Effect of anti-inflammatory regimen on early postoperative inflammation after cataract surgery

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Purpose: To investigate whether a combination of topical non-steroidal anti-inflammatory drugs (NSAIDs) and steroids were superior in controlling early postoperative inflammation after cataract surgery compared with topical NSAIDs alone and with dropless surgery where a sub-Tenon depot of steroid was placed during surgery.

Setting: Department of Ophthalmology, Rigshospitalet-Glostrup, Denmark.

Design: Prospective randomized controlled trial with masked statistical analyses.

Methods: Patients undergoing phacoemulsification for age-related cataract were randomized to 1 of 5 regimens: ketorolac and prednisolone eyedrops combined (Pred+NSAID-Pre [control group] and Pred+NSAID-Post group) vs ketorolac monotherapy (NSAID-Pre and NSAID-Post groups) vs sub-Tenon depot of dexamethasone (dropless group). Drops were used until 3 weeks postoperatively, starting 3 days preoperatively in the Pre groups and on the day of surgery in the Post groups. Aqueous flare was measured at baseline and 3 days postoperatively.

Results: Four hundred fifty-six participants, with a mean age of 72.1 (SD 7.0) years and 283 (62%) women, were included. Flare increased significantly more in the dropless group compared with the control group (Pred+NSAID-Pre), but none of the other groups differed significantly from the control group. Intracocular pressure decreased in all groups but significantly less in groups receiving prednisolone eyedrops (Pred+NSAID-Pre and Pred+NSAID-Post groups) compared with NSAID monotherapy and dropless groups. No differences in postoperative visual acuity were found compared with the control group.

Conclusions: No differences were found between groups randomized to NSAID monotherapy or combination of NSAID and steroid in controlling early inflammation after cataract surgery, but sub-Tenon depot of dexamethasone was less efficient. Initiating prophylactic eyedrops prior to surgery did not influence early postoperative anterior chamber inflammation.

Cataract surgery with extraction of the lens and implantation of an artificial intraocular lens (IOL) is one of the most commonly performed surgical procedures in westernized countries. Modern techniques and optimized surgical procedures have reduced the risk for complications. Successful outcome after cataract surgery is generally expected by patients and cataract surgeons and depends, among other factors, on controlling the surgically induced inflammatory response. If the inflammatory response is not controlled, not only patients might experience ocular pain and photophobia, but it might also lead to serious adverse events such as uveitis, posterior synechiae and secondary glaucoma, and pseudophakic cystoid macular edema. Hence, optimal anti-inflammatory prophylaxis is important.

Early postoperative inflammation is assessed by quantifying the inflammatory response in the anterior chamber of the eye. Inflammation is believed to arise from surgical manipulation and liberation of lens proteins that in turn release inflammatory mediators responsible for degradation of the blood–ocular barrier and migration of leukocytes. Thus, inflammation in the anterior chamber results in higher protein concentrations in the aqueous humor. As the concentration of protein in the aqueous humor rises, low-wavelength light is backscattered, referred to as Tyndall scatter or flare. Anterior chamber inflammation is commonly assessed with slitlamp examination by subjectively evaluating the amount of flare and by counting leukocytes in a 1 mm × 1 mm light beam. Objective
evaluation of anterior chamber inflammation can be performed by measuring flare with a laser flare photometer. The laser flare photometer quantifies Tyndall scatter present in the anterior chamber by counting the number of reflected photons.

The inflammatory response is amenable to prophylactic intervention by 2 main types of drugs: glucocorticoids (steroids) and nonsteroidal anti-inflammatory drugs (NSAIDs). Steroids inhibit phospholipase A2, which reduces levels of leukotrienes responsible for chemotaxis and arachidonic acid that is converted to prostaglandins by cyclooxygenase enzymes. NSAIDs are inhibitors of cyclooxygenase enzymes and mainly inhibit synthesis of prostaglandins. Traditionally, eyedrops containing steroids have been the mainstay of anti-inflammatory prophylaxis after cataract surgery. However, recent meta-analyses showed that NSAID eyedrops might be superior in controlling the postoperative inflammation and preventing pseudophakic cystoid macular edema compared with steroid eyedrops.

