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ORIGINAL ARTICLE

REGENERATIVE POTENTIAL OF DIFFERENT GROWTH FACTORS (PRP, PRF, AND CGF) IN SINUS AUGMENTATION PROCEDURES-A SYSTEMATIC REVIEW

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ABSTRACT

This study was conducted to assess the regenerative potential of blood derived growth factors such as Platelet Rich Plasma (PRP), Platelet Rich Fibrin (PRF), and Concentrated Growth Factor (CGF) used alone or in combination with graft materials during sinus augmentation procedures.

A detailed literature search was conducted of the major online databases including hand and bibliography search of all related international journals. Definite search variables were set, and specific inclusion exclusion criteria were applied to retrieve relevant articles.

Application of the definite search strategy and related parameters resulted in the retrieval of two hundred and thirty-four articles, of which only 14 articles satisfied the inclusion and exclusion criteria. Four articles were related to PRF, six to PRP and four to GCF. Only two of them reported a positive response to the use of these blood products. The clinical parameters reported were radiographic bone density, bone height changes, implant stability, marginal bone levels, implant survival rates, and histological changes.

It was concluded that further research with larger sample size and longer duration is warranted to determine the osteogenic effects of PRF, PRP and CGF. The available evidence fails to report long-term clinical outcomes on implant success rate and other related clinical parameters greater than six months period. The current literature on the clinical application of these blood derived growth factors is inadequate and limited.

Keywords: *regeneration, growth factors, sinus augmentation, implant survival rates, implant stability, bone height changes, radiographic bone density, histological change*

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INTRODUCTION

Dental implant placement requires adequate alveolar bone and appropriate soft tissue.[1] There has been plethora of research done to provide evidence for the effectiveness of bone grafting procedures pre-implant placement, during implant placement and post placement.[2]

Recent advancements have been done to introduce platelet derived growth factors showing both potential for improving outcomes of bone grafting procedures and providing antibacterial properties.[3,4,5] Growth factors have been reported to enhance healing in bone defects and play a pivotal role in angiogenesis, cell migration and cell proliferation hence, proving to be extremely beneficial for regenerative procedures around teeth and implants.[6] Techniques developed to extract growth factors have led to the development of platelet rich fibrin (PRF), platelet rich plasma (PRP) and concentrated growth factor (CGF).[7,8] PRP has been reported to augment haemostasis, angiogenesis, osteogenesis,

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and posses' anti-infective properties.[9] PRF mainly consists of autologous platelets and white blood cells present in a fibrin matrix[10], whereas CGF has a denser fibrin matrix aimed at producing better regenerative results.[11,12]

Maxillary sinus augmentation with simultaneous implant placement requires complex yet essential planning to provide adequate accommodation of implant dimensions[1]. Sinus lift procedures have been executed conventionally with or without the use of bone grafts[2]. Lately with the advent of blood derived growth factors and their application in regenerative procedures, sinus elevation procedures are undertaken together with growth factors to accelerate and improve the clinical outcomes of the concerned clinical treatment[3]. However, literature remains inconclusive regarding the use of growth factors alone or in combination with bone grafts that promises additional clinical benefits in comparison to conventional sinus lift techniques[7].

This review aims at systematically assessing the literature in order to effectively compare the regenerative effects of PRP, PRF and CGF that will deliver appropriate evidence and profound clinical protocol employed during sinus elevation procedures.

METHODS

A systematic review of literature encompassing the effectiveness of blood derived growth factors in terms of their regenerative effects in sinus augmentation procedures and other clinical outcomes.

Research Topic

The research topic in question was formulated according to the following PICO formula:

Population: Individuals with inadequate residual bone in their posterior maxilla.

Intervention: Sinus lift:

- PRP with/without grafting
- PRF with/without grafting
- CGF with/without grafting

Comparison: Sinus lift procedure without using any blood derived growth factor.

Outcomes: The outcomes were measured in terms of implant survival rates, mobility, pain, bone gain or loss, marginal bone levels and peri-implantitis when PRP, PRF or CGF used alone or together with grafting materials.

