
ORIGINAL ARTICLE

EFFICACY OF BETAXOLOL TO RECOVER UNEXPLAINED VISUAL LOSS AFTER UNEVENTFUL SMALL INCISION CATARACT SURGERY IN HYPERTENSIVE PATIENTS

Lakshmikanta Mondal¹, Anindita Mondal², Krishna Pada Baidya³, Goutam Bhaduri⁴

HOW TO CITE THIS ARTICLE:

Lakshmikanta Mondal, Anindita Mondal, Krishna Pada Baidya, Goutam Bhaduri. "Efficacy of Betaxolol to Recover Unexplained Visual Loss after Uneventful Small Incision Cataract Surgery in Hypertensive Patients". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 11, March 17; Page: 2789-2796, DOI: 10.14260/jemds/2014/2210

ABSTRACT: AIM: To test the efficacy of topical betaxolol to recover unexplained visual loss after uneventful cataract surgery in hypertensive patients. **Study design:** Randomized clinical trial. **MATERIALS AND METHODS:** One hundred patients of decreased visual acuity (20\40 to 20/50 after best correction after 6 weeks of uncomplicated small incision surgery in hypertensive patients were enrolled. Fifty eyes received topical betaxolol twice daily and fifty eyes received placebo eye drops as a randomized comparison group and followed up for more than six months. Change in best-corrected visual acuity was considered as change of five letters (0.1 log MAR) or more. **Statistical analysis:** Significance of difference of results between study and control groups is determined by Mann-Whitney U test and Fisher Exact test. **RESULTS:** 14 (28 %) patients demonstrated three lines and 31 (62 %) patients showed two line improvement in best-corrected visual acuity under treatment group. Whereas one (0.3 to 0.0) and 11 (0.4 to 0.2) eyes of the placebo group demonstrated same amount visual improvement. **CONCLUSION:** Topical betaxolol significantly improves visual acuity in unexplained visual loss after uneventful small incision cataract surgery in hypertensive patients. **KEYWORDS:** Unexplained visual loss, small incision cataract surgery (SICS), hypertension, topical betaxolol, best-corrected visual acuity (BCVA).

INTRODUCTION: Cataract is the leading cause of blindness all over the world and cataract surgery is the major work load of the most eye care hospitals.^{1,2} Usually uneventful cataract surgery yields good visual recovery. Though phacoemulsification with implantation of foldable intraocular lens has become the treatment of choice for cataract surgery over the past two decades, manual small incision cataract surgery (SICS) with implantation of non-foldable polymethyl methacrylate (PMMA) lens is safe, economic and effective for high volume surgeries in many developing countries including India.^{3,4}

On the other end, hypertension which is one of the most common diseases of morbidity and mortality all over the globe is more prevalent with aging.⁵ Most patients who suffer from blindness due to cataract are usually over 60 years old and these individuals are most affected by hypertension. Most commonly hypertensive patients present to the ophthalmologists seeking treatment for loss of vision owing to macular hemorrhage, edema, exudates, poor capillary perfusion, serous or exudative detachment of retina and ischemic optic neuropathy.⁶

Reduced visual acuity without ophthalmoscopic evidence of hypertension related pathology after uneventful cataract surgery in hypertensive patients encouraged us to search for systemic biochemical abnormality related to visual loss in these subjects. Previous study suggested that low-

ORIGINAL ARTICLE

grade ischemia induced biochemical derangement like increased anaerobic glycolysis and oxidative stress might be responsible for unexplained visual loss after uneventful SICS.⁷

Betaxolol, a selective β_1 -adrenoceptor blocker is one of the most commonly used class of antiglaucoma agent because of its ability to preserve visual field better. Evidence is accumulating for an ischemic/excitotoxic-like pathway of ganglion cell death in glaucoma with some similarities to that occurring in the brain after stroke or heart attack. Recent work indicates that β_1 -adrenoceptor antagonist is a retinal neuroprotective agent, since topical administration of the drug reaches the retina and can counteract the detrimental effects caused by ischemic/or N-methyl-D-aspartate (NMDA) –induced insults to the retina. Its neuroprotective action is generally thought to be due to its calcium channel blocking properties. Studies have shown that betaxolol interacts directly with L-type calcium channel and therefore is effective to ameliorate ischemic or NMDA induced injury of retina by its calcium channel blocking activity.^{8,9}

In the present study we tested the efficacy of topical betaxolol to improve visual acuity in unexplained visual loss after uneventful SICS in hypertensive patients.