Both steroids and NSAIDs have advantages and disadvantages. Steroids possess a wider anti-inflammatory effect than NSAIDs and the price is low, but they are associated with a risk for elevated intraocular pressure (IOP) and might impair wound healing and increase the risk for infections. Corneal melts have been reported with NSAID eyedrops, and application can be associated with discomfort. A systematic review and meta-analysis did not find any differences in the risk for adverse effects between NSAID and steroid eyedrops but found that IOP was significantly higher when steroid was used compared with NSAID.

Administration of eyedrops can be challenging to older patients because of dementia and arthritis. A study found that more than one third of patients were assisted in administering eyedrops and 36% were unable to use the eyedrops as prescribed. Dropless surgery, where a depot of steroid is administered during surgery, has been proposed as a way of avoiding the practical problems associated with eyedrops, but the risk for sustained IOP elevation might be a concern. The purpose of this study was to analyze the effect of anti-inflammatory prophylactic regimen on early postoperative inflammation after standard cataract surgery.

**METHODS**

A randomized controlled trial of 5 different anti-inflammatory prophylactic regimens after uneventful cataract surgery by phacoemulsification was conducted. Regimens were combination of prednisolone (Pred Forte 1%, prednisolone acetate, Allergan Inc.) and ketorolac (Acular 0.5%, Allergan, Inc.) eyedrops 3 times per day for 3 weeks (Pred+NSAID-Pre group and Pred+NSAID-Post group); ketorolac eyedrops alone (Acular 0.5%) 3 times per day for 3 weeks (NSAID-Pre group and NSAID-Post group); and dropless surgery where a sub-Tenon depot of 0.5 mL dexamethasone (Dexamethasone Krka 4 mg/mL, Krka or Dexamethasone 4 mg/mL, Vital Pharma Nordic) was administered during surgery (dropless group). In the Pred+NSAID-Pre and NSAID-Pre groups, treatment was initiated 3 days preoperatively, and in the Pred+NSAID-Post and NSAID-Post groups, treatment was initiated on the day of surgery. Participants in the dropless group were instructed not to use anti-inflammatory eyedrops in the study eye, and surgeons were instructed to place a sub-Tenon depot of dexamethasone at the conclusion of surgery. Sub-Tenon administration of dexamethasone for anti-inflammatory prophylaxis after cataract surgery was not approved by the U.S. Food and Drug Administration as an indication for usage. The combination of prednisolone and ketorolac eyedrops with preoperative initiation (Pred+NSAID-Pre) served as the control group. The study was registered at the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT, 2017-002666-47) and at wwwclinicaltrials.gov (NCT03383328) prior to initiation. The study was approved by the Danish Medicines Agency (Journal nr.: 2017064331), the Danish Committee on Health Research Ethics (Journal nr.: H-1702182), and The Danish Data Protection Agency (RH-2017-291, I-Suite nr.: 05860) and was monitored according to the Good Clinical Practice quality standard by the Good Clinical Practice unit at Copenhagen University Hospital. The study was conducted in accordance with the tenets of the Declaration of Helsinki. All study participants provided written informed consent.

**Participants**

Participants were recruited among patients who were referred for a preoperative evaluation for cataract surgery at the Department of Ophthalmology, Rigshospitalet-Glostrup, Denmark. Participants underwent surgery from February 2018 to October 2019. Inclusion criteria were age-related cataract scheduled for surgery, capacity to consent, and informed consent to participation. Women had to be at postmenopausal stage. Exclusion criteria were known allergy to any of the contents of the pharmaceuticals used in the study, medical history of retinal vein occlusion, epiretinal membrane, uveitis, glaucoma, retinal detachment, diabetes mellitus, exudative age-related macular degeneration or age-related macular degeneration with geographical atrophy, significant complications to surgery such as posterior capsule rupture/vitreous loss, choroidal hemorrhage, and dislocated lens material. Because surgical complications could not be assessed prior to surgery, detection of a significant surgical complication led to exclusion from study (Figure 1).

