

REGULAR ARTICLE

Efficacy and safety of breast milk eye drops in infants with eye discharge

Tetsu Sugimura¹  | Tomoko Seo² | Nami Terasaki¹ | Yukiko Ozaki³ | Noriko Rikitake¹ | Rumiko Okabe³ | Masami Matsushita³

¹Department of Pediatrics and Allergology, Sugimura Children's Medical Clinic, Chikugo City, Japan

²Department of Pediatrics, Green Woods Children's Clinic, Okazaki City, Japan

³Department of Pediatrics, Kurume University School of Medicine, Kurume City, Japan

Correspondence

Tetsu Sugimura, Department of Pediatrics and Allergology, Sugimura Children's Medical Clinic, 991-2 Mizuta, Chikugo City, Fukuoka 833-0027, Japan.
Email: sugimura@kurume.ktarn.or.jp

Abstract

Aim: Breast milk (BM) contains various protective components, such as immunoglobulins, lactoferrin, lysozyme, oligosaccharides and immune cell subsets. We evaluated the effectiveness of BM eye drops in infants with eye discharge in a randomised controlled study.

Methods: Subjects were breastfed infants aged ≤ 180 days, with eye discharge. We randomly assigned patients to receive eye drops of BM or sodium azulene sulphonate hydrate 0.02% ophthalmic solution (OS). The patients received drop of BM or OS for 7 days. Improvement score of eye discharge in the groups was compared using a non-inferiority test.

Results: The number of patients improved eye discharge was 119/155 (76.8%) and 119/157 (75.8%) in BM and OS groups, respectively. There were no significant differences between groups. The improvement score in eye discharge was 1.76 ± 0.91 in the BM group and 1.71 ± 0.96 in the OS group. The BM group was considered non-inferior to the OS group.

Conclusions: This study demonstrated that BM is no less effective than OS in infants with eye discharge aged ≤ 6 months. The results suggested that the use of breast milk as eye drops could be considered as a first-line treatment for infants aged ≤ 6 months with eye discharge.

KEYWORDS

breast milk, eye discharge, eye drops, infant, non-inferiority test

1 | INTRODUCTION

Eye discharge is a common complaint in paediatric primary care visits. The most common causes were bacterial and viral infections,^{1,2} with 54% of cases of conjunctivitis in children attributed to bacterial infection.^{2,3} In general, paediatric patients with a chief complaint of eye discharge underwent a microscopic examination and discharge

culture, and if diagnosed with bacterial conjunctivitis, they were then treated with antibiotic eye drops.⁴ In paediatric practice, infants presenting with a chief complaint of eye discharge may have conditions other than bacterial infection, such as viral infection, nasolacrimal duct stenosis, dacryocystitis and allergic conjunctivitis.⁴ However, physicians prescribed antibiotic eye drops 80%–95% of the time.^{5,6} The use of antibiotic eye drops in infants with

Abbreviations: OS, Sodium azulene sulphonate hydrate 0.02% ophthalmic solution; BM, Breast milk; CI, Confidence interval; HIV, Human immunodeficiency virus.

A summary of part of this work was presented at the 121st Annual Meeting of the Japan Pediatric Society, April 21, 2018, Fukuoka, JPN

© 2021 Foundation Acta Paediatrica. Published by John Wiley & Sons Ltd

non-bacterial conjunctivitis can increase medical costs and promote antibiotic-resistant bacteria.

Antibiotic eye drops were only effective for bacterial infection. In contrast, breast milk (BM) contains various protective components, such as immunoglobulins, lactoferrin, lysozyme, oligosaccharides and immune cell subsets (mainly macrophages).⁷⁻¹¹ In addition, the BM exhibits biological activity against a broad range of microorganisms, including Gram-negative and Gram-positive bacteria, fungi, viruses and amebae.¹⁰⁻¹⁵

Previous reports have suggested that BM eye drops had antibacterial effects in infant conjunctivitis¹⁶ and against the causative agents of conjunctivitis in children¹⁷ and that they helped treat congenital nasolacrimal duct obstruction.¹⁶ However, the effectiveness of BM eye drops in infant conjunctivitis had not been investigated in controlled studies. In a previous preliminary study, we used BM as eye drops in infants aged 6 months or younger ($n = 22$) who visited Sugimura Children's Medical Clinic with a chief complaint of eye discharge. We observed improvements in eye discharge in 72.7% of the patients, with no adverse events, demonstrating the feasibility and safety of BM eye drops.¹⁸

Here, we examined the effectiveness of BM eye drops in infants with eye discharge in a randomised controlled study. We hypothesised that BM eye drops were as effective as anti-inflammatory eye drops in the treatment of eye discharge in infant.

