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Efficacy of bromfenac sodium ophthalmic solution in preventing cystoid macular oedema after cataract surgery in patients with diabetes

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ABSTRACT.

Purpose: **To compare the efficacy of bromfenac sodium ophthalmic solution (BF) and a steroidal solution (ST) administered prophylactically against cystoid macular oedema and anterior-chamber inflammation after phacoemulsification and intraocular lens implantation and to assess macular thickness changes using optical coherence tomography (OCT).**

Methods: **In this prospective study, 62 eyes of 62 patients were randomized to either the BF group (n = 31) or the ST group (n = 31). The average perifoveal thickness (AFT) was measured by OCT preoperatively, and 1 day and 1, 2, 4 and 6 weeks postoperatively. The best-corrected visual acuity, intraocular pressure and flare in the anterior chamber were recorded at each visit. The same method was used to compare patients with non-proliferative diabetic retinopathy (NPDR) in the BF (n = 16) and ST (n = 11) groups.**

Results: **In the analysis of all patients, flare in the anterior chamber was significantly ($p = 0.007$) lower in the BF group 2 weeks postoperatively. In patients with NPDR, the anterior chamber flare values were significantly lower in the BF group at 4 weeks ($p = 0.0009$) and 6 weeks ($p = 0.005$). The AFT values were significantly lower in the BF group at 4 weeks ($p < 0.0001$) and 6 weeks ($p < 0.0001$). No adverse events occurred in either group.**

Conclusion: **BF suppressed anterior chamber inflammation and increasing retinal thickening after cataract surgery in patients with NPDR.**

Key words: after cataract surgery – bromfenac sodium – cystoid macular oedema – diabetic patients

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Introduction

Many trials have assessed the prophylactic effects of non-steroidal ophthalmic solutions on cystoid macular oedema (CMO) after cataract surgery (Miyake 1977; Yannuzzi et al. 1981; Kraff et al. 1982; Miyake et al. 1983, 2000; Flach et al. 1990; Rossetti et al. 1998; Rho 2003), in which ophthalmoscopy and fluorescein angiography were used to detect CMO. However, no studies have been published on the prophylactic efficacy of bromfenac ophthalmic solution alone to treat CMO and inflammation after cataract surgery in patients with diabetes who did not receive concurrent steroidal ophthalmic solutions. Optical coherence tomography (OCT) – a non-contact, non-invasive, reproducible investigation – quantifies early-stage macular oedema, which was impossible with previous methods (Huang et al. 1991; Hee et al. 1995; Puliafito et al.1995; Otani et al. 1999; Sourdille & Santiago 1999; Ching et al. 2006; Torron-Fernandez-Blanco et al. 2006; Degenring et al. 2007; Biro et al. 2008; Soliman et al. 2008). In the current study, we used OCT-3 to compare the prophylactic effects of the use of bromfenac ophthalmic solution

with the use of steroid ophthalmic solution to treat inflammation and CMO after cataract surgery in patients with diabetes.

Materials and Methods

A prospective open-label trial was conducted using the envelope method. Sixty-two eyes of 62 patients with diabetes (34 men and 28 women; age range 37–84 years) who underwent small-incision phacoemulsification with intraocular lens (IOL) implantation at our facility between March 2005 and May 2007 were included. The exclusion criteria were: foveal thickness of 250 μm or more; severe diabetic retinopathy (DR) for which ocular surgery (including photocoagulation) was indicated; use of topical medications for glaucoma, uveitis and other diseases that cause CMO; ocular allergies to bromfenac (Bronuck Senju Pharmaceutical Company Ltd, Osaka, Japan) (BF group) or steroids (ST group); use of systemic steroids or non-steroidal anti-inflammatory drugs (NSAIDs); and serious cardiac, cerebral or renal disease.

The study was conducted in accordance with the Declaration of Helsinki and received approval from the Tokyo Women's Medical University Hospital Institutional Review Board. All patients provided written informed consent before enrolment.

Patients were randomized to the BF group (n = 31) or the ST group (n = 31). Sixteen patients in the BF group and 11 patients in the ST group had non-proliferative diabetic retinopathy (NPDR).

