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Efficacy and safety of indomethacin 0.1% eye drops compared with ketorolac 0.5% eye drops in the management of ocular inflammation after cataract surgery

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ABSTRACT.

Purpose: **To determine whether indomethacin 0.1% eye drops are at least as effective as ketorolac 0.5% eye drops in treating ocular inflammation following cataract surgery.**

Methods: **Prospective, multicenter, investigator-masked, parallel-group, randomized, active-controlled clinical trial. Cataract patients were randomized in a 1:1 ratio to receive indomethacin or ketorolac administered QID for 3 weeks beginning 1 day before surgery. The primary end-point was aqueous flare measured by laser flare meter at postoperative Days 1 and 7. Secondary end-points included retinal thickness, slit lamp and funduscopic examinations and postsurgical pain ratings. Safety and tolerability were also assessed.**

Results: **A total of 86 patients were included in the per protocol population (n = 43 per treatment group). Indomethacin was found non-inferior to ketorolac for comparison of aqueous flare at postoperative Days 1 and 7 (Day 1: 95% CI: −2.37, 5.50; non-inferiority upper margin, 15 ph/ms and Day 7: 95% CI: −7.83, −0.94; non-inferiority upper margin, 8 ph/ms) and statistically better than ketorolac at Day 7 ($p = 0.013$). There were no significant between-group differences in aqueous flare and change from baseline in retinal thickness at postoperative Days 30 and 90. Indomethacin showed a higher subjective tolerance rating than ketorolac at postoperative Days 7 and 30 ($p \leq 0.044$).**

Conclusion: **Indomethacin 0.1% was at least as effective as ketorolac 0.5% at Day 1 and more effective than ketorolac 0.5% at Day 7 in treating ocular inflammation after uncomplicated cataract surgery. Indomethacin was better tolerated than ketorolac. There were no clinically meaningful safety concerns with either treatment.**

Key words: aqueous flare – cataract surgery – indomethacin – ketorolac – laser flare meter – ocular inflammation

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Introduction

Ocular inflammation, commonly observed after cataract surgery, is associated with a breakdown of the blood–aqueous barrier (BAB) as a result of surgical trauma-induced prostaglandin production (Perry & Donnenfeld 2006; Sandoval et al. 2007). Advanced surgical techniques including phacoemulsification, capsulorhexis, small clear corneal incisions, improved viscoelastics and foldable implants have helped optimize postoperative results and reduce surgical trauma. However, postoperative inflammation may still occur (Alió et al. 1996; Pande et al. 1996; Laurell et al. 1998) and can lead to complications such as corneal oedema, intraocular pressure (IOP) spikes, posterior capsule opacification and cystoid macular oedema (CME) (El-Harazi & Feldman 2001; Rotsos & Moschos 2008).

Corticosteroids are often used to control postoperative ocular inflammation (Korenfeld et al. 2008; Lorenz et al. 2008; Comstock et al. 2011); however, they are associated with adverse effects such as increased IOP, increased susceptibility to microbial

infections, as well as delayed corneal epithelial and stromal wound healing (McGhee et al. 2002). In routine cases, the use of ocular formulations of non-steroidal anti-inflammatory drugs (NSAIDs) for controlling postoperative inflammation may be an alternative treatment option to corticosteroids. Non-steroidal anti-inflammatory drugs exert their anti-inflammatory effect by inhibiting the enzyme cyclooxygenase, thereby decreasing the formation of prostaglandins (Vane & Botting 1998). Non-steroidal anti-inflammatory drugs have been shown to be safe and effective in the treatment of postoperative inflammation and pain and/or complications thereof in numerous controlled studies (Liou & Yen 1991; Le Rebeller et al. 1994; Roberts 1996; Arnaud & Trinquand 1997; Heier et al. 1999; Solomon et al. 2001; Papa et al. 2002; Scuderi et al. 2003; Donnenfeld et al. 2007; Lane et al. 2007; Donnenfeld et al. 2011), with equivalent (Flach et al. 1989; Roberts & Brennan 1995; Renard et al. 1996; Missotten et al. 2001; Holzer et al. 2002) if not sometimes greater efficacy (Kraff et al. 1990; Sourdille et al. 1993; Endo et al. 2010) when compared with corticosteroids. However, topical NSAIDs have been linked to varying degrees to a potential reduction in corneal sensitivity accompanied by an increased risk of superficial punctate keratitis and subjective symptoms of discomfort, including pain, burning or pricking, or a tingling sensation after instillation into the cul-de-sac (Shimazaki et al. 1995; Seitz et al. 1996; Aragona et al. 2000; Flach 2002; Aragona et al. 2005).

