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The Evidence-based Effect of Platelet-rich Fibrin in Osteogenesis: A Systematic Review and Meta-analysis

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Abstract

BACKGROUND: Platelet-rich fibrin (PRF) is a growth factor concentration functioning as an initiator of wound healing and bone regeneration and it is mainly reported in dentistry rehabilitation and rejuvenation.

AIM: The aim of the study was to summarize and analyze the evidence based on the effect of PRF on the bone osteogenesis.

METHODS: A comprehensive search was conducted on the bibliographic databases or medical subject headings in the PubMed. The search was conducted among articles that were published between 2010 and 2021. Required article information was extracted from each article by abstract and full paper availability that focuses on the platelet-rich fibrin (PRF) and osteogenesis. We recruited studies with the design was employed clinical trials with *in vitro* and *in vivo* approaches. The only study that provided osteogenesis outcome proceeded to the quantitative analysis.

RESULTS: Regarding literature search and screening processes, it yielded 24 studies for qualitative assessment and 11 studies for quantitative analysis. Most of the studies performed a combination of PRF with other materials such as Mg ring, BMSCs, gold nanoparticles, and PDLSCs. It showed that PRF combined with other materials enhanced the osteogenic ability. The assessment of PRF only showed the various result in multiple outcome markers. For the ALP, the mean difference is 1.40 [1.14–1.67] p = 0.001. It indicates that there is a significant effect of PRF application with the increase of ALP. For the RUNX2, there is a significant effect of PRF application with the increase of RUNX2 1.10 [0.93, 1.26]. For OCN, the mean difference of PRF in OCN is 0.77 [0.43, 1.12] p = 0.001. It showed a significant effect of PRF application with the increase of OCN. There is also a significant effect of PRF application for TRAP with the declining number of TRAP is –1.59 [–2.96, –0.22] p = 0.001.

CONCLUSION: PRF combined with other materials showed more promising results rather than PRF only. Moreover, in the assessment of PRF only, it was found that PRF has a significant effect in accelerating bone osteogenesis.

Introduction

The refinement of bone defects is one of the most frequent regenerative methods involving more than 2 million bone grafts in the global world annually. Bone defects are mainly caused by trauma, congenital anomalies, and tissue resection because of cancer [1]. Even though bone has an exquisite capacity performance in self-repairing, it is still limited, particularly in bridge extensive defects. Despite the advances in the treatment in medicine, autologous bone transplantation is deemed the gold standard to treat bone defects [1]. The transplantation procedure includes harvesting bone derived from other anatomical locations in the patient to be used as a transplantation material in the bone defect site. At present, there is an advanced development in bone repair using biomaterial for augmentation. Different biomaterials have been utilized in dentistry and proven to fill skeletal defects and improve wound healing. The previous materials such as tricalcium phosphate, freeze-dried bone graft, and hydroxyapatite bioactive glass have been commonly used and tested for their effect and significance in healing and regenerating soft and hard tissues [2].

Autologous bone transplantation utilizes the autologous graft for the treatment procedure. Autologous grafts are collected from patients, in which, they are to be used, commonly at the first surgical procedure. Allografts are collected from one patient or individual and they can be utilized for another patient in the same species. A xenograft, the third form of graft, is different from other graft forms because graft material can be used in individuals of different species. Grafts could be gathered from cortical bone, cancellous bone, a combination of the two (corticocancellous graft), or from cartilage (osteochondral) [3]. Grafts treat defect repairment by viable osteoblasts accouterment and their precursors through recruitment of MSCs that discern into osteoblast and chondrocytes (osteoinduction) and by administering new bone formation scaffold (osteoconduction) [3].

Recently, numerous studies have been centralized to study the utilization of platelet-rich fibrin

(PRF), an autogenous material. PRF provides scaffold osteoconduction and growth factors to prompt patients' cells toward a regenerative response [4]. PRF is a fibrin matrix in which growth factors, platelet cytokines, and cells are cornered and liberated after a specific time [5]. PRF acts as a growth factor and promotes the healing and regeneration of wounds. It is used in dentistry to heal various lesions and regenerate oral and dental tissues [2]. However, the development of PRF utilization, a limited study finds the evidence-based PRF effect on osteogenesis. Therefore, this study aims to summarize the effect of PRF on bone osteogenesis.

