Comparative role of 20% cord blood serum and 20% autologous serum in dry eye associated with Hansen's disease: a tear proteomic study

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ABSTRACT

Background To compare the role of topically applied serum therapy with preservative-free artificial tear (AT) drops in patients with moderate to severe dry eye in Hansen's disease along with change in tear protein profile.

Methods 144 consecutive patients were randomly divided into three groups. After a baseline examination of clinical parameters, each of the patients received designated modality of topical therapy six times a day for 6 weeks. Post-treatment documentation of clinical parameters was done at 6 weeks, and then at 12 weeks after discontinuation of topical therapy. Analysis of three tear proteins using gel electrophoresis (sodium dodecyl sulfate polyacrylamide gel electrophoresis) was done at baseline, at the first and second post-treatment visits.

Results In the cord blood serum (CBS) group, except for McMonnies score and staining score, all other clinical parameters showed continued improvement in the first and second post-treatment analyses. In the autologous serum (ALS) group, all the clinical parameters except Schirmer's I showed significant improvement in the first post-treatment analysis .This was sustained at a significant level in the second analysis except for tear film break-up time (TBUT) and conjunctival impression cytology grading. In the AT group, all the parameters improved at a non-significant level except for TBUT in the first analysis. In the next analysis, apart from McMonnies score and TBUT, other clinical parameters did not improve. In the ALS and CBS groups, tear lysozyme, lactoferrin levels improved in both post-treatment measurements (statistically insignificant).Total tear protein continued to increase at statistically significant levels in the first and second post-treatment analyses in the CBS group and at a statistically insignificant level in the ALS group. In the AT group, the three tear proteins continued to decrease in both the analyses.

Conclusions In moderate to severe dry eye in Hansen's disease, serum therapy in comparison with AT drops, improves clinical parameters and causes betterment in tear protein profile.

Trial registration number CTRI/2013/07/003802.

INTRODUCTION

Hansen's disease caused by lepra bacilli is one of the most ancient diseases affecting mankind .The socio-economic burden of the disease, especially in this part of the world, is huge. Misconceptions arising out of the fact that the disease is hereditary and incurable are still in vogue in some parts of our society. This causes considerable social apathy towards the sufferers of this disease resulting in high physical deformity. Leprosy currently affects a quarter of a million people throughout the world, with 70% of these cases occurring in India.[1] Against a national prevalence of 0.88/10 000 population (WHO global criteria for leprosy elimination), West Bengal (the area of our study) recorded a prevalence rate of 1–2/10 000 population.[2]

Corneal anaesthesia and xerosis are two important ocular anterior segment involvements in Hansen's disease. In patients with dry eye ocular surface becomes desiccated causing chronic discomfort and in severe cases may lead to a reduction of vision caused by ocular surface changes. These changes are characterised as squamous metaplasia. Several conventional treatments such as artificial tear (AT) drops, topical steroids, special type of contact lenses and punctal occlusion are available for treatment of dry eye. However, all these procedures provide temporary relief by decreasing symptoms and are not directed towards reversing the process of squamous metaplasia. The serum (derived from umbilical cord and autologous blood) contains epitheliotropic factors which are essential for the maintenance of the ocular surface epithelia and recovery of a damaged ocular surface. Formulating a remedy for dry eye in this cohort is of paramount importance because that may improve the quality of life. Against this background, this study is undertaken to compare the role of serum therapy with AT drops along with tear proteomics in patients with moderate to severe dry eye in Hansen's disease.

MATERIALS AND METHODS

One hundred and forty-four consecutive patients of Hansen's disease with bilateral moderate to severe dry eye (Schirmer's I value <5 mm) attending cornea clinic of our Institute between September 2008 and April 2011 were included for this prospective, double-blind, randomised trial. The patients with leprosy were given treatment in the Department of Leprology of our hospital. From there, they were referred to our cornea clinic for ophthalmic evaluation. A total of 276 patients were screened at our cornea clinic during this period. Institutional ethics committee approval and written informed consent from the patients were obtained. Patients having active ocular and lid infections, active keratitis, lid deformity, history of punctal occlusion within last 3 months, immunodeficiency, pregnancy and lactation, were excluded from the study.

