Efficacy and Safety of Topical Cysteamine in Corneal Cystinosis: A Systematic Review and Meta-Analysis

SUKHMANDEEP KAUR, PHULEN SARMA, HARDEEP KAUR, MANISHA PRAJAPAT, NISHANT SHEKHAR, JAIMINI BHATTACHARYYA, HARPINDER KAUR, SUBODH KUMAR, BIKASH MEDHI, JAGAT RAM, DIPANKAR DAS, PRAMOD AVTI, AJAY PRAKASH, RAHUL SINGH, AND ANUSUYA BHATTACHARYYA

• PURPOSE: To evaluate safety and efficacy of topical cysteamine ophthalmic solution for corneal cystinosis.

• METHODS: Seven databases were searched (PubMed, OVID, EMBASE, Web of Science, Cochrane Central, Google Scholar, and ClinicalTrials.gov) for relevant studies, using appropriate keywords. Comparative observational studies and randomized controlled trials comparing cysteamine with control or other formulations for treatment of corneal or ophthalmic cystinosis were included. Outcome measurements were improvement or response to therapy, change in corneal cystine crystal score (CCCS), in vivo confocal microscopy score (IVCM), cystine crystal depth, contrast sensitivity (CS), photophobia score, and safety.

• DESIGN: Systematic review and meta-analysis.

• RESULTS: Seven studies were included. Compared to placebo and control, the cysteamine arm was better in terms of improvements and responses to therapy (2 studies showed a risk ratio [RR] of 16; 95% confidence interval [CI]: 2.30-111.37) and crystal density score (1 study showed a mean difference [MD] of −0.80; 95% CI: −1.56 to −0.04). No significant differences were observed in terms of improvement in CS (1 study showed an RR of 7.00; 95% CI: 0.47-103.27). Compared to cystamine, cysteamine showed benefits in terms of crystal density score (MD −0.94; 95% CI: −1.64 to −0.24). Compared to a newer formulation, the standard formulation (cysteamine [Cystaran]; 0.55% cysteamine hydrochloride + benzalkonium chloride 0.01%) performed better in terms of decreasing CCCS. Another newer, viscous formulation, Cystadrops, performed better than the standard formulation in terms of change in CCCS, IVCM score, corneal crystal depth, and photophobia score; however, local adverse effects and blurring were higher in the group receiving Cystadrops.

• CONCLUSIONS: Conventional cysteamine (0.1% to 0.3%) performed better than placebo (control) in terms of response to therapy. In terms of decreasing corneal cystine density, cysteamine (0.55%) was better than cystamine (0.55%), and the viscous Cystadrops (0.55%) was better than the standard formulation (0.1%). (Am J Ophthalmol 2021;223:275–285. © 2020 Elsevier Inc. All rights reserved.)

CYSTINOSIS IS A RARE AUTOSOMAL RECESSIVE DISease associated with mutation of cystinosin, a lysosomal transporter protein (encoded by the *CTNS* gene located in the short arm of chromosome 17). Cystinosin is involved in facilitated transport of cystine from lysosome.[1] A defect in this transporter (caused by a mutation in the cystinosin gene) leads to defective accumulation of the disulfide amino acid cystine in lysosomes of various tissues, causing multiple organ damage.[1] Although kidneys are the organs most affected,[2] cystine crystals are also deposited in ocular structures and more specifically in the cornea, which makes it a disease of concern for ophthalmologists.[2] Typically, corneal cystine crystal deposition cases present with photophobia, blepharospasm, and corneal erosions.[3,4]

Cysteamine is a type of free aminothiol sulfhydryl compound which can enter lysosomes and form disulfide bonds with cystine at room temperature, forming a complex (the cystine-cysteamine complex),[2,5] which resembles lysine and leaves the cystinotic lysosome using a lysine transport system, making it an alternative pathway for clearance of cystine.[5,6] Oral cysteamine is effective in the management of nephropathic cystinosis. However, it fails to reduce the symptoms associated with corneal cystinosis (which may be due to suboptimal concentrations deposited in the cornea owing to its relative avascularity).[1,5,7] Thus, the need arose to develop a new treatment option or an alternative formulation of cysteamine, which shows significant corneal penetration and alters the disease pathology in patients with corneal cystinosis. In response, a topical preparation (eye drops) of cysteamine hydrochloride (CH) was

Accepted for publication Jul 24, 2020.

From the Department of Pharmacology (S.K., P.S., H.K., M.P., N.S., H.K., S.K., B.M., A.P., R.S.), PGIMER Chandigarh, India; Department of Management Studies (J.B.), IIT Madras, Chennai, India; Department of Ophthalmology (J.R.), PGIMER Chandigarh, India; Department of Ophthalmology (D.D.), Sri Sankaradeva Nethralaya, Guwahati, Assam, India; Department of Biophysics (P.A.), PGIMER Chandigarh, India; and the Department of Ophthalmology (A.B.), Government Medical College and Hospital, Chandigarh, Madras, Chennai, India.

First three authors S. Kaur, P. Sarma, and H. Kaur are joint first authors.

Inquiries to Anusuya Bhattacharyya, Department of Ophthalmology, Government Medical College and Hospital, Chandigarh, India; e-mail: anusuya.8k@gmail.com

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2020.07.052

developed, which showed efficacy in terms of reducing corneal cystine crystals and photophobia.[2–4,8] However, the formulation needed to be stored at −20-degrees after opening and required frequent instillation (up to 12 times/day), which was a major cause of poor patient compliance.[9,10] This form was followed by trials of topical cystamine,[6] however, it failed in clinical studies.[9] Following this, Sigma-Tau Pharmaceuticals (Gaithersburg, Maryland) developed a new cysteamine formulation in 2003 (0.55% CH solution in combination with 1.85% monosodium phosphate and disodium ethylenediaminetetraacetic acid (EDTA, 0.10% with 0.01% benzalkonium chloride [BAC]).[7] The new formulation had the advantage of greater stability at room temperature (stable free thiol formulation, storage up to 7 months at room temperature and 24 months in refrigeration)[7]; however, it performed poorly compared to the standard formulation. In 2012, the standard topical formulation (Cystaran) by Sigma-Tau Pharmaceuticals, having 0.44% cysteamine with a formulation of 0.01% BAC received U.S. Food and Drug Administration (FDA) approval.[1] This formulation was equivalent to the 0.55% CH topical formulation previously used in the U.S. National Institutes of Health (NIH) clinical trials. The differences that appeared in the concentrations of both formulations were due to different labeling practices as the NIH formulation also took the moisture content into account.[1,11] Another viscous formulation (Cystadrops) containing 0.55% cysteamine hydrochloride, was approved as an orphan drug for the treatment of corneal cystinosis in Europe in 2017.[12] Cystadrops had the advantages of being instilled 4 times daily and was stable at 25-degrees after opening for 7 days.[13]

