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Editorial Board Member of *World Journal of Clinical Cases*, Farooq Shahzad, FACS, MBBS, MS, Assistant Professor, Plastic Surgery Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, United States. fooqs@hotmail.com

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Platelet rich fibrin is not a barrier membrane! Or is it?

Amit Arvind Agrawal

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Amit Arvind Agrawal, Department of Periodontology and Implantology, Mahatma Gandhi Vidyamandir's Karmaveer Bhausaheb Hiray Dental College and Hospital, Nasik 422003, India

Corresponding author: Amit Arvind Agrawal, MDS, MPhil, Doctor, Professor, Department of Periodontology and Implantology, Mahatma Gandhi Vidyamandir's Karmaveer Bhausaheb Hiray Dental College and Hospital, Mumbai-Agra Road, Panchavati, Near Kannamwar Bridge, Nasik 422003, India. agrodent@rediffmail.com

Abstract

Platelet-rich fibrin (PRF) is widely used in dentistry and other fields of medicine, and its use has become popular in dental implantology. In several published studies, PRF has been used as a barrier membrane. A barrier membrane is a sheet of a certain material that acts as a biological and mechanical barrier against the invasion of cells that are not involved in bone formation, such as epithelial cells. Among the basic requirements of a 'barrier membrane, occlusivity, stiffness, and space maintenance are the criteria that PRF primarily lacks; therefore, it does not fall under the category of barrier membranes. However, there is evidence that PRF membranes are useful in significantly improving wound healing. Does the PRF membrane act as a barrier? Should we think of adding or subtracting some points from the ideal requirements of a barrier membrane, or should we coin a new term or concept for PRF that will incorporate some features of a barrier membrane and be a combination of tissue engineering and biotechnology? This review is aimed at answering the basic question of whether the PRF membrane should be considered a barrier membrane or whether it is something more beyond the boundaries of a barrier membrane.

Key Words: Platelet rich fibrin; Platelet rich plasma; Barrier membrane; Guided tissue regeneration; Guided bone regeneration

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Core Tip: Barrier membranes are an important aspect of guided bone and tissue regeneration in periodontics and implant dentistry. Extensive research has been conducted on barrier membranes; however, no single ideal barrier membrane available. Platelet-rich fibrin (PRF) is increasingly becoming popular in dentistry due to its growth factor-secreting properties and is also known to enhance wound healing and soft tissue thickness at the surgical site. However, PRF membranes are labelled as barrier membranes, although they do not fulfil the basic requirements of a barrier membrane.

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INTRODUCTION

Before discussing whether platelet-rich fibrin (PRF) is a barrier membrane, let us understand what PRF is, along with the concept of a barrier membrane. PRF, as the name suggests, contains a high number of platelets and leukocytes, in addition to a dense fibrin matrix. It is produced by the slow centrifugation of the patient's blood as a chair-side procedure. The fibrin matrix and platelets contribute to wound healing, whereas leukocytes contribute to the antibacterial effects. PRF clots are formed after the termination of the centrifugation cycle in the upper layer of the centrifuge tubes. Following their removal, they can be used in different modalities by either compression or using an extraction socket. They can be cut into small fragments and mixed with bone graft materials. Alternatively, they can be flattened to produce a membrane called the PRF membrane for eventual use in guided tissue regeneration (GTR) or guided bone regeneration (GBR) procedures. PRF exhibits a slow and sustained release of growth factors, such as transforming growth factor-beta1, platelet-derived growth factor, and vascular endothelial growth factor, all of which have been proven to promote wound healing and tissue regeneration[1,2].