After recruitment, each patient underwent subjective interview of symptoms (McMonnies

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questionnaire),[3] detailed slit lamp examination of anterior segment including tear film break-up time (TBUT) (expressed in seconds), Schirmer's I test (expressed in millimetres), fluorescein staining of ocular surface and sampling for conjunctival impression cytology (CIC).[4] Analysis of different proteins (lactoferrin, lysozyme and total tear protein) present in tear fluid collected on Schirmer's strips (Whatman number 41 filter paper, Millipore India Limited,Bengaluru, India) was done using gel electrophoresis (sodium dodecyl sulfate polyacrylamide gel electrophoresis, figure 1).[5]

Staining score of ocular surface

The visible area of the eye was divided into three zones formed by imaginary vertical lines at either side of the limbus. Each zone was given a score depending upon the degree of staining contained, from 0 for no staining, through 1 for mild staining and 2 for moderate staining to 3 for severe staining. A total score (range from 0 to 9) was calculated by adding the scores for the three zones of the ocular surface.

Conjunctival impression cytology sampling

Surface anaesthesia was obtained by putting a drop of 0.5% proparacaine hydrochloride. After excess of tear fluid was wiped out, cellulose acetate filter paper (5×7 mm) was pressed onto the nasal and temporal bulbar conjunctiva by flattened forceps. The cellulose acetate paper was smoothed onto ocular surface by stroking it with the forceps tip. The filter paper was removed by the forceps tip in a peeling manner. It was then kept in the properly labelled sample bottle having fixative solution (glacial acetic acid 5 mL, 37% formaldehyde 5 mL and 70% alcohol 100 mL). After proper staining as described by Tseng SC, the goblet cells were counted in 400× magnification. The mean total of ten such areas were recorded for each specimen. The mean nasal and temporal bulbar conjunctival densities for each eye were averaged and reported as goblet cell densities per high power field (field area=0.1885 mm^2). CIC sampling score was done based on epithelial cell morphology and goblet cell density (figure 2).

All the pretreatment baseline parameters were recorded. We initially recruited a total of 156 patients (52 patients for each of three groups). Subsequently 12 patients (four patients from the cord blood serum (CBS) group and eight patients from the AT group) were lost to follow-up and 144 patients completed the study. Total number of cases were randomised into three groups and were given 20% CBS (group A, n=48), 20% autologous serum (ALS) (group B, n=52) and preservative-free ATs (group C, n=44), each six times a day for 6 weeks.

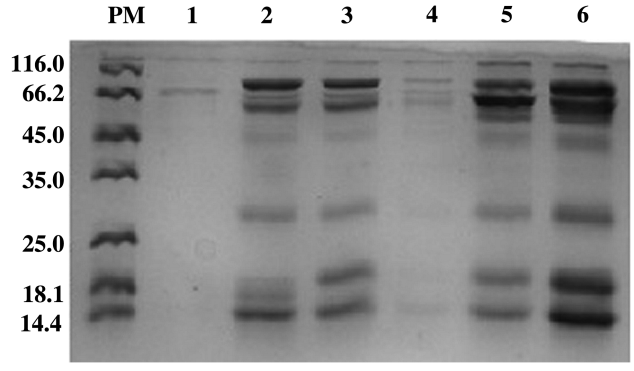

Figure 1 Gel electrophoresis pattern of tear proteins.

Preparation of cord blood serum

The umbilical cord blood was collected from the placenta obtained from elective caesarean section cases performed in the department of obstetrics of our medical college. Written informed consent was obtained from the mothers undergoing caesarean section. Screening for syphilis, hepatitis B, hepatitis C and HIV was done. The blood (100 mL) was collected by directly cannulating the umbilical vein under sterile conditions. The blood was allowed to drain by gravity from the placenta. No anticoagulant was used during the procedure. The blood was allowed to coagulate and the supernatant serum was centrifuged at 1500 rpm for 5 min. It was then diluted using sterile saline solution and given to the patients in glass containers as a 20% solution. No antibiotic preservative was used. The serum was dispensed in sterile glass dropper bottles labelled with date of production and a unique randomisation number. Similar looking glass bottles were used for dispensing the study medications. The patients were instructed to store the bottles (3 mL) frozen and to open a new bottle each day for application. The used bottles are to be returned to the cornea clinic in each visit. They were instructed to report to the clinic immediately if there was any discolouration or thread-like floating objects noted in the serum.