The aim of the current meta-analysis was to evaluate the safety and efficacy of different topical CH ophthalmic formulations in clearing corneal cystine crystal in corneal cystinosis patients. This is the first systematic review and meta-analysis addressing comparative efficacy and safety of different cysteamine formulations in patients with corneal cystinosis.

MATERIAL AND METHODS

THIS CURRENT META-ANALYSIS WAS PERFORMED IN accordance with Cochrane group guidelines,[14] an Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[15] were followed. PROSPERO registration number for the study is CRD42019146406. The PRISMA checklist is included in Supplemental Table.

• **PURPOSE:** To evaluate the efficacy and safety of topical cysteamine ophthalmic solution in patients with corneal cystinosis.

• **STUDY HYPOTHESIS:** The null hypotheses for the study were 1) there are no differences in efficacy and safety between conventional topical cysteamine and placebo/control in patients with corneal cystinosis; 2) there are no differences in efficacy and safety between topical cysteamine and cystamine in patients with corneal cystinosis; and 3) there are no differences in efficacy and safety between topical conventional cysteamine and newer formulations of cysteamine in patients with corneal cystinosis.

• **INCLUSION/EXCLUSION CRITERIA:** All published studies evaluating comparative efficacy of topical cysteamine versus placebo, cystamine, and newer formulations in patients with corneal cystinosis were included. Age and sex were not kept as a bar for inclusion. We included comparative observational studies and interventional clinical trials (both randomized and nonrandomized). Studies with no control group, case reports, and case series were excluded from the study.

• **DATABASE SEARCH:** Three independent reviewers (H.K., A.B., and S.K.) searched 7 databases (PubMed, OVID, EMBASE, ClinicalTrials.gov, Cochrane Central, Web of Science, and Google Scholar) independently. Searches were performed on February 2, 2020. Keywords were: "cystinosis," "cornea," "cystine," "corneal cystine crystal," "cysteamine," "Cystaran," and "Cystadrops." There were no language restrictions. For articles written in languages other than English, Google Translate was used to obtain relevant information. In cases where the translation was not understandable, data were collected only from the abstract. If neither the translation of the article nor the abstract were comprehensible, the article was excluded from the review.

• **SCREENING OF RELEVANT ARTICLES:** After databases were searched, the data files were extracted using EndNote. After removing duplicates, the EndNote file was exported as a.txt file and saved. This.txt file was uploaded in Rayyan QCRI, a Web-based application for systematic review. The title and abstract of all studies were screened for identification of relevant articles. The full article of studies fitting the present inclusion/exclusion criteria were retrieved and screened by 2 reviewers (S.K. and A.B.). In case of any discrepancy, P.S. and H.K. were consulted, and the issue was resolved.

• **DATA EXTRACTION (SELECTION AND CODING):** Data were extracted independently by 2 authors (P.S. and A.B.) using a pretested data extraction form. Information included study design, baseline demographic characteristics, treatment in the experimental and control group, and outcome details. After independent verification by B.M. and H.K., data were entered into Review Manager version 5.3 software (Cochrane, London, United Kingdom) by P.S.

• **OBJECTIVES:** Comparative evaluation of efficacy of cysteamine in terms of improvements and responses to

therapy, change in corneal cystine crystal score (CCCS) from the baseline and safety. Secondary objectives were evaluation of comparative efficacy of cysteamine in terms of change in in vivo confocal microscopy (IVCM) score from the baseline and change in cystine crystal depth from baseline.

• **TIMING AND EFFECT MEASUREMENTS:** A minimum of 1-month follow-up was carried out after the application.

• **COMPARISONS:** Comparisons were made among cysteamine, placebo, and cystamine and between cysteamine and newer formulations.

• **STATISTICAL ANALYSIS:** Review Manager 5.3 software was used for the meta-analysis. Data were presented as mean ± SD for continuous data and absolute change mean difference (MD) and 95% confidence interval (CI) were calculated. On the other hand, risk ratio (RR) was calculated for dichotomous data. Heterogeneity among the included studies was estimated using chi-squared and I^2 tests. I^2 more than 50% indicated significant heterogeneity, and in that case, random effects were used; otherwise, a fixed effect model was used for analysis.[16] A *P* value <.05 was considered statistically significant while calculating overall effect in each parameters.

• **RISK OF BIAS ASSESSMENT:** The methodological quality of included randomized controlled trials (RCTs) was assessed in accordance with the risk of bias criteria given by the Cochrane *Handbook for Systematic Reviews of Interventions*.[17] For nonrandomized studies ROBINS-I scale (Cochrane Methods) was used.[18] For observational studies, the Newcastle Ottawa scale was used.[19]

RESULT

• **STUDY SELECTION DETAILS:** A total of 527 articles were recognized after 7 different medical literature databases were searched. After duplicates were removal, 480 articles were carried forward for further screening using title and abstract. Full text was screened for 11 relevant articles, of which 7 studies fulfilling predefined inclusion and exclusion criteria were included in the systematic review and meta-analysis (Figure 1). Characteristics of included studies are described in Table 1.

• **CYSTEAMINE VERSUS PLACEBO:** Three articles compared cysteamine to placebo/control in patients with corneal cystinosis. However, in the study by MacDonald and associates,[20] treatment assignments among the eyes were not clear. Therefore, although that reference was included in a systematic review, it was not included for meta-analysis. For the analysis, a decrease was taken in crystal density score of 0.5 or higher from baseline as improvements and responses to therapy. In case of subjective assessment by a physician, response to therapy as judged by the clinician on the basis of crystal density was taken forward for the meta-analysis.

