ORIGINAL ARTICLE

Comparison of safety and efficacy of ofloxacin-dexamethasone combination with tobramycin-dexamethsone after cataract surgery

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Abstract

Purpose: The purpose of this study was to evaluate both efficacy and safety of dexamethasone-ofloxacin combination with that of tobramycin-dexamethasone in post surgical management of cataract surgery.

Methods: In total 223 patients were randomly treated with dexamethasone 1mg/ml plus ofloxacin 3mg/ml (n=148), or dexamethasone1mg/ml plus tobramycin 3mg/ml (n=75) 2 hourly in a day for 7± 1days starting 24 hours after surgery. Efficacy (anterior chamber (AC) inflammation, conjunctival hyperemia, corneal edema, lid edema, ocular infection, pain, photophobia and tearing) and safety (burning, stinging, blurred vision, intra-ocular pressure (IOP) and visual acuity) were analyzed in the operated eye after 7±1 days. A follow-up visit was performed at days 14 ±2 .The extent of AC inflammation ,measured by slit lamp according to a standard scoring system, was used as a primary efficacy parameter.

Results: At the primary end point (day 7) both fixed combinations were equally effective in reducing post-operative inflammation. The safety profile of dexamethasone/ofloxacin was excellent with no evidence of poor local tolerance or adverse reaction.

Conclusion: Combination of dexamethasone and ofloxacin was effective and safe in controlling ocular inflammation after cataract surgery.

Key words: Cataract, Fixed combination, Ofloxacin, Dexamethasone.

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Introduction:

Cataract surgery is one of the most frequently performed surgeries in the world[1]. The techniques of cataract extractions have evolved significantly during the past decade, resulting in decreased intraocular inflammation following this procedure[2].

Some patients can have surgery even with no inflammation, but it is not possible to date to predict such outcome and therefore anti-inflammatory agents are routinely used in nearly all patients[3].

Besides ocular inflammation, the major concern of ophthalmologists performing cataract surgery is the risk of ocular infection[4]. Surgical wound infection and postoperative endophthalmitis are relatively rare but potentially devastating events, and therefore there is uniform agreement on the need for antibiotic prophylaxis in the cataract surgery[5].

Thus, the postoperative pharmacology management of cataract extraction includes the use of a topical steroid with an antibiotic usually as a combination eye drop[6]. The concomitant administration of both agents in a single ophthalmic product overcomes the potential washout effect that may be seen when separate medications are used. In addition, single administration of a combination product leads to better compliance and patient comfort[7,8].

In the present study we evaluated both efficacy and safety of a new fixed combination of dexamethasone and ofloxacin in patients undergoing cataract surgery. The efficacy of such product was compared to TOBRADEX, a well accepted steroid/antibiotic combination that is currently marketed in several countries as a standard treatment to control postsurgical inflammation and prevent postsurgical infection[9].

Dexamethasone is a potent fluorinated synthetic corticosteroid derived from hydrocortisone with structural changes that give to dexamethasone an anti-inflammatory activity about six times stronger than that of prednisolone[10,11].

Ofloxacin is a semisynthetic, third generation, flouroquinolone antibiotic with a wider spectrum of activity than other antibiotics of the same class, such as tobramycin and gentamicin [12]. It is active against most of both Gram-negative and Gram-positive germs, including S. aureus, S. epidermidis and S. coagulase negative[13]. These organisms are the most common bacteria isolated in postoperative endophthalmitis and are usually recovered in the patient's external tissues, such as eyelids[14]. In addition, ofloxacin is less susceptible to attack from many of the aminoglycoside-inactivating bacterial enzymes and therefore is active against strains resistant to gentamicin and tobramycin[15].

Material and Methods:

Design:

Prospective, randomized, double blind, active controlled, parallel group study.

Patients:

Study was conducted at Department of Ophthalmology Hamdard University Hospital between October and June 2006 in patients scheduled for phacoemusification and ECCE with posterior chamber intra- ocular lens implantation, written and informed consent was obtained from all patients. A total 223 patients were included in the study (Table 1).

Table 1: *Patient demographics*

	Test	Controlled	Total
No. of Patients	148	75	223
Age Range	41-70	40-75	40-75
Gender			
Male	78	40	118
Female	70	35	105
Surgery Type			
Phacoemulsification	127	54	181
ECCE with IOL	21	21	42

Inclusion criteria: at least 40 years old, either sex, and suffered from pre-senile or senile cataract with no other ocular or systemic pathology, which were expected to show good post-op follow up.

Exclusion criteria included: Intra-ocular pressure (IOP) greater than 24mmHg, any concomitant ocular pathology, herpes infection, diabetic retinopathy, ocular medication other than artificial tears, previous ocular surgery or laser treatment, known or suspected allergy to any of the ingredients in the study medication and use of topical or systemic steroids or non-steroidal inflammatory agents in the 15 days preceding surgery.