The objective of this clinical trial was to compare the efficacy and safety of indomethacin 0.1% (Indocollyre® 0.1% ophthalmic solution; Laboratoire Chauvin, Bausch & Lomb, Montpellier, France) and ketorolac tromethamine 0.5% (Acular®; Allergan Inc., Courbevoie, France) in preventing ocular inflammation after uncomplicated cataract surgery. The study assessed ocular inflammation through the use of a laser flare meter (LFM). The LFM provides a precise, objective, non-invasive and quantitative method to measure the aqueous flare (Ino-ue et al. 1994) and is reported as the best method to study postoperative inflammation induced by surgical trauma of cataract surgery (Sourdille et al. 1993). To our knowledge, this is the first LFM-based study comparing the efficacy of indomethacin and ketorolac for the treatment of ocular inflammation after cataract surgery.

Patients and Methods

Study design

This was a prospective, multicenter, investigator-masked, parallel-group, randomized, active-controlled clinical trial (EUDRACT no. 2007-004686-18) conducted in 11 centres across four countries – France (four centres), Germany (five), Poland (one) and Portugal (one). The study was approved by the Institutional Review Boards/Independent Ethics Committees of the respective centres and was conducted in accordance with the ethical principles of the Declaration of Helsinki (2004) and ICH-GCP guidelines (CPMP/ICH/135/95). All patients were required to provide written informed consent.

Inclusion criteria for the study were as follows: patients ≥18 years of age who planned to undergo cataract surgery on one eye by phacoemulsification with posterior chamber IOL, using topical or general anaesthesia; patients with a preoperative flare of ≤15 photocounts/millisecond (ph/ms), measured with an LFM without pharmacological pupil dilation, within the 2 months before cataract surgery; and women participants of childbearing potential with a negative urine pregnancy test at baseline. Patients were excluded from the study if they had an inflammatory and/or infectious pathology of the eye and its adnexa, history of postoperative intraocular infection in the fellow eye, glaucoma or post-traumatic cataract in the study eye, exfoliative syndrome, diabetic retinopathy, history of uveitis, any progressive pathology requiring the use of topical or systemic anti-inflammatory or anti-infectious agents, and monocularity for any reason other than cataract. Additional exclusion criteria included an active peptic ulcer, severe hepatocellular or renal impairment, immunodepression, use of acetylsalicylic acid at doses >100 mg daily and inability to discontinue its usage during the study, history of asthma linked to acetylsalicylic acid or other NSAID administration, and any history of intolerance to the study drug or to any NSAID. Patients were excluded further from the efficacy analysis if they experienced an intraoperative complication of vitreous loss, complicated capsular rupture or were implanted with an anterior chamber IOL.

Study treatment and assessments

Patients who met the inclusion/exclusion criteria were randomized in a 1:1 ratio to receive either indomethacin 0.1% (test drug) or ketorolac 0.5% (active control). The patients were instructed to instil one drop of the allocated drug into the study eye QID for 3 weeks, beginning 24 hrs prior to surgery, in accordance with prescribing information of each treatment. Allocation of treatment was determined by a unique randomization table provided to the investigator by the sponsor. The randomization list was produced prior to study enrolment by an unmasked statistician who was not otherwise involved in the study. Randomization was stratified by site. Both drugs were labelled identically to preserve masking. As the drugs could not be completely masked because of different bottle designs, the study was investigator-masked, with the patients being masked to the treatment name. On the day of surgery, the study nurse instilled the drug before and after surgery to maintain masking of the investigator.