**Randomization**

Only 1 eye was included per patient. If both eyes were eligible, it was decided by a computerized coin toss which eye to be included in the study. Participants were randomly and evenly allocated to 1 of 5 randomization groups using the randomization instrument in Research Electronic Data Capture (REDCap) hosted at Capital Region, Denmark. A block-randomized list was created and uploaded to REDCap prior to initiation of the study by an independent researcher. The list was created using https://www.sealedenvelope.com/simple-randomiser/v1/lists. Block size was 5, 10, and 15, and length of the list was 470. Bottles with study eyedrops were given to participants along with oral and written instructions for self-administration, except if they were randomized to the dropless group.

**Surgical Procedure**

Participants went through standard cataract surgery by phacoemulsification and implantation of an IOL in the lens capsule. All procedures were performed with local anesthesia with topical oxybuprocaine. Phentolamine 10%, tropicamide 1%, and ketorolac 0.5% were instilled preoperatively. A main incision of 2.4 mm and a side-port incision of 1 mm were made, and intracameral lidocaine 1% and ophthalmic viscosurgical device were instilled, followed by capsulorhexis and hydrodissection. Ultrasonic phacoemulsification was
Table 1. CONSORT diagram for flare analysis. Pred+NSAID-Pre group used prednisolone 1% and ketorolac 0.5% eyedrops, 3 times per day from 3 days preoperatively until 3 weeks postoperatively. Pred+NSAID-Post group used prednisolone 1% and ketorolac 0.5% eyedrops 3 times per day from the day of surgery until 3 weeks postoperatively. NSAID-Pre group used ketorolac 0.5% eyedrops 3 times per day from 3 days preoperatively until 3 weeks postoperatively. NSAID-Post group used ketorolac 0.5% eyedrops 3 times per day from the day of surgery until 3 weeks postoperatively. Dropless group received a sub-Tenon depot of 0.5 mL dexamethasone 4 mg/mL at the conclusion of surgery and used no eyedrops (Excluded = number of participants who were randomly allocated but met a criterion for exclusion; Withdraw = number of participants who withdrew from participation preoperatively and before initiation of allocated regimen; Postop = postoperative; Outside timeframe = number of participants with 3-day visits placed >4 days or <2 days after cataract surgery).

Examinations and Outcomes
Participants were examined at the preoperative visit (baseline) and 3 days (±1 day) after cataract surgery. The primary outcome was change in anterior chamber flare from baseline to 3 days postoperatively. Anterior chamber flare was measured on undilated pupils by flare photometer (KOWA FM-600, KOWA Company) using an average of 5 reliable measurements. Secondary outcomes were number of anterior chamber cells at the postoperative visit, change in corrected distance visual acuity in logarithm of the minimum angle of resolution (logMAR) using an Early Treatment Diabetic Retinopathy Study chart, and change in IOP. Number of cells was counted in a 1 mm × 1 mm light beam, and IOP was measured with a rebound tonometer (Icare) and controlled with Goldman applanation tonometry if IOP was more than 25 mm Hg. Severity of cataract was determined according to the Age-Related Eye Disease Study system for classification of cataracts.18

Adverse events were noted at the postoperative visit as any events that were not expected as part of standard cataract surgery, were not part of baseline conditions, or led to additional treatment. Corneal edema or dryness was not noted as adverse events unless additional treatment was initiated. Additional anti-inflammatory treatment could be initiated at the discretion of an experienced physician if the participant presented with signs or symptoms of uncontrolled inflammation. Eye-related adverse events were grouped into 8 groups (pain/soreness, insufficiently controlled anterior chamber inflammation, dryness, corneal abrasion, swollen/red externa, elevated IOP more than 25 mm Hg, significant corneal edema, and others) and counted. Additional treatment with anti-inflammatory eyedrops, lubricating eyedrops or ointments, IOP-lowering medication, or antibiotic (eg, chloramphenicol) eyedrops or ointments was counted as well.