Inclusion Criteria

Studies that evaluated the regenerative effects of blood derived growth factors (PRP, PRF, CGF) in sinus augmentation surgeries using either lateral window or transcrestal approach with immediate or delayed implant placement were incorporated. A minimum number of ten patients were considered in case of case series, while no limit was set for other study designs. Clinical outcomes considered must have been reported with a mean follow-up period of not less than 4 months.

Exclusion Criteria

Studies in which primary outcome was not sinus augmentation were excluded. Publications reporting systemic conditions such as HIV, diabetes, osteoporosis, or bisphosphonate therapy were not included. Cleft palate/craniofacial surgeries and case reports were not incorporated in the review and case series involving less than ten patients were also not considered.

Literature search

A search was done using online databases including PubMed, MEDLINE, Cochrane Database, BioMed, Science Direct, and Google Scholar. The following search terms were used in combination 'platelet rich plasma' OR 'PRP', 'PRF' OR 'platelet rich fibrin', 'concentrated growth factor' OR 'CGF' AND 'Sinus augmentation' OR 'Sinus lift' OR 'Maxillary sinus elevation' OR 'Maxillary sinus lift' AND 'Implant Success Rate', OR 'Implant Failure', OR 'Implant Survival Rate'.

The search criteria were defined to incorporate human subjects of any gender or age having no underlying medical conditions. Articles published in all languages were included, and the search was limited to a period starting from of 1st January 2010 until 31st January 2022. Three levels of search were done which involved the keywords mentioned above, abstract reading and hand search utilising international peer reviewed journals. Fig.1 explains the search strategy.

Search Criteria

The titles and abstracts of all extracted articles were reviewed and analysed by the two main authors (IH and HS). Each title was read individually, and a third reviewer (MN) was involved where there was disagreement amongst the authors. The agreement percentage for each stage of screening was set at 95 percent. Full texts of articles which met the inclusion criteria were obtained. Studies which did not satisfy the inclusion criteria were excluded. Data was presented using tables (Tab.1-3) present in publications classified as study type, author name, test group, control group, mean patient age, number of implants placed, number of sinus elevations, follow up period, implant installation protocol and effect of intervention. Critical appraisal of the relevant studies added was done using the checklist of the critical appraisal skills program (CASP) tool. Jadad scale was used to analyse randomized clinical

trials where required.[13]

RESULTS

Outcome of literature search

Of the fourteen selected articles six belonged to PRP, four were related to PRF, and four were associated to CGF. The mean follow-up period for inclusion was initially set at 6 months; however, it was later reduced to four months to include more studies.

Seven studies utilised the lateral window technique, while four used the transcrestal approach to augment the sinus floor. Articles reported several different clinical variables to account for the regenerative potential of the blood derived growth factors such as radiographic bone density, radiographic bone gain or loss, implant success rates, implant survival rates, and histological measures. A detailed search strategy can be seen in Fig.1.

Platelet Rich Plasma (PRP)

Poeschel et al. 2012[14] and Taschieri et al. 2016[15] performed prospective studies using PRP enriched grafts in sinus elevation surgeries. Poeschl et al. 2012[14] employed venous blood mixed with HA in the test group and HA alone in the control group following delayed implant placement protocol. However, difficulty was encountered in assessing the concentration of growth factors present in a small volume of blood sample taken and thus, made the study results inconclusive. Taschieri et al. 2016[15] compared the regenerative potential of biphasic calcium phosphate (BCP) and PRP or deproteinized bovine bone matrix (DBBM) and PRP in sinus floor elevation and reported an excellent performance of both materials regarding implant survival rate after one year, however, the beneficial role of PRP was stated as controversial. Similarly, Inchingolo et al. 2012[16] and Kumar et al. 2014[17] executed prospective studies evaluating the effect of PRP when used with autogenous bone. Both studies displayed statistically significant results in the favour of PRP when used with autogenous bone.

