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The Role of Platelet-Rich Fibrin (PRF) Membrane in Regulating Interleukin (IL)-1 and Vascular Endothelial Growth Factor (VEGF) Expression in Strabismus Surgery

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ABSTRACT

Strabismus surgery is a common procedure for correcting ocular misalignment. However, a major challenge in achieving optimal surgical outcomes is the risk of excessive postoperative inflammation, which can lead to fibrosis. This inflammatory response is primarily driven by the release of pro-inflammatory cytokines such as Interleukin (IL)-1 and pro-angiogenic factors like Vascular Endothelial Growth Factor (VEGF). While these mediators are essential for wound healing by promoting fibroblast activity, angiogenesis, and vascular permeability, their uncontrolled expression may result in excessive fibrosis, ultimately impairing ocular motility. A promising solution is the use of Platelet-Rich Fibrin (PRF) membrane, a second-generation platelet concentrate with both anti-inflammatory and regenerative properties. A review of existing literature highlights PRF's potential in enhancing wound healing. Despite its well-documented benefits in various surgical fields, its application in ophthalmic procedures, including strabismus surgery, remains underexplored. Given these promising findings, further research on PRF's role in strabismus surgery is warranted. This study aims to investigate the effect of PRF on IL-1 and VEGF expression, offering insights into its potential as an alternative strategy for improving surgical outcomes. PRF is expected to be a promising approach for reducing inflammation, preventing excessive fibrosis, and minimizing postoperative complications in strabismus surgery. However, further experimental and clinical studies are needed to validate its effectiveness.

Keywords: *Strabismus Surgery, Vascular Endothelial Growth Factor, Interleukin, Platelet Rich Fibrin*

1. INTRODUCTION

Strabismus surgery is a standard procedure aimed at correcting ocular misalignment. However, postoperative inflammation that is not properly managed can compromise surgical success. Excessive inflammation following strabismus surgery often leads to fibrosis, characterized by irregular connective tissue accumulation, which can negatively affect ocular motility (1).

One of the key immune reactions following surgery involves the release of pro-inflammatory cytokines, including Interleukin-1 (IL-1) and the pro-angiogenic factor Vascular Endothelial Growth Factor (VEGF). IL-1 triggers inflammatory pathways by activating immune cells and stimulating the production of cytokines and inflammatory mediators. In contrast, VEGF functions as a tissue mediator, enhancing vascular permeability and angiogenesis, both of which are essential for wound healing. Both IL-1 and VEGF play crucial roles in tissue repair by stimulating fibroblast activity, which is fundamental for wound healing, and by promoting angiogenesis and vascular permeability. However, their expression levels must be carefully regulated to prevent excessive inflammation, which could potentially compromise surgical outcomes (2–4).

Various approaches have been investigated to manage fibrosis and minimize excessive scar formationinter in strabismus surgery, aiming to preserve ocular motility and prevent postoperative misalignment. These include the use of steroids, amniotic membranes, mitomycin-C, triamcinolone injections, extracellular matrix membranes, and fibrin glue (5–7). However, these methods have limitations in clinical practice due to complex intraoperative application procedures, inconsistent results, and associated complications (8).

PRF membranes have emerged as a modern alternative for enhancing wound healing and tissue regeneration. They promote growth factor expression and matrix proteins which contribute to wound healing while preventing excessive scarring and inflammation. The combination of PRF's chemotactic and mechanical properties makes it an excellent autologous biomaterial for preserving function and promoting tissue reconstruction (9).

Studies on rabbit models of strabismus surgery have demonstrated PRF's effectiveness in improving wound healing and minimizing fibrosis. However, further research is needed to evaluate PRF's role in modulating IL-1 and VEGF expression. The results of this study are anticipated to serve as a foundation for utilizing PRF as an alternative strategy to mitigate inflammation and minimize postoperative complications in strabismus surgery.

2. WOUND HEALING PROCESS

Wound healing is a complex biological process designed to restore tissue integrity and function after an injury. It relies on various cellular and molecular mechanisms that facilitate proper tissue repair. Traditionally, this process is divided into four interconnected phases: hemostasis, inflammation, proliferation, and remodeling. Each phase is essential for ensuring efficient healing and preventing complications (10). The time line of wound healing phase describe on figure 1.