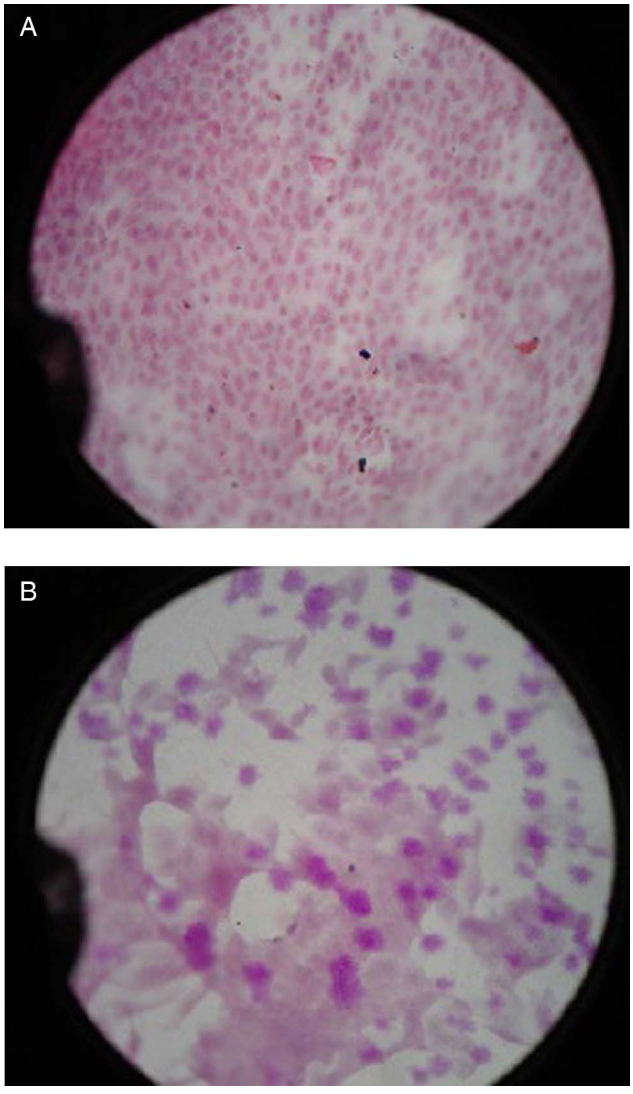

Figure 2 Goblet cell density before (A) and after (B) cord blood serum therapy in conjunctival impression cytology sampling.

Table 1 Change in different clinical parameters and tear protein profile in patients of group A (CBS)

Parameters	Pretreatment analysis (am±SD)	First post-treatment analysis (am±SD)	Second post-treatment analysis (am±SD)
Schirmer's I value	2.93±1.21	7.64±5.89, p=0.0097	10.36±9.79, p=0.1732
McMonnies score	13.71±2.46	8.57±2.87, p<0.0001	5.14±3.30, p<0.0001
Intensity value of tear lactoferrin	5.52±3.53	7.10±4.44, p=0.2482	8.49±5.96, p=0.07
Intensity value of tear lysozyme	3.04±5.30	3.67±6.35, p=0.35	4.00±7.56, p=0.60
Intensity value of total tear proteins	22.28±10.76	28.2±16.88, p=0.03	36.22±23.03, p=0.02
TBUT	6.28±1.50	21.78±7.17, p<0.0001	22.71±8.07, p=0.55
Staining score	8.71±0.47	4.93±1.68, p=0.0001	2.4286±2.90, p=0.0002
CIC grading	2.57±0.51	0.86±0.66, p<0.0001	0.86±0.66, p=0.05

p<0.05 is statistically significant.
am±SD: arithmetic mean±SD.
CBS, cord blood serum; CIC, conjunctival impression cytology; TBUT, tear film break-up time.

