Effects of dexamethasone, diclofenac, or placebo on the inflammatory response after cataract surgery

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Aim: To compare the inflammatory response after phacoemulsification and intracocular lens (IOL) implantation with postoperative treatment with dexamethasone, diclofenac, or placebo.

Methods: A prospective, randomised, controlled double masked study including 180 patients enrolled for cataract surgery. The patients were 64–85 years old and had no eye disease other than cataract. After phacoemulsification and IOL implantation the patients were randomised to topical treatment with dexamethasone phosphate 0.1% (group I), diclofenac sodium 0.1% (group II), or placebo (saline 0.9%) (group III). The drops were administered four times daily during the first week and twice daily during the second, third, and fourth weeks. The inflammatory reaction in the anterior chamber was measured with laser flare photometry preoperatively and 1, 3, and 8 days, 2 and 4 weeks, 2 and 6 months, and 1, 2, and 4 years postoperatively. Inflammatory symptoms were registered. Biomicroscopy and visual acuity determinations were performed. The rate of Nd:YAG laser posterior capsulotomies after 2 and 4 years was determined.

Results: After 3 and 8 days (p <0.0001), 2 weeks (p <0.0001), and 1 month (p = 0.0013) median flare was highest in group III. There were no significant differences between group I and II. Inflammatory symptoms and striate keratopathy were more common in group III.

Conclusion: Dexamethasone and diclofenac were equally effective in reducing postoperative inflammation after phacoemulsification and IOL implantation in eyes with no other disease than cataract. Both substances were more effective than placebo.
The surgery was uncomplicated in all cases. There were no statistically significant differences between the groups regarding operation time, phacoemulsification time, or phacoemulsification energy. In group I median flare rose from 5.0 photons/ms before surgery to 12.1 photons/ms on the first postoperative day. In group II the flare increased from 4.9 photons/ms to 12.4 photons/ms, and in group III from 5.1 photons/ms to 13.3 photons/ms. The differences between the groups were not significant.

The study solution was administered by the patients four times daily during the first week and twice daily during the second, third, and fourth weeks. At day 1 laser flare photometry (Kowa 500) was performed before the study treatment was given. The flare measurements were performed about 30 minutes after dilatation of the pupil at 1, 3, and 8 days, 2 and 4 weeks, 2 and 6 months, and 1, 2, and 4 years postoperatively. The flare value for each patient was averaged from 10 measurements. If an extreme value was found the highest and lowest measurements were eliminated before calculation. The patient was excluded if the coefficient of variation exceeded 35%.

There were no significant differences in pupil size between the groups. Eyes treated with Nd:YAG laser posterior capsulotomy were not included.

The presence of inflammatory symptoms (ciliary flush, pain, and/or photophobia) was registered. At all observation times, except after 3 days and 2 weeks, biomicroscopy was performed in all patients, as well as visual acuity and intraocular pressure (IOP) determinations. Patients were withdrawn from the study if a clinically unacceptable inflammation occurred. This implied a symptomatic inflammation, or more than a slight ciliary injection or aqueous flare.

After 2 and 4 years the rate of Nd:YAG laser posterior capsulotomies in each group was determined.

### Assignment
The patients were randomly allocated to three equal sized groups (n=60). Randomisation was done by a computer in blocks of six patients (randomly permuted blocks, SAS/PLAN procedure). On the first day after surgery, the patients received three coded bottles containing one of the treatment solutions.

### Masking
All bottles were white and non-transparent. They were delivered from the pharmacy with identical labels except for the randomisation number. There was a coding envelope for each number.

### Statistics
The sample size was determined from laser flare photometry data collected by the authors in a previous study. Using this information, a 5% significance level and 80% power, the number of patients needed in each treatment group was 56 to detect a 20% difference between the groups. The Kruskal-Wallis ANOVA with correction for multiple comparisons was used to detect differences in laser flare between the groups at different time points. Relations between categorical variables were analysed with the chi-square test. The Spearman rank correlation coefficient was used as a measure of correlation. Pupil diameters were analysed with the median test. The calculations were made by computer analysis using Statistica 5.0 (StatSoft).

### RESULTS

#### Inflammatory response: laser flare photometry
On the first postoperative day there were no significant differences between the groups. At 3 and 8 days, 2 weeks, and 1 month the flare values were significantly lower in group I (dexamethasone) and group II (diclofenac) compared to group III (placebo) (Table 1). Subsequently, no significant differences were found between the groups. There were no significant differences between groups I and II at any observation time.

The change of the flare from the preoperative measurement to day 1 after surgery was not correlated with the total phacoemulsification energy used (Spearman R = 0.007, p = 0.93, n = 180) (Fig 1).

