Treatment of acute neonatal bacterial conjunctivitis: a comparison of fucidic acid to chloramphenicol eye drops

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ABSTRACT.

Purpose: **To compare the clinical and bacteriological effects of fucidic acid (Fucithalmic®: 1.0%) and chloramphenicol (Minims®: 0.5%) eye drops in neonates with a clinical diagnosis of acute conjunctivitis of suspected bacterial origin.**

Methods: ***A total of 456 n*****ewborns with gestational age > 32 weeks with acute conjunctivitis of suspected bacterial origin acquired within the first 28 days of life were included in the study. They were randomly assigned to a 7-day treatment with eye drops using either fucidic acid (1.0%) (Fucithalmic®) applied twice per day, or chloramphenicol (0.5%) (Minims® Chloramphenicol) applied six times per day. The subjects were followed up with two visits (on days 1 and 8) and by telephone 2 weeks after the end of treatment.**

Results: **Eighty-nine per cent of the neonates treated with Fucithalmic® were cured, compared to 87.9% of those treated with Minims® Chloramphenicol (n.s). The drug was used as instructed in 90.7% of patients treated with Fucithalmic® and in 78.0% of those treated with Minims® Chloramphenicol ($P < 0.001$).**

Conclusion: **Treating neonatal conjunctivitis with fucidic acid is easier than with chloramphenicol and is equally effective.**

Key words: conjunctivitis – neonatal – fucidic acid – chloramphenicol

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Neonatal conjunctivitis, defined as conjunctivitis with discharge occurring during the first 28 days of life, is a common neonatal infection (de Toledo & Chandler 1992). Bacterial infection, often by *Staphylococcus aureus*, is a common aetiology of neonatal conjunctivitis (Solberg & Meberg 1991). The incidence of neonatal bacterial conjunctivitis in Norway is about 8% (Solberg & Meberg 1991). This incidence rate is comparable to that reported by other investigators (Hammerschlag 1993).

Therapy consists of topical antibiotics administered in the form of eye drops, applied in the lower conjunctival sac, and chloramphenicol eye drops have been found to be quite effective (Sinclair & Leigh 1988; Hørven 1993). However, the use of chloramphenicol in adults has been associated with the development of bone marrow dysplasia (Fraunfelder & Bagby 1983; Besamusca & Bastiaensen 1986). Consequently, other agents are now being sought for the treatment of neonatal conjunctivitis (Hørven 1994). While fucidic acid has been used to treat conjunctivitis in older children (> 6 months) and adults (Dirdal 1987; Hvidberg 1987; Sinclair & Leigh 1988; Hørven 1993), there are no studies documenting its efficacy and safety for use in neonates. The purpose of the current study is to compare the clinical and bacteriological effects of fucidic acid (1%) eye drops with those of chloramphenicol (0.5%) eye drops in neonates with a clinical diagnosis of acute neonatal conjunctivitis of suspected bacterial origin, and to compare the safety of the treatments.

Material and Methods

This is a prospective, randomized, multicentre study, comparing two parallel groups. The first of these was treated with Fucithalmic® eye drops (Leo Phar-

maceutical Products, Ballerup, Denmark) (1%, 0.2 mL/unit dose), applied twice per day to both eyes for 7 days. The second group was treated with Minims® Chloramphenicol eye drops (Smith & Nephew Pharmaceuticals Ltd, Hull, UK) (0.5%, 0.5 mL/unit dose), applied six times per day to both eyes for 7 days. The dosage was specified according to each product's registration. Each child was seen by an investigator on day 1 and day 8 (± 2) and a telephone interview was conducted 2 weeks after completion of treatment.

We calculated that in order to facilitate detection of a 10% difference in success rate (approximately 90%) between the two treatments with a significance level of 5%, and a power of 80%, we would need to involve 400 patients (200 in each group) at visit 2 (end of treatment). The study therefore had to include 450 patients.

The study was conducted from May 1993 to August 1994 in 17 European medical centres, located in Sweden (n = 5), Norway (n = 4), Denmark (n = 4), Finland (n = 3) and Switzerland (n = 1). It was approved by the institutional review boards and Ethics Committees of the participating institutions.