Statistical Analysis
All statistical analyses were performed according to a specified statistical analysis plan using the statistical software R, version 3.6.0.19,20 Flare measures and phacoemulsification energy were transformed to logarithmic scale to assume normal distribution. A constrained linear mixed model with inherent baseline adjustment was used to make pairwise comparisons of flare, corrected distance visual acuity, and IOP between experimental treatment groups and the control group. Number of cells in the anterior chamber was compared between the groups using Welch t test because no measurement was made at baseline. Dichotomous outcomes were compared between the groups with Fisher exact test. After unmasking, effects of combination treatment vs monotherapy with NSAID and effect of preoperative initiation vs postoperative initiation by pooling relevant eyedrop groups were reported. To correct for multiple comparisons, a Bonferroni adjustment was applied on the primary analysis concerning change in median flare relative to control, resulting in a significance level of 0.0125. All secondary analyses were corrected using the method of Benjamini and Hochberg, which controls the false discovery rate (FDR) to 1 in 20 reported significances (FDR correction).20 An adjusted P value (adj-P) less than 0.05 was considered statistically significant. Analyses were performed according to the intention-to-treat approach. Missing data were implicitly handled by maximum likelihood estimation in the linear mixed model, and the sensitivity of the results was tested with best-case/worst-case scenarios and analyses where extreme outliers were removed. In best-case/worst-case scenarios, missing values were substituted with 10th- and 90th percentiles of the observed data. Finally, analysis to check for possible postrandomization confounding was performed by adjusting analyses for baseline characteristics that seemed to differ between completers and dropouts and for amount of phacoemulsification energy used.

Because of the study design with 1 group not receiving eyedrops, participants and outcome assessors could not be masked to allocation status. Masking was achieved by

Note: Preoperative examinations and outcomes are not included in this CONSORT diagram.
performing data analyses without knowledge of allocation status. This was performed by renaming the interventional groups prior to analyzing. Renaming was performed by a researcher with no relation to the study, and the code was not revealed until analyses were completed.

RESULTS

A total of 470 participants was included and randomized with 94 participants in each interventional group. Fourteen participants were excluded after allocation, leaving 456 participants (283 women [62%]; 173 men [38%]) available to participate in the study. Another 14 participants withdrew preoperatively and before initiation of prophylactic regimen, and 4 participants attended the postoperative visit outside the prespecified timeframe. Thus, 438 participants provided data for the primary analysis. Baseline characteristics and mean use of phacoemulsification energy are presented in Table 1.

Anterior Chamber Inflammation

From a baseline value of 10.1 (95% CI, 9.7-10.6), anterior chamber flare increased by 74.0% (95% CI, 55.2%-95.1%) with Pred+NSAID-Pre, 78.8% (95% CI, 59.8%-100.1%) with Pred+NSAID-Post, 103.7% (95% CI, 81.5%-128.5%) with NSAID-Pre, 94.5% (95% CI, 73.6%-118.0%) with NSAID-Post, and 201.3% (95% CI, 167.9%-239.0%) with dropless prophylaxis. Anterior chamber flare in the droppless group increased significantly more than that of the control group (Pred+NSAID-Pre) (adj-P < .0001), but we found no statistically significant differences for the rest of the groups compared with the control group (Table 2 and Figure 2). The mean number of cells in the anterior chamber at the 3-day visit was 3.4 (95% CI, 3.0-3.9) with Pred+NSAID-Pre, 3.8 (95% CI, 3.3-4.4) with Pred+NSAID-Post, 4.1 (95% CI, 3.3-5.0) with NSAID-Pre, 4.0 (95% CI, 3.4-4.5) with NSAID-Post, and 5.5 (95% CI, 4.5-6.7) with dropless prophylaxis. The mean number of cells was statistically significantly larger for the droppless group compared with the control group (adj-P = .0011) (Table 2).

