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Autologous Blood Products and their Role within Dentistry

Abstract: Use of autologous blood products, such as platelet rich plasma (PRP) and platelet rich fibrin (PRF) is increasing within the field of dentistry. Such products aim to promote bone regeneration which is valuable in a range of procedures, including implant placement, post tooth extraction, and periodontal surgery. Dental practitioners should be aware of what these new materials are, and the beneficial role that they may play in modern dentistry.

CPD/Clinical Relevance: This article aims to inform the reader regarding the range of available autologous blood products, their uses in dentistry, how they are derived from whole blood, as well as cost and time implications.

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Blood comprises various components, which can be classified into 'formed' elements (red blood cells, white blood cells and platelets), and plasma elements (such as fibrinogen, water and albumin).[1] Blood not only transports oxygen from the lungs to the tissues, it also has a vital role in the transportation and storage of various nutrients and toxins, aids homeostasis and regenerative processes.[2,3] Techniques exist in which blood is separated out into its different parts, enabling components that aid regeneration to be harnessed and used to aid dental treatments.

These products are becoming more widely used within medical fields whereby patients have local injections of blood products. This is being used in the treatment of osteoarthritis, and some bodies recommend its use for facial cosmetics, however, currently there is an ongoing debate about its effectiveness in this role.

This article aims to inform the reader regarding the range of available autologous blood products, their uses in dentistry and oral surgery, how they are derived from whole blood, as well as the cost and time implications of their use.[1,3]

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What autologous blood products are available?

Autologous blood products can be classified based on the methods used in their production, namely if they are derived with or without the use of an anti-coagulant, or whether they undergo one centrifugation cycle or two. Four main blood products will be described within this article:

1. Platelet rich plasma (PRP);
2. Platelet poor plasma (PPP);
3. Platelet gel;
4. Platelet rich fibrin (PRF).

Platelet rich plasma is produced by adding sodium citrate (an anticoagulant) to 10 ml of whole blood (although this volume can vary depending on the amount of PRF or PRP required). The blood is generally harvested from a vein. The solution is then centrifuged (spun at high speed), and the plasma extracted (Figure 1). This plasma then undergoes further centrifugation to separate it into platelet rich and platelet poor plasma (Figure 2). Platelet rich plasma can be used alone, or may be combined with calcium chloride and thrombin, which initiate the coagulation cascade, forming platelet gel.[4,5] Platelet poor plasma (PPP) is rich in other substances, such as fibrinogen, and may therefore be used to form fibrin-based sealants.[1]

Platelet rich fibrin is produced by taking whole blood and centrifuging it without adding any anticoagulant. This results in separation of the blood constituents, leaving an area of a fibrin clot to form (Figure 3). This clot can then be manipulated into a membrane-like structure, as outlined later in this article. Due to the lack of anticoagulant, separation of the fibrin clot must occur promptly to prevent a diffuse clot forming instead of a discrete layer, and thus blood must be processed shortly after collection. During this process, free-floating platelets become incorporated into the resultant fibrin clot during the polymerization process of the fibrin mesh. PRF therefore has the added benefit of being able to release platelet cytokines

a

b

Figure 1. (a, b) Venepuncture (blood harvesting) and a centrifuge. Blood is typically withdrawn from the arm at the anterior cubital fossa (the image above shows a butterfly device used to harvest the blood, note the tubing coming from the back of the device). The blood samples are loaded into the central portion (black in colour), which spins at a speed pre-determined by the selection menu. A top cover is present for safety reasons.