Preparation of autologous serum

For preparation of ALS, 40 mL of blood was taken by venepuncture from the antecubital vein. After centrifugation at 1500 rpm for 15 min, the serum was extracted. This was diluted to 20% concentration using sterile normal saline solution. No antibiotic preservative was used. Mode of dispensing and storage protocol was same as the CBS group. Patients were asked to report to the institutional cornea clinic immediately if their symptoms worsened or if any unusual reactions developed.

Following discontinuation of topical therapy all the above-mentioned tests were repeated for 6 weeks (first post-treatment) and for 12 weeks (second post-treatment) later. All the results were documented and analysed. The statistical analysis was done using SPSS V.17. Paired t tests were carried out, separately for each eye, to compare differences in mean values between individual groups. Wilcoxon signed rank test was used as a test of significance involving non-parametric data. A p value <0.05 was considered statistically significant.

Randomisation: a register was maintained for all patients and each patient was assigned a serial number. Patients were assigned to any of the three groups with the help of a computer generated random number table (MS Excel).

RESULTS

In the first post-treatment visit among group A (CBS) patients, clinical parameters like Schirmer's I value, McMonnies score, TBUT, staining score and CIC grading were significantly improved, the p value being 0.0097, <0.0001, <0.0001, 0.0001 and <0.0001, respectively.The McMonnies score and staining score had significantly decreased in the second post-treatment visit, the p values being <0.0001 and 0.0002, respectively. The changes in the other clinical parameters in the second post-treatment visit (Schirmer's I score, TBUT and CIC grading) were not statistically significant, p values being 0.1732, 0.55 and 0.05, respectively. In the first post-treatment visit, there was an increase in the intensity value of tear lactoferrin and lysozyme (statistically not significant, p values being 0.2482 and 0.35, respectively). However, the increase in the intensity value of total proteins was found to be statistically significant (p=0.03). In the next post-treatment evaluation, there was an increase in the intensity values of tear lactoferrin and lysozyme (statistically not significant, p values 0.07 and 0.60, respectively). There was a statistically significant increase in the intensity value of total proteins at this visit (p=0.02) (table 1).

Among group B patients (ALS), clinical parameters like Schirmer's test I, McMonnies score, TBUT, staining score and CIC grading were improved at statistically significant levels in the first post-treatment visit except for Schirmer's I value, the p values being 0.13, 0.0002, 0.0046, 0.0136 and 0.0409, respectively. The Schirmer's I test value, McMonnies score and staining score had significantly improved in the subsequent analysis, the p values being 0.02, 0.0071 and 0.0274, respectively . The changes in the other clinical parameters in the second post-treatment visit (TBUT and CIC grading) were not statistically significant, p values being 0.2338 and 0.1747, respectively. In the first visit, there was an increase in the intensity value of tear lactoferrin, lysozyme and total protein (p values being 0.7703, 0.7397 and 0.49, respectively, statistically not significant). In the next visit there was an increase in the intensity values of tear lactoferrin, lysozyme and total protein but this change was not statistically significant (p values 0.8742, 0.8275 and 0.2407, respectively) (table 2).

Among group C (AT) patients, clinical parameters like Schirmer's I value, McMonnies score, TBUT and staining score

Table 2 Change in different clinical parameters and tear protein profile in group B (ALS)

Parameters	Pretreatment analysis (am±SD)	First post-treatment analysis (am±SD)	Second post-treatment analysis (am±SD)
Schirmer's I	3.67±1.21	9.83±8.68, p=0.13	12.17±8.38, p=0.02
McMonnies score	13±3.10	7.67±4.23, p=0.0002	4.33±3.72, p=0.0071
Intensity value of tear lactoferrin	8.19±4.82	8.84±4.28, p=0.7703	9.58±5.55, p=0.8742
Intensity value of tear lysozyme	7.1±3.32	7.66±3.48, p=0.7397	8.16±7.41, p=0.8275
Intensity value of total tear proteins	48.98±28.60	52.94±25.34, p=0.49	61.93±47.9, p=0.2407
TBUT	5.83±1.33	19.33±7.00, p=0.0046	21.5±10.15, p=0.2338
Staining score	8.33±0.52	5.83±1.83, p=0.0136	3.67±3.39, p=0.0274
CIC grading	2.33±0.52	1.33±0.52, p=0.0409	1±0.89, p=0.1747