Enrolled patients were randomly assigned to treatment groups in a 2:1 ratio to receive an ophthalmic formulation containing dexamethasone plus ofloxacin (n=148, group 1) or tobramycin plus dexamethasone (n=75, group 2). Both products were packaged in an identical fashion to guarantee an appropriate masking for both patients and investigators.

The treatment started 24hours after surgery (day1) and continued for 7 consecutive days. No other treatment was allowed until after the end of trial except in case of absolute necessity.

Five patients had intra-operative complications (capsule rupture followed by vitrectomy); these patients were considered not eligible and evaluated for safety.

Evaluation:

Patients were examined before surgery (day 0) and post-operatively at day1 and day 7 ±1 (end point evaluation).A follow-up visit was per-

formed at day14±2.The examination at each visit included best corrected visual acuity, slit lamp examination (SLE),fundoscopy,and applanation tonometry assessment of IOP. The primary variable chosen to assess drug efficacy was the anterior chamber (AC) inflammation.

AC inflammation was evaluated by SLE and scored from none to severe using a 0-4 point scale.

Grading of cells is performed with a 2mmx1mm slit beam with maximum intensity and magnification. The findings were recorded as in Table 2.[16]

Table 2: *Grading of A/C Cells*

Score	Cells in field
0	Occasional cells(upto 5 cells)
1	6-15 cells
2	16-25 cells
3	26-50 cells
4	>50 cells

Flare was scored by observing the degree of interface in the visualization of iris using the same setting as for cells as in Table 3 .

Table 3: *Grading of Flare*

Score	Description
0	Nil
1	Faint
2	Mild (iris & lens detail clear)
3	Moderate (iris & lens detail hazy)
4	Severe (intense;fibrinoid exudates)

Corneal edema was graded as none to severe by SLE as follows

None clear transparent cornea.

Mild edema involving central cornea along with folds in descemet membrane.

Moderate extensive edema throughout cornea but Iris detail still visible.

Severe Iris details not visible.

All patients were divided into following groups

Mild cell score upto 2, flare upto 2, mild corneal edema.

Moderate cell score upto 3, flare upto 3, moderate corneal edema.

Severe cells upto 4, flare upto 4, severe corneal edema.

Table 4: *Patient group according to degree of inflammation*

Total patients studied	218
Test(ofloxacin/dexamethasone)	145
Control(tobramycin/ dexamethasone)	73
Patients having none to mild inflammation	208(95.5%)
Patients having mild to moderate inflammation	10(4.5%)
Patients having moderate to severe inflammation	0

Results:

218 patients were studied in 09 months. Five patients had intra-operative complications (capsule rupture followed by vitrectomy); these patients were considered not eligible and evaluated for safety.

Efficacy data are displayed in Table 5.

Both treatments were effective in decreasing overtime ocular inflammation .No significant difference was observed in evaluation of efficacy parameters. All these data demonstrate therefore that fixed combination containing ofloxacin/ dexamethasone is effective and not inferior than tobramycin/dexamethasone combination.

Safety:

Three patients of ofloxacin/dexamethasone group and two patients of tobramycin/dexamethasone group did not complete the study due to adverse systemic events judged not related with treatment. The tolerance variable assessed were the degree of burning, stinging and blurred vision. Their intensity was generally related as none or mild at all study visits without any statistically significant difference between treatment groups. Moreover, within treatment comparison showed that such symptoms significantly improved overtime in both group of treatment. Safety variable that were monitored during the trial were visual acuity and IOP. No difference between treatment groups in mean change from screening was detected at any visit.

Table 5: *Efficacy data*

Parameter	Day after surgery	Responders			
		Test (145)		Control(73)	
		n	%	n	%
AC cells	7	143	98.6	73	100
	14	145	100	73	100
AC flare	7	117	80.6	59	80.8
	14	143	98.6	72	98.6
Conjunctval hyperemia	7	110	75.8	70	95.8
	14	140	96.5	72	98.6
Corneal edema	7	139	95.8	70	95.8
	14	143	100	73	100
Lid edema	Not applicable				
Pain	7	120	82.7	61	83.5
	14	139	95.8	70	95.8
Photophobia	7	139	95.8	71	97.2
	14	143	100	73	100
Tearing	7	117	80.6	60	82.1
	14	139	95.8	70	95.8

Table 6: *Safety data*

Safety Parameter	Day after surgery	Responders			
		Test n=145 (%)		Control n=73 (%)	
		Mild	None	Mild	None
Burning	7	15(10%)	130(90%)	3(4%)	70(96%)
	14	0	145(100%)	0	73(100%)
Stinging	7	21(14%)	124(86%)	7(9.5%)	66(90.5%)
	14	5(3.5%)	140(96.6%)	2(2.7%)	71(97.3%)
Blurred Vision	7	9(6.2%)	136(93.8)	4(5.5%)	69(94.5%)
	14	2(1.3%)	143(98.7%)	0	73(100%)
Visual Acuity	7	No change		No change	
	14				
IOP	7	Decrease		Decrease	
	14				

Discussion:

Cataract surgery with intraocular lens (IOL) implantation is the most common ophthalmic surgical operation. This procedure is usually associated with varying degrees of postsurgical inflammation. Although such inflammation is usually self-limited, the use of anti-inflammatory agents postoperatively can rapidly resolve this event[18].