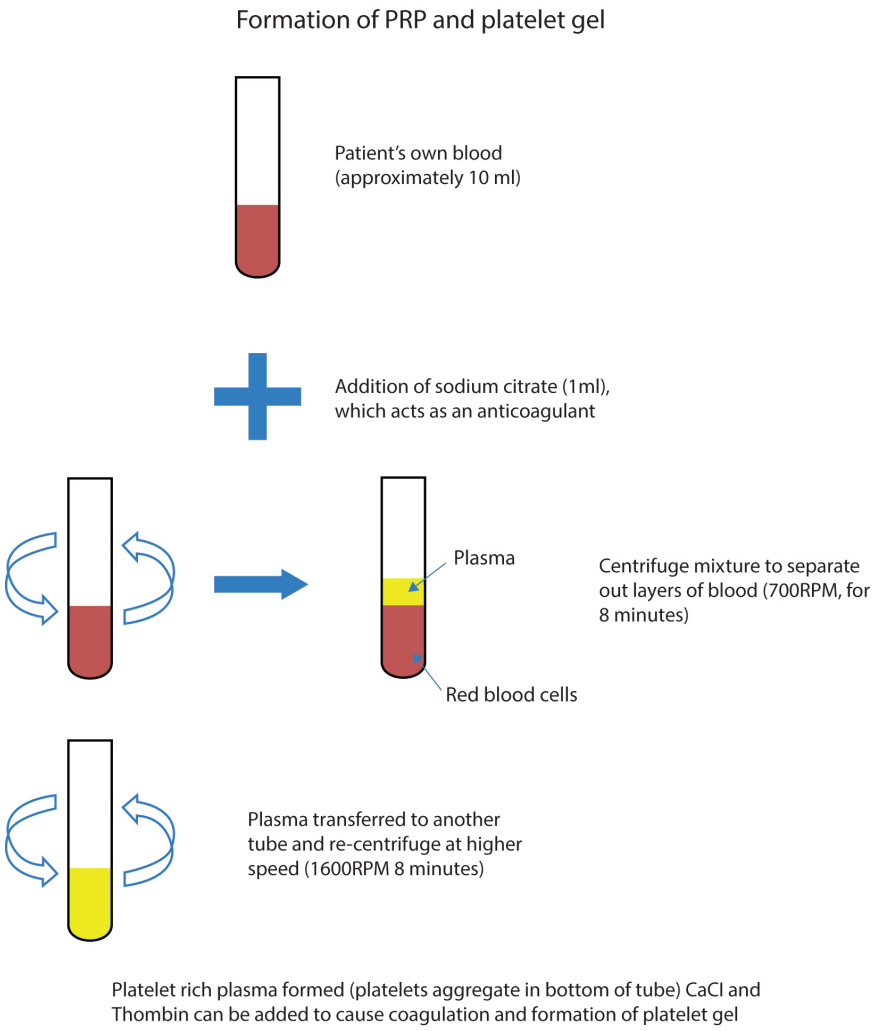

Figure 2. A diagrammatic representation of the formation of PRP and of platelet gel. Note that this process is more complex than creating PRF, as it requires the use of anticoagulants to halt the clotting process as the blood is separated.

gradually during the fibrin remodelling process, giving PRF its bioactive properties.[6]

Fibrin-based sealants can be fabricated by isolating fibrinogen either from platelet poor plasma or whole fresh blood, and is activated prior to clinical use by mixing the fibrinogen with thrombin and an anti-fibrinolytic, which creates a sticky fibrin mesh. Note that this needs to be done shortly before application of the fibrin glue.[7]

What benefits do autologous blood products have?

As autologous blood products are created from the patient's own blood, such products have the advantage that there are no concerns regarding spread of infection or immunologically-mediated reactions, as must be considered with other bone grafting products.[3]

Platelets contain alpha granules which contain various growth and repair cytokines such as platelet derived growth factor (PDGF). These cytokines help mediate various aspects of wound healing, including proliferation, chemotaxis, differentiation and morphogenesis of the locally influenced cells as part of the regenerative process.[8] In health, these cell mediators would normally be released in response to an injury, which results in the disruption in the normal blood vessel architecture, and are normally released following platelet activation and aggregation.[9,10,11] Autologous blood products use these naturally occurring cell mediators in a concentrated form and enable them to be used locally to promote a healing environment.[2,8] In animal studies, the release of these cytokines has resulted in angiogenesis, bone and cementum formation

