Original Article

Role of Topical Human Milk in the Treatment of Neurotrophic Corneal Opacity

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Purpose: To study the effect of topical human milk on neurotrophic corneal opacity.

Material and Methods: This observational clinical analysis was done at Departments of Ophthalmology, Liaquat University of Medical & Health Sciences Jamshoro, Azra Naheed Medical College Lahore, and College of Medicine and Dentistry Lahore from June 2005 to June 2011 to determine effects of human milk on forty three (28 male and 15 female) patients within 55 years of age, having neurotrophic corneal opacity. Three patients were dropped due to incomplete follow up. Forty patients with neurotrophic cornea, sixteen non insulin dependent diabetics, and twenty four with previous viral keratitis were included in the study After taking informed consent these patients were put on topical human milk and tobramycin 0.3% eye drops four times daily. Before treatment every patient was seen on slit lamp to assess size, site, level and density of opacity. Thickness and vascularization of cornea, condition of endothelium, and any reaction in the anterior chamber was also noted. Corneal staining was done to rule out ulcer and tear strip along the inner border of lower lid was also noted to see the level of dryness associated with neurotrophic cornea. Best corrected visual acuity was recorded and corneal sensitivity was tested with a cotton tip. Sensitivity to chemical stimulation was also determined with diclofenac sodium eye drops by noting intensity of burning sensation. Follow up was done for six months, on day 7, day 15 and monthly. The beneficial and adverse effects were noted and results were compiled. Only forty patients who completed six months follow up were included in the final result analysis.

Results: Treatment response began within 15 days of instillation of topical human milk, corneal sensitivity improved in 24 (60%) eyes and visual acuity improved in 28 (70%). Transient conjunctival hyperemia was noted in most of the patients. Out of forty patients (28 male 12 female) 32 patients (80%) achieved nearly complete recovery of corneal transparency by last follow up. 8 (20%) diabetic patients failed to respond completely. Bacterial conjunctivitis occurred in 6 (15%) patients.

Conclusion: Human milk helps in restoring corneal transparency in neurotophic corneal opacity, especially in patients with previous viral keratitis.

Corneal diseases are a major cause of blindness, second only to cataract in overall importance[1]. Furthermore, persons with corneal blindness are of a younger age group compared with those suffering from cataract. Therefore, in terms of total blind years, the impact of corneal blindness is greater. The cornea is a virtually avascular tissue, but it has very dense innervation (40 times more than the tooth pulp and 400 times more than skin)[2].

Nerve growth factor plays a special role in growth and differentiation of peripheral sensory nerve cells and help in repairing the damaged nerve fibers[3]. Thus, any inflammatory reaction and subsequent healing are controlled by this neuronal innervation[4]. Corneal

sensitivity threshold is significantly higher in male than female (females more sensitive). Reduction in corneal threshold (increase in sensitivity) occurs with age in females but not males[5]. Corneal nerves damage impairs epithelial healing and induces trophic keratopathy even in the absence of injury or infection[6]. According to Mackie classification[7,8], neurotrophic keratopathy is divided into three stages. Stage 1: is dry eye, with resultant vascularization and scarring of cornea. Stage 2: is non healing corneal epithelial defect. Stage 3: is stromal melting leading to perforation. Treatment of neurotrophic keratopathy at stage 1 is therefore necessary to prevent further complication, and to restore corneal function. Unfortunately available treatments do not help the patient to the level of their satisfaction.

Several ocular and systemic diseases, including fifth-nerve palsy, viral infections, chemical burns, corneal surgery, abuse of topical anesthetics, diabetes mellitus, leprosy, and multiple sclerosis, can cause sensory-nerve impairment[8].

Loss of corneal sensation leads to a decrease in the number of corneal stem cells[9], decreased metabolic and mitotic rates in the corneal epithelium[10]. The result is progressive corneal damage with epithelial defects, vascularization, stromal scarring, ulceration, and ultimately perforation even in the absence of injury or infection. In viral keratitis interaction with host immunity results in corneal opacity[11].

