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Topical nonsteroidal anti-inflammatory drugs in uncomplicated cataract surgery: Effect of sodium naproxen

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PURPOSE. To investigate whether topical nonsteroidal antiinflammatory drugs (NSAIDs) are useful, in the absence of concomitant corticosteroid therapy, in limiting postoperative inflammation after uncomplicated cataract surgery.
METHODS. A total of 328 patients were enrolled in a prospective, randomized, double-masked, parallel-group, active-controlled study. Anterior chamber inflammation (ACI) was evaluated as the primary efficacy parameter. Only patients with moderate inflammation (ACI score of ≤4) the day after surgery were randomized and treated with NSAIDs. A novel topical formulation containing 0.2% sodium naproxen was compared with 0.1% diclofenac. Both were administered three times a day for 14 consecutive days. Ocular inflammation was measured after 7 and 14 days by using slit-lamp biomicroscopy. Safety parameters were also evaluated at the same time.
RESULTS. Both treatments were equally effective in controlling postsurgical inflammation. No statistically significant differences between treatment groups were observed for the safety variables. No serious adverse events (AEs) occurred during the course of the study. The most frequent AE reported with naproxen was eye redness.
CONCLUSIONS. NSAIDs can effectively be used without concurrent administration of corticosteroids to control postoperative inflammation after uncomplicated cataract surgery. In addition, naproxen ophthalmic solution may be considered a suitable alternative to the currently available NSAIDs. (Eur J Ophthalmol 2005; 15: 598-606)

KEY WORDS. Naproxen, Cataract surgery, NSAID, Ocular inflammation

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INTRODUCTION

Recent advances in cataract surgery techniques and instrumentation have significantly reduced the extent of physical trauma associated with surgery. The decreased tissue damage results in less production of chemical mediators, which are responsible for postoperative ocular inflammation. Nevertheless, many patients experience some degree of postoperative inflammation or pain and require anti-inflammatory treatment (1, 2).

Historically, corticosteroids have been the drugs of choice for such therapy (3). Although effective, these drugs may interfere with wound healing, aggravate infections, or increase intraocular pressure (IOP) (4, 5). For this

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reason, during the last decade several topical ophthalmic nonsteroidal anti inflammatory drugs (NSAIDs) have been developed, and their use in the treatment of postoperative inflammation has progressively increased (2, 6, 7). NSAIDs are at present considered an effective and safe alternative to corticosteroids (1, 3, 6, 7), at least in patients who have not undergone complicated surgery (e.g., prolonged phacoemulsification, excessive iris manipulation, retention of cortical material).

Sodium naproxen is a well known NSAID with established anti-inflammatory properties (8, 9). Given systemically, naproxen is also able to reach the eye, reducing ocular inflammation (10-16).

The anti-inflammatory properties of sodium naproxen were also confirmed when given as ophthalmic solution even without concurrent corticosteroid treatment (17-19). In addition, we have recently demonstrated in two randomized clinical trials the efficacy of such solution in the prevention of surgically induced miosis (20).

The objective of the present study was to investigate whether NSAIDs (in the absence of corticosteroids) can effectively control ocular inflammation after uncomplicated cataract surgery.

For this purpose, we tested the new ophthalmic NSAID sodium naproxen versus diclofenac, which is considered the gold standard of this pharmaceutical group.

MATERIALS AND METHODS

Patient population

Patients of either sex, at least 40 years old and scheduled to undergo phacoemulsification with posterior chamber intraocular lens (IOL) implantation, were enrolled in the study. Main characteristics of patient populations (age, sex, and race) are displayed in Table I. Due to the type of study (phase III), it was decided not to follow a standard surgical operating procedure (type of tunnel incision, type of IOL, and so on) in order to keep the postoperative ocular conditions as close as possible to the clinical routine. Differences in the surgical procedures, and any subsequent deviation from most commonly followed procedures, reflect therefore the different approaches of surgeons and the clinical presentation of single cases.