METHODS:

Study subjects: This prospective double masked randomized clinical trial was carried out at the Regional Institute of Ophthalmology, Kolkata, India, from June 2006 to June 2008. One hundred hypertensive patients of 60 to 67 years age with advanced immature cataract having visual acuity less than 20/100 (logMar 1.0) underwent uneventful small incision cataract surgery with implantation of PMMA lens (US IOL) in the bag and such patients having best corrected visual acuity of 20/40 to 20/50 (logMar 0.3 - logMar 0.4) at 42nd day of post-operative period were included in the study. Patients were randomly assigned to receive topical betaxolol or placebo for two months and followed up for six months. Randomization of patients was done by using computer generated random number: odd number was to receive topical betaxolol and even number was to receive placebo eye drops. The patients were masked to the allocation procedure and the randomization state of patients was rigorously maintained to the evaluator.

All patients underwent complete curvilinear capsulorhexis and PMMA IOL implantation in the bag under one surgeon (LKM). Visual acuity was measured in every case on the first post-operative day, after six weeks of surgery, 2 months and 6 months topical administration of betaxolol and placebo eye drops. by other ophthalmologists (SG, CS). Cycloplegic refraction was performed and best corrected visual acuity (BCVA) was recorded by early treatment diabetic retinopathy study (ETDRS) chart at 4 meters. Visual acuity was assessed by letter-by-letter scoring in logarithmic units (log MAR). A change in visual acuity was defined as a change of 5 letters (0.1 of Log MAR) or more.

All subjects underwent detailed ocular and systemic examinations before and during the follow up period. Anterior segment was evaluated by slit-lamp examination to exclude corneal edema, anterior uveal tract pathology and thickening of posterior capsule which might affect visual acuity. Dilated fundoscopic examination by indirect ophthalmoscopy, slit-lamp biomicroscopy by +90D and three mirror lens were done to detect retinal abnormality before and at every visit of the follow up period. Visual evoked response (VER) was performed on those subjects with reduced visual acuity. Every patient of this study had optical coherence tomography (OCT) to map macular thickness and digital fundus fluorescein angiogram to detect angiographic macular edema and capillary drop out. OCT scan was performed with Stratus OCT-3 (Carl Zeiss Meditec, Inc, Dublin, CA, USA) at the

ORIGINAL ARTICLE

baseline, 2 months and 6 months after administration of topical betaxolol and placebo eye drops. The scan protocol used was the Fast Macular Thickness Map algorithm. The best quality macular thickness maps (signal strength five or more) at those visits were analyzed to produce macular thickness map, consisting of thickness values in central fovea. Data were entered into a Microsoft Excel spreadsheet and analyzed using spss (version 12.0, SPSS, Inc., Chicago, IL, USA). Macular thickness values in central fovea between treatment and placebo groups were compared by using student's t-test.

Goldman tonometry was used to determine intraocular pressure at baseline and 6 months visits. The patients were regularly questioned and examined for side effects of the drugs. Assessment of outcomes, complications and adverse effects were determined by another ophthalmologist (GB) of this hospital who is masked to the allocation procedure of this study.

Patients suffering from diabetes mellitus, neurodegenerative disease, grade III or grade IV hypertensive retinopathy, glaucoma, high refractive error or having history of uveitis, trauma, previous eye surgery and other ocular disease like optic neuropathy of any type and clinically angiographically or on OCT, cystoid macular edema were excluded from the recruitment for participation in this study. The study was approved by Institutional Ethical Committee and all patients were informed of the purpose of the study and gave their signed consent to participate.

