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Review

The Appliance of A-PRF and CGF in the Treatment of Impacted Mandibular Third Molar Extraction Sockets—Narrative Review

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Abstract: Tooth extractions, especially of impacted lower third molars, are among the most common procedures performed in dental practices. The continuity of the patient's oral mucosa, which is interrupted during them, can manifest itself in general discomfort, pain, swelling, and even trismus. In the age of cosmetic dentistry, when lost teeth are restored through implant, prosthetic, and orthodontic treatment, each tooth extraction actually reduces the amount of available alveolar bone. This has prompted researchers to develop extraction sockets treatment procedures that reduce the negative consequences of surgical intervention while also enhancing the rate of alveolar bone and soft tissue regeneration using minimally invasive approaches. This is expected to enable or significantly facilitate further stages of treatment. The aim of this paper is to review the literature on the use of autologous blood preparations, which are considered to aid regenerative processes when applied to extraction sockets.

Keywords: advanced platelet-rich plasma; concentrated growth factors; post-extraction sockets; A-PRF; CGF; regeneration; autologous blood products; dentistry

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1. Introduction

During the extraction, the periodontal ligaments are torn, and the tooth is luxated and removed, resulting in the tissues disruption. In the case of an impacted tooth, the surgical intervention is usually more invasive than a simple tooth extraction—procedures such as cutting, detaching the flap and often removing the bone around the tooth are required. The level of difficulty, and therefore the length of the extraction, has an impact on healing. It is influenced by factors such as the position of the tooth in the bone or its size and shape. A statistically significant correlation between the gonial angle and the position of lower third molars was shown by Barone S et al. in 2021, who confirmed that a higher incidence of impacted lower third molars was associated with a lower value of the gonial angle, which may facilitate the decision to extract germs of the lower wisdom teeth at an early stage of development [1]. The difficulty of extraction of impacted lower wisdom teeth in relation to various factors was examined by Park et al. They confirmed that older age, male sex, depth of impaction, position of the retained tooth, large or/and bulbous roots, ankylosis and blurred root image on panoramic radiographs are factors that increase the difficulty of extraction [2]. Unfortunately, tooth extractions, like all surgical procedures, are associated with postoperative complications. Cho et al., in their review article, showed that the use of painkillers such as paracetamol and ibuprofen reduce pain, and trismus and swelling could be reduced by using corticosteroids, while antibiotics administered immediately before extraction can reduce the risk of infection and alveolar osteitis (but postoperative use does

not seem to make sense), and gels and mouthwash with chlorhexidine reduce the incidence of alveolar osteitis [3].

Previously, the only way to heal the alveoli of extracted teeth was a natural dressing made of a blood clot. The recovery period was associated with swelling, discomfort and a dry socket, and there was a risk of hemorrhage and nerve damage during the procedure [4]. This prompted critics to seek alternative treatments such as dressings that modulate inflammatory responses and accelerate healing [5].

Human plasma derivatives, also known as tissue fibrin adhesives, were the first of their kind to be introduced in Europe in the late 1970s. The general mechanism of action relies on the formation of a fibrin clot, which is the end product of the blood clotting process. They are used to seal wound edges and provide a homeostatic surface, as well as a bonding substance for biomaterial particles in bone augmentation surgery. The commercial preparation was made from cryoprecipitated donor plasma and contained two lyophilized components: fibrinogen/fibronectin/factor–XIII dissolved in an antifibrinolytic solution (e.g., aprotinin), and thrombin concentrate dissolved in a dilute calcium chloride solution. Activated factor XIII catalyzes crosslinking between fibrin molecules in the presence of calcium cations, resulting in a water-insoluble fibrin matrix that serves as a clot scaffold.

However, the use of such treatment puts patients at risk of infection with pathogens such as hepatitis (HBV, HCV). This led researchers to seek procedures based on the use of autologous preparations derived from patients' serum. Combining whole plasma from patients with bovine thrombin produced fibrin glues. Unfortunately, their manufacture was characterized by very low physical reproducibility (in terms of viscosity and elasticity, for example) [6].

2. Materials and Methods

There are few studies and review articles in the scientific literature on modern techniques for the treatment of post-extraction sockets. Nonetheless, knowledge of this topic is essential for refining practice and advancing this field of dental surgery. With that in mind, the aim of this review is to present the current state of knowledge on the management of post-extraction sockets in the form of a narrative summary. Current treatment practices and research in the field of regenerative dentistry are discussed.