A corneal tunnel incision was used to gain entry into the anterior chamber for most of the surgeries (70%) and foldable IOL were implanted in approximately 60% of the patients (Tab. II). Although phacoemulsification is usually considered a sutureless surgical procedure, a suture was applied in 143 interventions (45%), possibly due to solid unfoldable IOL implant (87% of cases), tunnel incision other than corneal (5%), or routine surgical procedure of the center (8%).

TABLE I - DEMOGRAPHIC CHARACTERISTICS (N=328, all randomized population)

Characteristics	**Naproxen**		**Diclofenac**	
No. of patients	163		165	
Race	Caucasian	other	Caucasian	other
	161	2	163	2
Sex	M	F	M	F
	78	85	77	88
Age, yr	mean (SD)	range	mean (SD)	range
	71.7 (9.7)	40-99	73.7 (9.2)	48-99

TABLE II - SURGICAL PROCEDURES

	Surgical procedures	**Naproxen**	**Diclofenac**
Tunnel incision	Scleral	6.1	7.3
	Limbal	23.9	23.6
	Corneal	70.0	69.1
Suture	No	55.8	57.0
	Yes	44.2	43.0
Acrylic IOL	Foldable	58.9	59.4
	Solid	41.1	40.6
Duration of surgery	min <10	16.0	17.0
	>10<20	65.5	66.1
	>20<30	16.0	14.5
	>30	2.5	2.4

Values are %
IOL = Intraocular lens

The most important inclusion criterion to enter the study was the grade of anterior chamber inflammation (ACI) score measured as the sum of flare and cells (each graded from none to severe, according to a 0- to 3-point scale) (Tab. III). Only patients displaying mild to moderate inflammation (ACI score ≤4) in the operated eye the day after surgery (Day 1) were randomized and actually enrolled in the study. Exclusion criteria included IOP greater than 24 mmHg, any ocular pathology, herpes infection, proliferative diabetic retinopathy, ocular medications other than topical beta-blockers or artificial tears, previous ocular surgery or laser treatment in the operated eye in the 6 months preceding surgery, known or suspected allergy to any of the ingredients in the study medications, and use of topical or systemic steroids or NSAIDs in the 15 days preceding surgery.

Study design

The trial was designed as a prospective, randomized, double-blind, active controlled, parallel group study. Eligible patients were randomly assigned to one of the two treatment arms by using a computer generated randomization list. Patients were treated with either 0.2% sodium naprox-

TABLE III - SCORING SYSTEM TO MEASURE ANTERIOR CHAMBER INFLAMMATION

Score	Anterior chamber flare
0	None
1	Mild (barely detectable)
2	Moderate (iris and lens details clear)
3	Severe (iris and lens details not visible and fibrin in the anterior chamber)
Score	**Anterior chamber cells**
0	None
1	Mild (1 to 10 cells)
2	Moderate (11 to 50 cells)
3	Severe (>50 cells)

TABLE IV - SUMMARY OF EFFICACY RESULTS (N=311, full analysis population)

Efficacy parameter	Day after surgery	p value*
ACI (% change)	7±1	NS
	14±1	NS
Conjunctival hyperemia	7±1	<0.01
	14±1	NS
Lid edema	7±1	NS
	14±1	NS
Corneal edema	7±1	NS
	14±1	NS
Pain	8±1	<0.01
	14±1	NS
Photophobia	7±1	NS
	14±1	NS
Tearing	7±1	NS
	14±1	NS

*Mann-Whitney U-test (except anterior chamber inflammation [ACI] = analysis of variance)
NS = not significant

TABLE V - SUMMARY OF SAFETY RESULTS (N=328, all randomized population)

Safety parameter	Day after surgery	p value*
Burning	7±1	<0.01
	14±1	<0.01
Stinging	7±1	<0.01
	14±1	<0.01
Blurred vision	7±1	NS
	14±1	NS
IOP	7±1	NS
	14±1	NS
Visual acuity	7±1	NS
	14±1	NS

