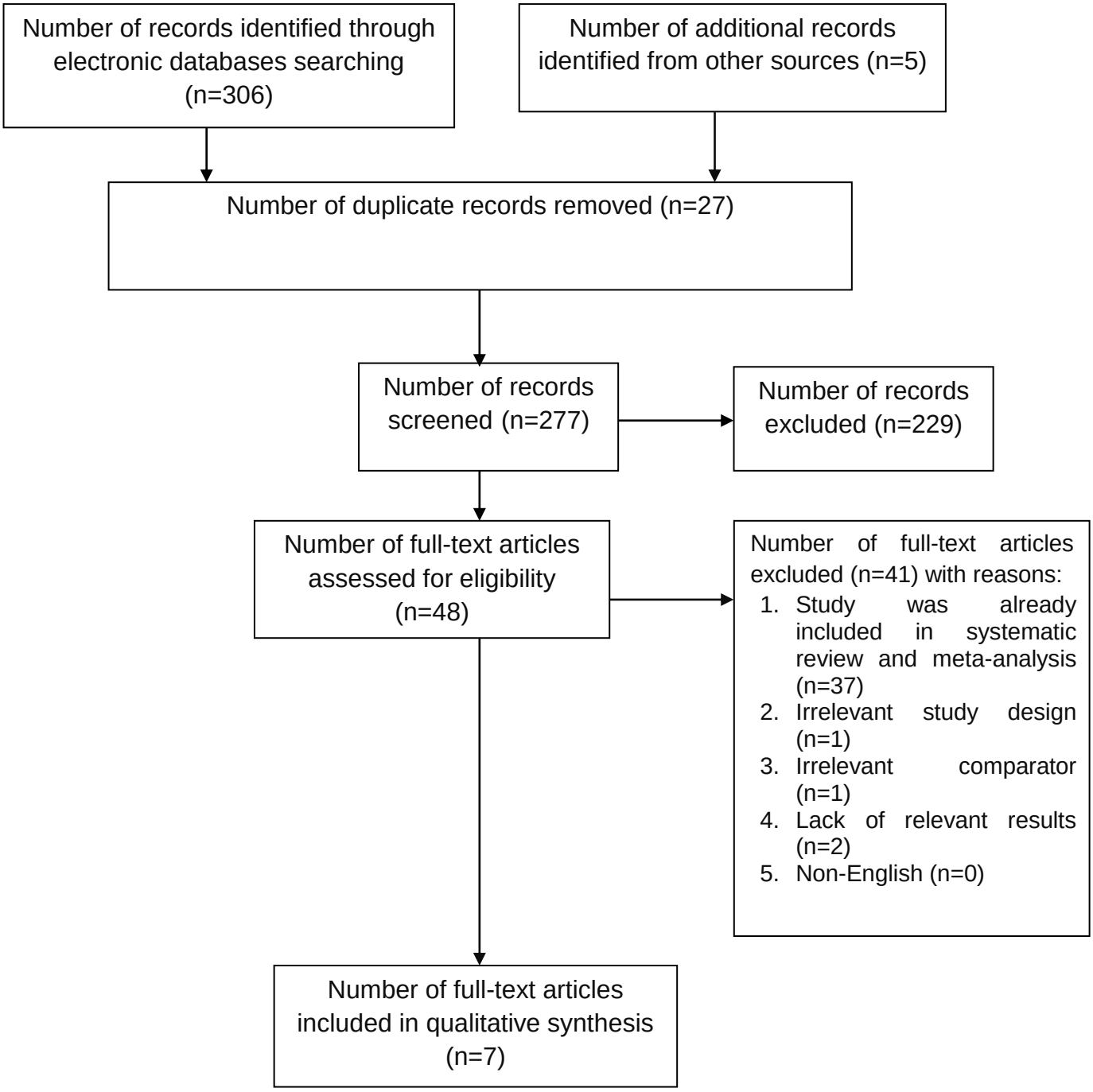

Figure 2: Flowchart of study selection

The seven full text articles finally selected for this review comprised of SR (seven for effectiveness, none for safety) and no study retrieved on cost-effectiveness. The included articles were published between 2016 and 2019. Most of the studies were multi-country.

Assessment of risk of bias in included studies

For systematic reviews included in the review, assessment of quality was conducted based on Critical Appraisal Skills Programme (CASP) checklist and the quality of evidence included in the SRs was summarised. Review author's judgements of risk of bias involved answering specific questions and assigning a judgement relating to the risk of bias as either:

+	Indicates YES (low risk of bias)
?	Indicates UNCLEAR risk of bias
-	Indicates NO (high risk of bias)

The assessment of risk of bias revealed that the SRs included were considered to have low risk of bias.

The results of risk of bias of included studies are summarised as below.

Criteria assessed	The right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Del Fabbro M et al., 2018	+	+	+	+
Zhou S et al., 2018	+	+	+	+
Li A et al., 2019	+	+	+	?
Hou X et al., 2016	+	+	+	+
Franchini M et al., 2019	?	+	+	+
Li F et al., 2017	?	?	+	+
Cãlin C et al., (2017	+	+	+	+

Figure 3. Assessment of risk of bias of systematic review.

5.1 EFFICACY/ EFFECTIVENESS

A Cochrane systematic review by Del Fabbro M et al., (2018) assessed the effects of autologous platelet concentrates (APC) used as an adjunct to periodontal surgical therapies [open flap debridement (OFD), OFD combined with bone grafting (BG), guided tissue regeneration (GTR), OFD combined with enamel matrix derivative (EMD)] for the treatment of infrabony defects. Quality of the evidence (GRADE) showed included studies were ranged from very low to low due to most of the included studies were not blinded. Included 38 RCTs compared treatment outcomes of a specific surgical technique combined with APC, with the same technique when used alone. The result showed:[2, level I]