The study groups included all neonates with conjunctivitis of suspected bacterial origin, defined as both general conjunctival redness and purulent discharge. All premature infants (32 weeks or less), neonates with known or suspected hypersensitivity to either medication, neonates with nonbacterial or gonorrhoeal conjunctivitis, neonates receiving systemic antibiotics, neonates receiving topical or systemic drugs such as corticosteroids which affect the course of conjunctivitis, and neonates born to mothers younger than 18 years of age were excluded from the study.

Parents of neonates with conjunctivitis were invited to participate in the study, and those who agreed gave written consent prior to enrolment. The neonates were then randomized to receive either Fucithalmic® or Minims® Chloramphenicol. Randomization code numbers were assigned in order, and contained an equal number of Fucithalmic® and Minims® Chloramphenicol assignments in blocks of four. The medications were supplied in identical boxes, and the investigators were blinded to which drug the neonates were receiving.

Bacterial swabs were taken from the lower conjunctival sac of the most affected eye. All the swabs were analysed at a central laboratory (Hazleton UK, Harrogate, UK) to identify micro-organisms and to determine *in vitro* susceptibility to fucidic acid and chloramphenicol by identifying the minimal inhibitory concentration (MIC). Conjunctival scrapings for chlamydia were taken at the initial visit.

During each visit, the investigator rated the severity of conjunctivitis from 0 to 3 as follows: absent = 0; mild = 1; moderate = 2; severe = 3. Each eye was rated separately and the sum of the scores for both eyes was used for all patients including those with unilateral infection. On completion of the course of treatment, response was rated as 'cured' (all signs of conjunctivitis had resolved), 'improved' (signs of conjunctivitis improved but still present, no further treatment required), or 'failed' (signs of conjunctivitis were unchanged or worsened after at least 72 h treatment). Neonates that failed to return to clinic were removed from analysis.

On the second visit, the investigators inquired about the use of the medications. Parents were asked whether the medication was used as instructed, when it was last used, and how convenient they found the treatment regimen.

The clinical and bacteriological 'success' rates were analysed by a log-linear model for the contingency table treatment × country × response with the treatment × country marginal fixed. The CATMOD procedure of SAS was applied (SAS 1989).

The time until disappearance of clinical symptoms was analysed by survival analysis using time until disappearance as 'survival' time. The median time until disappearance of symptoms was estimated from the product limit survival estimates and the two treatments were compared by the log-rank test. The LIFETEST procedure of SAS (SAS 1989) was applied.

The proportion of patients who had no problems at follow-up was compared between the treatments by a chi-square test. The data on compliance and convenience of the used drug were analysed by Wilcoxon test with calculation of the exact p-value (StatXact 1992).

Results

Of the 458 patients recruited, 230 were randomized to the Fucithalmic® group and 226 to the control group (Minims® Chloramphenicol). Two patients were withdrawn before randomization (Table 1). Of the 456 patients, the number of boys and girls was significantly different (268 boys and 188 girls). A total of 407 patients (89.3%) had a gestational age > 36 weeks. Demographic data for the two groups were similar in terms of age of patient, gestational age, duration of conjunctivitis, scores for clinical signs and bacteriological results (Tables 1–3).

Some patients in both groups were excluded from the final analysis for various reasons, e.g. chlamydia infections. Overall, 209 neonates in the group receiving Fucithalmic® and 215 in the group receiving Minims® were included in the final per protocol analysis. Of the 209 subjects in the Fucithalmic® group, 89.0% found their conjunctivitis was either cured or improved, as did 87.9% of the 215 subjects treated with Minims® Chloramphenicol. (P = 0.73; 95% CI −5.0% to 7.2%). Median resolution time of symptoms from onset of therapy was 4 days. The intention to treat analysis similarly showed no significant differences between the two groups. Success rates were similar for all participating institutions. The data

Table 1. Demographic data

	Randomized patients (n = 456)	Fucidic acid treated infants (n = 230)	Chloramphenicol treated infants (n = 226)
	Days	Days	Days
Mean postnatal age	6.0	6.2	5.9
SD	4.0	4.0	4.0
Range	1–27	1–25	1–27
Mean duration of ymptoms before treatment	2.5	2.6	2.3
SD	2.6	2.8	2.3
Range	0.1–21.0	0.1–21.0	0.2–15.0