*Mann-Whitney U-test (except IOP and visual acuity = analysis of variance)
IOP = Intraocular pressure; NS = Not significant

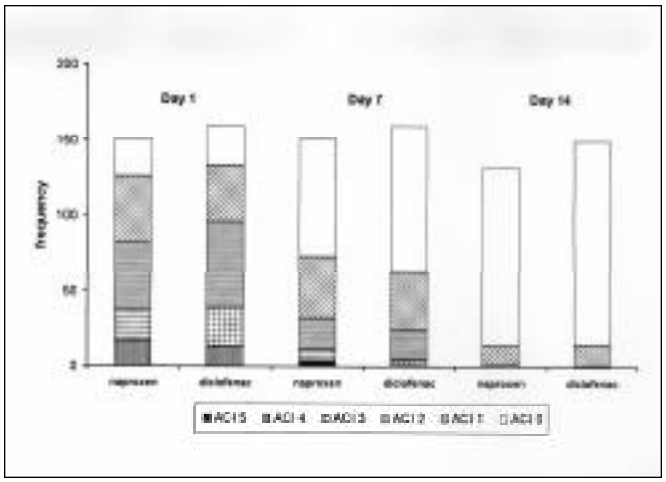

Fig. 1 - Distribution of the anterior chamber inflammation (ACI) score in the full analysis population (n=311).

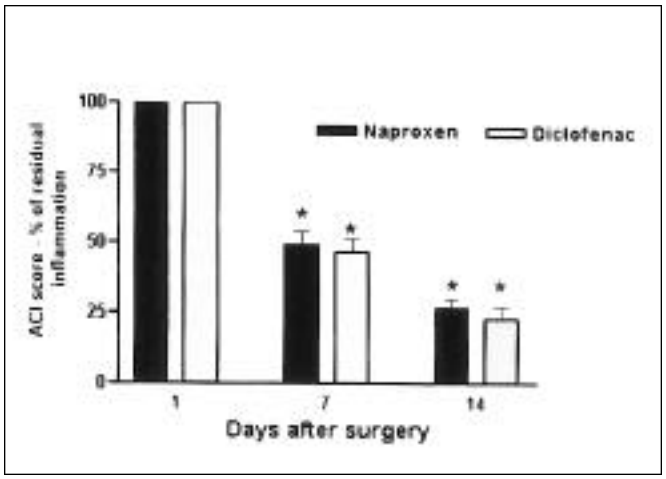

Fig. 2 - Anterior chamber inflammation (ACI) score improvement in the full analysis population (n=311). The ACI score is shown as percentage change from baseline (Day 1 after surgery). *Tests for paired observations within each treatment ($p<0.0001$).

en or 0.1% sodium diclofenac. Both formulations were preserved with 0.1% benzalkonium chloride.

Diclofenac was chosen as active control because it is considered worldwide as the gold standard in the NSAID group. In addition, diclofenac has been demonstrated to be superior to placebo and as effective as corticosteroids in reducing postoperative inflammation after cataract surgery (21-23). The use of placebo in the control group was not considered ethical.

The study was conducted in 19 centers located in Italy, Germany, and France. The study protocol was reviewed and approved by the local ethics committee at each center and conducted according to the Declaration of Helsinki and Good Clinical Practices. Written informed consent was obtained from all patients.

The NSAID treatment of patients displaying a mild to moderate inflammation started the day after surgery (Day 1) and continued (one drop three times in a day) until Day 14. According to the routine of each center, most of the patients (280 out of 328 = 85%) received an antibiotic coverage for approximately 1 week after surgery, whereas 48 patients (15%) did not receive any topical postoperative antibiotic.

The most used antibiotic (199 out of 328 patients = 61%) was the aminoglycoside netilmicin (24); the remaining patients treated received a fluoroquinolone antibiotic (44 ofloxacin, 16 ciprofloxacin, 15 lomefloxacin, and 6 norfloxacin). No other treatments were allowed. In particular, use of steroids or other NSAIDs in any dose form was not permitted from 15 days before operation until after the end of the trial.