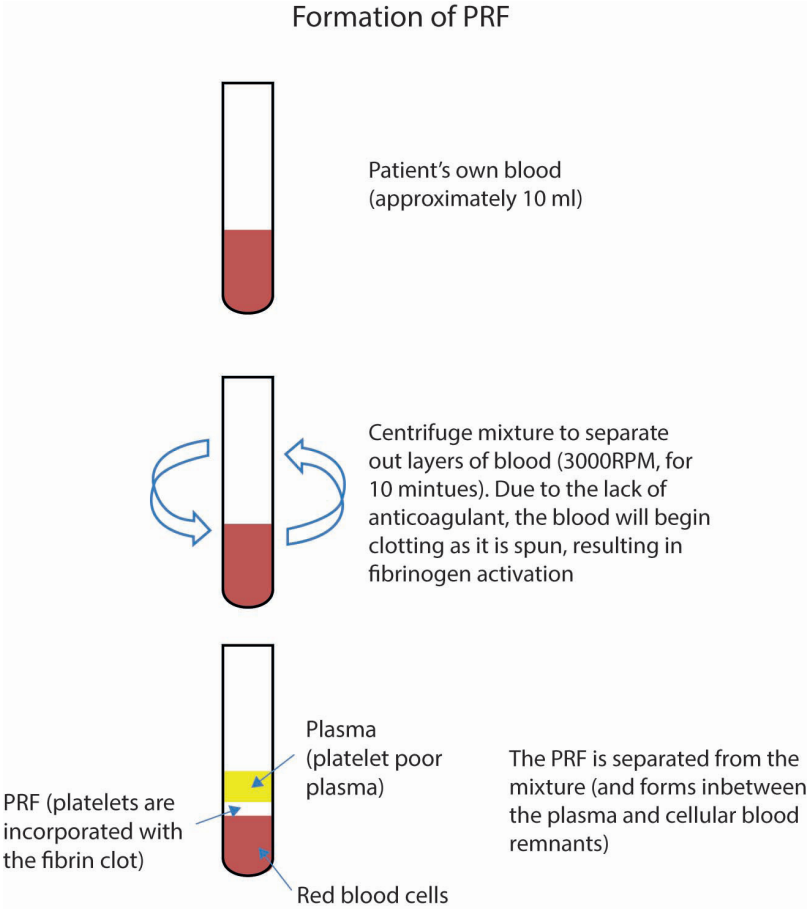

Figure 3. A diagrammatic representation of the formation of PRF. This process is much simpler, as the process of fibrin clotting continues uninterrupted, entrapping platelets within its mesh as it does so. Because of this, no anticoagulant is needed.

and periodontal healing.

What clinical applications do blood products have?

Autologous blood products aim to accelerate the healing process within any surgical-based procedure, and evidently this has many benefits to the modern dental practitioner. Outlined below are various examples where this benefit may be utilized.

Periodontal defect regeneration

Periodontal disease results from inflammation, generally triggered by oral pathogens, and results in destruction of the supporting structures of the teeth. Management and treatment aims to reduce bacterial load and disrupt biofilm accumulation, so reducing the inflammatory response and subsequent tissue destruction. Infra-bony defects and furcation involvements, however, can act as local risk factors for continued plaque build-up, despite best patient efforts of plaque control.[3] PRF and PRP have both been found in *in vitro* studies to stimulate the differentiation of osteoblast cells, and this is what a clinician may wish to exploit when using such material in periodontal defects.[12] Note that PRP/PRF, in this instance, should augment current periodontal therapy, so good oral hygiene, removal of calculus and granulation tissue, and other periodontal factors must also be appropriately managed. PRF has been used successfully by Panda *et al* and Thorat *et al* to produce infill of intra-bony defects with good results.[13,14]

PRF and PRP have also been used in conjunction with particulate bone grafts to promote bony healing, and have been shown to yield results comparable to the use of enamel matrix protein derivatives, such as Emdogain®.[15,16] Enamel matrix proteins are derived from late-bud stage developing teeth which are thought to stimulate periodontal ligament fibroblast activity.

