Journal of Clinical & Experimental Ophthalmology
ISSN: 2155-9570

Duong J Clinic Experiment Ophthalmol 2011, 2:8
DOI: 10.4172/2155-9570.1000177

Research Article Open Access

Comparing the Efficacy of Bromfenac 0.09% and Nepafenac 0.1% Post Cataract Surgery: A Prospective Evaluation

Hon-Vu Q. Duong[1,2]*, Kenneth C. Westfield[1] and Isaac C. Singleton[1]

[1]Westfield Eye Center, 2575 Lindell Road, Las Vegas, NV 89146, USA
[2]Nevada State College, 1125 Nevada State Drive, Henderson, NV 89002, USA

Introduction

The purpose of the study was to comparetwo FDA approved topical non-steroidal anti-inflammatory medications (NSAIDs): Bromfenac 0.09% (Ista Pharmaceutical, 50 Technology Drive, Irvine CA 92318) andNepafenac 0.1% (Alcon Laboratories, Inc. 6201 South Freeway, Fort Worth, TX 76134). This comparative study was designed to assess four end points: 1) optical coherence tomography (OCT) sensitivity in detecting early (subclinical) cystoid macular edema (CME); 2) the incidence of CME (clinical and subclinical) between bromfenac and nepafenac; 3) visual recovery and 4) changes in intraocular pressure.

Background

Bromfenac 0.09% andnepafenac 0.1% are both FDA approved topical nonsteroidal anti-inflammatory drugs. Bromfenac [1-4], a newer NSAIDs, and nepafenac [4-6] are two ophthalmic agents indicated in the treatment of post-operative inflammation and ocular pain from cataract surgery. Although both drugs have been reported to be efficacious in managing post-operative inflammation from cataract surgery and the mechanism of actions are similar, bromfenac and nepafenac differ in dosing: bromfenac dosing is twice-a-day while nepafenac dosing is three-times-a-day. Bromfenac displayed better ocular penetration due to its lipophilic property [2] and duration permitting twice-daily dosing [1]. One significant biochemical difference is that nepafenac is a prodrug [6]. Nepafenac penetrates the cornea and is hydrolyzed to the active metabolite: amfenac [6]. The active metabolite is believed to inhibit the action of prostaglandin H synthase [6] while bromfenac inhibit prostaglandin synthesis by inhibiting cyclooxygenase 1 and 2 [2]. Bromfenac chemical structure is identical to amfenac with the exception of the bromide atom at the C4 position [2]. The addition of bromine enhances lipophilicity [2], facilitates penetration [2], and increases duration of action (half-life) [2].

Method

This clinical trial was conducted as a comparative, prospective, masked study. Once the study was approved by the institutional review board (IRB), patientswere randomized toGroup I (bromfenac) or Group II (nepafenac). Patients with visually significant cataract were eligible for this study. Exclusion criteria included a history of allergic reaction to topical NSAIDs, proliferative diabetic retinopathy and mono-vision. To remove any confusion with respect to post-operative topical medications, all patients in the study were "first time" cataract extraction patient.

All patients were instructedto instill the respective medication 3 days prior to surgery in the operative eye to the regimen recommended for bromfenac (one drop in the operating eye, BID) and nepafenac(one drop in the operating eye, TID)and to continue with the respective NSAIDs 7 days after surgery. The standard post-cataract medical regimen, i.e., antimicrobial (Moxifloxacin for Group I & II, QID for 7 days) and topical steroid (Prednisolone acetate 1% for Group I & II, QID for 7 days with a tapering dose thereafter) was followed.

The study began in June 2008 and ended in September 2008. There were a total of 205 (Group I-bromfenac = 103; Group II-nepafenac = 102) eyes in the study. Preoperative data collected included medical and ocular co-morbidities, best-corrected visual acuity (BCVA), intra-ocular pressure (IOP) by Goldmann's applanation, dilated fundus examination (DFE), and a macular OCT. Clinical data were collected at the one-day, one-week, and one-month post-surgery.