Patients were examined four times: before surgery (up to 14 days) and postoperatively at Day 1, Day 7±1, and Day 14±1. Day 7 was considered for the endpoint evaluation. The examination at each visit included best-corrected visual acuity, funduscopy, applanation tonometry, and slit lamp examination.

As earlier described, the primary variable chosen to assess drug efficacy was the ACI score (19) (Tab. III). Other criteria of efficacy included conjunctival hyperemia, eyelid and corneal edema, and ocular discomfort. The tolerance variables assessed were the degree of burning, stinging, and blurred vision. All these clinical variables also were graded from none to severe using a 0 to 3 point scale as already described (19). Safety variables that were monitored during the trial were visual acuity, IOP, and funduscopy.

Statistical analysis

All statistical comparisons between treatment groups considered within-patient changes relative to the baseline after surgery (Day 1). The analyses of the primary efficacy parameter ACI score were performed on the percent change from baseline. A nonparametric evaluation by means of the Mann-Whitney U-test was performed for all categorical variables, excluding the primary efficacy parameter. An analysis of variance (ANOVA) model was used

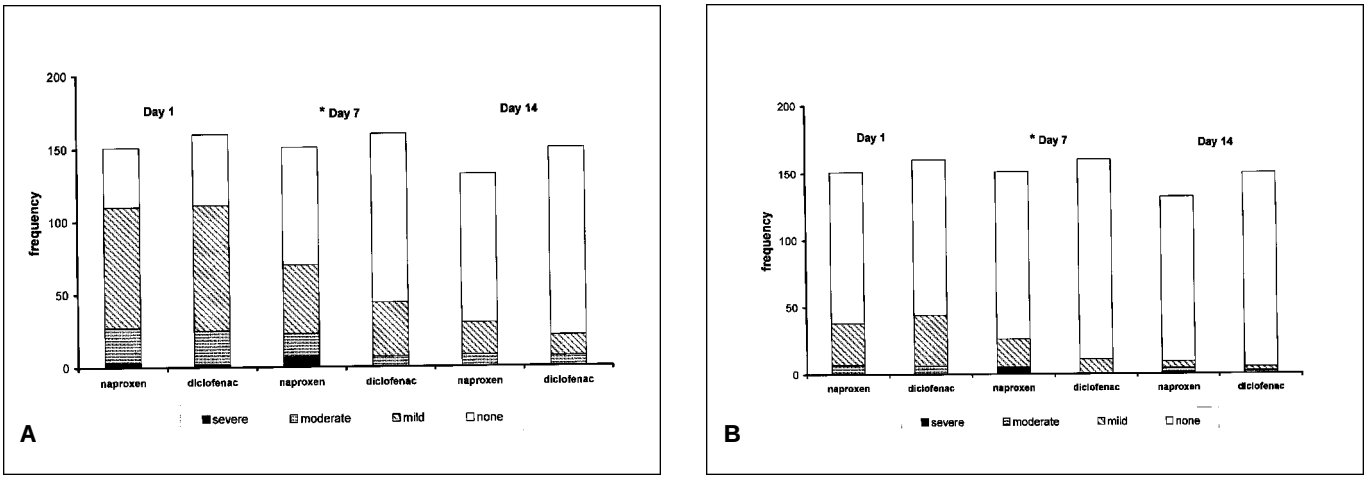

Fig. 3 - Effect of naproxen and diclofenac on conjunctival hyperemia **(A)** and pain **(B)** in the full analysis population (n=311). *Mann-Whitney U test (p<0.01).

