Efficacy of Nepafenac 0.3% Plus Dexamethasone 0.1% Versus Dexamethasone Alone in Prophylaxis of Irvine-Gass Syndrome After Cataract Surgery

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Abstract

Purpose: To determine whether nepafenac ophthalmic suspension 0.3% in co-administration with dexamethasone 0.1%, effectively reduces the incidence of Irvine-Gass syndrome, after uneventful cataract surgery.

Setting: Laserlens One Day Clinic. Ioannina-Greece

Design: Prospective, comparative, intervention and randomized study. (N=200).

Methods: We included 200 eyes that required phacoemulsification and uncomplicated cataract surgery. Patients were randomly divided into two groups: first group (right eye) included nepafenac 0.3% + dexamethasone 0.1% ophthalmic suspension. Second group (left eye) included dexamethasone 0.1% alone. On thirty and ninetieth day after surgery optical coherence tomography was carried out; fluorescein retinal angiography study was performed to confirm the CME.

Results: Mean age of study population was 60.97± 4.91 years. In both groups, presence of flare in the aqueous humor was found in 100% of the patients the first 24 hours. The intraocular pressure average in both groups was 13.04 mmHg ± 2.23. Symptoms associated with the use of NSAID in group 1, 53% of the patients referred sensation of foreign body the first and seventh day post surgery. In group 1, the patients did not develop macular edema unlike group 2 a significantly lower percentage of patients demonstrated Irvine-Gass syndrome within ninetieth day after surgery (two cases without pre-operative risk factors 2%) corroborated with optical coherence tomography and fluorescein retinal angiography.

Conclusion: The combination of nepafenac 0.3% with dexamethasone 0.1% is appropriate for the prophylaxis of Irvine-Gass syndrome, also for the control and the reduction of the postoperative inflammation.

Keywords: Non-steroidal anti-inflammatory; Cystoid macular edema; Optical tomography; Steroids; Nepafenac

Introduction

Nepafenac ophthalmic suspension 0.3% (Nevanac®; Alcon Research Ltd, Fort Worth, TX) is a non-steroidal anti-inflammatory prodrug (NSAID) indicated for the management of pain and inflammation associated with cataract surgery [1]. After topical ocular dosing, nepafenac penetrates the cornea and is hydrolyzed in the intraocular tissues including the ciliary body epithelium, retina, and choroid, to amfenac, that inhibits in a non-specifically way the activity of the COXI and COX2 cyclooxygenase enzymes, diminishing the production of pro-inflammatory factors as the prostaglandin and thromboxane that are generated during the tissue answer to the trauma. If an NSAID can penetrate to the retina, it could possibly reduce vascular permeability by inhibiting the inflammatory cascade [2,3].

The ocular bioavailability and permeability of nepafenac, combined with its rapid bio-activation by ocular tissues, make it a target-specific NSAID for the inhibition of prostaglandins (PG) formation in the anterior and posterior segments of of the eye [4]. Prostaglandins play an important role in the response to ocular trauma, causing inflammation, pain, trans-operative myosis, increased intraocular pressure, and pseudohaptic cystoid macular edema (PCME), among others [5]. The topical ocular dosing of an NSAID before and after cataract surgery has been proposed to prevent the myosis during the surgery, decrease or avoid the ocular inflammation, as well as the development of macular edema [6,7].

CME is caused by cystic accumulation of intraretinal fluid in the outer plexiform and inner nuclear layers of the retina, as a result of the breakdown of the blood–retinal barrier [8]. It is not a disease itself, rather the endpoint of a variety of processes that lead to the accumulation of fluid in the central retina. It can present with symptoms of blurred or declined central vision, and painless retinal inflammation or swelling [9], is a serious consequence of numerous ocular procedures and conditions, including cataract surgery, ocular inflammatory disease, retinal vascular diseases, and tractional disorders, resulting sometimes in transient or even permanent vision loss [10,11].

The incidence of CME is approximately 20%–30% of uncomplicated cataract surgery cases, while acute, clinically significant CME has been reported from 1%–2% of patients following uncomplicated phacoemulsification [12,13].

With the use of the optical coherence tomography (OCT) an incidence of 1.92% CME has been reported in patients with uncomplicated cataract surgery cases, this shows that this is a useful study to detect the presence of CME [14].