Gingival recession defects and coronally repositioned flaps

Studies have compared the use of PRP or PRF with enamel matrix protein derivatives and bone-derived xenografts, as adjuncts to coronally and laterally repositioned flap surgery in areas of gingival recession. The aim of such surgery is to create an environment conducive to formation of a long junctional epithelium and a stable gingival margin. Hanna *et al* found there to be a statistically measurable improvement in probing depth and clinical attachment loss at 6 months where PRP had been used in conjunction with a bone-derived xenograft material, when compared to the use of a bone-derived xenograft alone.[15] Padma *et al* also reported statistically significant improvements in clinical attachment level, width of keratinized gingivae, and recession depth when PRF was used in coronally repositioned flaps for the treatment of Miller Class I and II defects.[16] Other authors reported similar clinical attachment improvements with the use of PRP in coronally repositioned flap surgery when compared with enamel matrix protein derivatives.[17–19] Likewise, Anilkumar *et al* published a case report in which PRF was used successfully in combination with a laterally repositioned flap. A stable and aesthetic gingival margin was present six months post-operatively.[20]

Connective tissue graft substitute

PRF membranes have been used instead of connective tissue grafts (CTGs) when carrying out surgical procedures to correct gingival recessions, with comparable results.[21] CTG preparation not only requires significant surgical skill, but also creates a second surgical site with associated post-operative pain, giving PRF membranes obvious advantages. In a blinded split mouth randomized control trial, where patients underwent bilateral surgical periodontal procedures to treat gingival recession, using either CTG or PRF membranes, both CTG and PRF membranes had comparable effects on recession, clinical attachment level and pocket depth, with CTG having a slightly more significant increase in keratinized tissue, although the PRF-treated sites also had an increase in keratinized tissue as compared to baseline levels.[21]