Preoperatively, eyedrops were administered as follows. All patients received gatifloxacin (Gatiflo; Senju, Pharmaceutical Company Ltd, Osaka, Japan) four times daily for 1 day preoperatively; on the day of surgery, they received 0.5% tropicamide, 0.5% phenylephrine hydrochloride (Mydrin-P, Santen, Osaka, Japan) and 5% phenylephrine hydrochloride (Neosynesin Kowa 5% eye solution; Kowa, Tokyo, Japan) every 30 min 2 hr preoperatively. Postoperatively, eyedrops were administered as follows. In the BF group, the eyedrops (Bronuck; Senju) were instilled twice daily until week 6. In the ST group, betamethasone sodium phosphate and fradiomycin sulfate (Rinderon-A solution; Shionogi, Osaka, Japan) were instilled four times daily for 1 week followed by fluorometholone (Flumetholon 0.1%; Santen) for steroid withdrawal four times daily for 5 weeks. Considering the side-effects of long-term steroid administration, we substituted fluorometholone for betamethasone 1 week postoperatively because of ethical considerations. The patients also received gatifloxacin four times daily until week 6, and 0.5% tropicamide and 0.5% phenylephrine hydrochloride once daily for 1 week. The surgery included capsulorrhexis, small-incision (3 mm) phacoemulsification and in-the-bag implantation of an IOL (AcrySof SA60AT or MA60AC; Alcon Laboratories Inc., Fort Worth, Texas, USA).

We evaluated the patient's medical history, best-corrected visual acuity (BCVA) [the decimal VA data were converted to logarithm of minimum angle of resolution (LogMAR)], intraocular pressure (IOP), slit-lamp biomicroscopy, anterior chamber flare [measured by laser flare-cell photometry (FM-500; Kowa)] and average perifoveal thickness (AFT) using OCT (Stratus OCT-3; Carl Zeiss Meditec, Dublin, California, USA). The fast Macular Thickness Map protocol was used. The six radial scans were used to generate a retinal thickness map for areas within defined circles. The AFT (1 mm diameter) of the retinal map was used for statistical analyses. The measurements were taken preoperatively, and 1 day and 1, 2, 4 and 6 weeks postoperatively. The same method was used to compare patients with NPDR in the BF (n = 16) and ST (n = 11) groups.

The level of DR was recorded as: none; mild, moderate or severe non-proliferative; or proliferative, as described previously in the international clinical DR and diabetic macular oedema disease severity scale (Wilkinson et al. 2003).

Statistical analysis

The patient age and haemoglobinA_{1c} (HbA1c) and the surgical data were analysed using Student's t-test. Gender and the presence of hypertension and DR were analysed using Fisher's exact test. Creatinine and blood urea nitrogen data (BUN) were analysed using Welch's test. BCVA, IOP, anterior chamber flare and AFT were analysed using repeated measures ANOVA. $p < 0.05$ was considered significant.

Results

Seventy-five patients were included at the start of the study (40 in the BF group and 35 in the ST group). Three patients were excluded because of difficulty with the OCT measurement. Ten patients (10 eyes) dropped out of the study because of poor health (eight patients), posterior capsular rupture (one patient) and epidemic keratoconjunctivitis (one patient). Consequently, 62 eyes of 62 patients completed 6 weeks of follow-up. Sixteen eyes (51.6%) in the BF group and 11 eyes (35.5%) in the ST group had DR. Of the 16 eyes in the BF group, four had mild NPDR and 12 had moderate NPDR. Of the 11 eyes in the ST group, one had mild NPDR and 10 had moderate NPDR.

Table 1 shows the characteristics of the study participants. There were no significant differences between the two

Table 1. Clinical characteristics of the study patients.

	BF group (n = 31)	ST group (n = 31)	p-value
Mean age (years)	68 ± 7.8	69 ± 10.0	0.76
No. men/women	16/15	18/13	0.79
No. with hypertension (%)	16 (51.6)	16 (51.6)	1.0
BUN (mg/dl)	17.2 ± 7.02	16.6 ± 4.63	0.70
Creatinine (mg/dl)	0.84 ± 0.50	0.85 ± 0.27	0.82
No. with retinopathy (%)			
No DR	15 (48.4)	20 (64.5)	0.3
NPDR	16 (51.6)	11 (35.5)	
HbA1c	7.6 ± 1.22	6.8 ± 0.88	0.0035*

BF, bromfenac sodium ophthalmic solution; ST, steroidal solution; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; BUN, blood urea nitrogen; HbA1c, haemoglobinA_{1c}; *statistically significant.

groups in terms of age, sex, hypertension, BUN or creatinine. A significant ($p = 0.003$) difference was found in HbA1c despite randomization. However, the BF group had a higher HbA1c value (BF group 7.6 ± 1.22 mg/dl; ST group 6.8 ± 0.88 mg/dl), but this was not thought to affect the interpretation of results considering the risk of developing CMO.