- change in probing depth (PD) (mm):
  - significant improvement in APC and OFD (MD 1.29; 95% CI: 1.00 to 1.58)
  - significant improvement in using APC with OFD and BG (MD 0.54; 95% CI: 0.33 to 0.75)
  - significant improvement in using APC and GTR (MD 0.92; 95% CI: 0.02 to 1.86)
  - no significant difference between two groups APC and EMD vs EMD (MD 1.13; 95% CI: -0.05 to 0.30)
- change in clinical attachment level (CAL) (mm):
  - significant improvement in APC and OFD (MD 1.47, 95% CI 1.11 to 1.82)
  - significant improvement in APC with OFD and BG (MD 0.72; 95% CI: 0.43 to 1.00)
  - no significant difference between two groups for APC and GTR vs GTR alone
  - no significant difference between two groups for APC and EMD vs EMD alone
- change in radiographic bone defect filling (RBF) (%):
  - significant improvement in APC and OFD (MD 34.26, 95% CI 30.07% to 38.46%)
  - significant improvement in APC with OFD and BG (MD 8.10%; 95% CI: 5.26% to 10.94%)
  - no data were available in comparison APC and GTR vs GTR alone
  - no significant difference between two groups for APC and EMD vs EMD alone

According to the author of this study, there were very low-quality evidence that the addition of APC to two types of treatment: open flap debridement and open flap debridement with bone graft, may bring some advantages in the treatment of infrabony defects. However, for the other two types of treatment, guided tissue regeneration and enamel matrix derivative, showed insufficient evidence of benefit compared to treatment as usual.[2, level I]

Zhou S et al., (2018) conducted a systematic review (SR) and meta-analysis (MA) to evaluate adjunctive effects of bioactive materials such as platelet-rich plasma (PRP), platelet-rich fibrin (PRF), enamel matrix derivative (EMD), and amnion membrane (AM) on the outcomes of bone grafting treatment for periodontal intrabony defects. A total of nine moderate quality RCTs were included, involving 259 patients on the assessment of effectiveness of four biomaterials in conjunction with demineralized freeze-dried bone allografts (DFDBA) in the treatment of periodontal intrabony defects. DFDBA was chosen as the scaffold to fill the periodontal defect because it is the most commonly used bone replacement graft and is approved by the FDA as an osteoinductive material. The follow-up period ranged from 6 to 12 months. Sensitivity analysis was also performed, the results were stable, indicating that no single study interfered with the overall results significantly. Additional bioactive materials in conjunction with DFDBA in patients with periodontal intrabony defects comparing DFDBA alone showed:[5, level I]

- improved pocket depth (PD) reduction in:

  - PRP (MD 0.47; 95% CI: 0.14 to 0.80)
  - PRF (MD 0.88; 95% CI: 0.41 to 1.34)
  - PRF subgroup showed better reduction of PD compared to PRP subgroup
  - EMD and AM showed no significant difference
- clinical attachment loss (CAL) gain:
  - PRP (MD 0.80; 95% CI: 0.27 to 1.32)
  - PRF (MD 1.61; 95% CI: 1.10 to 2.12)
  - AM (MD 0.80; 95% CI: 0.37 to 1.24)
  - PRF subgroup showed best gain of CAL compared with the subgroups of PRP and AM
  - EMD subgroup failed to show any significant difference
- recession reduction (RecRed):
  - PRF subgroup showed positive result (MD 0.77; 95% CI: 0.31 to 1.22)
  - subgroups of PRP, EMD, and AM showed NS differences.
- increase in bone fill
  - PRP (MD; 0.71 (95% CI: 0.13 to 1.29)
  - subgroups of PRF, EMD and AM showed NS differences

This study concluded PRF exerts the most significant adjunctive effect on soft tissue healing, while PRP exhibits a unique impact on hard tissue reconstruction in the treatment of periodontal intrabony defect. This is because PRF failed to show any additionally favourable effect on bone fill according to the result of this analysis. The better soft tissue healing of PRF than that of PRP found in this analysis. However, EMD and AM demonstrated little additional benefit. Therefore, PRF/PRP could be taken as a preferred adjunctive treatment to promote periodontal regeneration due to its proven good biological effects and ease of preparation. Nevertheless, the author of this study also suggested standardisation of the protocol for the preparation and application of PRF/PRP is needed to obtain optimal effect of regenerative procedures.[5, level I]

Li A et al., (2019) conducted a meta-analysis with 12 RCTs of intermediate- to high-quality studies which methodological quality was assessed by the Cochrane Collaboration tool. Total number of patients analysed was 538 after follow up of 9 to 12 months. This study systematically evaluated the effectiveness of adding autologous PRF in the treatment of intrabony defects of chronic periodontitis patients They found:[3, level I]

- significant reduction of PD in OFD and PRF group compared to OFD only (WMD 1.14; 95% CI: 0.94 to 1.33)
- significant gaining of CAL in OFD and PRF group compared to OFD only (WMD 1.14; 95% CI 0.94 to 1.33)
- significant improvement of gingival marginal level (GML) in OFD+PRF group compared OFD only (WMD 0.45; 95% CI: 0.31 to 0.58)
- significant leser defect depth reduction (DDR) in OFD+PRF group compared to OFD only (WMD 1.73; 95% CI: 1.38 to 2.08)

They concluded, adjunctive use of PRF with OFD significantly improves fill defects when compared to OFD alone. However, according to the author of this SR, additional powered studies with much larger sample sizes were needed to obtain a more concrete conclusion.[3, level I]

Hou X et al., (2016) conducted a meta-analysis with 12 RCTs related to PRP in the surgical treatment of periodontal intrabony defects by comparing clinical outcomes between patients who received PRP as an adjunct to periodontal intrabony defect therapy

and those who did not. They found clinically and significantly greater CAL gains and PD reductions were observed in subjects who received PRP as an adjunct to periodontal intrabony defect therapy than in subjects who did not as below:[4, level I]

- PD reduction (WMD 0.53; 95% CI: 0.21 to 0.85)
- CAL gain (WMD 0.76 mm; 95 % CI: 0.34 to 1.18 mm)
- subgroup meta-analyses in CAL gain among studies that:
  - with GTR: not significantly affect treatment outcomes (WMD 0.08; 95 % CI: −0.30 to 0.46) without GTR (WMD 1. 22; 95 % CI 0.88, 1.57 mm)
- Univariate meta-regression analyses revealed that the use of GTR explained the heterogeneity among the included studies ($p< 0.05$)

They concluded, adjunctive use of PRP together with conventional grafting procedures may be a beneficial treatment approach. However, when combined with the use of a regenerative technique, such as GTR, the beneficial effect of PRP on the treatment of intrabony defects is negligible.[4, level I]