In this study, in terms of response to therapy or improvement, eyes treated with cysteamine showed higher improvements and responses to therapy than placebo-treated eyes (consisting of 2 studies [n = 25] in the cysteamine arm and n = 25 in the control/placebo arm, with a RR 16.00; 95% CI: 2.30-111.37) (Figure 2). As the heterogeneity among studies was low (I^2 = 0%), a fixed effect model was used for the analysis. Other efficacy parameters where cysteamine showed benefit compared to placebo was crystal density score (1 study [n = 5] in each arm; MD −0.80; 95% CI: −1.56 to 0.04) (Table 2). Although the cysteamine-treated eyes showed improvement in contrast sensitivity (CS) (in a single study, an improvement was seen in 3 of 4 eyes in the cysteamine-treated group and, in the placebo-treated eyes, 4 of 4 eyes, none of the eyes showed improvement); however, while pooling the results, the differences between the 2 groups were not found to be statistically significant (RR 7.00; 95% CI: 0.47-103.27) (Table 2).

Regarding vision, Kaiser-Kupfer and associates[3] reported improvement in visual acuity in 2 patients in the cysteamine (0.5%) arm (total sample size in the cysteamine arm was 25, but among those, 16 patients were below 4 years of age) after 6-9 months of treatment. Similarly, in the study by Bradbury and associates,[8] slight improvement in visual acuity was seen at 6 months in 3 patients (total sample size = 5). However, in the study by McDonald and associates,[20] no differences in visual acuity was were seen between the treated and untreated eye after a follow-up of 7 months (n = 4 in each arm). In the present study, although improvement was seen in terms of visual acuity in 2 patients, the authors inferred that the improvement was due to improved cooperation while testing and progression from symbol chart to Snellen chart (from a pediatric patient).

However, none of the studies compared adverse effects, and no adverse effects are reported in any of the studies.

• **CYSTEAMINE VERSUS CYSTAMINE:** Only 1 study, conducted by Iwata and associates,[6] compared cysteamine with cystamine. Cysteamine showed benefit in terms of crystal density score (1 study with 12 participants in each arm; MD −0.94; 95% CI: −1.64 to −0.24) (Table 2).

Regarding vision parameters, the study by Iwata and associates[6] reported that there was an improvement in best-corrected visual acuity (BCVA) (improvement of 5 or more letters from the Early Treatment Diabetic Retinopathy Study chart) in 3 of 14 eyes; however, the treatment arm in which improvement was seen was not clearly mentioned, although the authors mention that the better eye was always found to be the cysteamine-treated eye, so

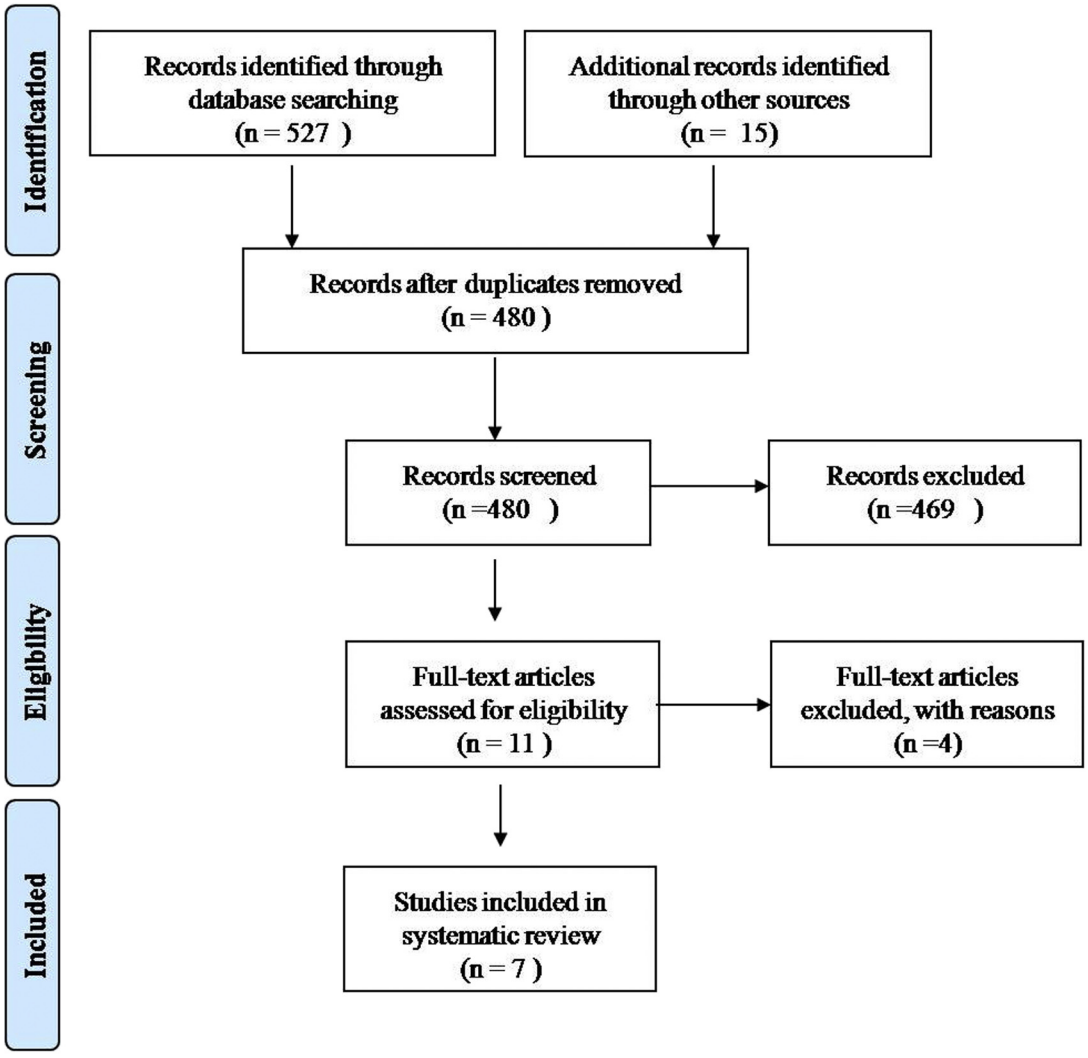

FIGURE 1. PRISMA flow diagram of the study.

we assume that the improved eyes were the cysteamine-treated eyes. None of the patients in any of the arm reported a decrease in vision.