2 | METHODS

2.1 | Study design

Patients for this randomised, investigator-masked, parallel-group, non-inferiority study were recruited at two sites: Sugimura Children's Medical Clinic and Green Woods Children's Clinic between 16 January 2014 and 9 February 2019. At each site, one investigator assessed ocular status in a masked fashion, while another assessed safety and acceptability parameters. A double-blind design was not feasible because the application of the two treatments differed: BM was instilled using a dropper, whereas eye drops were instilled from dispenser bottles. The parents of each patient were provided with full information about the objectives and protocol of this study, and written informed consent for each infant to participate was obtained.

This study was reviewed by the Investigation and Research Method Committee of the Society of Ambulatory and General Pediatrics of Japan and approved by the Ethics Committee of the society and registered for trial in the Committee on December 26, 2013 (approval number 201305).

2.2 | Patients

Eligible subjects were breastfed infants aged 180 days or younger, with purulent discharge in one or both eyes, who had been born to

Key Notes

- We evaluated the effectiveness of breast milk (BM) eye drops in infants with eye discharge in a randomised controlled study.
- The improvement score was 1.76 ± 0.91 in the BM group and 1.71 ± 0.96 in the sodium azulene sulphonate hydrate 0.02% ophthalmic solution (OS) group. The BM was considered non-inferior to the OS.
- The results suggested that the BM eye drops could be considered as a first-line treatment for infants with eye discharge.

healthy mothers at the gestational age of 36 weeks or more. Infants were ineligible if their birth weight was less than 2400 g. Patients with eyelid cellulitis, physical trauma, epidemic keratoconjunctivitis, corneal infiltrate or ulcers in either eye were excluded. Infants born to women who had a systemic or vulvar infection or were positive for HIV or human T-cell leukaemia virus were also excluded from this study.

The use of systemic or topical non-prophylactic antimicrobial therapy was disallowed within 96 hours of day one and for the duration of the study. Subjects who had received topical antimicrobial therapy for routine prophylaxis at birth could be enrolled 24 hours or more after the final dose of antibiotic.

2.3 | Study medications and dosing regimen

We assigned patients to receive eye drops of BM or the control drops using a block randomisation scheme (1:1 ratio) with Microsoft Excel 2008 (Microsoft Inc.). For the BM group, BM was collected using Tip bent dropper 2 ml (MI Chemical Co, Ltd.) (Figure 1). The patients' mothers collected their BM after gently wiping the nipple with clean gauze without sanitiser or alcohol. One drop of collected BM was applied to the patients' affected eyes three times daily (morning, afternoon and evening) for 7 days. In the control group (OS group), patients received one drop of sodium azulene sulphonate hydrate 0.02% ophthalmic solution (OS) (Zeria Pharmaceutical Co, Ltd.), a medicinal product approved in Japan for the treatment of conjunctivitis,¹⁹ in the affected eyes three times daily (morning, afternoon, and evening) for 7 days.

2.4 | Main outcomes

Eye discharge, conjunctival hyperaemia and tearing were evaluated at the first visit and after 4 and 7 days of eye drop instillation.



FIGURE 1 Tip bent dropper 2 ml. It is electronically sterilized. The tip is hemispherical and round (MI CHEMICAL Co., Ltd. Hyogo, Japan)

TABLE 1 Severity Score of eye findings

Signs	Score		Findings
Eye discharge	0	None	No eye discharge
	1	Mild	Outer and/or internal canthus with eye discharge
	2	Moderate	Between mild and severe
	3	Severe	Upper and under eyelid with eye discharge
Conjunctival hyperaemia	0	None	No conjunctival hyperaemia
	1	Mild	Several vasodilations
	2	Moderate	Many vasodilations
	3	Severe	Many and diffuse vasodilations
Tearing	0	None	Normal
	1	Mild	Tearing a little
	2	Moderate	Sometimes tearing
	3	Severe	Frequent tearing

2.5 | Clinical efficacy assessments

Patients had an initial eye examination to assess the severity of the clinical signs, which were graded on a Four point scale (0, none; 1, mild; 2, moderate; and 3, severe) using the Clinical Evaluation Criteria for General Purpose Antibacterial Eye Drops for Children as a reference.²⁰ The scoring system is shown in Table 1. For patients with discharge from both eyes, the eye with the higher severity score for discharge was assessed. If both eyes had the same score, the right eye was chosen for assessment.