Franchini M et al., (2019) included 21 RCTs in a systematic review to evaluate benefit of platelet rich plasma (PRP) in oral surgery. Meta-analysis was done on treatment given for periodontal defects in the PRP group compared to the control arm which included 12 RCTs. Quality assessment done using GRADE which ranged from very low to low quality of primary papers. They found:[9, level I]

- no significant difference between two groups (MD -0.39; 95% CI: -0.80 to 0.02) in terms of probing depth.
- slight improvement in clinical attachment level in PRP group (MD -0.57; 95% CI: -0.93 to -0.20)
- slight improvement in gingival recession in PRP group (MD -0.46; 95% CI: -0.77 to -0.15)
- slight improvement in bony defects in PRP group (MD -0.67; 95% CI -1.19 to -0.15)

Results of the meta-analysis, limited to studies in patients with periodontal defects, documented that PRP was slightly more effective compared to controls not-containing PRP.[4, level 1]

In a meta-analysis by Li F et al., (2017), clinical efficacy of recombinant human FGF-2 and PDGF-BB in periodontal regeneration with different specific concentrations in periodontal repair was evaluated. Quality assessment was done using the Cochrane “risk of bias**”** tool showed moderate quality RCTs were included in this study. Both split mouth RCTs and parallel RCTs were included to compare the impact of growth factors in conventional periodontal surgeries with control group (patients who did not receive growth factors for the treatment or placebo). This study showed:[1, level I]

- The effect of recombinant human FGF-2 on Periodontal Regeneration:
  - concentration 0.3% fibroblast growth factor 2 (FGF-2) groups was compared with control groups among patients with osseous defects:
    -in terms of bone fill percentage (BF%) (MD 22.37; 95% CI 13.46 to 31.27)
    -in terms of linear bone growth (LBG) (MD 1.13; 95% CI 0.78 to 1.49)
    -in terms of gains in clinical attach levels (CAL-G) (MD 0.27; 95%CI=−0.26 to -0.81)
  - concentration 0.1% FGF-2 groups was compared with control groups among patients with osseous defects showed no significant difference in terms of:
    -BF%
    -LGB
    -CAL-G

- concentration 0.4% FGF2 groups was compared with control groups among patients with osseous defects:
  -in terms of BF% (MD=22.27; 95% CI -1.46 to 45.99)
  -in terms of CAL-G no significant difference

- The effect of recombinant human FGF-2 on patients with osseous defect
  - 0.3mg/ml PDGF-BB groups was compared with control groups among patients with osseous defects:
    - in terms of BF% (MD=22.71; 95% CI 7.78 to 37.65)
    - LGB (MD=1.00; 95% CI 0.32 to 1.69)
    - no statistically significant difference in gingival recession
    - in terms of CAL-G (MD=0.76; 95% CI 0.28 to 1.24)
    - in terms of PDR (MD=1.12; 95% CI 0.28 to 1.96)

The result showed concentration of 0.3% rhFGF-2 and 0.3mg/ml rhPDGF-BB have better periodontal regeneration than other concentrations and superiority to control groups.[1, level I]

Cãlin C et al., (2017) analysed five RCTs in a meta-analysis to evaluate the effectiveness at six months follow-up of recombinant human platelet derived growth factor-BB (rhPDGF-BB) coated onto a beta-tricalcium phosphate (b-TCP) carrier compared to b-TCP alone, or to recombinant human growth/differentiation factor-5 (rhGDF-5) adsorbed onto a b-TCP scaffold in intraosseous periodontal defects. Quality of primary papers were assessed using CONSORT guidelines showed [high to low-quality (57% to 23%)] and the Cochrane risk of bias tool revealed moderate quality.They found for these outcomes:[10, level I]

- probing pocket depth reduction (PPD)
  - rhPDGF-BB vs β-TCP (p=0.0004)
  - rhPDGF-BB vs rhGDF-5/b (p=0.1313)
- clinical attachment level gain
  - rhPDGF-BB vs β-TCP (p= 4.748^{-8})
  - rhPDGF-BB vs rhGDF-5/b (p= 0.3598)
- linear bone growth (LBG)
  - rhPDGF-BB vs β-TCP (p< 2.2^{-16})
- % bone fill (%BG)
  - rhPDGF-BB vs β-TCP (p< 2.2^{-16})
- gingival recession (GR)
  - rhPDGF-BB vs rhGDF-5/b (p= 0.00048)

There were no significant differences in terms of safety profile and vital signs in patients receiving rhGDF-5/b-TCP compared to the control group.

5.2 SAFETY

There was no retrievable evidence on safety of platelet rich plasma (PRP), platelet – rich fibrin (PRF) and concentrated growth factor (CGF) for periodontal therapy.

5.3 ECONOMIC IMPLICATION / COST EFFECTIVENESS

No retrievable evidence on cost effectiveness of platelet rich plasma (PRP), platelet – rich fibrin (PRF) and concentrated growth factor (CGF) for periodontal therapy.

5.3.1 Cost Analysis

Introduction

A cost analysis was conducted to identify parameters and costs associated with the addition of platelet concentrates treatment, particularly platelet rich fibrin (PRF) and concentrated growth factor (CGF) in periodontal surgical procedures in public specialist dental clinics in Malaysia. Only direct medical cost related to the provider was taken into consideration to reflect the Ministry of Health Malaysia (MOH) perspective. The results of this analysis were based on limited data and input obtained from the experts in periodontic specialist services as well as publicly available reports and literature. The calculation for all estimations was carried out using Excel Microsoft 365 and externally reviewed.

Method

Statistics on patients that have been treated with either PRF or CGF and other related information as well as cost pertaining to machine procurement and maintenance were obtained from periodontists who have been performing these procedures in the MOH. Currently, there are two types of blood phase separator (BPS) machines available in two MOH specialist dental clinics, each located in Malacca and Penang. The capital cost is inclusive of procurement, delivery, as well as training costs for handling and operating those machines.

The yearly estimated maintenance cost is around three per cent of the estimated initial capital of the machine. In addition, the overall cost of this treatment would be driven by the amount of PRF or CGF required by a patient as it reflects the quantity of vacuum blood collection tubes being used to produce such PRF or CGF. Typically, a patient may require between one to three tubes during any surgical procedure. Depending on the complexity of a case, a patient may also require more than one surgery in a year with PRF/CGF administered during each procedure.