Over a period of approximately 90 days, patients were scheduled for six study visits: baseline (within 2 months prior to surgery), day of surgery (Day 0) and postoperative Days 1, 7 (±1 day), 30 (±3 days) and 90 (±7 days). After visual acuity measurement, aqueous flare was measured by LFM in darkness without pharmacological pupil dilation, and five measurements were averaged to a single score in ph/ms. Other study assessments included slit lamp examination, fluorescein staining for corneal epithelial erosions, IOP measured by means of Goldmann applanation tonometry, dilated funduscopy and optical coherence tomography (OCT 3) for measuring retinal thickness. Concomitant medications used to treat inflammation related to cataract surgery were recorded at baseline as

well as follow-up visits. Corticosteroids were to be administered at follow-up visits only in the following cases: conjunctival hyperaemia grade ≥3, ciliary flush grade ≥3, fibrinoid exudate, hypopyon, retrocorneal precipitates or posterior synechiae in the study eye. In other cases, corticosteroids were prohibited. The allowed postoperative antibiotic treatment was gentamicin or tobramycin eye drops, QID, for 1 week.

Outcome measures

The primary efficacy end-point was aqueous flare measured with an LFM at Day 1 and Day 7 after cataract surgery. These assessment times were chosen as primary based on previous reports showing that aqueous flare is higher on Day 1 postoperatively, with a quick decrease within the first 7 days and a return to preoperative values after 1 month (Pande et al. 1996; Laurell et al. 1998). Secondary efficacy end-points included aqueous flare at Day 30 and Day 90 after cataract surgery, change from baseline in retinal thickness measured by OCT (central thickness and mean of four pericentral quadrants) at Day 30 and Day 90, anterior chamber flare and cells as well as conjunctival hyperaemia and ciliary flush measured by slit lamp examination at all visits except the day of surgery, patient ratings of postsurgical pain or discomfort immediately after and 24 hrs after surgery (on a scale of 0–4, where 0 = absent and 4 = unbearable), change from baseline in the appearance of the macula and the rest of retina by dilated indirect funduscopy at Day 30 and Day 90, and percentage of patients using concomitant medications to treat postoperative ocular inflammation. OCT measurements were not performed earlier than Day 30 based on literature reports of increases in retinal thickness reaching a maximum 6 weeks after small-incision cataract surgery (Lobo et al. 2004).

Safety was assessed based on the incidence of Adverse events (AEs), serious adverse events (SAEs) and their relationship to the study drug. The subjective rating of tolerance upon drug instillation (very good, good, bad and very bad) was assessed at Day 0 (prior to surgery), Day 7 and retrospectively at Day 30. Corneal staining at Day 7 and Day 30 was graded using the Oxford Scale Scheme (0 = no staining to 5 = severe staining). Best-corrected distance visual acuity (BCDVA) was assessed at Day 7, Day 30 and Day 90. Change from baseline in IOP was assessed at Day 7, Day 30 and Day 90.

Statistical methods

To test the primary efficacy end-point of aqueous flare at Day 1, 55 patients (eyes) per treatment group would yield 90% power to detect non-inferiority of indomethacin to ketorolac. This calculation assumed a standard deviation of 24 ph/ms in both treatment groups, a non-inferiority upper limit of 15 ph/ms (indomethacin–ketorolac) and a one-tailed alpha of 0.025. This sample size would provide > 90% power to detect non-inferiority at Day 7, assuming a standard deviation of 8 ph/ms in both treatment groups, a non-inferiority upper limit of 8 ph/ms (indomethacin–ketorolac) and a one-tailed alpha of 0.025. Assuming a discontinuation rate of approximately 8%, 60 patients (eyes) would need to be enrolled per treatment group for a total of 120 patients (eyes).