Visual Acuity and IOP

Postoperatively, visual acuity improved significantly in all groups from a baseline mean at 0.29 logMAR (95% CI, 0.28-0.30) to 0.10 logMAR (95% CI, 0.07-0.13) with Pred+NSAID-Pre, 0.10 logMAR (95% CI, 0.06-0.13) with Pred+NSAID-Post, 0.07 logMAR (95% CI, 0.03-0.10) with NSAID-Pre, 0.10 logMAR (95% CI, 0.06-0.13) with NSAID-Post, and 0.11 logMAR (95% CI, 0.07-0.14) with droppless prophylaxis, but there were no statistically significant differences between the groups (Table 3). IOP decreased in all groups from a mean of 14.3 (95% CI, 13.9-14.6) mm Hg at baseline to 13.6 (95% CI, 12.9-14.2) mm Hg with Pred+NSAID-Pre, 13.4 (95% CI, 12.8-14.0) mm Hg with Pred+NSAID-Post, 11.5 (95% CI, 10.9-12.1) mm Hg with NSAID-Pre, 11.0 (95% CI, 10.4-11.6) mm Hg with NSAID-Post, and 10.3 (95% CI, 9.7-11.0) mm Hg with droppless prophylaxis (Table 3). The decrease was statistically significantly larger for groups that did not receive steroid eyedrops (NSAID-Pre, NSAID-Post, and droppless groups) compared with the control (Pred+NSAID-Pre) group (Table 3). None of the participants had elevated IOP (>25 mm Hg) at the postoperative visit, but 2 participants received IOP-lowering medications immediately postoperatively (Table 3).

Combination vs Monotherapy and Preoperative vs Postoperative Initiation

After combining Pred+NSAID groups (Pred+NSAID-Pre and Pred+NSAID-Post) and NSAID monotherapy groups (NSAID-Pre and NSAID-Post), anterior chamber flare increased more with NSAID monotherapy compared with combination of prednisolone and NSAID, but the difference was not statistically significant after FDR correction (Supplemental Digital Content, Table 1, available at http://links.lww.com/JRS/A246). IOP was statistically significantly lower for groups that did not receive prednisolone eyedrops (Supplemental Digital Content, Table 1, available at http://links.lww.com/JRS/A246). There were no statistically significant differences between eyedrop groups after combining groups with preoperative initiation (Pred+NSAID-Pre and NSAID-Pre) and groups with postoperative initiation (Pred+NSAID-Post and NSAID-Post) (Supplemental Digital Content, Table 2, available at http://links.lww.com/JRS/A246).

| Table 1. Baseline characteristics and use of phacoemulsification energy. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | All Participants| Pred+NSAID-Pre Group | Pred+NSAID-Post Group | NSAID-Pre Group | NSAID-Post Group | Dropless Group |
| Participants, n                | 456             | 91              | 94              | 90              | 92              | 89              |
| F/M, n (%)                     | 283/173 (62/38) | 54/37 (59/41)   | 58/36 (62/38)   | 67/23 (74/26)   | 57/35 (62/38)   | 47/42 (53/47)   |
| Age (y), mean (SD)             | 72.1 (7.0)      | 72.6 (7.1)      | 72.3 (7.0)      | 71.7 (7.1)      | 72.4 (6.8)      | 71.7 (7.1)      |
| AC flare, median (IQR)         | 9.8 (7.4, 14.3) | 9.6 (8.1, 14.3) | 9.8 (7.8, 12.6) | 9.7 (7.0, 13.6) | 10.2 (7.5, 13.0) | 9.8 (6.9, 13.2) |
| VA (logMAR), mean (SD)         | 0.29 (0.15)     | 0.30 (0.19)     | 0.31 (0.15)     | 0.29 (0.16)     | 0.27 (0.14)     | 0.29 (0.13)     |
| IOP (mm Hg), median (SD)       | 14.3 (3.9)      | 13.9 (3.7)      | 14.3 (4.1)      | 14.6 (4.0)      | 14.4 (3.8)      | 14.3 (4.0)      |
| AREDS, median (range)          | 2.0 (<1.0, >3.0)| 2.5 (1.0, >3.0) | 2.0 (1.0, >3.0) | 2.0 (<1.0, 3.0) | 2.0 (<1.0, >3.0)| 2.0 (<1.0, 3.0) |
| CDE, median (IQR)              | 7.7 (5.4, 11.3) | 9.2 (6.3, 14.2) | 8.7 (6.1, 11.4) | 7.2 (5.2, 10.6) | 7.9 (5.6, 10.8) | 6.5 (4.5, 10.7) |