The investigators examined both eyes of each patient on day 4, and those who had worsening clinical signs received antibiotic eye drops. The examination was repeated on day 7, and subjects who had no improvement in the severity score for eye discharge or worsening of clinical signs were treated with antibiotic eye drops or

referred to ophthalmology specialists. The investigators interviewed the patients when the eye symptoms disappeared at each visit.

2.6 | Vaccine assessments

History of vaccination against *Haemophilus influenzae* type b and *Streptococcus pneumoniae* (pneumococcus), common causative agents of infection in infants, was investigated. The number of vaccinated patients was compared between the BM and OS groups to determine whether vaccination status influenced improvement in eye discharge.

2.7 | Microbiological assessments

At their first visit, patients had a conjunctival swab taken from the affected eye. The eye discharge samples were cultured, and the number and type of isolated bacterial species were compared between the two groups and in relation to improvements in eye discharge.

2.8 | Safety assessments

The safety assessment included all patients enrolled in the study. They were carefully monitored by their parents, and the study investigators for adverse events and ophthalmic signs (such as eye redness, eruption, swelling, discharge and tearing) after instillation. If eye discharge did not improve by day 7, follow-up was continued until symptoms resolved. Patients who had been referred to ophthalmologists and those who did not return to our clinic after day 7 were followed up by telephone interview to determine the presence and severity of eye symptoms.

2.9 | Statistical analysis

Degree of improvement in eye discharge that defined as the severity score for eye discharge on day 7 subtracted from the pre-instillation score in the two groups was compared using a non-inferiority test with a 2-sided 95% confidence interval (CI). The non-inferiority margin was set at 10% of the mean value in the AZ group. Compared with the AZ group, the BM group was considered non-inferior if the lower limit of the CI was $\geq -10\%$ and $<0\%$ and considered superior if the lower limit was $\geq 0\%$. The means of the two groups were compared using *t* tests.

Improvements in conjunctival hyperaemia and tearing were calculated using the same method as for eye discharge and compared between the BM and OS groups. The number of subjects presenting with these signs was not large enough to perform a non-inferiority test, so data were assessed using Student's *t* test.

Continuous data were analysed using Student's *t* test, and percentage data were assessed using Fisher's exact test. Analyses were performed using the Statistics Calculators. socscistatistics.com.²¹

3 | RESULTS

3.1 | Patient demographics

A total of 346 subjects were enrolled and randomly divided into two groups: 155 in the BM group and 157 in the OS group. Improvements in eye discharge were compared between the two groups. Number of 34 subjects dropped out of the study. The numbers of subjects dropped out was 18 in the BM group and 16 in the OS group. The subjects had fever ($\geq 37.5^{\circ}\text{C}$) due to upper respiratory tract inflammation, hand-foot-and-mouth disease, enteritis or viral disease after enrolment. On the other hand, the subjects included those who visited ophthalmologists because of their parents' concern and received antibiotic eye drops during the 7-day study period, or visited other clinics because of febrile illness and were given oral antibiotics.

Demographic characteristics are shown in Table 2. The mean age at first visit was significantly higher in the OS group (92.1 ± 51.0 days) than in the BM group (75.3 ± 47.4 days) ($p = 0.003$). Accordingly, the OS group had a significantly higher body weight at first visit (5.6 ± 1.5 kg) than the BM group (5.3 ± 1.4 kg) ($p = 0.043$). There were no significant differences between groups in gender distribution or duration of eye discharge before first visit (days). The number of subjects vaccinated against *Haemophilus influenzae* b was significantly higher in the OS group than in the BM group (89 versus 64; $p = 0.007$), but no significant difference was observed between the groups in vaccination history against pneumococcus.

3.2 | Efficacy

Incidence of conjunctival hyperaemia and tearing, and the scores and improvements of these clinical signs are shown in Table 3.

The number of patients who showed improvement in eye discharge (responders) was 119/155 (76.8%) and 119/157 (75.8%) in the BM and OS groups, respectively. There were no significant

TABLE 2 Demographic characteristics

	BM group	OS group	p Value
N	155	157	
Age (day)	75.3 ± 47.4	92.1 ± 51.0	0.003
Body weight (Kg)	5.3 ± 1.4	5.6 ± 1.5	0.043
Sex (M/F)	68/87	78/79	0.310
Day of illness at day 0	5.1 ± 4.5	4.3 ± 3.3	0.060
Hib V (n)	64	89	0.007
Pneumo. V (n)	57	64	0.488

Note: Parameter was showed mean $\pm$ Standard deviation.