Badr et al. 2010[18] and Khairy et al. 2013[19] conducted randomized clinical trials (RCT) to analyse the efficacy of PRP in sinus augmentation procedures when implants were placed following the delayed protocol. Badr et al. 2010[20] observed no significant difference between the test and control groups when iliac crest graft was used alone or in combination with PRP. Khairy et al. 2013[19] assessed the change in bone density when PRP was used together with an autogenous bone graft and observed no significant improvement in bone density in PRP enriched graft at 3 months, however, at 6 month the bone density was higher in PRP enriched grafts.

Platelet Rich Fibrin (PRF)

Simonpieri et al. 2011[20] conducted a case series determining the effectiveness of PRF as a sole augmentation material in sinus lift procedures. Radiographic analysis using retroalveolar, panoramic and in some cases CT scan was carried out immediately post-operative, at 6 months, one year and following every year until 6 years. The results demonstrated no implant failure and substantial vertical bone gain during the period of follow up. The author concluded that the PRF was a reliable and stable grafting material when used in a sinus elevation surgery. Similarly,

Toffler et al. 2010[21] and Tajima et al. 2013[22] conducted prospective studies to determine the success of PRF used alone in sinus elevation procedures and reported it as a predictable material for sinus floor augmentation.

Inchingolo et al. 2010[23] conducted a prospective study to evaluate the significance of PRF use with Xenograft. The study results considered this treatment modality a highly successful protocol that leads to successful implant rehabilitation.

Concentrated Growth Factor (CGF)

Chen et al. 2016[24] conducted a retrospective study evaluating the clinical effects of osteotome mediated sinus elevation (OSFE) using CGF as grafting material and results showed remarkable bone augmentation with this protocol.

Sohn et al. 2011[25] executed a prospective study to analyse new bone formation when autologous fibrin rich blocks with CGF were used alone as an alternate to bone grafting. The authors found CGF to be an effective treatment modality that promises enhanced bone regeneration with simultaneous implantation during sinus elevation procedures.

Moreover, Kim et al. 2012[26] performed a prospective study aimed to assess the implant success rate

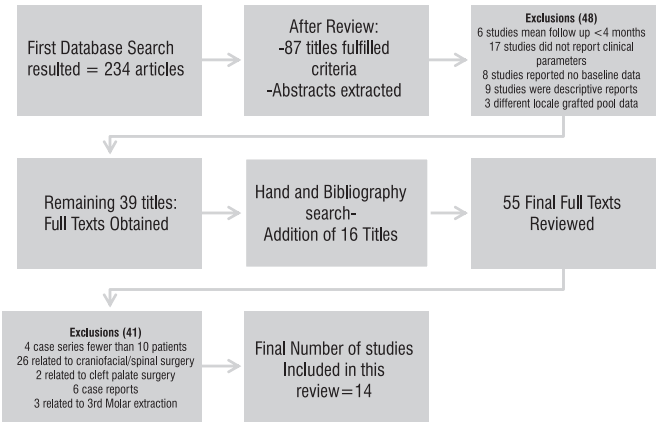

Fig 1: Search Strategy

TABLE 1: DETAILS OF STUDIES THAT EMPLOYED PRP. HA-HYDROXYAPATITE, PRP-PLATELET RICH PLASMA, RCT-RANDOMIZED CONTROL TRIAL, AB-AUTOGENOUS BONE, OB-ORGANIC BONE, A.B-ANORGANIC BONE, NI-NOT INCORPORATED, NR- NOT REPORTED

Authors	Study Design	Control Group	Test Group	No. of Patients Reported	Patient Mean Age (years)	No. of Implants Placed	Implant Protocol	Sinuses Augmented	Follow up Period (months)	Regenerative Potential of PRP
Badr.et al 201018	RCT	AB	PRP with AB	16	36	85	Delayed	16	5-6	Not significant
Inchingolo et. al 201216	Prospective	AB, OB and A. B	PRP with AB, OB and A.B	127	NR	NR	Immediate	127	5	Significant
Poeschl et al.201214	Prospective	HA	PRP with HA	25	55	28	Delayed	18	7	Significant
Khairy et al. 201319	RCT	AB	PRP with AB	15	38	NR	Delayed	15	3 and 6	Significant
Kumar et al. 201417	Prospective	AB with VB	PRP with AB	50	55	121	Delayed	NR	6 and 12	Not significant
Taschieri et al. 201615	Prospective	NI	PRP	23	55	60	Immediate	NR	14	Significant