Papers on PRF and CGF were searched in the Pubmed, Medline, and Scopus databases. Following the extraction of third molars, particular emphasis was placed on facts about their appliance. The articles were compiled in April 2021 and included most of the latest news from the previous 20 years.

D.S. and M.S. briefly assessed the abstracts of the resulting publications for inclusion in this review. If the article was relevant and presented unique findings, databases were also searched for the keywords included, allowing us to expand our review to include relevant but rarely published materials. This is due to the novelty of the recommended approach to the treatment of third molar sockets. The final list of items considered was selected after much deliberation. It resulted in a total of 58 articles.

This review is divided into two parts: A-PRF and CGF. The topic of their mechanisms of action, applications, and a discussion of their claimed results are presented.

3. Results

In 1998, Marx et al. [7]. developed platelet-rich plasma (PRP) as a breakthrough in the use of platelet preparations derived from blood with higher angiogenic or osteogenic potential than the clot found in the socket after extraction. He obtained it by centrifuging 400 to 450 mL of a patient's whole blood at 5600 RPM (revolutions per minute) with the addition of citrate phosphate dextrose (an anticoagulant). The previous procedure resulted in three layers of preparation, starting from the lowest: red blood cells, PRP (platelet-rich plasma, also called "buffy coat"), and PPP (platelet-poor plasma). After the PPP layer was collected, the remaining blood was centrifuged at 2400 RPM to properly separate the PRP from the red blood cells. To start the coagulation process, PRP must be mixed with 10%

calcium chloride and bovine thrombin. Individual 10 mL syringes were used for mixing, with 6 mL of PRP, 1 mL of calcium chloride + thrombin and 1 mL of air collected as a mixing element. A proper PRP preparation with a gel consistency is formed after mixing in the syringe for 6 to 10 s.

After extensive research, Jo et al. [8]. presented a modification to the PRP technique in 2013. According to the original concept, citrate phosphate dextrose is used as an anticoagulant, and calcium gluconate + bovine thrombin is used as a coagulant. After a 5-min centrifugation of 9 mL of the patient's blood at 900 RPM, three fractions are visible: red blood cells, buffy coat, and platelets with white blood cells. The top two fractions were collected and centrifuged again (1500 RPM, 15 min), after which this top layer of PPP is collected, leaving only 2 mL of PRP in the tube. When PRP is treated with 0.2 mL of 10% calcium gluconate, it forms a gel with 4.2 times the platelet concentration of peripheral blood. Both centrifuges use plastic tubes.

Anitua et al. [9,10] proposed another concept of an autologous blood derivative from the PRP family that accelerates the healing process, calling their product PRGF (Plasma Rich In Growth Factors). After a single 8-min centrifugation at 1850 RPM using 5 mL plastic tubes containing the anticoagulant sodium citrate, a fibrin clot was produced from the patient's blood. The centrifugation results in the three visible layers, starting from the bottom: a layer of red blood cells, a middle transitional layer called a buffy coat, and an upper layer of cell-free plasma, which includes two empirically defined layers: upper plasma with low-growth factors (PPGF), and lower plasma rich in growth factors (PRGF), which is collected from all centrifuged tubes and transferred to a pooled one, to which calcium chloride is added to induce clotting, and after 15 to 20 min PRGF gel is obtained. It is noteworthy that the authors do not use bovine thrombin (except from the previously mentioned modifications) for clot formation, and one of its salient features is the absence of both erythrocytes and leukocytes. According to the authors' findings, the absence of polynuclear neutrophils within the damaged tissues, which are the body's first line of defense against pathogens, may have a beneficial effect on healing. This is because they produce matrix metalloproteinases MMP-8 and MMP-9, which can impede tissue repair, as well as free radicals (active forms of oxygen and nitrogen), which can damage cells in surrounding tissues in addition to bacteria.

The aforementioned family of PRP preparations is the first generation of platelet concentrates. Their main disadvantage is the need for coagulants and anticoagulants in the manufacturing process, which usually involves repeated centrifugation. In addition, the use of bovine thrombin can cause coagulopathies by stimulating the formation of antibodies against blood clotting components V and XI, as well as thrombin [11]. Therefore, researchers conducted additional studies to develop an autologous biomaterial that would not require the use of chemicals in the manufacturing process.