A barrier membrane is a sheet of a certain material, which acts as a biological and mechanical barrier against the invasion of cells not involved in bone formation, such as epithelial cells, and allows for the migration of slow-migrating bone-forming cells into the defect sites[3]. In simple terms, as bone defects heal, there is competition between soft tissue and bone-forming cells to invade the surgical site. In general, soft tissue cells migrate at a much faster rate than bone-forming cells. Therefore, the primary goal of barrier membranes is to allow for selective cell repopulation and guide the proliferation of various tissues during the healing process[4]. Regeneration occurs below the membrane and involves angiogenesis and migration of osteogenic cells. The initial blood clot is replaced by woven bone after vascular ingrowth, which is later transformed into a load-bearing lamellar bone. This ultimately supports hard- and soft tissue regeneration[5]. If a barrier membrane is not utilised, the lack of space maintenance will result in soft tissue integration and compromised bone growth.

Literature has laid out various aspects of an ideal barrier membrane, including biocompatibility, the ability to create space, cell occlusiveness, tissue integration and handling, and resorption time. A membrane should be stiff and biocompatible enough to avoid soft tissue penetration or collapse into the regeneration area[6]. This stiffness is required because successful bone regeneration requires bone defects to be isolated from the soft tissues, permitting bone growth, which takes a minimum of 4-6 wk for periodontal tissues and 16-24 wk for bones[7,8]. Lee *et al*[6] reported that non-resorbable membranes are the best barrier membranes; although they do not require a second surgery, they have a low tensile strength, which can be a limitation when compared with expanded polytetrafluoroethylene membranes or a titanium mesh, thereby lowering their ability to maintain space.

Caballé-Serrano *et al*[7] performed a systematic review with a primary research question, 'which main criteria should a barrier membrane fulfil?' They concluded that an ideal membrane should maintain its barrier function for enough time for new bone formation and, if possible, should be resorbable so that a second surgery would not be needed, thereby reducing morbidity. With reference to degradation properties, porcine natural collagen membranes are the fastest to resorb (4-8 wk), whereas cross-linked membranes and bone lamina membranes offer more margins in terms of resorption (4-6 mo and 5-8 mo, respectively)[8].

In the context of resorbable membranes, Zellin *et al*[9] stated that even if resorbable barrier membranes can initially maintain space, they generally lose strength, collapse into the space, and lead to failed reconstruction. In contrast, PRF membranes are unable to maintain space even at placement; therefore, technically, when it comes to the space maintenance criterion, the PRF score is 0.

THE BIG QUESTION?

Having understood the basics of PRF and PRF membranes, and the ideal requirements of a barrier membrane, let us focus on the question, 'should PRF membranes be considered as a barrier membrane?' This question is important because there are thousands of articles published in literature in which the title itself mentions 'PRF used as barrier membrane'; there could be lakhs more where not in title *per se* but clinical studies, care series, case reports, *etc.* have included 'PRF was used in patient as a barrier membrane'. However, there is still much debate on whether PRF acts as a barrier membrane. This question should be answered because the literature needs to be evidence based. It is possible that PRF is a barrier membrane in some way or may be used as a barrier membrane, although it does not fulfil the criteria for a barrier membrane, and thus labels it incorrectly. This article discusses the available literature both as evidence against the belief that PRF is a barrier membrane and evidence in support of it. Finally, let the individual reader decide what is true: Should we continue to label PRF as a 'barrier membrane' or should we find other terminologies that are more relevant and appropriate? **Table 1** Lists all the terms related to membranes (in the context of dentistry) and their meanings for a basic understanding of different terms.