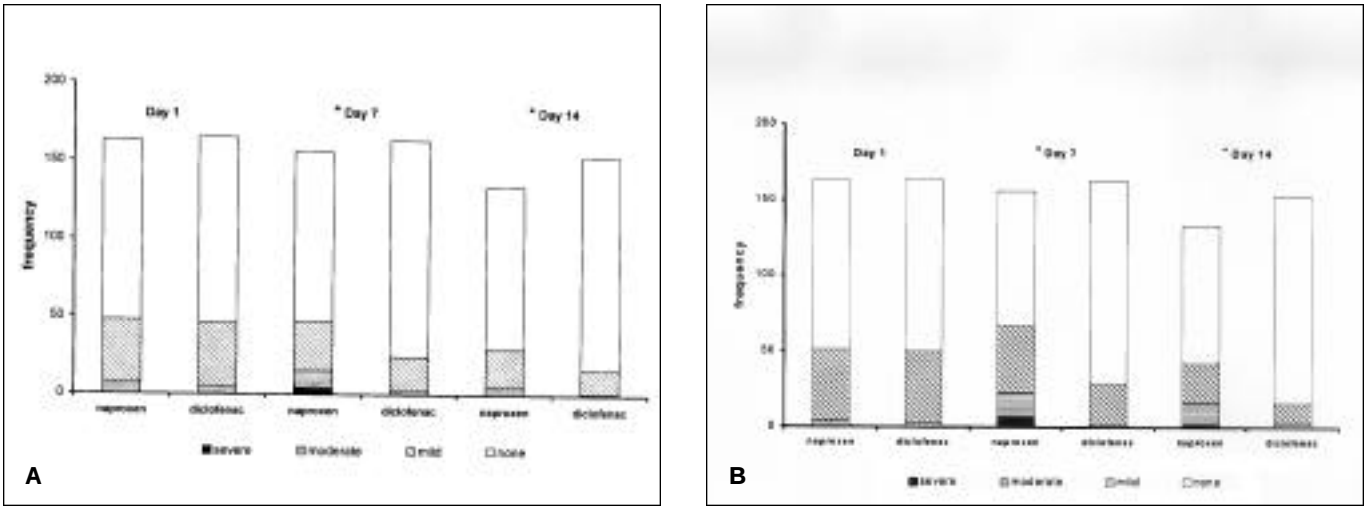

Fig. 4 - Effect of naproxen and diclofenac on burning **(A)** and stinging **(B)** in the full analysis population (n=311). *Mann-Whitney U-test (p<0.01).

to compare numerical data (IOP and visual acuity) and also to analyze the primary efficacy parameter. In addition, within each treatment group Wilcoxon tests for paired observations were performed comparing each treatment day with baseline.

The required sample size was estimated as 90 patients per group to give the study a power of 80% (25). A p value of 0.05 (two-tailed test) was considered statistically significant. Efficacy data were analyzed in both full analysis (FA) and per-protocol (PP) subsets.

Patients who dropped out prior to the Day 7 (endpoint) visit were excluded from the PP and FA populations. Safety data were analyzed in all the randomized patients (Safety subset).

RESULTS

During this prospective randomized study, 339 patients were screened. Only patients displaying a mild to moderate inflammation (ACI score ≤4, on a scale of 0 to 6) in the operated eye the day after surgery (Day 1) were randomized and actually enrolled in the study. A total of 328 patients fulfilled these criteria (Safety subset) and were assigned to one of the two treatment arms (163 patients received 0.2% naproxen and 165 received 0.1% diclofenac). Almost all enrolled patients were white, 47% were male and 53% female, the mean age (SD) was 72.7 (9.5) years. The two groups of treatment were comparable with respect to age, sex, race, and surgical procedures

(Tabs. I and II). For the assessment of efficacy, two populations were evaluated: 1) the FA population (including patients with minor-mild protocol deviations and study completion at least Visit 3, study endpoint) including 311 patients (naproxen = 151, diclofenac = 160) and 2) the PP population including 240 patients fully adhering to the study protocol (naproxen = 114, diclofenac = 126). Since results from both subsets were comparable, only data from the FA subset are shown and discussed.

