

Finger-Prick Autologous Blood (FAB) Eye Drops for Dry Eye Disease: Single Masked Multi-Centre Randomised Controlled Trial

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Purpose: To investigate the quantitative and qualitative efficacy of finger-prick autologous blood (FAB) eye drops versus conventional medical therapy for the treatment of severe dry eye disease (DED).

Methods: Two centre, single masked, randomised controlled trial. Sixty patients in total were recruited with thirty patients (sixty eyes) treated with FAB eye drops four times per day in addition to their conventional DED treatment, and thirty patients (fifty-eight eyes) served as control subjects on conventional treatment alone. Ocular surface disease index (OSDI), Schirmer's test, fluorescein ocular staining grade (OCSG) Oxford schema and fluorescein tear film break-up time (TBUT), were performed at baseline, at 4 and 8 weeks.

Results: OSDI scores significantly decreased in the FAB arm by greater than -17.68 (-37.67 to -2.96 , $p=0.02$) compared to the control arm. There were greater improvements in OCSG and TBUT in the FAB arm but these were non-significant ($p>0.05$).

Conclusion: This feasibility study demonstrates adding FAB eye drops to conventional medical therapy for DED improves mean OSDI symptom score compared to conventional medical therapy alone. It may have particular use in settings where serum is unobtainable. An adequately powered and well-designed randomised trial is needed to further evaluate the long-term clinical benefit of FAB.

Keywords: finger-prick, dry eye, serum, autologous

Introduction

The ocular surface is an epithelial membrane that requires the tear film to support and maintain its health. Loss of normal tear film function can result in ocular surface damage and a failure of epithelial healing.¹

Dry eye disease (DED) is a multifactorial abnormality of the tear film that can result in damage to the ocular surface.² In the United Kingdom (UK) the prevalence amongst women aged 60–79 years old is 22.45%.³ A recent systematic review concluded that DED has a substantial economic burden, with indirect costs making up the largest proportion of overall costs from loss of work productivity.⁴ Current treatments for DED have been comprehensively reviewed in the management and therapy report by the Tear Film & Ocular Surface Society.⁵

Haemoderivative treatments have trophic effects on epithelial cells⁶ and this makes them beneficial for managing ocular surface diseases. This has been recognised since the 1940s when their use was described for managing ocular blast injuries⁷ and persistent epithelial defects.⁸ Today autologous serum (AS) is the most widely utilised and studied haemoderivative eye drop for DED.^{9,10} However, various other haemoderivative therapies have demonstrated beneficial effects including allogeneic serum,¹¹ umbilical serum,¹² platelet rich plasma (PRP),¹³ plasma rich in growth factors (PRGF)¹⁴ and autologous platelet lysate.¹⁵

Restrictions in haemoderivative licencing, cost and availability can mean such treatments are reserved for severe and recalcitrant disease.^{16,17} In the UK, obtaining such treatment requires named patient application and can involve prolonged delays depending on service workload. The estimated UK cost of producing AS drops is ~£300 per month.

In 2017 our group described a technique utilising finger-prick autologous blood (FAB) eye drops as an ocular surface therapy.¹⁸ FAB was found to be safe, effective and well tolerated in single armed pilot studies for both DED^{18,19} and persistent epithelial defects (PED).²⁰ More recently, a group in Cambridge (UK) have successfully used maternal allogeneic fingerprick blood to treat a young only eye patient's PED.²¹ FAB benefits from being cheaper and instantaneously available compared to other haemoderivative treatments for the ocular surface.

The present study is the first investigator-masked randomised controlled trial (RCT) to investigate FAB as an add-on therapy for severe DED comparing it against conventional medical treatment alone.

Methods

The trial was conducted in accordance with the tenets of the declaration of Helsinki and received ethical approval from the Health Research Authority (REC 17/EE/0508) in England.

Patients were recruited from two hospital sites of Moorfields Eye Hospital, a major tertiary eye care centre in England. All patients had symptomatic DED fulfilling the inclusion and exclusion criteria (Table 1). Written informed consent was obtained from all patients in this study.

Patients were randomised to either add FAB four times daily to their conventional DED treatment or to continue with their conventional DED treatment alone. All FAB patients underwent training which involved watching a 5-minute instructional video demonstrating the technique (available publically online on Moorfields official YouTube channel for general public),²² this was followed by the patient performing the technique under supervision of an unmasked ophthalmic research nurse. They were instructed as follows: hands are first washed and dried and then the selected fingertip is wiped with 70% isopropyl alcohol and allowed to air dry; a safety lancet (UniStik 3 Comfort, Owen Mumford, UK) is used to extract a drop of blood from a fingertip which is instilled directly into the inferior conjunctival fornix.

