Anti-inflammatory medication following cataract surgery: a randomized trial between preservative-free dexamethasone, diclofenac and their combination

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ABSTRACT.

Purpose: To examine the anti-inflammatory efficacy and tolerance between preservative-free dexamethasone (DEX) and diclofenac (DICL) eye drops, and their combination following cataract surgery.

Methods: A randomized, double-blind, prospective single-centre study with 189 eyes of 180 patients undergoing routine cataract surgery. Laser flare meter measurement and spectral-domain optical coherence tomography imaging were conducted before surgery and at the 28-day postoperative visit. Clinical characteristics, surgical parameters and assessment of postoperative symptoms were recorded.

Results: Preoperative flare was 9.9 ± 0.5 pu/ms and central retinal thickness (CRT) 264.0 ± 1.9 μm (mean ± SEM). On day 28, flare was 22.1 ± 2.9 pu/ms for DEX, 17.4 ± 2.5 pu/ms for DICL and 13.0 ± 1.6 pu/ms (p < 0.05) for their combination. Central retinal thickness (CRT) increase was 31.6 ± 8.8 μm for DEX, 6.0 ± 0.8 μm (p = 0.001) for DICL, and 3.5 ± 0.5 μm (p < 0.001) for their combination. The incidence of ocular symptoms related to the eye drops was 11% for DEX, 37% for DICL and 34% for their combination (p < 0.001). Clinically significant pseudophakic cystoid macular oedema (PCME) was observed in seven eyes which were all treated with DEX (p < 0.001).

Conclusion: Diclofenac (DICL), as well as the combination of DEX and DICL, were superior to DEX monotherapy in minimizing CRT change and the incidence of PCME. Combination medication showed no added value compared to DICL monotherapy in uneventful cataract surgery.

Key words: aqueous flare – cataract – central retinal thickness – dexamethasone – diclofenac – nonsteroidal anti-inflammatory drug – phacoemulsification – pseudophakic cystoid macular oedema

Introduction

Postoperative management of cataract surgery has been a topic of discussion for a decade. The main interest revolves around the question whether the choice between topical corticosteroids or nonsteroidal anti-inflammatory drug (NSAID) affects postoperative inflammation or the risk of developing pseudophakic cystoid macular oedema (PCME; also, known as Irvine–Gass syndrome), and whether the choice has an impact on the speed of visual recovery and acuity gain. In addition, concerns of drug tolerability differences between NSAIDs and corticosteroids have emerged (Duong et al. 2014; Kessel et al. 2014; Kim et al. 2015; Cardascia et al. 2016; Coassin et al. 2016; Grzybowski et al. 2016; Lim et al. 2016; Malik et al. 2016; Duan et al. 2017; Pollack et al. 2017).

The measurement of aqueous flare, using automated laser flare metering technology, has enabled objective evaluation of anterior chamber reaction for postoperative inflammation. Excess sterile intraocular postoperative inflammation and breakdown of the blood–retinal barrier as marked by aqueous flare have been shown to be connected with the risk for PCME (Ersoy et al. 2013). Widespread use of optical coherence tomography (OCT) has facilitated...
Materials and Methods

Study design

This study was conducted as a randomized, double-blind, prospective single-centre study. Patients were admitted as per the national guidelines for the management of cataract in the Department of Ophthalmology, Kymenlaakso Central Hospital, Kotka, Finland. A total of 224 eyes of 214 patients scheduled for cataract surgery were enrolled between January 2016 and October 2016 for either preservative-free corticosteroid (Monopex®, DEX phosphate 1 mg/ml; Laboratoires Théa, Clermont-Ferrand, France), or NSAID (Voltaren Ophtha®, DICL sodium 1 mg/ml; Laboratoires Théa) eye drops, or a combination of these two drugs.

The data on efficacy in the management of anterior chamber inflammation between topical corticosteroids and NSAID remain conflicting; however, the choice of NSAID may result in less PCME (Henderson et al. 2007; Kim et al. 2010; Duong et al. 2014; Kessel et al. 2014; Wielders et al. 2015; Grzybowski et al. 2016; Malik et al. 2016; Duan et al. 2017). Prior randomized clinical trials often lack head-to-head comparison between the most potent corticosteroid and NSAID eye drops in prevention of PCME (Shimura et al. 2007; Miyake et al. 2011). The choice for patients at increased risk of PCME, such as those with diabetes, with or without retinopathy (Zaczek et al. 1999; Somiya et al. 2002; Kim et al. 2007; Chu et al. 2016), seems to include a combination of corticosteroids and NSAID (Henderson et al. 2007; Singh et al. 2012; Pollack et al. 2017). The combination of corticosteroids and NSAID results in lower PCME incidence when compared to topical corticosteroids, as well as with uneventful surgery for nondiabetic patients (Wolf et al. 2007; Wielders et al. 2015).