The first response to injury is hemostasis, which begins immediately to prevent excessive blood loss. Vasoconstriction occurs to minimize bleeding, followed by platelet aggregation at the injury site. The activation of the coagulation cascade results in fibrin clot formation, which acts as a temporary protective barrier against pathogens while providing a scaffold for the subsequent healing process. This initial phase is essential for stabilizing the wound and preparing it for further repair (10).

Once hemostasis is achieved, the inflammatory phase begins, lasting for several days. This stage is marked by the recruitment of immune cells, primarily neutrophils and macrophages, to the wound site. Neutrophils are the first responders, working to eliminate debris, pathogens, and necrotic tissue through phagocytosis (11). As the inflammation progresses, macrophages replace neutrophils and secrete cytokines and growth factors, which facilitate the transition to the next phase of healing. This inflammatory response is necessary for infection control and wound cleansing, ensuring a favorable environment for new tissue formation (12).

During the proliferative phase, which lasts from a few days to several weeks, the primary focus is on tissue regeneration and repair. This stage is crucial for lesion closure, involving angiogenesis, fibroplasia, reepithelialization, and wound contraction. These processes initiate within the first 48 hours in the lesion microenvironment and continue up to the 14th day post-injury. They collectively restore tissue integrity, accelerate recovery, and reduce complications (13).

The final stage of wound healing, remodeling phase, is lasting from months to years. During this period, the newly formed tissue undergoes maturation and structural reorganization. Type III collagen is progressively replaced by Type I collagen, enhancing tensile strength. Additionally, the extracellular matrix continues to be remodeled, improving wound stability, while unnecessary cells undergo apoptosis, refining the tissue structure (14). A comprehensive understanding of the wound healing phases is essential for developing therapeutic approaches that promote tissue repair and help manage complications like chronic wounds and excessive scarring.

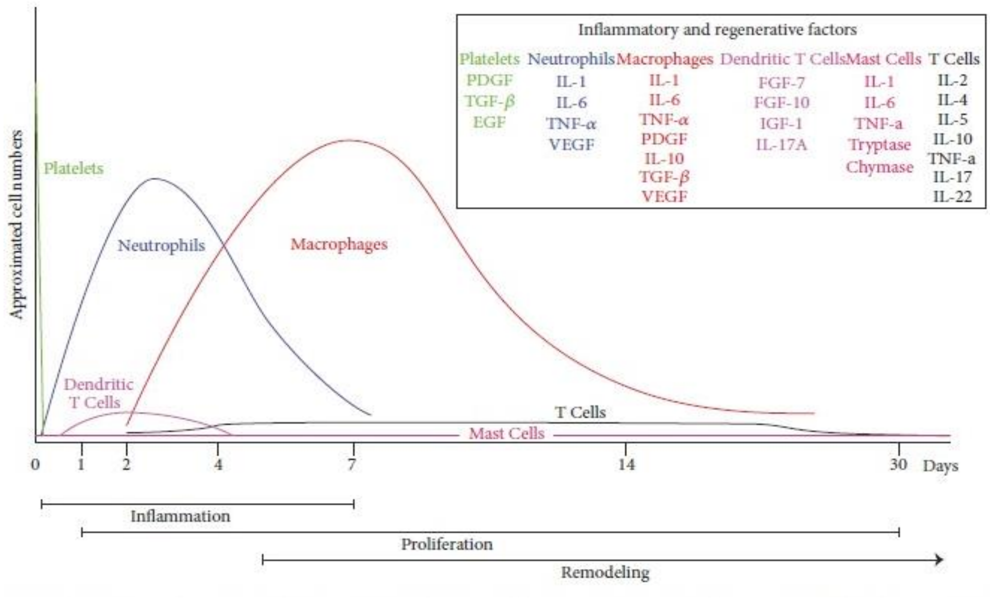

Figure 1. During the initial inflammatory phase, neutrophils rapidly peak and begin to decline after four days,

continuing to decrease until the end of the first week. As neutrophils decrease, macrophages progressively increase, reaching their highest concentration during the proliferation phase. Their numbers then gradually decline throughout the remodeling phase, playing a crucial role in tissue repair and inflammation resolution (11).