Methods

Data collection and assessment of the methodological quality of each included study referred to the standard method of preferred reporting items for systematic reviews and meta-analysis [6]

Literature search method

Inclusion criteria

The studies had to analyze the effect of platelet-rich fibrin application with bone osteogenesis (*in vitro* and *in vivo* study) and had to be published in English with published between January 2010 and May 2021.

Databases

Published studies were collected from PubMed. Using text words, medical subject headings (MeSH) and search terms were performed in the article search. The reference list of recaptured articles was assessed manually to identify further research studies relevant to the PRF effect in bone osteogenesis.

Participant

It was conducted on behalf of clinical trial studies. The studies also utilize either *in vitro* or *in vivo* design and it also recruited studies from dentistry and orthopedics studies.

Interventions

This review highlights platelet-rich fibrin's use with and without combining other grafting materials. The comparison was recorded using the significant outcome marker results such as bone alkaline phosphatase (ALP), RUNX2, OCN, and TRAP.

Critical appraisal

The selected relevant study was assessed by the primary investigator independently for methodological validity. An expressly designed checklist was employed to examine every study according to the inclusion criteria. Specific articles were not included because of limited information on the PRF outcome with one of the osteogenesis markers. The process of this systematic review was summarized with a PRISMA flow diagram (Figure 1).

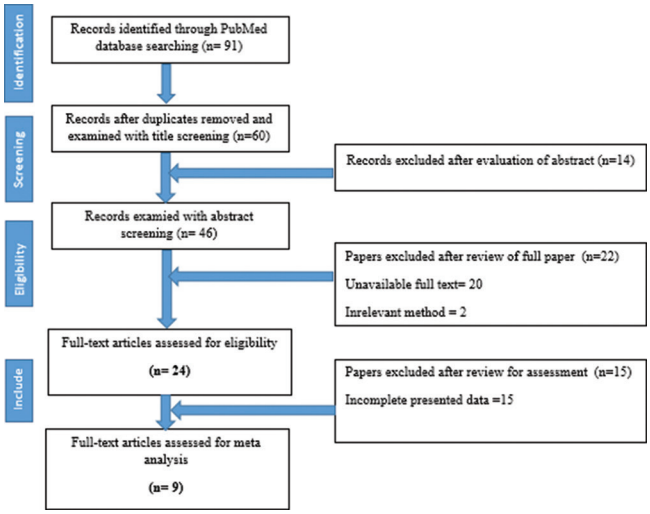

Figure 1: PRISMA flow diagram, summary of search process

Risk bias

The included studies were assessed for outcome reporting bias by utilizing PRISMA, 2009

