ClinicalEvidence

Uveitis (acute anterior)

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ABSTRACT

INTRODUCTION: Anterior uveitis is rare, with an annual incidence of 12/100,000 population, although it is more common in Finland (annual incidence of 23/100,000), probably because of genetic factors, such as high frequency of HLA–B27 in the population. It is often self-limiting, but can, in some cases, lead to complications such as posterior synechiae, cataract, glaucoma, and chronic uveitis. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of anti-inflammatory eye drops on acute anterior uveitis? We searched: Medline, Embase, The Cochrane Library and other important databases up to November 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found six systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: corticosteroids, mydriatics, and non-steroidal anti-inflammatory drug eye drops.

QUESTIONS

INTERVENTIONS

ANTI-INFLAMMATORY DROPS

Likely to be beneficial

Unknown effectiveness

To be covered in future updates

Slow taper of drug treatment

Treatment of chronic iridocyclitis

Footnote

*Based on consensus; RCTs unlikely to be conducted.

Key points

- Anterior uveitis is inflammation of the uveal tract, and includes iritis (inflammation of the iris) and iridocyclitis (inflammation of both iris and ciliary body).

  It is usually rare, with an annual incidence of 12/100,000 population, although it is more common in Finland (annual incidence of 23/100,000), probably because of genetic factors, such as high frequency of HLA–B27 in the population.

  It is often self-limiting, but can in some cases lead to complications such as posterior synechiae, cataract, glaucoma, and chronic uveitis.

- Corticosteroid eye drops have been the standard treatment for uveitis since the early 1950s, although the evidence supporting their effectiveness is somewhat sparse.

  Widely known adverse effects of topical corticosteroid eye drops include local irritation, hyperaemia, oedema, and blurred vision.

- The studies examining the effects of NSAID eye drops or mydriatics were either too small or of insufficient quality to allow us to judge their effectiveness in treating uveitis.

Clinical context

DEFINITION

Anterior uveitis is inflammation of the uveal tract, and includes iritis and iridocyclitis. It can be classified according to its clinical course into acute or chronic anterior uveitis, or according to its clinical appearance into granulomatous or non-granulomatous anterior uveitis. **Acute anterior uveitis** is characterised by an extremely painful red eye, often associated with photophobia, and occasionally with decreased visual acuity. [1] **Chronic anterior uveitis** is defined as inflammation lasting over 6 weeks. It is usually asymptomatic, but many people have mild symptoms during exacerbations.

INCIDENCE/ PREVALENCE

Acute anterior uveitis is rare, with an annual incidence of 12/100,000 population. [2] It is particularly common in Finland (annual incidence 22.6/100,000 population, prevalence 68.7/100,000 population), probably because of genetic factors such as the high frequency of HLA–B27 in the Finnish population. [3] It is equally common in men and women, and more than 90% of cases occur in people older than 20 years of age. [3] [4]

AETIOLOGY/ RISK FACTORS No cause is identified in 60–80% of people with acute anterior uveitis. Systemic disorders that may be associated with acute anterior uveitis include ankylosing spondylitis, Reiter's syndrome, Kawasaki's disease, infectious uveitis, Behçet's syndrome, inflammatory bowel disease, interstitial nephritis, sarcoidosis, Vogt–Koyanagi–Harada syndrome, and masquerade syndromes. [5] Acute anterior uveitis also occurs in association with HLA–B27 expression not linked to any systemic disease. Acute anterior uveitis may occur after surgery, or as an adverse drug or hypersensitivity reaction. [3] [4]

PROGNOSIS Acute anterior uveitis is often self limiting, but we found no evidence about how often it resolves spontaneously, in which people, or over what length of time. Complications include posterior synechiae, cataract, glaucoma, and chronic uveitis. In a study of 154 people (232 eyes) with acute anterior uveitis (119 people HLA–B27 positive), visual acuity was better than 20/60 in 209/232 eyes (90%), and 20/60 or worse in 23/232 (10%) eyes, including worse than 20/200 (classified as legally blind) in 11/232 (5%) eyes. [6]

AIMS OF INTERVENTION To reduce inflammation; to relieve pain; and to prevent complications and loss of visual acuity, with minimal adverse effects.