3. COMPLICATIONS POST-SURGERY FOR STRABISMUS

Strabismus surgery is generally safe and effective, but postoperative complications can occur and need to be diagnosed and treated early to optimize outcomes. Postoperative adhesions may develop in the conjunctiva, intermuscular membrane, Tenon's capsule, sclera, and extraocular muscles, potentially restricting eye movement even after extraocular muscle surgery. These adhesions, along with improper scar tissue formation, often result from poor wound healing (15).

When scar tissue stretches and invades normal muscle and scleral tissue, it can lead to progressive secondary strabismus, often accompanied by muscle weakness that may persist for months to years after the primary surgery. Management of secondary strabismus caused by scar tissue stretching requires surgical intervention, including exploration, scar excision, muscle reattachment to the sclera, and, if needed, additional surgery on the antagonist muscle (16–18).

Interleukin-1

Interleukin-1 (IL-1) is a key pro-inflammatory cytokine which plays a significant role in the body's immune response, primarily regulating inflammation. The IL-1 family comprises 11 cytokines that play a crucial role in initiating and controlling inflammatory processes. Among them, IL-1α and IL-1β are the most extensively studied due to their strong pro-inflammatory properties. These cytokines function by binding to specific receptors on target cells, triggering signaling pathways that regulate immune activation and inflammatory responses (19).

IL-1α and IL-1β are predominantly secreted by activated macrophages, though other cell types, including neutrophils, epithelial cells, and endothelial cells, can also produce these cytokines. They serve as key regulators of the inflammatory response, stimulating the expression of adhesion molecules on endothelial cells to enhance the recruitment of immune cells to areas of infection or injury(19).

While IL-1 is essential for initiating the healing process, its activity must be tightly regulated to prevent excessive inflammation, which can impede healing and lead to chronic wounds. The body naturally produces Interleukin-1 Receptor Antagonist (IL-1Ra) to inhibit IL-1 signaling, thereby modulating the inflammatory response (20).

Studies have demonstrated that interventions targeting IL-1 can modulate postoperative inflammation. For instance, the application of cryopreserved amniotic membrane in experimental strabismus surgery has been shown to reduce the expression of inflammatory cytokines, including IL-1β. This reduction correlates with decreased postoperative inflammation and fibrosis, suggesting that managing IL-1 levels can improve surgical outcomes. Moreover, the balance between pro-inflammatory and anti-inflammatory forms of IL-1 in ocular tissues is essential for maintaining tissue homeostasis. Disruption in this balance can exacerbate inflammatory conditions, highlighting the need for therapeutic strategies that modulate IL-1 activity to prevent adverse postoperative outcomes (21,22). IL-1 serves as a critical mediator of inflammation in strabismus surgery. Targeting IL-1 and its associated pathways offers a promising approach to controlling postoperative inflammation, thereby reducing the risk of fibrosis and enhancing surgical success.

4. VASCULAR ENDOTHELIAL GROWTH FACTOR

Vascular Endothelial Growth Factor (VEGF) is a signal protein essential for angiogenesis, the process of forming new blood vessels from existing vasculature. It belongs to family of growth factors that includes several isoforms, notably VEGF-A, VEGF-B, VEGF-C, VEGF-D, and also Placental Growth Factor (PlGF). These isoforms result from alternative mRNA splicing and have distinct functions in angiogenesis and lymphangiogenesis (23).

VEGF functions by binding to specific tyrosine kinase receptors on the surface of endothelial cells, primarily VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1). This interaction triggers a signaling cascade that stimulates endothelial cell proliferation, migration, and the formation of new blood vessels (24).

VEGF plays a key role in the wound healing process, especially during the inflammatory phase. Its main function is to stimulate angiogenesis, ensuring an adequate supply of oxygen and nutrients to support tissue repair and regeneration. During inflamatory phase, VEGF expression is upregulated in response to hypoxic conditions and inflammatory signals (25). In the context of ophthalmology, VEGF has been extensively studied, particularly concerning retinal diseases. However, its direct correlation with strabismus surgery remains an area with limited research, so further research is necessary to elucidate the potential impact of VEGF in strabismus surgery.