Pre-operative, post-op day 1, post-op week 1, and 1-month post-op visual acuities were recorded. The Snellen chart values were converted into LogMAR for statistical analysis.

All patients enrolled in the study had a pre-operative (baseline) macularOCT3 [Zeiss Stratus OCT] performed and all patients post cataract surgery had an OCT3 performed at the 1 week post-op visit with subsequent OCT3as indicated by clinical examination. All OCTs were performed by two experienced and certified ophthalmic technicians.The foveal thickness (FT), the mean thickness within the central 1000 micron diameter area of the fovea [7] and the central foveal thickness (CFT), the mean thickness measured at the point of intersection of the six radial scans by OCT [7] were analyzed. For the purpose of this study, FT and CFT two standard deviations outside the mean were considered to have CME by OCT.

All cataract surgerieswereperformed by one surgeon. The anesthesia of choicewas topical (tetracaine-HCl 0.5%) and intracameral lidocaine 4% if needed. The method of cataract extraction was the phaco-chop technique with bimanual irrigation and aspiration. All cataract surgeries wereperformed at one surgery center (SMA). The intra-ocular lens of choice was the AMO SI-40.

Statistical analysis

Results were recorded as mean and standard deviation. A p-value < 0.05 was regarded as statistically significant. Variable differences between two groups were tested using the unpaired and paired Student t-test (Microsoft Excel, Microsoft Inc.). The Fisher exact and chi-square tests were utilized to test for independence between variables.

Results

Patient data: Group I – Bromfenac 0.09%

Fifteen eyeswere lost to follow-up in Group I and seventeen eyes

***Corresponding author:** Hon-Vu Q. Duong, M.D., Nevada State College, 1125 Nevada State Drive 30 Desert Gallery Street, Henderson, Nevada 89012, USA, E-mail: tenthsfg@msn.com

Received May 27, 2011; **Accepted** August 08, 2011; **Published** August 10, 2011

Citation: Duong HQ, Westfield KC, Singleton IC (2011) Comparing the Efficacy of Bromfenac 0.09% and Nepafenac 0.1% Post Cataract Surgery: A Prospective Evaluation. J Clinic Experiment Ophthalmol 2:177. doi:10.4172/2155-9570.1000177

	Bromfenac	Nepafenac		Bromfenac	Nepafenac
Total Enrolled	103	102	Comorbidities		
Completed	88	85	Diabetic	29 (33%)	30 (35.3%)
Lost to F/U	15	17	ARMD	19 (21.6%)	22 (25.9%)
Average Age	69.39 ± 9.15	68.52 ±9.28	POAG	21 (23.9%)	24 (28.2%)
Age Range	40-85	41-84	GS/OHTN	11 (12.5%)	9 (10.6%)
Sex			ERM	2 (2.27%)	2 (2.35%)
Male	38 (43.2%)	49 (57.6%)	Other	14 (15.9%)	12 (14.1%)
Female	50 (56.8%)	36 (42.4%)	ARMD = age-related macular edema POAG = primary open angle glaucoma GS/OHTN = glaucoma suspect/ocular hypertension ERM = epiretinal membrane		
Eyes					
OD	52 (59.1%)	43 (50.6%)			
0S	36 (40.9%)	42 (49.4%)			

Table 1: Demographic.

	Baseline	POD#l	POD#7	POD#30
Visual Acuity in Log MAR ± SO				
Bromfenac	0.63± 0.53	0.5 ± 0.49	0.29 ± 0.34	0.15 ± 0.21
Nepafenac	0.54 ± 0.58	0.55 ± 0.53	0.28 ± 0.22	0.19 ± 0.2
Statistical Value(p < *0.05)*		***p = 0.23***	***P = 0.38***	***P = 0.06***
Mean IOP in mmHg ± SO				
Bromfenac	16.25 ± 3.45	20.57 ± 6.87	14.95 ± 2.84	14.52 ± 2.58
Nepafenac	16.19 ± 3.04	20.84 ± 7.69	16.08 ± 3.53	15.48 ± 2.87
Statistical Value *(p < 0.05)*		***p = 0.39***	***P = 0.23***	***P = 0.44***

POD = post-operative day

Table 2: Visual Acuity and Mean IOP.