EVIDENCE AGAINST PRF AS BARRIER MEMBRANE

Wang *et al*[10] laid the 'PASS' criteria for ideal regenerative procedure, wherein 'P' stands for primary, non-tension wound closure that enables healing by primary intention; 'A' for angiogenesis to promote blood supply to the regenerative area; 'S' for stability of clot to allow development and proliferation of osteogenic cell; and 'S' for space maintenance for undifferentiated mesenchymal cells platform. Dimitriou *et al*[11] performed an extensive review of barrier membranes and highlighted the importance of variability and the lack of control over the rate of resorption of commercially available resorbable membranes, which are influenced by factors such as the local pH and material composition. They also listed the requirements for desirable membrane pore size, topography, soft tissue ingrowth capacity, and mechanical stability. There was no mention of PRF membranes in any of the inclusions of the various barrier membranes. The pore size of a barrier membrane is crucial for preventing excessive penetration of fibrous tissue (soft tissue) into the bone defect while simultaneously allowing neovascularisation and bone formation. Different intensities of bone regeneration can be observed depending on the variability in pore size[12]. Pores in excess of 100 µm are required for the rapid penetration of highly vascular connective tissue, and small pores tend to become filled with more avascular tissue[13] because they are not adequate for the penetration of capillaries[14]. A pore size of 50-100 µm allows bone ingrowth, whereas a size > 150 µm is required for osteon formation[15,16]. As much variability has been reported in the preparation of PRF based on patient age, sex, time of blood aspiration, and type of centrifuge, there is no consensus regarding the pore size of a PRF membrane. In addition to porosity, the three-dimensional topography of the membrane with interconnecting pores and channels is important, as it can alter the cell occlusion properties and biological responses of different cell types to the membrane[17]. However, there is no strong literature on the internal topography of a PRF membrane; hence, the fulfilment of this parameter is questionable. In terms of membrane stability, micromovements between the bone and any implanted material prevent bone formation. These micromovements may result in the development of fibrous tissue[18,19]. Therefore, adequate stability and minimal stress on the graft site are required to allow early tissue infiltration through the pores to differentiate into bone by direct or appositional bone formation[20]. Membrane-fixing pins are generally recommended to achieve higher membrane stability. Bone formation is significantly enhanced when the resorbable membrane is tightly attached and immobilised on the bone surface[21]. The PRF membrane is extremely flexible; although heating or double heating of the PRF membranes is recommended to increase their tensile strength[22], there has been no evidence that any modification or treatment of the PRF membrane increases its stiffness or has been used along with fixation pins or tack pins for GBR procedures. In terms of space maintenance, the implanted barrier membrane is expected to provide a shielding effect for up to 6 wk for periodontal tissue regeneration and for approximately 24 wk for bone augmentation therapy[8,23,24]. As PRF membranes degrade in < 6 wk[25], their role in the shielding effect seems questionable.

In their review article, Rakhmatia *et al*[26] summarised more than 30 articles (between 1994 and 2012) on current barrier membranes, but did not include articles on PRF. Soheilifar *et al*[27] conducted an extensive review of barrier membranes and assessed articles published from 1982 to 2013; they highlighted the importance of space maintenance and specified that a particular barrier membrane should primarily act as a 'barrier'. However, their review did not include any articles on PRF or its variants. In a systematic review by Miron *et al*[28], the authors evaluated approximately 35 articles and concluded that the literature supports the use of PRF for periodontal and soft tissue repair; however, well-conducted studies demonstrating the role of PRF in hard tissue bone regeneration are lacking. Similarly, in a systematic review on the search for a barrier membrane, Caballé-Serrano *et al*[7] analysed 22 articles, none of which were related to PRF. Rodriguez *et al*[29], in their review article on barrier