There were no significant differences in the duration of surgery ($p = 0.51$) or phacoemulsification time ($p = 0.22$).

Analysis of all patients

BCVA (LogMAR) improved from 0.24 ± 0.35 in the BF group and 0.16 ± 0.13 in the ST group preoperatively to −0.09 ± 0.056 and −0.04 ± 0.085 after 6 weeks, respectively. However, there was no significant difference in BCVA between the groups ($p = 0.37$).

No patients in either group required additional postoperative treatment for elevated IOP, and there was no significant difference between the groups ($p = 0.91$).

The peak anterior chamber flare values were reached in the BF and ST groups on postoperative day 1 (BF group, 8.8 ± 6.6 pc/msecond; ST group, 9.1 ± 5.3 pc/msecond) (Fig. 1). One week after surgery, the degree of flare in the BF group was lower than that in the ST group. The flare value in the BF group decreased to the preoperative level (4.6 ± 3.91 pc/msecond) at week 2 and was significantly lower ($p = 0.007$, repeated measures ANOVA) than in the ST group (7.8 ± 6.82 pc/msecond) at that time-point. However, in the ST group, the value was still high at week 6.

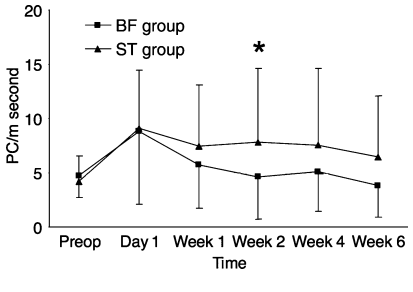

Fig. 1. Anterior-chamber flare values of all patients in the bromfenac sodium ophthalmic solution (BF) and steroidal solution (ST) groups. A significant difference was seen between the two groups by repeated measures ANOVA ($p = 0.007$). The flare value in the BF group was significantly (*$p = 0.007$) lower (4.6 ± 3.91 pc/msecond) at week 2 than in the ST group (7.8 ± 6.82 pc/msecond).

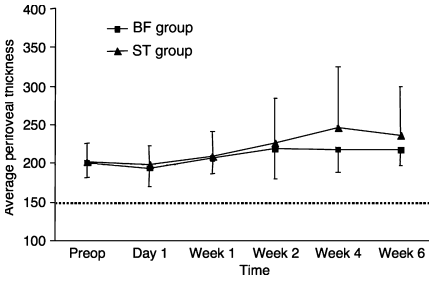

Fig. 2. Average perifoveal thickness (AFT) of all patients in the bromfenac sodium ophthalmic solution (BF) and steroidal solution (ST) groups. AFT was lower in the BF group than in the ST group, although this difference did not reach statistical significance.

The preoperative AFT was 200.9 ± 19.6 μm in the BF group and 203.1 ± 22.76 μm in the ST group (Fig. 2). In the BF group, the AFT values were 194.4 ± 24.1, 207.2 ± 20.2, 219.0 ± 39.0, 218.3 ± 29.2 and 216.9 ± 19.8 μm on postoperative day 1 and weeks 1, 2, 4 and 6, respectively. In the ST group, the AFT values were 199.0 ± 24.6, 209.8 ± 31.6, 226.2 ± 58.6, 246.6 ± 77.5 and 236.1 ± 63.6 μm on postoperative day 1 and weeks 1, 2, 4 and 6, respectively. Although repeated measures ANOVA showed no significant difference between the two groups ($p = 0.19$), AFT was lower in the BF group than in the ST group.

Analysis of NPDR patients

There were 16 cases of NPDR in the BF group and 11 in the ST group. The BCVA (LogMAR) improved from 0.15 ± 0.18 in the BF group and 0.14 ± 0.11 in the ST group preoperatively to −0.08 ± 0.075 in the BF group and −0.02 ± 0.087 in the ST group after 6 weeks. However, the difference between the groups was not significant ($p = 0.32$).

No patient in either group required additional postoperative treatment for elevated IOP, and there was no significant difference in IOP between the groups ($p = 0.82$).