The primary efficacy analysis (non-inferiority analysis) was conducted using the per protocol (PP) set, which included subjects in the intent-to-treat (ITT) set who did not deviate from the protocol in any way that would seriously affect the primary outcome of the study. Secondary efficacy analyses were conducted using the ITT set, which included all subjects who received at least one dose of the study drug and for whom data from at least one follow-up visit were available. Safety analysis was performed using the safety set, which included all subjects who received at least one dose of the study drug and for whom safety data were available.

To test the non-inferiority of indomethacin to ketorolac, a general linear model (ANOVA) adjusting for baseline aqueous flare and site was used to obtain a 95% confidence interval (CI) on the difference in the flare scores between the treatment groups. Inference of non-inferiority was made using the one-sided upper bound ($\alpha = 0.025$ because of multiple comparisons of the primary end-point). If non-inferiority was shown, superiority tests at $\alpha = 0.05$ level were performed as secondary analyses. Secondary efficacy analysis of the flare data was performed similar to the primary end-point analysis. The change in retinal thickness from baseline to each visit was compared using a general linear model (ANOVA) adjusting for baseline retinal thickness and site. Slit lamp measures, postsurgical pain/discomfort, subjective tolerance to the study medication and fluorescein staining of the cornea were used as ordinal variables and compared between the treatment groups using the Jonckheere–Terpstra tests. All statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 123 patients were randomized to the study treatments (indomethacin, $n = 59$; ketorolac, $n = 64$) with no site enrolling more than 20% of patients. Two patients in the ketorolac group did not receive the study treatment because of compliance failure, while one patient in the ketorolac group received study treatment but did not complete any efficacy assessments, resulting in 121 patients who were included in the safety population (indomethacin, $n = 59$; ketorolac, $n = 62$) and 120 patients included in the intent-to-treat (ITT) population (indomethacin, $n = 59$; ketorolac, $n = 61$). A total of 55 patients in the indomethacin group and 57 patients in the ketorolac group completed the study. Reasons for discontinuations included withdrawal of consent ($n = 2$ indomethacin), lost to follow-up ($n = 1$ indomethacin, $n = 2$ ketorolac), AE ($n = 1$ ketorolac), failure to follow required study procedure ($n = 1$ indomethacin, $n = 1$ ketorolac), intraoperative complication ($n = 1$ ketorolac) and postoperative complication ($n = 1$ ketorolac). Major protocol violations, primarily LFM measurements not made in accordance with protocol and/or use of prohibited medications, were identified for 34 subjects (indomethacin, $n = 16$; ketorolac, $n = 18$), leaving 86 patients for inclusion in the PP population ($n = 43$ per treatment).

Demographics were similar between treatment groups and as expected for a population having cataract surgery.

The mean (SD) age of the patients was 69.1 (10.3) years, and 55.8% of patients were women. Ocular and non-ocular medical histories were similar between treatment groups. The mean (SD) baseline aqueous flare was 6.46 (4.06) ph/ms for the indomethacin group and 6.16 (3.95) ph/ms for the ketorolac group (p = 0.372). The mean (SD) baseline central retinal thickness (CRT) was 219.7 (29.7) μm for the indomethacin group and 209.3 (31.0) μm for the ketorolac group (p = 0.206).