Table 1 Different names/terminologies related to membrane and their meanings

Sr. No.	Terminologies	Meanings/definition
1	Membranes	A thin pliable sheet of material or tissue forming a barrier or lining.
2	Resorbable membranes	Membranes that are biocompatible and are metabolised by hydrolysis or enzymatic activity over the course of time.
3	Non-resorbable membranes	Membranes that are bio-inert and require a second surgical procedure to remove after bone regeneration is complete.
4	Barrier membranes	A barrier membrane is a device used in oral surgery and periodontal surgery to prevent epithelium, which regenerates relatively quickly, from growing into an area in which another more slowly growing tissue type, such as bone, is desired.
5	Collagen membranes	Membranes made of collagen (mostly type-1 collagen) that are fabricated in different shapes and sizes and used in oral surgical procedures for bone and tissue regeneration.
6	Collagen barrier membranes	Selective collagen membranes that can act as barrier membrane for bone and tissue regeneration.
7	Natural membranes	Membranes made from natural materials or sources, such as collagen, dermis, tendons, sclera, amnion, pericardium, chorion, and silk.
8	Synthetic membranes	Membranes made from synthetic materials, such as polytetrafluoroethylene, titanium, and ceramic.
9	GTR membranes	Barrier membranes used for regeneration of lost PDL, cementum, and bone.
10	GBR membranes	Barrier membranes used for bone regeneration.
11	PRF membranes	Autologous membrane made <i>via</i> blood centrifugation followed by compression of clot to the desired thickness.
12	Multiphasic membranes	Multiphasic membranes that are designed in phases (or layers) to meet the various criteria of the periodontal tissue types.
13	3D-printed membranes	Customised zirconia printed <i>via</i> the CAD CAM technology to serve as new-generation barrier membranes.
14	Functional membranes	Membranes that are not passive barriers but are actively functioning in supporting the regeneration process.
15	Bioactive membranes	Membranes that are loaded with different biological activities, which are timed to play a role in different stages of bone healing and mimic the natural osteogenesis process.
16	Antimicrobial membranes	Barrier membranes loaded with antimicrobial components such as antibiotics, silver ion coating, PEG, superhydrophobic and structural coating.
17	Structurally layered membranes	Multiple layered membrane that are structurally engineered so that each layer has a different biological characteristic.
18	Polymer barrier membranes	Membranes made from polymers such as polylactic acid, polyglycolic acid, collagen, and alginate.

GTR: Guided tissue regeneration; PDL: Periodontal ligament; GBR: Guided bone regeneration; PRF: Platelet-rich fibrin; CAD CAM: Computer-aided design computer-aided manufacturing.

membranes used in dentistry, not only included almost all resorbable and non-resorbable membranes but also mentioned upcoming potential membranes such as BioXclude, hybrid and multiphasic barrier membranes, anti-infective membranes, and novel manuka honey advancement of membranes. However, no platelet concentrates, including PRF, were included in this study. On thermal manipulation of PRF membrane and using single syringe closed system, Kardos *et al*[22] found significant improvement in tensile strength, significantly higher cell adhesion, and lower degradation rate. Despite this, they advocated the use of PRF as an autologous biocompatible membrane for tissue regeneration and did not claim its use as a barrier membrane.

PRF membranes typically have very short resorption times, ranging from a 10- to 28-d period[25]. However, during their limited resorption time, a slow and gradual release of growth factors is observed within the PRF matrix[30]. This release of growth factors is higher than that of platelet-rich plasma. Miron *et al*[31], in one of their review articles, highlighted the question, 'Can we use PRF alone as a replacement to collagen barrier membranes?' However, they added that barrier membranes, in general, were developed to prevent fast-growing soft tissues from entering the slow-growing compartment containing bone. Therefore, the role of PRF remains controversial. They concluded that PRF membranes can be placed around the implant collars to facilitate more rapid soft tissue healing without utilising a collagen barrier membrane. They added that PRF can also be utilised in a 'poncho' technique and wrapped around the healing cap to favour soft tissue attachment and prevent infection. However, in both of these applications, the PRF membrane is not utilised as a barrier membrane but as a sheet of autologous fibrin intended to assist and improve soft tissue healing and thickness. The authors concluded that during GBR procedures (most notably during extensive GBR cases), PRF membranes