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Nepafenac 0.3% may improve postoperative outcomes with increased patient compliance and reduced treatment burden. In healthy patients and with macular edema history in the other eye, may be an indication for nepafenac prophylaxis [15]. However, each patient should be assessed individually in terms of benefits and adverse effects of the treatment [15].

There is no prophylactic protocol for PCME because there is a lack of strong randomized clinical trials and comparative effectiveness studies. The lack of large studies is perhaps due to the fact that most cases of acute PCME spontaneously resolve. However, the treatment of chronic PCME remains a challenge. For this reason, this study was designed to know if the co-administration of nepafenac ophthalmic suspension 0.3% + dexamethasone ophthalmic suspension 0.1%, is able to reduce the incidence of Irvine-Gass syndrome and provides a synergistic effect in controlling intraocular inflammation using each patient as his own control group, to avoid bias in the result of the study after uneventful cataract surgery. Thus, each patient should be judged individually in terms of benefits and adverse effects of the co-administration treatment.

Materials and Methods

This was a prospective, comparative, interventional and randomized study that was performed at the anterior segment department “Laserlens One Day Clinic”, Ioannina, Greece. The study followed the principles of the biomedical research on humans, not causing damage and keeping the confidentiality and respect to the patient. These principles were posted in the Helsinki declaration and were updated in the 1987 South Africa Congress. The protocol was presented to the Committee of Ethics in research studies at “Laserlens One Day Clinic”, and each one of the patients signed an un-disclosure agreement. This research includes the analysis of 200 eyes of 100 patients of any race/ethnicity and gender who were older than 40 years old with diagnosis of senile cataract and uncomplicated surgery. The intraocular pressure was less than 21 mmHg without ocular treatment. We included all patients with or without pre-operative risk factors, except those patients with conditions that may have caused macular edema, including preexisting histories of retinal vein occlusions in one eye, ocular surgeries, uveitis, keratitis, dry eye syndrome, conjunctivitis, allergy or hypersensitivity to the nepafenac, as well as those that had been under treatment with, steroids or NSAID 90 days prior surgery, were left out of the study.

The calculation of the intraocular lens power, was carried out with optical low coherence reflectometry (OLCR) (LENSSTAR LS900®, HAAG-STREIT AG, Switzerland), in all cases the power for emmetropia calculated was chosen.

Patients were randomly divided into two groups: first group (n=100 right eyes) included topical Nepafenac 0.3% (Nevanac®; Alcon Research Ltd) one drop per day starting one day before surgery until 30 days after surgery. Second group (n= 100 left eyes) included dexamethasone ophthalmic suspension 0.1% four times a day starting one day before surgery until 30 days after surgery. All patients received a standard regimen of moxifloxacin 0.5% drops dosed at four times a day, starting one day before surgery until 10 days after surgery. Each patient signed a consent authorizing the anterior segment specialist surgeon (ESD) and the institution (Laserlens One Day Clinic) to receive different therapy schemes in both eyes.

The surgical procedure was performed by anterior segment specialist surgeon (ESD) carried out under topical anesthesia with xylocaine 1%. Corneal incision in the XI meridian with a steel knife of 2.2 mm wide, after was injected a dispersive-cohesive viscoelastic material to maintain and pressurize anterior chamber (DioVisc Alcon Labs Fort Worth, Texas) ®. Circulate continuous capsulorhexis (CCC) was carried out, after that was made a hydro dissection. In some cases, when possible, the pre-fracture of the nucleus was practiced using the technique of Karate-Chop; when it was not possible because of the hardness of the nucleus, a second incision of 1 mm wide was carried out in the II meridian. The phacoemulsification of the cataract was done using torsional ultrasound or in a combination of it with a longitudinal ultrasound, according to the hardness of the nucleus. The same viscoelastic material was injected in the bag to be able to implant the acrylic hydrophobic intraocular lens inside the capsular bag (SN60WF or TORIC IOL, Alcon Labs. Fort Worth, Texas) ®, through the trans corneal injection. Viscoelastic material was removed and a simple suture with nylon 10-0 was made in cases that did not present airtightness of the corneal injury (4 cases).

The patients were checked (first, seventh, thirtieth and ninetieth day after the procedure) the visual acuity and capacity, refraction, presence of turbidity in the anterior chamber, as well as the intraocular pressure using Goldmann applanation tonometer. Spectralis optical coherence tomography (Heidelberg Engineering GmbH) was carried out in all patients and the presence of cystic intraretinal spaces was sought deliberately. All the cases were investigated with the use of fluorescein retinal angiography (FAG).