### Table 1 Laser flare values (photons/ms) in the three study groups preoperatively and during 4 years postoperatively (median and range). During the first postoperative month median flare was significantly higher in the placebo group (Kruskal-Wallis ANOVA). The flare value in the placebo group rose until 8 days after surgery and then it fell continuously, indicating a spontaneous regression of the BAB damage.

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone (No)</th>
<th>Diclofenac (No)</th>
<th>Placebo (No)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop</td>
<td>5.0 (0.5–15.0)</td>
<td>4.9 (2.1–17.4)</td>
<td>5.1 (2.3–18.3)</td>
<td>60</td>
</tr>
<tr>
<td>1 day</td>
<td>12.1 (8.7–21.2)</td>
<td>12.4 (10.3–89.2)</td>
<td>13.3 (12.5–52.6)</td>
<td>60</td>
</tr>
<tr>
<td>7 days</td>
<td>10.8 (2.4–63.4)</td>
<td>10.8 (2.4–46.7)</td>
<td>24.3 (2.7–145.1)</td>
<td>60</td>
</tr>
<tr>
<td>8 days</td>
<td>8.6 (3.0–64.4)</td>
<td>7.9 (2.7–38.4)</td>
<td>27.5 (4.0–156.0)</td>
<td>58</td>
</tr>
<tr>
<td>2 weeks</td>
<td>7.6 (2.7–24.8)</td>
<td>7.3 (1.5–19.0)</td>
<td>14.3 (3.2–67.3)</td>
<td>54</td>
</tr>
<tr>
<td>1 month</td>
<td>6.0 (1.5–15.0)</td>
<td>7.0 (2.6–18.7)</td>
<td>9.1 (2.8–34.2)</td>
<td>55</td>
</tr>
<tr>
<td>2 months</td>
<td>6.6 (2.8–18.9)</td>
<td>6.3 (2.2–15.8)</td>
<td>6.1 (0.9–20.8)</td>
<td>55</td>
</tr>
<tr>
<td>6 months</td>
<td>5.9 (2.6–12.4)</td>
<td>5.4 (1.8–18.3)</td>
<td>5.4 (0.5–14.9)</td>
<td>50</td>
</tr>
<tr>
<td>1 year</td>
<td>6.2 (3.6–21.1)</td>
<td>5.8 (2.8–20.8)</td>
<td>5.7 (1.7–12.8)</td>
<td>50</td>
</tr>
<tr>
<td>2 years</td>
<td>7.2 (3.6–19.8)</td>
<td>6.6 (2.9–21.8)</td>
<td>6.1 (3.7–22.7)</td>
<td>44</td>
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<tr>
<td>4 years</td>
<td>7.1 (4.2–16.6)</td>
<td>6.4 (4.4–21.4)</td>
<td>6.2 (3.9–19.3)</td>
<td>36</td>
</tr>
</tbody>
</table>

The difference in flare (photons/ms) between the placebo group rose until 8 days after surgery and then it fell significantly.

#### Figure 1
The difference in flare (photons/ms) between the preoperative examination and the first day after surgery was not significantly correlated with the total phacoemulsification energy used during the operation (Spearman R = 0.007, p = 0.93, n = 180).
There was no general consensual inflammatory response in the unoperated eye.

During the first month after the operation six patients were withdrawn from the study because of inflammatory reactions (see below). Three patients dropped out of the study because of intervening general diseases. A coefficient of variation exceeding 35% was measured in a few patients during the first month. None of these patients (18.3%) at day 3 and in 19 of 59 patients (30.5%) at day 8. Median flare was higher in these eyes than in the rest of the group, 40.4 (range 8.7–124.5) and 53.0 (9.7–156.0) photons/ms, respectively. Comparing group III to the other groups, the rate of patients with inflammatory symptoms was greater in group III at day 3 (p<0.001) and day 8 (p<0.001) but not at 2 weeks (Table 2). Subsequently all eyes were quiet. Thus at 2 weeks and subsequently, clinical outcome was similar in group III and the other groups. No significant differences were found between group I and II at any observation time.

Withdrawals due to inflammatory reactions

No patient in group I was withdrawn from the study. One patient in group II experienced an uveitis with hypopyon 6 days after surgery and was withdrawn from the study. Samples from the anterior chamber and the vitreous were culture negative. The eye improved promptly after treatment with topical dexamethasone.

In group III inflammatory symptoms were found in 11 of 60 patients (18.3%) at day 3 and in 18 of 59 patients (30.5%) at day 8. Median flare was higher in these eyes than in the rest of the group, 40.4 (range 8.7–124.5) and 53.0 (9.7–156.0) photons/ms, respectively. Comparing group III to the other groups, the rate of patients with inflammatory symptoms was greater in group III at day 3 (p<0.001) and day 8 (p<0.001) but not at 2 weeks (Table 2). Subsequently all eyes were quiet. Thus at 2 weeks and subsequently, clinical outcome was similar in group III and the other groups. No significant differences were found between group I and II at any observation time.