should be combined with either a collagen barrier membrane or titanium/titanium-reinforced membranes, further proving that PRF alone cannot be considered or should not be used as a barrier membrane'. In this context, PRF membranes can be placed over or under the barrier membrane. As PRF is known to rapidly promote greater soft tissue wound healing, its biological use involves contact with soft tissues on the outer surface of barrier membranes. However, it would be advantageous to place the PRF membrane under a non-resorbable membrane as the periosteum would not be able to supply angiogenesis through this membrane, and PRF placed under this membrane can supply the early growth factors responsible for new blood vessel formation within the underlying bone augmentation procedure. Therefore, PRF should be placed above or under the barrier membrane but should not be used as a barrier membrane by itself. Furthermore, Omar *et al*[32] presented a comprehensive narrative review and up-to-date survey of the available literature on in-vivo biological mechanisms related to GBR and the potential active role of the membrane. They summarised numerous membranes under various headings and subheadings but did not mention PRF anywhere. In their article, Higuchi *et al*[33] suggested that the current trend of designing membranes should focus not only on biodegradability or compatible growth for cells but also on additional functions such as bone stimulating or antibacterial properties. However, there was no mention of PRF in their description.

In their review article, Sasaki *et al*[34] summarised the fundamental characteristics of barrier membranes based on their components and provided an update from the material point of view; PRF was not included in the list of biodegradable and non-degradable membranes. In a recent narrative review by Alauddin *et al*[35], the authors summarised recent biomaterials and contemporary membranes utilised in periodontal regeneration and implant therapy in the market. Although the title was 'Barrier membranes in regenerative therapy', their aim was to evaluate all biological membranes and not just barrier membranes. Hence, PRF must have found its place in this review. However, in their description of autologous platelet concentrates (APCs), they concluded that in their literature search, APCs alone, as a barrier membrane, are lacking and, therefore, are recommended for future studies. Kim *et al*[36] reviewed various coated barrier membranes and reported that PRF-coated collagen membranes increased gingival thickness[37]. In another recent review on advances in barrier membranes by Yang *et al*[38], the authors summarised and described the ideal requirements of a barrier membrane. They also added notes on functional membranes, bioactive membranes, antimicrobial membranes, and structurally layered membranes. However, PRF was not mentioned under any heading or subheading of barrier membranes. Ren *et al*[39] mentioned PRF but specified that PRF should be used as a bioactive molecule as an adjunct to barrier membranes.

LITERATURE ADVOCATING PRF AS BARRIER MEMBRANE

Kawase *et al*[40] conducted a study on heat compression of PRF membranes and concluded that heat-compressed PRF membranes can be easily prepared on the chair-side and applied as a barrier membrane in the GTR procedure. However, in their in-vitro and in-vivo animal studies, they only evaluated the degradation rate of conventional gauze-pressed PRF against heat-compressed PRF. No other properties of barrier membranes have been studied; therefore, based on their observation, claiming that heat-compressed PRF can be used as a 'barrier membrane' does not seem justified. Isobe *et al*[41] studied the mechanical properties of fibrin membranes and associated them with their degradability compared with advance PRF, concentrated growth factors (CGFs), and platelet-poor plasma-derived fibrin membranes. They concluded that all three membranes were tough enough to serve as barrier membranes. Their statement was based on the evaluation of 'toughness as mechanical strength', but they evaluated the tensile strength of the membranes. Based on this, it can be concluded that certain membranes are mechanically resistant to stretching; however, their study did not provide any data on their space-maintaining capacity, stiffness, or delayed degradation time. Increased tensile strength of a membrane is useful for its ability to be sutured without tearing, as reported by Kardos *et al*[22].

A further extensive review by Aprile *et al*[42] presented the latest advancements in GBR membranes and described the process leading to the industrial development of materials for such biomedical applications. Among the exhaustive list, there was only a single sentence that mentioned PRF without any clear specification on whether PRF can be used as a barrier membrane. In another summary of barrier membranes[43], the authors particularly included PRF under the subheading of resorbable membranes but added that PRF should be used with other membranes where bone growth factors are indicated. Yu *et al*[44] demonstrated that double heating of a PRF membrane at 90°C for 10 s significantly improved its mechanical and degradation properties but decreased cell viability and fibroblast proliferation activity. Surmeli Baran *et al*[45] demonstrated that photobiomodulation of L-PRF resulted in better results than L-PRF alone (although not statistically significant) when used as a barrier membrane in animal studies. However, their study also included a collagen membrane group, which showed significantly improved results compared with all other study groups. In addition, the study was performed for 1 mo, which is too short to evaluate the regeneration and degradation of a membrane, and the defects were filled with bone substitutes, which again ruled out the stiffness or space-maintaining capacity of the membrane. In a recent descriptive review by Solomon *et al*[46] on identifying the perfect membrane, the authors