As all steps involved in preparing and producing these PRF and CGF are carried out chairside by trained dental staffs in a relatively short time, in addition to other routine surgical procedures, it is assumed that the availability of this treatment does not incur significant additional cost on resources used. Besides, patient's own whole venous blood is used to produce PRF and CGF, which unlike platelet rich plasma (PRP), do not require additional biomaterials and anticoagulant. For base case analysis, it is assumed that:

- a patient would use one vacuum blood collection tube for any periodontal surgical procedure during each visit,
- the number of visit for surgical procedures required by a patient remains the same either with or without PRF/CGF treatment, and
- average number of patient treated with PRF/CGF in each specialist periodontal clinic were similar to that of in 2019

Potential number of patients who might be suitable candidates for PRF/CGF treatment was obtained from the Health Information Management System (HIMS) Oral Health Sub-system.[11] Generally, there are four main surgical procedures that may benefit from the treatment, namely, soft, and hard tissue grafts, regenerative therapy, and dental implants. These data were compared to the number of actual cases treated with either PRF or CGF

in the two clinics in 2019. Since data from specific specialist dental clinic that have the BPS machines was not available from the report, proportion of patients treated with PRF or CGF were compared with the total number of cases reported for the previously mentioned procedures in their respective states, namely Penang and Malacca.

The cost of interest is the average cost of periodontal surgical treatment per patient per year and average cost per outpatient visit for patient requiring periodontal surgery. The information needed to compute these costs are obtained from a published cost analysis study on management of periodontitis patients who were receiving care and followed up for one year in select five MOH's specialist periodontal clinics. It was reported in the study that 90 per cent of the total cost for managing periodontitis patients was contributed by provider cost.[12].

Table 1: Summary of parameters from published literature used as reference[12]

Parameter	Number of patients	Reported value (mean)	Provider cost
All patients with periodontitis:	165		
• Average cost per patient per year		MYR 2,820	MYR 2,524
• Average number of outpatient visits per year		7.5	NA
• Average cost per outpatient visit per patient		MYR 376	MYR 337
By types of periodontitis:			
• Chronic (cost per patient per year)	131	MYR 2,636	MYR 2,359
○ Average number of outpatient visits per year per patient		7.1	NA
• Aggressive (cost per patient per year)	34	MYR 3,527	MYR 3,157
○ Average number of outpatient visits per year per patient		9.2	NA
By mix of treatment received (cost per patient per year):			
I - Nonsurgical treatment only	72	MYR 1,962	MYR 1,756
II - Nonsurgical and rehabilitative treatments	74	MYR 3,102	MYR 2,776

III - Nonsurgical treatment, rehabilitative treatment, and periodontal surgery	10	MYR 4,847	MYR 4,338
IV - Nonsurgical treatment and periodontal surgery	9	MYR 5,103	MYR 4,567

NA: not applicable; all costs were in MYR 2012

In this cost analysis, the estimated average cost of managing patients requiring periodontal surgery will be calculated by averaging the costs for those who had received mix of treatment III and IV. Meanwhile, the estimation of cost of follow-up visit after surgical procedure per year would be based on the average costs of treatment mix I and II (outpatient visits without surgical procedure). These parameters are as listed in Table 1.

Based on the input from the periodontists that are currently using this PRF/CGF treatment, one potential outcome that could be seen with PRF/CGF treatment is reduction in outpatient visit due to less surgical complications and faster wound healing. This assumes fewer number of outpatient visit is owing to assessment by the specialist that a patient can be discharged from the active treatment phase, not because of the no-shows. Hence, potential cost savings that could have been resulted from a reduction in at least one outpatient visit per patient will be estimated by comparing total outpatient visit costs for one year between those treated with or without additional treatment of PRF or CGF. All costs will be adjusted to the current cost based on Consumer Price Index published by Department of Statistics Malaysia (DOSM).[13]

Results

The estimated annualised cost per year for a BPS machine over 5 year is around MYR5,200. Overall, around 40 to 50 percent of total cases reported in HIMS to have undergone periodontal surgery for soft and hard tissue grafts, regenerative therapy as well as dental implants in Penang and Malacca in 2019, were treated with either PRF or CGF. The additional cost associated with PRF or CGF treatment then, was estimated to be around MYR 60 to MYR 70 per patient. The average cost of managing patients requiring periodontal surgery per patient per year in MYR 2020 was estimated to be around MYR 5,300 per patient per year, with average cost per visit estimated at about MYR 580. On the other hand, the average cost for managing patients without surgical procedures was estimated to be around MYR 2,690 per patient per year. Thus, the estimated average cost for a follow-up visit per patient was about MYR 360.

For the base case analysis, it was assumed that on average, a patient would require two outpatient visits for periodontal surgical procedures. Based on the experience and input from the experts, typically patients who had been treated with PRF/CGF required between two to five follow-up visits. In contrast, those who had not received the treatment required more frequent follow-up, between six to eight outpatient visits. The total cost per patient per year for those treated with PRF/CGF with five follow-up visits on average, was estimated to be around MYR 3,000. Meanwhile, the estimated total cost per outpatient visit for those receiving standard periodontal surgical procedure with six follow-up visits was about MYR 3,300. Consequently, the potential cost saving estimated for one

outpatient visit avoided per patient for each case treated with PRF or CGF was around MYR 300. Based on the average number of patients treated with PRF or CGF in 2019, if 50 per cent of patients achieved this potential outcome, the accumulated cost saving would be around MYR 13,000 per year for one specialist periodontal clinic offering the treatment. To expand the use of this BPS machine in periodontic services all over Malaysia within five years, the estimated overall expenditure is around MYR 288,000.

5.4 ORGANISATIONAL

No retrievable evidence on organisational issues pertaining to the use of platelet rich plasma (PRP), platelet – rich fibrin (PRF) and concentrated growth factor (CGF) for periodontal therapy.

5.5 SOCIAL/ ETHICAL / LEGAL

No retrievable evidence of social/ ethical/ legal aspects on platelet rich plasma (PRP), platelet – rich fibrin (PRF) and concentrated growth factor (CGF) for periodontal therapy.

6.0 CONCLUSION

Based on the above review, there was fair level of retrievable evidence on the use of platelet rich plasma (PRP), platelet-rich fibrin (PRF) and concentrated growth factor (CGF) for periodontal therapy. Evidence demonstrated that (PRP), (PRF) and (CGF) as adjunctive use for treatment of infrabony defects especially in open flap debridement and open flap debridement with bone graft were effective in reducing the pocket depth (PD) and improving the clinical attachment level (CAL) gain.

