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N-acetylcarnosine (NAC) drops for age-related cataract (Review)

Dubois VDJP, Bastawrous A

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[Intervention Review]

N-acetylcarnosine (NAC) drops for age-related cataract

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ABSTRACT

Background

Cataract is the leading cause of world blindness. The only available treatment for cataract is surgery. Surgery requires highly-trained individuals with expensive operating facilities. Where these are not available, patients go untreated. A form of treatment that did not involve surgery would be a useful alternative for people with symptomatic cataract who are unable or unwilling to undergo surgery. If an eye drop existed that could reverse or even prevent progression of cataract, then this would be a useful additional treatment option.

Cataract tends to result from oxidative stress. The protein, L-carnosine, is known to have an antioxidant effect on the cataractous lens, so biochemically there is sound logic for exploring L-carnosine as an agent to reverse or even prevent progression of cataract. When applied as an eye drop, L-carnosine cannot penetrate the eye. However, when applied to the surface of the eye, N-acetylcarnosine (NAC) penetrates the cornea into the front chamber of the eye (near to where the cataract is), where it is metabolised into L-carnosine. Hence, it is possible that use of NAC eye drops may reverse or even prevent progression of cataract, thereby improving vision and quality of life.

Objectives

To assess the effectiveness of NAC drops to prevent or reverse the progression of cataract.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 6), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to June 2016), Embase (January 1980 to June 2016), Allied and Complementary Medicine Database (AMED) (January 1985 to June 2016), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to June 2016), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 28 June 2016. We handsearched the American Society of Cataract and Refractive Surgery (ASCRS) and the European Society of Cataract and Refractive Surgeons (ESCRS) meetings from 2005 until September 2015.

Selection criteria

We planned to include randomized or quasi-randomised controlled trials where NAC was compared to control in people with age-related cataract.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We identified two potentially eligible studies from Russia and the United States. One study was split into two arms: the first arm ran for six months, with two-monthly follow-up; the second arm ran for two years with six-monthly follow-up. The other study ran for four months with a data collection point at the start and end of the study only. A total of 114 people were enrolled in these studies. The ages ranged from 55 to 80 years.

We were unable to obtain sufficient information to reliably determine how both these studies were designed and conducted. We have contacted the author of these studies, but have not yet received a reply. Therefore, these studies are assigned as 'awaiting classification' in the review until sufficient information can be obtained from the authors.

Authors' conclusions

There is currently no convincing evidence that NAC reverses cataract, nor prevents progression of cataract (defined as a change in cataract appearance either for the better or for the worse). Future studies should be randomized, double-masked, placebo-controlled trials with standardised quality of life outcomes and validated outcome measures in terms of visual acuity, contrast sensitivity and glare, and large enough to detect adverse effects.

PLAIN LANGUAGE SUMMARY

N-acetylcarnosine (NAC) drops for age-related cataracts

What is the aim of this review?

The aim of this Cochrane Review was to find out if NAC eye drops can prevent or reverse the progression of cataracts (cloudy lens in the eye).

Key messages

It is uncertain whether NAC eye drops prevent, or reverse, the progression of cataracts.

What was studied in the review?

The eye has a clear lens that focuses the light on the back of the eye. As people get older this lens can become cloudy, leading to vision problems. A cloudy lens is known as a cataract. Doctors can remove the cataract and replace it with an artificial lens. This is usually a very successful operation. But any operation has risks and can be an unpleasant experience. Cataracts are common in older populations and cataract surgery is expensive for health care systems. This is why there is interest in preventing, or treating cataract, so that surgery can be avoided.

As part of normal metabolism, our bodies produce chemicals that contain oxygen and are reactive ("reactive oxygen species"). One theory of ageing is that these chemicals may be harmful and might lead to age-related changes in our body, such as cataract. This is known as oxidative stress. N-acetylcarnosine (NAC) is thought to be able to combat some of the effects of oxidative stress as it has anti-oxidant properties. If NAC can stop the lens from becoming cloudy, or reduce the cloudiness, this might improve people's vision and quality of life.