Choukroun's breakthrough was classified as the second generation of platelet concentrates, called L-PRF (Platelet-Rich Fibrin) concentrates, which he produced and presented in 2001 [12,13]. Unlike previous concepts, the protocol for obtaining PRF does not require any additives; only the patient's blood, a glass tube and a centrifuge are needed to obtain a clot, and the process is physiological, using the autogenous thrombin present in the collected blood [14]. The original procedure used 10 mL plastic tubes with a glass cover on the inside, and the collected blood was centrifuged for 10 min at 3000 RPM. When the blood contacts the inside surface of the glass tube, the clotting cascade is activated; fibrinogen accumulated during the centrifugation process in the upper part of the tube, as a result of the action of thrombin, is transformed into a fibrin clot occupying the central part of the tube, inside which platelets, white blood cells and growth factors are trapped; the upper layer is platelet-poor plasma and the lower layer is red blood cells [5].

PRFM, T-PRF, liquid i-PRF, Vivostat PRF and A-PRF, A-PRF+, CGF are among the second generation formulations and are described below:

- PRFM (Platelet-Rich Fibrin Matrix), is a method of producing platelet-rich fibrin without the use of additional bovine thrombin. In the first stage (low speed centrifugation),

red blood cells are separated from platelets and plasma proteins in a 9 mL tube containing sodium citrate. In the second centrifugation, fibrinogen is converted to cross-linked fibrin containing platelets in the presence of $CaCl_2$ [15].

- T-PRF (Titanium-prepared Platelet-Rich Fibrin): the patient's blood is collected into 10 mL titanium tubes and centrifuged without anticoagulants at 3500 RPM for 15 min [16].
- i-PRF (injectable Platelet-Rich Fibrin): from 10 mL of a patient's blood drawn into a plastic tube, centrifugation at 700 RPM for 3 min produces a liquid form of fibrin without the use of anticoagulants [17].
- A Vivostat PRF-120 mL of whole blood is collected and processed in the Vivostat Processor Unit using the "platelet" program. After 26 min. of centrifugation, 6 mL of preparation is obtained (without the use of thrombin) [18].
- L-PRF (Leukocyte and Platelet-Rich Fibrin) was invented by Joseph Choukroun in 2001, and the clot was obtained by centrifuging the blood at 3000 RPM in 10 mL plastic tubes for 10 min [13].
- A-PRF (Advanced Platelet-Rich Fibrin), A-PRF+ (Advanced Platelet-Rich Fibrin +) and CGF (concentrated growth factors) will be described below.

In 2014, Ghanaati and Choukroun et al. [19] presented a modification of the original system for producing platelet-rich fibrin, called the new A-PRF (advanced platelet-rich fibrin) procedure. Blood was collected from patients and immediately centrifuged in sterile 10 mL vacuum glass tubes for 14 min at 1500 RPM. When the centrifugation speed was reduced while the process was prolonged, the researchers discovered an increase in the presence of neutrophils captured between fibrin fibers. Products of neutrophil degranulation influence the conversion and differentiation of monocytes into macrophages. In turn, growth factors secreted from macrophage granules can influence bone and soft tissue regeneration.

In collaboration with Choukroun, Fujioka-Kobayashi et al. [20] proposed a variation of the aforementioned procedure in 2017, naming the produced product A-PRF+. Patient blood was collected into a 10 mL glass vacuum tube and centrifuged at 1300 RPM for 8 min to obtain A-PRF+. In vitro, the researchers found that the A-PRF and A-PRF+ regimens released more growth factors (e.g., PDGF-Platelet-derived growth factor, TGF-1-Transforming growth factor beta 1, EGF-Epidermal growth factor, IGF-1-Insulin-like growth factor 1) from fibrin than the original L-PRF regimen. Furthermore, A-PRF+, a platelet rich fibrin, released more growth factors than A-PRF fibrin.

In 2006, another researcher, Sacco, named his unique method of generating fibrin clots by centrifugation with varying centrifugation settings "CGF". Unfortunately, until the publication of Rodella et al. in 2011 [21], there were no studies confirming the biological efficacy and histological aspect of this novel technique. Vacuum blood collection tubes are made out of PET plastic, and the centrifugation strategy for CGF is as follows:

- 30 s of acceleration,
- 2 min of centrifugation at 2700 RPM,
- 4 min at 2400 RPM,
- 4 min at 2700 RPM,
- 3 min at 3000 RPM,
- 36 s deacceleration till it fully stops

Platelets and growth factors TGF-1, PDGF-BB, and VEGF were found in equal amounts in CGF and A-PRF+ fibrin clots, with a slight predominance of the aforementioned numbers in A-PRF+ [22].