Parameter was analyzed using Student's t test. Categories was analyzed using Fisher's exact test.

Statistical significance was defined as $p < 0.05$.

Abbreviations: BM, Breast milk; Hib V, *Haemophilus influenzae* b Vaccine; OS, sodium azulene sulfonate hydrate 0.02% ophthalmic solution; Pneumo. V, *Pneumococcus* Vaccine.

differences between groups. The degree of improvement score in eye discharge was 1.76 ± 0.91 in the BM group and 1.71 ± 0.96 in the OS group. No significant differences between groups were noted in discharge score at first visit (mean $\pm$ standard deviation, 2.2 ± 0.7 and 2.1 ± 0.7 in the BM and OS groups, respectively) or time to improvement (5.6 ± 2.2 and 5.0 ± 2.1 days). Analysis of the group means (BM group minus OS group) revealed a difference of 0.05 between the means (95% CI, -0.158 to 0.258). Because the lower limit of the CI was above the non-inferiority margin of -0.171 , the BM group was considered non-inferior to the OS group (Table 4).

The incidence of conjunctival hyperaemia was 31 cases (20.0%) and 35 cases (22.3%), the score of first visit was 1.0 ± 0.0 and 1.0 ± 0.2 , or degree of improvement in conjunctival hyperaemia was 0.97 ± 0.17 and 0.91 ± 0.37 in the BM and OS groups, respectively. There were no significant differences between the groups (Table 3). The incidence of conjunctival hyperaemia was also not significantly different between responders and non-responders in either group (Table 5).

TABLE 3 Efficacy and Eye findings resolution of BM group versus OS group

	BM group (n = 155)	OS group (n = 157)	p Value
Efficacy rate of eye discharge. n (%)	119 (76.8)	119 (75.8)	0.894
Time to improvement of eye discharge	5.6 ± 2.2	5.1 ± 2.1	0.054
Eye discharge score at day 0	2.2 ± 0.7	2.1 ± 0.7	0.361
Eye discharge score at day 4	1.0 ± 0.8	0.8 ± 0.8	0.059
Eye discharge score at day 7	0.4 ± 0.8	0.4 ± 0.8	0.813
Degree of improvement of eye discharge	1.8 ± 0.9	1.7 ± 1.0	0.606
Conjunctival hyperaemia (CH). n (%)	31 (20.0)	35 (22.3)	0.678
CH score at day 0	1.0 ± 0.0	1.0 ± 0.2	0.344
CH score at day 4	0.0 ± 0.0	0.2 ± 0.4	0.120
CH score at day 7	0.0 ± 0.2	0.1 ± 0.3	0.203
Degree of improvement of CH	1.0 ± 0.2	0.9 ± 0.4	0.457
Tearing. n (%)	53 (34.2)	50 (31.8)	0.718
Score of tearing at day 0	1.1 ± 0.3	1.1 ± 0.4	0.495
Score of tearing at day 4	0.5 ± 0.5	0.5 ± 0.6	0.922
Score of tearing at day 7	0.3 ± 0.5	0.3 ± 0.5	0.817
Degree of improvement of tearing	0.8 ± 0.5	0.8 ± 0.6	0.524

Note: Parameter was showed mean $\pm$ Standard deviation.

Percentage data was analyzed using Fisher's exact test. Others was analyzed using Student's t test.

Statistical significance was defined as $p < 0.05$.

Abbreviations: BM, Breast milk; CH, Conjunctival hyperaemia; OS, sodium azulene sulfonate hydrate 0.02% ophthalmic solution.

No significant differences were observed between groups in the incidence of tearing. The incidence was 53 cases (34.2%) and 50 cases (31.8%) in the BM and OS groups, respectively. The score at first visit was 1.1 ± 0.3 and 1.1 ± 0.4 , or the degree of improvement in tearing was 0.76 ± 0.51 and 0.84 ± 0.55 in the BM and OS groups, respectively. There were no significant differences between groups (Table 2). The incidence of tearing in the BM group was significantly higher in non-responders (18/36, 50.0%) than in responders (35/119, 29.4%) ($p = 0.02$), and the incidence in the OS group was also significantly higher in non-responders (22/38, 57.9%) than in responders (28/119, 23.5%) ($p = 0.0001$) (Table 5).