The surgical characteristics of the two groups were comparable. Topical anaesthesia was used in most patients (76.3% and 77.4% in the indomethacin and ketorolac treatment groups, respectively). All IOLs were implanted with an IOL injector. Acrylic hydrophilic IOLs were implanted in 64.4% and 62.9% of eyes in the indomethacin and ketorolac treatment groups, respectively, while remaining eyes were implanted with hydrophobic IOLs. Corneal incisions were made in 52.5% and 54.8% of eyes, limbal incisions in 32.2% and 30.6% of eyes, and scleral incisions in 15.3% and 14.5% of eyes treated with indomethacin and ketorolac, respectively. The mean (SD) incision size was 2.71 (0.35) and 2.74 (0.3) in indomethacin- and keterolac-treated eyes, respectively; the mean (SD) duration of surgery was 15.04 (6.58) min and 15.55 (6.13) min, respectively; and the mean (SD) duration of phacoemulsification was 0.902 (0.930) min and 1.128 (1.460), respectively. The viscoelastic was retrieved in 100% of eyes treated with indomethacin and 98.4% of eyes treated with ketorolac. There were five intraoperative complications (indomethacin, n = 1, ketorolac, n = 4), all non-serious. Posterior capsular rupture with vitreous loss in one patient randomized to receive ketorolac met the criteria for exclusion from the efficacy analysis. Remaining intraoperative complications were one case of posterior capsular rupture in the indomethacin group, and one case of iris trauma (mild) and two cases of pain (n = 2) in the ketorolac group.

Exposure to the NSAIDs was similar between treatment groups. The mean (SD) days on treatment was 23.6 (4.3) for the indomethacin group and 23.2 (4.7) for the ketorolac group.

Efficacy

Primary end-point

At Day 1, the mean (SD) aqueous flare was 18.50 (9.67) ph/ms for the indomethacin group and 16.25 (8.71) ph/ms for the ketorolac group (95% CI of the mean difference between the treatment groups [indomethacin – ketorolac]: −2.37, 5.50). The upper limit of the 95% CI (5.50) was less than the upper limit of the non-inferiority margin (15), demonstrating non-inferiority of indomethacin. When testing the hypothesis of superiority, the differences in the mean aqueous flare between the indomethacin and ketorolac groups at Day 1 were not statistically significant (p = 0.431). At Day 7, the mean (SD) aqueous flare was 11.88 (7.23) ph/ms for the indomethacin group and 15.01 (9.58) ph/ms for the ketorolac group; indomethacin was found non-inferior to ketorolac (95% CI: −7.83, −0.94; upper limit of non-inferiority margin: 8). However, when testing the hypothesis of superiority, the difference in the mean aqueous flare between the indomethacin and ketorolac groups was significant at Day 7 (p = 0.013) (Fig. 1).

Secondary end-points

At Day 30, the mean (SD) aqueous flare for the indomethacin group was 9.2 (7.60) ph/ms and 8.94 (8.27) ph/ms for the ketorolac group (p = 0.559), while at Day 90, they were 9.20 (6.80) ph/ms and 8.12 (7.61) ph/ms, respectively (p = 0.571).

Fewer patients reported mild to moderate pain in the indomethacin group (19 of 59 patients, 32.2%) than in the ketorolac group (27 of 61 patients, 44.3%) at Day 0 (Table 1). However, there were no statistically significant differences observed in the distribution of pain scores between the indomethacin and ketorolac groups at Day 0 or Day 1.

The differences in the change from baseline in central retinal thickness at Day 30 and Day 90 between the treatment groups were not statistically significant. However, the increase from baseline in central retinal thickness was less marked in the indomethacin group compared with the ketorolac group (Table 2). The differences in the change from baseline in the pericentral retinal thickness at Day 30 and Day 90 between the treatment groups were also not statistically significant (data not shown).

No statistically significant differences were identified in the results of slit lamp examination and funduscopy between the treatment groups (data not shown). Furthermore, none of the study participants required concomitant medication to treat postsurgical inflammation.

