

ORIGINAL ARTICLE

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Epinephrine, but not dexamethasone, induces apoptosis in human retinal pigment epithelium cells *in vitro*

Possible implications on the pathogenesis
of central serous chorioretinopathy

ABSTRACT

Objective

The pathogenesis of central serous chorioretinopathy is poorly understood. It is believed to be due to dysfunction of the retinal pigment epithelium and/or choroid, and has been associated with elevated levels of epinephrine and administration of corticosteroids. Epinephrine and corticosteroids have previously been shown to induce apoptosis (programmed cell death) in various types of cells. It has also been shown that experimentally-induced central serous chorioretinopathy is associated with degeneration of the underlying retinal pigment epithelium. The objective of this study is to investigate whether epinephrine and dexamethasone, a corticosteroid, can induce apoptosis in cultured human retinal pigment epithelium cells. This may help elucidate the pathogenesis of central serous chorioretinopathy.

Methods

Third passage human retinal pigment epithelium cells were grown to confluence and incubated for 1 - 7 days in culture medium containing epinephrine (10^2 - 8×10^7 pg/ml) or dexamethasone (4 - 4×10^4 ng/ml). The cultures were evaluated for apoptosis by phase contrast microscopy and *in situ* terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling.

Results

Epinephrine (4×10^7 - 8×10^7 pg/ml) induced apoptosis in a dose- and time-dependent manner. Exposure to lower concentrations of epinephrine (10^2 - 2×10^7 pg/ml) and all tested levels of dexamethasone did not result in apoptosis.

Conclusions

Human retinal pigment epithelium cells may undergo apoptosis following exposure to elevated levels of epinephrine. These findings suggest a possible pathophysiologic mechanism for the development of central serous chorioretinopathy.

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APOPTOSIS (programmed cell death) is a gene-regulated process that plays an important role in the normal physiologic turnover of cells and in various pathological processes. It differs from necrosis in a variety of morphologic and biochemical features. Morphologic changes in necrosis include cell swelling, degradation of organelles, rupture of cell membranes, and spillage of cellular contents into the extracellular space, resulting in an inflammatory response.^{1,2,3} In contrast, apoptosis is characterized by condensation of the nucleus and cytoplasm, compaction and margination of chromatin, structural disorganization of the nucleus, and formation of cell fragments or "apoptotic bodies". Apoptotic bodies maintain intact organelles and cell membranes, and are engulfed by neighboring phagocytic cells, thus no inflammatory response is elicited.^{1,2,3,4} Biochemical changes in apoptosis are characterized by enzymatic cleavage of DNA by endogenous endonuclease, often into multiples of 180 - 200 base pairs.^{1,3,5} In necrosis, DNA is cleaved into segments of random length.⁶

Apoptosis may occur spontaneously or in response to physiologic stimuli which trigger cellular and molecular transformations that result in cell death. It may also be induced by a variety of exogenous toxic agents.^{1,2,3,4,5,7,8,9,10,11,12} In particular, it has been demonstrated that epinephrine can induce apoptosis in trabecular meshwork cells⁷ and thymocytes,⁸ and that corticosteroids can cause apoptosis in thymocytes,^{5,9,10} eosinophils,¹¹ and leukemia cells.¹²

The retinal pigment epithelium (RPE) performs a variety of functions, which include maintenance of homeostasis of the subretinal space and prevention of free water movement from choroid to retina. Central serous chorioretinopathy (CSCR) is a condition characterized by accumulation of fluid in the subretinal space, resulting in blurring of vision and metamorphopsia. The mechanism by which CSCR is caused is poorly understood. However, it is believed to result from dysfunction of the RPE and/or choroid.^{13,14,15,16,17}

CSCR has been noted to be more prevalent among "hard-driving, tense, type-A" individuals who have high levels of endogenous catecholamine (i.e., epinephrine).¹⁸ In experiments performed in monkeys, it has been shown that intravascular administration of epinephrine can induce CSCR, and that the RPE underlying areas of CSCR undergoes degeneration.¹³ CSCR has also been noted to develop following systemic,^{19,20,21,22,23} epidural²⁴ and inhalatory or intranasal²⁵ administration of corticosteroids. Whether apoptosis plays a role in the degeneration of human RPE cells and pathogenesis of CSCR has thus far not been investigated.

The aim of this study is to investigate whether epinephrine and dexamethasone, a corticosteroid, can induce apoptosis in human RPE cells *in vitro*. These findings may

help elucidate the pathophysiologic mechanisms involved in CSCR.

METHODOLOGY

Retinal Pigment Epithelium Cell Cultures

Primary RPE cell cultures were prepared from the eyes of human donors after securing the necessary consent. The donors ranged in age from 28 to 50 years. The cells were processed within 48 hours of death. Methods similar to those described by Sheu et al.²⁶ were used to harvest the cells. Each eye was incised along the equator, and the anterior segment and vitreous were removed. The retina was carefully peeled off and cut away from the optic disc. The posterior half of the globe was then incised radially and the RPE was mechanically scraped with a cell scraper. The RPE was transferred to culture medium consisting of Dulbecco's Modified Eagle's Medium with 10% fetal bovine serum and 1% penicillin-streptomycin (Gibco, Buffalo, NY, USA), and grown to confluence in 25 cm² tissue culture flasks (Greiner, Frickenhausen, Germany) maintained in an atmosphere of 5% carbon dioxide, 95% relative humidity, at a temperature of 37° C. Upon reaching confluence, the cells were trypsinized and subcultured in 75 cm² tissue culture flasks (Greiner, Frickenhausen, Germany). All cells used for the experiments were in the third passage and were grown to confluence on 4-well chamber slides (Lab-Tek/Nalge Nunc, Naperville, IL, USA).

All cells in the primary cell culture had regular polygonal epitheloid shapes and melanin granules, indicating that the cells were of homogenous RPE origin. In addition, the epithelial origin of the cultured RPE cells was confirmed by positive staining with mouse-derived anti-pancytokeratin Lu-5 (Dianova, Hamburg, Germany).

For cytokeratin staining, the following technique was used. RPE cultures were fixed in 4% paraformaldehyde in phosphate buffered saline (PBS) for 30 minutes. They were then rinsed in PBS and incubated in 1% bovine serum albumin (BSA) for 10 minutes to block non-specific binding sites. The cultures were subsequently incubated with antipancytokeratin antibody diluted in PBS (working dilution = 1:20) for 60 minutes in a humidified chamber at 37° C. Negative controls were obtained by substituting the antipancytokeratin antibody with PBS. Following incubation, the cultures were washed in PBS and incubated in a 1:100 dilution of fluorescein-conjugated rabbit antimouse antibody (Sigma, St. Louis, MO, USA) at room temperature for 45 minutes in a humidified chamber. The slides were given a final rinse with PBS, coverslipped using the Slow Fade Light Antifade Kit (Molecular Probes, Eugene, OR, USA) as a mounting medium, and viewed with a fluorescence microscope (Leica Model DMRBE, Heerbrugg, Switzerland).

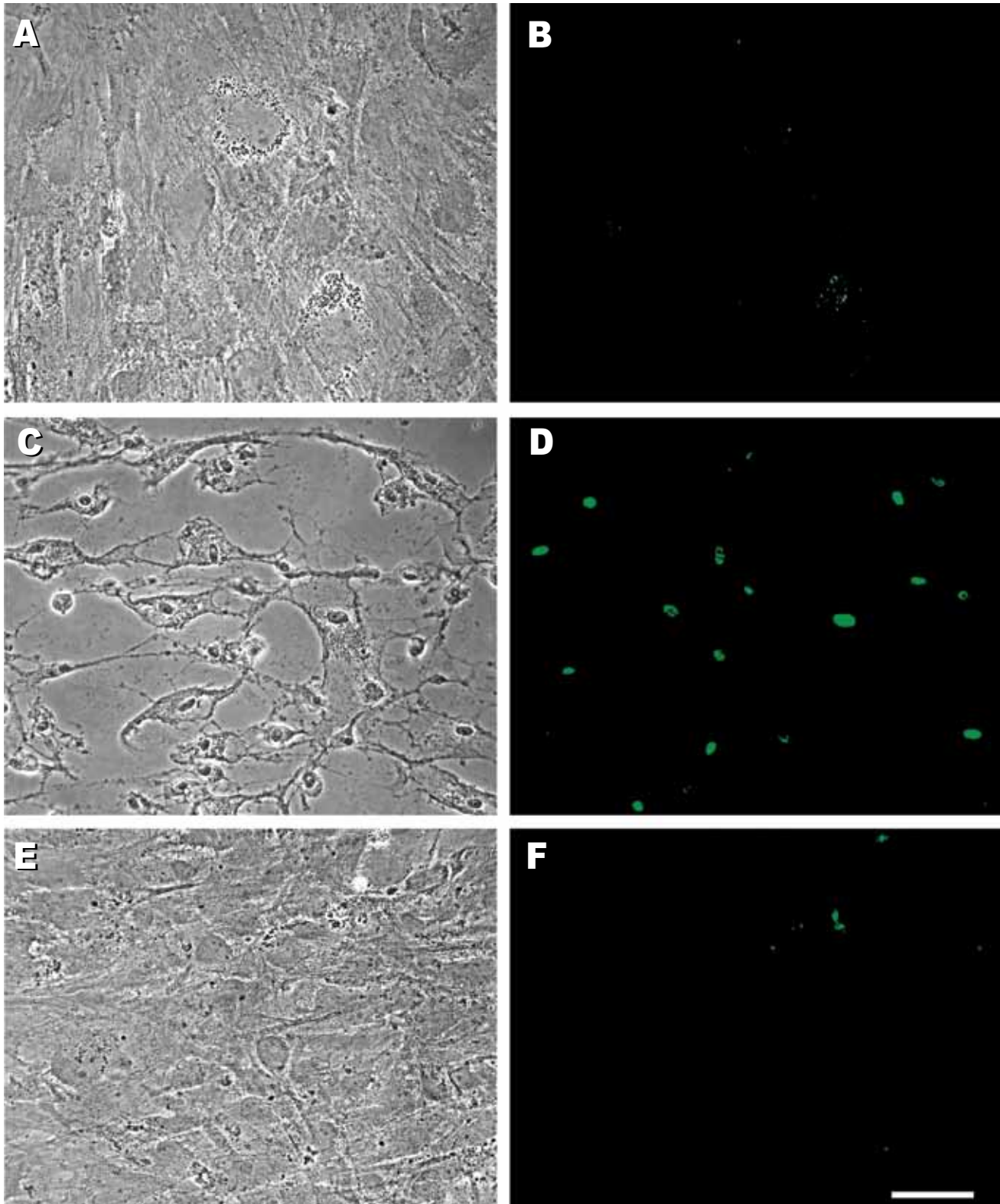


Figure 1. Phase contrast photomicrographs and fluorescent TUNEL labeling of drug-treated human RPE cells *in vitro*. (A) Control cells do not exhibit morphologic features characteristic of apoptosis. (B) The same field viewed under fluorescence does not demonstrate TUNEL staining. (C) Epinephrine-treated cells (6×10^7 pg/ml x 1 day) exhibit morphologic changes characteristic of apoptosis (condensation of the nucleus and cytoplasm; compaction and margination of chromatin). (D) The corresponding fluorescence photomicrograph shows positive TUNEL staining of nuclei. (E) Dexamethasone-treated cells (4×10^4 ng/ml x 7 days) do not exhibit morphologic changes characteristic of apoptosis. (F) TUNEL staining of dexamethasone-treated cells is also negative. (All photomicrographs - same magnification; bar = 50 μ m)

Drug Solutions

RPE cell cultures were incubated in the following drugs (Sigma, St. Louis, MO, USA) dissolved in the previously described culture medium at specified concentration ranges: epinephrine (10^2 - 8×10^7 pg/ml); dexamethasone (4 - 4×10^4 ng/ml). The drug concentrations used in this study are similar to those used in previous experiments involving cultured bovine trabecular meshwork cells.⁷ In addition, concentrations of epinephrine and dexamethasone similar to those found in circulating human plasma (epinephrine = 5×10^1 - 5×10^2 pg/ml²⁷; dexamethasone = 3.7 - 13.16 ng/ml following oral administration in normal subjects²⁸) were tested. Cell cultures incubated in drug-free culture medium served as controls. All experiments were performed in quadruplicate.

Morphology Studies

RPE cell cultures were evaluated serially for morphologic changes by phase contrast microscopy with the use of an inverted microscope (Olympus Model CK2, Tokyo, Japan).

In Situ Apoptosis Staining

RPE cells were processed for *in situ* apoptosis labeling using the terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) technique. The *In Situ* Cell Death Detection Kit (Boehringer Mannheim, Mannheim, Germany) was utilized. This assay is a histochemical stain that labels 3'-OH ends of DNA fragments that are generated during the process of apoptosis. Non-apoptotic cells have relatively insignificant amounts of 3'-OH overhangs, and thus are not stained.

The following is a summary of the *in situ* staining procedure. After incubation with the drugs, the RPE cell cultures were fixed with 4% paraformaldehyde in PBS for 30 minutes. The cells were subsequently washed three times in PBS for 5 minutes each wash. The PBS was aspirated, fluorescein-conjugated TUNEL reaction mixture was applied, and parafilm slips were placed over the specimens to spread the reagent evenly. The specimens were then incubated for 90 minutes in a humidified chamber at a temperature of 37° C. The parafilm slips were removed, the specimens were rinsed three times in PBS, and coverslips were applied on the slides using the Slow Fade Light Antifade Kit as a mounting medium. The slides were then examined with a fluorescence microscope.

Positive controls were obtained by incubating nondrug-treated RPE cells in DNase I (1 mg/ml) (Boehringer Mannheim, Mannheim, Germany) for 10 minutes at room temperature between the fixation and TUNEL reaction steps of the staining procedure.²⁹ Negative controls were obtained by substituting TUNEL reaction mixture with terminal-transferase-free label solution.

Quantitation of Apoptotic Cells

Quantitation of apoptotic cells was performed by counting the number of apoptotic cells per 200x field. This figure was divided by the total number of cells within the same field, yielding the percentage of apoptotic cells per specified field (the total number of cells per field ranged from 55 - 90 in the epinephrine series and 62 - 92 in the dexamethasone series). Statistical analyses were performed using the Student's *t*-test, with a *p* value less than 0.05 considered statistically significant.

RESULTS

Epinephrine

Following treatment with epinephrine (4×10^7 - 8×10^7 pg/ml), RPE cells underwent apoptosis, as evidenced by development of characteristic morphologic changes (condensation of the nucleus and cytoplasm; compaction and margination of chromatin) (Figure 1C) and positive TUNEL staining (Figure 1D). Apoptosis was induced in a dose- and time-dependent manner (Figure 2). Exposure to lower concentrations of epinephrine (10^2 - 2×10^7 pg/ml) for up to 7 days did not result in apoptosis.

Dexamethasone

No morphologic changes consistent with apoptosis were observed in any of the specimens treated with dexamethasone even after 7 days of incubation (Figure 1E). TUNEL staining was also negative in all specimens (Figure 1F).

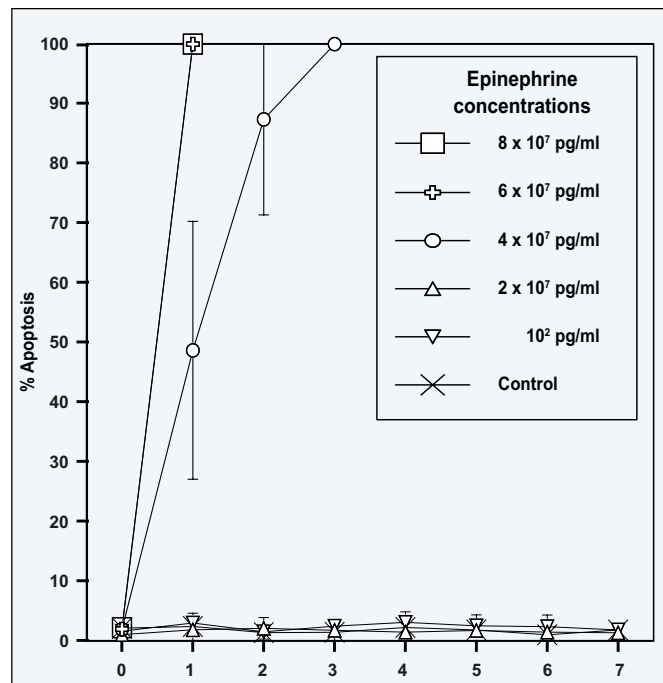


Figure 2. Epinephrine (4×10^7 - 8×10^7 pg/ml) induced apoptosis in RPE cells in a dose- and time-dependent manner. Lower concentrations (10^2 - 2×10^7 pg/ml) did not result in apoptosis even after 7 days of incubation. (Error bars represent standard deviation.)