SD = standard deviation

Table 2. Bacteriological data

	Randomized patients ($n = 456$)	Fucidic acid treated infants ($n = 230$)	Chloramphenicol treated infants ($n = 226$)
	Number	Number	Number
S. aureus	148	75	73
Strep. viridans	72	33	39
S. epidermidis	54	34	20
Coliform	29	14	15
Strep. pneumoniae	6	1	5
Diphtheroids	5	4	1
Moraxella species	5	2	3
Neisseria species	5	2	3
H. influenzae	4	3	1
Streptococus species	2	1	1
Bacillus species	1	1	0
H. parainfluenzae	1	0	1
Neisseria species or moraxella species	1	0	1
Total number of CFU	333	170	163
Number of patients with bacteria (%)	299 (65.6)	153 (66.5)	146 (64.6)
Number of patients with no growth (%)	155 (34.0)	76 (33.0)	79 (35.0)
Number of patients with no data (%)	2 (0.4)	1 (0.4)	1 (0.4)

(CFU = colony forming units)

Table 3. Clinical assessment, sum score for both eyes at baseline

	Fucidic acid treated infants ($n = 230$)	Chloramphenicol treated infants ($n = 226$)
	Mean score (SD)	Mean score (SD)
Conjunctival redness	2.6 (1.2)	2.6 (1.1)
Eyelid redness	1.8 (1.3)	1.9 (1.3)
Eyelid stuck	2.3 (1.2)	2.4 (1.2)
Purulent discharge	2.8 (1.1)	2.9 (1.1)
Periorbital oedema	2.0 (1.2)	2.1 (1.3)
Watery discharge	1.7 (1.2)	1.6 (1.3)
Total	13.3 (5.0)	13.5 (5.2)

0 = absent, 1 = mild, 2 = moderate, 3 = severe
SD = standard deviation

are summarised in Table 4. Side-effects were minor in both groups. Four parents in the Fucithalmic® group reported one of the following: crying at application, oral candidiasis, stuck-together eyelids, and assistance for application by a nurse.

Table 4. Overall assessment of treatment response (per protocol)

	Fucidic acid treated infants ($n = 209$)		Chloramphenicol treated infants ($n = 215$)	
	Number	%	Number	%
Cured	130	62.2	139	64.7
Improved	56	26.8	50	23.3
Failed	23	11.0	26	12.1

The Minims® group registered five reports of difficulties consisting of worsening symptoms, sleep disturbances, dislike of treatment, redness of eyelids and skin irritation in lateral eyelid corner.

The *in vitro* studies results were similar for both drugs. Micro-organisms were eradicated in 73.6% of samples by Fucithalmic® and in 75.6% of samples by Minims® ($p = 0.72$; 95% CI: −13.4% to 9.4%).

Parents of neonates treated with Fucithalmic® were found more likely to have complied with the application schedule, and over 90% reported applying the medication as instructed. Compliance rates among parents of neonates treated with Minims® were lower, with only 78% reporting compliance with the treatment schedule ($P < 0.001$) (95% CI: 87.0% to 94.5%). The less onerous regimen associated with Fucithalmic® also resulted in a higher degree of satisfaction among parents using it, 30% of whom reported the application regimen to be 'very convenient' compared with only 17.9% of parents using Minims® ($P = 0.026$). There was no difference between the groups in their application of the descriptors 'inconvenient' or 'very inconvenient'. Satisfaction rates are depicted in Table 5.

Discussion

In this study we have shown that when fucidic acid (1.0%) and chloramphenicol (0.5%) are equally effective when administered as eye drops. Cure rates and *in vitro* studies show no differences between the two groups. These findings are similar to those reported by Sinclair & Leigh (1988). However, parents who used Fucithalmic® had to apply the medication only twice per day, rather than the more demanding four-hourly regimen required by chloramphenicol. Not surprisingly, the simpler regimen of Fucithalmic® was more acceptable to parents, and consequently, they were more likely to comply with the schedule and to report a higher degree of satisfaction.