Anterior chamber flare peaked in the BF group on postoperative day 1 (9.8 ± 8.01 pc/msecond) (Fig. 3). However, in the ST group, it peaked on day 1 (10.9 ± 6.4 pc/msecond) and again at week 4 (11.6 ± 10.0 pc/msecond) and remained higher than the preoperative value at week 6 (8.8 ± 8.0 pc/msecond). The anterior chamber flare was lower in the BF group than in the ST group, and repeated measures ANOVA showed a significant ($p = 0.004$) difference between the two groups. The flare value was significantly lower in the BF group (4.8 ± 2.6 pc/msecond at week 4; 3.1 ± 1.0 pc/msecond at week 6) than in the ST group (11.6 ± 10.0 pc/msecond at week 4; 8.8 ± 8.0 pc/msecond at week 6) at weeks 4 and 6 ($p = 0.001$ and $p = 0.005$, respectively).

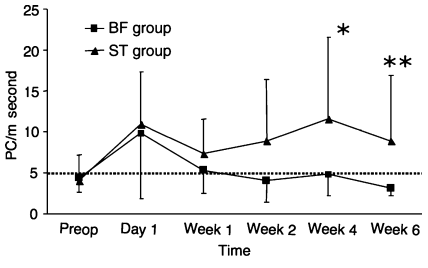

Fig. 3. Anterior-chamber flare in patients with NPDR in the bromfenac sodium ophthalmic solution (BF) and steroidal solution (ST) groups. A significant ($p = 0.004$) difference between the groups was seen by repeated measures ANOVA. In a comparison of the two groups by time-point, the flare value was significantly (*$p = 0.001$ and **$p = 0.005$, respectively) lower in the BF group than in the ST group at weeks 4 and 6.

AFT did not differ between the BF and ST groups preoperatively, with respective values of 196.9 ± 17.5 μm and 210.5 ± 18.1 μm. In the BF group, AFT values were 190.9 ± 29.8, 205.9 ± 23.6, 222.9 ± 46.0, 211.1 ± 19.4 and 214.5 ± 18.0 μm on postoperative day 1 and weeks 1, 2, 4 and 6, respectively. In the ST group, AFT values were 207.3 ± 19.2, 226.9 ± 35.5, 254.5 ± 85.6, 276.6 ± 86.8, and 272.5 ± 86.3 μm on postoperative day 1 and weeks 1, 2, 4 and 6, respectively (Fig. 4). Repeated measures ANOVA showed a significant difference between the two groups ($p = 0.01$). Postoperatively, a comparison of the two groups by time-point showed that AFT was significantly lower in the BF group at weeks 4 ($p < 0.0001$) and 6 ($p < 0.0001$). In the ST group, two patients were diagnosed with cystoid degeneration by OCT; the preoperative AFT in these two patients were 187 μm and 237 μm and at week 6 458 μm and 422 μm, respectively.

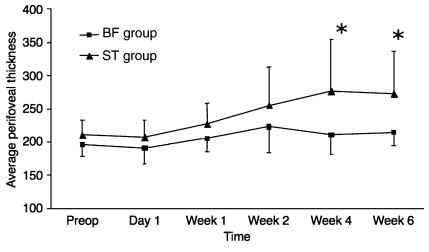

Fig. 4. Average perifoveal thickness (AFT) in cases of NPDR in the bromfenac sodium ophthalmic solution (BF) and steroidal solution (ST) groups. A significant ($p = 0.01$) difference between the groups was seen by repeated measures ANOVA. In a comparison of the two groups by time-point, the AFT was significantly (*$p < 0.0001$ for both comparisons) lower in the BF group at weeks 4 and 6.

In patients without DR, no significant difference was seen between the BF and ST groups in terms of VA, IOP, anterior chamber flare or AFT. No adverse events were noted in either group.

Discussion

Various hypotheses have been proposed for the underlying cause of CMO after cataract surgery. One hypothesis is that mechanical trauma promotes cyclooxygenase (COX-2) expression at the mRNA and enzyme levels, which triggers synthesis of various prostaglandins and other inflammatory mediators and the breakdown of the blood–aqueous barrier, accompanied by increased protein concentration in the anterior chamber. Substances that cause inflammation accumulate in the aqueous humour and are dispersed in the vitreous, where they increase the permeability of the retinal blood vessels leading to CMO (Miyake 1977; Vane et al. 1998; Funk 2001). NSAIDs are efficacious as prophylaxis to reduce the incidence of CMO after cataract surgery (Miyake 1977; Yannuzzi et al. 1981; Kraff et al. 1982; Miyake et al. 1983, 2000; Flach et al. 1990; Rossetti et al. 1998; Rho 2003). NSAIDs inhibit the COX-2 pathway, which leads to the production of prostaglandins (Vane et al. 1998). Bromfenac, an NSAID in the class of phenylacetic acids, inhibits COX activity in the arachidonate cascade 11 times more than indomethacin (Sancilio et al. 1987).