Indeed, despite growing number of studies and meta-analyses, assessment of clinical care guidelines for postoperative medication congruent with the study outcomes in uneventful cataract surgery remains a challenge. Multiple treatment protocols, even within a single unit, are common. Here, we aimed to determine the tolerability and compliance, and the effectiveness for postoperative aqueous flare and PCME between a potent treatment with topical preservative-free dexamethasone (DEX), diclofenac (DICL), and a combination of these regimens.

Patients

A total of 224 eyes of 214 patients scheduled for cataract surgery were enrolled between January 2016 and October 2016. Thirteen patients did not want to continue in the research and gave no specific reason or could not attend the predetermined control visit within ± 2 days. Five patients left the study group because they had symptoms from the eye drops and their medication was changed. Ten subjects did not use the medications as prescribed (oral and written instructions were given), and two subjects had mild corneal oedema which led to changes in medication. On a later review, five patients were found not to fill the inclusion/exclusion criteria to the study; one patient (DEX group) did not meet the age criterion, one patient (DEX) was revealed to have wet age-related macular degeneration (AMD), two patients (DEX) had iris prolapsed during surgery and one patient (DEX + DICL) was found to have an old branch retinal vein occlusion. Baseline variables were evaluated according to intention to treat (Tables 1 and 2) and per protocol (Tables S1 and S2) analysis. After these dropouts, a total of 189 eyes of 180 patients were included in the analysis (Fig. 1).

Randomization

The study was conducted as a randomized, double-blind, prospective single-centre study (hrrg.fi/en/clinicaltrials/cataract/). The patients were randomized into three groups for postoperative anti-inflammatory medication: (i) preservative-free corticosteroid eye drops (Monopex®, DEX phosphate 1 mg/ml; Laboratoires Théa) three times a day (t.i.d.) for 3 weeks; (ii) preservative-free NSAID eye drops (Voltaren Ophtha®, DICL sodium 1 mg/ml; Laboratoires Théa) t.i.d. for 3 weeks; or (iii) a combination of both drops with similar dosing. No preoperative anti-inflammatory drops were used.

The drug pipettes were covered with tape by hospital pharmacy and put into marked envelopes. After the cataract operation, the research technician randomized the operated patient into a study group and distributed the marked envelopes accordingly. The blinding was uncovered after the data was analyzed.

Inclusion criteria

The study subjects were aged 60–90 years and were eligible for cataract surgery under the Current Care Guidelines of Cataract Surgery of the Finnish
Table 1. Baseline variables (intention to treat analysis).

<table>
<thead>
<tr>
<th></th>
<th>DEX (n = 78)</th>
<th>DICL (n = 78)</th>
<th>DEX + DICL (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F) n/%</td>
<td>36.42 (46.54%)</td>
<td>30.48 (38.62%)</td>
<td>25.43 (37.63%)</td>
</tr>
<tr>
<td>Age (years) n/%</td>
<td>77.1 ± 0.8 (63–96)</td>
<td>76.0 ± 0.7 (62–88)</td>
<td>76.2 ± 0.9 (62–90)</td>
</tr>
<tr>
<td>Diabetes n/%</td>
<td>15 (19%)</td>
<td>17 (22%)</td>
<td>12 (18%)</td>
</tr>
<tr>
<td>Smoking n/%</td>
<td>10 (13%)</td>
<td>5 (6%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>BCVA (Snellen decimals) n/%</td>
<td>0.32 ± 0.02 (&lt;0.1–0.70)</td>
<td>0.37 ± 0.02 (&lt;0.1–1.00)</td>
<td>0.36 ± 0.02 (&lt;0.1–0.80)</td>
</tr>
<tr>
<td>IOP (mmHg) n/%</td>
<td>15.4 ± 0.4 (8–22)</td>
<td>16.8 ± 0.5 (7–32)</td>
<td>16.0 ± 0.5 (9–32)</td>
</tr>
<tr>
<td>PFX n/%</td>
<td>17 (22%)</td>
<td>15 (19%)</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>CRT mean (μm) n/%</td>
<td>270.7 ± 3.9 (177–415)</td>
<td>275.6 ± 3.0 (228–374)</td>
<td>264.7 ± 3.4 (208–378)</td>
</tr>
<tr>
<td>AMD n/%</td>
<td>22 (28%)</td>
<td>24 (31%)</td>
<td>21 (31%)</td>
</tr>
<tr>
<td>iERM (packer) n/%</td>
<td>6 (8%)</td>
<td>7 (9%)</td>
<td>2 (3%)</td>
</tr>
</tbody>
</table>