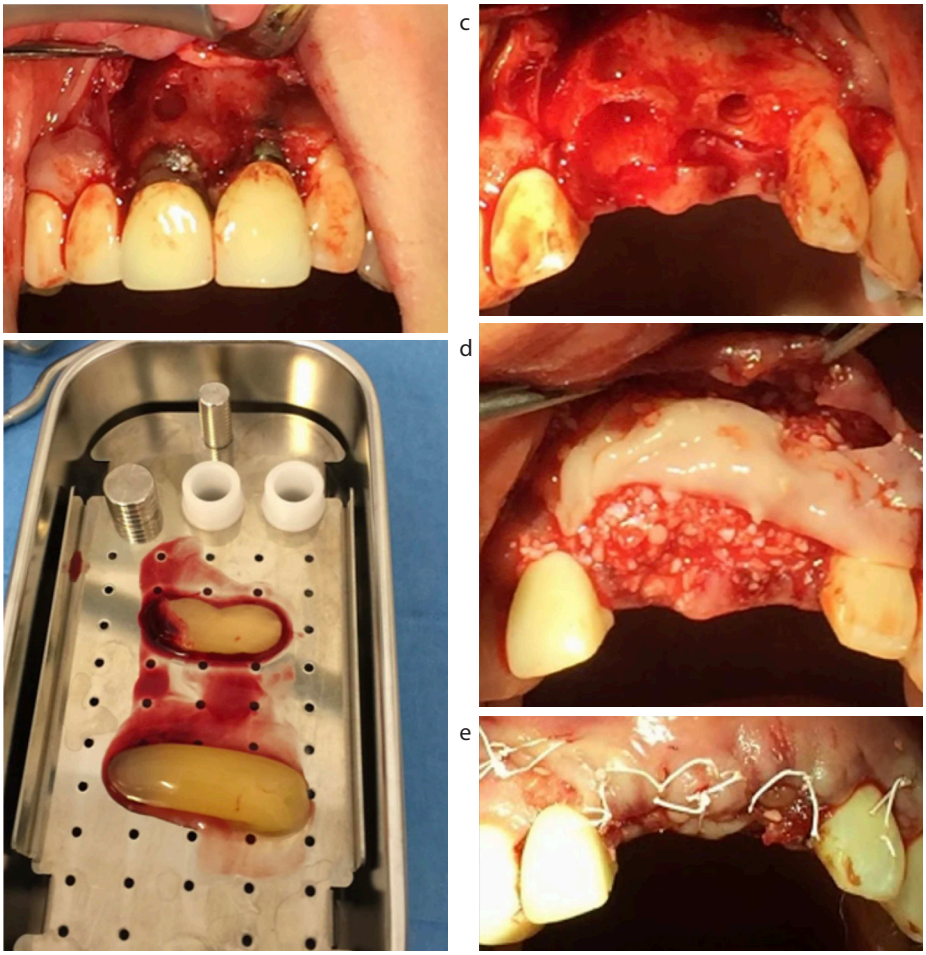

Figure 4. (a–e) The use of a PRF membrane used to augment anterior maxillary extraction sockets in preparation for future implants. The prepared PRF with its yellow colour is shown. (Images kindly supplied by Dr Rajesh Handa of Aesthetics Dental and Implant Surgery.)

Suture substitute

Fibrin-based sealants may be used in place of sutures in some instances to secure flap closure after periodontal surgery.[22] Fibrin sealants may be superior to traditional suture placement because there is less plaque and debris accumulation without the presence of sutures. Friable flaps may be easily torn by a suture, whereas this is not the case with a fibrin-based sealant. Prato *et al* also found haemostasis was achieved more rapidly after modified Widman flap procedures when comparing fibrin glue to suture placement (although for this study, silk sutures were used, which have become largely outdated today).[23]

By using sealants, the whole flap surface may also be sealed in contrast to interrupted suture points at the flap margin with suture placement, and this potentially reduces the possibility of bacterial ingress to the surgical site. It must, however, be born in mind that not all surgical sites will be amenable to fibrin-based sealant placement. Cases where a large underlying surgical defect lies beneath a gingival flap would be unsuitable for fibrin glue closure due to insufficient surface area for sealant placement.

Sinus lift and augmentation surgery

PRF has been used solely and in conjunction with other bone substitutes in sinus lift and augmentation surgery. Many studies have suggested that using PRF alone to augment a sinus can be effective, and a systematic review by Ali *et al* concluded that PRF had promising results when used independently as a sinus-lifting biomaterial, or when used in conjunction with bone allograft.[24] PRF membranes have also been used instead of a porcine-derived collagen membrane to aid in the repair of Schneiderian membrane damage (the mucosal sinus floor), and it has been suggested that, during sinus augmentation, the use of PRF may help prevent damage to this membrane.[25] PRP and PRF have also been used to aid in the repair of oral-antral communications, although there is a lack of clinical studies in this area, with most evidence being gained from case reports.[26]

Implant placement

PRP and PRF have both found use in implant surgery, with some authors advocating the use of PRP around the surface of an implant prior to implantation, which may result in superior osteointegration of the implant. Two studies have suggested an improvement in implant prognosis, and early bone apposition, with the use of PRP and PRF.[27,28] PRF membranes have been used as a barrier membrane to cover newly placed implants, and this has been shown to result in good soft tissue aesthetics, as well as providing good coverage for the implant (Figure 4).[27]

Osteonecrosis of the jaw management

Osteonecrosis is death of the bone tissue. Patients are more susceptible if the bone has received radiotherapy, known as osteoradionecrosis (ORN), or if the patient has received antiresorptive or antiangiogenic medications, known as medication-related osteonecrosis of the jaw (MRONJ). Both ORN and MRONJ have proved difficult conditions to resolve, and there has therefore been interest in the use of autologous bone products which contain platelet-derived growth factors (which are known to have a positive influence on the healing process) as both a prevention and a management.[3] Curi *et al* presented a case series where PRP was used successfully in combination with local resection of necrotic bone and primary gingival closure in patients affected by MRONJ.[29] The author reports 80% of the 25 patients who underwent this treatment had complete mucosal covering after healing.