Statistical analysis: Age and sex differences between the patients and controls were investigated by Student's t-test and chi-square (χ^2) test respectively. The significance of differences of visual acuity between corresponding groups of observations was evaluated by the Mann-Whitney U test and all values were expressed as mean (SD) and range. For all other two-by-two comparisons, the Fisher exact test was used [by GraphPad Software]. The level of statistical significance was set at $P < 0.05$

Results: Baseline data are summarized in Table – 1. 100 patients subject to SICS with posterior chamber lens implantation were randomized to receive topical betaxolol or placebo for 6 months.

At the baseline best corrected visual acuity was 20\40 to 20\50 (Log MAR BCVA 0.3 – 0.4) in the treatment and placebo groups. Treatment group consisted of 34 (68%) eyes having Log MAR BCVA 0.4 and 16 eyes having Log MAR BCVA 0.3.

Placebo group consisted of fifty eyes of which 39 eyes had baseline Log MAR BCVA 0.4 and 11 eyes had Log MAR BCVA 0.3.

At the baseline (on 42nd postoperative day) the mean macular thickness in central fovea was $207.6 \pm 26.3 \mu\text{m}$ and $207.8 \pm 26.1 \mu\text{m}$ respectively.

After 2 months of administration of topical betaxolol 14(28%) eyes of baseline Log MAR BCVA of 0.3 attained 2 lines improvement whereas only 3 (6 %) eyes of placebo group having same baseline visual acuity showed 2 line improvement ($p = 0.006$).

One line improvement was seen in 30(60%) eyes of the treatment group having Log MAR BCVA of 0.4 whereas 18 (36%) eyes of the placebo group of same baseline visual acuity demonstrated one line improvement ($p = 0.02$).

After 6 months of administration of topical betaxolol 3 lines improvement was detected in 14 (28%) eyes of treatment group compared to one (2%) eye of the placebo group ($p=0.003$). Improvement of 2 lines in BCVA was seen in 31 (62 %) eyes of treatment group in comparison to 11 (22%) eyes of placebo group ($p < 0.0001$).

ORIGINAL ARTICLE

No improvement in BCVA was significantly more found in 30 (60 %) eyes of placebo group compared to only 4 (8 %) eyes of the treatment group ($p < 0.0001$).

Macular edema was not detected clinically or on OCT in any patient of both groups, but resolution of macular thickness was significantly higher in betaxolol group ($p < 0.04$).

Mean intraocular pressure at baseline were 15.5 ± 1.6 and 15.5 ± 1.7 mm of Hg and at 6 months visit were 12.9 ± 1.4 and 15.5 ± 1.8 in the treatment and placebo groups respectively. Mean systolic blood pressure at baseline and at 6 months was 160 ± 10.1 and 158 ± 9.1 in the treatment group. Placebo group showed no change in systolic blood pressure e.g. 160 ± 11 and 160 ± 10.9 mm of Hg at baseline and 6 months visit (Table – 4).

Betaxolol showed mild decrease in blood pressure.

DISCUSSION: This study demonstrated efficacy of topically applied betaxolol to recover unexplained visual loss after uneventful cataract surgery in some hypertensive patients. Forty six (92 %) eyes of decreased visual acuity showed improvement of 10 letters (0.2 Log MAR) or more in BCVA owing to treatment with topical betaxolol while only 8 (16 %) eyes of placebo group gain one line (log MAR 0.2) improvement after 6 weeks of follow-up. Here the observed difference is greater than twice the standard error of difference. So a strong evidence of efficacy of topical betaxolol to recover visual loss is found. So betaxolol improved visual acuity significantly compared with untreated eyes.

Medically unexplained visual loss is not an uncommon problem in ophthalmic practice.¹⁰ Patients of essential hypertension usually seek the advice of the Ophthalmologists owing to loss of vision caused by venous or arterial occlusion, hemorrhage, exudates, serous or exudative detachment, ischemic optic neuropathy or papilledema. When patients with grade I or grade II hypertensive changes in retinal vessels present visual loss after uncomplicated good cataract surgery, it stimulated us to search for ischemia induced biochemical derangement associated with such diminished visual recovery.