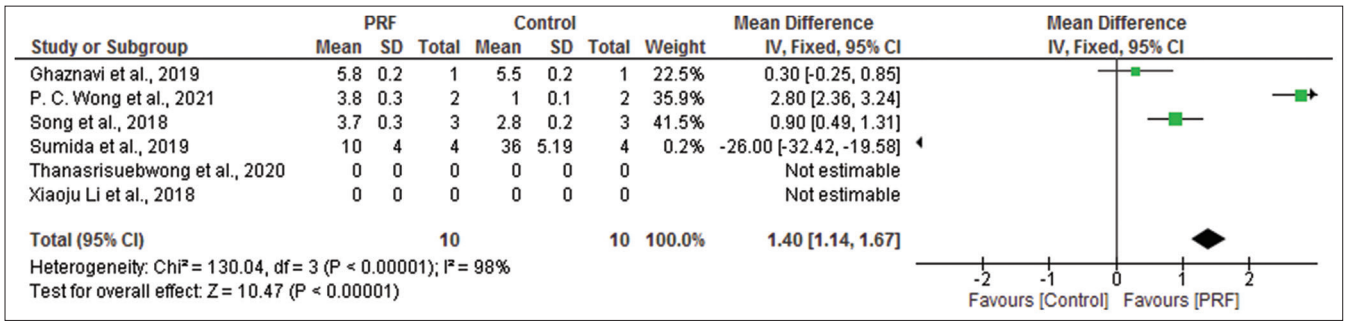

Figure 2: Forest plot of PRF and ALP

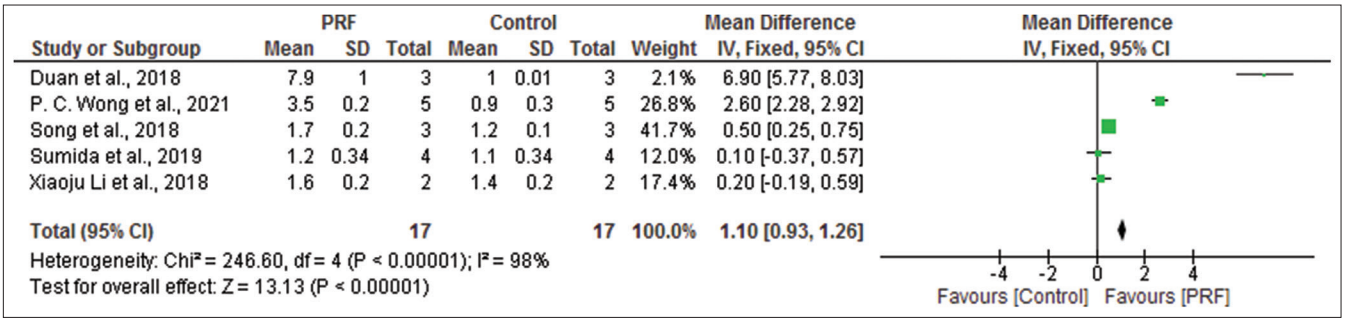

Figure 3: Forest plot of PRF and RUNX2

guidelines. These were examined by contrasting the study objective, intervention, and outcomes. All included studies were categorized it low, high, or unclear bias by the initial analyst regarding reported results. Articles with low bias were only selected to be synthesized and analyzed in quantitative analysis.

Data analysis strategy

We employed a random-effects model with a restricted maximum likelihood approximate to assess the summary relative risk. The effect of homogeneity across the studies was estimated using v^2 statistic and quantified by I^2, showing the total variation of percentage among studies related to heterogeneity than chance.

Results and Discussion

The effect of PRF in osteogenesis

It showed that PRF intervention was less effective in osteogenesis than PRF combination with other materials. However, the studies that only employed PRF indicated an inclining number of OPG/RANK ratio by OPG expression induction, implying PRF enhancement in early-stage osteogenesis with improving osteoblastic differentiation [7]. PRF positively affects the process of wound healing, especially in angiogenesis, in the *in vitro* coculture [8]. PRF membrane soluble extracts reduced the expression level of Cathepsin K, nuclear factor of activated T-cells (NFATc1), osteoclast marker genes TRAP, osteoclast-associated receptor (OSCAR), and dendritic cell-specific transmembrane protein (DC-STAMP) [9]. Clinical studies reported that PRF's advantages in bone regeneration depend on its combined competency as cell migration, proliferation, and agent of wound-healing, along with its tissue-specific capacity to result in osteoblast differentiation [10].

PRF combined with other materials has revealed better effectiveness in bone regeneration and osteogenesis rather than PRF alone. The use of an Mg ring enhanced the osteogenic ability and migration capacity of Mg ions during degradation. Large-pore platelet-rich fibrin (LPRF) combined with Mg ring showed more effect in repairing long bone defects [11]. Other studies showed that red i-PRF might be advisable for bone rejuvenation because of its capability to induce growth and mobilization of bone regeneration cells without affecting premature mineralization. Moreover, red i-PRF combined with bone substitute material application may be more effective than the yellow i-PRF [12]. Intervention using the combination of BMSCs and PRFr has more significant results in improving osteogenesis, which served as an understanding for further developing a novel therapeutic strategy in treating osteoporosis [13]. Gold nanoparticles to the advanced PRF and fibrin and platelet byproducts could be new substitute strategies to enhance the osteogenesis capacity of the stem cells [14]. PRF transplantation along with rat PDLSCs reported a higher expression of collagen I (COL1A), RUNX2, and osteopontin (Opn) at both 12 and 24 days after surgery. Regarding the histological analysis and micro-computed tomography, more bone formation was found in the PRF + cells group 24 days after surgery. Stereology and histologic examination revealed a higher composition of bone development in the defects treated with PRF mixed β-TCP compared to the treatment of