DISCUSSION

Using a monkey model of epinephrine-induced CSCR, Yoshioka and Katsume¹³ have demonstrated degeneration of the RPE underlying areas of CSCR. Our finding that epinephrine can induce apoptosis in RPE cells may help substantiate this mechanism of degeneration and may contribute to the explanation of the pathogenesis of CSCR.

It has previously been shown that stimulation of beta-adrenergic receptors in RPE cells *in vitro* causes a net increase in cyclic adenosine 3',5'-monophosphate (cAMP) levels.³⁰ It has also been demonstrated that agents that elevate cAMP levels (i.e., epinephrine) can induce apoptosis.³¹ These findings suggest that apoptosis in RPE cells may be induced by a beta-adrenergic/cAMP-mediated process.

Clinical observations suggest that systemic administration of beta-blockers to patients with CSCR may improve vision and hinder recurrence of CSCR.³² If RPE cell apoptosis indeed occurs in CSCR, these observations further support the hypothesis that it is mediated by a beta-adrenergic mechanism.

Another possible mechanism by which apoptosis could be induced may involve oxidative byproducts of epinephrine. Epinephrine is metabolized by monoamine oxidase (MAO) into 3,4-dihydroxyphenylglycolaldehyde (DOPEGAL) and hydrogen peroxide,³³ both of which could act as inducers of apoptosis.^{33,34,35} Experimental evidence suggests that MAO is present in RPE cells.³⁶ RPE cells could therefore metabolize epinephrine and undergo apoptosis in response to its metabolites.

Drug doses used in toxicity studies include high, intermediate and low levels of a test compound. High doses allow one to observe toxic effects more readily.³⁷ In the current study, epinephrine levels at which apoptosis was observed were 8×10^4 to 1.6×10^6 times higher than endogenous *in vivo* levels. Since apoptosis could be difficult to detect due to its rapid kinetics and the relative paucity of cells that undergo apoptosis at any specific time point,³⁸ the administration of such high drug doses could facilitate observation of this process. Further toxicokinetic studies would however be necessary to determine how these high-dose acute findings correlate with the *in vivo* situation where prolonged exposure to lower drug levels is present.³⁷

Dexamethasone did not induce apoptosis at any of the tested concentrations. However, corticosteroids may cause an upregulation of adrenergic response by increasing the number of adrenergic receptors and/or increasing the responsiveness of each receptor.³⁹ A corticosteroid-induced increase in adrenergic response could possibly result in a cAMP-mediated apoptotic response similar to that observed in epinephrine-treated cells, and could

also account for CSCR observed following treatment with corticosteroids. Such responses however could not be evaluated in these studies since no adrenergic agents were present in the cell cultures treated with dexamethasone.

Although the pathophysiology of CSCR is poorly understood, various theories regarding its pathogenesis have been proposed. Spitznas¹⁴ hypothesized that it is due to a cAMP-mediated reversal of the RPE fluid pumping action. According to this model, fluid is pumped in a chorioretinal, instead of a retinochoroidal direction. This leads to accumulation of fluid in the subretinal space. Initially, the fluid movement occurs transcellularly. However, the diffusion barrier (i.e., RPE) eventually breaks down, leading to direct leakage of fluid into the subretinal space. Although Spitznas proposed that the disruption of the barrier is due to strong fluid flow, it could also be due to degeneration of the RPE. Applying our findings to this model, the increase in cAMP could account not only for the reversal of the pumping action, but also for the breakdown of the diffusion barrier.

Gass¹⁵ suggested that CSCR is due to focal areas of increased permeability in the choriocapillaris. Yoshioka and Katsume¹³ and Marmor^{16,17} proposed that defects in both the choroid and RPE are necessary for leakage of fluid into the subretinal space. The latter proposal is supported by the experimental observation that, in addition to degeneration of the RPE, diaphragms of the fenestrated endothelial cells on the inner surface of the choriocapillaris disappear.¹³ These defects in the choroid and RPE create a pressure head, resulting in such leakage. While our findings cannot fully explain the observed anatomic changes and proposed pathophysiologic mechanisms involved in CSCR, they could contribute to the explanation of the RPE component of this condition.

Whether epinephrine causes CSCR by inducing apoptosis in RPE cells *in vivo* cannot be determined from this study. However, our findings provide a possible pathophysiologic mechanism for this poorly understood disease entity.

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ORIGINAL ARTICLE

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A prospective, randomized clinical trial comparing the effects of three viscoelastics on the corneal endothelium after cataract surgery

ABSTRACT

Objective

To compare the effects of Amvisc Plus (AP), Duovisc (DV), and Viscoat (VC) on the corneal endothelium of patients who have undergone uncomplicated phacoemulsification cataract surgery.

Methods

This is a prospective, randomized trial that involved 60 eyes of 48 patients with age-related cataracts. The eyes were randomly assigned to receive AP, DV, or VC during phacoemulsification. The main outcome measures were postoperative intraocular pressure (IOP), endothelial cell counts, and corneal thickness.

Results

The mean postoperative IOP were 15.13 ± 2.99 mmHg in the AP group, 15.42 ± 2.35 mmHg in the DV group, and 14.86 ± 5.56 mmHg in the VC group. The average postoperative endothelial cell counts were 2531 ± 420 cells/mm² in the AP group, 2330 ± 674 cells/mm² in the DV group, and 2678 ± 471 cells/mm² in the VC group. The mean postoperative corneal thickness measurements were 566 ± 49 μ m for the AP group, 561 ± 21 μ m for the DV group, and 552 ± 27 μ m for the VC group. No significant differences in all parameters were noted among the three groups.

Conclusion

The results of this study suggest that AP, DV, and VC may be comparable in terms of their ability to protect the corneal endothelium during phacoemulsification.

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PRIOR to the use of viscoelastic materials (VEMs), corneal edema was the most common cause of failed cataract surgery.¹ Postoperative corneal edema or corneal decompensation results from corneal endothelial damage during surgery.^{2,3} The introduction of VEMs in the 1970s greatly improved the outcome and safety of anterior segment surgery. The use of VEMs facilitates lens implantation by deepening the anterior chamber, protecting the corneal endothelium and iris surfaces from mechanical and thermal damage, and absorbing offending molecules on the surface of intraocular lenses (IOL).

VEMs are classified as being either cohesive or dispersive. Cohesive agents have high molecular weights and surface tension. They are primarily used to maintain the anterior chamber. Dispersive agents, meanwhile, have lower molecular weights and surface tension. They are primarily used to protect the corneal endothelium. Different VEM products and formulations have already been developed. These include sodium hyaluronate and chondroitin sulfate.⁴⁻¹²

Combining the use of cohesive and dispersive agents during surgery has been advocated by some authors.¹³ While many previous studies have compared the protective abilities of other products, the authors of this study believe that this is the first simultaneous comparison of Amvisc Plus (AP) (1.6% sodium hyaluronate, Bausch & Lomb, Rochester, NY, USA), Viscoat (VC) (3% Na hyaluronate + 4% chondroitin sulfate, Alcon, Fort Worth, TX, USA), Duovisc (DV) (a dual system consisting of Viscoat and Provisc [1% sodium hyaluronate], Alcon, Fort Worth, TX, USA).

Parallel improvements in phacoemulsification techniques and instrumentation have also enhanced the safety and efficiency of cataract surgery. In the light of these advances, the authors conducted this study to determine whether the choice of VEM has a critical effect on endothelial cell count and corneal edema following cataract surgery.

METHODOLOGY

Adult patients from the University of the Philippines-Philippine General Hospital and the Asian Eye Institute who were scheduled to undergo phacoemulsification cataract surgery were prospectively enrolled in the study. Patients with a history of corneal pathology, corneal decompensation, trauma, glaucoma, and uveitis were excluded from the study. Also excluded were eyes with intraocular pressure (IOP) higher than 22 mmHg as measured via Goldmann's applanation tonometry, endothelial cell count of under 700 cells/mm², and corneal thickness of more than 650 μm. Sixty eyes of 48 patients were included in the study.

Approval of the study protocol and informed consent

were obtained from the Institutional Review Board of the two centers prior to the start of the study.

Measurements

All patients underwent a standard preoperative eye examination, which included history taking, visual acuity measurement, IOP measurement, and biomicroscopic examination of the anterior and posterior segments. The following data were collected in preoperative and postoperative periods: best corrected visual acuity (BCVA), IOP, central corneal thickness (CCT) as measured by ultrasonic corneal pachymetry (Pachette 2, DGH, Exton, PA, USA), and corneal endothelial cell density as measured by noncontact specular microscopy (SP1000, Topcon Corporation, Japan).

A single observer (KEB), masked as to which treatment group a patient belonged in, interpreted specular microscopy results and determined the endothelial cell count. Masked observers measured visual acuity and IOP, as well as graded cataract nuclear density according to the Lens Opacities Classification System II (LOCS II).¹⁴ There were no statistically significant differences in preoperative visual acuity, IOP, endothelial cell count, and corneal thickness among the three groups (Table 1).

Surgical Technique

At the time of surgery, the patients were randomly assigned to one of three VEM treatment groups using a random number generator. Twenty-two (36 %) of 60 eyes were assigned to receive AP, 19 (32 %) were assigned to receive VC, and 19 (32 %) were assigned to receive DV. Because of unique packaging and handling properties concerning the agents used, it was not possible to mask the surgeon as to which VEM was used.

All surgeries were performed by a single surgeon (HSU). Phacoemulsification was performed under topical anesthesia using proparacaine 0.5%. A side port was made with a 15-degree keratome. The assigned VEM was injected through the side port until the anterior chamber was filled. For eyes assigned to receive DV, the Viscoat component

Table 1. Baseline preoperative characteristics of eyes within each viscoelastic material (VEM) group (N = 60 eyes)

Parameter	Amvisc Plus	Duovisc	Viscoat	ANCOVA*
Visual acuity (decimal units)	0.32 ± 0.27	0.24 ± 0.21	0.24 ± 0.21	p > 0.468
IOP (mmHg)	15.58 ± 0.76	14.44 ± 0.74	14.00 ± 0.81	p > 0.335
Cell count (cells/mm ²)	2692.50 ± 545	2440.00 ± 610	2918.89 ± 299	p > 0.05
Corneal thickness (μm)	546 ± 41	544 ± 34	544 ± 23	p > 0.969

*Analysis of covariance

was used to fill the anterior chamber. A clear corneal incision was made using a 3.2mm keratome. Continuous curvilinear capsulorhexis was done, followed by hydrodissection and hydrodelineation with balanced saline solution. Phacoemulsification was performed using the same machine for all eyes (Legacy 2000, Alcon Laboratories, Fort Worth, TX, USA). Nuclear disassembly was performed using a stop-and-chop technique.

After removing the remaining cortical material using an irrigation and aspiration (I/A) probe, the anterior chamber and capsular bag were filled with viscoelastic. For the DV group, the Provisc component was used to fill the chamber prior to insertion of the IOL. All eyes were implanted with a foldable one-piece acrylic IOL. The VEM was removed using I/A until the anterior chamber was cleared of all visible VEM. The phacoemulsification time, ultrasound power, and total operative time were recorded (Table 2). The patients were examined on the first, eighth, and fifteenth days after the operation.

Statistical Analysis

An analysis of covariance (ANCOVA) model was used to evaluate differences in visual acuity, intraocular pressure, endothelial cell count and pachymetry after adjusting for patient factors, surgery time, phacoemulsification time, phacoemulsification power, gel type, nuclear sclerosis, and period of observation. Tukey's multiple comparison procedure was used to perform post-hoc analysis during the follow-up period. A significance level of 0.05 was used to test all hypotheses.

RESULTS

The mean patient age was 67 ± 12 years (Figure 1). Eighteen patients (37.5%) were male. Thirty-seven (70%) patients underwent single-eye surgery while the rest underwent bilateral surgery.

The main outcome measures included postoperative visual acuity, IOP, endothelial cell count, and corneal thickness (Table 3).

The mean visual acuity in decimal units on Day 15 were 0.75 ± 0.21 in the AP group, 0.74 ± 0.21 in the DV group, and 0.83 ± 0.25 in the VC group. Visual outcomes were not affected by the type of VEM used during surgery when other factors were kept constant ($p > 0.740$). Patient factors and period of follow-up demonstrated statistical significance in the differences in visual acuity ($p < 0.001$).

Post-hoc analysis using Tukey's method demonstrated that visual acuity significantly improved on Days 1, 4, 8, and 15 after surgery. From baseline, there was an average of 0.5 units (50%) of improvement on Day 1, 0.8 units (80%) of improvement by Day 8, and 0.4 units (40%) on Day 15. This suggests that the best improvement in vision after phacoemulsification was achieved between Day 1 and

8. The amount of visual improvement declined after Day 8 regardless of VEM used and phacoemulsification time and power.

The mean postoperative IOPs on the first postoperative day were 15.13 ± 2.99 mmHg in the AP group, 15.42 ± 2.35 mmHg in the DV group, and 14.86 ± 5.56 mmHg in the VC group. Postoperative IOP was not affected by the type of VEM used during surgery ($p > 0.347$). Surgical factors (phacoemulsification time and power, surgical duration) had no effect on IOP ($p > 0.206$). Only patient factors such as age and cataract density had an effect on IOP ($p = 0.007$). The model accounted for 59.2% of the variability in IOP.

The average endothelial cell counts on Day 15 were 2531 ± 420 cells/mm² in the AP group, 2330 ± 674 cells/mm² in the DV group, and 2678 ± 471 cells/mm² in the VC group (Table 4). Regardless of VEM type, analysis of within-

Table 2. Cataract nuclear density grading and surgical parameters during phacoemulsification using three different VEMs (N = 60 eyes)

Parameter	Amvisc Plus	Duovisc	Viscoat	ANCOVA*
Nuclear sclerosis	2.2 ± 0.8	2.4 ± 0.8	2.4 ± 0.8	$p > 0.50$
Phaco time (mins)	1.23 ± 0.66	1.41 ± 0.68	1.25 ± 0.71	$p > 0.41$
Phaco power (%)	15.82 ± 6.11	15.50 ± 3.49	14.16 ± 5.44	$p > 0.31$
Surgery duration (mins)	19.73 ± 6.48	21.47 ± 6.42	19.21 ± 5.55	$p > 0.26$

*Analysis of covariance

Table 3. Postoperative characteristics of eyes within each VEM group (N = 60 eyes)**

Parameter	Amvisc Plus	Duovisc	Viscoat	ANCOVA*
Visual acuity (decimal units)	0.75 ± 0.21	0.74 ± 0.21	0.83 ± 0.25	$p > 0.740$
IOP (mmHg)	15.13 ± 2.99	14.42 ± 2.35	14.86 ± 5.56	$p > 0.335$
Cell count (cells/mm ²)	2531 ± 420	2330.00 ± 674	2678 ± 471	$p > 0.05$
Corneal thickness (m)	566 ± 49	561 ± 21	552 ± 27	$p > 0.992$

*Analysis of covariance

**Values measured on day 15 except IOP, which was measured on first postoperative day

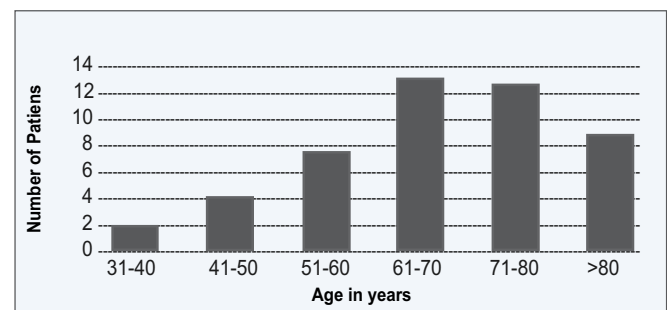


Figure 1. Age distribution of patients undergoing cataract surgery (n=48)

Table 4. Preoperative and postoperative endothelial cell count (cells/mm²)

VEM	Preoperative	Postoperative	Change (%)
Amvisc Plus	2692	2531	- 6.0
Duovisc	2440	2330	- 4.5
Viscoat	2919	2678	- 8.3

Table 5. Preoperative and postoperative corneal thickness (mm)

VEM	Preoperative	Postoperative	Change (%)
Amvisc Plus	546	566	+ 3.7
Duovisc	544	561	+ 3.1
Viscoat	544	552	+ 1.5

subjects effects showed a significant decrease in cell count, with a mean of 167 cells/mm², between baseline and Day 1.

Endothelial cell counts were not affected by type of VEM used during cataract surgery, when other independent variables were kept constant ($p > 0.05$). Phacoemulsification time ($p = 0.522$), power ($p = 0.631$), and surgical duration ($p = 0.143$) had no significant effect on endothelial cell count after surgery. However, patient factors, nuclear sclerosis, and follow-up period independently but significantly affected cell count ($p < 0.001$). The model accounted for 94.5% of the variability in cell count regardless of VEM type.