4. APRF

4.1. General Mechanism

A-PRF, a biomaterial used in current tissue engineering procedures, has been developed to accelerate healing processes at the application site. During the centrifugation process, no additives are used to activate coagulation, resulting in a tube with three distinct layers, starting from the bottom: a layer of red blood cells, a PRF fibrin clot with a layer

tangential to the red blood cells called the buffy coat (the highest concentration of white blood cells and platelets), and a top layer of cell-free plasma [5].

The fibrin clot formed during the production of traditional PRF or its modification, A-PRF, is a three-dimensional scaffold that replaces the extracellular matrix in cell regeneration and newly formed vessels. Platelets trapped between fibrin fibers, B and T lymphocytes, monocytes, stem cells and neutrophils, as well as secreted growth factors such as TGF-1, PDGF, and VEGF, play a role in healing. As previously reported, neutrophils influence monocyte differentiation and conversion to macrophages by releasing the contents of their granules, which contain growth factors that can positively influence soft tissue and bone regeneration [19,23].

As a result, A-PRF, like other second generation preparations, is highly regarded by clinicians worldwide and is used in the treatment of musculoskeletal trauma [24], drug-induced bone necrosis in the form of a membrane applied to exposed jawbone to reduce bacterial contamination and risk of reinfection [25], in periodontal reconstructive procedures [26], in implants, and maxillary sinus floor lifts [27], and as a local hemostatic agent, specifically recommended after multiple extractions in patients taking antiplatelet drugs [28].

The extraction of molars is one of the most common surgical procedures performed in dental clinics worldwide. As with any medical procedure, it carries the risk of intra- or postoperative complications. The most common of these are dry socket, post-operative socket infection and damage to the inferior alveolar nerve, which may be reversible or irreversible. In addition, postoperative discomfort, swelling of the surrounding tissues, trismus and, in rare cases, hemorrhage, are associated with the extraction process [29]. As a result, clinicians are looking for better, more effective techniques for dealing with extraction sockets that are also cheap and simple to use to reduce the negative consequences of the procedure. One of these has been fibrin clots taken from the patient's own blood before surgery, such as L-PRF, A-PRF, and CGF.

4.2. Regeneration of Soft Tissues and Bones

When extracting an impacted tooth, it is often necessary to remove a significant amount of surrounding bone. Improper management of the post-extraction socket can lead to a significant loss of alveolar height after extraction, resulting in recession on the second molar in the distal/buccal region of the tooth. Therefore, in order to preserve the height of the ridge, the alveolus needs to be adequately protected, which is achieved with bone substitute materials, fibrin preparations derived from the patient's blood, or a combination of both.

Three months after extraction, Talal M Zahid et al. [30] found no significant differences between the test side (with A-PRF augmentation) and the control side (without A-PRF augmentation). CAL (clinical attachment level) and GR (gingival recession) measurements yielded similar results. In conclusion, the authors of the aforementioned study did not discover any additional benefit of A-PRF over natural healing in terms of pocket shallowing, reconstruction of the connective tissue attachment and minimization of the recessions formed; a slight advantage in healing with A-PRF could be seen by analyzing data from different measurement points around the tooth at different times after extraction. Unfortunately, this benefit did not include improved bone healing.

Gupta et al. [31] discovered a significant difference between alveolar healing using postoperative A-PRF and bone healing as gauged by measures of bone density using extraoral RVG imaging (performed on controls after 1, 3, and 6 months). The researchers found comparable improvements in soft tissue healing after A-PRF.

The findings of the above in vivo studies do not seem to confirm the results of in vitro studies comparing L-PRF (low-speed centrifugation) and A-PRF+ (high-speed centrifugation) and L-PRF, A-PRF, and A-PRF+ in terms of content, including growth factors, which have been shown to have higher concentrations in A-PRF+ compared to L-PRF [20,32].