Efficacy

The distribution of ACI scores through the study is shown in Figure 1. Differences between naproxen and diclofenac for the primary efficacy parameter (percent change from baseline of ACI score) were not statistically significant at Day 7 (endpoint visit) or Day 14 (Tab. IV, Fig. 2). Both treatments led to a time dependent reduction of the ACI score of high statistical significance ($p<0.0001$ at both Day 8 and Day 14), thus indicating treatment efficacy (Fig. 2).

On Day 7, conjunctival hyperemia and pain were noted slightly more frequently under naproxen treatment compared to diclofenac (Fig. 3). None of the other efficacy parameters (lid or corneal edema, photophobia, tearing) could discriminate between treatments (Tab. IV).

Local tolerance and safety

No statistically significant differences between treatment groups were observed for blurred vision and visual acuity, whereas in the evaluation of burning and stinging diclofenac appeared to be better tolerated (Fig. 4 and Tab. V). IOP values were similar in the two groups of treatment at all visits (mean ± SD, naproxen vs. diclofenac: 15.8 ± 2.4 vs. 15.6 ± 2.6 mmHg at Day 1; 15.2 ± 3.1 vs. 15.7 ± 3.3 mmHg at Day 7; 14.4 ± 2.7 vs. 14.8 ± 2.3 mmHg at Day 14).

Fifteen patients (14 in the naproxen group = 8.6% of treated patients) experienced adverse events (AEs) that were classified as possibly drug-related. AEs' clinical severity was rated mild to moderate in 64% of cases. Only one AE (iritis) required hospitalization to remove the IOL as a precautionary measure and therefore was considered serious. Most AEs in the naproxen group were associated with eye redness (80%) and additional therapy with corticosteroids was required in 86% of cases. Complete recovery was observed in the totality of cases. One case of keratitis was observed in the diclofenac group.

DISCUSSION

Traditionally, topical corticosteroids have been used in ophthalmology to control postoperative inflammation after cataract surgery. However, during the last decade, several ophthalmic solutions containing NSAIDs have been developed. All commercially available NSAIDs generally have good ocular penetration with minimal systemic absorption and are widely used in the pre- and postoperative management of cataract surgery (2, 6). Currently, there are three justifications for the use of NSAIDs in ocular surgery: 1) control of postoperative inflammation, 2) prevention of cystoid macular edema, and 3) prevention of intraoperative miosis subsequent to iris manipulation during cataract extraction (2, 6, 7).

Several studies have compared the anti-inflammatory effectiveness of topical NSAIDs and corticosteroids and have found them equally effective, though some studies have reported NSAIDs to be only partially effective in resolving severe levels of inflammation (2, 6, 7, 26). However, many studies on NSAIDs' effects on postoperative inflammation include the concomitant administration of corticosteroids. Such combination therapy is also widely used in common practice. NSAIDs and corticosteroids have a potential, though still unproven, synergistic activity (2, 27, 28). Therefore it is often difficult to discriminate the effects of NSAIDs alone from those due to the combined activity of NSAIDs and corticosteroids.

Since the most recent technical advances in ocular surgery have dramatically reduced the extent of ocular trauma and, consequently, of postoperative inflammation, an increasing number of patients is likely to be overtreated with a combined NSAIDs/corticosteroid therapy. Furthermore, this therapy can mask any ocular irritation eventually caused by NSAIDs and increase the risk of corneal toxicity (26). For this reason a therapeutic flowchart based upon actual levels of postoperative inflammation could be advisable.

In order to study a subset of patients who might better benefit of NSAID treatment in the absence of corticosteroids, we assumed that patients with medium to high postsurgical inflammation might be better controlled by short corticosteroid coverage (4 to 7 days). NSAID might therefore be the drug of choice in controlling a less severe inflammation. Accordingly, in the present study NSAID treatment was reserved only for patients displaying a moderate inflammation (ACI score ≤4, on a scale of 0 to 6) in the operated eye the day after surgery. Since the use of

corticosteroids was not allowed, it was not ethically advisable to use a placebo; therefore, an active control was included in the study. Diclofenac was chosen as a control because it is considered the gold standard of the NSAID category. In addition, diclofenac has been demonstrated to be superior to placebo and as effective as corticosteroids in reducing postoperative inflammation after cataract surgery (21-23).

