

Evaluation of the Efficacy of Concentrated Growth Factor in Regenerative Endodontics: A Narrative Review

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Abstract

Regenerative endodontic procedures are the treatment of choice when managing non-vital immature permanent teeth. Various autologous platelet concentrates are being used as scaffolds such as blood clot, platelet-rich plasma, platelet-rich fibrin (PRF), and concentrated growth factor (CGF). CGF is a novel scaffold that can be used in regenerative endodontic procedure. No additives are added in its production and it has higher adhesive and tensile strength as well as higher viscosity when compared to other platelet concentrates. Hence, the objective of this narrative review is to assess the efficacy of CGF in regenerative endodontic treatment.

Keywords: Autologous platelets concentrates, Concentrated growth factor, Regenerative endodontics, Scaffolds.

INTRODUCTION

Traumatic dental injuries to the teeth and/or other hard and soft tissues of the oral cavity commonly occur in children and young adults.^[1] Pulp necrosis and consequent infection of the root canal system may be caused by such injuries with a prevalence of 17–100%.^[2]

Immature permanent teeth with necrotic pulps are difficult to treat with conventional root canal fillings due to the presence of blunderbuss canals and large open apices.^[3] Management of these teeth is of great concern and apexification used to be the treatment of choice earlier. Such teeth have thin and weak roots which are susceptible to fracture. Apexification procedures necessitate the long-term insertion of calcium hydroxide in the root canal to induce the creation of an apical hard tissue barrier. The mechanical properties of dentin are altered when calcium hydroxide is used in the canals for a long time. It resolves the signs and symptoms of the disease, but the immature tooth is left with thin fragile dentinal walls, thus increasing its susceptibility to fracture and lower survival rates.^[4]

As an alternative method, regenerative endodontics is being used to promote better tooth prognosis and function of non-vital immature permanent teeth.^[5]

A complete tooth regeneration that seemed to be impossible few years ago is now possible with the introduction of scaffold-based tooth regeneration techniques and tissue engineering. A scaffold is a three-dimensional porous solid biomaterial

used for regeneration that should offer the framework for cell growth, differentiation, and organization at a local site, be porous enough to allow cell implantation, and be biocompatible with host tissue. It should be biodegradable, decay gradually, and transfer nutrients and trash efficiently.^[6] Both natural and artificial scaffolds are being used with advantages over each other; however, natural scaffolds are more bioactive and biocompatible than the artificial one.^[7]

Natural scaffolds include collagen, chitosan, silk, and fibrin, as well as autologous scaffolds such as blood clots, platelet-rich plasma, and platelet-rich fibrin while synthetic scaffolds include polyglycolide, polyglycerol sebacate, etc.^[8] Autologous platelet concentrates (APCs) have recently emerged as potential scaffolds for improving regeneration procedures, as they play a key role in raising the predictability of both hard and soft-tissue regeneration. APCs are hemo components that are extracted from a patient's blood sample by centrifugation. The goal of this method is to gather the blood sample's most active components.

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One such novel scaffold containing increased level of platelet concentrates and a denser fibrin clot is concentrated growth factor (CGF). Sacco developed CGF, an upgraded second-generation platelet concentrate, in 2006.^[9]

CGF contains abundant cytokines and can be used in the study of bone regeneration.^[10] CGF promotes proliferation and osteoinduction of PDL stem cells *in vitro* and bone tissue engineering *in vivo*^[11] due to the presence of numerous growth factors such as fibroblast growth factors (FGF), transforming growth factor (TGF), platelet derived growth factor (PDGF), insulin-like growth factor, and vascular endothelial growth factor (VEGF). The growth factors regulate cell proliferation, migration, matrix remodeling, differentiation, and angiogenesis.^[12]

Therefore, the aim of this narrative review is assess the efficacy of CGF in regenerative endodontics treatment.

LITERATURE SEARCH

A thorough literature search was carried out between January 1, 2010, and June 1, 2023, using electronic search engines including PubMed, Cochrane Library, and Google Scholar as well as hand search, to find published studies on the efficacy of CGF in regenerative endodontics. The keywords used in the preliminary search were as follows: “CGF,” “Regenerative endodontics,” and “autologous scaffolds.” The articles to be selected for the review were required to fulfill the following eligibility criteria:

1. Studies published between the year 2011 and 2023
2. Studies in which CGF was used as an autologous scaffold
3. Studies in which CGF was used exclusively for regenerative endodontic procedures and/or for regeneration of the dentin-pulp complex
4. Disclosure of at least one of the following outcomes: Effect of CGF on cell proliferation, differentiation, migration, root regeneration, resolution of periapical pathology, and resolution of signs and symptoms.
5. Case reports, randomized controlled trials, clinical trials, and original studies.

