Mineralocorticoid receptor antagonists in chronic central serous chorioretinopathy

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Abstract

Introduction

Central serous chorioretinopathy consists of the leakage of fluid from the choroid and its accumulation into the subretinal space. Its chronic form is associated with permanent vision loss. Mineralocorticoid receptor antagonists are an alternative treatment for this condition, although there is no clear evidence about their effectiveness.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified three systematic reviews including 22 studies overall and four of them are randomized trials. We concluded that in chronic central serous chorioretinopathy, mineralocorticoid receptor antagonists probably make little or no difference to best-corrected visual acuity. We are uncertain whether this intervention reduces subretinal fluid height because the certainty of the evidence is very low. Furthermore, this intervention may make little or no difference in terms of adverse effects, but the certainty of the evidence is low.

Problem

Central serous chorioretinopathy consists of the leakage of fluid from the choroid and the retinal pigment epithelium into the subretinal space, which generate a serous retinal detachment. There is not a universally accepted classification for this disease, but in general terms, it is chronic when its course is longer than three months. In this case, there is a high risk of permanent vision loss.

There is not a standard treatment for chronic central serous chorioretinopathy and there are several alternatives of management: photodynamic therapy, focal laser photocoagulation, micropulse diode laser, intravitreal anti-vascular endothelial growth factor agents (anti-VEGF) and mineralocorticoid receptor antagonists (eplerenone and spironolactone). The association between central serous chorioretinopathy and the overactivation of mineralocorticoid receptors localized in the choroid supports the employment of these drugs.

Mineralocorticoid receptor antagonists are an affordable treatment especially when there is not a leakage point in fluorescein angiography, or when it has a macular localization. Nevertheless, their effectiveness is unclear.

Key messages

- Mineralocorticoid receptor antagonists in chronic central serous chorioretinopathy probably make little or no difference to best-corrected visual acuity.
- We are uncertain whether mineralocorticoid receptor antagonists in chronic central serous chorioretinopathy reduce subretinal fluid height because the certainty of the evidence has been assessed as very low.
- Mineralocorticoid receptor antagonists in chronic central serous chorioretinopathy may make little or no difference to adverse effects (low certainty evidence).

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We identified three systematic reviews[1-3] with 22 primary studies[4-25], four of which are randomized control trials[4-7]. The table and summary are based on the randomized trials, as the observational studies did not increase the level of certainty of the evidence nor added any additional relevant information.
What types of patients were included*	All trials included patients with chronic central serous chorioretinopathy, defined by the systematic reviews as central serous chorioretinopathy with a course longer than three months. The best-corrected visual acuity for the control group (placebo or observation) on average was 0.24 logMAR scale units. For the intervention group, this parameter was 0.36 logMAR[4-7]. The baseline subretinal fluid height was on average 198.5 micrometres (µm) for the control group and 210.5 µm for the intervention group[4-7].
What types of interventions were included*	All trials evaluated mineralocorticoid receptor antagonists. Two of them[4,5] evaluated eplerenone, one trial[6] evaluated spironolactone and another trial[7] evaluated the combination of spironolactone and eplerenone. Two trials[4,5] evaluated the administration of 25 mg daily of oral eplerenone for one week followed by 50 mg daily for nine weeks[4] or 12 weeks[5]. Another trial[6], evaluated the administration of 50 mg daily of spironolactone for four weeks. In the last trial[7], the patients received 50 mg daily of eplerenone, followed by 50 mg daily of spironolactone for four weeks. Three trials[4-6] compared the intervention with placebo and one trial[7] compared it with placebo and spironolactone.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

What types of outcomes were measured	The trials evaluated several outcomes grouped by the systematic reviews as follows: • Best-corrected visual acuity, in logMAR scale. • Subretinal fluid height in micrometres (µm). • Choroidal thickness in micrometres (µm). • Adverse effects. The average follow-up was 8,5 weeks with an interval between four to 24 weeks.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of findings

The information about the effect of mineralocorticoid receptor antagonists (spironolactone and eplerenone) in chronic central serous chorioretinopathy is based in four randomized controlled trials (75 eyes) [4-7].