AC = anterior chamber; AREDS = Age-Related Eye Disease Study classification of cataract score for nuclear cataract; CDE = cumulative dissipated energy (phacoemulsification energy); IOP = intraocular pressure; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug; VA = visual acuity.
Adverse Events and Additional Anti-inflammatory Treatment

Eye-related adverse events were registered in 89 participants (20.1%) after cataract surgery. In the dropless group, 44 participants (53.0%) had an eye-related adverse event, which was statistically significantly more than the rest of the groups (adj-P < .0001) (Table 4). The most common adverse events were insufficient control of inflammation and pain/soreness. Additional anti-inflammatory treatment was initiated in 3 (3.4%), 3 (3.2%), 3 (3.3%), and 1 (1.1%) of participants in the Pred+NSAID-Pre, Pred+NSAID-Post, NSAID-Pre, and NSAID-Post groups, respectively, but 30 (36.1%) in the dropless group (Table 4).

Sensitivity Analyses

Results from best-case/worst-case scenarios, analyses where extreme outliers were removed, and analyses for postrandomization confounding are presented in Tables 3–6 (see Supplemental Digital Content, available at http://links.lww.com/JRS/A246). Extreme outliers were found in analyses of cells in anterior chamber, and visual acuity and sensitivity analyses were made where number of cells more than 14 and visual acuity more than 0.80 logMAR were removed. These analyses did not change the overall results from the intention-to-treat analyses.

DISCUSSION

The purpose of this study was to assess the effect of 5 different anti-inflammatory regimens on early postoperative inflammation after uneventful, standard cataract surgery. We found no statistically significant differences between combination of steroid and NSAID eyedrops and NSAID eyedrops alone, and we found no statistically significant effects of initiating eyedrop prophylaxis prior to surgery, but postoperative inflammation was insufficiently controlled in the dropless group. Although we did not find an increase in IOP in groups receiving steroids, we found a statistically significantly lower reduction in postoperative IOP in these groups. Visual acuity improved in all participants with no statistically significant differences compared with the control subjects.

Postoperative inflammation causes breakdown of the blood–ocular barrier and might lead to complications. It is, therefore, highly relevant to test the efficacy of prophylactic anti-inflammatory regimens on early postoperative inflammation. We used an objective measurement: flare photometry. Previous clinical trials have tested prophylactic anti-inflammatory regimens in cataract surgery, and meta-analyses suggest a beneficial effect of using NSAID eyedrops, but reluctance against recommending routine use of NSAID eyedrops exists.6–9 A report by the American Academy of Ophthalmology did not recommend the use of NSAIDs in cataract surgery and argued that NSAIDs should be tested.

Figure 2. Change in anterior chamber flare from baseline to 3 days ±1 day after cataract surgery. Error bars represent median and 95% confidence intervals (Pred = prednisolone 1% eyedrops; NSAID = ketorolac 0.5% eyedrops; Dropless = 0.5 mL sub-Tenon depot of dexamethasone 4 mg/mL; Pre = initiation of eyedrop treatment 3 days preoperatively; Post = initiation of eyedrop treatment on the day of surgery, ph/ms = photon counts per millisecond).
against prednisolone eyedrops instead of eyedrops containing more potent steroids, such as dexamethasone, because of a greater penetration of prednisolone into the anterior chamber. The report also argued that the increased effect of adding NSAID to steroid treatment might simply be caused by increased dosing.21 We tested the combination of prednisolone and NSAID eyedrops against NSAID eyedrops alone to counter these arguments, and we did not find an effect of adding prednisolone eyedrops to NSAID eyedrops on early postoperative inflammation. A study that compared flare measures in eyedrop treatment with diclofenac against dexamethasone eyedrops and combination of the 2 also concluded that there was no significant benefit from combining steroid and NSAID compared with NSAID alone.22 A large European multicenter study concluded that adding steroid eyedrops to NSAID eyedrops did not improve the effect of NSAID monotherapy on macular thickness 12 weeks postoperatively, which supports our conclusions.23 However, the study reported that odds for developing clinically significant cystoid macular edema was lowest for combination of steroid and NSAID eyedrops, but the difference was not statistically significant compared with NSAID monotherapy. This study did not report data on early postoperative inflammation. Other studies compared dropless surgery with steroid eyedrop monotherapy and found no statistically significant differences.15,24 These studies did not compare dropless surgery with NSAID eyedrops, and they administered depots of betamethasone and triamcinolone. We used dexamethasone because of its potency and short period of action, which we theorized would minimize risk for sustained IOP elevations.14 In addition, the other studies measured anterior chamber flare 4 weeks postoperatively, whereas we measured flare 3 days postoperatively.15,22,24 Anterior chamber flare peaks on the first postoperative day and rapidly declines during the first postoperative week, except if inflammation is not