The mean corneal thickness measurements on Day 15 were 566 ± 49 μ m for the AP group, 561 ± 21 μ m for the DV group, and 552 ± 27 μ m for the VC group (Table 5). Postoperative corneal thickness measurements did not differ significantly among the VEM groups ($p > 0.992$). Postoperative corneal thickness was independent of phacoemulsification time ($p = 0.536$) and power ($p = 0.326$), surgical duration ($p = 0.996$), and nuclear sclerosis ($p = 0.286$). Patient factors and period of follow-up significantly affected postoperative corneal thickness ($p < 0.001$).

DISCUSSION

Endothelial cell loss is a primary indicator of corneal injury. Since endothelial cells do not regenerate, adjacent cells expand to fill in the gaps. As a result, endothelial cell density or count decreases and cell size increases in response to injury. Endothelial cell hexagonality and corneal thickness have been shown to increase as a result of corneal stress.^{2, 3}

Corneal thickness is regulated partly by active transport of ions across endothelial cell membranes. Chemical, thermal, or mechanical insult that interferes with endothelial cell function may disturb its pump function, resulting in corneal edema.

VEMs are used to protect the corneal endothelium during anterior segment surgery. While several products are available, it is unclear which products provide the best protection. Numerous studies have compared the perfor-

mance of cohesive and dispersive types of viscoelastics during phacoemulsification. However, these studies have yielded mixed results. It has been suggested that dispersive viscoelastics provide better coating and protection of the endothelium while the use of cohesive agents, which are more easily removed from the anterior chamber, results in a decreased frequency of postoperative IOP rise. Other reports suggest that dispersive and cohesive agents do not differ significantly in terms of endothelial cell protection and tendency to cause postoperative IOP rise.^{6-12, 15-17}

Glasser et al.⁶ and Probst et al.¹⁵ found no significant differences in endothelial cell loss after phacoemulsification using either Amvisc Plus or Viscoat. These studies found that Viscoat has a higher likelihood of being retained during surgery and may confer better endothelial cell protection.

The necessity of removing VEM completely at the end of the surgery to prevent postoperative IOP rise has also been investigated.¹⁵⁻¹⁷ Davis and coauthors compared AP, VC, and OcuCoat (Bausch & Lomb, Rochester, NY, USA) and found that postoperative visual acuity and corneal thickness were similar, no matter what VEM was used.¹²

It is possible that advances in phacoemulsification instrumentation and techniques may have sufficiently improved the safety and efficiency of cataract surgery such that the type of VEM used is of secondary importance. This belief is supported by a recent study by Kiss et al. It revealed similar changes in corneal edema and endothelial cell morphology, whether the VEM used during phacoemulsification was expensive or low-cost.¹⁸

The results of this study support the findings of Kiss et al., showing that similar corneal endothelial and IOP changes occur regardless of the VEM used. The results of this study also suggest that other factors, such as patient age and degree of nuclear sclerosis, may be important determinants affecting the way the corneal endothelium recovers from surgery. The process of endothelial damage is likely to be multifactorial in nature. Surgical skill and technique are also likely to be important factors in determining surgical outcomes.

While this study suggests that the type of VEM may not be critically important in most surgeries, it is possible that the type of VEM used may be important in selected situations such as in Fuchs's endothelial dystrophy as well as other instances where there is endothelial compromise. More studies are needed to determine whether any VEM offers additional safety advantages in these selected cases.

This study shows that the type of VEM used does not significantly affect postoperative IOP, endothelial cell count, and corneal thickness after uncomplicated phacoemulsification with foldable intraocular lens implantation.

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ORIGINAL ARTICLE

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Association of ocular manifestation and disease activity among Filipinos with systemic lupus erythematosus

ABSTRACT

Objective

To determine the distribution of ophthalmologic manifestations of systemic lupus erythematosus (SLE) in Filipinos and correlate them with disease activity.

Methods

SLE patients seen at the Rheumatology Section of the Philippine General Hospital (PGH) underwent complete work-up to determine disease activity and referred for a comprehensive ocular evaluation at the Department of Ophthalmology. One ophthalmologist performed all ocular examinations. The findings were correlated to disease activity using the chi-square test.

Results

Seventy-eight (78) patients diagnosed with SLE were included in the study. Ninety-eight percent (98%) were female. The mean age of the study population was 31.73 ± 9.58 years. The mean duration of the disease was 3.63 ± 3.70 years. The mean disease activity index was 10.36 ± 8.35 . Most of the patients (84.4%) had no ocular complaints at the time of examination. Posterior subcapsular cataract (PSC) was the predominant ocular finding in patients with no disease activity, occurring in 14.3% of patients. PSC was also the most common ocular finding in patients with mild to moderate disease activity (21.4%) and lupus retinopathy (16.7%) in those with greater disease activity.

Conclusions

Ocular manifestations among Filipinos with SLE include lupus retinopathy, optic atrophy, glaucoma, periorbital edema, keratoconjunctivitis sicca, and posterior subcapsular cataract. PSC was the most common ocular finding in patients with mild to moderate disease activity and lupus retinopathy in those with greater disease activity.

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SYSTEMIC lupus erythematosus (SLE) is a chronic, immunologic disorder that affects multiple organ systems. It is characterized by hyperactivity of the immune system and prominent autoantibody production. The disease can manifest in many forms, ranging from mild cutaneous or joint involvement to more serious and lethal involvement of the kidney, heart, and brain.¹

The estimated incidence of SLE ranges from 1.8 to 20 cases per 100,000 per year. Almost 80 to 90% of SLE patients are women. The average age of onset is 30, with a range from infancy to old age.¹ The ten-year mortality in SLE is 71%.² Renal failure and septicemia are the main causes of death.¹

Diagnosis of SLE is arrived at if four or more of the following criteria are present: malar rash, discoid rash, photosensitivity, oral or nasopharyngeal ulcers, nonerosive arthritis, serositis, renal disorder, neurological disorder, hematological disorder, immunological disorder, and presence of antinuclear antibodies.² Patients with SLE may present with various systemic manifestations. The general symptoms include fever, malaise, arthralgia, myalgias, headache, and loss of appetite and weight.²

Several ways of scoring disease activity have been proposed. The most widely used was introduced by Bombardier et al. in 1992. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was developed to standardize outcome measures in SLE. Three indices that could adequately describe outcome (disease activity, damage from disease, and health status) were identified. Twenty-four variables were identified as important factors in a disease activity index, including clinical and laboratory findings, which were rated on a disease activity scale of 0 to 10 by 14 rheumatologists. This yielded a "weighted" index for 9 organ systems (the SLEDAI) as follows: 8 for central nervous and vascular systems; 4 for renal and musculoskeletal; 2 for serosal, dermal, and immunologic; and 1 for constitutional and hematologic. The maximum theoretical score is 105. SLE has *no disease activity* if the score is 0, *mild to moderate* if ≤ 10 , and *greater disease activity* if >10 .³

Dysfunction in immune regulation plays a major role in the pathogenesis of SLE. Hyperactivity of B-cells, producing a spectrum of autoantibodies is mainly responsive to the immune dysregulation, although T-cells are involved as well. The tissue injury is caused by immune complexes, deposition of which induces cell infiltration and damage to the tissue by proteolytic and collagenolytic enzymes. Histopathology of affected tissues reveals vasculitis with fibrinoid necrosis and deposition of immunoglobulin and complement in small vessels and capillaries.²

The ophthalmic manifestations of SLE range from lesions of the eyelid to sight-threatening disorders such as retinal vascular diseases and neuro-ophthalmic involve-

ment. Keratoconjunctivitis sicca and lupus retinopathy are frequent.⁴ Blindness is rare in SLE, and may be caused by retinopathy in severe cases.⁵

Several studies on the ocular manifestations of SLE among Caucasians^{1,4} and Asians⁶ have been done, but there are no data among Filipinos. This study determined the distribution of ophthalmologic manifestations of SLE in Filipino patients seen at the University of the Philippines-Philippine General Hospital (UP-PGH), and correlated these with disease activity.

METHODOLOGY

Consecutive patients who were newly diagnosed with SLE based on the criteria set by the American College of Rheumatology and patients with SLE who were being followed up by the Rheumatology Section of the Department of Medicine, University of the Philippines-Philippine General Hospital were recruited into the study from August 2002 to June 2003. The disease activity score (SLEDAI) was determined for each patient by the rheumatologists.

The patients were referred to the UP-PGH Department of Ophthalmology and Visual Sciences for a comprehensive ocular examination consisting of (1) detailed ocular history, (2) best corrected visual acuity, (3) applanation tonometry, (4) gross examination, (5) extraocular muscle evaluation, (6) slit-lamp examination, (7) indirect ophthalmoscopy, (8) examination of the cornea and conjunctiva following installation of rose bengal stain in the conjunctival sac (9) Schirmer's Test I, (10) gonioscopy and (11) color vision testing using the Ishihara's Color Vision Chart (Kanehara, Tokyo, Japan). All patients with ocular manifestations were referred to the appropriate subspecialty and managed accordingly.

Excluded from the study were patients who were incoherent and unable to complete the standardized ocular examination, those who had preexisting retinal lesions, and those who required examination under general anesthesia.

Ocular findings in those with no disease activity, mild to moderate disease activity, and severe disease activity were compared using the chi-square test.

RESULTS

Eighty-one (81) patients diagnosed with SLE were recruited into the study. Seventy nine (98.0%) were female and 2 (2%) male. Three (3) patients (2 females and 1 male) were excluded from the study for failure to complete the examination. The mean age of the study population was 31.73 ± 9.58 years with a range of 19 to 63 years. The mean duration of the disease was 3.63 ± 3.70 years with a range of 1 to 18 years. The remaining 78 patients were divided into 3 groups based on their disease activity index score determined by the rheumatologists (Table 1). Most were in the mild to moderate disease activity group (36%) and greater

Table 1. Distribution of SLE patients by disease activity

Disease Activity	Male	Female	Total	Activity Index
No Activity	1	13	14	0
Mild to Moderate	-	28	28	6.96 ± 2.33 (4-10)
Greater	-	36	36	18.37 ± 6.04 (11-32)

Table 2. Visual acuity of SLE patients according to disease activity

Visual Acuity	No Disease Activity (n=14) (no. of eyes)	Mild to Moderate Disease Activity (n=28) (no. of eyes)	Greater Disease Activity (n=36) (no. of eyes)
20/30 or better	24	46	62
20/50 or better	2	9	4
20/70 or better	-	3	5
Counting Fingers	2	1	1
Hand Movement	-	1	-

Table 3. Mean tear measurement by Schirmer's test of SLE patients according to disease activity

Disease Activity	Mean Measurement of Tears (mm)		Range (mm)	
	OD	OS	OD	OS
No Activity	15.57 ± 2.27	15.07 ± 2.28	13 - 20	13 - 20
Mild to Moderate	16.54 ± 2.78	17.25 ± 2.78	13 - 23	13 - 23
Greater	16.83 ± 4.33	17.33 ± 3.85	7 - 24	9 - 24

p > 0.500, OU

Table 4. Distribution of fundus findings of patients diagnosed with SLE according to disease activity

Fundus Findings	No Disease Activity (n=1)	Mild to Moderate Disease Activity (n=3)	Greater Disease Activity (n=6)
Soft Exudates	-	+	+
Hemorrhage	+	-	+
Vasculitis	+	+	-
Ghost Vessels	-	+	-
Vitreous Hemorrhage	-	+	+
Optic Atrophy	+	+	+
Preretinal Membrane	-	+	+

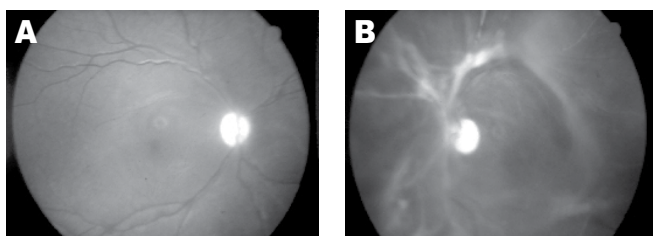


Figure 1. Fundus photos of a 27-year-old female with SLE of mild to moderate disease activity for 8 years: optic atrophy and vasculitis in the right eye (A), optic atrophy with preretinal membranes on the vascular arcades in the left eye (B).

disease activity (46%) with mean disease activity index of 10.36 ± 8.35.

Most of the patients (75.6%) were previously diagnosed cases of SLE undergoing follow-up while 24.4% were recently diagnosed cases. 84.7% of those previously diagnosed were outpatients while 73.7% of the new cases were inpatients.

Sixty-five of the patients were asymptomatic at the time of examination while 13 complained of blurring of vision of 1 to 84 months duration.

Most eyes (84.6%) had a visual acuity of 20/30 or better. Fifteen (9.61%) of 156 eyes had a visual acuity of 20/50 or better. Eight (5.13%) of 156 eyes had a visual acuity of 20/70 or better. Visual acuity of counting fingers was seen in 2.56% of eyes. Only 1 eye had a visual acuity of hand movement (Table 2).

There was no difference (*p* > 0.5) in mean intraocular pressure (IOP) of the 3 patient groups (range of 10-20 mmHg).

Fifty percent of the patients who had posterior subcapsular cataracts had mild to moderate disease activity.

There was no difference (*p* > 0.5) in the mean tear measurement by Schirmer's Test I in the 3 patient groups (Table 3). One patient had a measurement of less than 10mm and staining of the conjunctiva using rose bengal. This patient had a disease activity index score of 14.

Lupus retinopathy was present in 10 (12.8%) out of 78 patients. Most of them (60%) were in the greater disease activity group (Table 4). One patient with no disease activity had a visual acuity of counting fingers on both eyes, hemorrhages in one eye, and vasculitis in both eyes. Bilateral optic atrophy was present.

Three patients with mild to moderate disease activity had lupus retinopathy. One patient had vitreous hemorrhage in one eye and ghost vessels in the other. Another had optic atrophy and vasculitis in both eyes. Preretinal membranes along the vascular arcade were seen in the left eye (Figure 1). One patient with greater disease activity had periorbital edema in both eyes. None had abnormal color vision.

DISCUSSION

The prevalence of ocular manifestations in patients with SLE varies from one study to another. The most common ocular finding reported was dry eye.⁶ In our study, however, only one patient exhibited dry eye, defined as an abnormal Schirmer's test and positive rose bengal staining. Though keratoconjunctivitis sicca (KCS) or dry eye is strongly associated with HLA-DRW52 antigen and Anti-Ro (SSA) and Anti-La (SSB) antibodies,¹ there are no clinical studies to date establishing this association. Another way of establishing the presence of KCS is through lacrimal gland biopsy, but it was abandoned for being invasive.

The correlation between corticosteroid and posterior subcapsular cataract (PSC) is well documented.⁴ This occurs whether the corticosteroid administered is topical or systemic, but is more common with the latter. PSC development is related to duration of use, dosage, and patient susceptibility. In a study by Yap et al., 14 out of 70 patients diagnosed with SLE had PSC.⁶

In this study, two patients with no disease activity had PSC and had used oral steroids for a mean period of 15.86 months. In the mild to moderate disease activity group, 6 patients had PSC and their mean duration of corticosteroid use was 20 months. In the greater disease activity group, four patients had PSC and their mean duration of oral corticosteroid use was 85 months. However, most patients with mild to moderate disease activity had longer oral steroid use (56 months average) than patients with greater disease activity (24.5 months). Overall, 12 (15.4%) out of 78 patients were found to have posterior subcapsular cataracts related to steroid use.

Retinal involvement in SLE is a common ocular manifestation. A prospective clinical study showed that 88% of patients with lupus retinopathy had active disease.⁴ The retina is often involved and the appearance and disappearance of retinal lesions parallel the course of the disease. Cotton-wool spots and retinal hemorrhages are the most frequently reported findings.⁵ Other findings include retinal edema, hard exudates, microaneurysms, arterial narrowing, venous engorgement, and vascular thrombosis.

Retinopathy is believed to reflect vascular damage from vasculitis or thromboembolism. Hemorrhages may be caused by vasculitis, thromboembolism, or hypertension. Pathological examination of cotton-wool spots discloses disciform thickening of the retinal nerve fiber layer.⁷ Vasculitis and microaneurysm of the retinal arteries may cause destruction of the vessel walls or nerve fiber layer or both, resulting in the formation of cotton wool spots. In this study, exudates in the form of cotton wool spots were seen mostly in patients with greater disease activity. This is consistent with other studies^{5, 7} where vasculitis, hemorrhages, and vitreous hemorrhage predominate. Preretinal membranes that might be evidence of proliferative lupus retinopathy were seen in this study.

Vitreous hemorrhage, which is usually seen in cases with proliferative lupus retinopathy, was present in 2 eyes. This is believed to be due to retinal neovascularization secondary to severe retinal ischemia.^{5, 8}

Optic atrophy was present in 5 eyes in 3 patients, 1 patient from each group. Direct involvement of the optic

nerve may occur as acute retrobulbar neuritis, acute anterior optic neuropathy, or anterior ischemic neuropathy. Both optic neuropathy and retinal occlusive disease may result in optic atrophy, the latter being the more plausible explanation on the prevalence of optic atrophy in this study. Reported retrochiasmatal visual problems in lupus include geniculocalcarine blindness, homonymous hemianopsia, visual hallucinations and transient amaurosis.⁴ These neuro-ophthalmologic findings were not evident in this study.