What are the main results of the review?

The Cochrane researchers found two potentially relevant studies. The studies compared NAC eye drops with placebo or no treatment. These studies were from Russia and the United States and were conducted by the same research group.The Cochrane researchers were unable to find out enough information about these studies to include in the review. These studies are assigned as 'awaiting classification' in the review until sufficient information can be obtained from the authors.

How up-to-date is this review?

The review authors searched for studies that had been published up to 28 June 2016..

BACKGROUND

Description of the condition

Cataract is opacification of the lens within the eye, which can cause symptoms due to poor, or altered quality of vision. This can lead to a reduced ability to carry out activities of daily living, driving and working (Steinberg 1994).

Recent figures show that cataract is responsible for 48% of world blindness, representing some 17.6 million people making it the leading cause of blindness (Resnikoff 2004).

Description of the intervention

Currently, the only widely-accepted treatment for cataract is removal. This is done through an operation. As the cataract is the natural lens of the eye that has reduced clarity, its removal usually precedes replacement of the natural lens with an artificial one.

There were 320,000 cataract operations carried out in the UK between 2012 and 2013 (HSCIC 2013). In the United States, the figure is estimated at 1.7 million operations carried out in Medicare beneficiaries in 2004 (Schein 2012).

Currently there is no treatment for cataracts aside from surgery. One of the causes of cataract may be oxidative stress within the lens. Oxidative stress results from the formation of free radical species. Carnosine is a naturally occurring dipeptide, implicated in reducing free radicals in the body (Dahl 1988).

Anti-cataract drops are instilled onto the affected eye twice a day. A course of treatment is recommended for a minimum of two months and may be required indefinitely to prevent progression of the cataract.

How the intervention might work

Topical application of carnosine onto the ocular surface does not result in penetration into the eye. Hence, a vehicle has been developed, called N-acetylcarnosine (NAC). When NAC is instilled onto the eye it penetrates the anterior chamber of the eye through the cornea. Subsequent metabolism of NAC within the eye produces L-carnosine, the active drug (Babizhayev 1996).

L-carnosine has been shown to have an antioxidant effect on the cataractous lens (Babizhayev 1989). Consequently, it is possible that topical administration of NAC could lead to a reduction in cataract by either slowing down the progression of the cataract or indeed reversing the cataractous change.

Why it is important to do this review

The current forms of management are either conservative (do nothing) or surgical. The cataract(s) may cause the patient to cease or downgrade certain activities such as driving, working and self-caring.

Overall success rates for cataract surgery include 95% of patients being satisfied with the results of the surgery (Lum 2000); the quoted risk of sight-threatening infection is 0.1% (Montan 2002).

In high-income countries a medical treatment or prophylactic agent such as NAC eye drops would add to the treatment options available to the ophthalmologist and medical practitioners in the primary care setting; fewer people may need to consult an ophthalmologist and of those who did, fewer may require surgery. Individuals may be able to choose which treatment option they prefer and fewer surgical complications would arise from fewer operations. In countries with emerging economies, it may mean the difference between survival and death. Ultimately, more people may have improved vision and fewer may have worse vision.

It is important to identify whether the evidence supports the theory. There are multiple freely-available brands of eye drops purported to reverse cataract. These can be obtained without prescription and over the Internet. Unless there is evidence to support their use, they should not be distributed. Conversely, manufacturers of machinery, consumables and intraocular lenses relevant to cataract surgery may not be motivated to advance research in this field or share study results due to the possible loss of income that would follow the successful use of such an eye drop. Conducting this review could eliminate this bias.

OBJECTIVES

To assess the effectiveness of carnosine to prevent or reverse the progression of cataract.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized and quasi-randomised controlled trials. We excluded cross-over trials due to the uncertainty regarding carry-over effects.

Types of participants

We included trials where participants are over 50 years of age with measurable cataract, specifying which eye is affected (or both eyes), as defined by a suitably qualified medical practitioner or researcher, which is shown to be affecting their quality of life through reduced or abnormal vision. We did not make any demographic differentiations. We excluded participants with any ocular comorbidity,

as this condition may make it difficult to diagnose the cause of reduced vision.