3.3 | Bacteriological resolution

Bacterial species from eye discharge cultures are shown in Table 6. There were no significant differences between the groups in positive or negative cultures. In the BM and OS groups, *Staphylococcus epidermidis* was detected in 43/160 (26.9%) and 43/165 (26.1%) patients, respectively, *Haemophilus influenzae* in 41/160 (25.6%) and 43/165 (26.1%), *Streptococcus* spp. in 29/160 (18.1%) and 32/165 (19.4%), *Moraxella catarrhalis* in 19/160 (11.9%) and 13/165 (7.9%), *Streptococcus pneumoniae* in 11/160 (6.9%) and 13/165 (7.9%), *Corynebacterium* spp. in 11/160 (6.9%) and 14/165 (8.5%), *Staphylococcus aureus* in 3/160 (1.9%) and 6/165 (3.6%), *Staphylococcus haemolyticus* in 3/160 (1.9%) and 1/165 (0.6%) and negative cultures in 29/160 (18.1%) and 32/165 (19.4%). However, among non-responders, *Staphylococcus epidermidis* was isolated significantly more frequently in the BM group (12/44, 27.3%) than in the OS group (5/47, 10.6%) ($p = 0.04$), with no differences in other bacteria. Multiple bacterial species were identified in a single eye discharge sample from several subjects, and the total number of isolated species was higher than the number of subjects.

3.4 | Safety

No adverse events or complications were observed in responders from either group. Of non-responders from the BM and OS groups, 35/36 (97.2%) and 28/38 (73.7%) received antibiotic eye

drops, 9/36 (25.0%) and 7/38 (18.4%) had nasolacrimal duct stenosis, 2/36 (5.6%) and 5/38 (13.2%) visited ophthalmologists, and 1/36 (2.8%) and 3/38 (7.9%) had increased eye discharge. The frequency of antibacterial eye drop use was significantly higher in the OS group than in the BM group. Time to resolution of eye discharge was not significantly different between non-responders from the BM group (13.8 ± 4.2 days; range, 9–26 days) and the OS group (14.2 ± 10.6 days; 8–62 days). Other than increased eye discharge, no adverse events, such as inflammation of the eyelids or ophthalmic complications, were noted in the present study. All non-responders had a good prognosis (Table 7).

4 | DISCUSSION

Verd reported that comparison of the treatment of epiphora with an antibacterial agent and breast milk instillation and the BM instillation was effective.¹⁶ His survey was not randomly assigned, and the number of cases was as small as 20 in the antimicrobial group. In addition, Baynham et al. reported that investigation of the antibacterial effect of BM against pathogenic bacteria of conjunctivitis in children. They suggested the effects of breast milk on *Neisseria gonorrhoeae*, *Moraxella catarrhalis* and *Streptococcus viridans*.¹⁷ Our study was the first randomised controlled clinical study to examine the effectiveness and safety of BM eye drops as a treatment for eye discharge in infants.

Despite the patients being randomly assigned to the two groups, the OS group had a significantly higher age (and therefore body weight) at first visit than the BM group. The higher age of the patients in the OS group may also explain their higher rate of *Haemophilus influenzae* b vaccination. However, the percentage of patients with positive cultures for *Haemophilus influenzae* was not significantly different between the two groups; therefore, the difference in vaccination history was unlikely to have affected the comparison of improvement in eye discharge.

No significant differences were seen between the BM and OS groups in the percentages of responders or time to improvement. In degree of improvement score, BM group was considered non-inferiority to the OS group (Table 4). This indicated that the use of BM as eye drops was no less effective than a conventional anti-inflammatory ophthalmic solution in the treatment of eye discharge in infants aged 6 months or younger.

The incidence and severity score of conjunctival hyperaemia at first visit were not significantly different between the BM and OS groups, and neither was the incidence of conjunctival hyperaemia different between responders and non-responders, suggesting that this condition did not influence improvements in eye discharge or affect comparisons between the groups.

Similarly, the incidence and severity score of tearing at first visit were not significantly different between the BM and OS groups, so tearing did not affect comparisons of improvement in eye discharge. However, incidence of tearing was significantly higher in non-responders than responders in both groups (Table 5). All

TABLE 4 Change in eye discharge score at day 7

	BM group	OS group
n	155	157
Mean $\pm$ SD	1.76 ± 0.91	1.71 ± 0.96
Non-inferiority analysis (BM minus OS)		
Means difference	0.05	
Difference 95% CI	−0.158, 0.258	
Non-inferiority	Accepted	

Abbreviations: BM, Breast milk; CI, Confidence interval; OS, sodium azulene sulfonate hydrate 0.02% ophthalmic solution; SD, Standard deviation.