There was no retrievable evidence of safety/ social/ ethical/ legal aspects/ organisational issues in the use of platelet rich plasma (PRP), platelet – rich fibrin (PRF) and concentrated growth factor (CGF) for periodontal therapy.

Cost analysis showed the estimated additional cost associated with PRF or CGF treatment ranged from RM62 to RM 68 per patient per year. A decrease by at least one outpatient visit would yield an estimate of MYR293 of potential cost saving per patient.

7.0 REFERENCES

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APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS / DIAGNOSTIC STUDIES

I	evidence from at least one properly randomised controlled trial
II - 1	evidence obtained from well-designed controlled trials without randomisation
II - 2	evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II - 3	evidence from multiple time series with or without intervention
III	opinions of respected authorities based on clinical experience; descriptive studies & case reports; or reports of expert committees

Source: Canadian/US Preventive Services Task Force (Harris 2001)

APPENDIX 2: SEARCH STRATEGY

Date	Database	Keywords	Limit	No. Of Search
	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to August 17, 2018	1 PERIODONTITIS/ 2 pericementiti*.tw. 3 periodontiti*.tw. 4 CHRONIC PERIODONTITIS/ 5 (adult adj1 periodontitis*).tw. 6 (chronic adj1 periodontiti*).tw. 7 AGGRESSIVE PERIODONTITIS/ 8 periodontos*.tw. 9 ((juvenile or aggressive or prepubertal) adj1 periodontitis).tw. 10 early onset adj1periodontiti*.tw. 11 early-onset adj1periodontiti*.tw. 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (36067) 13 PLATELET-RICH PLASMA/ 14 ((platelet rich or platelet-rich) adj1 plasma).tw. 15 PLATELET-RICH FIBRIN/ 16 ((platelet-rich or plateletrich) adj1 fibrin).tw. 17 l-prf.tw. 18 (((leukocyte and platelet rich) or leukocyteand platelet-rich) adj1 fibrin).tw. 11 "INTERCELLULAR SIGNALING PEPTIDES AND PROTEINS"/ 20 (factor * adj1 growth*).tw. 21 (paracrine adj1 peptide factor*).tw. 22 (intercellular signaling peptide* adj4 protein*).tw. 23 concentrated growth factor.tw. 24 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (1568603) 25 12 and 24 26 limit 25 to (english language and humans and yr="2015 -Current")	English language, human	306
	EBM Reviews - Health Technology Assessment 4th Quarter 2016		English language, human	0
	EBM Reviews - Cochrane Database of Systematic Reviews 2005 to August 15, 2018		English language, human	1
	EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016		English language, human	
	PUBMED		No limit	27
	INAHTA			0
	FDA			0
	HS			0

APPENDIX 3: EVIDENCE TABLE

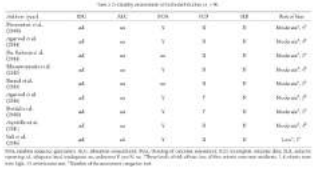
Evidence Table :
Question :

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
Li F, Yu F, Xu X, Li C, Huang D, Zhou X, Ye L, Zheng L. Evaluation of Recombinant Human FGF-2 and PDGF-BB in Periodontal Regeneration: A Systematic Review and Meta-Analysis. Sci Rep. 2017 Mar 6;7(1):65. doi: 10.1038/s41598-017-00113-y. PMID: 28246406; PMCID: PMC5427916.	**Study design:** **MA** **Objectives:** 1. ascertain whether rhPDGF-BB and rhFGF-2 can be deemed effective in regeneration of periodontium among patients suffering from either osseous defect or gingival recession. 2. the impact of periodontal therapy based on rhPDGF-BB and rhFGF-2 is affected by the concentration. 3. to identify whether periodontal hard tissue and soft tissue manifest different regeneration effects when treated with the same growth factors. **Data source:** Cochrane Central Register of Controlled Trials (CENTRAL; 2016), MEDLINE (via OVID, 1948 to August 2016), Embase (1984 to August 2015) and Pubmed **Quality assessment**: The Cochrane "risk of bias"= moderate	**I**	**Inclusion**: Both split mouth RCTs and parallel RCTs were included . **Exclusion**: case report, retrospective study, cohort study	growth factors treatment	control group: patients who did not receive growth factors treatment but who received conventional periodontal surgeries, placebo plus surgeries, or the carriers of growth factors plus surgeries		**Results:** **The Effect of Rhfgf-2 on Periodontal Regeneration** 1. 0.3% FGF2 groups was compared with control groups among patients with osseous defects: • BF% (MD=22.37; 95% CI 13.46 to 31.27) • LGB (MD=1.13; 95% CI 0.78 to 1.49) 2. 0.1% FGF2 groups was compared with control groups among patients with osseous defects: • BF% (MD=0.89; 95% CI -11.41 to 13.20) • LGB (MD=0.03; 95% CI -0.57 to 0.62) 3. 0.4% FGF2 groups was compared with control groups among patients with osseous defects: • BF% (MD=22.27; 95% CI -1.46 to 45.99) **The Effect of Rhfgf-2 on Patients with Osseous Defect** 1. 0.3mg/ml PDGF-BB groups was compared with control groups among patients with osseous defects: • BF% (MD=22.71; 95% CI 7.78 to 37.65) • LGB (MD=1.00; 95% CI 0.32 to 1.69)	CASP

	Outcomes: • bone fill percentage (BF%) • linear bone growth(LBG) • gains in clinical attach levels (CAL-G • probing depth reduction (PDR) • gingival recession (GR) **Statistical analysis**: MD						• no statistically significant difference in gingival recession among patients with osseous defect and gingival recession. 4. CAL-G (MD=0.76; 95% CI 0.28 to 1.24) 5. PDR (MD=1.12; 95% CI 0.28 to 1.96) 6. **Sensitivity analysis:** **Conclusion:** Our findings indicate that 0.3% rhFGF-2 and 0.3mg/ml rhPDGF-BB show a greater capacity for periodontal regeneration than other concentrations and superiority to control groups with statistical significance. In the case of patients suffering only from gingival recession, however, the application of rhPDGF-BB produces no significant regenerative advantage. The findings of this study can potentially endow clinicians with guidelines for the appropriate application of these two rhGFs	