TABLE 2: DETAILS OF STUDIES THAT EMPLOYED PRF. NI-NOT INCORPORATED, PRF-PLATELET RICH FIBRIN

Author	Study Design	Control Group	Test Group	No. of Patients Reported	Patient Mean Age (months)	No. of Implants Placed	Implant Protocol	Sinuses Augmented	Follow up (months)	Regenerative Potential of PRF
Inchingolo et al. 201023	Prospective	NI	PRF with xenograft	23	45	95	Immediate	31	6	Significant
Toffler et al. 201021	Prospective	NI	PRF	110	58.4	138	Immediate	138	5	Significant
Simonpieri et al. 201120	Case Series	NI	PRF	20	59.8	52	Immediate	23	6	Significant
Tajima et al. 201322	Prospective	NI	PRF	6	67.8	17	Immediate	9	6	Significant

TABLE 3: DETAILS OF STUDIES THAT EMPLOYED CGF. NI – NOT INCORPORATED, CGF – CONCENTRATED GROWTH FACTOR

Author	Study Design	Control Group	Test Group	No. of Patients Reported	Patient Mean Age (months)	No. of Implants Placed	Implant Protocol	Sinuses Augmented	Follow up (months)	Regenerative Potential of CGF
Sohn et al. 201125	Prospective	NI	CGF	53	51.3	113	Immediate	61	5	Significant
Kim et al. 201226	Prospective	NI	CGF	33	51.4	74	Immediate	51	5	Significant
Kim et al. 2014a27	Prospective	NI	CGF	10	50.7	16	Immediate	11	5	Significant
Chen et al.201624	Retrospective	NI	CGF	16	54.2	25	Immediate	15	6 and 12	Significant

and vertical bone gain using hydrodynamic piezoelectric internal sinus elevation (HPISE) technique with fibrin rich blocks of CGF. The study found crestally approached HPISE technique comparable to laterally sinus augmentation that provides favourable implant success rate and enhanced new bone formation.

On the contrary, Kim et al. 2014a[27] performed another prospective study comparing new bone formation in PRP, PRF and CGF and observed no considerable difference between the three blood derivates in terms of their osteogenic effects.

DISCUSSION

Sinus augmentation is necessary in patients with inadequate residual bone height in the posterior maxilla. Therefore, the foremost aim of this procedure is to augment the height of the residual alveolar bone for the placement of endosseous implants.[28]

There are various methods described in the literature to perform sinus augmentation procedures. However, this systematic review focuses on the use of PRP, PRF and CGF when employed solely or in combination with a graft in sinus lift situations either before or at the time of implant placement. These blood derived factors are expected to promote new bone formation and improve implant related clinical outcomes.

The complexity of the theme can be overtly simplified, and any conclusions drawn cannot stand alone as evidence, however this paper aims to provide an overall comparison for which a systematic study design is considered acceptable.

PRP, PRF, and CGF can be used alone or in combination with autografts, xenografts, or alloplastic bone substitutes. They have shown to increase bone regeneration, induce rapid tissue healing and stabilise the placed implant.[3] Moreover, they have proven to reduce the treatment window between bone augmentation and implant placement due to enhanced tissue healing.[3]

Platelet Rich Plasma (PRP)

PRP has displayed to promote increased bone formation and bone density when used with autogenous bone, and alloplastic bone substitutes like HA.[8,30] Some authors have reported positive clinical outcomes; however, the net beneficial effect is not statistically significant.[31] Whilst the extracted data reported increased regenerative potential of PRP, the long-term clinical outcomes are not well reported in the recent literature.[30] This might be on account of the evolution of second-generation blood derived products such as PRF and CGF. [3,25]