The present results expand the currently published literature regarding the possible clinical use of a new ophthalmic NSAID based on sodium naproxen as active principle. In fact, it has been well known for many years that oral naproxen is able to reduce ocular inflammation (10-16). In addition, sodium naproxen ophthalmic solution reduces clinical and biochemical signs (i.e., proteins, polymorphonuclear leukocytes and PGE2 levels in aqueous humor) of ocular inflammation in different experimental animal models (17, 18). In humans, such solution penetrates the cornea (20) and effectively maintains intraoperative mydriasis (20). We have also recently shown that naproxen eyedrops are effective in reducing postsurgical inflammation as evaluated by both laser cell and flare meter (LCFM) and biomicroscopy (19). The close agreement of these two methods has been previously documented (21). In the present study, in an attempt to confirm those findings, we decided to test the effectiveness of naproxen in a routine clinical setting. Therefore, inflammation was only evaluated by clinical biomicroscopy.

During the course of the study both naproxen and diclofenac led to an almost complete reduction of the ACI (primary efficacy parameter). Within each treatment group, the decrease from baseline of ACI values was statistically highly significant, thus indicating treatment efficacy. Treatment groups were compared statistically with respect to the intraindividual percent changes from baseline ACI score. Differences were evaluated in order to give a higher weight to changes from a low baseline score, e.g., reduction from a baseline score of 2 to a postdose score of 1, corresponding to –50%, compared to higher baseline scores, e.g., a reduction from a baseline score of 3 to a postdose score of 2, corresponding to –33%. Changes were compared by ANOVA in order to estimate confidence intervals. The 90% confidence interval for the percent change of ACI score under naproxen treatment, expressed as percentage of the mean percent change under diclofenac treatment, was (-9%, +14%) on Day 7 and (-5%, +12%) on Day 14 as derived in course of this ANOVA. Accepting a ±14% difference in efficacy as clinically irrelevant, and considering also that none of the efficacy parameters lid edema, corneal edema, photophobia, or tearing yielded values that could discriminate between treatments, the two NSAIDs then may be considered equivalent in terms of clinical efficacy.

Local irritant effects of topical ophthalmic NSAIDs include conjunctival hyperemia, burning, stinging, and corneal anesthesia (26). These events are for the most part short-lived and self-resolving. A more serious complication involves the association of topical ophthalmic NSAIDs with indolent corneal ulceration and full-thickness corneal melts (29). In fact, a higher incidence of corneal complications has been recently described primarily with a generic formulation of diclofenac (2, 30, 31). In the present study the only reports of possible relevance were conjunctival hyperemia, burning, stinging, and pain, which were mainly associated with the use of sodium naproxen. The lower scores observed in the diclofenac group for burning, stinging, and pain may be explained by differences in the two formulations but also by the known ability of diclofenac to induce a reduction in corneal sensitivity (32). The overall percentage of patients treated with sodium naproxen with eye redness was <10%, whereas transient burning was reported in approximately 4% of patients. These percentages are not higher than those reported for other topical ophthalmic NSAIDs such as diclofenac or ketorolac (PDR info). Only one case of keratitis, in the diclofenac group, was observed during the study. Interestingly, no corneal AEs have been reported in the entire clinical series involving about 400 patients treated with naproxen (19, 20, 33). Larger studies are needed to confirm this safety profile.

In conclusion, the results of the present study suggest that the new ophthalmic NSAID sodium naproxen may be useful in controlling signs and symptoms of ocular inflammation after uncomplicated cataract surgery in the absence of concomitant corticosteroid therapy and presumably without expectations of corneal complications.

APPENDIX

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The authors have no proprietary interest in any products object of the study.

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