OUTCOMES Degree of inflammation using scores that register a range of different variables as markers of disease severity: number of anterior chamber cells per examination field, flare in the anterior chamber, keratic precipitates, ciliary flush, clinical cure, and severity of symptoms (photophobia and pain), quality of life, and adverse effects of treatment.

METHODS *Clinical Evidence* search and appraisal November 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to November 2009, Embase 1980 to November 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 7). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of anti-inflammatory eye drops on acute anterior uveitis?

OPTION CORTICOSTEROIDS

Disease severity

Compared with placebo eye drops We don't know whether corticosteroid eye drops are more effective than placebo eye drops at reducing symptom severity at 14–21 days as we found insufficient evidence from one small RCT (very low-quality evidence).

Corticosteroid eye drops compared with each other We don't know whether prednisolone 1% eye drops are more effective than rimexolone 1% eye drops or loteprednol 0.5% eye drops at reducing the number of anterior chamber cells per examination field after 28 days (low-quality evidence).

Compared with non-steroidal anti-inflammatory drug (NSAID) eye drops We don't know whether corticosteroid eye drops are more effective then NSAID eye drops at increasing clinical cure rates (not further defined) at 14–21 days in people with acute anterior uveitis some of whom were also receiving atropine eye drops (very low-quality evidence).

Note
Topical corticosteroids have been standard treatment for anterior uveitis since the early 1950s, especially for people with acute or severe uveitis. Placebo controlled RCTs are unlikely to be conducted. We found no direct information from RCTs about oral or subconjunctivally injected corticosteroids in the treatment of people with acute anterior uveitis.

For GRADE evaluation of interventions for acute anterior uveitis, **see table, p 7 .**

Benefits:

We found no systematic review.

Corticosteroid eye drops versus placebo eye drops:
We found one RCT (60 people), which compared three treatments: betamethasone phosphate 0.1% (2 drops every 2 hours), clobetasone butyrate 0.1% (2 drops every 2 hours), and placebo. [7] The RCT found no significant difference with steroid (betamethasone phosphate/clobetasone butyrate) compared with placebo eye drops in symptom severity after 14 or 21 days (results presented graphically; see comment below).

Corticosteroid eye drops versus each other:
We found two papers reporting four RCTs. [8] [9] Two RCTs compared prednisolone 1% eye drops versus rimexolone 1% eye drops. [8] The larger RCT (183 people) found no significant difference in the number of anterior chamber cells per examination field after 28 days (see comment below; 0.4 cells/examination field with rimexolone *v* 0.2 cells/examination field with prednisolone, difference 0.2 cells/examination field, CI not reported; P = 0.16). The smaller RCT (83 people) also found no significant difference in the number of anterior chamber cells per examination field after 28 days (see comment below; 0.3 cells/examination field with rimexolone *v* 0.2 cells/examination field with prednisolone; difference 0.1 cells/examination field; CI not reported; P = 0.40). [8] Two RCTs compared prednisolone 1% versus loteprednol 0.5% eye drops. [9] The larger RCT (175 people) found that prednisolone significantly increased the proportion of people with fewer than five anterior chamber cells per examination field after 28 days compared with loteprednol (5 people lost to follow-up; 77/89 [87%] with prednisolone *v* 58/81 [72%] with loteprednol; RR 1.20, 95% CI 1.03 to 1.42; NNT 7, 95% CI 4 to 35). The smaller RCT (70 people) found that more people had fewer than five anterior chamber cells per examination field with prednisolone compared with loteprednol but the difference was not significant (see comment below). [9]

Corticosteroid eye drops versus NSAID eye drops:
See benefits of topical NSAID eye drops, p 4 .

Oral corticosteroids:
We found no systematic review or RCTs.

Subconjunctival corticosteroid injection:
We found no systematic review or RCTs.