Types of interventions

We included all trials where topical NAC is compared to a control (such as saline or artificial tear) or to cataract surgery. Included trials had a minimum treatment period of two months at any dose and frequency.

Types of outcome measures

Primary outcomes

- Cataract appearance as defined on LOCS III grading slides or Scheimpflug photography (pixel counting).

We planned to assess the primary outcome as short-term (less than one year) and long-term (more than one year). Change was defined by the trial investigators.

Secondary outcomes

- Quality of life as measured by validated quality of life questionnaires, namely VCM1, IVI, VFQ-25, AVL, Van Dijk, NHI, Carta, SQDL-DVI, ADVS, VF-14, VDA, CSS, TyPE, HVAT, MIOLS VFQOL, Catquest, Mone-stam and VFI.
- Visual acuity as measured by Snellen (imperial or metric), LogMAR or ETDRS charts.
- Contrast sensitivity as measured by validated printed optotype or grating tests, namely Mentor B-VAT, CSV-1000, MCT 8000, Pelli-Robson, ETDRS, Cambridge, Regan and Joyce.
- Glare disability as measured by validated glare disability tests, namely Mentor BAT, Miller-Nadler and Berkely glare test.

Adverse effects

As reported.

We planned to assess all secondary outcomes as short-term (less than one year) and long-term (more than one year). Change was defined by the trial investigators.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 6), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to June 2016), Embase (January 1980 to June 2016), Allied and Complementary Medicine Database (AMED) (January 1985 to June 2016), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to June 2016), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 28 June 2016.

See Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), Embase (Appendix 3), CINAHL (Appendix 4), AMED (Appendix 5), ISRCTN (Appendix 6), ClinicalTrials.gov (Appendix 7) and the WHO ICTRP (Appendix 8) .

Searching other resources

We searched the reference lists of included studies and searched the Science Citation Index database to identify any additional trials. We handsearched the society meetings of the American Society of Cataract and Refractive Surgery (ASCRS) and the European Society of Cataract and Refractive Surgeons (ESCRS) from 2005 to September 2015.

Data collection and analysis

Selection of studies

Both review authors (VD, AB) searched through the results and independently extracted data in duplicate. We included studies on the basis of the criteria specified above. For studies that we labelled as 'include' or 'unsure', we obtained a full-text report of the study. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009), and Characteristics of excluded studies table. The two review authors resolved any disagreement by discussion.

Data extraction and management

We designed a paper data collection form. The form consisted of study and version ID, review author ID, citation and contact details, confirmation of eligibility for review, any reasons for exclusion of participants, study design, study duration, evidence of sequence generation and allocation sequence concealment, masking and documentation of any concerns over bias.

- Participant factors: number, setting, diagnostic criteria, age, sex, country and study dates.
- Intervention data: number of groups, number of participants per group and details of intervention for all groups.
- Outcomes: quality of life (differences in scores between baseline and study endpoint), cataract severity (differences in

LOCS III scores and density (Scheimpflug) between baseline and study endpoint) and visual function (differences in measured visual acuity and contrast sensitivity between baseline and study endpoint).

We planned to collect these data at short-term (less than one year) and at long-term (more than one year) intervals. We based the outcome criteria on change from the baseline; we recorded scales, including limits and units of measurement.

- Results: any missing participants, summary data as detailed above including means, confidence intervals and P values.
- Adverse event data: (worsening in quality of life scores, visual function, or cataract within the study period, or adverse effects from topical application of NAC drops, i.e. pain, eye infection, allergy and scarring to ocular surface) and relevant notes.

We documented sources of funding, along with key conclusions from study authors, any references to related studies and any comments from the review authors.

Both review authors independently collected all the data in duplicate. One review author (VD) entered the data from both review authors into Review Manager 5 (RevMan 2014), and the second review author (AB) then checked that the data had been correctly entered.