Baseline variables regarding (i) patient (ii) ophthalmic (iii) posterior segment and parameters. Data are given as mean (±SEM) or range and absolute number and proportion.

AMD = age-related macular degeneration, BCVA = best-corrected visual acuity, CRT = mean central retinal thickness, DEX = dexamethasone, DICL = diclofenac, iERM = idiopathic epiretinal membrane, IOP = intraocular pressure, PFX = pseudoxefoliation syndrome.

Table 2. Surgical variables (intention to treat analysis).

<table>
<thead>
<tr>
<th></th>
<th>DEX (n = 78)</th>
<th>DICL (n = 78)</th>
<th>DEX + DICL (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time (min) n/</td>
<td>19.2 ± 1.2 (7–75)</td>
<td>19.1 ± 1.3 (5–70)</td>
<td>21.7 ± 1.3 (6–56)</td>
</tr>
<tr>
<td>Phaco energy (CDE)</td>
<td>17.2 ± 1.0 (5.6–43.2)</td>
<td>17.6 ± 1.0 (6.3–51.3)</td>
<td>20.7 ± 1.6 (5.4–68.4)</td>
</tr>
<tr>
<td>Pupil extension device n/%</td>
<td>10 (13%)</td>
<td>6 (9%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>CTR n/%</td>
<td>3 (4%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Baseline variables regarding surgical parameters. Data are given as mean (±SEM) or range and absolute number and proportion.

CDE = cumulative dissipated energy, CTR = capsular tension ring, DEX = dexamethasone, DICL = diclofenac.

Medical Society, Duodecim (updated in year 2013).

Exclusion criteria

Exclusion criteria of the study were (i) prior or active wet AMD, retinal vein/artery occlusion, retinal detachment, retinal necrosis, vitritis/endophthalmitis, vitreous haemorrhage, retinal phlebitis or optic neuritis, previous intraocular procedures (including fundus laser photocoagulation), planned anti-vascular endothelial growth factor treatments, myopia above 6.0 dioptres, alcohol abuse, hypothyroidism with thyroid-stimulating hormone (TSH) above physiological range, continuous use of anti-inflammatory drugs and sensitivity to any of the medications used in the operation or postoperatively. Intraoperative complications such as iris prolapse, use of sutures or posterior capsule tear, failure to attend the postoperative control visit at 28 ± 2 days and failure to use the postoperative anti-inflammatory medication as prescribed were criteria for exclusion. Prior enrollment of contralateral eye was not considered as an exclusion criterion. However, (i) no simultaneous bilateral cataract surgeries were performed to study patients, (ii) randomization of treatment group was performed before every surgery independently from prior contralateral eye surgery and (iii) the minimum gap between the surgeries was 1 month giving sufficient time to recover from the first surgery.