Extraction site healing

The placement of PRP in extraction sockets has been shown to improve healing times. Alisa *et al* showed that patients in which PRP was placed in extraction sockets reported less pain and better radiographic signs of healing.[30] In this particular study, all the patients who were found at follow-up to have a dry socket were in the control group not receiving PRP therapy but, due to the small size of the study, it is difficult to ascertain if PRP had a significant effect on this risk.[30]

Some studies have demonstrated

greater increases in post-extraction radiographic socket bone density, suggesting increased bony healing,[3] although this is not universally accepted in the literature. Autologous bone products may therefore find more use in patients who are at higher risk of poor bony healing post extraction, such as patients who are immunocompromised, or at risk of ORN or MRONJ.

PRF has also been used itself to try and treat dry sockets, and has been compared to more traditional zinc-oxide eugenol dressing, showing comparable results in resolution of pain and increased radiographic signs in bony healing.[31] More work will be required in this area, however, this is another area where autologous substances may be used in the future.

Risks and complications

There are theoretical risks associated with autologous blood product use. The use of products containing growth factors may promote tumour growth, due to upregulation of mitogenesis, cell differentiation and general cell growth. However, the growth factors within PRP and PRF mixtures degrade after 7–10 days and, for sustained tumour growth, a more continuous growth factor stimulus would be required.[3] It is reassuring that there are no reported cases of tumour growth in an area where PRP or PRF substances have been used, and this is a more likely theoretical risk.

The process of blood harvesting carries its own risks. While adverse effects of this are unlikely to be serious, they must be considered when considering using autologous bone products. The main risks include a haematoma formation at the venepuncture site, as well as syncope, but phlebitis (inflammation of the vein wall) and ecchymosis (bruising) can also result.

Autologous blood product use may be unwise in patients who have a severe needle phobia, as blood harvesting may be distressing to the patient. Also, patients with a coagulopathy carry a higher risk of bleeding and may therefore be unsuitable candidates for autologous blood product use (although patients who have such severe coagulopathy would likely be poor candidates for dental surgery anyway).

Overall, autologous products carry a very small risk, with no complications being reported in the literature.

Cost and time implications

The main drawback surrounding the use of autologous bone products within dentistry and oral surgery is the cost involved. In order to set up a service to obtain and process blood to create these products, a significant outlay to invest in equipment is required. This includes equipment for blood harvesting, a centrifuge machine, 10 ml syringes, and instruments for manipulating the PRF into a membrane. Another factor to consider is that time must also be allocated to gaining blood and subsequent processing. It takes around 30 minutes to create PRF. Such cost and time implications should be appreciated at the treatment planning stage and, with appropriate time management, may be mitigated by having an assistant prepare the PRF whilst other treatment progresses.

Discussion

The use of autologous blood products has been shown to be safe and effective. To the authors' knowledge, there have been no reported complications resulting from the use of these products. Unfortunately, at present, there is limited long-term data on the benefit provided by these substances, and there is a need for future clinical trials to evaluate long-term benefits of autologous bone products compared to other treatment methods. Further clinical trials are required to evaluate properly whether autologous blood products provide real benefit to patients.

At present, costs involved in autologous bone product production may be prohibitive in all but specialist practices. Prices of centrifuges are likely to reduce in the future, however, and it is possible that PRF- and PRP-based substance use will become more common, particularly within specific patient groups, such as those at risk of MRONJ and ORN, and in conjunction with implant placement and periodontal defect surgery.

Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Informed Consent: Informed consent was obtained from all individual participants included in the article.

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