Poeschl et al. 2012[14] reported a statistically significant osteogenesis when a mixture of PRP enriched

grafts of autogenous bone and HA were used. Moreover, Inchingolo et al. 2012[16] found PRP to significantly enhance bone regeneration when mixed with autogenous, organic and anorganic bone substitutes. Surprisingly, Kumar et al. 2014[17] demonstrated significantly improved osteogenesis with PRP enriched autogenous bone grafts at 6 months; however, the difference was not significant at one year postoperatively, thus suggesting that the addition of PRP may increase new bone formation at an initial healing stage. Similarly, Khairy et al. 2013[19] observed a considerable increase in bone density at four months in comparison to six months postoperatively, additionally supporting the findings of Kumar et al. 2014.[17] These findings are in accordance with other published studies.[31]

Studies performed on PRP have demonstrated to increase bone regeneration at least during the initial phase of healing; however, the current evidence on its osteogenic properties is still controversial and cannot be pertinent at large. [31]

Platelet Rich Fibrin (PRF)

Currently, there appears to be a consensus on its use as being broadly useful. Whilst the data collected in this review is sufficient to support this statement, however, the available literature is inadequate, and most of the studies were conducted by a small number of investigators who possess a special interest in this field.[34] Evidence suggests that the effects of PRF may be related to the adjunctive graft material used and the adhesion provided by PRF to particulate grafts.[34]

PRF has demonstrated enhanced bone regeneration, reduced healing time, and increased bone density.[32] It has also been described as successful when used as a sole graft material[33] however, without statistical analysis and the presence of a control group the results cannot be considered as conclusive.

Moreover, PRF was found to promote Schneiderian membrane repair and help reduce sinus graft healing time particularly during Osteotome Mediated Sinus Floor Elevation (OMSFE) procedures.[35]

Implant survival rate of up to 100% after six months had been reported in literature with the use of PRF during sinus augmentation procedures.[34] However, operator experience with specific technique employed, and the effect of primary implant stability were highlighted as the most important factors governing the outcome. The use of PRF is considered contraindicated whenever an implant lacks primary stability. This is because the apical end of an implant tents the overlying Schneiderian membrane and secures the placed graft. In addition, the constrictive ability of PRF does not allow an adequate bone volume to form especially in cases of delayed implant placement in larger defect sites.[22]

Concentrated Growth Factor (CGF)

Fibrin rich blocks are known to slowly release CGFs, such as platelet-derived growth factor, transforming growth factor B-1 and vascular endothelial growth factor, and accelerate new bone formation when mixed with bone grafts in the maxillary sinus augmentation.[6] CGF a second-generation blood derivative used solely as a graft substitute in either transcrestal or lateral sinus elevation approaches promises enhanced bone regeneration.[25]

Chen et al. 2016[24] revealed significant bone resorption at 6 months and further resorption after 12 months period that was considered insignificant when OSFE technique was employed with CGF. Authors reported OSFE with CGF to be a viable treatment option in severely atrophic maxillae especially in cases of residual bone height of 2-4mm.

High implant success rate (97.2-98.2%) and significant vertical bone gain had been reported when autologous fibrin-rich blocks with concentrated growth factors (CGFs) were used alone as an alternative to graft material.[25,26] On the other hand, Kim et al. 2014a[27] observed enhanced new bone formation when CGF was filled in a rabbit skull defect following a healing period of 6 months, however, the osteogenic effects of CGF and PRF were not seen to be greater than PRP. It may be because the researcher did not compare CGF with a control group. The authors further recommended the use of CGF in combination with bone grafts to obtain accelerated tissue healing that allows early implant placement.[27]

CGF has proven to be a viable blood derived factor than can be used as an alternate to bone grafts which promises enhanced bone augmentation in sinus elevation procedures. However, current evidence is insufficient, therefore, further research is required to validate the results.

CONCLUSION

PRF and CGF were seen to outperform PRP in terms of enhanced bone regeneration, advanced soft and hard tissue healing and Schneiderian membrane repair, however the evidence is limited and therefore, further research is warranted to evaluate the osteogenic properties of PRP, PRF and CGF in the form of randomized clinical trials with a follow up period greater than 6 months. Current literature is inadequate and cannot be applied to clinical practice at large.

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