Four trials measured the outcomes best-corrected visual acuity (logMAR scale) and subretinal fluid height (µm) (75 eyes) [4-7].

None of the systematic reviews enabled data extraction regarding adverse effects to perform a meta-analysis. In consequence, the information about this outcome is presented as a narrative synthesis.

The summary of findings is the following:

- Mineralocorticoid receptor antagonists in chronic central serous chorioretinopathy probably make little or no difference to the best-corrected visual acuity (moderate certainty evidence).
- We are uncertain whether mineralocorticoid receptor antagonists in chronic central serous chorioretinopathy reduces subretinal fluid height because the certainty of the evidence has been assessed as very low.
- Mineralocorticoid receptor antagonists in chronic central serous chorioretinopathy may make little or no difference in terms of adverse effects (low certainty evidence).

Mineralocorticoid receptor antagonists in chronic central serous chorioretinopathy

Patients Chronic central serous chorioretinopathy (lasts more than three months)

Interven-tion Mineralocorticoid receptor antagonists (eplerenone and/or spironolactone)

Comparison Placebo

Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT mineralocorticoid receptor antagonists	**WITH mineralocorticoid receptor antagonists**		
Best-corrected visual acuity**	0.2 logMAR units	0.14 logMAR units	--	⨁⨁⨁◯[1] Moderate
	MD: 0.06 logMAR units less (Margin of error: 0.1 to 0.02 logMAR units less)			
Subretinal fluid height	183.5 µm	99.9 µm	--	⨁◯◯◯[1,2] Very Low
	MD: 83.6 µm less (Margin of error: 178.7 µm less to 11.6 µm more)			
Adverse effects	One systematic review [1] reported that spironolactone and eplerenone were well tolerated by most of the patients and the adverse effects did not cause treatment withdrawal. Two systematic reviews [2], [3] reported cases of patients with diarrhoea (n=1), sedative effect (n=1) and fatigue (n=1), without specifying in which group they appeared. One patient who received spironolactone reported gynecomastia [7]. No patient had hyperkalemia nor hypotension [5], [6], [7].			⨁⨁◯◯[1,4] Low

Margin of error: 95% confidence interval (CI).
MD: Mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).

*For the best-corrected visual acuity, the mean **WITHOUT mineralocorticoid receptor antagonists** is based on the average of the trial with higher weight in the meta-analysis [7]. For subretinal fluid height, the mean **WITHOUT mineralocorticoid receptor antagonists** is based on the average of the trials control groups. The risk **WITH mineralocorticoid receptor antagonists** (and its margin of error) is calculated from the mean difference (and its margin of error).
**The outcome best-corrected visual acuity is defined as the best visual acuity with optical correction reached by each patient. LogMAR scale is a logarithmic scale in which a lower value indicates a better visual acuity.

[1] We downgraded the certainty of the evidence in one level for risk of bias, because of the limitations related to random sequence generation (selection bias), blinding of participants and personnel (performance bias), attrition bias and selective reporting (reporting bias).
[2] We downgraded the certainty of the evidence in one level for imprecision since different clinical decisions would be taken at each extreme of the confidence interval.
[3] We downgraded the certainty of the evidence in one level for inconsistency because one trial [5] had an opposite effect compared with the other trials (I^2=90%).
[4] We downgraded the certainty of the evidence in one level for imprecision, since there are so few events and it cannot be ruled out that the observed effect is explained by chance.

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

About the certainty of the evidence GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

The results exposed in this article apply to patients with central serous chorioretinopathy for more than three months.

These results could be extrapolated to patients with this disease when there is not a leakage point in fluorescein angiography or when it has a macular localization because laser therapy is not indicated in these cases.

About the outcomes included in this summary

The outcomes included in this summary coincide with those reported by the systematic reviews and according to the authors' opinion, they are critical for decision-making.