The standard treatment of corneal opacity is expensive, often ineffective, and the outcome may be loss or severe impairment of vision. New drug modalities such as epidermal growth factor, nerve growth factor, fibroblast growth factor (FGF-2), vascular endothelial growth factor etc have been found effective in achieving normal corneal integrity. Majority of these growth factors are present in the human milk including NGF[12]. Growth factor activity is present throughout the lactation period in the human milk but in bovine milk only during the colostral phase[13].

Human breast milk is still in use as Traditional Eye Medicine (TEM) for corneal ulcer in rural areas. However, no clinical research has been conducted so far to see its beneficial or adverse effects on the human eye. This study will therefore be the first of this nature.

MATERIAL AND METHODS

Before treatment, informed consent was taken from all the patients. Dignity, honor, and privacy of patient and the human milk provider were always maintained. Observational clinical analysis was then carried out on patients of either sex having corneal opacity accompanied with decreased corneal sensitivity and negative conjunctival swab culture. Patients having neurotrophic corneal opacity due to viral keratitis (Mackie classification stage 1), long standing disciform keratitis, recurrent viral keratitis and long standing diabetes with neurotrophic cornea were registered for study. Initial examination was performed in outpatient department. After getting informed consent, detailed history was taken which included; age, sex, residency, occupation, any previous history of trauma to eye, and socioeconomic condition. The data was also collected related to any surgery which can damage trigeminal nerve, topical medication, corneal surgery, associated systemic disease and family history.

Best – corrected visual acuity was noted using Snellen's chart. Slit lamp examination of normal and affected eye was done, and where possible dilated indirect ophthalmoscopy with 90D was also performed. Corneal staining of affected eye was done to rule out active ulcer, for which one drop of fluorescein 1% was used. The corneal opacity was examined for size, site, density, location and invasion of blood vessels. All layers of cornea and anterior chamber were examined carefully on slit lamp. Corneal sensitivity was tested with cotton tip at the center of the cornea of affected eye. When the cornea was touched with cotton tip, the sensitivity was considered normal if a blink reflex was present. If the patient felt contact but had no blink reflex corneal hypoesthesia was diagnosed, and if no response was present corneal anesthesia was diagnosed. Corneal/ conjunctival sensitivity to chemical stimulation was also determined by noting a burning sensation after conjunctival instillation of a pungent substance in the affected eye of patient[14] for which Naclof (diclofenac sodium) eye drops were used in the affected eye. Short term use of non steroidal anti-inflammatory drugs (NSAID) are harmless to ocular surface and do not decrease corneal sensitivity and tear secretion[15].

Intraocular pressure was checked with air puff tonometer in both eyes. Conjunctival swab sampling, culture, and random blood glucose assessment was performed by the pathologist in the laboratory.

The patients were then put on topical human milk four times daily. Every patient requested the healthy nursing woman at his or her home or any other

nursing woman for fresh milk four times daily. The milk was taken in a clean stainless steel spoon and used by the patient with the help of sterilized dropper immediately. Topical tobramycin 0.3% ophthalmic drops were also used four times daily to prevent bacterial infection.

Follow up was done on day 7, day 15, and then every month up to 6 months. On every follow up visit complete assessment including visual acuity, size and thickness of corneal opacity, corneal sensitivity, and any complication was noted. Same research protocol was used by all the authors and all patients were discussed online to maintain uniformity.

DATA ANALYSIS

SPSS 14.0 (Statistical Package for Social Sciences) was used for statistical analysis. Paired t-test was used to assess visual acuity in numbers of eyes before and after treatment with human milk in patients with diabetic neurotrophic and viral neurotrophic corneal patients. For data analysis visual acuity was used in decimals. Mean visual acuity before management was 0.2 and after management was 0.7, independent sample test was performed to see significant difference between two groups. There was significant difference in visual outcome between viral and diabetic neurotrophic corneal opacity patients, P value 0.004.