Assessment of risk of bias in included studies

We used Cochrane's tool for assessing risk of bias as per Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* assessing the following (Higgins 2011): sequence generation, allocation concealment, masking (blinding) of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. We assessed all parameters as 'low', 'high' or 'unclear' risk of bias.

Measures of treatment effect

We planned to analyse ordinal data such as visual acuity and LOCS III grading as continuous data, using their respective standardised mean differences (SMDs).

We planned to analyse continuous data such as cataract density (measured by pixel counting on a Scheimpflug camera system) and quality of life data, with respective SMDs, as the measurement scales may vary depending upon which equipment or method(s) are used in each study.

We planned to consider data on glare sensitivity and contrast sensitivity as ordinal or continuous, depending upon the measurement method used.

Unit of analysis issues

We included only studies where people are randomized to treatment. We excluded trials where one eye receives treatment and the other placebo.

Trialists may use two main methods to deal with the problem of non-independence of data from eyes: (i) they may enrol one eye per person into the trial, or (ii) they may analyse data from both eyes making corrections for within-person correlation.

For (i), we documented the criteria used to define which eye is to be included in the trial.

For (ii), if the trialist has not adjusted for within-person correlation, we planned to take statistical advice, but as no trials were included this is not relevant for this version of the review.

Dealing with missing data

We planned to document the reasons why participants were not followed up, if reported. We planned to contact study trialists for further clarification as needed. At that stage we planned to be able to make judgements as to whether the data are missing at random or not. We planned to address the potential impact of missing data in the Discussion section.

Assessment of heterogeneity

We planned to investigate clinical heterogeneity by examining differences in population, intervention and outcomes. We planned to investigate statistical heterogeneity by looking at the forest plots and statistical tests (Chi^2 and the I^2 statistic) since tests for statistical heterogeneity are underpowered when the number of studies is low.

Assessment of reporting biases

We planned to use funnel plots to help in our assessment of bias as per Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011), but as there was not enough data, we did not create funnel plots.

Data synthesis

As we cannot assume that the intervention will have the same effect in different groups of people, that is, that each included study will be measuring the same effect, we planned to pool the data using a random-effects model (providing there are three or more included trials providing relevant data). A random-effects model will allow for differences in the effect of the intervention between the included trials. If the heterogeneity is too great, then meta-analysis will not be possible.

Subgroup analysis and investigation of heterogeneity

We planned to consider the following subgroups but in the event there were not enough data to do these analyses.

- Smokers versus non-smokers.
- Diabetics versus non-diabetics.

Sensitivity analysis

We did not plan to conduct any sensitivity analysis for this review.

Summary of findings

We planned to include a 'Summary of findings' table, but due to the sparse and uncertain data we did not do this. In future updates of this review, if we identify further trials, we will include a 'Summary of findings' table including our primary and secondary outcomes.

We assessed the overall quality of the evidence using GRADEpro GDT (GRADEpro GDT 2014). This was done against the following GRADE parameters (Atkins 2004): study limitations, consistency of effect, imprecision, indirectness and publication bias .The following outcomes were assessed: cataract appearance, quality of life, visual acuity, contrast sensitivity and glare disability.