Glaucoma is a known complication of corticosteroid treatment. Systemic corticosteroid may cause a rise in IOP in some individuals. In this study, one patient had elevated IOP in both eyes attributed to corticosteroid use. No study is available on the direct relationship of SLE with the trabeculum or ciliary body.

Ocular symptoms and findings are not currently part of the diagnostic criteria of SLE. Since the mortality rate is high, it is important that ophthalmologists recognize patients with SLE so that they could be properly treated and monitored. Rheumatologists and other specialists must not ignore ocular manifestations of SLE in the diagnosis and monitoring of disease activity.

In summary, systemic lupus erythematosus is a chronic immunologic disorder that may affect multiple organ systems. The most common ocular manifestation found among Filipinos diagnosed with SLE was lupus retinopathy, occurring in 10 (12.8%) of 78 patients seen. Sixty percent of this occurred in patients with greater disease activity. Optic atrophy occurred in 3 (3.8%) out of 78 patients and retinal vaso-occlusive disease was the probable etiology. Twelve (15.38%) out of 78 patients had posterior subcapsular cataracts, 6 of whom had mild to moderate disease activity. Less common ocular findings were glaucoma, periorbital edema, and keratoconjunctivitis sicca.

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ORIGINAL ARTICLE

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Use of hollow polymethylmethacrylate as an orbital implant

ABSTRACT

Objectives

To establish the physical properties of a low-weight hollow polymethylmethacrylate (PMMA) implant and determine its suitability as an orbital implant.

Methods

Hollow implants were molded by fusing 2 half-sphere shaped implants made from medical-grade PMMA powder. The water absorption capacity, bulk density, and hardness of the hollow implants were determined. Twelve patients were randomly divided into two equal groups: one group receiving the standard solid acrylic implant and another receiving the hollow PMMA implant. The anophthalmic socket was examined for complications due to surgery and type of implant used. Serial CT (computed tomography) scans were performed to detect implant migration.

Results

The hollow PMMA implant had the following physical properties: water absorption = 0.65%, bulk density = 0.57 g/cm³, and hardness = 71.2kg. Most of the implants remained in the socket at least 6 weeks in both groups with 1 case of early implant extrusion in the solid acrylic group. Small degree of implant migration was observed on CT scan in 4 patients in the solid acrylic group and 3 in the hollow PMMA group at 12 weeks follow-up. In the solid acrylic group, the implant migrated posteriorly in those that were eviscerated and anteriorly in those that were enucleated. No pattern was observed in the type of operation and direction of the implant migration in the hollow PMMA group.

Conclusion

Hollow polymethylmethacrylate implants are comparable substitutes for solid acrylic implant. Multicenter clinical trials with adequate sample size and longer follow-up are needed to establish the long-term stability of the implant.

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THE SEARCH for the ideal eye implant for anophthalmic sockets continues notwithstanding the availability of orbital implants for years. Size, shape, composition, and cost determine the ideal type of implant. It must approximate the normal eye, resemble the globe in shape, occupy the excess orbital volume, and compensate for the missing viscera. It must also be made of material that the body would not reject. In the Philippines, the solid acrylic implant is commonly used because of its low cost.

A five-year survey of cases at the Plastic and Lacrimal Clinic of the Philippine General Hospital reported that the most common anophthalmic socket problems were socket contraction and implant extrusion (Pagkatipunan PN and Mangubat LR, Anophthalmic socket in the plastic and lacrimal clinic, Department of Ophthalmology and Visual Sciences-Philippine General Hospital, 1996). Surgical technique, infection, and type of implant used were the usual causes. A five-year survey of 2,775 cases found 110 (3.9%) socket problems with 11 cases of implant extrusion (Tecson JV and Mangubat LR, Plastic and lacrimal clinic: A five-year survey, Department of Ophthalmology and Visual Sciences-Philippine General Hospital, 2001).

Integrated implants such as hydroxyapatite (HA) and porous polyethylene (PPE) are preferred because they allow tissue ingrowth and are associated with low incidence of migration. But these cannot be used for immunocompromised patients or those who have infections because the pores may serve as nidus for infection. Nonintegrated implants such as solid silicone and polymethylmethacrylate (PMMA) have been widely used because of their inert properties and low cost. However, these are associated with a high incidence of extrusion and migration. To date, no randomized clinical trial has been conducted to evaluate the stability of the various nonintegrated implants.

We hypothesized that for most cases of migration of nonintegrated implants, weight may be a cause. A hollow implant would be expected to be more stable compared with a solid implant of the same size as it would be subjected to less gravitational force.

We conducted this study to evaluate the suitability of an experimental hollow PMMA implant for the anophthalmic socket. We determined its physical properties (water absorption capacity, bulk density, hardness strength) and identified complications (infection, wound dehiscence, and implant extrusion and migration) vis-à-vis solid acrylic spheres.

METHODOLOGY

Nito-Seiki Manufacturing Corporation (Baesa, Quezon City, Philippines) molded the hollow implant (Figure 1). Medical-grade PMMA powder was used to form half-spheres by plastic injection technique. Pairs of half-spheres were fused ultrasonically to form 20-mm hollow PMMA

spheres. The physical properties of the hollow PMMA implant were tested by the Department of Science and Technology (Taguig, Metro Manila, Philippines). The following parameters were measured: water absorption, bulk density, hardness. The ultra structure of the implants was observed under scanning electron microscopy.

The study complied with the protocol established in the Declaration of Helsinki and was approved by the bioethics committee of the University of the Philippines-Philippine General Hospital (UP-PGH).

Study subjects seen consecutively at the Department of Ophthalmology and Visual Sciences of the PGH were selected based on the following inclusion criteria: male or female 18 years old or older with clinically diagnosed nonseeing eyes secondary to traumatic globe injuries, ruptured corneal ulcers, or staphyloma who were advised to undergo evisceration or enucleation with orbital implantation or reimplantation for extruded orbital implants. Patients were excluded from the study if their normal eye had an axial length of less than 21mm determined by A-scan or an intraoperative determination showed the socket would have difficulty accommodating a 20-mm implant. Subjects were randomly assigned into the control group, which received the solid acrylic implant, or the treatment group, which received the hollow PMMA implant.

All participants were interviewed and underwent a complete eye examination consisting of visual acuity assessment, gross orbital exam, extraocular muscle function, intraocular pressure (IOP) determination, funduscopy, and slit-lamp examination. The clinical diagnosis was recorded. The mean axial length (average of 3 measurements) of the fellow normal eye measured by A-scan was used to estimate the length of the affected eye.

Prior to implantation, the orbital implant was weighed and its volume measured by water displacement. A standardized posterior sclerostomy and insertion of the

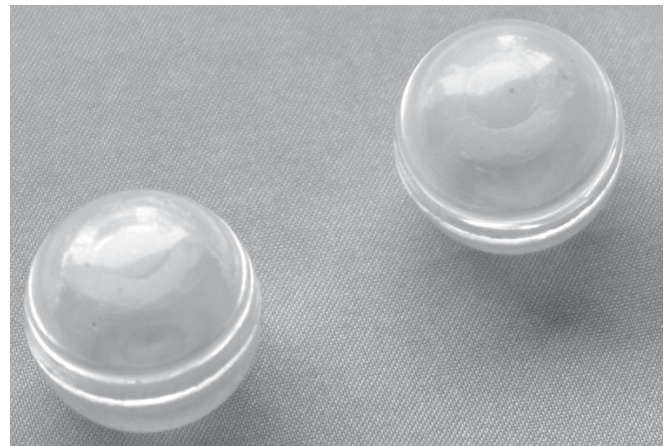


Figure 1. Hollow polymethylmethacrylate implant

implant at the retrobulbar space were followed for evisceration. A three-layer closure of the Tenon's capsule over the implant was performed for enucleation or reimplantation.

Six surgeons performed the surgeries. All patients were given topical steroid antibiotic ointment. All underwent tarsorrhaphy, which was released after 1 week. Patients were followed up at 2 weeks, 6 weeks, and 12 weeks postoperatively for signs of infection, dehiscence, and migration.

Orbital (computed tomography) CT scan was performed the day following surgery and on the 12th week of follow-up. The implant was considered in place if it was not visible through the overlying conjunctiva, palpable within the center of the socket, and not obliterating the fornices. The distance between the orbital apex and posterior surface of the implant on axial cuts was measured to determine implant migration. A single blinded radiologist performed all measurements.

RESULTS

Physical properties

Tests done by the Industrial Technology Development Institute (ITDI) of the Department of Science and Technology (DOST, Reference No. MSD-0211-062) yielded the following physical properties of the hollow PMMA spheres compared with those of the solid acrylic: water absorption 0.65% versus 0.2%; bulk density, 1.19g/cm³ versus 0.57g/cm³; hardness, 71.2kg versus 92-100kg.

Microstructure determination by Scanning Electron Microscopy showed ridges on both inner and outer surfaces of the hollow orbital PMMA implant.

Patient profile

Twelve patients (6 males and 6 females) with mean age of 35 were enrolled in the study. Three patients (2 solid acrylic, 1 hollow PMMA) underwent reimplantation (following implant extrusion), 5 had enucleation (2 solid acrylic, 3 hollow PMMA), and 4 had evisceration (2 solid acrylic, 2 hollow PMMA) with posterior sclerostomy for such conditions as anterior staphyloma (3), neovascular glaucoma (2), infection (2), trauma (1), and phthisis bulbi (1).

All were seen on the 6th-week of follow-up. However, 5 patients (2 solid acrylic, 3 hollow PMMA) did not return for the final follow-up.

Axial length measurements and weight of implants

The mean axial length of the fellow eyes was 23.38mm ±0.817 in the solid acrylic group and 23.34mm ±1.424 in the hollow PMMA group (Table 1). The hollow PMMA implant weighed 2.5g, half the weight of the solid acrylic implant.

Implant Status

At 6 weeks, 11 of 12 implants remained in the socket; 1 in the solid acrylic group extruded. At 12 weeks, only 7 patients (4 solid acrylic, 3 hollow PMMA) completed the follow-up, and all implants were in place.

Results of orbital CT scan at 12 weeks follow-up are shown in Table 2. A migrating implant is one that has been displaced from its original position but has not yet extruded from the socket on eye exam.

Complications

There was 1 incidence each of wound infection, dehiscence, ptosis, and superior sulcus defect in the solid acrylic group, as well as 1 case each of conjunctivitis and ptosis in the hollow PMMA group.

DISCUSSION

In the design of orbital implants, several factors, namely size, shape, composition, weight, and volume, must be considered to minimize migration.

An implant smaller than the volume of the affected eye yields a volume deficit and poor aesthetic results. This study showed that for eyeballs that have an axial length of at least 21.98mm by A-scan ultrasound, a 20mm implant can be placed. These results are consistent with the findings in a 2000 study, which showed that many anophthalmic sockets could accommodate implants of

Table 1. Axial lengths of fellow eyes

Patient	Solid Acrylic	Hollow PMMA
1	23.18	23.75
2	22.65	25.95
3	24.65	22.46
4	23.71	22.49
5	22.41	23.41
6	23.70	21.98

Table 2. Implant displacement determined by CT scan

Solid Acrylic	Anterior-Posterior	Superior-Inferior	Medial-Lateral
1	1.0mm posterior	1.0mm superior	-
2	5.0mm posterior	2.5mm superior	0.5mm lateral
3	2.0mm anterior	1.0mm superior	-
4	-	-	-
5	3.0mm posterior	1.5mm superior	0.5mm lateral
6	Extruded	Extruded	Extruded
Hollow PMMA	Anterior-Posterior	Superior-Inferior	Medial-Lateral
1	-	-	-
2	4.0mm anterior	1.5mm inferior	1.0mm lateral
3	-	-	-
4	-	-	-
5	11.0mm anterior	0.5mm superior	0.5mm medial
6	2.0mm posterior	-	0.5mm medial

22mm diameter or larger based on the axial length measurements of the fellow eye.¹ But there are no studies that correlate the size with implant migration.

Implant shape also plays a role in the mechanics of the prosthesis.¹ It may be spherical or irregularly-shaped (pyramidal,¹ conical,² or egg-shaped³.) We used the traditional spherical shaped implants to simulate the shape of the eyeball.

Orbital implants may be classified according to their composition. Nonintegrated implants have no apparatus for attachments of the extraocular muscles and therefore do not allow ingrowth of organic tissue. They have no direct attachments to the ocular prosthesis. Examples are those made from glass,⁴ rubber, silicone, steel, gold, silver, acrylic, and PMMA. Integrated implants^{5, 6, 7, 8, 9, 10, 11} have an apparatus for attaching extraocular muscles and allow ingrowth of fibrovascular tissue on its surface.^{12, 13, 14} Examples are the porous polyethylene (PPE)^{15, 16} and hydroxyapatite (HA) orbital implants that are nontoxic, nonallergenic and biocompatible materials made from salt of calcium phosphate. We used PMMA because of its inert properties, low cost, and long history of use as orbital implant.

Weight and volume^{17, 18} are also important. If the adult eye is assumed to have a spherical diameter of 24mm, the volume of the sphere is 7.2 mL ($V = 4\pi r^3/3$). The average artificial eye has a volume of 2.5 mL. The volume of the orbital implant is the difference between the volume of the eye removed (7.2 mL) and the volume of the artificial eye or prosthesis (approximately 2.5 mL). An implant should therefore provide a volume of 4.7 mL. A spherical implant with such volume would have a diameter of 21 mm. Since the goal of implant insertion is volume replacement, only the implant's volume and not its weight is needed to replace the enucleated globe. We used a lighter implant to avoid weight-related problems such as extrusion and implant migration due to gravity.

One case of early implant extrusion in the solid acrylic group was seen on the third week following enucleation. This could have been due to incomplete Tenon's closure.

In the solid acrylic group, the implants migrated posteriorly in patients who underwent evisceration and anteriorly in those who had enucleation. Coronal cuts showed that the implants migrated supero-laterally.

In the hollow PMMA group, no pattern was observed between the type of operation and the direction of the implant migration, possibly because the lighter weight of the implant made it more mobile inside the eye socket.

Caution should be used when analyzing results of displacement based on CT scan. The values are measured in millimeters and the results may be affected by the position of the patient's head during the scan and the size of cuts.

Early wound dehiscence with threat of implant extrusion because of infection was seen in the solid acrylic group in a patient who underwent evisceration and whose preoperative diagnosis was panophthalmitis (*Pseudomonas aeruginosa*). First week postoperatively, purulent discharge with breakdown of tissues and exposure of the underlying sclera was seen. There was reepithelialization of the conjunctiva 2 weeks later and lower lid margin laxity on later follow-up. Patient was given oral cefuroxime for 1 week.

Infection is less frequent with nonintegrated than integrated implants because of the lack of pores which act as areas for potential infection.^{19, 20, 21, 22} A case of postoperative viral conjunctivitis characterized by severe chemosis and prolapse of the conjunctiva was seen in the hollow PMMA group which was managed by cold compresses, pressure patching, and repeat tarsorrhaphy. The implant did not extrude and no shortening of fornices was noted on last follow-up.

Anterior granulomatous uveitis in the fellow eye of a patient in the hollow PMMA group occurred 8 weeks postoperatively and responded to topical steroids. Cases of mild ptosis were seen in each group and one case of superior sulcus defect in the solid acrylic group. These are commonly seen as late complications resulting from downward and anterior migration of the implant with deepening of the superior sulcus.¹⁵

The patients in both groups were satisfied with their prosthesis fit and no further surgical intervention was done.

This study is limited by its small sample size and the short follow-up period, which could not establish the long-term stability of the hollow implant. Nevertheless, the study showed that hollow polymethylmethacrylate implants are comparable substitutes for solid acrylic implants with similar rates of complication. A larger sample size with longer follow-up period is needed to establish the long-term stability of the implant.

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ORIGINAL ARTICLE

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In vitro evaluation
of natamycin 5% suspension
against *Aspergillus flavus*, *Fusarium
solani*, and *Candida parasilopsis*

ABSTRACT

Objective

This study compared the minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) of two available brands of natamycin 5% suspension (Natacyn and Elmycin) against three ocular fungi (*Aspergillus flavus*, *Candida parasilopsis*, *Fusarium solani*).

Methods

Antifungal susceptibility testing by broth microdilution was performed. The MIC and MFC of both brands were determined and paired *t*-tests were compared.

Results

Results of MIC and MFC of Elmycin and Natacyn against *Aspergillus flavus* showed no significant difference ($p = 0.05$). The same values were obtained for *Fusarium solani* and *Candida parasilopsis*, showing no difference in their MIC and MFC.