Our previous studies have suggested that systemic biochemical abnormality like increased anaerobic glycolysis and oxidative stress may be associated with decreased visual acuity in certain number of diabetic and hypertensive patients without visible retinopathy.^{7, 11}

Hypertension is associated with narrowing of arteriolar lumens causing impairment of blood supply to the affected organs like brain, kidney and retina and induces downstream ischemic injury.¹² The first point of attack of ischemia or hypoxia is cell's oxidative phosphorylation by mitochondria. As the oxygen tension within the cell decreases, there is less oxidative phosphorylation and decreased generation of ATP resulting wide spread effects within the cells like reduction of the activity of Na⁺K⁺ATPase pump in plasma membrane and alteration of cellular metabolism. It is assumed that densely packed and metabolically highly active foveal cones which dominantly determine visual acuity may suffer from slow grade ischemia induced cell injury and dysfunction.

Different studies have demonstrated the efficacy of betaxolol to relax retinal microarteries to improve ocular microcirculation and protect retinal neurons from ischaemia.¹³

The vasodilating effects of betaxolol on ocular vessels have recently been demonstrated in vivo and in vitro studies acting via Ca⁺⁺ channel blocking activity and those studies also showed long-term effects of topically applied betaxolol to increase retinal blood flow.¹⁴ In addition to improvement of microcirculation and brain derived neurotropic factor upregulation, the ability of

ORIGINAL ARTICLE

betaxolol to interact with Na⁺ channel and to reduce Na⁺ influx into neurons may have a role in paradigm of ischaemia.¹⁵

Another randomized clinical trial has shown the efficacy of topical betaxolol to resolve macular edema and regain visual acuity after vitrectomy for epiretinal membrane.¹⁶

Another important point of discussion should include the risk of development of cystoid macular edema (CME) especially on the background of topical use of antiglaucoma agents in SICS.

Use of antiglaucoma agents particularly prostaglandins like latanoprost, bimatoprost, travoprost and beta-blocker like timolol have been associated with increased incidence of CME in patients with postoperative pseudophakia.^{17, 18} Literature does not show such side effect of topical betaxol.

Our recent study did not demonstrate any increased risk of CME, either clinically or on OCT following manual small incision cataract surgery.¹⁹

The present study did not find any incidence of CME after application of topical betaxolol but showed higher resolution of macular thickness following this medication.

As in our study betaxolol improves visual acuity in more than ninety percent of treated patients, biochemical explanation may be amelioration of ischemia induced foveal dysfunction by long-term effects of betaxolol. It is speculated that topical betaxolol may result in improvement of microcirculation and reduction of swelling of foveal cones.

It is best assumed that slow grade ischemia of highly active mosaic of foveal cones may be the determining factor for unexplained visual loss after uncomplicated cataract surgery in some hypertensive patients and betaxolol is effective to regain this loss.

The weakness of this study is the small sample size and unicentre trial. A multicentre study with large number of patients is invited to prove the efficacy of betaxolol to recover decreased visual acuity after uneventful cataract surgery.

Characteristics	Treatment group	placebo group	P value
Ratio of men to women	24: 26	20: 30	
Mean age in years \pm SD	62.9 \pm 2.8	63.2 \pm 3.5	0.63
Log MAR BCVA	0.367 \pm 0.058	0.35 \pm 0.071	0.1929

Table 1: Demographics of patient groups

	Treatment group	placebo group	P value
Baseline Log MAR BCVA	0.367 \pm 0.058	0.35 \pm 0.071	0.1929
Log MAR BCVA after 2 months	0.267 \pm 0.153 ($<$ 0.0001)	0.3 \pm 0.168 (0.0554)	0.307
Log MAR BCVA after 6 month	0.2 \pm 0.2 ($<$ 0.0001)	0.297 \pm 0.178 (0.0534)	0.011