The number of randomized boys and girls was significantly different (268 *versus* 188). We do not have any explanation for this and believe the difference is obtained by chance. The difference has no implication for the results since bacterial conjunctivitis to our knowledge has the same pathology and manifestation in boys and girls.

In Fucithalmic®, fucidic acid is suspended in a carbomer vehicle, appearing in a gel-like formulation. Because of the carbomer the fucidic acid persists in the lacrimal fluid and aqueous humour for at least 12 h (van Bijsterveld et al. 1987a; Sinclair & Leigh 1988). The viscosity of the carbomer makes it easy to administer. As the carbomer becomes clear on contact with electrolytes in the tear fluid, it causes less blurring than eye ointment. Some paediatricians recommend using ointment during the night because chloramphenicol in eye drops is an aqueous suspension and is rapidly washed out of the eye. This requires parents to purchase eye drops for daytime use and ointment for use during the night.

The use of chloramphenicol in neo-

Table 5. Convenience of use. In comparing the four categories together, fucidic acid was seen to be significantly more convenient than chloramphenicol ($P = 0.026$)

	Fucidic acid treated infants ($n = 227$) Number	%	Chloramphenicol treated infants ($n = 223$) Number	%
Very convenient	68	30	40	17.9
Convenient	106	46.7	130	58.3
Inconvenient	41	18.1	46	20
Very inconvenient	6	2.6	5	2.2
Missing information	6	2.6	2	0.9

nates may cause aplastic anaemia and give rise to 'gray baby syndrome', which describes the clinical signs of toxicity with cyanosis and vascular collapse in the neonatal period. While rare, aplastic anaemia caused by chloramphenicol eye drops has been reported (Besamusca & Bastiaensen 1986). The chloramphenicol passes through the nasal lacrimal ducts to the nasal cavity and the epipharynx where it may be absorbed directly through the nasal mucosa, or swallowed and absorbed in the intestine. Because aplastic anaemia may be dose-independent, even the small amounts absorbed may be of concern (Fraunfelder & Bagby 1983; Besamusca & Bastiaensen 1986). However, a recent study by Walker et al. (1998) investigated whether serum accumulation of chloramphenicol occurred after topical therapy in 40 patients. The investigators were unable to detect chloramphenicol in serum from the patients and concluded that treatment with topical chloramphenicol is not a risk factor for inducing dose-related bone marrow toxicity.

Fucidic acid provides an alternative to chloramphenicol. Its safety and efficacy have been evaluated and documented in older children (> 6 months) with conjunctivitis (van Bijsterveld et al. 1987b; Dirdal 1987; Hvidberg 1987; Sinclair & Leigh 1988; El-Shami 1989; Dy-Liacco et al. 1991; Hørven 1993). Its use in younger children has been evaluated in a previous study (Holt et al. 1991), but the current study is the first to evaluate the use of the drug in a large group of neonates.

Older children cry, wriggle their heads and resist parental attempts to instil eye drops. We anticipate that parents of this age group will also be more likely to comply with and be satisfied by the simpler application regimen of fucidic acid.

S. aureus was the predominant organism isolated in this study. The flora isolated in this group of patients is similar to that reported in other studies (Dirdal 1987; Solberg & Meberg 1991; Dannevig et al. 1992; Hammerschlag 1993). Since chlamydial eye-infection is a rare condition (Solberg & Meberg 1991; de Toledo & Chandler 1992) and ophthalmia neonatorum caused by Neisseria gonorrhoeae is very rare, appearing in fewer than 1% of cases (Solberg & Meberg 1991; Hammerschlag 1993), fucidic acid may be utilized as a first line therapy in neonatal conjunctivitis.

The study aimed to blind the investigators as to which medication the patient received. However, in some of the participating institutions, the physician was responsible for instructing parents in how to apply the medication. Because of the different application regimens, these physicians were able to tell whether the patients were to receive fucidic acid or chloramphenicol. However, the results from these institutions were similar to those obtained from centres in which the instructions were given by nursing staff and the physicians did not know which drug the neonates received. Therefore, we believe that no measurable bias was introduced and the data obtained are valid.

Conclusion

Fucithalmic® is as effective as Minims® Chloramphenicol for treatment of neonatal bacterial conjunctivitis. It is easier to use, resulting in significantly higher rates of compliance and satisfaction.

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