In 2019, Masahiro To et al. [33] confirmed the osteogenic effect of A-PRF+ in sockets after extraction. In a study on Beagle dogs with removed premolars, the researchers observed significantly faster bone recovery in A-PRF-dressed sockets compared to control sockets (without A-PRF), including post mortem histology and immunofluorescence of healing tissues after 14 and 30 days.

Animal studies were also carried out in 2012 by Dominiak et al. in the group of 36 New Zealand White (NZW) rabbits, in which a bone defect 5 mm in diameter and 10 mm deep was made in the femur under general anesthesia. Subsequently, in 12 rabbits (group I), the defect was filled with bone substitute material (xenograft Bio-Oss Collagen®) and covered with a collagen membrane (Bio-Gide Perio®); in 12 rabbits from group 2, a layer of platelet rich plasma (PRP) was placed to the defect after application of the biomaterial. Group 3 (also 12 rabbits) was the control group that was treated without the regenerative techniques. After the animals were sacrificed, a histological examination of the dissection preparations was performed, which showed the most intense osteogenesis 1 month after treatment in group 2 (with PRP application). At subsequent stages of healing (after 3, 6 and 12 months), more intense osteogenesis was shown in group 1 (xenogenic material and resorbable collagen membrane). The worst results were obtained in the control group, while the use of two regenerative methods influenced the speed, quality and overall healing of intraosseous defects [34].

4.3. Analgesic and Antiedemic Effect

Tooth extraction, as with any surgical procedure, causes tissue disruption and a subsequent inflammatory response by the body during the healing phase.

Under normal conditions, the extraction socket fills with blood, which forms a clot within a few to several minutes. The clot is quickly replaced by richly vascularized granulation tissue (day 3), which is replaced by connective tissue (day 21) which fills 2/3 of the socket and gives rise to bone formation (osteoid). After 6 weeks, the socket is filled with immature bone.

In a 2018 study by Talal M Zahid and Mohammed Nadershah [30], which was the first randomized study of alveolar healing using A-PRF, augmentation of the post-extraction socket with A-PRF clot significantly reduced postoperative pain and swelling within 7 days of surgery according to the authors. Gupta et al. [31] also observed a reduction in post-extraction discomfort when A-PRF was used (compared to a control group without augmentation). On day 1, there was no difference in post-extraction swelling or trismus between the groups, but on day 3 in the A-PRF group, both pain and the potential for a broad opening of the mouth were significantly reduced, and patients showed significantly greater potential for a broad opening of the mouth.

Caymaz et al. [35] conducted a study in 2018 comparing the healing process using a primary PRF (L-PRF) and A-PRF regimen. Patients with bilaterally retained third molars underwent surgical extraction (twice, with at least 21 days between procedures), with L-PRF inserted into one of the extraction sockets (group 2) and A-PRF inserted into the other (group 1). Discomfort on days 1, 2, and 3 days after extraction was significantly greater in group 2 (L-PRF) than in group 1 (A-PRF). On day 7, there was no discernible difference in discomfort between group 1 and group 2. The aforementioned relationship can also be seen in the amount of analgesics used; patients with the L-PRF dressing took significantly more pain medication on days 2 and 3 after surgery. There were no differences in the amount of painkillers consumed by the groups on days 1 and 7. There were no differences in swelling and trismus between the groups on the first, second, third and seventh postoperative days.

The above study shows that the use of A-PRF instead of L-PRF after extraction of the lower third molar has a significant effect on reducing postoperative pain, while no association favoring one of the above techniques in reducing swelling and trismus was found.

Torul et al. [36] obtained additional findings by evaluating the effects of A-PRF and CGF on the incidence of swelling, trismus, and postoperative discomfort after lower third molar extraction. The researchers found that the CGF group had greater trismus and horizontal postoperative swelling, as well as greater vertical swelling, than the A-PRF group in a study of 75 patients (25 in each group). Although not statistically significant, the above results can be attributed to the higher concentration of white blood cells and growth factors in the A-PRF and CGF fibrin clots compared to classic PRF, which may result in an increased inflammatory response in the early postoperative period. In addition, the researchers found no reduction in pain symptoms with the administration of A-PRF and CGF compared to the control group.