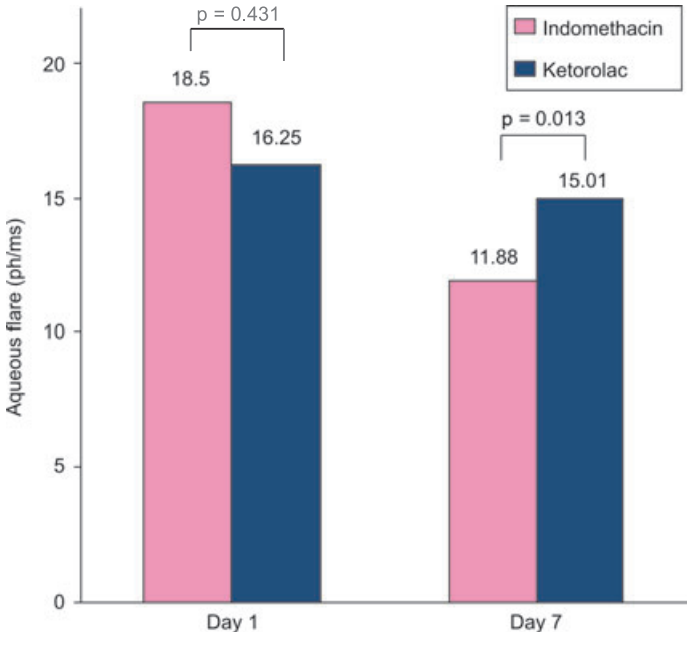

Fig. 1. Mean aqueous flare measured by laser flare meter in the indomethacin and ketorolac groups at Day 1 and Day 7 after cataract surgery (ph/ms: photocounts/millisecond).

Table 1. Postsurgical pain ratings after cataract surgery (intent-to-treat population).

Postsurgical pain rating	Indomethacin (n = 59) n (%)	Ketorolac (n = 61) n (%)	p-value*
Day 0 (immediately after surgery)			
Absent	40 (67.8)	34 (55.7)	0.228
Mild	16 (27.1)	25 (41.0)	
Moderate	3 (5.1)	2 (3.3)	
Severe	0 (0.0)	0 (0.0)	
Day 1			
Absent	42 (71.2)	46 (75.4)	0.537
Mild	14 (23.7)	14 (23.0)	
Moderate	2 (3.4)	1 (1.6)	
Severe	1 (1.7)	0 (0.0)	

No patients rated their pain as 'unbearable' at either visits and in treatment groups.
* p-values for the difference in distribution of pain scores from the Jonckheere–Terpstra test.

Table 2. Central retinal thickness measurements at baseline and after cataract surgery (intent-to-treat population).

Characteristic	Indomethacin (n = 59) mean (SD)	Ketorolac (n = 61) mean (SD)	p-value
Mean CRT, μm			
Baseline	219.7 (29.7)	209.3 (31.0)	0.206
Day 30	221.6 (34.1)	232.1 (55.6)	0.160
Day 90	227.9 (39.5)	227.5 (37.5)	0.852
Change in CRT from baseline, μm			
Day 30	4.3 (24.2)	21.9 (62.1)	0.131
Day 90	12.4 (33.3)	16.2 (43.3)	0.763

CRT = central retinal thickness.