Results

200 eyes of 100 patients were included in the study; 58 of them were females and 42 males, with mean age of study population was 60.97 ± 4.91 years. The average visual preoperative capacity was of 0.82 (1 to 0.5 LogMAR units). In both groups, presence of flare in aqueous humor was found in 100% of the patients the first 24 hours, which was reduced in group 1 to 0% and in group 2 to 13% on 7th day and 3% on the fourth week. The visual capacity in both groups was 0.08 LogMAR, with a spherical average equivalent by the fourth week of +0.08 D. The intraocular pressure average in both groups was 13.04 mmHg ± 2.23 at the first 24 hours and it was maintained without significant changes through the study.

As for the apparition of symptoms associated with the use of NSAID in group 1 the 53% of the patients referred sensation of foreign body the first and seventh postoperative day, being reduced to 12% of the cases by the fourth week.

Spectralis optical coherence tomography was carried out in all patients at the beginning of the first and third month. In group 1, the patients did not develop macular edema after cataract surgery unlike group 2 a significantly lower percentage of patients demonstrated Irvine-Gass syndrome within the ninetieth day after surgery (two cases without pre-operative risk factors 2%) corroborated with the Spectralis optical coherence tomography and fluorescein retinal angiography (Figure 1). One of them presented decrease of the visual capacity under 0.20/0.5 LogMAR, associated with a macular edema on the third postoperative month (Figure 2). Two cases out of 20 from group 2 had a small increase of the visual capacity under 0.20/0.5 LogMAR, and fluorescein retinal angiography showed a delay in the macular edema conditions. In group 1, no cases of macular edema was found. 11% of the patients in group 1 and 10% of the patients in group 2 presented an increase of macular edema under 0.20/0.5 LogMAR, however, we do not consider this an indication for the postoperative treatment.
and received acetazolamide 250 mg 1 pill four times a day for 2 weeks, prednisolone acetate 1% 1 drop four times a day for 15 days and timolol maleate 1 drop twice a day for 15 days (Figure 3).

**Discussion**

In the present study we found that the new higher concentration nepafenac 0.3% (Nevanac(®); Alcon Research Ltd) one drop a day in co-administration with dexamethasone 0.1% ophthalmic suspension four times a day, appears well tolerated, safe and also enhanced the efficacy of steroids to reduce macular edema, furthermore this combination could control the inflammation in the postoperative and use as a prophylaxis of PCME. These findings are similar to other studies that show the use of topical nepafenac 0.3% reduces pseudophakic cystoid macular edema (PCME), also known as Irvine-Gass syndrome, in patients with pre-operative risk factors for PCME compared to placebo but shows no benefit in patients without pre-operative risk factors [16,17]. This type of medicine acts inhibiting the activity of the 1 and 2 cyclooxygenase enzyme in a not selective form, diminishing the formation of proinflammatory precursors such as the prostaglandin, prostacyclin and thromboxanes. Nevertheless, the formation of leukotrienes is not affected because the lipoxygenase enzyme is not inhibited by these medicines [1,2].

The nepafenac was well tolerated by all the patients, although symptoms of little intensity were presented in an important number of the cases. The sensation of foreign body and heat were the most often found symptoms, which agrees with reported in use of other NSAID [3,4].

In the present study no data of keratitis or wound of the corneal epithelium was found, demonstrable by staining of the ocular surface with sodium fluorescein nevertheless, due to the reports that exist about the presence of punctate keratitis or even in the nuclear liquefaction, all the cases were revised exhaustively [11-13].
Conclusion

We consider that nepafenac 0.3% in co-administration with dexamethasone 0.1% is useful for the prophylaxis of Irvine-Gass syndrome and for the control of the postoperative inflammation. This joint treatment with both types of medicines turns out to be appropriate and could enlarge the efficacy of the treatment due to the synergic action with the different action mechanisms of these medicines. Numerous prior reports have evaluated the efficacy of this therapeutic strategy and have found an important reduction in the incidence of PCME in combined therapy with steroids in comparison with the use of only steroids. Therefore, future investigations should indicate which patients achieve the greatest long-term benefit to topical NSAID + topical steroids prophylaxis.

References