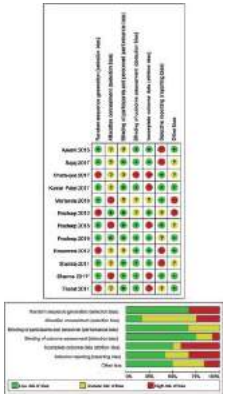
Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comme
Del Fabbro M, Karanxha L, Panda S, Bucchi C, Nadathur Doraiswamy J, Sankari M, Ramamoorthi S, Varghese S, Taschieri S. **Autologous platelet concentrates for treating periodontal infrabony defects**. Cochrane Database Syst Rev. 2018 Nov 26;11(11):CD011423. doi: 10.1002/14651858.CD011423.pub2. PMID: 30484284; PMCID: PMC6517213.	**Study design** Cochrane SR **Objectives** To assess the effects of APC used as an adjunct to periodontal surgical therapies **Data source:** Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 1) in the Cochrane Library (searched 27 February 2018); MEDLINE Ovid (1946 to 27 February 2018); Embase Ovid (1980 to 27 February 2018); and LILACS BIREME Virtual Health Library (from 1982 to 27 February 2018). The US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform were searched for ongoing trials on 27 February 2018. No restrictions were placed on the language or date of publication when searching the electronic databases. **Quality assessment**: GRADE: very low **Outcomes**: **Primary outcomes** Change in probing depth (PD), change in clinical attachment level	**I**	**Inclusion**: 38 RCTs: parallel (16) and split-mouth design (22), involving patients with infrabony defects requiring surgical treatment. Studies of a specific surgical technique combined with APC, with the same technique when used alone **Exclusion**: Studies: 1. no randomisation 2. no control group 3. gingival recession, not infrabony defects 4. same patients reported in a previous study 5. non-independence of analysing unit 6. incomplete data 7. no APCs (fibrin glue) 8. APC not the only difference between groups 9. studies with mixed (parallel/split-mouth) design	1. APC + OFD 2. APC + OFD + BG 3. APC + GTR 4. APC + EMD	1. OFD 2. OFD + BG 3. GTR 4. EMD	1. 12 trials 2. 17 trials 3. 7 trials 4. 2 trials	**Results:** 1. Primary outcome: i. Change in probing depth (PD) (mm) advantage in using APC (MD 1.29, 95% CI 1.00 to 1.58; P < 0.001) advantage in using APC (MD 0.54, 95% CI 0.33 to 0.75; P < 0.001) advantage in using APC (MD 0.92, 95% CI -0.02 to 1.86; P = 0.05) insufficient evidence of an advantage in using APC (MD 1.13, 95% CI -0.05 to 0.30; P = 0.16) ii. Change in clinical attachment level (CAL) (mm) advantage in using APC (MD 1.47, 95% CI 1.11 to 1.82; P < 0.001) advantage in using APC (MD 0.72, 95% CI 0.43 to 1.00; P < 0.001) insufficient evidence of an advantage in using APC (MD 0.10, 95% CI -0.13 to 0.32; P = 0.40) insufficient evidence of an advantage in using APC (MD 0.42, 95% CI -0.02 to 0.86; P = 0.06) iii. Change in radiographic bone defect filling (RBF) (%)	CASP

	(CAL), and change in radiographic bone defect filling (RBF). **Secondary outcomes** Tooth survival, pocket closure, and oral health-related quality of life. **Statistical analysis**:						advantage in using APC (MD 34.26%, 95% CI 30.07% to 38.46%; P < 0.001) advantage in using APC (MD 8.10%, 95% CI 5.26% to 10.94%; P < 0.001) NIL Insufficient evidence of an advantage in using APC (MD -0.60%, 95% CI -6.21% to 5.01%; P = 0.83; 49 participants) **Sensitivity analysis:** Done but no explanation **Conclusion:** There is very low-quality evidence that the adjunct of APC to OFD or OFD + BG when treating infrabony defects may improve probing pocket depth, clinical attachment level, and radiographic bone defect filling. For GTR or EMD, insufficient evidence of an advantage in using APC was observed.	

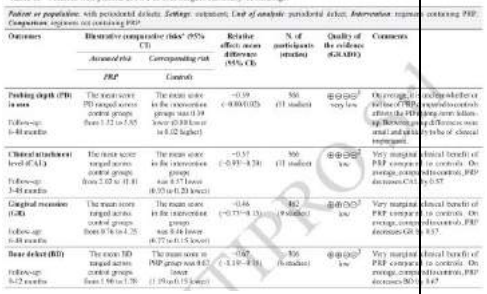
Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
Zhou S, Sun C, Huang S, Wu X, Zhao Y, Pan C, Wang H, Liu J, Li Q, Kou Y. Efficacy of Adjunctive Bioactive Materials in the Treatment of Periodontal Intrabony Defects: A Systematic Review and Meta-Analysis. Biomed Res Int. 2018 May 27;2018:8670832. doi: 10.1155/2018/8670832. PMID: 29977919; PMCID: PMC5994283.	**Study design:** MA **Objectives:** evaluate the adjunctive effects of bioactive materials such as platelet-rich plasma (PRP), platelet-rich fbrin (PRF), enamel matrix derivative (EMD), and amnion membrane (AM) on the outcomes of bone grafing treatment for periodontal intrabony defects. **Data source:** electronically in three databases (PubMed, Embase, and Cochrane Central) **Quality assessment**: Cochrane Handbook (available at: http:// training.cochrane.org/handbooks): 1 low, 8 moderate  **Outcomes**: PD reduction, CAL gain, RecRed, bone fll, and bone resorption between baseline and ultimate follow-up **Statistical analysis**: mean diference (MD)	**I**	**Inclusion**: RCTs compared DFDBA with or without one of the 4 bioactive materials (EMD, PRP, PRF& AM) in patients with periodontal intrabony defects **Exclusion**: retrospective cohort studies, animal studies, in vitro studies, case reports, case series, and reviews	DFDBA+PRP/PRF /EMD/AM	DFDBA alone	>=6 months.	**Results:** 1. PD reduction because of the low heterogeneity that was found among the subgroups (I^2 = 39.3%). • subgroups of PRP and PRF showed statistically significant differences compared with DFDBA alone, MD 0.47; 95% CI 0.14 to 0.80) & MD 0.88; 95% CI = 0.41 to 1.34) • PRF subgroup showed better reduction of PD compared to PRP subgroup 2. CAL gain: the random-effects model was employed because of the high heterogeneity (I^2 = 72.1%). • showed statistically significant differences between subgroups compared with DFDBA alone: - PRP (MD 0.80; 95% CI 0.27 to 1.32) - PRF (MD 1.61; 95% CI 1.10 to 2.12) - AM (MD 0.80; 95% CI = 0.37 to 1.24) • PRF subgroup showed best gain of CAL compared with the subgroups of PRP and AM. 3. EMD subgroup failed to show any significant difference. 4. RecRed: the random-efects model was used on account of the high heterogeneity (I^2 = 70.7%). • Only PRF subgroup showed a statistically signifcant diference compared with DFDBA alone, (MD of 0.77 (95% CI = 0.31 to 1.22). • The subgroups of PRP, EMD, and AM showed NS differences. 5. Bone fill: the random-efects model was used due to the high heterogeneity (I^2 = 78.2%). • Only PRP subgroup showed a statistically significant difference compared with DFDBA alone (MD of 0.71 (95% CI = 0.13 to 1.29). • subgroups of PRF, EMD, and AM showed NS differences. 6. Bone resorption: the fxed-efects model was used because of the low heterogeneity (I^2 = 0%). Nevertheless,	CASP