Harms:

Corticosteroid eye drops:
Widely known adverse effects of topical corticosteroid eye drops include local irritation, hyperaemia, oedema, and blurred vision. Topical eye drops have been associated with an increase in intraocular pressure within 3–6 weeks of the start of treatment in susceptible people, and more prolonged use may lead to the formation of posterior subcapsular cataracts. Another potential effect is increased risk of herpes simplex keratitis. [1]

Corticosteroid eye drops versus placebo eye drops or versus each other:
In the RCTs, adverse events were generally mild, resolved without treatment, and did not result in permanent damage. [7] [8] [9] The first RCT did not report on harms. [7] In the smaller RCT comparing loteprednol versus prednisolone eye drops, 4/70 (6%) people were withdrawn because of adverse effects — cystoid macular oedema and ocular symptoms in the loteprednol group, and interstitial keratitis and increased age-related macular degeneration in the prednisolone group. [9] The largest RCTs found clinically relevant increases in intraocular pressure (defined as greater than 10 mm Hg from baseline) more frequently with prednisolone compared with rimexolone, and with prednisolone compared with loteprednol, although the differences were not significant (11/94 [12%] people with prednisolone *v* 6/89 [7%] people with rimexolone; RR 1.7, 95% CI 0.7 to 4.5; [8] 6/91 [7%] people with prednisolone *v* 1/84 [1%] people with loteprednol; RR 5.5, 95% CI 0.7 to 45.0 [9]).

Corticosteroid eye drops versus NSAID eye drops:
See harms of topical NSAID eye drops., p 4

Oral corticosteroids:
We found no RCTs.

Subconjunctival corticosteroid injection:
We found no RCTs.

Comment: Topical corticosteroids have been standard treatment for anterior uveitis since the early 1950s, especially for people with acute or severe uveitis.

Corticosteroid eye drops versus placebo eye drops:
In the RCT comparing corticosteroid eye drops versus placebo, 12/60 (20%) people did not complete the trial, and analysis of data was not by intention to treat. [7] Of these, 4/12 (33%) people were withdrawn from the placebo group because of the severity of their anterior uveitis. The trial was too small to detect any clinically important effect of topical steroids.

Corticosteroid eye drops versus each other:
In the RCTs comparing prednisolone versus rimexolone, people were excluded from analysis for a variety of reasons (23/183 [13%] in the larger RCT and 8/93 [9%] in the smaller RCT). [8] The smaller RCT comparing prednisolone versus loteprednol enrolled people in the USA and the UK; however, it only reported results for the subgroup of people recruited from the USA, [9] making the results difficult to interpret.

OPTION NSAID EYE DROPS

Disease severity
Compared with placebo We don't know whether NSAID eye drops (tolmetin) are more effective than placebo at increasing cure rates (not further defined) at 21 days in people with acute anterior uveitis who were also receiving atropine eye drops (very low-quality evidence).

Compared with corticosteroid eye drops We don't know whether NSAID eye drops are more effective than corticosteroid eye drops at increasing clinical cure rates (not further defined) at 14–21 days in people with acute anterior uveitis some of whom were also receiving atropine eye drops (very low-quality evidence).

For GRADE evaluation of interventions for acute anterior uveitis, see table, p 7 .

Benefits: We found no systematic review.

NSAID eye drops versus placebo eye drops:
We found one RCT (100 people) that compared three types of eye drops: NSAID (tolmetin 5%), corticosteroid (prednisolone 0.5%), and placebo (sterile saline 0.9%). [10] People were asked to instil two drops every 2 hours during waking hours plus atropine 1% eye drops once daily. The RCT found no significant difference between NSAID eye drops and placebo eye drops in clinical cure rate after 21 days (15/32 [47%] with tolmetin *v* 16/32 [50%] with placebo; RR 0.9, 95% CI 0.6 to 1.6). [10]