With regard to adverse effects, in the cysteamine arm, 2 patients reported a burning sensation. No other adverse effects were reported by that study.

• **EFFICACY OF NEW FORMULATIONS OVER STANDARD CYSTEAMINE FORMULATION:** A total of 3 studies evaluated efficacy of 2 new formulations (Cystaran in 1 study and Cystadrops, the viscous formulation, in 2 studies, one of which was a phase I/IIa study and the other one was a phase III study). Detail of the formulations are shown in Table 3.

• **STANDARD CYSTEAMINE (CYSTARAN) VERSUS NEWER FORMULATION:** In the case of Cystaran, a proportion of patients showing ≥1 unit of improvement in CCCS was higher in the Cystaran group than in the group treated with the newer formulation (47% showed improvement in the standard cysteamine group compared to 7% in the new formulation group; n = 15 in each arm; $P = .004$); and the median change in CCCS from baseline in the standard formulation group (Cystaran) was −0.75 and 0.00 in case of the newer formulation.[7] These findings highlight that the standard formulation (Cystaran) performed better than the newer formulation in terms of efficacy.

Both the newer formulation and the standard formulation (Cystaran) showed comparable adverse effects, most commonly, redness, itching, discomfort, irritation, and burning sensation.[7]

• **NEWER VISCOUS FORMULATION (CYSTADROPS) VERSUS STANDARD FORMULATION:** Although there were 2 studies[4,21] comparing the new viscous formulation (Cystadrops) to the standard cysteamine, results of both the studies were not combined (efficacy part) owing to their

TABLE 1. Characteristics of Included Studies in the Systematic Review and Meta-Analysis

Study Y	Study Design	Study Population	Diagnosis of Cystinosis	Intervention/Sample Size	Comparison or Control/ Sample Size	Study Parameters	Follow-Up (mo)	Oral Cysteamine
Kaiser-Kupfer 1990[3]	RCT	2 mo-31 y	Typical clinical features, leukocyte cystine concentration	0.1% CH/25	Placebo NS/25	CSSS, VA, CS, subjective assessment	4-24 mo	Yes
Mc Donald 1990[19]	Controlled clinical trial	All age groups	Typical clinical signs and symptoms and demonstration of corneal cystine crystal deposition in slit lamp examination.	0.3%CH drop in NS eyes 4 times daily/4	NS/4 4 times daily	VA	7 mo	Yes
Bradbury 1991[8]	RCT	≥8 y	Typical clinical features, diagnosis confirmed by either leukocyte cystine concentration or fibroblast culture	Topical CH 0.2% in NS/5 6 times daily	Placebo NS/5	VA, CCCS, subjective assessment	6 mo	Yes
Iwata 1998[12]	RCT	≥3 y	Clinical feature and leukocyte cystine content.	CH 0.5%/12	Cystamine 0.5%/12	CCCS, subjective assessment	8- 20 mo	Yes
Tsilou 2003[7]	RCT	>1 y	Clinical features, demonstration of corneal crystals and leukocyte cystine content measurement.	0.55% CH+ $MnPO_4$ 1.85% + DSEDTA 0.10% + benzalkonium chloride 0.01%.	0.55% CH+ benzalkonium chloride 0.01%	ADE, CCCS, CS, VA	1 y	Yes
Lobbe 2014[20]	Phase I/IIa clinical trial: open label, dose-response pilot study	All age groups	Typical clinical features and leukocyte cystine concentration	vCH 0.55% 3-5 times daily/8 (treatment 90 days)	CH 0.1% 3-5 times daily/8 (initial run-in period of 30 days)	IVCM, CCCS, OCT DCD, OCT CCT, VA, IOP, ADE, subjective assessment	4 y	Yes
Liang 2017[4]	RCT	≥2 y	Typical clinical features and cysteamine concentration in WBC	vCH 0.55%/15 4 times daily	CH 0.1%/16 4 times daily	IVCM, CCCS, ADE, subjective assessment	3 mo	Yes

ADE = adverse effect; CCCS = corneal cystine crystal score; CCT = central corneal thickness; CH = cysteamine hydrochloride; CS = contrast sensitivity; DCD = depth of crystal deposition; DSEDTA = disodium ethylene diamine tetraacetic acid; IOP = intraocular pressure; IVCM = in vivo confocal microscopy; $MnPO_4$ = monosodium phosphate; NS = normal saline; RCT = randomized control trial; VA = visual acuity; vCH = viscous cysteamine hydrochloride; WBC = white blood cell.

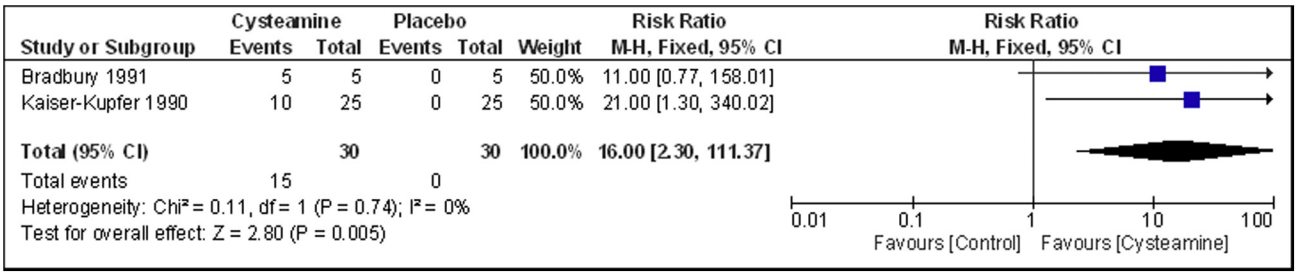

FIGURE 2. Comparative evaluation between cysteamine and placebo in terms of improvements and response to therapy.

differences in study design.[23] The first study, by Labbe and associates,[21] was a Phase I/IIa open label, dose-response pilot study. There was an initial run-in period of standard cysteamine, which was followed by switching over to the newer viscous formulation (Cystadrops). During the 4-year study period, treatment with Cystadrops resulted in a significant decrease in IVCM score from baseline.[21]

The second study, by Liang and associates,[4] was a Phase III study. In that study, treatment with Cystadrops resulted in more decrease in the change of CCCS from baseline, IVCM score (total score at day 90), corneal crystal depth change from baseline at day 90, and change of photophobia score from baseline on day 90 compared to the standard formulation (Table 2).