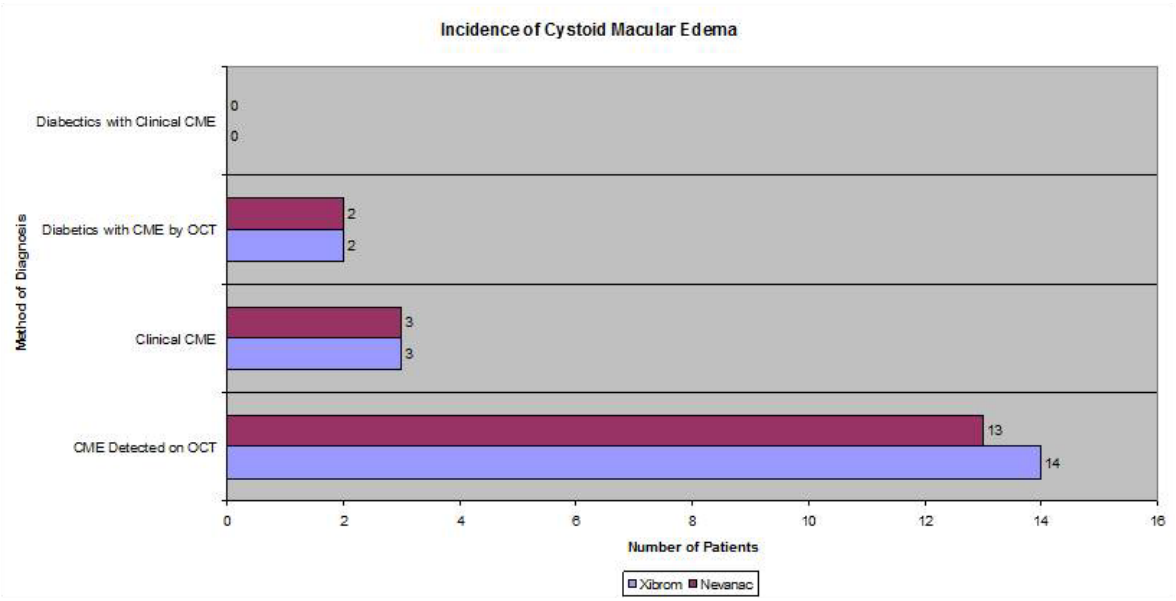

Figure 1: Incidence of Subclinical Cystoid Macular Edema.

were lost to follow-up in Group II.Comorbidities for both groups included ectropion, entropion, pseudohole, epiretinal membrane, and dry eyes. Medical comorbidities included hypertension, diabetes mellitus II, hypercholesteremia, coronary artery disease, peripheral vascular disease, breast, lung, prostate and colorectal cancers (Table 1).

Visual outcomes

The baseline, i.e., pre-operative, visual acuity for Group I (bromfenac group) was 0.63 ± 0.5 (20/30 – 20/400). The baseline visual acuity for Group II (nepafenac group) was 0.54 ± 0.6 (20/30 – CF @ 6"). Clinically, visual recovery i.e., best correct visual acuity at one month,was not statistically between the two Groups with the mean *p value*> 0.05 (Table 2).

Intraocular pressure

Group I and Group II had comparable inflammatory responseto the respective topical NSAIDs at the respective post-op visits with a mean *p-value*> 0.05.There was no statistical significance between the two NSAIDs with respect to IOP. On post-op day 1, there was an average of 3mmHg spike in IOP in both groups but statistically insignificant (Table 2).