Corneal epitheliopathy is an adverse effect of topical NSAIDs (Szerenyi et al. 1994; Shimazaki et al. 1996). However, the primary ocular side-effects of topical corticosteroids include corneal infections, steroid-induced glaucoma and delayed wound healing. In the current study, there were no adverse events in the BF group – even among the patients with diabetes, who were considered more likely to develop corneal epitheliopathy, indicating that bromfenac is a relatively safe drug. IOP did not increase in any patient in the ST group, although steroids reportedly increase IOP in about 40% of patients receiving 4–6 weeks of steroid eyedrop treatment, among whom 4–6% have marked IOP increases (Becker et al. 1966, 1971; Jones & Rhee 2006). Because eyedrops must be applied for several months after surgery, use of bromfenac may be more advantageous.

In the current study, there was no surgical difference between the two groups in terms of anterior chamber flare – an indicator of inflammation – on postoperative day 1. A significant decline was observed in the BF group from week 1. At week 1, betamethasone was replaced with 0.1% fluorometholone for steroid-sparing treatment and ethical considerations; however, bromfenac is considered to be more effective than 0.1% fluorometholone in suppressing anterior-chamber inflammation in the early postoperative stage. Moreover, in patients who received bromfenac, no significant difference was observed in postoperative flare values between the NPDR group and the group without DR. While previous reports showed the efficacy of prophylactic NSAIDs for CMO after cataract surgery without concurrent corticosteroid therapy in healthy participants (Flach et al. 1990), bromfenac is thought to have sufficient anti-inflammatory efficacy in patients with diabetes with NPDR.

The foveal thickness values in the current study were similar to those reported in the literature. Sanchez-Tocino et al. (2002) reported values of 156 ± 28 μm in patients without DR and 169 ± 33 μm in patients with NPDR without macular oedema; Yang et al. (2001) found 175 ± 38 μm in patients with diabetes without macular oedema; and Degenring et al. (2007), using OCT-3, reported 187 ± 28 μm in patients without DR and patients with NPDR. Degenring et al. (2007) concluded that retinal thickening corresponds with a worse VA outcome based on the observations that patients with diabetes had decreased VA at postoperative week 4 and the minimal foveal thickness increased to 204 ± 54 μm on OCT images. In the current study, the AFT in the BF group with NPDR was 222.9 ± 46.0 μm at week 2 and 211.1 ± 19.4 μm at week 4. However, the postoperative VA was also stable. OCT may be a more sensitive means of detecting CMO postoperatively. The VA changes seem to be less dramatic than changes in retinal thickness. Two patients in the ST group with NPDR had cystoid degeneration seen on OCT at weeks 1 and 2, respectively. The postoperative VA values in both patients were −0.1 LogMAR at week 1 and 0.1 LogMAR at week 6. Kim et al. (2007) reported a poor VA prognosis in patients with advanced DR and CMO caused by foveal thickening after cataract surgery. However, our two patients were the non-proliferative type and did not have macular oedema before cataract surgery. In the BF group, no patients showed marked thickening accompanied by cystoid degeneration. The current study suggested that postoperative application of steroid eyedrops alone may be insufficient to prevent increases in foveal thickness after cataract surgery in patients with NPDR. In a quantitative evaluation of retinal oedema using OCT-3, bromfenac was as effective as prophylaxis against postoperative CMO in patients with NPDR.

Bromfenac was probably more effective in patients with NPDR partly because of the difference in the mechanism of action between NSAIDs and steroids: NSAIDs inhibit COX-2 in the arachidonate cascade, while steroids inhibit the COX-2 and lipoxygenase pathways by inhibiting phospholipase A2. The results of the current study will be assessed further in association with the onset of DR to clarify the underlying pathology.

In the current study, bromfenac was safe based on the absence of side-effects in patients with NPDR. Bromfenac suppressed anterior-chamber inflammation after cataract surgery and was significantly more

effective in suppressing retinal thickening at postoperative weeks 4 and 6 than 0.1% flumetholon in patients with NPDR. Because the sample size in the current study was small, further investigation is needed to clarify the usefulness of bromfenac after cataract surgery.

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