Table 2 List of review articles on barrier membranes

Sr. No.	Ref.	Was PRF included in the list of barrier membranes?
1	Dimitriou <i>et al</i> [11], 2012	No
2	Rakhmatia <i>et al</i> [26], 2013	No
3	Soheilifar <i>et al</i> [27], 2014	No
4	Lee <i>et al</i> [6], 2014	No
5	Rodriguez <i>et al</i> [29], 2018	No
6	Caballé-Serrano <i>et al</i> [7], 2018	No
7	Omar <i>et al</i> [32], 2019	No
8	Higuchi <i>et al</i> [33], 2019	No
9	Caballé-Serrano <i>et al</i> [47], 2019	No
10	Aprile <i>et al</i> [42], 2020	Yes (only mentioned)
11	Sasaki <i>et al</i> [34], 2021	No
12	Ren <i>et al</i> [39], 2022	Yes (as a supportive bioactive molecule to other barrier membranes)
13	Yang <i>et al</i> [38], 2022	No
14	Alauddin <i>et al</i> [35], 2022	Yes (as a supportive membrane)
15	Solomon <i>et al</i> [46], 2022	Yes (for increasing the soft tissue thickness)

PRF: Platelet-rich fibrin.

included PRF under the subheading of trends in the development of barrier membranes. However, all studies supported either mixing bone grafts with PRF for better regeneration, management of gingival recession, or improvement in the thickness of soft tissue due to PRF. There was no evidence or justification for including PRF in the category of barrier membranes[47]. A summary of different review articles on barrier membranes is presented in Table 2, with a mention of whether they included PRF in their list of barrier membranes.

FUTURE POTENTIAL OF USING PRF MEMBRANE AS A BARRIER MEMBRANE

Wong *et al*[48] enlarged the pores in the structures of PRFs by repeated freeze-drying and used Mg rings to create a scaffold. They found that the use of an Mg ring enhanced the osteogenic ability and migration capacity of Mg ions during degradation. Although they did not study any property fulfilling it to be a barrier membrane, the concept of modifying the pore size and incorporating Mg rings might be a potential area of future research to study its ability to improve the space-maintaining capacity, delay degradation time, and potentially increase the stiffness of PRF membranes. CGF, developed by Sacco, produces an autologous membrane that is thicker, denser, and more durable than conventional PRF [49]. Future research on the potential use of CGFs, rather than PRF, as barrier membranes should also be explored.

CONCLUSION

Although PRF can mimic and be handled like a GTR membrane, its main disadvantage is that it resorbs within approximately 7 d[5] to 28 d[25], which is substantially shorter than the 4-6 wk required for most periodontal regeneration applications. In addition, owing to its high resorption rate, its ability to maintain space is compromised. The quest for an ideal barrier membrane depends on the operator's preference, skills, and experience rather than specific guidelines implemented for bone and tissue generation. The incorporation of metal ions and nanoparticles to improve the stiffness and space-maintaining properties of PRF may be useful as a barrier membrane and can potentially be used alone. Thus, it is better to label PRF membranes as a supportive, revitalising, rejuvenating, biological, autologous, or biocompatible membrane for tissue regeneration.

FOOTNOTES

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Country/Territory of origin: India

ORCID number: Amit Arvind Agrawal 0000-0002-2235-7305.

Corresponding Author's Membership in Professional Societies: Indian Dental Association, No. 51827; Indian Society of Periodontology, No. A25-621.

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