Total Patient	FT Baseline	FT 1 –week	CFT Baseline	CFT 1-week
Bromfenac (N = 88)	206.65 ± 16.38	220.58 ± 22.21	174.44 ± 8.99	184.86 ± 12.28
Nepafenac (N = 85)	207.84 ± 12.88	222.84 ± 22.03	176.68 ± 11.31	187.79 ± 15.29
P < 0.05	***P = 0.30***	***P = 0.25***	***P = 0.07***	***p = 0.08***
Diabetic	FT Baseline	FT 1 –week	CFT Baseline	CFT 1-week
Bromfenac (N = 29)	218.03 ± 20.18	226.86 ± 22.02	175.41 ± 7.89	182.38 ± 10.05
Nepafenac (N = 30)	214.27 ± 12.35	225.30 ± 16.03	178.57 ± 13.49	186.70 ± 13.60
P < 0.05	***P = 0.19***	***P = 0.38***	***P = 0.14***	***P = 0.085***

FT = foveal thickness in micrometer: rhe mean thickness within the central 1000 micron diameter area of the fovea[4]
CFT = central foveal thickness in micrometer: the mean thickness easured 01 the poim of intersection o/the si.x radial scans by OCT[4]

Table 3: Foveal & Central Foveal Thickness.

CME by OCT	FT Baseline	FT 1-week	CFT Baseline	CFT 1-week
Bromfenac (N = 14)	215.15 ± 15.42	225.15 ± 20.01	177.46 ± 4.86	184.08 ± 7.54
Nepafenac N = 13)	207.08 ± 10.32	220.92 ± 17.44	183.25 ± 14.47	193.92 ± 15.48
p-llalue (p < O.OS)	***p = 0.68***	***P = 0.29***	***P = 0.11***	***P = 0.032***

FT = foveal thickness; CFT = central foveal thickness
CME = cystoid macular edema
OCT = optical coherency tomography

Table 4: Incidence of Cystoid Macular Edema.

Cystoid macular edema

The baseline (pre-operative) FT for Group I (n = 88) was 207 ± 16 µm and for Group II (n = 85) was 208 ± 13µm (*p-value* = 0.30). The 1-week post-surgery FT for Group I was 221 ± 22 µm and 223 ± 22 µm for Group II (*p-value* = 0.25). The baseline (pre-operative) CFT for Group I was 174 ± 9 µm and 177 ± 11 µm for Group II (*p-value* = 0.07). The 1-week post-operative CFT for Group I was 185 ± 12 µm and for Group II, the thickness was 188 ± 15 µm (*p-value* = 0.08) (Table 3 & 4; Figure 1).

The baseline FT for diabetics in Group I (n = 29) was 218 ± 20µm and in Group II (n = 30), the baseline FT for diabetics was 214 ± 12µm (*p-value = 0.19*). The FT for diabetics at the 1-week post-op was 227 ± 22 µm for Group I and 225 ± 16 µm for Group II (*p-value = 0.38*). The baseline CFT was 175 ± 8 µm and 179 ± 14 µm for Group I and II respectively (*p-value* = 0.14). The 1-week CFT for Group I was 182 ± 10 µm and for Group II, 188 ± 14 µm (*p-value* = 0.09).

The incidence of CME was assessed in two ways: clinically and by OCT and within the total population and among diabetics. There were a total of four CME (2 in each Group) suspected on clinical exam for the entire studied population. There were 12 CME detected by OCT for Group I (12/88 = 14%) and 14 CME by OCT for Group II (14/85 = 17%). Among the diabetic population in our study, there were 4 diabetics (two in each group) with CME as detected by OCT (Group I - 2/12 [16.7%]); Group II - 2/14 [14.3%]). None of our diabetic patients were diagnosed with clinical CME.