5. PLATELET-RICH FIBRIN (PRF)

The platelet-rich fibrin (PRF) membrane is a second-generation blood concentrate containing platelets, which function to aid in tissue regeneration. PRF is a derivative of platelet-rich plasma (PRP) that undergoes further processing to concentrate cytokines and growth factors (26).

PRF facilitates cell growth, proliferation, migration, differentiation, and integration of new tissue with the original tissue, ensuring optimal wound healing. PRF biomaterial is a solid fibrin matrix rich in platelets, leukocytes, and essential proteins for wound healing, supporting the formation of new tissue. The PRF membrane also contains and gradually releases growth factors, including FGF, VEGF, TGF, and PDGF (27).

The PRF membrane is a biocompatible and biodegradable. Three-dimensional biopolymer that simply produced without the need for additional substances. Its preparation begins with collecting venous blood sample into a sterile tube without anticoagulants, followed by immediate centrifugation at 3,000 rpm for 10 minutes (28). The centrifugation process separates the blood sample into three distinct layers: the top layer consists of Platelet-Poor Plasma (PPP), the middle layer contains the fibrin clot used for PRF, and the bottom layer is composed of red blood cells. The fibrin clot from the middle layer is carefully extracted using forceps and placed in a PRF box, where it undergoes gentle compression. This compression process converts the dense fibrin clot into a thin, membrane-like sheet while simultaneously expelling residual fluids trapped within the fibrin and erythrocyte sediment (29). The procedure of making PRF membrane was describe on figure 2.

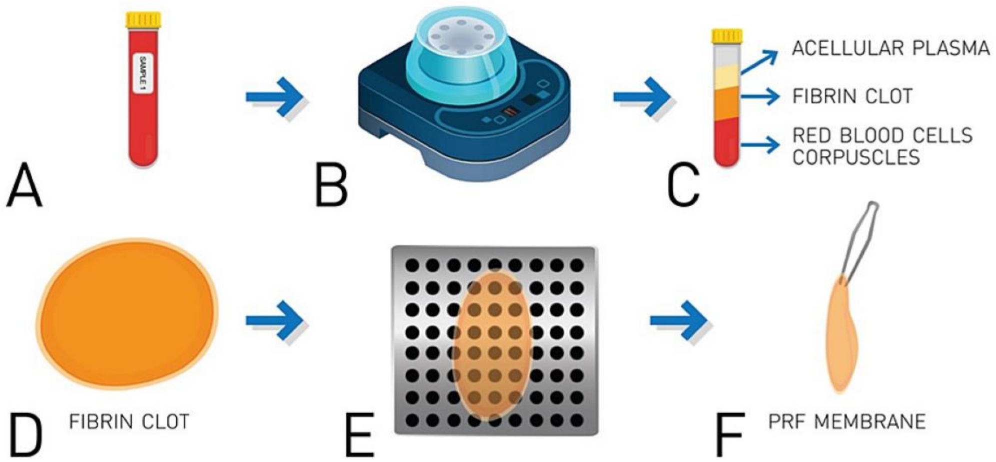

Figure 2. (A) A venous blood sample is collected from the patient and transferred into a sterile tube without anticoagulants. (B) The sample centrifuged at 3,000 rpm for 10 minutes. (C) This process concentrates fibrinogen in the upper two-thirds of the tube, leading to its polymerization into a fibrin clot (D). (E) The fibrin clot is carefully separated and drained, (F) resulting in the formation of the PRF membrane (28).

The use of PRF membranes has expanded across multiple medical fields, including dentistry, otolaryngology, plastic surgery, orthopedics, and ophthalmology. In ophthalmology, PRF supports healing in ocular surface diseases such as ocular alkaline trauma and enhances postoperative recovery following procedures like pterygium and strabismus surgery (29–31)

Effective wound healing after strabismus surgery is essential to prevent restrictive strabismus. Excessive scar formation and postoperative adhesions often restrict ocular movement, leading to complications. Various strategies have been explored to minimize adhesions, with PRF emerging as a promising approach. Acting as an adjuvant and biocatalyst, PRF enhances wound healing by promoting inflammatory cell recruitment and hemostasis. (16).