Studies not available in the English language as well as reviews, editorials, and letters were excluded from the study.

DISCUSSION

After searching all databases, eight studies^[13-20] qualified the inclusion criteria and were selected for this narrative review.

Effect of CGF on proliferation, migration, and differentiation of human dental pulp stem cells (hDPSCs):^[13,14]

Two studies^[13,14] evaluated the effect of CGF on proliferation, migration, and differentiation of hDPSCs *in vitro*. The results of these studies were similar and showed that the proliferation of hDPSCs was significantly higher with CGF than in the control group (medium in which no CGF was used). In comparison to the controls, CGF also increased cell migration, alkaline phosphatase (ALP) activity, and mineralized tissue deposition.

Jin *et al.* (2018)^[14] also evaluated the effect of different concentrations of CGF on the proliferative activity of hDPSCs. About 100% of CGF was prepared by soaking each CGF gel into 9 mL blank Dulbecco's Modified Eagle Medium (DMEM) at 37°C for 2 weeks. Then, 100% CGF was diluted with DMEM into 80%, 50%, 20%, 10%, or 5% (v/v) CGF as required. Lower doses of CGF (<50%) showed significantly higher rates of cell differentiation in comparison to the controls, while this difference was not significant for higher doses of CGF (50–80%).

These studies also evaluated the messenger RNA expression levels of various genes related to dentinogenesis and angiogenesis such as dentin matrix protein 1 (DMP-1), dentin sialophosphoprotein (DSPP), osteopontin, Runt-related transcription factor 2, osteocalcin, VEGF receptor-2, and cluster of differentiation. In both these studies, CGF significantly upregulated the expression of these genes thus confirming that CGF is a growth factor-loaded scaffold that promotes dentinogenesis and angiogenesis, thus facilitating regeneration of the dentin pulp complex.

Effect of CGF on proliferation, migration, and differentiation of Stem Cells of Apical Papilla (SCAPs)^[15,16]

Two studies^[15,16] evaluated the effect of CGF on proliferation, migration, and differentiation of SCAPs *in vitro*. In both the studies, the growth rate and migratory cell numbers of the CGF groups were significantly greater than those in the control groups ($P < 0.05$). The mineralization areas in the CGF groups were significantly larger than those in the control groups ($P < 0.05$).

These studies also evaluated the gene expression of ALP, DSPP, and DMP-1. In both the studies, the expression levels of these genes were down-regulated after incubation in the CGF for 7 days ($P < 0.05$); however, they were significantly enhanced after incubation in the CGF for 14 days.

In vivo effects of CGF^[13,19]

Nivedhitha *et al.*^[17] used CGF as a scaffold for regenerative endodontic treatment in two cases with incomplete root formation and periapical lesion. In both the cases, following bleeding induction CGF was prepared, placed, and condensed into the root canal followed by the placement of mineral trioxide aggregate up to the level of CEJ. The extent of apical closure increase in root lengthening thickness and reduction in periapical radiolucency was evaluated using CBCT analysis. Post-operative CBCT at 1 year follow-up showed a reduction in the apical diameter as well as increase in the root dentin thickness in both the cases. There was also a reduction in the size of periapical radiolucency by 18.57% in case 1 and by 19.85% in case 2.

Xu *et al.* (2019)^[13] also studied the *in vivo* effects of CGF when used as a scaffold for the regeneration of immature single-rooted teeth in beagle dogs. In the CGF-treated group, radiographic analysis, hematoxylin-eosin, and mason trichrome staining showed continuation of root formation and

ingrowth of soft tissues into the root canal which resembles normal tooth development in the positive control group. Immunohistochemical staining showed VEGF and nestin which were both moderately expressed in the regenerated pulp-like tissues indicating vascularization and innervation.

Comparison of CGF with other scaffolds^[18-20]

Three studies compared CGF with other platelet concentrates such as blood clot, platelet-rich fibrin (PRF), advanced PRF (A-PRF), and platelet-rich plasma (PRP). Lee *et al.*^[18] compared the tensile strength, growth factor concentration, and proliferative activities of CGF with PRF. Masuki *et al.*^[19] compared the growth factor and proinflammatory cytokine content of CGF with PRP, A-PRF, and plasma rich in growth factors (PRGF). Yang *et al.* compared CGF with blood clot.^[20]

Concentrations of TGF-beta 1, platelet-derived growth factor (PDGF), and epidermal growth factor were significantly higher in CGF and A-PRF (A-PRF>CGF) than in other scaffolds. In the study by Masuki *et al.*, the level of proinflammatory cytokines (interleukin [IL]-1B, IL-6) was significantly higher for CGF and A PRF in comparison to other scaffolds. In the study by Lee *et al.*, tensile strength of CGF clot was significantly higher than PRF. Number of osteoblast in the fibrin clot from CGF was significantly greater than PRF. However, in the study by Yang *et al.*, the success rate of CGF and blood clot had no significant differences, and hence, CGF can be used as an alternative scaffold in regenerative endodontic procedures.