Table 2: Change in best corrected visual acuity after 2 and 6 months of treatment

ORIGINAL ARTICLE

	Treatment group	placebo group	P value
0.3 to 0.1	14 (28%)	3 (6%)	0.0006
0.3 to 0.2	2 (4%)	8 (16%)	0.09
0.4 to 0.3	30 (60%)	18 (36%)	0.02
0.4 to 0.4	4 (8%)	21 (42%)	

Table 3: At 2 months

	Treatment group	placebo group	P value
0.3 to 0.0	14 (28%)	1 (2%)	0.0003
0.3 to 0.2	1 (2%)	8 (16%)	0.03
0.4 to 0.2	31 (62%)	11 (22%)	<0.0001
0.4 to 0.4	4 (8%)	30 (60%)	<0.0001

At 6 months

	Treatment group	Placebo group	P Value
At baseline	207.6 ± 26.3 μ m	207.8 ± 26.1	NS
After 2 months	193.1 ± 19.3	198.9 ± 21.4	0.04
After 6 months	193.1 ± 21.2	198.7 ± 17.3	0.04

Table 4: Showing changes in central macular thickness (μ m ± SD) on OCT following treatment with betaxolol and placebo drops

	Treatment Group	Placebo Group
Intraocular pressure (mm of Hg)		
At baseline	15.5 ± 1.6	15.5 ± 1.7
At 6 months	12.9 ± 1.4	15.5 ± 1.8
Blood pressure		
At baseline		
Systolic (mm of Hg)	160 ± 10.1	160 ± 11.1
Diastolic (mm of Hg)	98 ± 3.2	98 ± 4.2
At 6 months		
Systolic (mm of Hg)	158 ± 9.1	160 ± 4.1
Diastolic (mm of Hg)	96 ± 2.1	98 ± 4.2

Table 5: Showing change in intraocular pressure and blood pressure

REFERENCES:

1. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP and Mariotti SP. Global data on visual impairment in the year 2002. Bull World Health Organ 2004; 82: 844 – 851.
2. Ellwein LB and Urato CJ. Use of eye care and associated changes among medicare population: 1991 – 1998. Arch Ophthalmol 2002; 120: 804 – 811.