At each assessment (baseline, week 4 and week 8) patients were seen by a masked research ophthalmologist and underwent the following objective assessments: best corrected distance visual acuity (BCVA), Schirmer's without local anaesthesia, fluorescein Oxford corneal surface grading (OCSG)²³ and fluorescence TBUT. Patients reported symptoms and impact-on-life measures were collected using the OSDI at each visit with the end point being week 8. A final telephone consultation at week 12 (at which point they had been off FAB treatment for 4 weeks) was carried out to assess safety. All assessments were carried out by several masked ophthalmologists with the majority being carried out by a single study-dedicated research fellow; patients could not be masked as they were administering the treatment themselves. The full study protocol is published with open access.²⁴

Table 1 Study Inclusion and Exclusion Criteria

Inclusion	Exclusion
<ul style="list-style-type: none"> • Aged over 18-years • Moderate to severe symptomatic dry eye disease diagnosed by any one of following: <ul style="list-style-type: none"> – Ocular surface disease index (OSDI) score of greater than 33 – Ocular surface staining grade ≥ 2 Oxford – Schirmer's without anaesthesia < 5mm at 5 minutes • Patients on artificial tears and/or lubricating drops/gel four times a day 	<ul style="list-style-type: none"> • Needle / fingerpick phobia • Systemic infection or on systemic antibiotics • Active ocular infection, active immunological corneal melt, or recurrent corneal erosion • Pregnant or breast-feeding women • Systemic illness causing immune system deficiency • Graft versus host disease • Previous use of autologous serum • Previous use of fingerprick autologous blood (FAB) • Diabetes mellitus

Statistical Analysis

The full analysis set (FAS) comprised all patients randomized into the study. Those who received FAB were analysed according to randomized treatment (intention-to-treat principle). Exploratory tests were performed which suggested that the data was consistent with what is implied by missing at random. Missing data were therefore input as follows: patients who had discontinued after baseline for whom both time point 2 (4 weeks) and time point 3 (8 weeks) evaluation was missing were classified as withdrawn (no actual treatment received) and were subsequently excluded. For patients who completed the end point outside of the protocol window (+14 days) but did not discontinue before month 2, a last observation carried forward (LOCF) was used. Analysis was also performed for the primary efficacy endpoint on the per-protocol set (PPS) which excluded FAB patients with any major protocol deviation.

Descriptive statistics were used to summarize all continuous variables with frequencies used to present categorical variables. The primary efficacy endpoint was OSDI at 8 weeks. Secondary endpoints assessed included: total OSDI score, OCSG, Schirmer's test and TBUT. Data from both eyes was used for OCSG, Schirmer's and TBUT. This was a feasibility study and therefore no sample size calculation is applicable.

Analysis of covariance was used to derive the treatment effect (ie the additional benefit or detriment due to FAB above and beyond control treatment) between baseline and week 8 on OSDI and other continuous endpoints. In addition multivariate analyses were conducted with the following fixed factors: currently on ciclosporin, comorbid auto-immune disease and demographics (age, and ethnicity [non-white vs white]).

Results

A total of sixty patients from two sites were cluster randomised to either the FAB intervention or control arms. Thirty patients were allocated to the intervention and thirty allocated to control arms (Figure 1). Demographics at baseline and