Surgery

A standardized phacoemulsification technique was used in all cataract surgeries (hrgrg.fi/en/videos/cataract/). Cataract surgeries were performed by three specialists and three experienced residents in ophthalmology. A 2.75 mm clear cornea incision was followed by capsulorhexis, phacoemulsification (divide and conquer) and intraocular lens placement into the capsular bag. An Ozil phacoemulsification handpiece and a 0.9 mm 30-degree beveled Kelman tip were used in the phacoemulsification system (InfiniF1™; Alcon, Fort Worth, TX, USA). In all cases, anaesthesia was topical. Hyaluronic acid 1.6%-chondroitin sulphate 4.0% (DisCoVisc®; Alcon) was used as ophthalmic viscosurgical device. Preloaded aspheric hydrophobic single-piece monofocal intraocular lenses were used (PCB00, Tecni® IOL in iTec® delivery system; Abbott Medical Optics Inc., Santa Ana, CA, USA; AU00T0, AcrySof® IQ, SN60WF in UltraSert™ delivery system; Alcon). Antimicrobial medication included intraoperative intracameral cefuroxime (Aprokam®, Laboratoires Thea) and postoperative levofloxacin 5 mg/ml eye drops t.i.d. for 1 week (Oftaquix®, Santen Pharmaceutical Co. Ltd, Osaka, Japan). Duration of operation, phaco energy (cumulative dissipated energy; CDE) and use of intraocular surgical aid (StabilEye® capsular tension ring (CTR); Abbott Medical Optics Inc., 6.25 mm Malyugin Ring® pupil extension device; Micro-Surgical Technology, Redmond, WA, USA) were recorded.

Clinical evaluation

Biometry was evaluated at the day of surgery using swept-source optical coherence tomography (SSOCT) technology (OA-2000; Tomey GmbH, Nürnberg Germany) (McAlinden et al. 2017). Best-corrected visual acuity (BCVA) was preoperatively evaluated by the referring ophthalmologist and postoperatively with an autorefractometer.
Randomization

\[ N = 224 \text{ eyes (214 patients)} \]

Intention to treat analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>N = 78 eyes</th>
<th>N = 78 eyes</th>
<th>N = 68 eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion (do not fill study criteria)</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Withdrewn at patient’s own request / failure to attend on control visit</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Medication misuse</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Medication intolerance</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Adverse event / drug inefficiency</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Per protocol analysis

\[ N = 64 \text{ eyes} \quad N = 70 \text{ eyes} \quad N = 55 \text{ eyes} \]

(B)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dexamethasone</th>
<th>Diclofenac</th>
<th>Dexamethasone diclofenac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective symptoms</td>
<td>7</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>Visual recovery over 1 week</td>
<td>11</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>PCME</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BCVA at day 28</td>
<td>0.83 ± 0.04</td>
<td>0.99 ± 0.03</td>
<td>0.93 ± 0.04</td>
</tr>
<tr>
<td>Overall satisfaction (grade 1–10)</td>
<td>9.21 ± 0.16</td>
<td>9.43 ± 0.09</td>
<td>9.14 ± 0.15</td>
</tr>
</tbody>
</table>

Fig. 1. Per protocol analysis and outcome measures between study groups (A) Study flow chart and (B) subjective symptoms from anti-inflammatory drops, delayed visual recovery, PCME, BCVA at day 28 and overall satisfaction. BCVA = best-corrected visual acuity, PCME = pseudophakic cystoids macular oedema.

(A-RIs; NIDEK Co. Ltd, Aichi, Japan) at standardized light conditions. Intraocular pressure (IOP) was measured by rebound tonometry (iCare® tonometer; Revenio Group, Vantaa, Finland) to rule out differences regarding IOP adverse effects between the tested groups.

Follow-up 30-frame scans were performed with AutoRescan™ software, and preoperative OCT analyses were compared to those obtained 28 days after surgery (Heidelberg Eye Explorer Version 1.9.10.0 and HRA/SPECTRALIS® Viewing Module Version 6.0.9.0; Heidelberg Engineering GmbH).

Aqueous flare was measured preoperatively and at 28-day postoperation with a laser flare meter (FM-600; Kowa Company, Ltd.). The mean of five reliable measurements was used in the analysis.

The diagnosis for PCME was based on clinical appearance together with typical OCT findings taken at the 28-day control visit (Antcliff et al. 2000; Kusbeci et al. 2012).

Power analysis

The power analysis was based on sample size estimate for aqueous flare as it required higher number of enrolled patients than the second primary outcome, change in CRT. Aqueous flare at day 28 was estimated 10...
were given topical DEX, 26 (37%) topical diclofenac (p < 0.001; Fig. 1B), and 18 (34%) combination of both (p < 0.001; Fig. 1B). Forty-six of 51 (90%) of these symptoms were reported as stinging/burning sensation, one reporting symptoms in visual field after administering medication (DICL), one reporting pain after administering medication (DEX + DICL), three not being able to specify the symptom (1 DEX and 2 DICL).