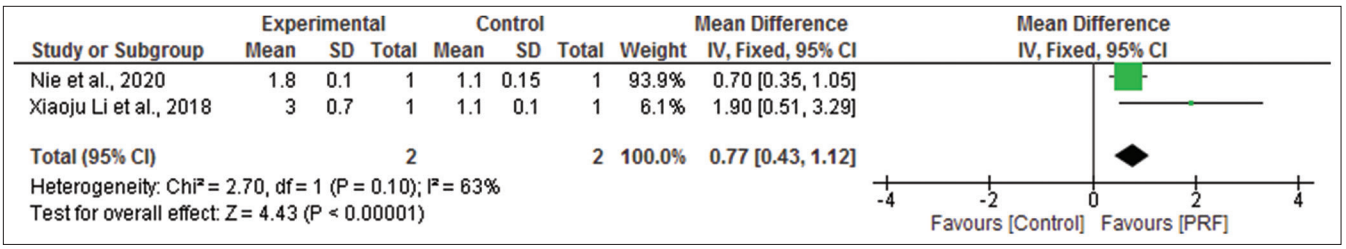

Figure 4: Forest plot of PRF and OCN

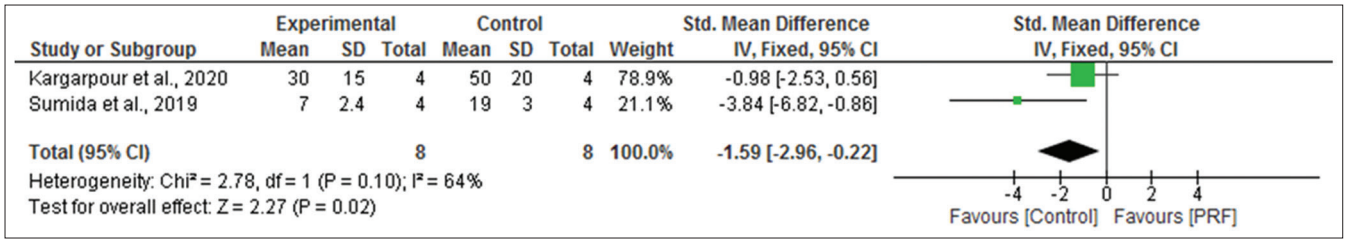

Figure 5: Forest plot of PRF and TRAP

either β-TCP or PRF alone [15].

Quantitative analysis

Nine studies were included in the meta-regression analysis as shown in Table 1. The studies were divided into four different outcome parameters, such as ALP, RUNX2, OCN, and TRAP, to assess the effectiveness of PRF in bone osteogenesis.

The alkaline phosphatase test (ALP)

Bone ALP is a primary regulator of bone mineralization. ALP has a principal function in bone mineralization in the process of bone-forming through hydrolyzing phosphate esters and ALP has been screened during human bone regeneration. In addition, ALP has been categorized as an initial marker for cells osteogenesis [16]. Four experimental studies were analyzed for PRF and bone ALP. The result found that the fixed effect size is 1.40 [1.14–1.67] p = 0.001, I^2= 98%. It indicates a significant effect of PRF application with the increase of ALP compared to the control group (Figure 2).

RUNX2

Runt-related transcription factor 2 (RUNX2) is a transcription factor associated closely with the osteoblast phenotype. RUNX2 is required for the osteoblast progenitor proliferation of osteoblast progenitors and proliferation inductor [17]. Our result showed that the effect size of PRF in RUNX2 is 1.10 [0.93, 1.26] p = 0.001, I^2= 98%. It indicated a significant effect of PRF application with the increase of RUNX2 compared to the control group (Figure 3).