Intraocular pressure

No patient in group I was withdrawn from the study. One patient in group II experienced an uveitis with hypopyon 6 days after surgery and was withdrawn from the study. Samples from the anterior chamber and the vitreous were culture negative. The eye improved promptly after treatment with topical steroids and intravitreal and subconjunctival antibiotics. Visual acuity was 20/20 1 month postoperatively. During the first 2 weeks after surgery anti-inflammatory treatment was added in four of the 60 eyes in group III because of an clinically unacceptable inflammatory reaction. These four eyes had a ciliary flush and a moderate flare at slit lamp examination and the patients complained of pain. Keratic precipitates were found in two cases. The flare values in these four patients were 27.6, 34.7, 37.6, and 124.5 photons/ms. There was a rapid improvement in all four cases after treatment with topical dexamethasone.

After 1 month a patient in group III had developed a maculopathy with dot haemorrhages causing a decrease of visual acuity. After anti-inflammatory treatment visual acuity was 20/30.

Visual acuity

There were no significant differences in visual acuity between the groups comparing the number of patients achieving the prospectively defined visual acuity limit of 20/25 except 8 days postoperatively, when visual acuity was significantly lower in group III than in group I (p<0.05) (Table 3).

Cornea

Regarding the rate of striate keratopathy (one or more MD folds found in the upper and/or central cornea) there were no significant differences between the groups at day 1. However, at day 8 striate keratopathy was more frequent in group III than in the other groups (p=0.01) (Table 4). Subsequently no corneal reactions were found. No epithelial complications occurred in any of the groups.

Capsulotomy rate

The rate of Nd:YAG laser posterior capsulotomies was equal in the three groups after 2 years. After 4 years it was significantly lower in group III than in group II (p<0.05) (Table 5).
DISCUSSION

Previously a greater need for anti-inflammatory treatment after ECCE than after intracapsular cataract extraction was suggested. An explanation might be induction of inflammation by remaining lens epithelial cells in the capsular bag. Later phacoemulsification has been shown to induce less inflammation and BAB breakdown than ECCE. Interestingly, in this study we found no significant correlation between the postoperative inflammatory reaction and the amount of phacoemulsification energy used during surgery (Fig 1).

Because of the improvements in surgical technique and the reduction of BAB damage the actual need for anti-inflammatory therapy after modern cataract surgery has been questioned. It has been only in the past several years that randomised studies including placebo have been performed. In the present trial we compare placebo drops to treatment with dexamethasone phosphate 0.1% or diclofenac sodium 0.1% drops after phacoemulsification and implantation of HSM IOL, an IOL that has been shown to induce a low inflammatory response.

Whereas steroids interfere with the inflammatory response in a variety of ways, one of which is the inhibition of arachidonic acid synthesis, NSAIDs decrease inflammation specifically by inhibition of the activity of cyclo-oxygenase, thus decreasing the production of prostaglandins from arachidonic acid. Unlike other NSAIDs, however, diclofenac indirectly modulates also the lipoxygenase pathway in the arachidonic acid cascade. This dual mechanism of action of diclofenac may make it comparable in anti-inflammatory activity to the corticosteroids. The results of the present study are in agreement with this presumption, since no significant difference in inflammatory reaction was found between group I (dexamethasone) and group II (diclofenac) at any observation time.

In group III (placebo) median flare in eyes with inflammatory symptoms was higher than in the group as a whole, confirming that an elevated laser flare meter value was pertinent to a clinically significant inflammation. We found that a higher rate of striate keratopathy was associated with a higher inflammatory activity to the corticosteroids. The rate of Nd:YAG laser posterior capsulotomies was low in the placebo group after 4 years (Table 5), although this group experienced a higher inflammatory response during the first postoperative month. However, capsulotomy rate is a less accurate measure of the development of after-cataract. We therefore intend to evaluate posterior capsular opacification using retroillumination images taken with a Scheimpflug camera.

No typical steroid responders were found, but a slight IOP rising effect of steroids was noted during and immediately after the treatment period, in accordance with previous information.

In conclusion, dexamethasone and diclofenac were equally effective in the treatment of postoperative inflammation in otherwise normal eyes after phacoemulsification and HSM IOL implantation. Both substances were more effective than placebo. The results support and extend the knowledge obtained from other studies and indicate that topical anti-inflammatory treatment is generally warranted after modern cataract surgery in order to alleviate the inflammatory response and the possible risk for complications such as corneal damage and cystoid macular oedema.

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The authors have no proprietary interest in any of the products or equipment mentioned in this article.

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REFERENCES