Twenty-two of the 189 study eyes (12%) were reported to have taken a week or more for VA to rise to its eventual postoperative state. Eleven (17% incidence) were treated with an eventful postoperative state. Forty-six of 51 (90%) of these were reported as stinging/burning sensation, one reporting symptoms in visual field after administering medication (DICL), one reporting pain after administering medication (DEX + DICL), three not being able to specify the symptom (1 DEX and 2 DICL).

**Statistical analyses**

Data were given as mean ± SEM, except for the absolute numbers and proportions for the nominal scale. IBM SPSS Statistics 24 (SPSS Inc., Somers, NY, USA) was used for statistical analysis. For two-group comparisons, data were analysed for continuous variables with Student’s t-test and nonparametric Mann–Whitney U-test for groups without normal distribution. Multiple groups were compared with the one-way ANOVA test using Bonferroni correction. Qualitative data were analyzed with the two-factor chi-squared test or Fisher–Freeman–Halton test for multiple groups. A linear regression model was used to estimate the relationships between variables. p ≤ 0.05 was considered statistically significant.

**Results**

**Baseline variables**

Baseline variables were comparable between DEX, DICL and combination treatment groups regarding (i) patient (gender, age, smoking), (ii) ophthalmic [BCVA, CRT, IOP, pseudoexfoliation syndrome (PFX)], (iii) posterior segment [existence of AMD and epiretinal membrane (macular pucker)] and (iv) surgical characteristics [operation time, phaco energy (CDE), aid of pupil expansion devices and CTRs; p = NS, Tables 1 and 2].

**Subjective irritation symptoms reported from anti-inflammatory medication**

Subjective symptoms, visual recovery and overall satisfaction were documented at 28-day postoperative visit using a structured questionnaire and interview by research technician. In 51 of the 189 study eyes (27%), symptoms were reported from the anti-inflammatory eye drops. Seven (11% incidence) photons/ms for the DICL group and 12 photons/ms for the DEX group with standard deviation 15 for both. Non-inferiority margin was set at 5 with 80% power and sampling ratio 1:1. The sample size estimated at 57 for single group adding to 71 with 25% estimated dropout rate. It was safe to assume similar difference will be detected for the inferior product comparing to combination treatment.

Central retinal thickness (CRT) increase was 31.5 ± 8.8 μm in DEX, 6.0 ± 0.8 μm in DICL (p = 0.001; Fig. 3A) and 3.5 ± 0.5 μm in the combination group (p < 0.001; Fig. 3A). At day 28, CRT was 302.3 ± 9.9 μm in DEX, 281.1 ± 3.2 μm in DICL (p = 0.047; Fig. 3B) and 266.4 ± 3.1 μm in the combination group (p < 0.001; Fig. 3B).

**Effect of anti-inflammatory medication on aqueous flare**

Compared to the day of surgery, aqueous flare increased by 11.4 ± 2.6 pu/ms in DEX, 9.0 ± 2.5 pu/ms in DICL and 3.6 ± 2.2 pu/ms in the combination group (p = NS; Fig. 2A). At day 28, aqueous flare was 22.1 ± 2.9 pu/ms in DEX, 17.4 ± 2.5 pu/msec in DICL and 13.0 ± 1.6 pu/ms (p = 0.042; Fig. 2B) in the combination group.

**Effect of anti-inflammatory medication on central retinal thickness**

Central retinal thickness (CRT) increase was 31.5 ± 8.8 μm in DEX, 6.0 ± 0.8 μm in DICL (p = 0.001; Fig. 3A) and 3.5 ± 0.5 μm in the combination group (p < 0.001; Fig. 3A). At day 28, CRT was 302.3 ± 9.9 μm in DEX, 281.1 ± 3.2 μm in DICL (p = 0.047; Fig. 3B) and 266.4 ± 3.1 μm in the combination group (p < 0.001; Fig. 3B).

**Effect of anti-inflammatory medication on aqueous flare**

Compared to the day of surgery, aqueous flare increased by 11.4 ± 2.6 pu/ms in DEX, 9.0 ± 2.5 pu/ms in DICL and 3.6 ± 2.2 pu/ms in the combination group (p = NS; Fig. 1B). At day 28, aqueous flare was 22.1 ± 2.9 pu/ms in DEX, 17.4 ± 2.5 pu/msec in DICL and 13.0 ± 1.6 pu/ms (p = 0.042; Fig. 2B) in the combination group.