ORIGINAL ARTICLE

3. Rwt S, Tabin G, Chang D, Bajracharya L, Kline DC, Richhmer W et al. Prospective randomized clinical trial of phacoemulsification versus manual SICS in Nepal. *Am J Ophthalmol* 2007; 143: 32 – 38.
4. Gogate P, Deshpande M, Nirmala PK. Why do phacoemulsification, manual SICS is almost as effective, but less expensive. *Ophthalmology* 2007; 114 (5): 965 – 8.
5. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart disease and Stroke statistics – 2009 update: A report from the American Heart Association Statistics Committee and Stroke statistics subcommittee. *Circulation* 2009; 119: 480 – 486.
6. Gass JDM. A fluorescein angiographic study of macular dysfunction secondary to retinal vascular disease. *Arch Ophthalmol* 1968; 80: 569 – 572.
7. Mondal LK, Baidya KP Shaw CR, Bhaduri G. Biochemical derangement behind unexplained visual loss after uneventful small incision cataract surgery in hypertensive patients. *J Indian Medical Biochemistry*.
8. Drance SM. A comparison of the effects of betaxolol, timolol, and pilocarpine on visual function in patients with open-angle glaucoma. *J Glaucoma* 1998; 7: 247 – 252.
9. Vorwerk CK, Gorla MSR, Dreyer EB. An experimental basis for implicating excitotoxicity in glaucomatous optic neuropathy. *Surv Ophthalmol* 1999; 43: S 142 – S 150.
10. Osborne NN, Cazevielle C, Carvalho AL, Larsen AK, De Santis L. In vivo and in vitro experiments show that betaxolol is a retinal neuroprotective agent. *Brain Res* 1997; 751: 113 – 123.
11. Wood JP, De Santis L, Chao HM, Osborne NN. Topically applied betaxolol attenuates ischemia induced effects to the rat retina and stimulates BDNF mRNA. *EX Eye Res* 2001; 72: 79 – 86.
12. Griffiths PG, Eddyshaw D. Medically unexplained visual loss in adult patients. *Eye* 2004; 1: 196-200.
13. L K Mondal, K P Baidya, B Bhattacharya, A Giri, G Bhaduri. Relation between increased anaerobic glycolysis and visual acuity in long-standing type-2 diabetes mellitus without retinopathy. *Indian J Ophthalmol* 2006; 54 (1): 43 – 44.
14. Schoen FJ, Cotran RS. Blood vessels. IN: Cotran RS, Kumar V, Collins T, editors. *Pathologic basis of disease*. 6th ed. Philadelphia: W.B. Saunders Company; 1999. pp 514 – 15.
15. Hester RK, Chen Z, Becker EJ, Mclaughlin M, Desantis L. The direct vascular relaxing action of betaxolol, carteolol and timolol in porcine long ciliary artery. *Surv Ophthalmol* 1994; 38 (suppl): 125 – 34.
16. Harris A, Arend O, Chung HS, Kagemann L. A comparative study of betaxolol and dorzolamide effect on ocular circulation in normal tension glaucoma patients. *Ophthalmology* 2000; 107: 430 – 434.
17. Chidlow G, Melena J, Osborne NN. Betaxolol, a β_1 -adrenoceptor antagonist, reduces Na^+ influx into cortical synaptosomes by direct interaction with Na^+ channels: comparison with other β -adrenoceptor antagonists. *Br J Pharmacol* 2000; 130: 759 – 766.
18. Hiroshi Kobayashi, Kaori Kobayashi, Satoshi Okinami. Randomized clinical trial of topical betaxolol for persistent macular edema after vitrectomy and epiretinal membrane removal. *Am J Ophthalmol* 2003; 136: 244 – 51.
19. Arcieri ES, Santana A, Rocha FN, Guapo GL, Costa VP. Blood-aqueous barrier changes after the use of prostaglandin analogue in patients with pseudophakia and aphakia: a 6 month randomized trial. *Arch Ophthalmol* 2005; 123: 186 – 192.

ORIGINAL ARTICLE

20. Miyake S, Ota I, Ibaraki N, Akura J, Ichihashi S, Shibuya Y, Maekubo K, Miyake S. Enhanced disruption of blood-aqueous barrier and the incidence of angiographic cystoid macular oedema by topical timolol and its preservative in early postoperative pseudophakia. Arch Ophthalmol 2001, 119: 387 – 394.
21. Ghosh S, Roy Indranil, Biswas PN, Maji D, Mondal LK, Mukhopadhyay S, Bhaduri G. Prospective randomized comparative study of macular thickness following phacoemulsification and manual small incision cataract surgery. Acta Ophthalmologica 2010; 88: e102 – e106.

AUTHORS:

1. Lakshmikanta Mondal
2. Anindita Mondal
3. Krishna Pada Baidya
4. Goutam Bhaduri

PARTICULARS OF CONTRIBUTORS:

1. Professor, Department of Ophthalmology, Regional Institute of Ophthalmology, Medical College, Kolkata.
2. Associate Professor, Department of Ophthalmology, Regional Institute of Ophthalmology, Medical College, Kolkata.
3. Associate Professor, Department of Ophthalmology, Regional Institute of Ophthalmology, Medical College, Kolkata.

4. Professor, Department of Ophthalmology, Regional Institute of Ophthalmology, Medical College, Kolkata.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. L. K. Mondal,
Regional Institute of Ophthalmology,
Medical College, Kolkata.
E-mail: lakshmi.mondal62@gmail.com

Date of Submission: 31/01/2014.
Date of Peer Review: 01/02/2014.
Date of Acceptance: 07/02/2014.
Date of Publishing: 12/03/2014.