Regarding vision, in the study by Labbe and associates,[21] although photophobia decreased (compared to baseline photophobia score), BCVA remained unchanged during the study compared to baseline values (n = 16 eyes). However, in the phase III parallel group RCT by Liang and associates[4] (n = 22 eyes in viscus cysteamine hydrochloride (vCH) 0.55% arm and n = 20 eyes in the standard CH 0.1% formulation arm), both reduction in photophobia and improvement in visual acuity and contrast sensitivity were seen in the Cystadrops arm (vCH 0.55%) compared to the standard formulation (0.1%).

With regard to safety of new viscous formulation (Cystadrops), although there were no differences seen in terms of occurrence of serious adverse events (RR 1.07; 95% CI: 0.17-6.64), but local adverse events occurred more often in the new viscous formulation-treated group (RR 1.47; 95% CI: 1.10-1.97). Blurring of vision (RR 2.70; 95% CI: 1.09-6.69) was more common in the Cystadrops-treated arm (Figure 3). Among local adverse effects, burning sensation (RR 2.67; 95% CI: 1.06-6.70) occurred more commonly in the viscous group than in the conventional group (Table 4).

• **RISK OF BIAS ASSESSMENT:** Overall high risk of bias was seen in the domain in terms of blinding of participants and personals (performance bias). In the other domains, risk of bias assessment, the risk of bias was either low or unclear (Figure 4).

DISCUSSION

IN OPHTHALMIC CYSTINOSIS, THE SYMPTOMS ARE DUE TO severe anterior stromal disease, which stimulates the sensory nerve endings at the level of the basal epithelial cells.[8] It has been shown that cysteamine (HS-CH2-CH2-NH3) depletes cystine from cystinotic cells. It first crosses the plasma and lysosomal membranes and then gets concentrated in the acidic lysosomes (owing to positively charged amine groups). Inside the lysosome, free thiol groups and stored cystine form a complex (disulfide interchange reaction) which freely exits from the cystinotic lysosome using lysine transport system.[9]In this way topical cysteamine treatment bypasses the defective lysosomal-cystine carrier-mediated transport, thus accumulated cystine crystals are depleted.[6]

• **CYSTEAMINE VERSUS PLACEBO:** Pooling the results of 2 studies comparing cysteamine with placebo[8,24] resulted in the cysteamine-treated patients showing higher improvements and responses to therapy. Topical application of cysteamine also resulted in improvement in crystal density score compared to placebo (1 study; small sample size of n = 5 in each arm). Although in the study by Bradbury and associates[8] 3 of 4 eyes in the cysteamine arm and 0 of 4 eyes in the placebo arm showed improvement in terms of improvement in contrast sensitivity, the association was not statistically significant (Table 2). Regarding vision, Kaiser-Kupfer and associates[3] reported definite improvement in visual acuity in 2 patients who received cysteamine treatment. Although Bradbury and associates also reported improvement in visual acuity in some proportion of patients, they concluded that improvement in visual acuity could be attributed to improvement in photophobia and blepharospasm rather than improvement in corneal transparency.[8] Again, Mc Donald and associates[20] reported that the improvement in visual acuity was due to improved cooperation while testing and progression from symbol chart to Snellen chart. None of the studies compared adverse effects.

In terms of evaluation of the formulations, Bradbury and associates and Kaiser-Kupfer and associates[3,24] used

TABLE 2. Efficacy Comparison among Standard Cysteamine Drop, Placebo, Cystamine and Newer Formulations of Cysteamine

Comparison	Parameter	Number of Studies	Sample Size		MD/SMD (95% CI)	RR (95% CI)	Heterogeneity		
			A	B			Chi-squared/*df*	*P* Value	I^2
Cysteamine (A) versus. Placebo (B)	Improvement/response to therapy	2	25	25	NA	16.00 (2.30-111.37)	0.05/1	.82	0
	Crystal density score	1	5	5	−0.80 (−1.56 to −0.04)	NA	NA	NA	NA
	Improvement in contrast sensitivity	1	4	4	NA	7.00 (0.47-103.27)	NA	NA	NA
Cysteamine (A) versus cystamine (B)	Cysteine density score	1	12	12	−0.94 (−1.64 to −0.24)	NA	NA	NA	NA
Cysteamine new viscous formulation (Cystadrops) (A) versus. conventional Cysteamine formulation (B)	CCCS score (CFB on day 90)	1	30	30	−0.70 (−0.90 to −0.50)	NA	NA	NA	NA
	IVCM score (Total score on day 90)	1	17	17	−3.80 (−5.86 to −1.74)	NA	NA	NA	NA
	Corneal crystal depth (CFB on day 90)	1	28	29	−56.90 (−82.81 to −30.99)	NA	NA	NA	NA
	Photophobia score (CFB on day 90)	1	30	31	−0.70 (−1.02 to −0.38)	NA	NA	NA	NA

CFB = change from baseline; CI = confidence interval; *df* = degree of freedom; CCCS = corneal cystine crystal score; IVCM = in vivo confocal microscopy (score); MD = mean difference; SMD = standard mean difference; RR = risk ratio.

TABLE 3. Comparative Details of the Two Formulations of Cysteamine (Cystaran and Cystadrops)

	Cystaran	Cystadrops
Manufacturer	Sigma-Tau Pharmaceuticals	Orphan Europe France
Composition	Cysteamine (6.5 mg/ml CH = 0.44% active cysteamine = 0.55% CH according to NIH labeling practices[1]] with 0.01% BAC.[7]	Gel-like formulation of cysteamine containing cysteamine, 3.8 mg/mL (equivalent to 0.55% CH, also known as vCH 0.55%) containing carmellose sodium as a viscous agent.[4] Other ingredients are BAC, disodium edetate, citric acid monohydrate, sodium hydroxide, and 0.1 M hydrochloric acid.[21]
Frequency of instillation (1 drop in each eye)	Every waking hour	4 times per day
Storage	Pre-use: −25 to −15°; During use: 2-25° for 7 days[22]	Pre-use: 2-8° (refrigerated).[22] During use: refrigerated for 7 days (can be refrigerated at night, kept at room temperature during the daytime,[21] however it can also be stored at room temperature after opening.[4])

BAC = benzalkonium chloride; CH = cysteamine hydrochloride; NIH = US National Institutes of Health; vCH = viscous cysteamine hydrochloride.