RESULTS

Out of 43 recruited patients of neurotrophic corneal opacity, only 40 patient completed full follow up of six months. Three patients with incomplete follow up were dropped from study. Among these 40 patient 16 were diabetic and 24 with previous viral keratitis. Majority of these patients were from rural areas and most of them were poor. Most of these patients were previously treated with acyclovir due to decreased corneal sensitivity (table 1).

These patients had either central or paracentral corneal opacity which was visible with naked eye (Figure 1 and 2) and reduced corneal sensitivity. Size of corneal opacity ranged between 2 to 5 mm. In diabetic patients skin sensitivity was also affected on the extremities along with corneal sensitivity but in viral patients peripheral skin sensation was normal. Best corrected visual acuity ranged between hand movements to 6/24 before treatment (table 2).

Table 1: Bio-data of patients

Total recruited patients	43
Dropped from study (incomplete follow up)	03
Patients completed follow up of 6 months	40
Male	26
Female	14
Age	20 to 55 years
Diabetic more than 10 years	16 Patients
Previous Viral keratitis	24 Patients
Socioeconomic condition	Middle and lower class
Residency	32 Rural 8 urban
Past medical history	acyclovir eye ointment

Table 2: Clinical status of the patients before treatment n = 40

Clinical Findings	Diabetics n = 16	Viral Keratitis n = 24
Size of corneal opacity	1 - 4 mm	2 -5 mm
Density of opacity	Visible with naked eye	Visible with naked eye
Level of corneal	Hypoesthesia to	Hypoesthesia
Insensitivity	Anesthesia	
Visual acuity	Hand movement to 6/24	6/60 to 6/24

Response to treatment was observed within 15 days following topical use of human milk. Viral induced neurotrophic corneal opacity responded much better than diabetic neurotrophic opacity. 32 patients (80%) achieved nearly complete transparency of cornea within 30 to 90 days of treatment (figure 3 and 4). Corneal sensitivity improved in 24 (60%) eyes and reported a burning sensation after conjunctival instillation of Naclof (diclofenac sodium) eye drops. Eight patients in whom corneal clarity occurred

without significant improvement in sensitivity were diabetic.

Best corrected visual acuity improved in 28 (70%). Visual acuity did not improve in two diabetic patients due to cataract although cornea became clear. Transient conjunctival hyperemia was noted in nearly all cases during initial treatment. 8 (20%) patients did not respond completely. Bacterial conjunctivitis occurred in 6 (15%) patients which recovered with frequent use of tobramycin eye drops. Post-treatment findings are given in table 3. Complications were mostly encountered in diabetic and malnourished patients.

Table 3: After treatment with topical human milk
n = 40

Clinical Findings	Diabetic	Viral	Total n (%)
Improved corneal transparency	10	22	32 (80)
Improved corneal sensitivity	02	22	24 (60)
Visual acuity achieved 6/18 to 6/6	06	22	28 (70)
Fully satisfied in relation to opacity	08	22	30 (75)
Conjunctivitis	06	00	06 (15)

The mean duration of treatment was 55 days. The first sign of good response on slit lamp examination was reduction in scar size in subepithelial layers (bowman's and stroma). Feeling of burning to Naclof eye drops was also noted. Burning sensation indicates recovery of corneal sensation. These ocular findings gradually disappeared and cornea became completely clear.

The improvements in corneal sensitivity and visual acuity were maintained throughout the follow-up period. None of the patients had systemic side effects during treatment with human milk. Moreover, none had a relapse of their eye disease during follow-up.