5. CGF

Concentrated Growth Factors (CGF) are derivatives of PRF and were developed by Sacco in 2006 [14,37]. CGF is a fibrin-rich organic matrix obtained by centrifuging of the patient's venous blood, and is considered a third generation platelet enrichment that does not require any additional reagents to induce platelet activation as well as fibrin polymerization [38]. It contains growth factors, platelets, fibronectin, immune cells and CD34+ stem cells that play a vital role in regeneration processes, immunomodulatory responses, as well as having the ability to induce angiogenesis, chemotaxis and tissue remodeling, while being a matrix for cell migration [39–42].

Due to the use of a different centrifugation speed, CGF contains a denser matrix that has more growth factors than both PRP and PRF, making it also more efficient at releasing them into the surrounding space, which can be especially useful in dentistry [43]. Among the numerous growth factors identified within CGF are platelet-derived growth factor (PDGF), transforming growth factor β-1 and 2 (TGF-β1 and TGF-β2), fibroblast growth factor (FGF), bone morphogenetic protein 2 (BMP-2), vascular endothelial growth factor (VEGF), brain derived growth factor (BDGF), and insulin-like growth factor (IGF). They stimulate cell proliferation, matrix remodeling, and promote angiogenesis [5,12,21,44]. It is noteworthy that CGF is associated with a sustained release of growth factors over 7–10 days, which can be used in aesthetic facial rejuvenation procedures, such as the treatment of wrinkles [45]. The ability to promote angiogenesis has applications in the regeneration of immature necrotic teeth in endodontics as an effective alternative to apexification [46]. It has been confirmed that CGF fibrous membrane is able to promote periodontal tissue regeneration involving hUCMSCs, which is achieved by upregulating the expression of TAZ and osteogenic differentiation-related genes [47]. The use of CGF together with a coronally advanced flap (CAF) leads to an increase in the amount of keratinized gingiva 6 months after maxillary recession coverage compared to a simple CAF procedure [48].

On the other hand, according to Akcan and Ünsal, CTG is superior to CGF in covering recessions, with CGF having a more positive effect on postoperative pain [49]. The biological properties of CGF, together with its viscosity and mechanical properties, allow it to improve the handling of other graft materials, promote wound healing, bone growth and maturation, as well as to stabilize bone grafts when used simultaneously [50]. Because of these properties, CGF has been widely used in jawbone regeneration procedures. Numerous studies have shown positive results with CGF as a biomaterial used in sinus lift procedures, which induces rapid and reliable bone formation [51–53].

CGF also induces osteoblastic differentiation promoting the early osseointegration of dental implants, leading to an increase in bone density around them [54]. There are some limitations to the use of CGF. First of all, platelet counts are affected by blood pH; changes in blood pH can interfere with cell proliferation. Furthermore, the time of CGF preparation and the volume of blood can affect the results [43,45] (See Table 1).

Table 1. Summary of the purpose and results of individual authors' research on A-PRF/CGF; + positive outcome, − negative outcome, +/− non-conclusive outcome.

	Material	Aim of the Research	Results	Effect	Authors/Year	Ref.
1	A-PRF	histochemical study of the clot and its composition	A-PRF might influence bone and soft tissue regeneration, especially through the presence of monocytes/macrophages and their growth factors. The relevance and feasibility of this tissue-engineering concept have to be proven through in vivo studies.	+ (in vitro)	Ghanaati et al., 2014	[19]
2	A-PRF	To evaluate the potential of advanced platelet-rich fibrin (A-PRF) as a regenerative biomaterial for bone regeneration and postoperative sequlae after impacted third molar extractions.	Placement of A-PRF clot in the extraction socket could lessen postoperative pain and increase patient comfort after third molar extraction	+ (in vivo)	Zahid et al., 2019	[30]
3	A-PRF	To evaluate the efficacy and healing potential of modified formulation of PRF, commonly known as advanced PRF (A-PRF) in impacted mandibular third molar extraction sockets.	A-PRF has enhanced the healing potential of soft tissue as well as bone in extraction socket. Using A-PRF as well relief of immediate postoperative symptoms like pain, swelling and trismus.	+ (in vivo)	Gupta et al., 2020	[31]
4	A-PRF	To evaluate the potential of advanced platelet-rich fibrin (A-PRF) on bone formation after extraction of beagle dogs premolars.	A-PRF application may result in enhanced new bone formation and may aid in accelerating bone formation.	+ (in vivo)	Masahiro et al., 2019	[33]
5	A-PRF	To investigate and compare the postoperative effects of leukocyte- and platelet-rich fibrin (L-PRF) and advanced platelet-rich fibrin (A-PRF) in terms of pain, swelling, and trismus after mandibular third molar surgery.	Using of A-PRF after mandibular third molar extraction significantly reduces postoperative pain compared to the L-PRF group. However, there was no significant difference between groups in terms of swelling and trismus.	+/− (in vivo)	Caymaz et al., 2018	[35]
6	A-PRF, CGF	To investigate the effects of concentrated growth factors (CGF) and advanced platelet-rich fibrin (A-PRF) on edema, pain, and trismus after mandibular third molar surgery.	A-PRF and CGF seem to have no positive effects on pain, edema, and trismus after third molar surgery.	− (in vivo)	Torul et al., 2020	[36]
7	CGF	To investigate the biological effects of concentrated growth factor on human dental pulp stem cells.	Concentrated growth factor (CGF) promoted cell proliferation, migration, and the dental pulp stem cell–mediated dentinogenesis and angiogenesis process.	+ (in vitro)	Jin et al., 2018	[42]
8	A-PRF, CGF	to evaluate the effect of platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and concentrated growth factor (CGF) on bone healing	The addition of PRP, PRF, and CGF had significantly increased bone formation at the 6th week. The effect of PRP, PRF, and CGF was similar.	+ (in vivo)	Kim et al., 2014	[50]