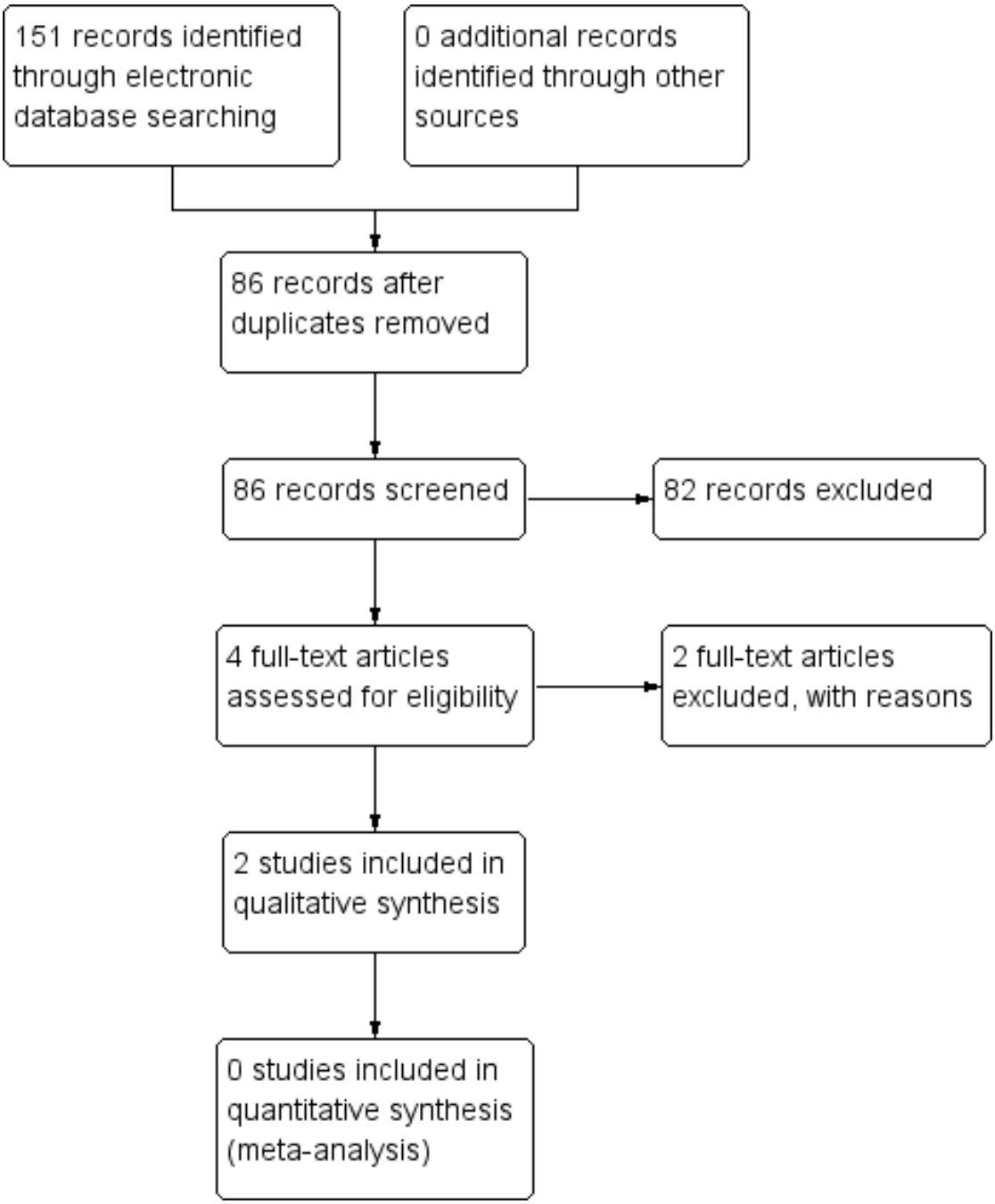
RESULTS

Description of studies

Results of the search

The electronic searches yielded a total of 151 references (Figure 1). The Cochrane Information Specialist removed 65 duplicate records and we screened the remaining 86 reports. We rejected 82 records after reading the abstracts and obtained the full-text reports of four references for assessment. All four studies were conducted by Dr Babizhayev - after assessing the studies, we considered Babizhayev 2002; and Babizhayev 2004 were potentially eligible and we excluded Babizhayev 2009 and Babizhayev 2011; see below for details.

Figure 1. Study flow diagram.



Studies awaiting classification

We identified two potentially eligible studies (Babizhayev 2002; Babizhayev 2004).

In Babizhayev 2002, 49 people (76 eyes) were enrolled in Russia and the United States. Some participants were followed up to six months and others to 24 months, however, the rationale for this was not clear, and these were described as two different studies. Participants were randomized to NAC 1% (26 people, 41 eyes) or control. Some of the control group received placebo (13 people, 21 eyes) and others received no treatment (10 people, 14 eyes), but again it was not clear why this was the case. Outcomes measured included cataract appearance (image analysis), visual acuity (Snellen), a measure of glare sensitivity and adverse effects.