p Value <0.5 is statistically significant.
am±SD: arithmetic mean±SD.
ALS, autologous serum; CIC, conjunctival impression cytology; TBUT, tear film breakup time.

Table 3 Change in different clinical parameters and tear protein profile in group C (AT)

Parameters	Pre treatment analysis (am±SD)	First post treatment analysis (am±SD)	Second post treatment analysis (am±SD)
Schirmer's I	4±1.55	4.25±0.96, p=0.3910	4±1.55, p=0.1753
McMonnies score	14±2.31	12.5±0.58, p=0.1871	10.75±0.96, p=0.006
Intensity value of tear lactoferrin	9.26±3.99	7.06±2.52, p=0.3910	4.90±3.42, p=0.0113
Intensity value of tear lysozyme	2.56±3.16	1.36±2.71, p=0.2701	0, p=0.3910
Intensity value of total tear proteins	25.45±9.34	23.04±3.89, p=0.506	14.17±4.74, p=0.07
TBUT	7.25±1.71	12.5±1.91, p=0.0087	9.25±0.96, p=0.0227
Staining Score	8.25±0.5	8.0±0.82, p=0.3910	8.0±0.82, p=0.0852
CIC grading	2±0	2±0	2±0

p Value <0.05 is statistically significant.
am±SD: arithmetic mean±SD.
AT, artificial tear; CIC, conjunctival impression cytology; TBUT, tear film breakup time.

improved in the first post-treatment analysis but the change was not statistically significant except for TBUT, the p values being 0.3910, 0.1871, 0.0087 and 0.3910, respectively. There was no change in the CIC grading. The McMonnies score and TBUT had significantly improved in the second post-treatment evaluation, the p values being 0.006 and 0.0227, respectively. The other clinical parameters in the second post-treatment evaluation did not improve. In the first visit, there was a decrease in the intensity value of tear lactoferrin, lysozyme and total proteins (p values being 0.3910, 0.2701 and 0.506, respectively, statistically not significant). In the next analysis, there was a decrease in the intensity value of tear lactoferrin (statistically significant, p=0.0113). There was a further decrease in the intensity of tear lysozyme and total proteins which was not statistically significant (p values 0.3910 and 0.07, respectively) (table 3).

DISCUSSION

The anterior segment of eye involvement in leprosy includes lagophthalmos, ectropion, corneal anaesthesia and dry eye. Abnormal TBUT, reduced mucin secretion in tear film coupled with high relative humidity is responsible for corneal morbidity among patients with leprosy in India. Corneal anaesthesia (due to involvement of trigeminal nerve) is an important cause of dry eye as proper corneal sensation is required for production of tear.[6] A lack of proper and prolonged wetting of ocular surface also contributes to pathogenesis of dry eye in patients with leprosy.[7]