NSAID eye drops versus corticosteroid eye drops:
We found three RCTs. [10] [11] [12] The first RCT (described above) [10] found no significant difference between NSAID eye drops and corticosteroid eye drops in clinical cure rate after 21 days (see comment below; 15/32 [47%] with tolmetin *v* 22/32 [69%] with prednisolone; RR 0.7, 95% CI 0.4 to 1.1). The second RCT (71 people) compared three treatments: prednisolone disodium phosphate 0.5%, betamethasone disodium phosphate 0.1%, and tolmetin sodium dihydrate 5%. [11] People were asked to instil one drop every 2 hours during waking hours, and all received atropine 1% eye drops once daily. The RCT found no significant difference between the NSAID (tolmetin sodium dihydrate) eye drops and corticosteroid (prednisolone disodium phosphate/betamethasone disodium phosphate) eye drops in clinical cure rate after 21 days (see comment below; 12/21 [57%] people with tolmetin sodium dihydrate *v* 31/39 [79%] with prednisolone disodium phosphate/betamethasone disodium phosphate; RR 1.4, 95% CI 0.9 to 2.1). [11] The third RCT (49 people) compared NSAID eye drops (indometacin [indomethacin] 0.1%) with corticosteroid (dexamethasone 1%) eye drops given six times daily. [12] Most people (equal numbers in each group) also received atropine eye drops three times daily. The RCT found a lower proportion of people clinically cured after 14 days with indometacin, but the difference was of borderline significance (see comment below; 12/25 [48%] people with indometacin *v* 18/24 [75%] people with dexamethasone; RR 0.6, 95% CI 0.4 to 1.0).

Harms: **NSAID eye drops versus placebo eye drops or corticosteroid eye drops:**
The first RCT did not report on harms. [10] In the second RCT 6/20 (30%) people receiving NSAID eye drops reported a transient stinging sensation in their eyes. [11] In the third RCT, more people receiving indometacin reported eye irritation, although the difference was not significant (7/25 [28%] with indometacin *v* 3/24 [13%] with dexamethasone; RR 2.2, 95% CI 0.7 to 7.8). [12]

Comment: Two RCTs used "clinical cure" as an outcome measure, although neither defined this term. [10] [11] The third RCT defined "clinical cure" as absence of clinical signs or symptoms suggestive of inflammation. [12] The RCT comparing NSAID with placebo eye drops reported that 6/71 (8%) people did not complete the trial, [10] and the second RCT reported that 11/71 (15%) people did not complete the trial. [11] Neither of these RCTs analysed data by intention to treat.

OPTION MYDRIATICS (DIFFERENT DRUGS OR POTENCIES)

We found no direct information from RCTs about different mydriatic drugs or different potencies of mydriatic drugs in the treatment of people with acute anterior uveitis.

For GRADE evaluation of interventions for acute anterior uveitis, **see table, p 7 .**

Benefits: We found no systematic review or RCTs comparing different mydriatic drugs or different potencies of mydriatic drugs for acute anterior uveitis.

Harms: We found no RCTs.

Comment: None.

GLOSSARY

Iridocyclitis Inflammation of both iris and ciliary body. Cells are present in the anterior chamber and in the vitreous.

Iritis Inflammation of the iris. Cells are seen in the anterior chamber but not in the vitreous.

Masquerade syndromes Comprise a group of disorders that occur with intraocular inflammation and are often misdiagnosed as a chronic idiopathic uveitis.

Posterior synechiae Adhesions between the iris and the lens capsule.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

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TABLE **GRADE evaluation of interventions for acute anterior uveitis**

Important outcomes	**Disease severity, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of anti-inflammatory eye drops on acute anterior uveitis?									
1 (60) [7]	Disease severity	Corticosteroid eye drops *v* placebo eye drops	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, poor follow-up, and no intention-to-treat analysis
4 in 2 reports (516) [8] [9]	Disease severity	Corticosteroid eye drops *v* each other	4	–2	0	0	0	Low	Quality points deducted for no intention to treat analysis in 2 RCTs (people excluded from analysis) and only reporting results for subgroup of people enrolled in 1 RCT
1 (64) [10]	Disease severity	NSAID eye drops *v* placebo eye drops	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and no intention-to-treat analysis. Directness points deducted for unclear outcome (clinical cure) and co-intervention (atropine)
3 (173) [11] [10] [12]	Disease severity	NSAID eye drops *v* corticosteroid eye drops	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and no intention-to-treat analysis. Directness point deducted for unclear outcome (clinical cure) and co-intervention (atropine)

Type of evidence: 4 = RCT. Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio