Commentary: Biological tear substitutes: Overview, evidence, and future

Artificial tear eye drops available over the counter are the primary tear substitutes used in the management of dry eyes and ocular surface disease with poor epithelial healing. When conventional therapy with the above, or combination with topical anti-inflammatory medications fail, biological tear substitutes (BTS) are one of the alternatives. Like artificial tears, BTS provide lubrication to the ocular surface; however, it differs by closely mimicking the biochemical properties of the natural tears produced by the lacrimal gland. The osmolarity and pH of serum and natural tears are similar,[1] and in addition, BTS contains growth factors, vitamins, enzymes, and other substances, which provide the nutrients necessary for epithelial healing.[2]

BTS include a range of products based on the preparation process. Serum-based products include autologous serum (AS) and cord blood serum (CBS), and platelet-derived products include platelet-rich plasma (PRP), plasma rich in growth factors (PRGF), and platelet lysate (PL). All the above could be autologous or allogenic based on the source. Currently, there are no specific guidelines on when to initiate BTS in patient care, and which type of BTS should be used based on the underlying condition.

Overview of preparation
The preparation of blood-derived products should be carried out in a sterile fashion to avoid contamination and infection. Testing for blood-borne diseases including Hepatitis B, Hepatitis C, CMV, HIV, and syphilis should be routinely carried out. Identifying the indication for use is also important. Patients with graft versus host disease (GVHD) after bone marrow transplant, an ocular surface disease associated with systemic autoimmune disorders may have severe anemia and this may alter the approach to obtaining BTS for them.

After phlebotomy for blood collection, the processing determines the type of BTS obtained. The blood is collected without an anticoagulant and allowed to clot while preparing autologous or allogenic serum or CBS.[3] Hence, patients who are on systemic anticoagulants are not good candidates for AS formulations. On the contrary, for preparing PRP, PRGF, and PL, the blood needs to be anticoagulated,[3] and such patients on anticoagulants are eligible to donate. While preparing platelet-based BTS, packed red blood cells (RBCs) are obtained at the end and may be infused back into the patient. This can help in countering the anemia that blood donation often causes. During AS preparation, packed RBCs cannot be obtained for re-infusion as the blood is allowed to clot during the preparation process. Hence, AS donors have a risk of worsening anemia with the blood donation compared to platelet-based BTS donors.

A brief overview of the preparation is presented below. For AS preparation, blood is first allowed to clot in the absence of an anticoagulant. After the clotting phase is complete, the blood will be centrifuged at 3,000 g for 15 min to separate the serum and the solid components.[4] The serum is then removed from the sample and diluted with a BSS or preservative-free normal saline. The final dilution factor also varies in the reported literature, ranging from 20% to 100%. A 100% solution will provide the greatest concentration of nutrients and viscosity, enhancing the lubrication effect; however, it will produce far less AS for a given blood sample. Furthermore, AS drops contain transforming growth factor-β (TGF-β), which inhibits the proliferation of corneal epithelial cells. Therefore, dilution will also decrease the concentration of TGF-β,[1] and most centers use a 20% concentration of AS. The above process is similar for allogenic serum and CBS as well. Once preparation is complete, the drops can be stored at −20 degrees Celsius. Once opened, a new bottle should be used daily and stored at 4°C.[1] Although autologous and allogenic sera are rich in growth factors, CBS has more growth factors, especially EGF (epidermal), NGF (nerve), and VEGF.[5]

Platelet-based BTS preparation involves centrifugation (10 min @ 1600 rpm) of patients’ whole blood (with added anticoagulant) to obtain PRP, which contains additional platelet-derived growth factors, such as Platelet derived growth factor (PDGF), TGF-β, and platelet factor-4.[4] Preparation of PL and PRGF involve slight modifications or additional steps in the above process, and they basically contain higher quantities of PDGF and other platelet-based factors.[3]

The preparation of BTS drops can be costly. The exact costs vary; however, it is typically a few hundred dollars for a supply ranging 3–12 months. This presents a significant barrier limiting their use in patients with lower socioeconomic backgrounds. Also, given the facilities required to prepare and store the drops, some patients may be forced to travel hundreds of kilometers to a supplier, further limiting the use.

Current evidence and applications
Clinical research on dry eye management has several limitations. Different studies utilize different parameters for assessment, and hence it is difficult to pool the data. Although Schirmer’s, Tear Break Up Time (TBUT), and corneal staining may show objective evidence of change, it is the patient-reported subjective change (OSDI) that matters finally at the end.

A recent study shows the superiority of autologous PRP over artificial tears in the short-term management of moderate-to-severe dry eyes.[9] Although an initial Cochrane analysis was not able to show any significant efficacy of BTS over artificial tears,[6] a recent meta-analysis has been able to show that BTS are superior to artificial tears and secretagogues.[7] The meta-analysis also shows that platelet-based BTS outperforms AS in reducing OSDI and corneal staining scores, emphasizing the relationship between the percentage of growth factors and healing of the ocular surface. The number of adverse events was not statistically significant between treatments.[3]

Although the literature demonstrates the advantages of BTS, there are limitations. Firstly, there is evidence only for short-term improvement up to 3 months, and there are no long-term data. Another challenge in applying this information clinically is the lack of standardization between preparation protocols, resulting in significant variation between the critical steps of preparation.

Future of biological tear substitutes
Although there is evidence of short-term benefits of BTS in the management of dry eyes and ocular surface healing,[5,7] there is
so much more to be done. Currently, there is a need to develop a standardized protocol for the preparation of various BTS, and more studies are needed to assess the long-term efficacy of these preparations. It is important for tertiary centers dealing with ocular surface diseases to have facilities to dispense all forms of BTS at an affordable cost. Among the growth factors available in BTS, different ones are specific to various pathways in wound healing on the ocular surface. Pooled allogenic sera can be manufactured in different formulations, each containing different growth factors specific for the treatment of different ocular surface diseases.[10] This can be a step forward toward personalized medicine in the treatment of ocular surface disorders.

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