Conclusion

Elmycin and Natacyn have similar MIC and MFC against *Aspergillus flavus*, *Fusarium solani*, and *Candida parasilopsis* as determined by *in vitro* tube dilution technique. Elmycin may be used as an alternative agent against these organisms in fungal keratitis.

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THE INCIDENCE of fungal keratitis has increased over the past 30 years. In the United States, it ranges from 2% of all keratitis cases in New York to 35% in Florida.¹ *Fusarium* is the most common cause of fungal corneal infection in southern states (45-76% of fungal keratitis) while *Candida* and *Aspergillus* are more common in northern states.² In South Florida, *Fusarium oxysporium* was the most common isolate (37%) followed by *F. solani* (24%), *Candida*, *Curvularia*, and *Aspergillus*.²

But elsewhere in the world, *Aspergillus* is the most common isolate. In India, it accounts for 2-64% of cases followed by *Fusarium* (6-32%) and *Penicillium sp.* (2-29%).¹ In the Philippines, a review by Valenton of 3,256 microbial keratitis cases treated at the Philippine General Hospital from 1972 to 1996 reported 349 laboratory confirmed cases of fungal keratitis. Of these, 105 were caused by *Fusarium sp.* and 26 by *Aspergillus sp.*³

The current treatment protocol for fungal keratitis recommends 0.1% amphotericin B or 5% natamycin as first-line antifungal agents. Also used are polyene antibiotics (nystatin, amphotericin B, natamycin); pyrimidine analogs (flucytosine); imidazoles (clotrimazole, miconazole, ketoconazole); triazoles (fluconazole, itraconazole); silver sulfadiazine; chemotherapeutic agents; and corticosteroids.^{4,5,6}

Valenton studied 309 fungal keratitis patients treated with topical antimicrobial after superficial keratectomy of ulcer infiltrate. The response rate was 33% for patients treated with plain topical antibiotics, 55% for those treated with topical amphotericin B (Fungizone, Bristol-Myers Squibb, New York, NY, USA), 54% for those treated with topical natamycin (Natacyn, Alcon Laboratories, Fort Worth, TX, USA) applied 6 times daily, and 33% for those treated with miconazole suspension (GynoDaktarin ovule 40mg in 5cc liquifilm ophthalmic solution, Janssen-Cilag, Mexico).³

Natamycin is the only commercially available topical antifungal. It is a polyene macrolide produced by *Streptomyces natalensis*, which is structurally related to amphotericin B and nystatin. *In vitro*, natamycin concentrations of 1-25 ug/ml (Pimaricin, Haorui Pharma-Chem, Edison, NJ, USA) and 1-10 ug/ml (Natacyn) usually inhibit *Aspergillus*, *Candida*, *Cephalosporium*, *Curvularia*, *Fusarium*, *Penicillium*, *Microsporium*, *Epidermophyton*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Sporothrix schenckii*.⁷ It also has some activity *in vitro* and *in vivo* against *Trichomonas vaginalis*.

Two brands of natamycin ophthalmic suspension are available in the Philippines: Natacyn 5% (Alcon Laboratories, Fort Worth, TX, USA) priced at PhP22,000/15 ml and Elmycin 5% (Elder Group, Mumbai, India) costing PhP150/3ml. This study compared the two brands *in vitro*

to determine if the cheaper brand has the same drug concentration and efficacy.

METHODOLOGY

Both brands of natamycin 5% suspension were subjected to antifungal susceptibility testing by broth microdilution. The MIC and MFC were determined as follows.

Ten-milliliter solutions were prepared in Pyrex test tubes by adding 1% chemically pure H₂SO₄ and 1% chemically pure BaCl₂ in increasing amounts. The test tubes were covered with rubber stopper, sealed with melted paraffin, and labeled 1 to 10.

Five-day-old cultures of *Aspergillus flavus*, *Fusarium solani*, and *Candida parasilopsis* were used as test organisms. These were prepared in Sabouraud's broth and agar slant. A standard inoculum containing about 300,000,000 cells was prepared based on the McFarland tubes (tube number 1). A 0.1cc of the standard inoculum was inoculated in the experimental and control tubes (about 3,000,000 cells/10 ml).

All the tubes were incubated at 25-degree-Celsius room temperature for 6 weeks and shaken for 10 minutes daily to make sure that the inoculum gets uniform contact with the antifungal agent. Three test tubes were prepared for each concentration level.

To confirm the presence of growth in each test tube, all Sabouraud's broth tubes were sampled weekly and streaked in a Sabouraud's agar, which was prepared by mixing 40g/L dextrose, 10g/L neopeptone, and 15g/L agar-agar. These slants were incubated at 25° Celsius for 6 weeks. Once growth was confirmed, a culture mount was done from all the slants that grew organisms to check if the samples collected were similar to the test organisms.

The drug-free control and the drug-inoculum tubes were observed and compared for possible signs of growth daily for 6 weeks. The MIC (the highest concentration with positive fungal growth after six weeks incubation) and the MFC (the lowest concentration where there is no growth after 6 weeks incubation) were determined for each drug.

A confirmatory test for MFC concentration was done by subjecting the tubes with negative growth to centrifugation, washing the sediments three times with sterile NSS, and culturing the washed sediments in Sabouraud's dextrose agar. A negative growth after 6 weeks incubation period confirmed the death of the organism.

Student *t*-test for paired samples was done.

RESULTS

Results of the tube dilution against *Aspergillus flavus* showed no growth for concentrations of 150-40000 g/ml for both Natacyn and Elmycin at the end of the 6 weeks

observation period. Both had the same MFC (150 µg/ml) and MIC (75 µg/ml) and showed positive growth (all 3 test tubes for Elmycin and 1 of 3 for Natacyl) on day 7. On day 13, all three test tubes of Natacyl were positive for growth. All concentrations below the MIC showed positive growth in the first week of observation period for both brands. *T*-tests for paired samples showed no significant difference between the MIC and MFC at 150mg/ml of both brands at $\alpha=0.05$.

For *Fusarium solani*, both the MFC (10µg/ml) and MIC (5µg/ml) were similar. All test tubes with this concentration showed signs of growth on day 1 of the observation period.

For *Candida parasilopsis*, both brands remained negative until the end of six weeks at concentrations 300 to 4000µg/ml. Both had the same MFC (300µg/ml) and MIC (150µg/ml) and showed positive growth concentration on day 12.

DISCUSSION

No difference in the MIC and MFC were noted between Natacyl and Elmycin in all the test fungi (*Aspergillus flavus*, *Fusarium solani*, and *Candida parasilopsis*). The MIC and MFC were lowest with *Fusarium solani* for both brands. Results for all the test tube replicates were consistent for both brands except in *Aspergillus flavus*, which showed a slight difference between the means of each brand. *T*-test paired samples of weekly results, however, showed that the difference was not significant. The results with *Fusarium solani* and *Candida parasilopsis* were exactly the same.

Natacyl and Elmycin have the lowest *in vitro* MIC (5µg/ml) in *Fusarium solani* compared with amphotericin B (20mg/µl). Clinically, the cure rate for fungal keratitis caused by *Fusarium solani* is higher with topical natamycin than with amphotericin B. Nakamura et al. reported a cure rate of 16 out of 18 culture-proven *Fusarium* corneal ulcers for natamycin 5% suspension applied hourly compared with only 7 out of 20 cases for amphotericin B.⁸ These results were reflected in a larger series where natamycin 5% suspension had a cure rate of 29 out of 35 *Fusarium* keratitis cases.⁹

Amphotericin B is the drug of choice for treatment of infections resulting from *Coccidioides immitis*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Candida* species, and other less common fungi. The extent to which it can damage the cell wall is dose-related. However, a more rapid death of the yeasts cannot be achieved clinically by increasing the drug dosage because the same cytoplasmic membrane damage also affects human cells, causing unpleasant and potentially dangerous side effects which are almost inevitable even at therapeutic levels.

Systemic side effects include renal damage, anemia, nausea, vomiting, GI cramps, and diarrhea. Topical application of 1% amphotericin B in a Deoxycholate vehicle causes progressively worsening corneal epithelial defects, stromal opacities, and severe iridocyclitis.¹⁰

The MIC of Elmycin for *Fusarium solani* was comparable with those of Primaricin and Natacyl. However, its MIC for *Aspergillus flavus* (75µg/ml) and *Candida parasilopsis* (150µg/ml) was higher compared with MIC or Primaricin reported by Mauger (1-25µg/ml).⁷ This could be explained by the differences in the antibiotic responses of different species and strains of fungi. The lower MFC of Elmycin and Natacyl for molds (*Fusarium* and *Aspergillus*) vis-à-vis yeasts (*Candida*) may be accounted for by the difference in the cell-wall thickness of the organisms. Cell walls of yeasts are generally thicker (300 nm) than that of molds (200 nm), making it difficult for the drug to bind to ergosterol in susceptible cellular membranes, altering membrane permeability and inducing electrolyte imbalance with resultant cell death.¹¹

This is an *in vitro* experiment to determine the minimum drug concentration at which two brands of natamycin can inhibit or kill the fungi. Its results may not correspond with *in vivo* clinical scenario because of host factors, corneal penetration of the antifungal, and difficulty in standardizing antifungal sensitivities. Several studies have shown that natamycin was not effective for deeper stromal involvement and that drug absorption depends on the state of damage to the epithelium.

However, based on the *in vitro* study, Elmycin may be used as a cheaper alternative agent against fungal keratitis, particularly if caused by *Fusarium solani*.

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ORIGINAL ARTICLE

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Freeze-dried human cancellous bone as orbital implant in an animal model

ABSTRACT

Objective

To determine if freeze-dried human cancellous bone is biocompatible and can be used as an integrated orbital implant.

Methods

This is an experimental study of 10 rabbits that underwent unilateral enucleation with placement of a 14mm spherical orbital implant made from freeze-dried cancellous bone of human femoral heads. The implants were harvested after six weeks. Grossly, the rabbits were observed for occurrence of inflammation and implant extrusion. Histologically, the extent of fibrovascular ingrowth was assessed.

Results

Six rabbits completed six weeks of observation. All implants were exposed at the time of harvest, although there was no evidence of gross infection or inflammation. None of the implants were extruded. Fibrovascular ingrowth was observed in the outer third zone. A few plasma cells were seen, mostly in the periphery, and scattered among red blood cells in the center of the implant.

Conclusions

Orbital implant made from freeze-dried human cancellous bone is comparable to commercially available porous implants with regard to the presence of fibrovascular ingrowth when implanted in rabbit eyes. This lessens the chance of implant extrusion. The absence of implant rejection in this study is an encouraging indication that it should be tested in humans.

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The authors developed the freeze-dried human cancellous bone orbital implants described in this study.

THERE is a growing interest in the use of porous orbital implants following enucleation. These implants permit fibrovascular ingrowth from the surrounding tissues with biologic anchoring and vascular access. Theoretically, these minimize the incidence of migration and extrusion seen in nonporous orbital implants.¹ Two commercially available porous implants are coralline hydroxyapatite and porous polyethylene.

Hydroxyapatite is a complex calcium phosphate salt occurring naturally in the body. It is the primary mineral in the human bone. Porous hydroxyapatite is made from a specific genus of reef-building coral.² Animal studies have shown that when implanted into a soft tissue area, this material becomes invested with the animal's tissue without forming a pseudocapsule around it. It tends to be covered by the surrounding fibrovascular tissue and epithelium.³ Other studies, however, have shown that the implant is brittle and may require a wrapping of sclera or other material to reduce the incidence of exposure.⁴

Porous polyethylene (Medpor, Porex Surgical, Atlanta, GA, USA) is a polymer composed of simple hydrocarbon chains highly resistant to biological degradation. Its pore size ranges from 100 to 200µm. Porous polyethylene is not brittle and produces less tissue friction during implantation. Extraocular muscles may be sutured directly to the implant surface.⁴ It is well tolerated in enucleated patients and is associated with low risk of exposure or extrusion.⁵

Cadaver bone, prepared by heating spheres of cancellous bone that destroys all organic matter and leaves only the calcium phosphate mineral framework, has been used since the 19th century. Long-term follow-up of hydroxyapatite implants prepared from fine-textured, three dimensional porous bovine cancellous bones, showed limited exposure that healed spontaneously with low incidence (7.5%) of explantation.⁶

Human bone has been processed primarily for grafting. These bone grafts undergo degreasing to prevent tissue reaction in the host. Red marrow and other proteinaceous materials are removed to reduce their antigenicity.

Nonviable foreign bone undergoes freeze-drying to remove moisture. This reduces antigenicity and makes it possible to store the bone at room temperature for a long period and to transport it easily.⁷

Cortical and cancellous bones may be used as allografts. Cancellous bone is ideal as defect filler. Its porosity provides a scaffold for fibrovascular ingrowth.

Taking these characteristics of freeze-dried human bone into consideration, this study determined whether freeze-dried human bone can be used as an orbital implant. Its biocompatibility, integration to host tissues, presence of fibrovascular ingrowth, and adverse effects were assessed.

METHODOLOGY

Ten (10) rabbits weighing between 2 and 3kgs each were placed under ketamine anesthesia (Ketaject 50 mg/kg, Astrapin/PharAsia-Curest) combined with lidocaine-(Abbot 2% Lidocaine, Abbot Laboratories, Abbott Park, IL, USA) bupivacaine (Sensorcaise, AstraZeneca, London, Great Britain) local anesthesia. Unilateral enucleation was performed in each rabbit; the eye was randomly chosen. A 360° conjunctival peritomy was performed. Subtenon's space was explored and the rectus muscles were isolated and severed from the globe. The optic nerve was cut and the globe was removed intact. The 14mm freeze-dried human cancellous bone implant was placed into the muscle cone. The Tenon's capsule and conjunctiva were closed using interrupted 6-0 Vicryl (Alcon Laboratories, Fort Worth, TX, USA) suture. Tarsorrhaphy was performed at the close of the surgery using a single bite of Vicryl 6-0. Tobramycin ointment (Tobrex, Alcon Laboratories, Fort Worth, TX, USA) was instilled into the enucleated eye postoperatively. Each rabbit was observed daily for adverse reactions and signs of implant extrusion.

All rabbits were euthanized after six weeks, using an overdose of intramuscular (IM) ketamine. The bone implants were explanted and immediately fixed with 10% buffered formalin solution. The specimens were placed in 5% nitric acid solution for decalcification. Microscopic sections were taken from the center of the orbital implant sphere in the sagittal plane. Sections were stained with hematoxylin and eosin and examined microscopically for evidence of tissue integration and inflammation. The extent of tissue integration was described as to its location—whether the fibrovascular tissue is within the outer, middle, or inner third of the implant.

Treatment of the rabbits adhered to the guidelines of the Association for Research in Vision and Ophthalmology (ARVO).

Preparation of the orbital implant sphere

The freeze-dried human cancellous bone orbital implants (Figure 1) were processed in the hospital's tissue bank. Cancellous bones derived from human femoral head were harvested from post-trauma patients of the Department of Orthopedics who had undergone hip arthroplasties. The cortex was removed and the cancellous part rinsed in warm water to remove surface grease. Spheres measuring 14mm were shaped using an electric saw. These were placed in a washing machine with cold water for approximately four hours to remove red marrow and other proteinaceous material. The completion of the washing period was signaled by the absence of red coloration from the bone. The bone spheres were placed for 24 hours in the freeze-drying apparatus with vacuum

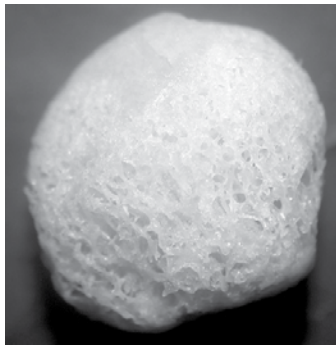


Figure 1. Freeze-dried human cancellous bone implant

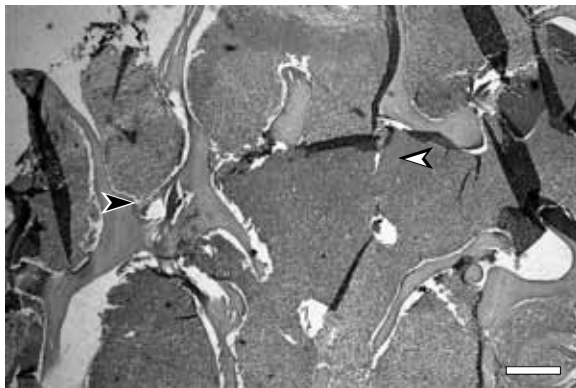


Figure 2. Photomicrograph of cross-section of bone implant showing bony matrix (▶) and red blood cells in the interstitium (▷). Hematoxylin and eosin stain. (bar = 500 μm)

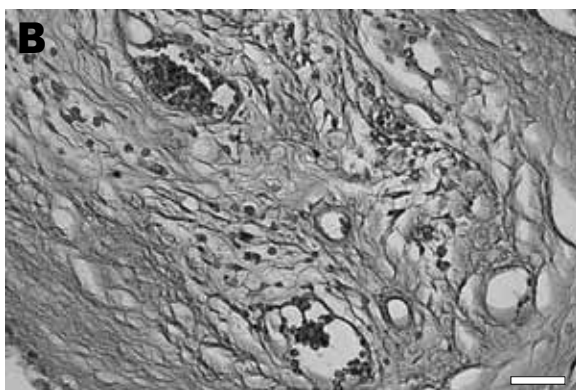
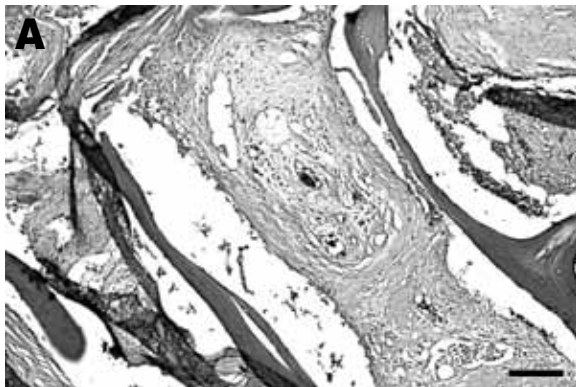


Figure 3. Fibrovascular ingrowth into the outer third of the implant. Fibrous tissue with accompanying blood vessels penetrated the interstitial spaces of the bone implant. Hematoxylin and eosin stain. (A: bar = 200 μm; B: bar = 50 μm)

pressure of 30 millibars and temperature at -30°C . The freeze-dried bones were then placed in individual plastic packets and sterilized using ethylene oxide gas.