Patients with long-standing dry eye develop features of squamous metaplasia on the ocular surface which contributes to conjunctiva-corneal morbidity and visual loss. Serum therapy is the only proven modality to reverse the surface changes in such patients as it provides a good source of growth factors (nerve growth factor, transforming growth factor (TGF)-β, substance P and fibronectin). Tsubota *et al*[8] have demonstrated that 20% ALS is a good source of epidermal growth factor, TGF β and vitamin A. Concentrations of these proteins remained stable when stored at 4° C for 1 month. When used in a 2-month placebo-controlled trial in patients with bilateral severe dry eye, ALS is found to be safe and effective in improving subjective symptoms and objective signs significantly (staining score and CIC grading). But the Schirmer's I and TBUT scores didn't improve.[9] This was similar to our study where we found an improvement of clinical parameters at a statistically significant level (except Schirmer's I) after a 6-week 20% topical ALS therapy. The improvements were sustained for 12 weeks after discontinuation of ALS therapy for most of the clinical parameters at statistically significant levels except CIC grading and TBUT in our study. Similar observations were reported by Kojima *et al*[10] who had demonstrated significant improvement in the subjective symptom score, break-up time and staining score in patients with severe dry eye after a 2 week course of ALS as compared with preservative-free AT drops. Safety and efficacy of ALS in keratoconjunctivitis sicca and persistent epithelial defect (as compared with unpreserved 0.3% hydroxymethylcellulose drops) had been reported in the literature.[11] Yoon *et al*[12] used 20% CBS in neurotrophic keratitis cases and concluded that it hastens the healing of epithelial defect and improves corneal sensitivity. Similar studies also establish the efficacious role of CBS in healing persistent epithelial defects.[13 14] When both CBS and ALS are compared, 20% CBS had been more effective in decreasing symptoms and keratoepitheliopathy in severe dry eye syndrome and increasing goblet cell density in Sjogren's syndrome than 20% ALS drops.[15] When applied in patients with severe dry eye, both ALS and CBS improved symptom score, keratoepitheliopathy score, break-up time and CIC grading at 1 month and 2 months after serum therapy.[16] In our study though, we did not find any statistically significant difference of response between the CBS and the ALS groups.

Danjo *et al* in a tear proteomics study established that the secretory function of the lacrimal gland can be assessed by estimating the tear lactoferrin level that is reduced in Sjogren's syndrome.[17] Reduced tear lysozyme may be used as a subclinical marker of lacrimal gland involvement in collagen diseases.[18] Tear lipocalin and total protein are reduced in Sjogren's syndrome as compared with keratoconjunctivitis sicca (p<0.0001).[19] In the ALS and the CBS groups in our study, tear lysozyme, lactoferrin and total tear protein continued to increase in the first and the second post-treatment analyses. In the AT group the three tear proteins continued to decrease in both the analyses. Literature search did not yield any references of the tear proteomics study in Hansen's disease. With serum therapy we did find a favourable response in tear protein profile among patients with moderate to severe dry eye in Hansen's disease. As the ATs lack trophic factors, they simply act as lubricants. The epitheliotropic factors present in serum play an important role in the proliferation, differentiation and maturation of ocular surface epithelium. This helps in the amelioration of symptoms of keratoepitheliopathy in patients with dry eye of various aetiologies including Sjogren's syndrome and Graft-versus-host disease.[20]

The site of the current study is India with a high prevalence of patients with Hansen's disease with ocular involvement. Not all of them have access to institutes with tissue banking facilities, which prepares and dispenses CBS. In that perspective and

against our background, ALS may be advantageous as it is readily available from the patients themselves. The need for a functioning tissue bank with facilities for collection, processing, storage and disposition of serum obviously demands increased cost of therapy as compared with the tear drops group. This justifies the decreasing cost of therapy from the CBS through the ALS to the AT groups.

Our study has a few limitations. The patients, depending on their clinical classification (multibacillary or paucibacillary), received standard multidrug therapy as advocated globally by WHO along with the designated modality of topical therapy. This systemic antileprosy therapy may act as a confounding factor influencing clinical outcomes.

Clinical response to serum therapy supplemented by laboratory work showing in vitro toxicity profile of ATs and serum on corneal epithelial cells along with effect of serum on mucin expression on cultured conjunctival epithelial cells in vitro would have been a better study design. Perhaps, a proteomics study with longer follow-up might answer whether the improvement in tear protein profile after serum therapy is sustained or not. We may conclude that serum therapy was superior to AT drops among patients with moderate to severe dry eye in Hansen's disease.

Contributors SM and SS contributed to the clinical studies, data acquisition, literature search, data analysis and manuscript preparation. SS contributed to laboratory work and statistical analysis. HD contributed to the concept, study design, definition of intellectual content, data analysis, literature search and manuscript review.

Competing interests None.

Ethics approval Institutional Ethical Committee, RIO, Kolkata.

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Notes