TABLE 5 Comparison between responders and non-responders for CH or tearing

BM group	Responders	Non-responders	p Value
N	119	36	
CH. n (%)	24 (20.2)	7 (19.4)	1.000
Tearing. n (%)	35 (29.4)	18 (50.0)	0.028
OS group	Responders	Non-responders	p Value
n	119	38	
CH. n (%)	24 (20.2)	11 (28.9)	0.269
Tearing. n (%)	28 (23.5)	22 (57.9)	0.0001

Note: In BM and OS group, tearing was significantly higher in non-responders than in responders.

Fisher's exact test was used for analysis. Statistical significance was defined as $p < 0.05$.

Abbreviations: BM, Breast milk; CH, Conjunctival hyperaemia; OS, sodium azulene sulfonate hydrate 0.02% ophthalmic solution.

TABLE 6 Bacterial species cultured from the eye discharge at the first visit

Identification bacteria	BM group				OS group				p Value 1	p Value 2
	Total (n = 160)	%	NR (n = 44)	%	Total (n = 165)	%	NR (n = 47)	%		
<i>Staphylococcus epidermidis</i>	43	26.9	12	27.3	43	26.1	5	10.6	0.497	0.038
<i>Haemophilus influenzae</i>	41	25.6	11	25.0	43	26.1	17	36.2	0.502	0.177
<i>Streptococcus</i> species	29	18.1	7	15.9	32	19.4	7	14.9	0.440	0.561
<i>Moraxella catarrhalis</i>	19	11.9	5	11.4	13	7.9	4	8.5	0.153	0.458
<i>Streptococcus pneumoniae</i>	11	6.9	3	6.8	13	7.9	3	6.4	0.447	0.630
<i>Corynebacterium</i> species	11	6.9	3	6.8	14	8.5	6	12.8	0.369	0.277
<i>Staphylococcus aureus</i>	3	1.9	1	2.3	6	3.6	4	8.5	0.447	0.328
<i>Staphylococcus haemolyticus</i>	3	1.9	2	4.5	1	0.6	1	2.1	0.300	0.475
Negative	29	18.1	1	2.3	32	19.4	2	4.3	0.440	0.525

Note: p Value1: Comparison between total BM group and OS group. p Value2: Comparison between BM group and OS group in non-responders.

In non-responders, BM group had a significantly higher *Staphylococcus epidermidis* positive rate than OS group.

Fisher's exact test was used for analysis. Statistical significance was defined as $p < 0.05$.

Abbreviations: BM, Breast milk; NR, non-responders; OS, sodium azulene sulfonate hydrate 0.02% ophthalmic solution.

non-responders who had tearing also suffered from nasolacrimal duct stenosis. It was suggested that nasolacrimal duct stenosis might have impaired the effectiveness of BM and OS eye drops in improving eye discharge.

There was no significant difference between the BM and OS groups in the number of bacterial species isolated from eye discharge. The percentage of subjects with negative cultures was also not significantly different between the groups, suggesting that the patients' eye discharge might be attributed to viral infection, nasolacrimal duct stenosis, dacryocystitis, allergy and other causes. The cause of eye discharge was nasolacrimal duct stenosis in several non-responders but could not be identified in others.

Chlamydia and *gonococci* are common causative agents of eye discharge in newborns⁴ but, owing to the routine postnatal administration of antibiotic eye drops to newborns in obstetrics and gynaecology clinics, bacterial conjunctivitis caused by these pathogens had rarely been reported in recent years. Indeed, they were not isolated from eye discharge samples in our culture. *Haemophilus influenzae*, the most common aetiological agent of bacterial conjunctivitis

in infants,⁴ was isolated from 26.5% and 27.4% of subjects in the BM and OS groups, respectively, and was the second most frequent species after *Staphylococcus epidermidis* (Table 6). Although *Staphylococcus epidermidis* was most commonly identified in this study, the evidence is too limited to attribute bacterial conjunctivitis to this agent. The significantly higher frequency of positive cultures for *Staphylococcus epidermidis* in non-responders from the BM group than their OS counterparts remains to be explained.

No adverse events were observed in responders from either group. Among non-responders, one and three subjects from the BM and OS groups, respectively, had a 1-point increase in the severity score for eye discharge at day 7, but their conditions resolved after treatment with antibiotic eye drops. Eye discharge in patients with nasolacrimal duct stenosis was relieved by massaging the area between the inner canthus and the nasal root. The absence of serious adverse events or ophthalmic complications indicates the safety of BM eye drops.

