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Review

Quality standards, safety and efficacy of blood-derived serum eye drops: A review

Pieter F. van der Meer [a], Jerard Seghatchian [b,*], Denese C. Marks [c]

[a] Sanquin Blood Supply, Department of Product and Process Development, Amsterdam, The Netherlands
[b] International Consultancy in Blood Components Quality/Safety Improvements, Audit/Inspection and DDR Strategies, London, UK
[c] The Australian Red Cross Blood Service, Sydney, Australia

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ABSTRACT

Serum eye drops (SEDs) are being used increasingly to treat dry eye syndrome and persistent corneal epithelial defects, and are usually prescribed when conventional treatments fail. SEDs are commonly sourced from the patient's own blood via an autologous collection. Although SEDs are clearly beneficial, they are not available for those patients that cannot donate sufficient blood, and some centres are moving to allogeneic SEDs. Many studies have reported that both allogeneic and autologous SEDs are effective. However, few large randomised controlled trials have been conducted to date, and clinical evidence is therefore limited to smaller studies. Alternatives to serum are also being explored, such as platelet lysate and products made from platelet rich plasma, as they are a rich source of growth factors. This article reviews how some centres are approaching allogeneic collections for SEDs, and alternatives to serum that are currently being explored.

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1. Background

Dry eye syndrome and other diseases of the ocular surface are often difficult to treat as they are complex and multifactorial in their aetiology and symptoms. Serum eye drops (SEDs) are being used increasingly to treat a variety of ocular surface defects. Serum, made from clotted whole blood, is a biological mix of growth factors, and studies indicate that not one single factor but rather the combination of growth factors provides the healing effect of SEDs. This complicates studying the effectiveness of SEDs, and makes production of SEDs difficult to standardise. SEDs are considered a last resort if more conventional therapies do not work, making clinical trials difficult to perform, as patients requiring SEDs cannot be treated with a placebo or an alternative therapy. SEDs are commonly sourced from

* Corresponding author. International Consultancy in Blood Components Quality/Safety Improvements, Audit/Inspection and DDR Strategies, London, UK.
E-mail address: jseghatchian@btopenworld.com (J. Seghatchian).

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the patient's own blood (autologous). SEDs are clearly beneficial for patients, but are not available for those that cannot donate sufficient blood, and therefore, ophthalmologists and blood banks are currently working together to move to SEDs sourced from allogeneic donor serum. Some of the challenges encountered in this process and questions yet to be answered are described in this review.

2. The source of SEDs

Platelet lysate, platelet-rich plasma (PRP) and serum contain high concentrations of growth factors, cytokines and other biological response modifiers. Of the three, serum is currently the most widely used to treat ocular surface defects, which may be caused by many underlying diseases. Until now autologous serum has been predominantly used to treat patients, although several blood centres are currently exploring whether allogeneic serum can be used as an alternative.

Autologous SEDs have been used since the mid-1980s [1], with more widespread use in the last decade. With increasing use, it has become apparent that not all patients are able to donate their own blood to produce the serum, due to underlying disease, poor venous access or low haemoglobin, and that the logistics of blood collection is at times challenging for these patients, which on occasion is a reason to stop the therapy. For these reasons, the use of allogeneic donor serum to treat ocular surface damage is being explored. However, moving from autologous collections to the provision of allogeneic SED is not without further challenges. Because serum is not a traditional blood product, and is not administered by a blood transfusion, there is still debate as to whether SEDs should be regarded as a blood product or as a medicine, and more clarity should be provided by the regulatory authorities. Collection of serum for culturing of human cells for gene therapy, cell therapy or tissue engineering intended for retransfusion in patients is performed in blood banks, but it is not a high-volume blood product, and serum collection and processing are sometimes infrequent. Nonetheless, serum collection and processing have the same validation, training and GMP requirements as other blood products; therefore, the cost of SEDs is relatively high, and a cost–benefit analysis of SEDs is warranted, both from the blood bank and the hospital's viewpoint.

Until now, autologous SEDs have been used when conventional therapies such as artificial tears or prednisone eye drops are ineffective. Laboratory studies, and particularly clinical studies, are therefore difficult to perform due to ethical aspects, as treatment cannot be withheld from patients, and thus, comparison of SEDs to a control is not possible. The available literature shows benefit, but it remains unclear as to whether no treatment or placebo treatment would have led to healing as well. Based on laboratory studies, it appears that single compound approaches have been unsuccessful [2–4], as it is the combination of growth factors, biological response modifiers, proteins and vitamins in serum, rather than a single constituent that contributes to its beneficial effects. Many *in vitro* studies have demonstrated that serum can promote epithelial proliferation and differentiation. Serum has been shown to support migration of human corneal epithelial cells in a dose dependent manner [5], as well as further differentiation, as characterised by mucin production, in immortalised conjunctival epithelial cells [6]. Further, serum was found to maintain morphology and support proliferation of primary human corneal epithelial cells far better than pharmaceutical tear substitutes [7]. Additionally, incubation of primary cultures of human keratocytes with undiluted serum increased transcription of RNA for nerve growth factor (NGF) and TGF-β receptors [8], as well as suppressing apoptosis in conjunctival and corneal epithelium [9]. Overall, serum and SEDs can induce cell mobility, proliferation and differentiation in vitro. However, one of the main challenges that remains is to demonstrate the mechanisms through which SEDs are effective in treating ocular surface diseases, and animal models need to be developed to achieve this. Such models will also be useful for assessing alternatives to SEDs when they are developed.

3. Practical issues encountered during implementation in a blood bank

Espinosa *et al., 2015* recently reported on the important methodological and clinical aspects of implementing a standardised method for the production of allogeneic serum eye drops from regular blood donors in a Norwegian University Hospital [10]. These authors emphasised that allogeneic SEDs are a good alternative when autologous eye drops cannot be collected or their use is otherwise clinically not possible. The requirements to become a serum donor at this institution were similar to those for whole blood or apheresis donors. However, only male donors that have never received blood products will be recruited to avoid possible HLA-related allo-immunisation in recipients. Additionally, donors must not be taking any kind of medication, to avoid the presence of medication and/or preservative traces in the serum. Moreover, only AB group blood donors will be recruited to make the logistics easier, although ABO-compatible SEDs are a possibility. Informed consent will be required to inform the donors about the clinical use of their serum. The Netherlands will use a similar approach, obtaining blood for SEDs from male, blood group AB, blood donors who have never received a transfusion [11].

The shelf life of the eye drops at the Norwegian institution will be six months, which was specified by the Norwegian regulatory authorities. In a similar environment in Denmark, allogeneic whole blood donations from regular male blood donors have been used to produce serum eye drops under GMP conditions. The eye drops are produced for each ABO blood type. In the Danish recommendations, the bottles are stored at –30 °C for up to 12 months following production [12].

At this point, it is still unclear how many patients require this product, and how the SEDs will be financed. In Norway, the cost of autologous SEDs is usually covered in the general cost of a hospital; however, allogeneic SEDs need a form of reimbursement. Regardless, these centres in Norway and Denmark have shown that the standardised production of allogeneic serum eye drops from regular blood donors is feasible. To evaluate the clinical benefits, the safety and

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