DISCUSSION

Persistent corneal epithelial defects due to decreased corneal sensitivity result in corneal scarring, neovascu-

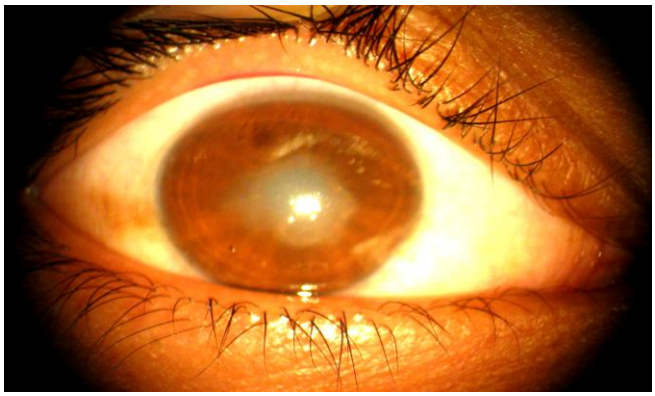

Fig. 1: Central corneal opacity.

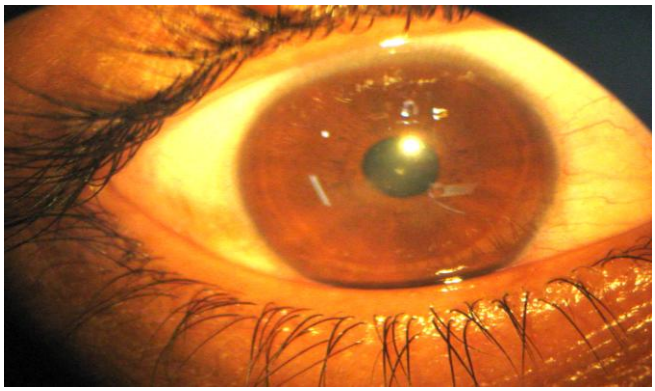

Fig. 2: Clear cornea after treatment

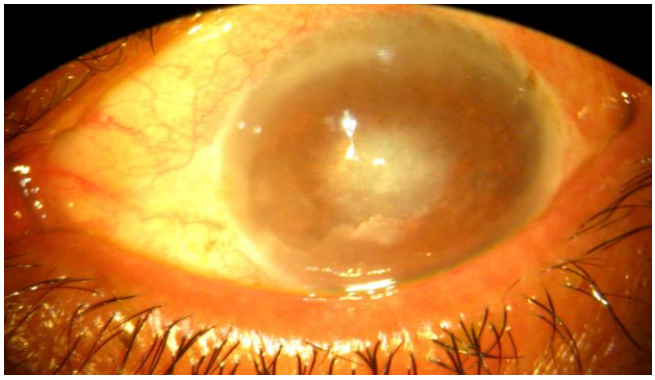

Fig. 3: Before treatment

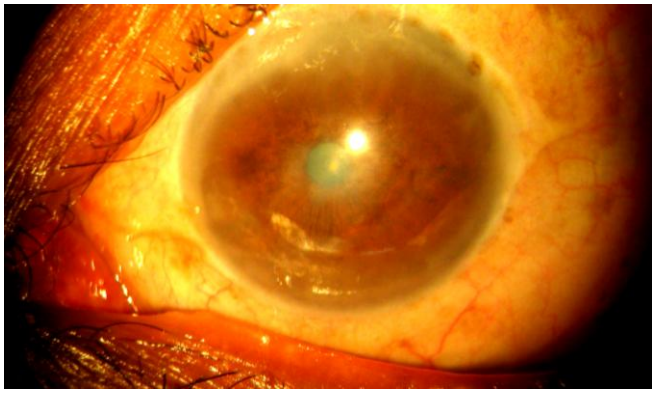

Fig: 4: after treatment

larisation, and decreased vision. Threshold corneal sensitivity level is required which can maintain anatomical and functional integrity of cornea[16].