OCN

OCN is derived from mature osteoblast and mainly accumulated in the extracellular matrix (ECM) of bones. OPN and OCN have an essential function in bone mineralization and are associated with the differentiation of osteogenesis. They are commonly treated as osteogenesis differentiation markers [18]. Our result showed that the effect size of PRF in OCN is 0.77 [0.43, 1.12] p = 0.001, I^2 = 63%. It is indicated a significant effect of PRF application with the increase of OCN compared to the control group (Figure 4).

Table 1: Studies included in meta-regression

Author and Year	Treatment comparison	Number of experiment	Result
(Nie *et al*., 2020)	OCN and OPN	n=1	OCN (Mean, SD) • Control (1.1, 0.1) • L-PRF (3, 0.7) OPN (Mean and standard deviation) • L-PRF (2.3, 0.7) • Control (1, 0.1)
(Sumida *et al*., 2019)	• OPG positive cells mean • TRAP-positive cell scale bars • ALP mg • RUNX2	OPG n=4, TRAP n=4, ALP=3, RUNX2 n=3	OPG positive cells Mean, 10 µm (Mean, SD) • PRF = (170, 60) • Control = (60, 20) TRAP positive cell scale bars, 10 µm (Mean, SD) • PRF = (7, 4,8) • Control = (19, 6) ALP mg (Mean, SD) • PRF = (10, 6.9) • Control = (36, 5.19) RUNX2 (Mean, SD) • PRF (1.2, 0.34) • Control (1.1, 0.34)
(Song *et al*., 2018)	• ALP activity nmol/min/mg protein • RUNX2 • OPN expression	N=3	ALP Activity nmol/min/mg protein (Mean, SD) • PRF = (85, 10) • Control= (51, 10) RUNX2 (Mean, SD) • PRF = (1.7, 0.2) • Control = (1.2, 0.1) ALP (Mean, SD) • Control; (2.8, 0.2) • PRF: (3.7, 0.3) OPN (Mean, SD) 14 Days • PRF (3.3 , 3.5) • Control (2.6, 0.1)
(Wong *et al*., 2021)	• ALP expression • RUNX2	N=5	ALP expression (Mean, SD) • PRF (3.8, 0.3) • Control (1.0, 0.1) RUNX2 (Mean, SD) • PRF (3.5, 0.2) • Control (0.9, 0.3)
(Kargarpour *et al*., 2020)	TRAP	N=4	TRAP (Mean, SD) • Control (50, 20) • PRF (30, 15)
(Thanasrisuebwong *et al*., 2020)	ALP (microgram)	N=2	ALP microgram (Mean, SD) • Control (0.006, 0.007) • Yellow PRF (0.018, 0.019) • Red PRF (0.015, 0.018)
(Xiaoju Li *et al*., 2018)	• RUNX2 • OCN	N=1	RUNX2 (Mean, SD) • PRF = (1.4, 0.2) • Control= (1.6, 0.2) OCN (Mean, SD) • PRF = (1.8, 0.1) • Control = (1.1, 0.15)
(Ghaznavi *et al*., 2019)	ALP	N=1	ALP (Mean, SD) • Control (5.5, 0.2) • PRF (5.8, 0.2)
(Duan *et al*., 2018)	RUNX2	N=3	RUNX2 (Mean, SD) Control = (1.0, 0.01) PRF = (7.9, 1)

TRAP

Tartrate-resistant acid phosphatase (TRAP) is mainly expressed in bone through osteoclasts; it is also found in osteoblast and osteoblasts. TRAP agitates mesenchymal lineage cells differentiation, that

is, osteoblasts and adipocytes progenitors [19]. Our analysis showed that the effect size of PRF in TRAP is −1.59 [−2.96, −0.22] p = 0.001, I2 = 64%. It indicates that there is significant effect of PRF application with the declining number of TRAP compared to the control group.

Conclusion

PRF combined with other materials showed more promising results rather than PRF only. Otherwise, in the assessment of PRF only, it was found that PRF has a significant effect in accelerating bone osteogenesis. PRF increases the alkaline phosphatase test (ALP), RUNX2, and OCN and decreases tartrate-resistant acid phosphatase (TRAP).

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