In Babizhayev 2004, 65 people were enrolled in the United States. People with cataract were identified from the medical notes and the participants were randomly allocated to NAC (35 people) or placebo (30 people) and followed up for four months. Outcomes included visual acuity (logMAR) and the halometer glare disability test.

We were unable to obtain sufficient information to reliably determine how both these studies were designed and conducted. We have contacted the author of these studies, but have not yet received a reply. Therefore, these studies are assigned as 'awaiting classification' until sufficient information can be obtained from the authors.

Excluded studies

We excluded two studies (Babizhayev 2009; Babizhayev 2011), and reasons for exclusion can be found in the Characteristics of excluded studies table.

Risk of bias in included studies

No studies were found that met the inclusion criteria.

Effects of interventions

No studies were found that met the inclusion criteria.

DISCUSSION

Summary of main results

Two studies potentially met the inclusion criteria for this review but we were unable to obtain further information from the study authors to enable us to judge whether they were eligible for inclusion in the review.

Overall completeness and applicability of evidence

There is insufficient good quality evidence to be able to answer the review question.

Potential biases in the review process

We followed procedures expected by Cochrane.

Agreements and disagreements with other studies or reviews

Other reviews currently focus on the biochemical and structural aspects of cataractogenesis. As far as we are aware there have been no other independent assessment of the clinical trials of NAC drops in the prevention of cataract.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence that NAC reduces the progression of cataract, nor reverses cataract.

Implications for research

The subject of non-surgical treatments for cataract remains topical and valid. There is room for a well-designed, randomized, placebo-controlled trial evaluating the efficacy of L-carnosine in the treatment of cataracts. Future studies in this area should be well-powered, randomized, double-masked, placebo-controlled trials with standardised quality of life outcomes and validated measures of visual acuity, contrast sensitivity and glare. Follow-up should be a minimum of two months.

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• Jennifer Evans and Anupa Shah for their advice and assistance throughout the development of the protocol/review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Babizhayev 2009	Review article
Babizhayev 2011	Biochemistry article

Characteristics of studies awaiting assessment *[ordered by study ID]*

Babizhayev 2002

Methods	Randomised, partly placebo-controlled study - some of the control group were untreated
Participants	Country: Russia and United States Number of people (eyes) randomized: 49 (76) Average age: 65 +/- 7.0 years 49% women Inclusion criteria: • confirmed diagnosis of age-related cataract "according to the medical history, clinical observations and epidemiological study", availability for study of both lenses • presence of a cataract in at least one eye • cataracts judged not to require surgery in the near future (2 years) based on the patients' visual needs and ocular symptomatology • 52 to 80 years of age • pupillary dilation could be performed safely Exclusion criteria: • any other ocular disease such as glaucoma or clinically significant diabetic retinopathy • previous laser retinal photocoagulation • prior corneal or anterior segment surgery or corneal scars that would interfere with visualisation or photography of the anterior segment • mature cataract (VA less than 0.1) in both eyes, and were likely to be candidates for cataract surgery within 1 year • monocular aphakia or secondary cataracts (e.g. cataracts associated with steroid intake, total body or local irradiation, local inflammatory or degenerative process or ocular trauma) • known or presumed hypersensitivity to any component of the ophthalmic preparations (active substances or excipients) • treated with drugs that could interfere with the trial • wearing contact lenses • concomitant ocular diseases
Interventions	Intervention: • Topical NAC 1% eye drops twice daily n = 26 (41 eyes) Comparator: • Placebo n = 13 (21 eyes)

Babizhayev 2002 (*Continued*)

	• No treatment n = 10 (14 eyes) Unclear why some people received placebo and others did not
Outcomes	All participants were evaluated at entry and followed up every 2 months for a 6-month period (trial 1), or at 6-month intervals for a 2-year period (trial 2), for best-corrected visual acuity and glare testing. In addition, cataract was measured using stereocinematographic slit-images and retro-illumination examination of the lens. Digital analysis of lens images displayed light scattering and absorbing centres in two- and three-dimensional scales
Notes	Date study conducted: not reported Funding source: Innovative Vision Products, Inc, County of New Castle,Delaware, USA Declarations of interest: No declarations of interest in the paper but NAC is marketed by the lead author under the auspices of Innovative Vision Products Trial id: not reported