Taken together, these results demonstrated that BM eye drops were no less effective than OS, an approved anti-inflammatory drug

TABLE 7 Clinical course in non-responders

	BM group (n = 36)	OS group (n = 38)	p Value
Time to improvement of eye discharge (day)	13.8 ± 4.2 (9, 26)	14.2 ± 10.6 (8, 62)	0.810
Antibacterial eye drops (n)	35 (97.2%)	28 (73.7%)	0.004
Nasolacrimal duct stenosis (n)	9 (25.0%)	7 (18.4%)	0.343
Ophthalmology consultation (n)	2 (5.6%)	5 (13.2%)	0.238
Adverse event	1 (2.8%)	3 (7.9%)	0.328
Eye complication	0	0	1.000
Others	7	11	0.457

Note: Time to improvement was showed mean ± SD (Min, Max). Min; minimum, Max; maximum.

The parameter was analyzed using Student's *t* test. Categories was analyzed using Fisher's exact test.

Statistical significance was defined as *p* < 0.05.

Abbreviations: BM, Breast milk; OS, sodium azulene sulfonate hydrate 0.02% ophthalmic solution; SD, standard deviation.

for ophthalmic use, in the treatment of eye discharge in infants, with more than 75% of the patients in this study showing improvement. This might result from the antimicrobial activity of BM components, such as immunoglobulins, lactoferrin, lysozyme, oligosaccharides and immune cell components.⁷⁻¹¹ Considering that these components were active against a wide range of microorganisms, including Gram-negative and Gram-positive bacteria, fungi, viruses and amebae,¹⁰⁻¹⁵ BM eye drops might also improve conjunctivitis of non-bacterial origin.

In infants presenting with eye discharge, positive/negative bacterial cultures of eye discharge should ideally be confirmed before initiating treatment with eye drops. However, because culture results take several days to obtain, by which time the conjunctivitis may worsen, paediatricians often prescribe antibiotic eye drops at the first visit to infants with conjunctivitis accompanied by eye discharge in view of suspected bacterial infection. The recent increase in antibiotic-resistant bacteria has led to a reduction in the use of antibiotics in children with febrile illnesses, such as upper respiratory tract inflammation. We also recommend considering the use of non-antibiotic eye drops before prescribing antibiotic eye drops for eye discharge in infants and children. BM eye drops can serve as such a non-antibiotic treatment option. Furthermore, given the differences in availability of medical services around the world, BM eye drops may be particularly useful in regions where proprietary eye drops are not readily available.

5 | LIMITATIONS

Breast milk used as eye drops improved eye discharge in approximately 75% of patients in this study. However, a limitation of the study design was that we were unable to investigate why the remaining 25% showed no improvement. It might be due to insufficient efficacy of BM eye drops in microbial infection, but it was equally possible that these patients had structural diseases or allergies, which require specific treatment. Future studies with closer follow-up of patients, including through subsequent changes of treatment, are warranted.

6 | CONCLUSION

The present randomised controlled study demonstrated that breast milk eye drops are no less effective than sodium azulene sulphonate hydrate ophthalmic solution 0.02% in resolving eye discharge in infants aged 6 months or younger. The treatment was safe, without any serious adverse events or side effects. The results suggested that the use of breast milk as eye drops could be considered as a first-line treatment for infants aged 6 months or younger presenting with a chief complaint of eye discharge.

ACKNOWLEDGEMENTS

We thank Professor Kiyoshi Ichihara (Yamaguchi University School of Medicine), Dr. Hiroki Mishina (Kobe City Child and Family Policy Bureau) and Assistant Professor Nobuaki Michihata (The University of Tokyo) for their help with statistical analyses, and the Investigation and Research Method Committee of the Society of Ambulatory and General Pediatrics of Japan for advice concerning the study design. We thank Hiromi Fujisaki (Secretary, Department of Pediatrics, Kurume University School of Medicine), Dr. Satoko Tanaka (Kurume University Medical Center) and the medical staff in Sugimura Children's Medical Clinic for assistance in clinical record collection and their cooperation throughout this study. We also thank Mrs. Hisayo Sugimura (Secretary, Department of Pediatrics and Allergology, Sugimura Children's Medical Clinic) for her assistance with this study.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare. This work was not funded.