### Table 3. Postoperative results on intraocular pressure and visual acuity.

<table>
<thead>
<tr>
<th></th>
<th>Pred+NSAID-Pre Group</th>
<th>Pred+NSAID-Post Group</th>
<th>NSAID-Pre Group</th>
<th>NSAID-Post Group</th>
<th>Dropless Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP* (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean (CI)</td>
<td>13.6 (12.9, 14.2)</td>
<td>13.4 (12.8, 14.0)</td>
<td>14.3 (13.9, 14.6)</td>
<td>11.0 (10.4, 11.6)</td>
<td>10.3 (9.7, 11.0)</td>
</tr>
<tr>
<td>3 d postop, mean (CI)</td>
<td>0.10 (0.07, 0.13)</td>
<td>0.10 (0.06, 0.13)</td>
<td>0.01 (0.05, 0.04)</td>
<td>0.10 (0.06, 0.13)</td>
<td>0.11 (0.07, 0.14)</td>
</tr>
<tr>
<td>P value/adj-P value</td>
<td>.6761/.9156</td>
<td>0.29 (0.28, 0.30)</td>
<td>0.07 (0.03, 0.10)</td>
<td>0.00 (0.06, 0.04)</td>
<td>.7116/.9474</td>
</tr>
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### Table 4. Adverse events and need for added treatment.

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Pred+NSAID-Pre Group</th>
<th>Pred+NSAID-Post Group</th>
<th>NSAID-Pre Group</th>
<th>NSAID-Post Group</th>
<th>Dropless Group</th>
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<tbody>
<tr>
<td>Total</td>
<td>10 (11.4)</td>
<td>11 (11.8)</td>
<td>10 (11.4)</td>
<td>14 (15.6)</td>
<td>44 (53.0)*</td>
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<tr>
<td>Pain/soreness</td>
<td>1 (1.1)</td>
<td>2 (2.2)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
<td>22 (26.5)*</td>
</tr>
<tr>
<td>Insufficiently controlled inflammation</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>30 (36.1)*</td>
</tr>
<tr>
<td>Dryness</td>
<td>2 (2.3)</td>
<td>3 (3.2)</td>
<td>4 (4.5)</td>
<td>5 (5.6)</td>
<td>7 (8.4)</td>
</tr>
<tr>
<td>Corneal abrasion</td>
<td>2 (2.3)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
<td>4 (4.4)</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Swollen/red externa</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>IOP &gt;25 mm Hg</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
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<tr>
<td>Corneal edema</td>
<td>3 (3.4)</td>
<td>3 (3.2)</td>
<td>1 (1.1)</td>
<td>1 (1.1)</td>
<td>1 (1.2)</td>
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<tr>
<td>Other</td>
<td>2 (2.3)</td>
<td>0 (0.0)</td>
<td>2 (2.3)</td>
<td>3 (3.3)</td>
<td>3 (3.6)</td>
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<td>Added treatment</td>
<td>3 (3.4)</td>
<td>3 (3.2)</td>
<td>3 (3.3)</td>
<td>1 (1.1)</td>
<td>30 (36.1)*</td>
</tr>
</tbody>
</table>

*Adjusted P < .0001.
controlled. Hence, we chose to measure flare 3 days postoperatively where we expected the prophylactic regimen to have greatest influence on flare measurements.