Comparing the NSAIDs among all the CME as detected by OCT, the baseline FT for Group I was 215 ± 15 µm and 207 ± 10 µm for Group II (*p-value* = 0.7). The FT at 1-week was 225 ± 20µm and 221 ± 17 µm for Group I and II, respectively (*p-value* = 0.3). The baseline CFT was 178 ± 5 µm and 183 ± 15µm with a *p-value* of 0.1 for Group I and II. The CFT at 1-week post-surgery was 184 ± 8 µm for Group I and 194 ± 16 µm for Group II (*p-value*< 0.05 [*p value* = 0.032]).

Discussion

In this study, we reported the clinical outcomes betweenbromfenac and nepafenac for patients that underwent cataract extraction. The data collected include: visual acuity, intraocular pressure, degree of anterior and posterior segments inflammation.

Visual acuities were measured at the 1-day, 1-week, and 1-month post cataract extraction and the outcomes were comparable and not statistically significant between groups.

In this study, the primary post-operative complication assessed was cystoid macular edema. To ensure readability and to minimize confusion, CME detected by OCT will be referred to as "subclinical CME" while those suspected on clinical exam will be referred to as "clinical CME."The incidence of subclinical and clinical CME was comparable for both groups and the values were not statistically significant. Except for two patients in each group, patients suspected of clinical CME did not have any medical or ocular co-morbidity, e.g., diabetes mellitus or BDR. The two diabetic patients diagnosed with subclinical CME, both had the HA1C levels below 7.0 for a minimum of six months prior to surgery. All the patients diagnosed with subclinical and clinical CME were followed closely with serial OCT with all cases resolved by week 8 post cataract surgeries. None of the patients with clinical CME progressed to debilitating visual function and none required retinal consultation. Further evaluations for those with clinical CME, there were no evidence of intra-operative complications, i.e., rupture capsule with or without anterior vitrectomy.

According to Lindstrom et al. [6], nepafenac'sability to inhibit prostaglandin synthesis plays a role in suppressing inflammation and cystoid macula edema following cataract surgery. Miyanaga et al. [12] reported that bromfenac is effective in minimizing inflammation after cataract surgery. Our study mirrored the findings by Lindstrom [6] and Miyanaga [12]. Our diabetic population was well controlled and the incidence of clinical CME was non-existent and only two were diagnosed subclinically. Our findings follow the trend suggested by Endo et al. [13].

Cystoid macular edema was determined both clinically as well as by OCT3. Previous versions of OCT have been found by some to not be as reliable as other methods in determining retinal thickness as it relates to CME [8]. Our findings seem to be consistent with others showing that OCT 3 is highly sensitive in diagnosing subclinical CME [7,11-13]. In this study, CME was defined as foveal and central foveal thickness 2 SD outside the mean. Foveal thickness (FT) as defined by Chan et al., is the mean thickness within the central 1000 micron diameter area of the fovea. Central foveal thickness (CFT) was defined as the mean thickness measured at the point of intersection of the six radial scans by OCT [4]. Only baseline and 1 week post-op OCT were performed in this study with no 1 month scan, except for patients with clinical CME, they were followed with subsequent scans accordingly. Our study also finds and is consistent with those of others, that OCT 3 is very sensitive in detecting early subclinical CME, especially if the CFT was the main criteria in determining CME [7].

Despite having two different technicians performing the OCT, Polito et al. found that repeatability and reproducibility were consistent in using OCT among experienced and certified OCT technicians [11]. Our findings suggest similar trend. We recognize that further OCT3 scans for longer term follow up would be advisable to better determine any differences in the efficacy between these two medications.

Conclusion

The study demonstrated that bothNSAIDs performed reliably well in the areas tested. There appears to be no statistically significant differences (*p-value > 0.05*) between the two pharmacological agentsand both are efficacious in their purported pharmacological properties.

Acknowledgments/Disclosure

I want to express my appreciation tothe pharmaceutical representatives from Ista and Alcon; the staff members andophthalmic technicians at the Westfield Eye Center and the nurses Southwest Medical Center for their assistance throughout the study period.

All ophthalmologists participating in this study do not have any financial nor proprietary interests in any of the products included in this study. There were no public or private financial supports provided for this study.

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