Babizhayev 2004

Methods	Randomised, placebo-controlled study
Participants	Country: United States Number of people (eyes) randomised: 65 (?) Average age: 68 years (range 55 to 80) 47% women Inclusion criteria: • cataract in one or both eyes with best-corrected visual acuity of 20/40 or worse in one or both eyes as indicated by the medical record • no previous cataract surgery in either eye • a primary diagnosis of cataract in the medical record • living independently in the community • legally licensed to drive and drove during the 5 years prior to enrolment Exclusion criteria: • known or presumed hypersensitivity to any component of the ophthalmic preparations (active substances or excipients) • treated with drugs that could interfere with the trial The report also provided data on drivers without cataract. These data are not included in this review
Interventions	Intervention: • Topical NAC 1% eye drops twice daily (n = 35) Comparator: • Placebo (n = 30)
Outcomes	All participants evaluated at entry and at 4 months with visual acuity and glare sensitivity Better and worse eyes were reported and sometimes the eyes were averaged within person
Notes	Date study conducted: not reported Funding source: see declaration of interest Decarations of interest: *"This work was planned, organized, and supported by Innovative Vision Products, Inc. (County of New Castle, DE). Innovative Vision Products, Inc. is a holder of the worldwide patent (including PCT International Publication Number WO 2004/028536 A1) for the application of N-acetylcarnosine for the treatment of ophthalmic*

Babizhayev 2004 (*Continued*)

	disorders, including cataracts" Trial registration id: not reported

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Cataract
#2 cataract*
#3 eye*
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Carnosine
#6 carnosine*
#7 NAC
#8 (#5 OR #6 OR #7)
#9 (#4 AND #8)

Appendix 2. MEDLINE (Ovid) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. cataract/
14. cataract$.tw.
15. eye$.tw.
16. or/13-15
17. carnosine/
18. carnosine$.tw.
19. NAC.tw.
20. or/17-19
21. 16 and 20
22. 12 and 21

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase (Ovid) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp cataract/
34. cataract$.tw.
35. eye$.tw.
36. or/33-35
37. carnosine/
38. carnosine$.tw.
39. NAC.tw.
40. or/37-39
41. 36 and 40
42. 32 and 41

Appendix 4. CINAHL (EBSCO) search strategy

S7 S3 AND S6
S6 S4 OR S5
S5 NAC
S4 carnosine*
S3 S1 OR S2
S2 cataract*
S1 (MH "Cataract")

Appendix 5. AMED (Ovid) search strategy

1. cataract/
2. cataract$.tw.
3. eye$.tw.
4. or/1-3
5. carnosine$.tw.
6. NAC.tw.
7. or/5-6
8. 4 and 7

Appendix 6. ISRCTN search strategy

"Cataract AND (Carnosine OR NAC)"

Appendix 7. ClinicalTrials.gov search strategy

Cataract AND (Carnosine OR NAC)

Appendix 8. WHO ICTRP search strategy

Cataract AND (Carnosine OR NAC)

CONTRIBUTIONS OF AUTHORS

- Conceiving the review: Cochrane Eyes and Vision
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- Co-ordinating the review: VD
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    - undertaking manual searches: VD
    - screening search results: VD, AB
    - organising retrieval of papers: Cochrane Eyes and Vision Group editorial team
    - screening retrieved papers against inclusion criteria: VD, AB
    - appraising quality of papers: VD, AB

- extracting data from papers: VD, AB
- writing to authors of papers for additional information: VD
- providing additional data about papers: VD
- obtaining and screening data on unpublished studies: VD

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- Providing a clinical perspective: VD
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DECLARATIONS OF INTEREST

VD: None known

AB: None known

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Adverse effects were omitted from the protocol but have been included in the review. Using the GRADE approach was not included in the protocol but was adapted for the review.