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Innovation in regeneration – Concentrated growth factor

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Abstract
Regenerative medicine is one of the most dominant objectives of today's rehabilitation therapies. In dentistry, many researches of growth factors applicable to bone regeneration techniques recognised that the best tissue regenerative stimulus are present amongst the autologous growth factors, which have clinically proven to induce regeneration and tissue healing. Growth factors are bioactive proteins which control the process of wound healing. Concentrated growth factor is an advanced 2nd generation platelet concentrate. Difference in centrifugation speed permit the isolation of a much larger and denser fibrin matrix richer in growth factors than typically found in platelet rich plasma and platelet rich fibrin.

Keywords: Regeneration, growth factors, concentrated growth factor (CGF)

Introduction
Concentrated growth factor is a novel 2nd generation platelet concentrate (Sacco in 2006) [1, 2]. CGF is fibrin rich organic matrix which contains growth factors, platelets, leukocytes and CD34+ stem cells which help in regenerating process [3, 6]. In dentistry, many researches of growth factors applicable to bone regeneration techniques recognised that the best tissue regenerative stimulus are present amongst the autologous growth factors, which have clinically proven to induce regeneration and tissue healing.

Preparation
CGF is an autologous preparation taken from venous blood collected in sterile Vacuette tubes without anticoagulant solutions. The tubes are centrifuged (Medifuge, Silfradent, Sofia, Italy) (Figure 1) with one step centrifugation protocol: 30sec -acceleration, 2min - 2700 rpm, 4min - 2400 rpm, 4min - 2700 rpm, 3min - 3000 rpm, 36sec – deceleration and stop. This results in 4 different phases which are as follows [4] (Figure 2)

Phases of CGF
1. Superior phase – Serum
2. Interim phase – Fibrin buffy coat
3. Liquid phase – Growth factors
4. Lower phase – Red blood cells

Phase 1
Superior phase is represented by Serum. It is a clear straw coloured fluid which is lightest and most liquid part of blood. It contains 92% of water and 7% of other concentrates which includes proteins, glucides, amino acids, lipids, enzymes, hormones and inorganic electrolytes. It is used to seal the bleeding capillaries, wash the surgical site, coat and protect the regenerated portions.

Phase 2
Interim phase is a fibrin buffy coat with polymerised fibrin block containing 3 dimensional polymer networks of fibrinogen molecules with interwoven fibres united to form a single phase in the form of gel. (Figure 3) When viewed under electron microscope this layer is constituted by thick and thin fibrillar elements. During polymerisation reaction the diameter of fibres grow until end of the reaction. During polymerisation it allows for volume growth of chains in all directions.

The fibrin blocks are of higher quality because of the high concentration of fibrinogen, factor XIII and thrombin. Factor XIIIa, which is activated by thrombin stabilizes the fibrin clot and provides protection from plasmin degradation, resulting in higher fibrin tensile strength and stability and prolong the duration of growth factor activity, which is conducive for growth factor synergy & enhances cell proliferation and osteogenic differentiation [5]. It is used as an autologous membrane support, filling material as a whole or mixed with bone particles.

Phase 3

Liquid phase contains growth factors, white blood cells and stem cells. (Figure 3) These stem cells are able to differentiate into their specialized cell types. This liquid phase is mixed with autologous bone graft to get high performance activated graft.

Phase 4

This lower phase is dark reddish dense gel. It consists of high concentration of red blood cells and also few white cells, platelets and clotting factors. It is used in pure form or mixed with bone grafts to fill large cavities.

Mechanism

CGF releases various growth factors such as Platelet-derived growth factor (PDGF), Transforming growth factor-β1 (TGF-β1) and β2 (TGF-β2), Fibroblast growth factor (FGF), Vascular endothelial growth factor (VEGF), Brain derived growth factor (BDGF) and Insulin-like growth factor (IGF) which stimulate cell proliferation, matrix remodelling and angiogenesis [6]. *In vitro* study have proved that growth factors like TNF-α and BDGF showed fast kinetic release from the concentrate and reached its maximum accumulation in 1st and 3rd day respectively. Similarly PDGF-AB, TGF- β1 and IGF-I had constant kinetic release and reached its maximum in 3rd and 6th day respectively. VEGF and BMP-2 had slow kinetic release and reached its maximum in 8th day. These growth factors predominantly play a role in osteoblast proliferation and differentiation [7].

CGF acts by degranulation of the alpha granules in platelets that contain growth factors which play a vital role in early wound healing [8]. The biphasic platelets in CGF is accelerated by thrombin, induce the release of growth factors and other substances which enhance the wound-healing process by increasing cellular proliferation, matrix formation, osteoid production, connective tissue healing, angiogenesis and collagen synthesis.

Functions

CGF is a fibrin tissue adhesive with haemostatic and tissue sealing properties. It promotes wound healing and accelerates osteogenesis. The CGF improve the wound stability, which is essential for the establishment of a new connective tissue attachment to a root surface. It also provides a scaffold supporting cytokine attachment and cellular migration. Act as a carrier for growth factors. It is an effective surgical haemostatic agent, promotes epithelial, endothelial and epidermal regeneration and decreases dermal scarring. Possess antimicrobial effect due to high concentration of leukocytes. It has anti-angiogenic property on chronic non healing wounds.

Applications

- CGF has wide range of healing property in patients undergoing cosmetic surgeries like facelifts, neck lifts, breast augmentation, cardiovascular surgeries, oral and maxillofacial surgeries.
- In dentistry CGF is used to fill extraction sockets, fill the cavity after cystectomy [9]. In a study CGF have proved to exhibit superior potential in sinus lift procedure and ridge augmentation surgeries [10]. CGF act as a membrane support in recession coverage as it constantly releases growth factors to produce tissue regeneration. [11] CGF is also mixed with autologous bone particles or biomaterials to fill the bone defects to induce bone regeneration. [4] In implants CGF is used as a membrane support to accelerate bone integration [12].

Fig 1: Medifuge, Silfradent, Sofia, Italy
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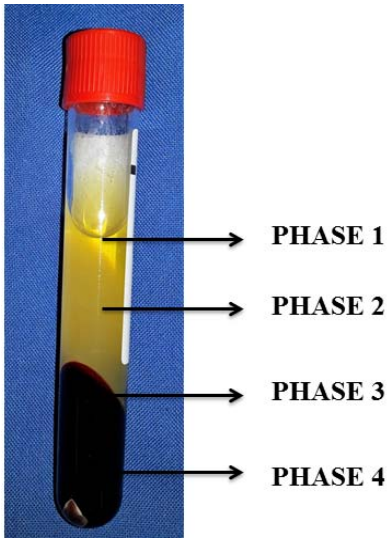

Fig 2: Four blood fractions obtained by centrifuge process. Phase 1: Superior phase represented by the serum; Phase 2: Interim phase represented by a very large and dense polymerized fibrin block; Phase 3: Containing growth factors, white blood cells and stem cells; Phase 4: Lower red blood cell layer.
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Fig 3: CGF separated from platelet-poor plasma.
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Conclusion

The autologous CGF is a relatively new biotechnology auto-graft that evidently demonstrates significant stimulation and acceleration of soft-tissue and bone, healing and formation. The efficacy of this therapy lies in the local delivery of a wide range and high concentration of growth factors and proteins, mimicking and supporting physiologic wound healing, reparative tissue process and local infiltration therapy, taking the practice of regenerative techniques to a sophisticated higher level.

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