**Effect of anti-inflammatory medication on central retinal thickness**

Central retinal thickness (CRT) increase was 31.5 ± 8.8 μm in DEX, 6.0 ± 0.8 μm in DICL (p = 0.001; Fig. 3A) and 3.5 ± 0.5 μm in the combination group (p < 0.001; Fig. 3A). At day 28, CRT was 302.3 ± 9.9 μm in DEX, 281.1 ± 3.2 μm in DICL (p = 0.047; Fig. 3B) and 266.4 ± 3.1 μm in the combination group (p < 0.001; Fig. 3B).
Visual acuity gain in patients with and without pseudophakic cystoid macular oedema

At day 28, BCVA was 0.83 ± 0.04 decimal units in DEX, 0.99 ± 0.03 decimal units in DICL (p = 0.006; Fig. 4A) and 0.93 ± 0.04 decimal units in the combination group. Best-corrected VA (BCVA) gain was 0.54 ± 0.04 decimal units in DEX, 0.63 ± 0.04 decimal units in DICL and 0.58 ± 0.04 decimal units in the combination treatment group (p = NS; Fig. 4A).

Clinically, refractory PCME was observed in seven eyes of seven patients (among which five eyes had CRT increase more than 30%). All seven eyes with PCME were in the DEX group (p < 0.001; Fig. 1B). Baseline values in eyes with and without PCME did not differ with regard to the patient age (76.9 ± 3.1 versus 76.3 ± 0.5 years), gender distribution (3:4 versus 72:110 male:female), smoking (1:6 versus 15:167 smoking:nonsmoking), aqueous flare (9.4 ± 1.7 versus 9.0 ± 0.6 pu/ms), CRT (296.3 ± 21.0 versus 268.5 ± 1.8 μm) and IOP (15.2 ± 2.5 versus 16.2 ± 0.3 mmHg; p = NS; data not shown).

Central retinal thickness (CRT) increase was 173.4 ± 2.5 μm versus 276.3 ± 2.3 μm in those with PCME versus without PCME, respectively (p = 0.001; data not shown). Central retinal thickness (CRT) at 28 days was 469.7 ± 33.6 μm for those with PCME and 276.3 ± 2.3 μm for those without PCME (p < 0.001; data not shown). Best-corrected VA (BCVA) at day 28 was markedly impaired in the eyes with PCME from those without PCME (3.2 ± 0.5 versus 8.8 ± 0.6 decimals for those with PCME and 276.3 ± 2.3 μm for those without PCME (p = 0.006; Fig. 4B).

Effect of anti-inflammatory medication on intraocular pressure 28 days after cataract surgery

In the study eyes, at 28 days IOP reduction was 5.5 ± 0.3 mmHg, the level of IOP being 10.7 ± 0.2 mmHg. The IOP change and mean IOP at 28 days was −5.1 ± 0.5 mmHg and 10.4 ± 0.4 mmHg in DEX, −6.1 ± 0.5 mmHg and 10.9 ± 0.4 mmHg in DICL, and −5.4 ± 0.5 and 10.8 ± 0.4 mmHg in the combination group (p = NS; Fig. 5A,B).

Effect of surgical parameters on the main outcome measures

Aqueous flare at 28 days and CRT increase did not correlate with phaco energy (R² = 0.019, p = 0.068 and R² = 0.004, p = 0.391, respectively) nor operation time (R² < 0.001, p = 0.938 and R² = 0.015, p = 0.110, respectively). Eyes with and without PCME did not differ for phaco energy (19.6 ± 5.6 versus 18.3 ± 0.7 CDE) nor operation time (25.4 ± 8.8 versus 19.8 ± 0.8 min, p = NS; data not shown).

Aqueous flare at 28 days remained statistically insignificant between eyes with pupil expansion device (33.4 ± 12.7 pu/ms) and CTR (30.2 ± 18.1 pu/ms) and those without (17.3 ± 1.5 pu/ms and 16.6 ± 1.4 pu/ms, respectively, p = NS; data not shown). Furthermore, CRT increase was comparable between eyes with pupil expansion device (15.1 ± 5.2 μm) and CTR (5.8 ± 4.1 μm) and eyes without (13.1 ± 3.2 μm and 13.5 ± 3.0 μm, respectively, p = NS; data not shown).