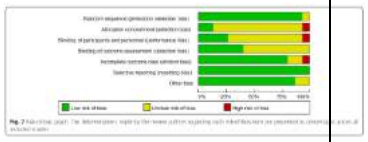
							all of the subgroups showed NS difference compared with DFDBA alone. **Sensitivity analysis:** removing one study each time to assess the infuence of an individual study on the overall outcomes. The results were stable, indicating that no single study interfered with the overall results significantly (Figure 3) **Publication Bias:** In the process of Begg's and Egger's test, no publication bias was detected in all assessments (Figures 4, 5, 6, 7, and 8) **Conclusion:** Within the limitation of this analysis, it is indicated that PRF exerts the most significant adjunctive effect on soft tissue healing, while PRP exhibits a unique impact on hard tissue reconstruction in the treatment of periodontal intrabony defect. EMD and AM demonstrated little additional benefit. Therefore, it seems reasonable to suggest that the autologous PRF/PRP could be taken as a preferred adjunct to promote periodontal regeneration due to its proven good biological efects, low costs, and ease of preparation. Nevertheless, standardization of the protocol for the preparation and application of PRF/PRP is needed to obtain an optimal efect in regenerative procedures.	

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
Călin C, Pătraşcu I. Growth factors and beta-tricalcium phosphate in the treatment of periodontal intraosseous defects: A systematic review and meta-analysis of randomised controlled trials. Arch Oral Biol. 2016 Jun;66:44-54. doi: 10.1016/j.archoralbio.2016.02.007. Epub 2016 Feb 11. PMID: 26897256.	**Study design:** MA **Objectives:** effectiveness at different points in time, of recombinant human platelet derived growth factor-BB (rhPDGF-BB) coated onto a beta-tricalcium phosphate (b-TCP) carrier compared to b-TCP alone, or to recombinant human growth/differentiation factor-5 (rhGDF-5) adsorbed onto a b-TCP scaffold in intraosseous periodontal defects **Data source:** MEDLINE/PubMed **Quality assessment**: • CONSORT guidelines: High to low-quality of reporting (57% to 23%) • Cochrane risk of bias tool: low in 2, medium in 1 study and high in 2 studies **Outcomes**: • probing pocket depth (PPD) reduction • clinical attachment level (CAL) gain • LBG • %BF **Statistical analysis**:	**I**	**Inclusion**: 5 RCTs **Exclusion**: As stated in the page 46 (2.3)	• human platelet derived growth factor-BB (rhPDGF-BB) coated onto a beta-tricalcium phosphate (b-TCP) • human growth/differentiation factor-5 (rhGDF-5) adsorbed onto a b-TCP	beta-tricalcium phosphate (b-TCP) alone	6 months	**Results:** • probing pocket depth reduction (PPD) ○ rhPDGF-BB vs β-TCP (p=0.0004083) ○ rhPDGF-BB vs rhGDF-5/b (p=0.1313) No significant difference • clinical attachment level gain ○ rhPDGF-BB vs β-TCP ($p= 4.748^{-8}$) ○ rhPDGF-BB vs rhGDF-5/b (p= 0.3598) No significant difference • linear bone growth (LBG) ○ rhPDGF-BB vs β-TCP ($p< 2.2^{-16}$) • % bone fill (%BG) ○ rhPDGF-BB vs β-TCP ($p< 2.2^{-16}$) • gingival recession (GR) ○ rhPDGF-BB vs rhGDF-5/b (p= 0.00048) **Sensitivity analysis:** **Conclusion:** In the treatment of periodontal intraosseous defects the application of rhPDGF-BB/b-TCP improved all outcomes when compared to b-TCP at 6 months follow-up. Either rhPDGF-BB/b-TCP or rhGDF-5/b-TCP seemed to provide similar results in terms of probing pocket depth (PPD) reduction and clinical attachment level (CAL) gain. The application of rhGDF-5/b-TCP resulted in a more pronounced reduction in gingival recession (GR) depth at 6 months follow-up compared to rhPDGF-BB/b-TCP.	CASP