RESULTS

Among the 10 rabbits that underwent enucleation and implantation of the bone implant, six were able to complete the six-week observation period. One died immediately postoperatively, one expired within the first postoperative week, while the other two died two weeks after enucleation.

There was no extrusion of the bone implant among the enucleated rabbits. But there was exposure of the anterior surface of the bone implant associated with minimal mucoid discharge. The exposed surface was eroded, with loss of the normal porous appearance. On explantation, there was no change in the size of the implants, no gross tissue infection or evidence of dystrophic calcification and heterotopic bone formation.

Histological examination of the implants revealed the presence of fibrovascular tissues in all (Figures 2 and 3). Growth of the fibrovascular tissue was confined mostly to the outer third of the implants; none was seen in the middle two-thirds. Two of the six implants were invested with a thin fibrous capsule (Figure 4). Minimal inflammatory cells were present. A few plasma cells were scattered in the center of the bone implants, mixed with numerous red blood cells (Figure 5). More plasma cells were observed in the bone implant margins. Granulomatous reaction was absent.

DISCUSSION

In the study by Goldberg et al., two out of 12 porous polyethylene implants (17%) and two out of four (50%) hydroxyapatite implants in rabbits extruded in the early postoperative course.⁴ The absence of extrusion at the sixth-week follow-up in our study is favorable compared with the earlier study. The histological findings in the bone implants support previous reports that porous implants provide structure for fibrovascular tissue ingrowth,^{3, 4, 8, 9} which minimizes the occurrence of extrusion. In our study all six specimens have fibrovascular tissue ingrowth and none of the implants extruded after six weeks.

None of the implants, however, had complete fibrovascularization into the inner zone. Previous animal studies showed that porous hydroxyapatite implants had complete ingrowth at six weeks and that porous polyethylene had fibrovascularization into the outer third zone during the first six to eight weeks, followed by a slower rate of tissue growth into the middle zone by the 48th week.⁴ In our study, it is possible that the tissue ingrowth was in the early stage at the sixth week and complete fibrovascularization would have occurred much later. Capsule formation in two implants indicated that the implants would be integrated well into the anophthalmic socket. Growth of the animal's own tissue around the implant may indicate lesser chances of extrusion.

The bone implants appeared to be well tolerated grossly and histologically. There were no evidence of gross tissue infection nor inflammation. Histologically, there was paucity of inflammatory cells. Plasma cells were found in the periphery and scattered among red blood cells in the center of the implant, an indication of chronic inflammatory reaction seen in fibrovascularization. Increased inflammation causes greater excitation of myofibroblasts, leading to increasing socket contraction and risk of extrusion.⁴ The absence of extrusion in our study is a good indicator that the bone implants were well tolerated by the body.

The absence of changes in the size of the bone implants after explantation is an indication that resorption of the implant did not take place. Suter et al. observed spontaneous breakdown of orbital implants involving bovine bone-derived hydroxyapatite orbital implants. Hydroxyapatite crystals contained in normal bones (along with collagen) were found to break down when exposed to conjunctival secretions.⁶ This may explain why there was erosion of the exposed anterior surface of the bone implants in this study, which may be prevented by covering it with autologous sclera, as frequent rubbing of the rough bone spicules in the implant surface may result in thinning of the overlying conjunctiva.

This study showed that spherical freeze-dried human cancellous bone is a viable material for orbital implants. It does not induce significant inflammation grossly and histologically. Its porosity encourages growth of fibrovascular tissue into the implant, ensuring good tissue integration and minimal implant extrusion. Capsule growth around some implants also ensures better soft tissue integration.

Further studies should include implants wrapped in autologous sclera to determine whether they would prevent exposure and implant erosion. The time to explantation should be prolonged to observe whether complete fibrovascularization occurs and if bone resorption or implant extrusion would eventually occur. Human trials are needed to determine whether the material is tolerated by the human body.

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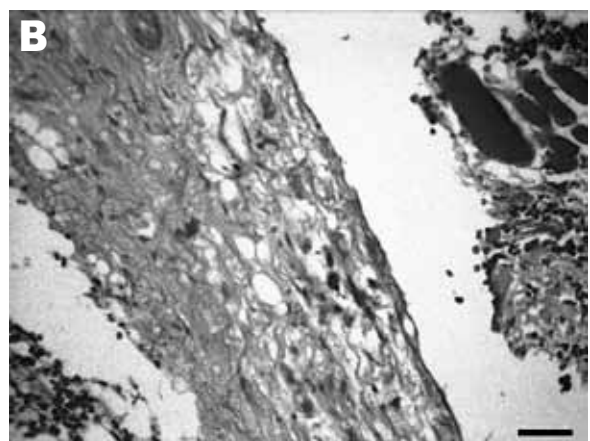
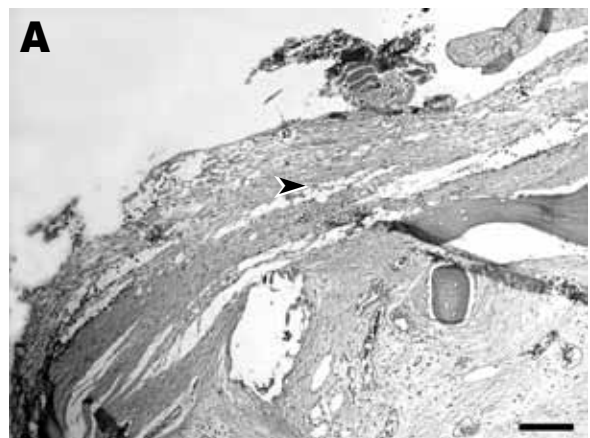


Figure 4. (A) Fibrous capsule (▶) investing the surface of the bone implant; (B) Magnified view showing fibrous tissue on outer surface of implant with muscle tissue on the right side. Hematoxylin and eosin stain. (A: bar = 200 μm; B: bar = 50 μm)

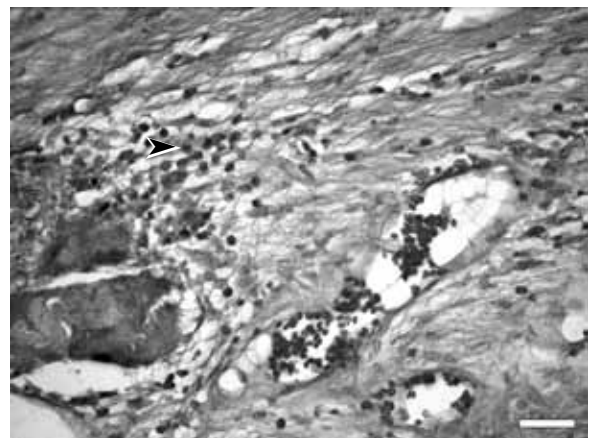


Figure 5. Plasma cells (▶) scattered among fibrous tissue and red blood cells. Hematoxylin and eosin stain. (bar = 50 μm)

ORIGINAL ARTICLE

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Comparison of higher-order aberrations

Wavefront-guided versus standard laser *in situ* keratomileusis in low to moderate myopia

ABSTRACT

Objective

To compare the pre- and postoperative changes in higher-order aberrations after standard LASIK (PlanoScan, Bausch & Lomb) and wavefront-guided LASIK (Zyoptix, Bausch & Lomb) and determine their effects on visual acuity, contrast sensitivity, and refractive outcomes at one year postoperatively.

Methods

In a prospective, randomized clinical trial, 15 patients with low to moderate myopia had standard LASIK on one eye and wavefront-guided LASIK on the contralateral eye. A Hartmann-Shack aberrometer (Zywave, Bausch & Lomb) was used to measure the aberrations. Root-mean-square (RMS) values were determined. Uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), refractive errors, and contrast sensitivity were also measured.

Results

Thirteen (87%) of the 15 eyes treated with Zyoptix and 12 (80%) of the 15 treated with PlanoScan had UCVA of 20/20 at one year postoperatively. The mean difference in the pre- and postoperative contrast sensitivity showed no significant changes in all spatial frequencies in both groups ($p > 0.05$). The difference in attempted versus achieved refraction was not significant between the two groups ($p = 0.794$). In all eyes, the total RMS increased postoperatively ($p < 0.001$), but the mean RMS difference from the preoperative values between the two groups was not statistically significant ($p = 0.257$).

Conclusion

LASIK in low to moderate myopia increases overall high-order aberrations. Zyoptix LASIK offers no advantage over PlanoScan LASIK in decreasing high-order aberrations postoperatively and in achieving better visual and refractive outcomes.

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ADVANCES in refractive surgery have given rise to sophisticated techniques for correcting visual errors, hoping not only to correct spherocylindrical refractive errors (low-order aberrations), but also to decrease a spectrum of higher-order aberrations and achieve optimum quality of vision.

In wavefront-guided LASIK, these aberrations are measured with a wavefront analyzer to establish an ablation pattern and correct them through a scanning-spot excimer laser. This procedure aims to reduce the amount of existing aberrations after corneal refractive surgery. But evidence also shows that refractive procedures may increase naturally occurring higher-order aberrations because of the creation of a corneal flap and the effects of variable healing patterns unique to each eye, which cannot be predicted before operation.¹ These may account for reported cases of "glare and haloes," decreased contrast sensitivity, and irregular astigmatism, resulting in deterioration in the quality of vision even in customized ablation.² Thus, it is important to determine whether wavefront-guided LASIK (Zyoptix, Bausch & Lomb, Hiedelberg, Germany) is better than standard LASIK (PlanoScan, Bausch & Lomb, Rochester, NY, USA) in achieving visual outcome and significantly decreasing the overall higher-order aberrations.

Using the root-mean-square (RMS) wavefront error, this study compared the changes in higher-order aberrations before and after standard LASIK and wavefront-guided LASIK and correlated them clinically in terms of their effect on visual acuity, contrast sensitivity, and refractive outcomes after one year.

METHODOLOGY

This is a randomized clinical trial involving 30 eyes of 15 patients with low to moderate myopia and astigmatism who agreed to have standard LASIK on one eye and wavefront-guided LASIK on the contralateral eye. The study was approved by the Ethics Committee of the St. Luke's Medical Center. All patients submitted written informed consent in accordance with the Declaration of Helsinki. All were able to complete at least one year of follow-up (November 2001 to January 2003).

All patients underwent a complete ophthalmic examination. Their uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) were determined using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart (Lighthouse Vision Products, Long Island, NY, USA).

Manifest and cycloplegic refractions, corneal topography and pachymetry (Orbscan II v. 3.10.31 Bausch & Lomb, Rochester, NY, USA), determination of wavefront aberration (Zywave v. 3.21 Bausch & Lomb, Rochester, NY, USA), contrast sensitivity testing, scotopic pupil size determination, slit-lamp evaluation of the anterior segment, applanation tonometry, and dilated fundus examination

were also performed. Functional Acuity Contrast Test (FACT, Vision Sciences Research Corporation, San Ramon, CA, USA) was used to determine contrast sensitivity using five spatial frequencies (1.5, 3.0, 6, 12, and 18 cycles per degree) with 9 sequences per frequency. All patients had best corrected visual acuity of 20/25 or better, no ocular abnormalities other than refractive errors, no collagen/autoimmune diseases, no previous ocular surgeries or history of trauma.

Postsurgical emmetropia was intended in all cases. UCVA, BCVA, refraction, contrast sensitivity testing, and slit-lamp examination were performed 1 and 7 days; 1, 3, 6 months; and one year postoperatively. Wavefront analysis using the Hartmann Shack-based Zywave aberrometer was performed at least one year postoperatively with eyes dilated with phenylephrine 2.5% (Mydrin, Alcon Laboratories, Fort Worth, TX, USA). The results were then evaluated using a CT-view (version 3.17, Sarver and Associates) software program for RMS comparison. To minimize technical error, the average of 3 wavefront measurements using a standard pupil size of 6.0 mm was used for data analysis.

Calculation of the Wavefront-Guided Ablation

Wavefront aberrations are measured, defined, and quantified in terms of Zernike polynomials. Up to 20 coefficients are measured showing the lower-order aberrations of the first- and second-order and the higher-order aberrations of the third to the fifth order.³ The RMS wavefront error is used to quantify the irregularity of the wavefront. It is expressed as the square root of the squared mean deviation of the higher-order aberrations.⁴ The higher the RMS value, the greater are the wavefront aberrations.

Three consecutive Zywave measurements were taken with and without pupil dilation under standardized conditions. A single drop of phenylephrine 2.5% was used to dilate each eye instilled twice at 5 minutes interval. Thirty minutes after the second drop, the 3 measurements were repeated. The Zylink (v. 2.3, Bausch & Lomb, Rochester, NY, USA) software for the Zyoptix wavefront-guided LASIK combines the measurements of the Orbscan II and the Zywave aberrometer into a program that calculates the treatment profile of each patient. A single technician performed all Zywave and Orbscan II procedures.

Surgical Technique

Standardized and uniform LASIK procedures were performed on all eyes at the Vision Laser Center, St Luke's Medical Center by three coinvestigators (RLBS, WLW, JMS) in this study. After instillation of the topical anesthetic proparacaine HCl (Alcaine, Alcon Laboratories), a superior hinge flap with a diameter of 8.5/9.5mm and a thickness of 160/180 μ m was created using a Hansatome

microkeratome (Bausch & Lomb, Hiedelberg, Germany). The 193nm 217z Technolas scanning-spot excimer laser (Bausch & Lomb, Rochester, NY, USA) system with a combined 2.0mm and 1.0mm spot was used in the Zyoptix group, and only a 2.0mm spot in the PlanoScan group. The PlanoScan and Zyoptix software programs dictated the ablation patterns for the standard and wavefront-guided treatments, respectively. The mean treatment zones were 6.47 ± 0.48 mm and 6.33 ± 0.33 mm for the PlanoScan group and Zyoptix group, respectively. After the photoablation, the corneal flap was repositioned and the interface irrigated with a balanced salt solution. Postoperatively, patient used tobramycin 0.3% + dexamethasone 0.1% (Tobradex, Alcon Laboratories, Fort Worth, TX, USA) QID for 1 week and artificial tears as needed. No intraoperative or postoperative complications were encountered.

Statistical Analysis

The RMS and spherical equivalents between groups were compared using independent *t*-test. Paired *t*-test was used to compare pre- and postoperative findings in each parameter. Contrast sensitivity results were analyzed using the

Marginal Homogeneity Test. Other nonparametric data were compared using the chi-square test. α was set at 0.05.

RESULTS

Visual Outcomes

Thirteen (87%) of 15 eyes treated with Zyoptix and 12 (80%) of 15 eyes treated with PlanoScan had UCVA of 20/20 at one year postop (Figure 1). The mean difference in the pre- and postoperative contrast sensitivity showed no significant change in all spatial frequencies in both groups (Marginal Homogeneity Test, $p < 0.05$).

Refractive Outcomes

The mean preoperative spherical equivalent refraction of the Zyoptix group was -3.99 ± 1.30 D with a range of -1.75 to -6.50 D. This was not statistically different ($p = 0.638$) from the PlanoScan group, with a mean preoperative spherical equivalent refraction of -3.77 ± 1.28 D (range -1.88 to -6.62 D).