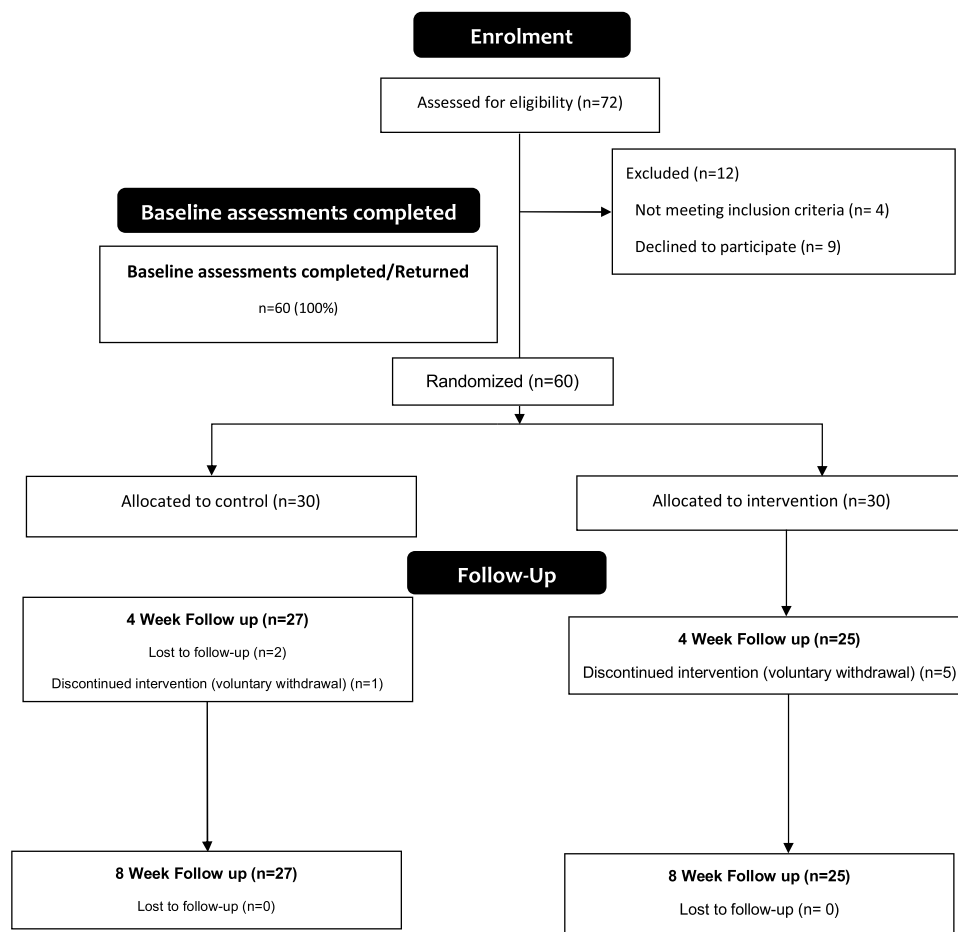


Figure 1 Flow diagram of recruitment.

clinical parameters at baseline and end of follow-up (week 8) are presented in Tables 2 and 3 respectively. The medications at baseline for each arm are in Table 4.

The OSDI decreased by -17.68 in the FAB group compared to -7.04 in the control group ($P=0.02$). Multivariate adjusted results demonstrated a beneficial effect of FAB on OSDI with additional decrease compared to control treatment of 17.50 (95% CI -0.02 to 35.02 , $p=0.05$). Unadjusted intention-to-treat total OSDI scores at week 8 in the FAB arm were also statistically significantly lower than that of the control arm by a mean of 10.14 (95% CI 1 to 50.02 , $p<0.05$). At week 12, after which FAB had been stopped for 4 weeks in the treatment arm, the FAB group maintained their decreased OSDI score with 38.14 (25.47) as did the control group 37.59 (23.28) ($p>0.05$). The other clinical parameters are summarised in Table 4 ($p>0.05$). There were no differences in BCVA at any time point ($p>0.05$). No adverse safety events occurred in either group. There were four withdrawals in the FAB group and two in the control group. Only one withdrawal was due to patient deciding after consent and training that they did not want to administer FAB. No safety issues were identified with the FAB intervention or in the control arm.

Table 2 Patient Demographics in Intervention and Control Arms

Demographics	Randomised Treatment Group		
	Intervention (N= 30)	Control (N= 30)	Total (N= 60)
Age years, n (%)	30 (100)	30 (100)	60 (100)
Mean (SD)	64.07 (9.95)	61.63 (11.57)	62.85 (10.77)
Median (min, max)	65 (41, 82)	61.50 (31, 89)	63 (31, 89)
Sex, n (%)	30 (100)	30 (100)	60 (100)
Male	4 (13.3)	8 (26.7)	12 (20.0)
Female	26 (86.7)	22 (73.3)	48 (80.0)
Ethnicity, n (%)	30 (100)	29 (96.7)	59 (98.3)
White Caucasian	26 (86.7)	24 (82.8)	50 (83.3)
Black African/Caribbean	0 (0)	3 (10.3)	2 (3.3)
Indian/Asian	4 (13.3)	2 (6.9)	7 (11.7)
Autoimmune aetiology of dry eye disease	17	6	23

Table 3 Clinical Parameters in Intervention and Control Arms

Mean Clinical Measure (Standard Deviation)	Schirmer's Total Score		TBUT (Seconds)		OCSG		OSDI	
	FAB	Control	FAB	Control	FAB	Control	FAB	Control
Baseline (N=30 in FAB, N=30 in Control)	7.83 (8.72)	9.45 (9.59)	5.32 (2.89)	5.20 (2.88)	2.35 (1.05)	2.37 (0.96)	57.28 (22.14)	48.19 (20.20)
Week 8 (N=26 in FAB, N=28 in Control)	8.12 (9.83)	10.30 (9.98)	7.06 (3.98)	7.00 (4.64)	1.81 (1.08)	1.91 (0.88)	36.96 (38.58)	41.15 (22.75)
Per-protocol adjusted treatment effect; week 8 – baseline (mean, 95% CI, p-value)	-0.55 (-5.38 to 4.27 , $p=0.82$)		-0.69 (-3.54 to 2.16 , $p=0.63$)		0.13 (-0.51 to 0.77 , $p=0.68$)		-17.68^* (-37.67 to -2.96 , $p=0.02$)	

Note: *p-value <0.05 .