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
Li A, Yang H, Zhang J, Chen S, Wang H, Gao Y. Additive effectiveness of autologous platelet-rich fibrin in the treatment of intrabony defects: A PRISMA-compliant meta-analysis. Medicine (Baltimore). 2019 Mar;98(11):e14759. doi: 10.1097/MD.0000000000014759. PMID: 30882646; PMCID: PMC6426538.	**Study design:** MA **Objectives:** evaluate the additive effectiveness of autologous PRF in the treatment of intrabony defects of chronic periodontitis patients when used along with OFD in terms of clinical and radiological outcomes **Data source:** Medline, EMBASE, the Web of Science, and the Cochrane Library **Quality assessment**: Cochrane Collaboration tool  **Outcomes**: **Statistical analysis**: **Limitation** the small size of the included RCTs.	**I**	**Inclusion**: 1. trials had to be properly randomized; 2. no additional agents or interventions confounded the comparison; 3. histologically proven intrabony defects of chronic periodontitis; 4. no systemic diseases that could potentially influence the outcome **Exclusion**: 1. study only featured comparisons of other types of chemotherapy regimens; 2. early studies published as a series of articles from the same institution or author that contained significant overlapping data were excluded for fear of multiple publication bias; 3.case reports, editorials, experimental studies, conference articles, and other studies that failed to provide detailed results were excluded.	1. probing depth (PD) reduction for intrabony defects (OFD+PRF) 2. clinical attachment level (CAL) for infrabony defects (OFD+PRF) 3. gingival marginal level change (GML) for infrabony defects 4. defect depth reduction (DDR) for intrabony defects	1. OFD only 2. OFD only 3. OFD only 4. OFD only	1. 9 months 2. 9-12 months 3. 9 months 4. 9 months	**Results:** weighted mean difference (WMD) • WMD=1.14, 95% CI 0.94 to 1.33 Significantly reduced PD in OFD+PRF group compared OFD only • WMD=1.14, 95% CI 0.94 to 1.33 Significantly gain CAL in OFD+PRF group compared OFD only 3. WMD=0.45, 95% CI 0.31 to 0.58 Significant improvement GML in OFD+PRF group compared OFD only 4. WMD=1.73, 95% CI 1.38 to 2.08 Significantly reduced DDR in OFD+PRF group compared OFD only **Sensitivity analysis: NIL** **Conclusion:** Adjunctive use of PRF with OFD significantly improves fill defects when compared to OFD alone. However, additional powered studies with much larger sample sizes are needed to obtain a more concrete conclusion. Although the interpretation of the study results was limited, we believe that to a certain extent, our analyses may provide valuable information for physicians	

							who need to decide the best treatment strategy among all possible regimens for patients with intrabony defects.	

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
Franchini M, Cruciani M, Mengoli C, Masiello F, Marano G, D'Aloja E, Dell'Aringa C, Pati I, Veropalumbo E, Pupella S, Vaglio S, Liumbruno GM. The use of platelet-rich plasma in oral surgery: a systematic review and meta-analysis. Blood Transfus. 2019 Sep;17(5):357-367. doi: 10.2450/2019.0177-19. PMID: 31577533; PMCID: PMC6774927.	**Study design:** MA **Objectives** to evaluate the benefit of platelet rich plasma (PRP) in oral surgery **Data source:** A computer-assisted literature search of the MEDLINE (through PUBMED), EMBASE, SCOPUS, OVID and Cochrane Library electronic databases **Quality assessment**: Cochrane Handbook for Systematic Reviews of Interventions **Outcomes**: 1. probing depths 2. clinical attachment level 3. gingival recession 4. radiographic bony defect **Statistical analysis**: mean difference (MD)	**I**	**Inclusion**: original, concerned with RCTs performed in adult patients, published in full in English in the last 20 years (1999- 2019) **Exclusion**: Studies less than • 20 patients • 2 months of follow up were excluded.	Regimens containing PRP	Regimens NOT containing PRP		**Results:**  1. **probing depths** (MD= -0.39, 95% CI -0.80 to 0.02) No significant difference between two groups 2. **clinical attachment level** (MD= -0.57, 95% CI -0.93 to -0.20) Slight decrease in clinical attachment level in the PRP group compared to the control arm 3. **gingival recession** (MD= -0.46, 95% CI -0.77 to -0.15) Slight decrease in gingival recession in the PRP group compared to the control arm 4. **radiographic bony defect** Slight decrease in bony defects in the PRP group compared to the control arm **Sensitivity analysis:** **Conclusion:** Evidence from a comparison between the use in oral surgery of PRP-containing regimens compared to other regimens not-containing PRP was of low quality. The results of the meta-analysis, limited to studies in patients with periodontal defects, document that PRP was slightly more effective compared to controls not-containing PRP	CASP

Bibliographic citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
Hou X, Yuan J, Aisaiti A, Liu Y, Zhao J. The effect of platelet-rich plasma on clinical outcomes of the surgical treatment of periodontal intrabony defects: A systematic review and meta-analysis. BMC Oral Health. 2016 Aug 17;16(1):71.	**Study design** MA **Objectives** evaluate the efficacy of PRP in the surgical treatment of periodontal intrabony defects by comparing clinical outcomes between patients who received PRP as an adjunct to periodontal intrabony defect therapy and those who did not **Data source:** PubMed, Embase, Web of Science and the Cochrane Central Register of Clinical Trials **Quality assessment**: Cochrane Handbook for Systematic Reviews of Interventions And reported  **Outcomes**: 1. Change in CAL 2. Change in PD **Statistical analysis**:	**I**	15 studies included in SR 12 were included in MA **Inclusion**: 1. RCT in which an intervention group receiving PRP was compared with a control group not receiving PRP 2. had no systemic illness or abnormal platelet counts that could affect the clinical outcome of periodontal therapy 3. f/up ≤ 6 mths **Exclusion**: 1. inadequate comparison of the results of PRP for the treatment of periodontal intrabony defects 2. PRP administered to both the intervention and control groups 3. the use of a biologic material that would hamper meaningful comparisons 4. reviews, case reports, animal studies	5. clinical attachment level (CAL) for infrabony defects (OFD+PRF) 6. probing depth (PD) reduction for intrabony defects (OFD+PRF)	1. Control (no PRP) 2. Control (no PRP)		**Results:** 1. PRP showed a significantly positive effect on periodontal intrabony defect treatment WMD=0.76, 95% CI 0.34 to 1.18 2. PD reduction was significantly greater in the intervention group treated with PRP than in the control group based on the random-effects model WMD=0.53, 95% CI 0.21 to 0.85 3. Subgroup meta-analyses: • with GTR: not significantly affect treatment outcomes (CAL: WMD 0.08, 95 % CI −0.30 to 0.46) • without GTR (CAL: WMD 1. 22, 95 % CI 0.88 to 1.57 mm) • Univariate meta-regression analyses revealed that the use of GTR explained the heterogeneity among the included studies (P < 0.05) **Conclusion:** The adjunctive use of PRP together with conventional grafting procedures may be a beneficial treatment approach. However, when combined with the use of a regenerative technique, such as GTR, the beneficial effect of PRP on the treatment of intrabony defects is negligible	CASP

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