ORCID

Tetsu Sugimura  <https://orcid.org/0000-0002-5468-2081>

REFERENCES

1. Buznach N, Dagan R, Greenberg D. Clinical and bacterial characteristics of acute bacterial conjunctivitis in children in the antibiotic resistance era. *Pediatr Infect Dis J*. 2005;24:823-828.

2. Patel PB, Diaz MC, Bennett JE, Attia MW. Clinical features of bacterial conjunctivitis in children. *Acad Emerg Med*. 2007;14:1-5.
3. Gigliotti F, Williams WT, Hayden FG, et al. Etiology of acute conjunctivitis in children. *J Pediatr*. 1981;9:531-536.
4. Japanese Association of Pediatric Ophthalmology. Conjunctivitis. http://www.japo-web.jp/info_ippan_page.php?id=page04. (2020-May-12 accessed).
5. Everitt H, Little P. How do general practitioners diagnose and manage acute infectious conjunctivitis? A general practitioner survey. *Fam Pract*. 2002;19:658-660.
6. Rietvelt RP, van Weert HCPM, ter Riet G, Sloos JH, Bindels PJE. Predicting bacterial cause on infectious conjunctivitis: cohort study on informativeness of combinations of signs and symptoms. *BML*. 2004;329:206-210.
7. Reddy V, Bhaskaram C, Raghuramulu N, Jagadeesan V. Antimicrobial factors in human milk. *Acta Paediatr Scand*. 1977;66:229-232.
8. Tomita M, Takase M, Bellamy W, et al. A review: the active peptide of lactoferrin. *Acta Paediatr Japonica*. 1994;36:585-591.
9. Yamauchi K. Science of breast milk ingredients: infection protection and immunological components. *Perinatal Med (Tokyo)*. 2008;38:1231-1234.
10. Nakano T. Science of breast milk ingredients: carbohydrate. *Perinatal Med (Tokyo)*. 2008;38:1225-1229.
11. Bowdish DM, Davidson DJ, Hancock RE. A re-evaluation of the role of host defence peptides on mammalian immunity. *Curr Protein Pept Sci*. 2005;6:35-51.
12. Oda H, Murata M, Yamauchi A. Function of healthcare in lactoferrin. *Bullet Japan Dairy Technical Assoc*. 2010;60:9-22.
13. Tomita S, Hasegawa S, Uotani T, et al. Amoebicidal activity of lactoferrin against *Acanthamoeba* cell. Lactoferrin 2011 edited by the Japan Lactoferrin Society 4th Scientific Meeting Executive Committee. Nihon-igakukan, Tokyo, pp. 35-40; 2011.
14. Venkatesh MP, Rong L. Human recombinant lactoferrin acts synergistically with antimicrobials commonly used in neonatal practice against coagulase-negative staphylococci and *Candida albicans* causing neonatal sepsis. *J Med Microbiol*. 2008;57:1113-1121.
15. Berlutti F, Pantanella F, Natalizi T, et al. Antiviral properties of lactoferrin—A natural immunity molecule. *Molecules*. 2011;16(8):6992-7018.
16. Verd S. Switch from antibiotic eye drops to instillation of mother's milk drops as a treatment of infant epiphora. *J Trop Pediatr*. 2007;53(1):68-69.
17. Baynham JT, Moorman MA, Donnellan C, Cevallos V, Keenan JD. Antibacterial effect of human milk for common causes of paediatric conjunctivitis. *Br J Ophthalmol*. 2013;97:377-439.
18. Sugimura T, Ozaki Y, Iemura M, et al. Breast milk eye drops in infants with eye discharges: a preliminary study. *J Jpn Pediatr Soc*. 2013;117:549.
19. Azulen sulfonic acid sodium hydrate (Sodium gualenate hydrate): Japan Pharmaceutical Information Center Tokyo Japan ed. *Drugs in Japan*. 2014 edition. Tokyo, : Jiho Inc.; 2013: p. 67-69.
20. Miyanagai Y, Nishida T, Ohno S. Clinical evaluation criteria for general purpose antibacterial eyedrops for children. *Atarashii Ganka (Journal of the Eye)*. 2012;29:425-429.
21. Statistics calculators. socscistatistics.com. <https://www.socscistatistics.com/tests/>. (2020-May-12 accessed).

How to cite this article: Sugimura T, Seo T, Terasaki N, et al. Efficacy and safety of breast milk eye drops in infants with eye discharge. *Acta Paediatr*. 2021;110:1322-1329. <https://doi.org/10.1111/apa.15628>