Discussion

Our present results favour topical NSAIDs over corticosteroids as a first-line choice in postoperative inflammation management. According to our data, DICL was more effective than DEX in preventing PCME. To our knowledge, this is the first report investigating added benefit of combination...
treatment over NSAID monotherapy. In this sample of patients with unselected cataract, combination therapy of both topical DEX and DICL presented better results on primary outcomes over DEX monotherapy. Combination therapy did not, however, promote added benefit to DICL monotherapy. Our data are clinically relevant, considering that steroid monotherapy is still primary treatment in many clinics.

The suggested mechanisms contributing to the development of PCME include increase in vascular permeability through inflammatory mediators such as prostaglandins (Flach 1998; Kessel et al. 2014). Corticosteroids prevent inflammation by pleiotropic mechanisms (including inhibition of prostaglandin synthesis), whereas NSAIDs specifically inhibit prostaglandin production (Kim et al. 2010). Combination therapy of corticosteroids and NSAID may offer limited synergistic anti-inflammatory effects. Comparison between NSAID and combination therapy in high-risk groups such as diabetic patients would be of interest to challenge the hypothesis.

Of note, in this study of patients with unselected cataract, we chose not to use preoperative anti-inflammatory medication. In our study population, age, gender, presence of posterior segment comorbidities (macular pucker or dry AMD) and surgical parameters (use of a CTR or a pupil expansion device) did not have a significant effect on the change in aqueous flare or CRT. Furthermore, the operation time or phaco energy did not affect the change in aqueous flare or CRT either. Several known risk factors for PCME were considered as exclusion criteria for the study. In high-risk patients, preoperative anti-inflammatory medication may be warranted (Kessel et al. 2014).

The number of dropouts was somewhat high in relation to the length of the follow-up. Baseline variables according to intention to treat gives an accurate image of successful randomization (per protocol data presented as supplement), while follow-up according to per protocol represents the study population within the limits of strict exclusion criterion. Here, the single major reason for dropout was failure to attend the control visit on the postoperative 28 ± 2 days, which we considered as a strict exclusion criterion for the study. Patients treated with DICL or combination therapy reported more irritation symptoms than those treated with DEX only. One could anticipate better compliance among DEX users when compared to those of DICL. The number of dropouts was comparable between DEX, DICL and combination therapy groups despite the difference in tolerability. Ten eyes were case specifically excluded due to misuse of prescribed anti-inflammatory regimen (regardless detailed instructions given in oral and written form), while occasional memory slips were accepted. Patients seemed to report medication use accordingly, but chance of report error and recall bias exists and needs to be acknowledged.

Another limitation of our study is the lack of long-term 3–12 months of follow-up. Our follow-up was only 1 month, which was adopted according to the Current Care Guidelines of Cataract Surgery of the Finnish Medical Society, Duodecim (updated in year 2013). The need for such control visit as a routine clinical practice was recently questioned (Eloranta & Falck 2017). However, 1-month control visit is suitable to pick up prolonged inflammation after the course of topical anti-inflammatory treatment. Even though most cases of refractory PCME occur later at 4–10 weeks (giving the definitive conclusion regarding incidence of refractory PCME only after 3 months), differences in CRT with modern OCT imaging are apparent already at 28 days.

During postoperative treatment, preservative-free products may reduce ocular discomfort and even exhibit superior anti-inflammatory efficacy (Maca et al. 2010; Yasuda et al. 2012). Dexamethasone (DEX), among another potent corticosteroid prednisolone acetate, have been proven effective in postoperative use (Laurrell & Zetterström 2002; Kessel et al. 2014). Nepafenac has established a wide market share (Margulis et al. 2017). Lack of sufficient data on potent NSAID head-to-head comparison in cataract surgery limits establishment of one drug over another. Keeping in mind the considerable incidence of irritation after topical preservative-free DICL that did not, however, reflect as compliance problems, our findings favour choosing DICL instead of DEX as the first-line postoperative medication after cataract surgery in preventing PCME, and to reserve DEX for the combination therapy for patients with highest risk of postoperative complications. Further studies are needed to optimize the length of treatment and follow-up, to investigate the potential of preoperative medication (Grzybowski et al. 2016) and to elucidate the effectiveness, tolerability and compliance between topical NSAID regimes.

References
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