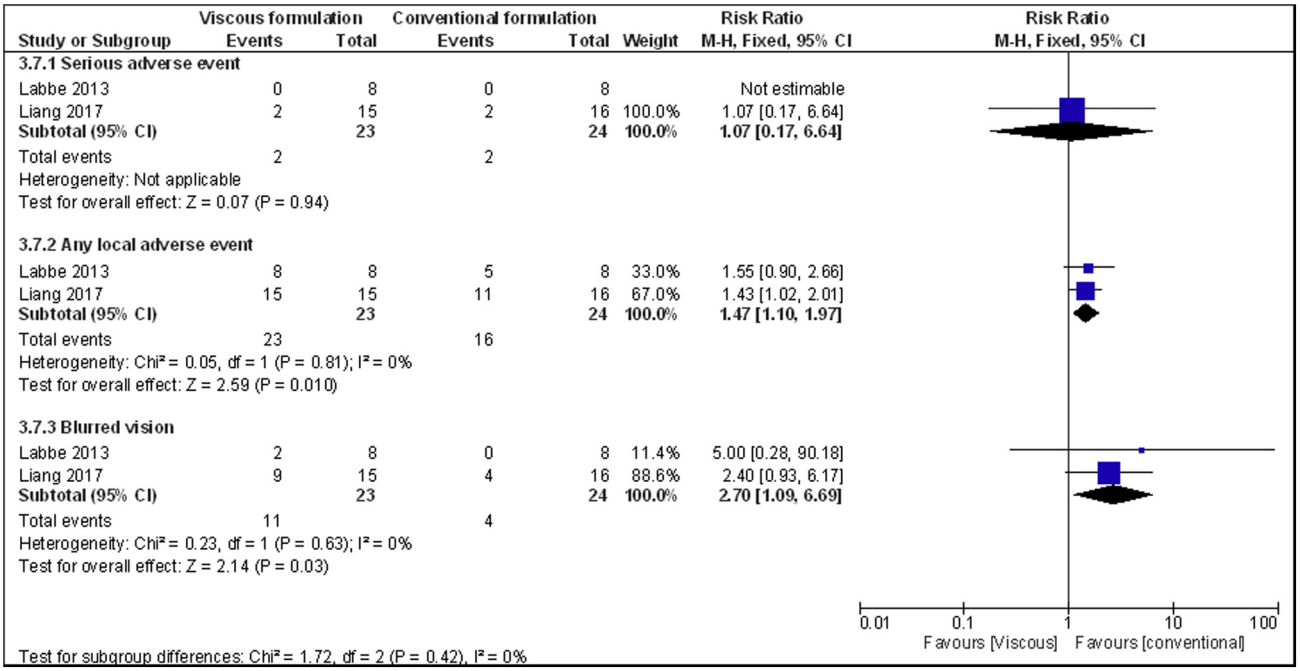

FIGURE 3. Comparison of adverse event between the new viscous formulation (Cystadrops) and the standard cysteamine formulation.

aqueous solutions of cysteamine ranging from 0.1%-0.5%.[8] As the efficacy of cysteamine 0.1% was low in terms of clearing cystine crystals, Kaiser-Kupfer and associates[3,24] advocated the use of 0.5% cysteamine drops.[3] In their study, they had to switch patients from 0.1% cysteamine to 0.5% cysteamine because of nonresponses with the lower dose.[3] The concentration of cysteamine used by Bradbury and associates was 0.2%, and the authors recommended 0.5% CH for better clearing of corneal crystals.[8] CH in a conventional formulation was well tolerated by all patients. However, the eye drops were required frequent instillation (6 times per day according to Bradbury and

TABLE 4. Comparison of the Adverse Events Between New Viscous Formulation (Cystadrops) And Standard Formulation of Cysteamine

Comparison	Adverse Effect	Number of Studies	Sample Size		RR (95% CI)	Heterogeneity		
			A	B		Chi-squared/*df*	*P* Value	I^2
Cysteamine new viscous formulation (cystadrops) (A) versus. conventional cysteamine formulation (B)	Itching	1	15	16	1.60 (0.56-4.58)	NA	NA	NA
	Burning sensation	1	15	16	2.67 (1.06-6.70)	NA	NA	NA
	Redness	1	15	16	1.37 (0.69-2.74)	NA	NA	NA

CI = confidence interval; *df* = degree of freedom; NA = not applicable; RR = risk ratio..

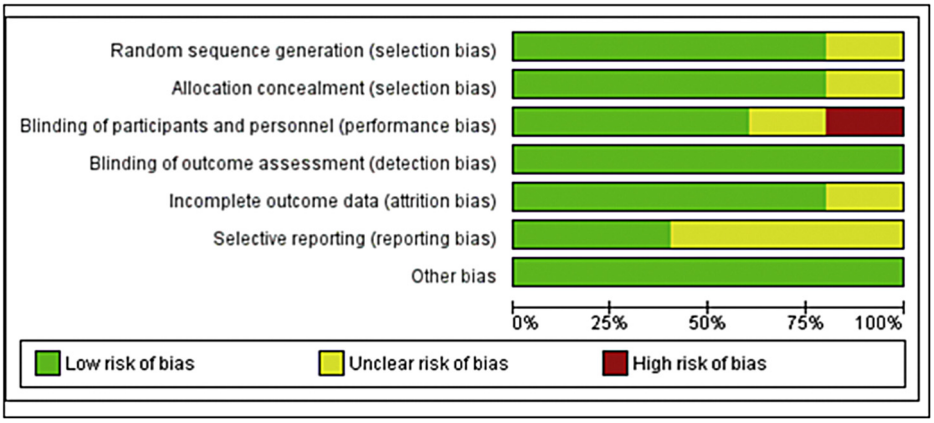

FIGURE 4. Risk of bias of the included randomized controlled trials.

associates[8] and hourly while awake according to Kaiser-Kupfer and associates[3]), which creates compliance issues and is difficult to maintain in the long term.