Many ocular and systemic conditions provoke a loss in corneal sensitivity sufficient to alter anatomical and physiological integrity of cornea: surgical treatment of trigeminal neuralgia and acoustic neuroma, ocular viral infection, diabetes, corneal graft, LASIK, chemical burns, multiple sclerosis, local anesthetics and anti-inflammatory medication, contact lenses, familia dysautonomia. It is not possible to reverse corneal sensory loss in all these conditions, however corneal sensitivity can be improved where the cause of sensory loss is viral, contact lens, or local anesthetic.

Topical use of growth factor, sensory neurotransmitter or human milk cannot restore corneal sensory loss in systemic disease with[17] generalized neuropathy, however local neurotrophic corneal opacity do respond to topical treatment; with human milk, individual growth factor, or neurotransmitter which is deficient in neurotrophic cornea. The effect of NGF is mediated through $TrkA^{NGFR}$ and $p75^{NTR}$ receptors[18]. Several studies showed that loss of NGF receptor $TrkA^{NGFR}$ (tropomyosin receptor kinases) develop corneal opacity and impairment of corneal sensitive nerves.

Human milk contains nerve growth factor in reasonable concentration which is maintained throughout the lactational period. Lactoferrin plays an important role in the defense against infections, including herpes simplex virus (HSV) keratitis[19]. Lactoerrin is an iron binding protein. It is very abundant in colostrum. Lactoferrin can inhibit viral infection by binding tightly to the viral envelope protein.

Neurotrophic cornea is usually accompanied by a reduction of tears or a reduced blinking of the lids which further aggravates the condition. Human milk contains not only growth factors and lactoferin but also tear components, like fat water and electrolytes, which helps in maintaining tear film. Human milk therefore covers all aspects of the problem.

We have found human milk very effective in eliminating corneal opacity associated with corneal hypoesthesia. These are the growth factors and lactoferrin in the human milk which play important role in the elimination of neurotrophic corneal scar. Nutritional factors in the human milk may also have positive effect in this process. However extent of response to human milk varies from patient to patient depending on cause of neurotrophic corneal opacity, age and general health of the patient.

Human milk therefore, inhibits viral infection, clears corneal opacity, improves corneal sensitivity, and restores corneal integrity with minimal complications and little expense. Human milk contains significantly more lactose, even more than cow's milk and this may also stimulate the growth of microorganisms[20] but this can be prevented by topical use of antibiotic (tobramycin 0.3%).

During treatment some patients had photophobia and burning of their eyes during slit-lamp examinations, which suggests functional recovery of corneal innervation. The maintenance of corneal sensitivity after treatment with human milk suggests that such treatment completely restores sensory innervation of the cornea mainly in viral patients.

Conjunctivitis was main side effect reported during the treatment. No relapse of the disease was observed during the follow-up period in the patients who responded to treatment, but relapse is possible in neurotrophic cornea due to systemic disease, as in diabetes.

Because no other study has been so far conducted directly on human milk therefore results cannot be compared with other studies, however individual growth factors like epidermal growth factor[21], nerve growth factor[22], and vascular endothelial growth factor[23] are effective in neurotrophic keratopathy. Our results are comparable with nerve growth factor which restores corneal integrity.

CONCLUSION

Human milk is effective in restoring corneal transparency in neurotophic corneal opacity, especially in viral neurotrophic cornea, if risk of bacterial infection is controlled with topical antibiotics. The treatment is easy to use, available everywhere, and cost effective especially in developing country. However we do not recommend its use until the facts are fully established by case and control study. The results can be improved further by using bensalkonium chloride free antibiotic and good nutrition for malnourished patients.