6. Study Limitations

The paper itself is narrative in nature. The efficacy of narrative reviews is irreplaceable in tracking the development of a scientific principle or a clinical concept. This ability to conduct a wider exploration could be lost in the restrictive framework of a systematic review.

Author bias may be present in this type of review topic. When reading and evaluating a narrative review, keep in mind that the author's bias may or may not be present. Furthermore, due to the scarcity of literature on the use of platelet concentrates in the treatment of post-extraction teeth, especially lower third molars, it is impossible to perform a meaningful systematic review.

7. Conclusions and Perspectives

Autologous platelet concentrates were thought to revolutionize both bones and soft tissue regeneration, thus indirectly affecting the quality of life of patients throughout the postoperative recovery period. Therefore, they have found their application in many medical fields, including dentistry [55]. Many authors of clinical studies involving the aforementioned tissue-engineering technologies confirm their efficacy in reducing post-extraction pain and emphasize the anti-inflammatory component of their action, which manifests itself, among other things, in the reduction of trismus and postoperative swelling.

A number of studies have been conducted to determine the efficacy of A-PRF and CGF in the treatment of edema, pain, and trismus. The therapeutic effect is clearly evident in some publications, but appears to have no significant impact on the recovery process in others. Instead, some studies highlight the lack of benefit associated with the use of the aforementioned approaches, casting doubt on their use.

In line with the above, the vast majority of publications treating the topic of blood concentrates either state their beneficial effect on the healing of post-extraction wounds or extraction sockets, or indicate that there is no perceived benefit from their use. However, it should be remembered that autologous platelet concentrates are not the panacea of bone healing. PRP, PRGF, A-PRF and CGF, depending on their generation, show differences in the quantitative composition of platelets, leukocytes, growth factors (including TGF-β1, PDGF-BB, VEGF) and pro-inflammatory cytokines (including IL-1β, IL-6) [22]. The amount of the latter increases in the blood of people who have an ongoing inflammatory process or who suffer from systemic diseases such as diabetes. This may result in a prolongation of the inflammatory phase of post-extraction wound healing by increasing the production of local pro-inflammatory cytokines [56]. They result in an imbalance between polarized pro-inflammatory M1 macrophages and inflammation-silencing M2 macrophages in favor of the former. Activated M1 macrophages continuously produce pro-inflammatory cytokines, causing bone resorption through increased osteoclast activity and the inhibition of bone formation by osteoblasts, resulting in impaired and prolonged soft and hard tissue healing [57,58].

Unfortunately, there is a lack of studies in the current literature comparing the amount of pro-inflammatory cytokines in a patient's peripheral blood with their levels after centrifugation in blood concentrates. Undoubtedly, more studies are needed to clarify the correlation between pro-inflammatory cytokine levels and alveolar healing after extraction and to assess the risk of treatment with blood concentrates in patients with systemic diseases causing chronic inflammation.

The tissue-engineering technologies discussed in the article above are relatively new and are constantly being refined by a large number of researchers, necessitating additional clinical trials on large groups of patients to collect more data.

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