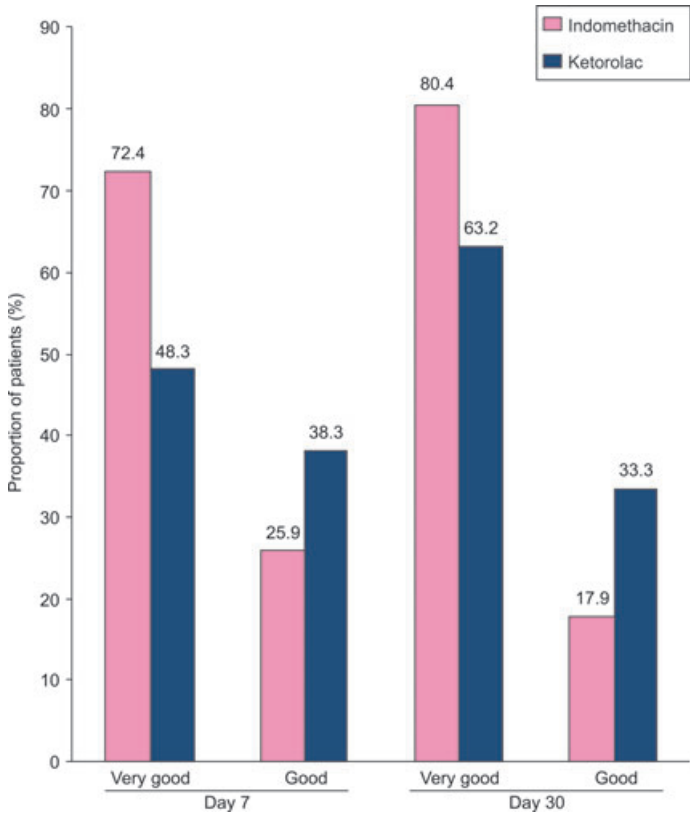

Fig. 2. Comparison of subjective tolerance ratings of "very good"and "good"in the indomethacin and ketorolac groups at Day 7 and Day 30 after cataract surgery. The between-group differences in the distribution of scores at Days 7 and 30 were significant ($P < 0.05$).

Safety

A total of 69 treatment-emergent AEs (indomethacin, n = 36; ketorolac, n = 33) were reported. Five treatment-emergent AEs (four patients), all ocular, were considered drug related. These included one case each of conjunctival hyperaemia and superficial punctate keratitis in the indomethacin group and one case each of follicular conjunctivitis, CME, and allergic reaction to the study medication in the ketorolac group. A total of five SAEs were reported in the study; none of the SAEs were considered related to the study drug or procedure.

At Day 0, the distribution of subjective tolerance ratings between the indomethacin and ketorolac groups was not statistically significant (p = 0.417); the majority of patients rated tolerance as 'very good' or 'good'. However, at Day 7 and Day 30, the distribution of subjective tolerance ratings was significantly better in the indomethacin group (p = 0.004 and p = 0.044, respectively), with a rating of 'very good' in 72.4% versus 48.3% of patients at Day 7 and 80.4% versus 63.2% of patients at Day 30, than in ketorolac group, respectively (Fig. 2). For all 'bad' or 'very bad' subjective tolerance ratings, the most important ocular sensation was burning, smarting or stinging.

A slightly lower proportion of patients in the indomethacin group had positive corneal staining at Day 7 in comparison to the ketorolac group, but the difference was not statistically significant (Table 3).

The distributions of BCDVA at the baseline, Day 7, Day 30 and Day 90 visits were comparable between the indomethacin and ketorolac groups (data not shown). The mean postoperative IOP was slightly reduced for both treatment groups at the Day 7, Day 30 and Day 90 visits when compared with baseline (data not shown).

Discussion

Several studies have established the safety and efficacy of 0.1% indomethacin in the treatment of postoperative inflammation and pain (Strobel et al. 1991; Colin et al. 1993; Sourdille et al. 1993; Le Rebeller et al. 1994; Renard et al. 1996; Arnaud & Trinquand 1997; Goes et al. 1997; Missotten

Table 3. Fluorescein staining of the cornea (safety population).

Visit	Grade	Indomethacin (n = 59) n (%)	Ketorolac (n = 62) n (%)	p-value*
Baseline	Grade 0	48 (81.4)	50 (80.6)	1.000
	Grade 1	8 (13.6)	11 (17.7)	
	Grade 2	2 (3.4)	1 (1.6)	
	Grade 3	1 (1.7)	0 (0.0)	
Day 7	Grade 0	42 (72.4)	39 (66.1)	0.532
	Grade 1	10 (17.2)	14 (23.7)	
	Grade 2	4 (6.9)	5 (8.5)	
	Grade 3	2 (3.4)	1 (1.7)	
Day 30	Grade 0	44 (77.2)	46 (78.0)	0.970
	Grade 1	10 (17.5)	9 (15.3)	
	Grade 2	3 (5.3)	3 (5.1)	
	Grade 3	0 (0.0)	1 (1.7)	