Another issue was instability of the solution at room temperature and short shelf life. At room temperature, the cysteamine preparation oxidizes to cystamine disulfide, which mandates compliance to stringent storage conditions.[6]

• **CYSTEAMINE VERSUS CYSTAMINE:** Iwata and associates evaluated the comparative efficacy of 0.5% cystamine versus 0.5% cysteamine topical solution.[6] In that study, cysteamine was better than cystamine in terms of crystal density score. However, none of the patients showed decrease in vision[6] compared to baseline. However, subjective improvement of photophobia and/or discomfort was reported in 5 of 6 patients, which resulted in remarkably increased quality of life.[6]With regard to adverse effects, in the cysteamine arm, 2 patients reported burning sensation. No other adverse effect was reported in the other arm.[6]

Although there are reports stating that cystamine depletes granular fraction of cystine in cystinotic fibroblasts, its efficacy is less than that of cysteamine in dissolving corneal crystal, and it is postulated that corneal cells do not have the ability to reduce cystamine to cysteamine, which is a primary requisite for its action.[7]

• **NEWER FORMULATIONS OF CYSTEAMINE:** In order to overcome the problems associated with the conventional cysteamine solution, 2 newer formulations have been delivered. One study compared a new preparation consisting of monosodium phosphate, BAC, and EDTA to the existing standard cysteamine (Cystaran) formulation.[7] Two studies compared a new viscous formulation (Cystadrops) with the standard cysteamine formulation (Table 3).[4,21]

In 2003, Tsilou and associates[7] developed a formulation containing cysteamine hydrochloride 0.55% along with 0.10% disodium EDTA, 1.85% monosodium phosphate, and 0.01% benzalkonium chloride (Investigational New Drug 40593; Sigma-Tau Pharmaceuticals), with the intention of enhancing patient convenience and compliance due to its longer shelf-life. Cysteamine in its stable free thiol form can be maintained in this new formulation for 7 months at room temperature and for 24 months in refrigeration.[8]Benzalkonium chloride (BAC) was used as a preservative.[1] BAC enhances penetration of cysteamine and also decreases surface tension and increases dispersion of gel formulations on ocular surface.[11,25] In the formulation by Tsilou and associates,[7] the change in CCCS from

baseline in the standard formulation group (Cystaran) was −0.75, and the change was 0.00 in case of the newer formulation, thus the newer formulation performed below the standard cysteamine formulation in terms of efficacy[7]; however, its adverse effect profile was similar to those of both formulations. In 2012, Sigma-Tau Pharmaceuticals received FDA approval for its standard cysteamine formulation Cystaran (containing 6.5 mg/ml CH = 4.4 mg/ml of cysteamine[1] = 0.44% free cysteamine base[22] = 0.55% CH according to NIH labeling practices[1]; the NIH version takes into account the moisture content, whereas Cystaran does not[1]) with benzalkonium chloride 0.01%,[1] but cold storage was still required.[1]

Following this, Labbe and associates[21] and Liang and associates[4] in their Cystadrops OCT study evaluated a new viscous formulation of cysteamine (Cystadrops), which was supposed to be used less frequently (4 times per day) in comparison to the standard formulation.[4,21,23] In their study, switching to Cystadrops was associated with a significant decrease in IVCM score from baseline at 4 years.[21] In the Phase III study with Cystadrops, significant decrease was seen in terms of change of CCCS from baseline, IVCM score (total score on day 90), corneal crystal depth change from baseline (at day 90), and photophobia score change from baseline (at day 90). However, the effect of Cystadrops on visual outcomes was still variable with no improvement in BCVA despite improvement in photophobia in the early phase study (phase I/IIa).[21] In the subsequent larger sample-sized parallel group phase III RCT, both improvements in visual parameters (visual acuity and contrast sensitivity) and improvement in photophobia were seen in the Cystadrops arm.[4] With regard to safety of the new viscous formulation, occurrence of local adverse effects (2 studies), blurring of vision (2 studies), and burning sensation (1 study) were higher in the new viscous formulation group. However there were no differences in occurrence of serious adverse events. The most common local adverse events were itching, redness, and burning sensation. The common local symptoms with the use of all CH solutions are associated with the requirement of maintenance of acidic pH for stability and use of BAC as preservative, which is a known irritant.[4,7] The increased frequency of local reactions seen in the vCH 0.55% arm could be because of 5-fold higher concentration of CH (concentration of CH in the control arm was 0.1%) and owing to its longer contact period with the ocular surface.[4] In both studies, all adverse events were manageable, and none of the patients discontinued treatment.

However, the findings of the studies by Liang and associates,[4] Labbe and associates[21] are limited by the use of 0.1% CH drops as control, as earlier studies recommended use of higher dose (0.5%) of cysteamine for treatment.[6–8,24] Previous animal studies reported occurrence of blepharitis with 2% cysteamine, but the side effect profile was similar to that of the placebo in cysteamine ranging from 0.5% to 1% range (Iwata and associates, unpublished data, 1998).[6] Again previous studies also used cysteamine in the range of 0.1% to 0.5%[6,8,24] without any increase in safety issues compared to placebo. Many earlier studies recommended use of 0.5% cysteamine for better clearance of corneal crystals.[8,24]

The new viscous formulation (Cystadrops) of cysteamine hydrochloride was approved as the first orphan drug to treat corneal cystinosis in Europe in 2017.[12] This viscous formulation offers instillation of only 4 times per day, refrigeration before use and storage at 25 C after first use, it needs no pre-use freezing and is stable for 7 days after opening.[12] However, the earlier formulations of cysteamine required freezing and storage away from an oxidizing environment to preserve their potency.[6] Cysteamine 0.1% has been discontinued due to lack of efficacy.[5]

CONCLUSIONS

TOPICAL CYSTEAMINE IS EFFECTIVE IN REDUCING THE corneal cystine burden. cysteamine is better than cystamine in treatment of corneal cystinosis. The viscous formulation of cysteamine (vCH 0.55%) is better than standard formulation of cysteamine 0.1% in terms of efficacy. The lack of efficacy of the standard formulation may be due to use of low dose (0.1% in the CH group compared to 0.55% in the vCH group). However, relative stability and requirement of less frequent application of the viscous solution gives us an added advantage. Although, occurrences of local adverse events were more in the viscous formulation group, they were manageable. More trials with equivalent dose between the standard and viscous formulation to evaluate the comparative safety and efficacy are needed.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported.

