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Review

Implementation of a standardised method for the production of allogeneic serum eye drops from regular blood donors in a Norwegian University Hospital: Some methodological aspects and clinical considerations

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A B S T R A C T

The use of autologous serum eye drops has been shown to be effective for the treatment of many ocular diseases. For patients were repeated blood sampling is not possible, allogeneic serum eye drops have been shown to be an effective and safe alternative. In our institution, we have managed to produce allogeneic serum eye drops from regular blood donors using a standardised procedure. The effectiveness and safety of this product will be evaluated in a clinical trial.

Contents

1. Introduction

Autologous serum eye drops contain vitamin A, epidermal growth factor, fibronectin, plasminogen and other growth factors and cytokines, useful for hard/soft tissue repair and wound healing and regenerative medicine. These factors have been shown to be successful for the treatment of persistent corneal epithelial defect in many ocular disorders [1]. The treatment with autologous serum eye drops seems to be safe and superior to conventional artificial eye solutions [2].

Traditionally, the production of autologous serum eye drops in Norway has been performed by the hospital laboratory, without any specific quality requirements or indication for the treatment being in place. In 2010, the Norwegian Agency of Medicines requested specific authorisation for the production of autologous eye drops. This demand from the national authorities resulted in the stop of the production in hospital laboratories, leaving these patients without any other commercially available preparation than artificial eye drop solutions. Some caregivers opted to

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continue the production of autologous serum in spite of the new regulations, finding them to be in clear conflict with patient needs.

Autologous production and treatment with serum eye drops have been in use at our institution until recent years, and no serious adverse events have been reported. Disadvantages with autologous drops are frequent blood sampling, limited stability of the product, lack of quality requirements and risk of infection [3]. To solve this problem, our hospital decided to implement the production of allogeneic serum eye drops from regular blood donors, based on the positive experience of a Danish research group [4].

2. Indications for serum eye drops

The main indication for serum eye drops is the chronic graft vs host disease (cGVHD), but patients with Sjögren's syndrome, rheumatoid arthritis, as well as patients other immune diseases may benefit from this treatment. cGVHD is caused by alloreactive donor-derived T lymphocytes and it is a well-known cause of keratoconjunctivitis sicca, and frequently accompanied by other manifestations, including xerostomia. The xerophthalmia is often severe, with frequent problems including blepharitis, conjunctivitis and corneal ulcerations. Incidence of cGVHD is increasing over time, mostly because of matched unrelated donors being used more and more frequently due to advances in tissue typing and because stem cell harvested from peripheral blood is increasing in use for practical and logistic reasons. In addition, older patients (up to 75 years old) may now be treated with allogeneic transplantation due to reduced intensity conditioning which decreases acute toxicity but does not preclude cGVHD. The majority of old patients suffer from cGVHD and xerophthalmia is therefore a frequent manifestation [5–7].

3. Methods

Serum from regular male AB blood donors was produced as it follows. Briefly, approximately 450 mL whole blood was donated from AB blood type, male regular donors, who never had received blood transfusion and not taking any kind of medication. The whole blood was allowed to clot at room temperature for approximately 2–6 hours after collection, followed by overnight storage at 2–6 °C. The whole blood was centrifuged at 4393 *g* for 13 minutes at 22 °C (Hettich Roto Silenta 630RS). The serum, containing red blood cells, was pressed manually (Fig. 1) under sterile conditions (Terumo Sterile Connection Device II) to a new bag. The serum was then centrifuged once more under the same conditions, and thereafter transferred sterilely to a new bag. The double centrifugation provides a cellular free serum. The serum (approximately 200 mL per donation) was sent to the Hospital Pharmacy (Pharmaceutical Department) for further processing. The blood bank service provides the serum, but the production and distribution will be performed by the Hospital Pharmacy. The bacterial and viral testing (HIV, HCV, HBV) is performed by the Hospital Microbiology Dept. at our institution.

The Hospital Pharmacy in Trondheim is able to perform the manufacture of sterile allogeneic serum eye drops in accordance to Good Manufacturing Practice (GMP). Required specifications like clean rooms, equipment and trained personnel are already implemented.

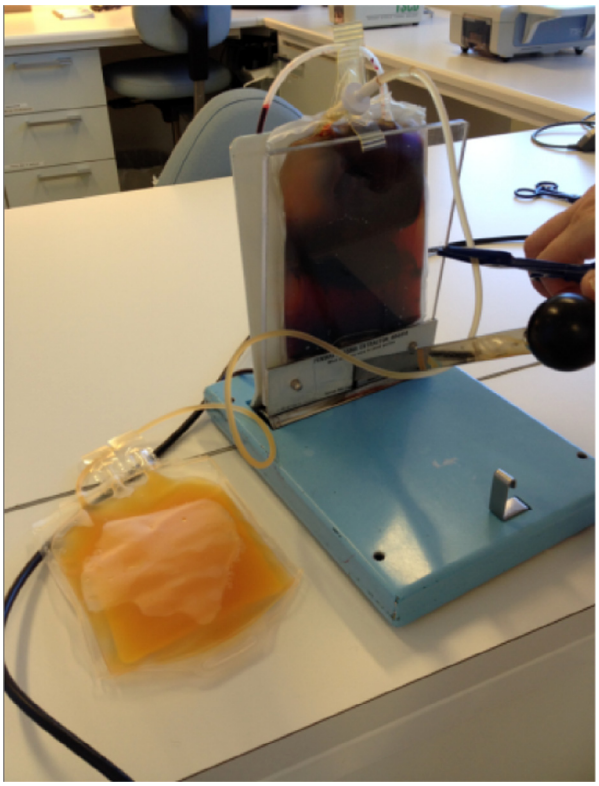

Fig. 1. Manual pressing of the serum is required to manufacture serum eye drops.

The serum from the blood bank service is diluted to 20 % (w/w) with sodium chloride 0.9%. No serum goes to waste in this process. After dilution, the solution is then filtered through a 0.22 µm filter (Millipak 20 express, Merck Millipore) into a sterile bottle or bag (Fig. 2). The serum solution is distributed in individual 5 mL eye drop bottles (Apodan Nordic, Denmark), using a pump (Baxa repeater pump, Baxter) (Fig. 3) and a suitable transfer set (Baxa fluid transfer set nr 11, Baxter).

The bottles are labelled with product specifications, batch number and storage conditions, packed in boxes (Cryo box, Fisher Scientific), containing 15 bottles in each box, and then stored in a plasma freezer (Dometic FR 490 G) at –36.5° C. Shelf life is defined as 6 months from serum donation date due to the Pharmacy's licence from the Norwegian Medicines Agency. The manufacture of serum eye drops follows existing regulations for extemporaneous production, and bacterial testing of each batch is not required. The quality of the product is assured by following GMP standard in the entire manufacturing process.

Each donation typically gives rise to about 180 bottles. The Cryo boxes are packed in a box with cooler elements prior to patient delivery (Fig. 4). The patients will be