In the Zyoptix group, only 1 eye was undercorrected by more than 0.50 D. Four eyes (27%) were overcorrected within 0.75 D. In the PlanoScan group, 2 (13%) eyes were

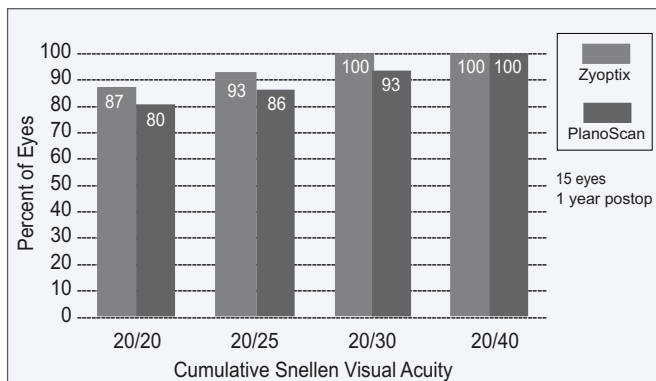


Figure 1. Uncorrected visual acuity at 1 year

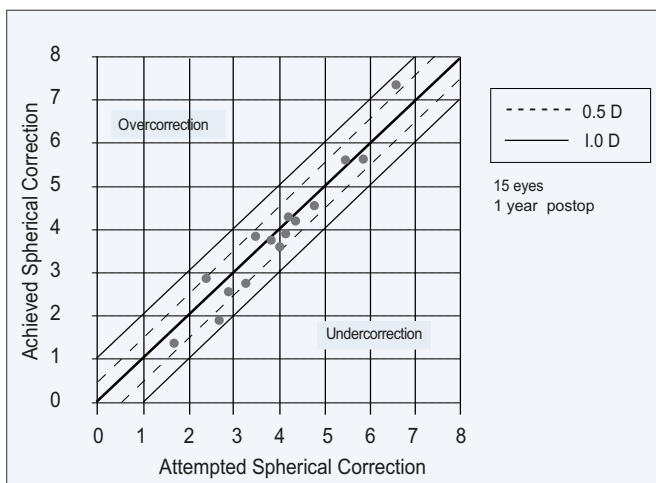


Figure 2. Attempted v. achieved refractive results 1 year after Zyoptix

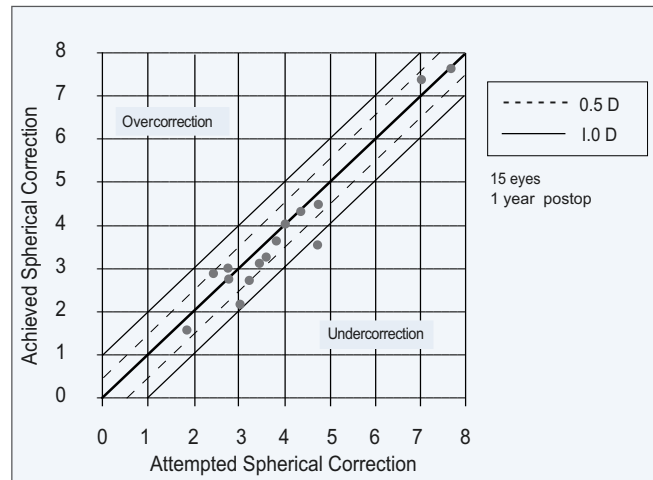


Figure 3. Attempted v. achieved refractive results 1 year after PlanoScan

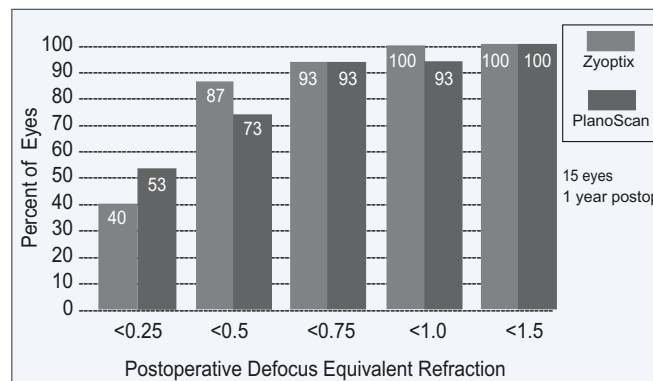


Figure 4. Postoperative defocus equivalent refraction at 1 year

Table 1. Average root mean square values in 30 eyes pre- and post-LASIK

Zernike Coefficient (μm)	PlanoScan			Zyoptix		
	Pre	Post	p	Pre	Post	p
3rd order						
Z_3^{-3} (trefoil w/ base on x-axis)	0.527808	0.601682	0.674	0.598078	0.695976	0.698
Z_3^{-1} (coma along x-axis)	0.642042	1.225225	0.044	0.405405	1.263784	0.002
Z_3^1 (coma along y-axis)	0.459700	0.560000	0.358	0.442763	0.881802	0.059
Z_3^3 (trefoil w/ base on y-axis)	0.383664	0.487447	0.462	0.323003	0.655495	0.008
4th order						
Z_4^{-4} (quadrafoil)	0.240000	0.486366	0.003	0.146667	0.513634	0.004
Z_4^{-2} (2 nd astigmatism on y-axis)	0.243483	0.486366	0.011	0.201922	0.513634	0.020
Z_4^0 (spherical aberration)	0.823423	2.426306	<0.001	0.679399	2.732973	<0.001
Z_4^2 (2 nd astigmatism on x-axis)	0.375255	0.478198	0.342	0.400841	0.439520	0.756
Z_4^4 (quadrafoil)	0.212492	0.387868	0.107	0.266186	0.436877	0.137
5th order						
Z_5^{-5} (pentafoil)	0.243243	0.311832	0.175	0.183904	0.332132	0.211
Z_5^{-3} (2 nd trefoil)	0.165285	0.188228	0.573	0.132973	0.266787	0.173
Z_5^{-1} (2 nd coma)	0.248769	0.237718	0.846	0.181622	0.280841	0.136
Z_5^1 (2 nd coma)	0.069189	0.170330	0.043	0.093574	0.140661	0.170
Z_5^3 (2 nd trefoil)	0.107628	0.180541	0.064	0.133934	0.219099	0.047
Z_5^5 (pentafoil)	0.080120	0.265586	0.002	0.113754	0.318559	0.119

undercorrected by more than 0.50 D, 3 (20%) were overcorrected within 0.50 D. In the Zyoptix group, the average difference between the attempted and achieved correction was 0.33 ± 0.24 D (Figure 2), which was not statistically significant ($p = 0.794$) compared with the average difference of 0.31 ± 0.30 D in the PlanoScan group (Figure 3).

In the Zyoptix group, 13 (87%) of 15 eyes treated had a postoperative defocus equivalent refraction (the sum of the absolute value of the sphere and one-half the absolute value of the cylinder⁵) within ± 0.50 D of the target refraction and 15 (100%) eyes were within ± 1.0 D. In the PlanoScan group, 11 (73%) of 15 eyes treated had a postoperative defocus equivalent within ± 0.50 D of the target refraction and all but 1 were within ± 1.0 D (Figure 4).

Higher-Order Aberrations

Higher-order aberrations (RMS) significantly increased postoperatively in both the PlanoScan and Zyoptix groups compared with preoperative RMS values ($p < 0.001$). However, no significant difference in the postoperative total RMS ($p = 0.257$) was noted between the two groups (Table 1).

An increase in postoperative wavefront error is seen as a trend in all Zernike modes, but not all proved to be statistically significant. In the PlanoScan group, there was significant increase only in the third-order coma along the x-axis ($p = 0.044$), quadrafoil ($p = 0.003$), secondary astigmatism on y-axis ($p = 0.011$), spherical aberration ($p < 0.001$), secondary coma ($p = 0.043$), and pentafoil ($p = 0.002$). In the Zyoptix group, a noticeable rise was likewise seen in the spherical aberration ($p < 0.001$) including

third-order coma along the x-axis ($p = 0.002$), trefoil with base on y-axis ($p = 0.008$), quadrafoil ($p = 0.004$), secondary astigmatism on y-axis ($p = 0.020$), and secondary trefoil ($p = 0.046$). Despite the statistically significant postoperative increase, no significant difference was noted in terms of comparing the coefficients (pre- and postoperative difference) of each Zernike mode between the two groups ($p > 0.05$).

DISCUSSION

In general, higher-order aberrations increase after LASIK. Several studies have shown that this can be due to factors related to the creation of a corneal flap, varied healing patterns, and possibly keratodynamic changes secondary to the effect of corneal tissue loss.^{1,6}

In this study, however, no advantage can be attributed to wavefront-guided (Zyoptix) over standard (PlanoScan) LASIK in terms of decreasing higher-order aberrations. This exists despite the ability of wavefront-guided LASIK to identify higher-order aberrations and create an ablation pattern to correct them. Although it has been demonstrated that image quality after customized procedures is improved over that of standard procedures (based on decreased higher-order aberrations⁷), there are still significant aberrations induced after a wavefront-guided procedure that are neither expected nor predicted. It seems that it is not only related to corneal flap; equally important is the effect of corneal healing and tissue reorganization over time.

A trend has been observed showing increased wavefront error in all Zernike modes after undergoing standard and

wavefront-guided LASIK. Most noticeable is a significant increase in the induction of spherical and coma-like aberrations and secondary astigmatism postoperatively, which is very comparable with the results obtained by Pallikaris et al.¹ describing resulting higher-order aberrations following creation of a LASIK flap. This can be explained partly by the overall central flattening and peripheral steepening of the cornea following LASIK procedures, thereby altering the tension carried in the lamellae, the internal fluid pressure, interlamellar crosslinking, and the load imposed by the intraocular pressure.⁶

Several other factors contribute to the existence of these and other higher order aberrations. It has to be accepted that any procedure that circumferentially severs corneal lamellae will produce a biomechanical response that will alter corneal shape in a manner that cannot be predicted with wavefront analysis alone.⁹ In fact, in the Third International Congress on Wavefront Sensing and Aberration-Free Refractive Corrections, an esteemed panel of experts voted corneal biomechanics the number one problem that limits the ability to achieve the “ideal” refractive correction.

In terms of the impact of the amount of higher-order aberrations on visual and refractive outcomes, there is no direct correlation that exists between them. As Applegate et al. pointed out, not all aberrations are “equal,” meaning Zernike modes when combined can interact to improve visual acuity despite the increase in total wavefront error.⁸ Nevertheless, this study revealed no significant difference in terms of postoperative visual acuity, change in contrast sensitivity, and postop refraction between the two groups, independent of the total RMS obtained.

The number of subjects, however, posed as a limitation to this study. Also, patients included in the study were limited to those with low to moderate myopia and astigmatism, making the findings not applicable to those with high myopia.

On the other hand, the results were obtained at one year postop, which is the longest follow-up period to date compared with those in published articles that had postoperative follow-up period of 3 to 6 months.^{7,10} Moreover, this study was able to account for inherent variables by using the same patients for both treatments.

Although wavefront-guided LASIK proves superior in treating patients with thin corneas and large scotopic pupil sizes³, as long as there is creation of a flap, correction of higher-order aberrations cannot be predicted. Experts are now, in fact, looking into the possibility of a two-staged procedure (create a flap first and analyze the induced aberrations before doing wavefront-guided ablation) or even customized procedures not involving the creation of a corneal flap, like in laser-assisted subepithelial keratectomy (LASEK) or photorefractive keratectomy (PRK), to solve this problem. Undoubtedly, much still has to be done, and the future bids optimistic for combined instrumentation for next-generation customized refractive surgery with the integration of topographic and wavefront analysis.

LASIK procedures for low to moderate myopia with low astigmatism, in general, increase overall higher-order aberrations (especially spherical and coma-like aberrations and secondary astigmatism). Zyoptix LASIK offers no advantage over PlanoScan LASIK in decreasing higher-order aberrations postoperatively and in obtaining better visual and refractive outcomes based on the treatment software used in this study. It is recommended that future studies have a larger sample base and include patients with high myopia and astigmatism to validate the findings in this study.

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ORIGINAL ARTICLE

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Low-cost electromagnet for extraction of metallic intraocular foreign body

ABSTRACT

Objective

To develop a low-cost electromagnet for extraction of metallic intraocular foreign body.

Methods

This is an experimental study of an improvised electromagnetic device for extraction of intraocular metallic foreign body in a porcine eye.

The device is an electromagnet made from locally available electronic materials. It is equipped with two sizes of solenoid coil heads acting as the reservoir of magnetic field. The coils are fitted with two types of probes for intraocular and external magnetic extraction in a porcine eye.

The device is compared with a rare earth permanent magnet to demonstrate its strength over existing magnets used in ophthalmology. The strength of the device is quantified by magnetizing a series of weighted iron plates and determining the maximum weight it held.

The porcine eye was cut and the anterior hyaloid phase preserved. A 6 x 5-millimeter metallic fragment was introduced intravitreally; magnetic extraction was done with the use of the electromagnetic device through a 3mm sclerostomy.

Results

The device is 100 times less expensive than its commercial counterpart and stronger than the permanent magnet. It has a maximum lifting capacity of 8.5 pounds. The electromagnetic probe extracted the 6 x 5 mm metallic fragment from the porcine eye.

Conclusion

The low-cost electromagnet has a potential use in internal and external extraction of metallic intraocular foreign bodies in human patients.

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The authors developed the electromagnetic surgical
device described in this study.

METALLIC objects are often involved in penetrating injuries to the eye. In the United States alone, 18 to 40% of penetrating injuries have at least one intraocular foreign body (IOFB). Most of these occur at work. About 80% of cases are caused by metal striking metal. The number of such injuries increases during times of leisure.¹

The metallic IOFB must be removed immediately from the eye to stop infection and avoid leeching of ferrous materials, which are both damaging to the eye.²

Magnetic extraction has been around for over a century. In 1869, Dixon deliberately incised an eye to deliver a metallic foreign body. In 1874, Mckeown went further by exploring an eye with the tip of a magnet introduced in the vitreous. William Sturgeon developed the first electromagnet by the mid-1800s. In 1875 Julius Hirschberg pioneered its use in ophthalmology.³ Although the size of a minivan, it performed quite well.

Chiquet et al. prefer magnetic extraction provided that the metallic IOFB is within the vitreous.⁴

Rare earth magnets are commonly used to extract metallic IOFBs. However, their strength is unpredictable and they do not offer much flexibility.

Electromagnet uses electric current converted into a magnetic field. It is this variable source of energy that makes it stronger, flexible, and predictable compared with large rare earth magnets. Commercial models available today do not come cheap. A basic unit plus peripherals will cost around US\$6,000.

Electromagnets work by collecting electrons at the negative terminal of a battery. These electrons will flow to the positive end through a conductor. When a wire is connected between the positive and negative terminals of a battery, three things will successively occur:

1. Electrons will flow from the negative to the positive end of the battery.
2. Within several minutes, the battery—if its two terminals are connected directly—will drain.
3. A small magnetic field is generated in the wire, which is the basis of the electromagnet.

A higher load of current will make a stronger magnet. But there is a limit to how much current can flow through the wire before it heats up. If the probe gets too hot, it may damage ocular tissues. This may be avoided by having a capacitor installed in the unit. Since a stronger current would waste a lot of energy it is wise to use a regulator. Adding coils to the electromagnet also adds power.

METHODOLOGY

A test model that included a 24-volt battery and a soldering-iron holster with a metal bar the size of a pen acting as the material to be magnetized was used. The iron bar was magnetized but it absorbed most of the heat. By replacing the iron holster with solenoid coils, heat was

localized instead of being absorbed by the material to be magnetized. A capacitor was also installed to provide successive storage and discharge of electrical energy to avoid a surge of current that would generate heat.

High magnetic power is equivalent to a high source of energy. To turn alternating current (AC) into a turned-down direct current (DC), a transformer was installed. These modifications were necessary to reduce heat while supplying a strong adjustable source of electromagnetic field.

Alternating current from the electric outlet will go to the transformer, where a rectifier will convert it to pulsating DC with 50-volt maximum power (Figure 1). This will then go to the capacitor for filtering to become pure DC, which in turn will supply the solenoid coils with current to generate the electromagnetic field.

For the electromagnet to work, the probe must be capable of transmitting the magnetic field and fit into a small pars plana incision. This posed a problem because magnetic power is affected directly by surface area and inversely by the distance the magnetic energy has to travel from the power source. Thus, if the medium is thin and long, magnetic power will be markedly diminished. A stainless ophthalmic curette was fashioned similar to a dart tip and mounted on a 5/32 x 3/8 GI-stove bolt to serve as probe. The intraocular probe excluding the bolt was 22mm in length with a tip diameter of .05mm. For external extraction through a sclerostomy site, a probe with a blunt tip and a bigger surface area was designed.

Two kinds of coils were designed:

- A small coil that gives more flexibility to the surgeon but with less magnetic power for use with the thinner, sharper probe for intraocular extraction via pars plana
- A bigger coil with more magnetic power that could be fitted with the blunt tip probe for external extraction via sclerostomy.