To use a laser flare photometer is generally accepted as the method of choice for measuring anterior chamber inflammation but the method has some limitations. We found that the machine was not easy to use, especially on small pupils, and it required thorough training to master. It is reported that flare measurements might also be influenced by use of mydriatic eyedrops, age, protein composition in the anterior chamber, use of medicines, and postsurgical corneal edema. We included a large number of participants in a randomized setup to minimize risk for bias. The study could not be fully masked because 1 group did not receive eyedrops and because participants who had received a sub-Tenon depot were recognizable at the postoperative visit. Instead, we did all statistical analyses masked to allocation status. The total rate of registered adverse events was generally high, even in the control group (11.4%), which was probably caused by thorough registration of even minor complaints. We included a broad sample of patients from our department, but we did not include patients with comorbidities such as diabetes mellitus, glaucoma, or uveitis, and our conclusions might not apply to such patients.

Monotherapy with NSAID reduces the need for eyedrops compared with combination of steroid and NSAID. Thus, monotherapy with NSAID eyedrops might be preferred to combination of steroid and NSAID eyedrops as standard prophylactic anti-inflammatory regimen after uneventful cataract surgery. We did not find a statistically significant difference in anti-inflammatory effect between combination of steroid and NSAID and NSAID alone, and CIs support that any true difference is likely small and, hence, not clinically relevant. In addition, the IOP-lowering effect of cataract surgery was statistically significantly lower for groups that used combination of steroid and NSAID compared with groups that only used NSAID. The clinical importance of this finding is uncertain because the mean IOP of all groups were low in the normal range and no participants had elevated IOP more than 25 mm Hg at the postoperative visit. But our results showed that IOP was affected using topical steroids a few days after initiation.

Although droplet surgery was less efficient in controlling early postoperative inflammation than eyedrops containing steroids and/or NSAIDs, it was found to be safe regarding risk for elevated IOP and visual outcome. We found no elevations more than 25 mm Hg, and IOP was significantly lower for those in the droplet group than for those in the combination groups, but the data only covers 3 days postoperatively.

We performed all statistical analyses according to the principles of intention-to-treat analysis, and we tested the reliability of our analyses. Our overall results were not affected by sensitivity analyses. The mean age of participants who dropped out was higher, and they were more likely to be men. Therefore, we analyzed whether these baseline variables, along with phacoemulsification energy, biased our primary analysis. Age, sex, and phacoemulsification energy had no effect on change in anterior chamber flare.

In conclusion, the effect of combining prednisolone and ketorolac eyedrops and initiating treatment preoperatively was not significantly different from ketorolac eyedrops alone, with or without preoperative initiation, in controlling early postoperative inflammation after standard cataract surgery. However, dropless surgery with a sub-Tenon depot of 0.5 mL of 4 mg/mL dexamethasone was less efficient in controlling early postoperative inflammation compared with combination of prednisolone and ketorolac eyedrops initiated 3 days preoperatively. Of interest, the combination of prednisolone and ketorolac eyedrops led to a smaller decrease in IOP 3 days postoperatively. Monotherapy with NSAID eyedrops might be preferred to a combination of steroid and NSAID, but long-term effects need to be investigated.

WHAT WAS KNOWN
- Eyedrops containing nonsteroidal anti-inflammatory drugs (NSAIDs) are beneficial compared with high-potency steroid eyedrops after standard cataract surgery.
- Dropless surgery has been compared with steroid monotherapy but has not been compared with NSAID monotherapy or combination of steroids and NSAID.
- Prednisolone eyedrops penetrate the eye better than more potent steroids but previous studies have used other steroids for comparisons with NSAIDs.

WHAT THIS PAPER ADDS
- Combining prednisolone and NSAID eyedrops was not better than NSAID eyedrops alone at controlling early postoperative inflammation after cataract surgery.
- Sub-Tenon depot of dexamethasone as dropless surgery was less efficient than eyedrops.
- Early postoperative inflammation was not better controlled when therapy was initiated preoperatively than on the day of surgery.

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