Abbreviations: FAB, fingerprick autologous blood; TBUT, tear breakup time; OCSG, Oxford corneal surface grade; OSDI, ocular surface disease index.

Table 4 Medications at Baseline in Each Arm

	Treatment	Control	Difference Between Groups
Topical Ciclosporin	20	18	$\chi^2 = 2.87$, $p > 0.05$
Topical Steroid	5	4	$\chi^2 = 1.31$, $p > 0.05$
Systemic immunosuppression (for systemic autoimmune disease)	16	6	$\chi^2 = 7.18$, $p < 0.01$
Mean no of lubricants	1.7	1.7	
Doxycycline	4	2	$\chi^2 = 0.74$, $p > 0.05$
Pilocarpine	4	2	$\chi^2 = 0.74$, $p > 0.05$
Acetylcysteine 5%	7	4	$\chi^2 = 1.00$, $p > 0.05$

Discussion

FAB is an emerging haemoderivative treatment for the ocular surface, and it involves the direct application of autologous whole blood to the ocular surface.²⁵ Whole blood is a complex adaptive organ which can take on both liquid and solid forms depending on need²⁶ and is a valuable source of nutritive components and trophic peptides which support ocular surface health and integrity.²⁷ Blood includes components naturally found in tears such as growth factors and fibronectin^{28,29} and is the source of haemoderivative eye drops. Compared to other haemoderivatives, fresh whole blood is unaltered, containing no additives, anticoagulants or excipients. FAB benefits from being cost effective, not requiring refrigeration and available instantly at the time of need.¹⁰

We found significant improvement in symptoms as per the OSDI but not for objective signs of DED which are comparable to findings from a meta-analysis which showed OSDI score is reduced by AS but not Schirmer's, staining or TFBUT.³⁰ Furthermore a Cochrane systematic review of five RCTs comparing AS eye drops with artificial tears found a mean -10.75 (95% CI, -18.12 ; -3.39) reduction in OSDI scores which compares to our -20.32 point reduction. Additionally they found no statistically significant changes in either TBUT or Schirmer's test scores in any of the five RCTs with only one finding surface fluorescein stain improvement.³¹

Limitations of this study include that it was a feasibility study and a larger powered RCT may be able to detect differences in the objective markers of DED such as staining, TFBUT and Schirmer's score. Another limitation is that autoimmune patients were over represented in the FAB arm, however, on multivariate adjustment the OSDI differences were still significant after correcting for this. This study was also not powered by a sample size calculation due to it being a feasibility study and therefore subsequent confirmatory trials for this technique should be powered. A key concern from clinicians is the acceptability to patients of having to prick their fingers several times a day, however, the FAB technique is chiefly suited to those patients who cannot access AS either because of the aforementioned lack of funding or access to appropriate licensed laboratory services to process blood such as in developing nations. Finally, modern finger-lancing devices used primarily by diabetic patients have been described as "virtually pain-free" compared to less comfortable older devices.³² Furthermore, interviews with patients were conducted to ascertain the acceptability of the technique with all saying they would recommend this to family and friends if they had severe DED. The full qualitative data results will be published in a separate manuscript. A further concern is that many patients who require this treatment may be within the elderly group and therefore not comfortable with pricking their fingers. Despite this study being single-masked we could not mask patients themselves as they were self-administering the treatment therefore a placebo effect cannot be entirely discounted.

FAB is potentially a cost effective and readily available treatment option for patient with DED. An adequately powered and well-designed randomised trial is needed to further evaluate the long-term clinical benefit of FAB eye drops in DED and other ocular surface disorders.

Summary

- Serum is an effective but difficult to obtain treatment for ocular surface disease in many clinical settings but particularly in low-to-middle income countries.
- Finger-prick autologous blood (FAB) showed improvement in symptoms as evaluated by ocular surface disease index score was significantly reduced in patients using FAB. No significant effect was demonstrated in the control arm.

Data Sharing Statement

No further data will be shared.

Compliance with Ethics Guidelines

The study conformed to the principles of the Helsinki Declaration 1964 and its later amendments. All patients gave informed consent. Ethical approval from the Health Research Authority (REC 17/EE/0508) in England. No patient identifiable information is published.

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Disclosure

Ali Hassan and Shafi Balal are co-first authors for this study. Shafi Balal, Ali Hassan, Erica Cook, Hakim-Moulay Dehbi, Shahina Pardhan, Rupert Bourne, Sajjad Ahmad and Anant Sharma declare no completing interests or financial conflicts of interest for this work.

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