No patients had corneal staining >Grade 3 at any visit in either treatment group.
* p-value from the Jonckheere–Terpstra test.

et al. 2001; Badalà et al. 2004) and in the prevention and/or treatment of CME (Miyake 1984; Liou & Yen 1991; Peterson et al. 1992; Ginsburg et al. 1995; Solomon 1995; Yavas et al. 2007; Kim et al. 2010). The objective of our study was to compare the efficacy and safety of indomethacin 0.1% with those of ketorolac tromethamine 0.5% in preventing ocular inflammation after uncomplicated cataract surgery. Laser flare meter measurements showed indomethacin 0.1% was at least as effective as ketorolac 0.5% on postoperative Day 1 and statistically more effective than ketorolac 0.5% on postoperative Day 7 ($p = 0.013$) in reducing aqueous flare after uncomplicated cataract surgery. Laser flare meter was used as the primary method of assessment because slit lamp examination or other scoring methods can be less sensitive, prone to observer bias and/or error and may lack reproducibility (Colin 2007). Indeed, in our study, there were no significant between-group differences in the aqueous flare as measured by slit lamp examination at Day 7, attesting to the higher sensitivity of LFM.

There were no significant between-group differences in secondary efficacy end-points. These included aqueous flare measured by means of LFM at Days 30 and 90; change from baseline in retinal thickness measured by OCT at Days 30 and 90; anterior chamber cells, anterior chamber flare, conjunctival hyperaemia and ciliary flush assessed by slit lamp examination; patients' ratings of postsurgical pain and discomfort at Day 0 and Day 1; and change from baseline in the appearance of the macula and the rest of the retina by fundoscopy at Days 30 and 90. Although the change from baseline in CRT in the indomethacin group was smaller than that in the ketorolac group at Day 30, the difference was not significantly different ($p = 0.131$). Phacoemulsification has been reported to lead to significant clinical macular oedema in some studies (Biro et al. 2008). In other studies, macular thickness increase was subclinical and significantly less with phacoemulsification than with manual cataract surgery (Ghosh et al. 2010). According to Cagini et al., although small postoperative increases in retinal thickness may be asymptomatic, they may represent the process that in its most advanced stages leads to the formation of CME (Cagini et al. 2009). Based on our results, indomethacin may offer advantages in controlling the physiological changes contributing to CME. Clinical studies powered to assess CRT changes are needed to better interpret these data.

Both eye drops were safe and well tolerated. Most AEs reported were not related to study drugs and were consistent with expected postcataract surgery events. The distribution of BCDVA did not differ between treatment groups at any visits, while mean postoperative IOP was slightly reduced compared with baseline for both the treatment groups at Days 7, 30 and 90. In addition, corneal staining did not differ between treatment groups. Subjective ratings of tolerability upon treatment instillation were significantly better in the indomethacin group with 'very good' tolerance observed in a greater percentage of indomethacin patients. These findings are in agreement with the previous studies showing better tolerability with indomethacin compared with other NSAIDs (Arnaud & Trinquand 1997).

The lack of a vehicle control group is a limitation of our study, especially in the framework of moderate levels of postoperative inflammation present after phacoemulsification. Although a placebo arm would have shown the absolute effect of the anti-inflammatory eye drops in the management of ocular inflammation following cataract surgery, such a design may also raise some ethical concerns.

In conclusion, indomethacin 0.1% eye drops were at least as effective as ketorolac 0.5% eye drops at postoperative Day 1 and statistically more effective at Day 7 for preventive treatment of ocular inflammation following uncomplicated cataract surgery. Indomethacin 0.1% instillation was better tolerated than ketorolac 0.5% instillation. No clinically meaningful safety concerns were identified with either treatment.

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