Two studies^[13,14] (Jin *et al.* and Xu *et al.*) confirmed that CGF promoted cell proliferation, migration, and the DPSC-mediated dentinogenesis and angiogenesis process *in vitro* and two studies by Hong *et al.*^[15,16] confirmed that CGF promoted the proliferation, migration, and differentiation of SCAP *in vitro*. This can be attributed to the high concentration of growth factors in CGF such as VEGF, TGF-B, and PDGF. Such results may also be caused by the abundant chemotactic factors released from the CGF, including PDGF-BB and bFGF. The dense fibrin network of CGF not only provided matrix surface for cell adhesion and migration but also protected those bioactive components from proteolysis.^[14]

In the study by Jin *et al.*,^[14] CGF extracts were diluted into low concentrations at 5% and 10% to imitate the slow release of growth factors from CGF scaffold *in vivo*. CGF improved the proliferative potential of DPSCs in a dose-dependent manner and achieved maximal promotion when the concentrations reached 50%. However, it displayed a pleiotropic effect on cell migration and odontoblastic differentiation, showing promotion effect dose-dependently at low concentrations (<50%), while high concentrations (50% or 80%) of CGF exerting negligible or no effect.

Qin *et al.*^[21] suggested that it may be associated with the unsuitable pH of culture medium resulting from too much platelets. The high level of leukocytes, IL-1 β , and IL-6 might also be responsible for the negative role of high-dosage CGF.

A low-dosage CGF at 5% had a synergistic action with VEGF on the DPSC-EC differentiation. However, 80% of CGF conversely repressed this process. Based on previous studies which reported that blocking TGF- β signaling enhanced endothelial differentiation,^[22,23] it could be hypothesized that the negative role of high-dosage of CGF may also be associated with the increasing content of TGF- β .

Masuki *et al.*^[19] compared the growth factor and proinflammatory cytokine content of CGF with PRP, A-PRF, and PRGF. The main finding of this study was that both A-PRF and CGF preparations contained TGF- β 1, PDGF-BB, VEGF, IL-1 β , and IL-6 at levels similar to or higher than PRP preparations. This may be because the prime source of growth factors in PRP was only exudate. It was also observed that WBCs, as well as platelets, were highly concentrated in A-PRF preparations. Similarly, WBCs were found to be concentrated in CGF preparations. In addition, the inflammatory cytokines were not exceptionally concentrated at higher levels in PRP preparations.

Lee *et al.*^[18] compared the tensile strength, growth factor concentration, and proliferative activities of CGF with PRF. A thicker and a more regular pattern of fibrin were observed in CGF than that in PRF. This is responsible for the greater tensile strength and growth factor content observed in CGF compared to those in PRF. Although the exact mechanism related to the mechanical and biological properties was still uncertain, the mode of polymerization of the final fibrin matrix in the absence of anticoagulant has considerable influence on these properties.^[24] Switching the centrifugation speed from one to another may produce fibrin clots with a stronger tensile strength, richer growth factors, and higher ability to induce the proliferation of osteoblasts and gingival fibroblasts.^[25]

Yang *et al.*^[20] compared CGF and blood clot as scaffolds in regenerative endodontic procedures and found a total success rate of 91.74% between both the groups over a period of 23.15 months. There was insignificant difference between the success rates of the blood clot group and the CGF group. Nonetheless, invoking adequate apical bleeding may not always be possible, and the concentration of growth factors in the BC is limited leading to unfavorable outcomes. This may be due to decreased inflammatory reactions after disinfection procedure or smaller canal diameters with smaller apical openings limiting the use of larger files for irritating apical tissues. In addition, intracanal calcification (50.0%) is a common complication for REPs with BC scaffold, leading to complicating future endodontic treatment.

CONCLUSION

This narrative review is designed to provide clinical information regarding the use of CGF in regenerative endodontics. Regenerative endodontic procedures have the potential to save teeth which have compromised structural integrity. It has emerged as an alternative for the treatment of immature teeth with pulpal necrosis. APCs have recently emerged as a possible

tool for enhancing the outcome of regeneration procedures as they play an important role in increasing the predictability of hard and soft tissue regeneration. CGF has appeared as a popular novel scaffold in the field of regenerative endodontics due to its higher adhesive strength, tensile strength, and higher viscosity as compared to other platelet concentrates. Further research is however still needed to open newer prospects in the future, regarding the use of CGF in regenerative endodontic procedures.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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