6. RABBIT AS A ANIMAL MODEL STRABISMUS SURGERY

The use of animal models is essential in ophthalmic research, particularly for investigating surgical interventions and therapeutic approaches in strabismus cases. Among various models, New Zealand White rabbit (*Oryctolagus cuniculus*) have been extensively utilized due to their physiological and anatomical similarities to the human ocular system. Their ocular size and structure closely resemble those of humans, facilitating the extrapolation of research findings. Additionally, the ease of handling rabbits a practical choice for experimental studies (32). The superior view of rabbit eye anatomy was describe on figure 3.

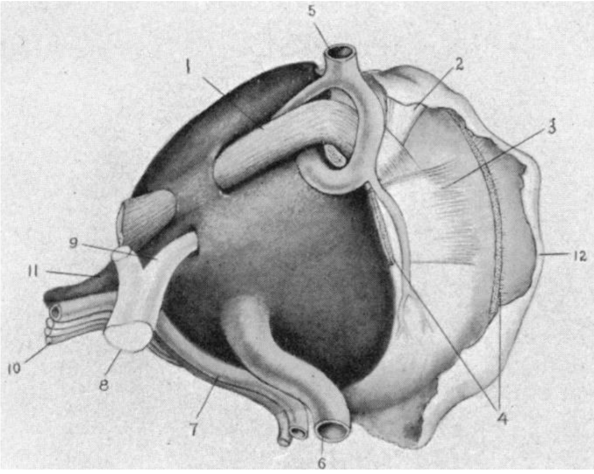

Figure 3. Superior view of orbital content dissection. 1. Superior oblique. 2. Retractor palpebre tertia. 3. Superior rectus. 4. Cut ends of levator palpebra superioris. 5. Supra-orbital vein. 6. Posterior ophthalmic vein. 7. Lacrimal artery and nerve. 8. Optic chiasm. 9. Optic nerve. 10. Branch of fifth nerve to lower lid. 11. Internal ophthalmic vein. 12. Cut margin of Tenon's capsule and conjunctiva (33)

The adult rabbit eye measures approximately 18 mm (horizontal) × 17 mm (vertical) × 16 mm (anterior-posterior), closely resembling the human eye. Rabbits possess large, prominent globes and laterally positioned orbits, with their orbital axis aligning with the visual axis, similar to human ocular anatomy (32,33).

Rabbits possess nine extraocular muscles that control eye movement, including the orbicularis muscle, levator palpebrae superioris, depressor palpebrae inferioris, retractor bulbi, four rectus muscles and two oblique muscles. Among these, superior rectus muscle is essential for vertical eye movement. It originates from the inner orbital wall, positioned above and behind the optic foramen, and extends diagonally forward. The insertion site is located at the mid-dorsal sclera near the limbus, with a broad and thick tendon measuring 6–8 mm in width. The insertion is oblique, with the anterior border situated approximately 2 mm from the limbus. Additionally, the superior oblique muscle's tendon passes beneath the superior rectus muscle (32,33). This systematic anatomical structure supports precise surgical interventions, making rabbits an ideal model for studying strabismus surgery techniques and postoperative healing responses.

7. CONCLUTION

Strabismus surgery aims to correct ocular misalignment, but postoperative inflammation can lead to fibrosis, negatively affecting surgical success. IL-1 and VEGF play crucial roles in the wound healing process, but their excessive expression can result in excessive scarring and inflammation. While traditional methods such as steroids, amniotic membrane transplantation, and Mitomycin-C have been used to control fibrosis, they have clinical limitations. PRF has emerged as a promising alternative, offering anti-inflammatory, pro-regenerative, and mechanical protective properties to enhance wound healing and reduce fibrosis risk. Further experimental and clinical studies are necessary to validate its efficacy in strabismus surgery.

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