Funding/Support: None.

Financial disclosures: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Huynh N, Gahl WA, Bishop RJ. Cysteamine ophthalmic solution 0.44% for the treatment of corneal cystine crystals in cystinosis. *Exp Rev Ophthalmol* 2013;8(4):341–345.
2. Gahl WA, Kuehl EM, Iwata F, Lindblad A, Kaiser-Kupfer MI. Corneal crystals in nephropathic cystinosis: natural history and treatment with cysteamine eyedrops. *Mol Genet Metab* 2000;71(1–2):100–120.
3. Kaiser-Kupfer MI, Gazzo MA, Datiles MB, Caruso RC, Kuehl EM, Gahl WA. A randomized placebo-controlled trial of cysteamine eye drops in nephropathic cystinosis. *Arch Ophthalmol* 1990;108(5):689–693.
4. Liang H, Labbé A, Le Mouhaër J, Plisson C, Baudouin C. A new viscous cysteamine eye drops treatment for ophthalmic cystinosis: an open-label randomized comparative phase III pivotal study. *Invest Ophthalmol Vis Sci* 2017;58(4):2275–2283.
5. Makuloluwa AK, Shams F. Cysteamine hydrochloride eye drop solution for the treatment of corneal cystine crystal deposits in patients with cystinosis: an evidence-based review. *Clin Ophthalmol* 2018;12:227–236.
6. Iwata F, Kuehl EM, Reed GF, McCain LM, Gahl WA, Kaiser-Kupfer MI. A randomized clinical trial of topical cysteamine disulfide (cystamine) versus free thiol (cysteamine) in the treatment of corneal cystine crystals in cystinosis. *Mol Genet Metab* 1998;64(4):237–242.
7. Tsilou ET, Thompson D, Lindblad AS, et al. A multicentre randomised double masked clinical trial of a new formulation of topical cysteamine for the treatment of corneal cystine crystals in cystinosis. *Br J Ophthalmol* 2003;87(1):28–31.
8. Bradbury JA, Danjoux JP, Voller J, Spencer M, Brocklebank T. A randomised placebo-controlled trial of topical cysteamine therapy in patients with nephropathic cystinosis. *Eye (Lond)* 1991;5(Pt 6):755–760.
9. Pescina S, Carra F, Padula C, Santi P, Nicoli S. Effect of pH and penetration enhancers on cysteamine stability and trans-corneal transport. *Eur J Pharm Biopharm* 2016;107:171–179.
10. Pisoni RL, Park GY, Velilla VQ, Thoene JG. Detection and characterization of a transport system mediating cysteamine entry into human fibroblast lysosomes. Specificity for aminoethylthiol and aminoethylsulfide derivatives. *J Biol Chem* 1995;270(3):1179–1184.
11. McKenzie B, Kay G, Matthews KH, Knott R, Cairns D. Preformulation of cysteamine gels for treatment of the ophthalmic complications in cystinosis. *Int J Pharm* 2016;515(1–2):575–582.
12. Ricordati. Recordati Announces Marketing Approval For Cystadrops. Milan, Italy. Milan. Available at: ; 2017. https://www.recordati.com/resources/Pubblicazione/___db0005479c8c4280aef43608c297244f_/approval-cystadrops.pdf;. Accessed February 16, 2020.
13. Lyseng-Williamson K. Cystadrops (cysteamine hydrochloride 0.55% viscous eye-drops solution) in treating corneal cystine crystal deposits in patients with cystinosis: a profile of its use. *Drug Ther Perspectives* 2017;33:1–7.
14. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (2020). Cochrane, 2020. Available at www.training.cochrane.org/handbook. Accessed June 28, 2020.
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Br Med J* 2009;339:e1000100.
16. Sarma P, Kaur H, Kumar H, et al. Virological and clinical cure in COVID-19 patients treated with hydroxychloroquine: a systematic review and meta-analysis. *J Med Virol* 2020;92(7):776–785.
17. Higgins JPT, Altman DG, Sterne JAC. Assessing risk of bias in included studies. cochrane reviews syst database. Available at: https://handbook-5-1.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm. Accessed February 14, 2020.
18. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Br Med J* 2016;355:i4919.
19. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for Assessing The Quality Of Nonrandomised Studies In Meta-Analyses. Ottawa Hospital Research Institute; Ottowa, ON, Canada. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed March 24, 2020.
20. MacDonald IM, Noel LP, Mintsioulis G, Clarke WN. The effect of topical cysteamine drops on reducing crystal formation within the cornea of patients affected by nephropathic cystinosis. *J Pediatr Ophthalmol Strabismus* 1990;27(5):272–274.
21. Labbe A, Baudouin C, Deschênes G, et al. A new gel formulation of topical cysteamine for the treatment of corneal cystine crystals in cystinosis: the cystadrops OCT-1 study. *Invest Ophthalmol Vis Sci* 2014;55(13):462.
22. Radojkovic B. Cysteamine eye drops in the treatment of cystinosis – an Australian perspective. *J Pharm Pract Res* 2015;45(4):440–445.
23. Labbe A, Baudouin C, Deschênes G, et al. A new gel formulation of topical cysteamine for the treatment of corneal cystine crystals in cystinosis: The cystadrops OCT-1 study. *Mol Genet Metab* 2014;111(3):314–320.
24. Kaiser-Kupfer MI, Gazzo MA, Datiles MB, et al. A randomized placebo-controlled trial of cysteamine eye drops in nephropathic cystinosis. *Arch Ophthalmol* 1990;108(5):689–693.
25. Center for Drug Evaluation and Research. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/200740Orig1s000OtherR.pdf. Accessed February 18, 2020.