Balance between benefits and risks, and certainty of the evidence

The use of mineralocorticoid receptor antagonists in chronic central serous chorioretinopathy probably does not generate an improvement on visual acuity, since there are no differences between the groups (moderate certainty of evidence).

Furthermore, it is not possible to establish if the intervention affects subretinal fluid height because the certainty of the evidence is very low.

Finally, although the intervention could be safe, the use of mineralocorticoid receptor antagonists in chronic central serous chorioretinopathy do not seem to produce a clear benefit.

Resource considerations

The cost of the mineralocorticoid receptor antagonists is lower compared with other interventions for chronic central serous chorioretinopathy such as photodynamic therapy, laser photocoagulation and antiangiogenic agents.

Nevertheless, it is not possible to perform a cost-benefits balance due to the unclear benefit of mineralocorticoid receptor antagonists.

Cost-effectiveness studies comparing this intervention with other alternatives of treatment are necessary to ease decision-making.

What would patients and their doctors think about this intervention

Given the evidence presented in this summary, we expect variability in the decision-making process about the intervention.

Although the intervention seems to be safe and low cost, the clinical decision should be individualized according to the patient characteristics and preferences, resource availability and clinician experience regarding the alternatives of treatment for chronic central serous chorioretinopathy.

Differences between this summary and other sources

The conclusions of this summary are similar to those obtained by the systematic reviews.

A recent broad synthesis[26] assessed different alternatives of treatment, the available evidence and proposes an algorithm for management. In general terms, the authors recommend photodynamic therapy as the first line of treatment because the evidence is less convincing for mineralocorticoid receptor antagonists compared with micropulsed laser and photodynamic therapy.

We did not identify specific international clinical guidelines about the management of chronic central serous chorioretinopathy.

Could this evidence change in the future?

Futhermore, we found two ongoing systematic reviews[30,31] in PROSPERO database. In one of them[30], the authors evaluate the effect of mineralocorticoid receptor antagonists in chronic central serous chorioretinopathy and in the second one[31], the authors do not specify if they are assessing the intervention in the acute or the chronic form of the disease.

The probability that future evidence changes the conclusions of this article is low for visual acuity, high for subretinal fluid height and moderate for adverse effects.

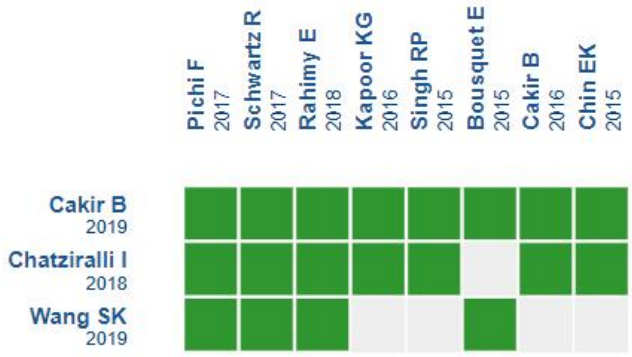
We identified one randomized controlled trial[27] published in January of 2020 in which authors compare eplerenone with placebo for chronic central serous chorioretinopathy. This trial was not included by the systematic reviews because of the date of publication.

There are two ongoing randomized controlled trials[28,19] registered in the International Clinical Trials Registry Platform of the World Health Organization whose objective is to evaluate the use of mineralocorticoid receptor antagonists in chronic central serous chorioretinopathy. The first one[28], compare the effect of half-dose photodynamic therapy with eplerenone and the other trial[29] will assess the use of spironolactone versus placebo.

Furthermore, we found two ongoing systematic reviews[30,31] in PROSPERO database. In one of them[30], the authors evaluate the effect of mineralocorticoid receptor antagonists in chronic central serous chorioretinopathy and the second one[31] does not specify if the intervention is used for the acute or chronic form of the disease.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Mineralocorticoid receptor antagonists in chronic central serous chorioretinopathy.

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

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