To date, topical corticosteroids still form the mainstay of the anti-inflammatory management of cataract extraction[19]. Corticosteroids offer the widest range of activity by ameliorating the effect of the preformed mediators of inflammation as well as attenuating the release of newly formed mediators[20].

Besides ocular inflammation, the major concern of ophthalmologists performing cataract surgery is the risk of ocular infection. Surgical wound infection and postoperative endophthalmitis are relatively rare but potentially devastating events, and therefore there is uniform agreement on the need for antibiotic prophylaxis in the cataract surgery[21]. The use of antibiotics in cataract surgery includes a variety of practices, such as preoperative topical antibiotics, intraoperative antibiotics in the irrigating solution, subconjunctival antibiotics, and postoperative topical antibiotics. Although many of these practices are largely empirical, the evidence that most of the postsurgical infections result from the intraocular introduction of bacterial flora from the eye and adjacent skin during surgery has led to the increasing importance of the use of perioperative antibiotics. Accordingly, also the Center for Disease Control and Prevention (CDC) included in 1999 for the first time ophthalmology in the 'Recommendations for Prevention of Surgical Site Infection[22].

Antibiotics and corticosteroids are usually given after surgery to patients either separated from or in combination[6]. The use of the latter option is usually preferred since it improves patients compliance and reduce cost. In addition, such therapy reduces the chance of an imprecise dosing or the potential washout effect that may be seen when separate medications are used[7]. The reduced number of administrations provided by the combination product may be of particular benefit for elderly patients, who make up the majority of cataract surgeries.

The currently approved fixed combinations of steroids and antibiotics contain dexamethasone, hydrocortisone, predisolone, or fluorometholone combined with sulphonamides or aminoglycosides (neomicin, gentamicin or

tobramycin)[9]. The efficacy and safety of a new steroid/antibiotic fixed combination containing dexamethasone/ofloxacin has been investigated in the present study.

The main objective of this study was to demonstrate the noninferiority of a combination of dexamethasone plus ofloxacin compared to a standard effective combination of steroid plus antibiotic tobramycin in controlling postoperative inflammation and preventing postoperative ocular infections. The design of the study was consistent with the standard postoperative care of patients undergoing cataract extraction. However, due to the excellent wound closure obtained with modern cataract surgery, it was decided to reduce the duration of treatment to 7 days. This restriction of the duration of therapy should ensure at the same time an effective control of postoperative inflammation and a lower incidence of both antibiotic resistance and corticosteroid-related side effects. As a potential limitation of the study, AC inflammation was measured, for practical reasons, by slit-lamp examination. Even if the scoring system used to measure flare and cells by slit-lamp examination is subjective and semiquantitative, yet it corresponds to the actual daily routine of practice.

The present findings indicate that new fixed combination of dexamethasone plus ofloxacin was as effective as tobramycin in reducing ocular inflammation after cataract surgery. There was a significant decrease in the amount of aqueous flare and cells, as well as of all other parameters of inflammations after 1 week of treatment. All parameters studied were comparable in the control and test group with no statistical significant differences. There was no evidence of rebound of signs after cessation of therapy. With respect to safety, dexamethasone/ofloxacin combination had a favorable safety profile, including ocular tolerance. A common safety concern with topical corticosteroids is the potential to cause an increase in IOP in susceptible individuals. There was no issue with elevation in IOP in this study. A decrease of IOP is a common feature in the follow-up of cataract surgery and, as expected, a significant decrease of IOP mean levels from baseline through study visits was observed in the present clinical trial.

Dexamethasone/ofloxacin fixed combination has several advantages over tobramycin. First, ofloxacin is a third generation fluoroquinolones. It has an excellent clinical profile and (as opposed to tobramycin) a very low prevalence of resistance against the most common microorganisms involved in ocular infections[23]. Second, Ofloxacin penetrates corneal tissue better than tobramycin; hence achieve higher aqueous humor concentration. Ofloxacin has the best aqueous penetration in human eyes, as compared with ciprofloxacin and tobramycin, which suggests ofloxacin, could be the preferred topical medicine for the prevention and treatment of endophthalmitis[24]. Moreover, the mean aqueous humor levels of ofloxacin were more than the MICs levels for most of the ocular pathogens which may cause postoperative endophthalmitis.Also, prolonged application and the presence of inflammation increased the penetration of ofloxacin into the vitreous humor[25]. Third the new combination is economical.

In conclusion, the fixed combination of dexamethasone and ofloxacin resulted to be safe, well tolerated, effective, and economical in controlling ocular inflammation after routine cataract surgery. This formulation can be considered for use in a wide spectrum of post surgical prophylaxis regimens and to achieve better patient compliance with medication.

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