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REFERENCES

1. **Oliva MS, Schottman T, Gulati M.** Turning the tide of corneal blindness Indian J Ophthalmol. 2012; 60: 423-7.
2. **Bonini S, Lambiase A, Aloe L, Mantelli F, Sacchetti M, Rocco ML.** Capsaicin-induced corneal sensory denervation and healing impairment are reversed by NGF treatment. Invest. Ophthalmol. Vis. Sci, 2012; 53: 8280-7.
3. **Levi-Montalcini R**. The nerve growth factor 35 years later. Science. 1987; 237: 1154-62.
4. **Tervo K, Latvala TM, Tervo TM.** Recovery of corneal innervation following photorefractive keratoablation. Arch Ophthalmol. 1994; 112: 1466-70.
5. **Golebiowski, Blanka Boptom, Papas, Eric B, Faao; Stapleton, Fiona Mcoptom.** Faao Factors affecting corneal and conjunctival sensitivity measurement Optometry and Vision Science. 2008; 85: 241-6.
6. **Price FW Jr, Whitson WE, Marks RG.** Graft survival in four common groups of patients undergoing penetrating keratoplasty. Ophthalmology. 1991; 98: 322-8.
7. Groos, E. Cornea, 2004; 94: 1189–1196.
8. **Mackie IA.** Neuroparalytic keratitis. In: Fraunfelder FT, Roy FH, eds. Current ocular therapy, Philadelphia W.B. Saunders; 1995: 506-8.
9. **Puangsricharern V, Tseng SCG.** Cytologic evidence of corneal diseases with limbal stem cell deficiency. Ophthalmology. 1995; 102: 1476-85.
10. **Sigelman S, Friedenwald JS.** Mitotic and wound-healing activities of the corneal epithelium: effect of sensory denervation. Arch Ophthalmol. 1954; 52: 46-57.
11. **Shtein RM, Elner VM.** Herpes simplex virus keratitis: histopathology and corneal allograft outcomes Expert Rev Ophthalmol. 2010; 5: 129-34.
12. **Gaull GE, Wright CE, Isaacs.** Significance of growth modulators in human milk pediatrics. 1985; 75: 142-5.
13. **YW Shing, M Klagsbrun** Human and bovine milk contain different sets of growth factors. Endocrinology. 1984; 115:273-82.
14. **Faulkner WJ, Varley GA.** Corneal diagnostic technique. In: Krachmer JH, Mannis MJ, Holland EJ. Cornea: fundamentals of cornea and external disease. St. Louis: Mosby–Year Book, 1997: 275-81.
15. **Yanai K, Huang J, Kadonosono K, Uchio E.** Corneal sensitivity after topical bromfenac sodium eye-drop instillation Clinical Ophthalmology. 2013; 7: 741-4.
16. **Dogru M, Yildiz M, Baykara M, Ozçetin H, Erturk H.** Corneal sensitivity and ocular surface changes following preserved amniotic membrane transplantation for non healing corneal ulcers Eye. 2003; 17: 139-48.
17. **Nishida, Teruo, Yanai, Ryoji.** Advances in treatment for neurotrophic keratopathy Current Opinion in Ophthalmology. 2009; 20: 276-81.
18. **You L, Kruse FE, Hans E.** Volcker Neurotrophic Factors in Human Cornea Investigative ophthalmology and visual science. 2000; 41: 692-702.
19. **Keijser S, Jagar MJ, Dogterom – Ballering, Schoonderwoerd, Krose, JJ. Houwing – Duistermaat.** Lactoferrin Glu561Asp polymorphism is associated with susceptibility to herpes simplex keratitis. Experimental eye research. 2008; 86: 105-9.
20. **Prajna VN, Pillai MR, Manimegalai TK, Srinivasan M.** Use of traditional eye medicines by corneal ulcer patients presenting to a hospital in South India Indian Journal of Ophthalmology. 1999; 47: 15-8
21. **G Carpenter.** Science promoting agent in breast milk. Science, 1980; 210: 198-9.
22. **Lambiase A, Rama P, Bonini S, Caprioglio G, Aloe L.** Topical treatment with nerve growth factor for corneal neurotrophic ulcers. The New England journal of medicine, 1998; 17: 1174-80.
23. **Yu CQ, Zhang M, Matis KI, Kim C, M. I.** Rosenblatt. Investigative Ophthalmology and Visual Science. 2008; 49: 3870-8.