The whole circuitry was housed in an old automatic voltage regulator casing fitted with voltage and ampere

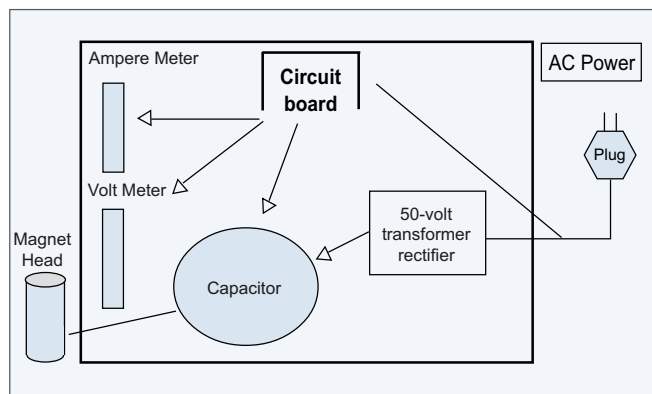


Figure 1. Circuit diagram

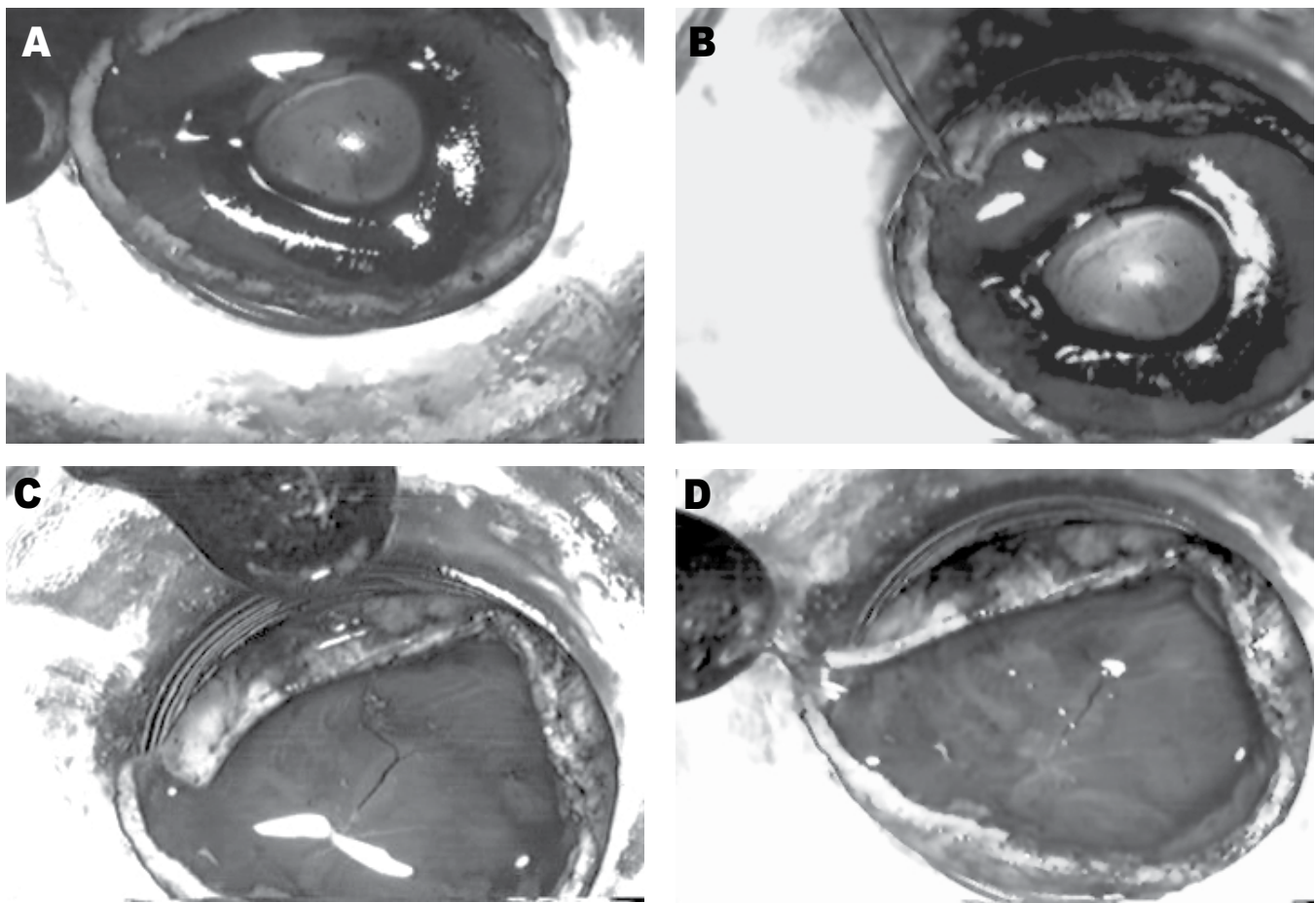


Figure 2. Electromagnetic extraction of intraocular foreign body: (A) tenting of the sclera caused by fragment while being magnetized, indicating its location near the choroid; (B) extraction through the slit using the pars plana probe; (C) blunt-tipped probe magnetizing the fragment even without sclerostomy; (D) external extraction through site of exit.

meter. Separate switches were installed—a power switch and a voltage switch that would activate the electromagnetic power.

The electromagnetic probe was compared with a larger permanent circular magnet to determine how many paper clips each of the magnets could pick up from end to end. This was to measure not the magnetic strength but magnetic accuracy.

Magnetic strength is measured with a gauss meter, which is not available locally. But it is possible to devise simpler methods of measuring magnetic capacity.

The magnetic strength of the electromagnet with the blunt tip was quantified by determining the maximum weight it could carry using a metal plate and lifting it. The electromagnetic probe was compared with a strong rare earth permanent magnet used in ophthalmology by putting a metallic object between the two magnets and engaging them in a tug-of-war.

1% sodium hyaluronate gel (Alcon Laboratories, Fort Worth, TX, USA) was used as a substitute for vitreous. A 3mm x 1mm metallic fragment was suspended in a tube

of this polymer. The capability of the electromagnetic probe to magnetize a particle with an interface (cohesive viscoelastic) between its tip and the metallic fragment to be magnetized was tested. The magnetic extraction of the metallic shard was videotaped.

The porcine eye was cut circumferentially anterior to the equator. The lens and parts of the iris remained intact while part of the sclera was removed. The anterior hyaloid phase was not disturbed. Using a pair of 0.12mm forceps, a 6x5mm metallic fragment was placed intravitreally near the optic nerve. Through a 3mm sclerostomy where the electromagnetic probe was inserted, magnetic extraction was performed.

RESULTS

The device and peripherals cost PhP3,500 compared with commercial models costing 100 times more.

The pars plana magnetic probe can hold four paper clips end to end vis-à-vis the bigger and heavier permanent magnet that can hold three paper clips.

The electromagnetic coil had a maximum lifting capacity of 8.5 lbs or 4.25 kgs at 50-volt setting.

During the pretesting of the device, the pars plana probe magnetized a 3mm x 1mm metal fragment suspended in a tube of 1% Na Hyaluronate gel at a distance of 6mm.

The extraction proceeded smoothly with the device set at 24 volts, below the full setting of 50 volts (Figure 2).

DISCUSSION

Poor final vision (20/400 or less) following posterior segment IOFB removal by electromagnet has been associated with these factors: initial vision less than 20/200, IOFB 3mm or longer, and presence of posttraumatic retinal detachment.⁴

With the post operative visual acuity (VA) as the main outcome measure, Chiquet et al. used electromagnetic extraction without vitrectomy to retrieve metallic IOFB. The authors reported that in 26 (65%) eyes, a significant improvement in VA after surgery occurred ($p = 0.0001$), with 23 (58%) patients attaining functional success and nine (23%) retaining preoperative VA. Seventy (70) of the patients obtained a final VA $\geq 20/40$.⁴

In a study by Greven et al. where 64% of IOFB retrieval was done through pars plana vitrectomy and the rest by scratch-down sclerostomy and forceps, a final VA $\geq 20/40$ or higher was achieved in 42 (71%) of 59 consecutive patients, 20/50 to 20/200 in 7 patients, 20/300 to 5/300 in 1 patient, and $<5/200$ in 9 patients. Ambulatory vision, defined as $>5/200$, was achieved in 50 (85%) patients. The authors, however, noted that comparing visual acuity results among studies was difficult because of the variable circumstances involved in ocular trauma.²

At the East Avenue Medical Center, electromagnetic extraction is preferred over vitrectomy because it preserves the vitreous and may be performed regardless of the depth of the IOFB.

Chiquet et al. noted that most surgeons prefer electromagnetic extraction in posterior segment IOFB regardless of the presence of small or moderate vitreous hemorrhage, whereas pars plana vitrectomy is reserved for nonmagnetic IOFB, intraretinal or encapsulated IOFB, dense vitreous hemorrhage, and management of late complications.⁴

The strength of the device we developed lies in the simple theory of electromagnetism. It presented the pos-

sibility of assembling an electromagnetic device from cheap locally available electronic parts. In this study, we were able to demonstrate that the assembly worked. At 24-volt setting (half the device's actual power), the electromagnetic probe easily extracted—internally using a pointed probe and externally using a blunt probe—the metallic foreign body placed intravitreally in porcine eye. At a lower setting the device could orient the foreign body to its long axis for better and safer extraction through sclerostomy.

Electromagnets may also be used to remove foreign bodies in the anterior chamber generally found at the iris plane. Removal of the foreign body in the entry wound is not recommended. Rather, a shelved incision through clear cornea or sclera is done depending on the size and location of the foreign bodies. A gauge 20 electromagnetic probe is inserted through this incision. The objects align themselves along the plane of the magnet, facilitating their removal.

In summary, this study presents the techniques for assembling a low-cost electromagnet for removal of metallic intraocular foreign body. It has the following limitations:

- The device could only be used in extraction of magnetic nonencapsulated IOFB.
- Compared with permanent magnets, the device needs an electrical source to operate.
- In the absence of a foot switch, a second individual is needed to operate the voltage regulator during sterile conditions.

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XXV JOSE RIZAL MEMORIAL LECTURE

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The Blind Filipino: What have we done? What needs to be done?

The Jose Rizal Memorial Lecture was established in 1955 by the Philippine Ophthalmological and Otolaryngological Society, the progenitor of the Philippine Academy of Ophthalmology (PAO), to honor Filipino and foreign ophthalmologists for their work in advancing the science and practice of the specialty. The previous 24 lecturers were honored for their work on specific areas of ophthalmology. Their works, taken collectively, address the social agenda of sight conservation and blindness prevention.

For this edition of the Lecture, we mark a paradigm shift. We will honor the contributions of not one but a group of ophthalmologists—the public service ophthalmologists. I accepted the honor of delivering the XXV Jose Rizal Memorial Lecture in the name of the countless and faceless ophthalmologists and nonophthalmologists alike who have made a collective effort to address sight conservation and blindness prevention as a public health concern.

The choice of this subject is not without reason. One hundred years after our national hero introduced the practice of ophthalmology in this country; 50 years after Filipino ophthalmologists organized themselves; and 25 years after we formulated the National Sight Plan that made us the 51st country to join the World Health Organization (WHO) in the fight against blindness, it is time we ask the question: How have we shown our concern for the blind Filipino?

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THE VISION

On his inauguration as the third president of the Philippine Ophthalmological and Otolaryngological Society in 1950, Dr. Geminiano de Ocampo, the father of Philippine ophthalmology, said: "The ultimate goal of Philippine ophthalmology should be that any Filipino with an eye disease is given adequate treatment, and that no blindness should come to any Filipino [given] the benefit of modern ophthalmologic knowledge and practice."¹

The PAO declares in the preamble to its constitution its goal to build "a blind-free society and establish an organization that shall...implement an integrated and comprehensive plan for sight promotion, sight conservation, blindness prevention, cure, and rehabilitation."²

The public service ophthalmologists have given meaning to this vision and goal. They believe that the sight of the Filipino blind is worth saving and restoring.

Many people often say, "If you are not part of the solution, you are part of the problem." For those who fall short of this vision, I hope this lecture will enlighten them on what they can do to be part of the solution rather than the problem.

In this lecture, I will answer the question: *The Blind Filipino: What have we done? What needs to be done?*

WHAT HAVE WE DONE?

Blindness prevalence in the Philippines has been reduced by 46 percent from 1.07% in 1987³ to 0.58% in 2002 (Olivar-Santos EO. Third National Survey of Blindness Philippines 2002). This rate, however, remains 0.08 percentage point higher than the WHO blindness prevalence goal of 0.5%, and 0.38 percentage point short of the 0.2% prevalence rate in developed countries.

This achievement did not come easy. We have had a long and continuing fight against blindness.

We have tried to sensitize the ophthalmologist and the public on the problem of blindness

- 1930: Blindness: Its causes and prevention (Dr. Conrado Ayuyao)⁴
- 1954: Sight-Saving Week through Presidential Proclamation No. 49¹
- 1959: Prevention of Blindness: A challenge to all (Dr. Antonio Fernando)⁵
- 1959: Preventive ophthalmology in the Philippines (Dr. Edmundo Reyes)⁶
- 1961: On preventive ophthalmology (Dr. Geminiano de Ocampo)⁷
- 1961: The role of the ophthalmologist in the prevention of blindness (Dr. E. Caparas)⁸
- 1978: Sight-Saving Week was expanded to Sight-Saving Month



Alejandro S. De Leon, MD, MHA *XXV Jose Rizal Memorial Lecturer*

Our XXV Jose Rizal Memorial Lecturer I admire, respect, and love. For all his work much can be said about him.

As a student, our Lecturer possesses that insatiable drive to learn. Beyond being a physician with ophthalmology as his specialty, he holds a degree of Master in Hospital Administration. He has mastered the science and art of management.

As a teacher, he rose from the rank of Instructor to full Professor at the University of the Philippines. He meets Sir William Osler's definition of a great teacher—"a senior student earnestly interested in the welfare of his junior students."

As a researcher, he is Hawking's disciple. He subscribes to the simple truth that man's desire for new knowledge is justification enough for his continuing quest for new knowledge. In his early years, he worked on the immunology of the corneal graft at Hopkins with A. Silverstein and on the retinopathy of prematurity with J. Elliot, both of whom I happened to know.

As an administrator in the academe (UP-Manila) and outside (Department of Health), he is not the pedantic bureaucrat. Nonetheless, he gets work done through people.

He is a planner par excellence.

He is a devoted husband and father. Both his wife, Angie, and his son are ophthalmologists.

I have never known a friend who is as loyal. When I had the opportunity to help establish and organize the Cardinal Santos Department of Ophthalmology, Eye Referral Center, formulate the Philippine Eye Research Institute (PERI) to Institute of Ophthalmology (IO) and craft the Philippine Program of Research in Ophthalmology, our Lecturer was there to lend a helping hand.

In 1993, our Lecturer was the Philippine Society of Ophthalmology Awardee for work on the Prevention of Blindness in the Philippines; the following were the words I said about him: "His is the crisp clarity of intellect, unequalled capacity to translate concepts and ideas into print, tenacity of purpose, and the natural disposition to accomplish work with the quiet dignity of a man to whom material gain and public accolade are strangers—ennobling values he truly embodies."

Is it any wonder then that GOD decided to keep our Lecturer, a Panglossian optimist, to be with us still for him to continue HIS work here on earth? — *Salvador R. Salceda, MD*

Our leaders have constantly admonished the ophthalmologists, various health workers, and the public on the problem of blindness. We continue this effort of social marketing through the Sight-Saving Month, celebrated every August of each year with scientific meetings, educational forums, radio and television interviews, vision screening, free eye and surgical clinics.

We have defined the magnitude and causes of blindness

- 1969: A survey of blindness in Bay, Laguna (Fojas M, de Ocampo G, Portes J)⁹
- 1976: A study on the incidence of blindness (Alianza LC)¹⁰
- 1977: Frequency of blindness in Davao City (Gestuvo RVG)¹¹
- 1987: The Institute of Ophthalmology blindness survey (Ramirez RL)³
- 1995: Second National Survey of Blindness, Philippines (Olivar-Santos EO)¹²
- 2002: Third National Survey of Blindness, Philippines (Olivar-Santos EO)

Cataract, vitamin A deficiency, trachoma, onchocerciasis, and glaucoma are the leading causes of blindness worldwide. Trachoma and onchocerciasis are not public-health problems in the Philippines. We have successfully eliminated blindness due to vitamin A deficiency.

Prior to 1980, numerous definitions of blindness made it difficult to convince decision-makers to take cognizance of blindness and give it priority. Using the 1980 WHO definition of blindness and a prevalence goal of 0.5%, the 1987 First National Blindness Survey showed that blindness was a public-health problem and cataract was the main cause. Thus, we have made the elimination of cataract blindness the centerpiece of our national blindness prevention program.

We have established organizations to address the prevention and elimination of blindness

- 1945: Philippine Ophthalmological and Otolaryngological Society (POOS) – Philippine Ophthalmological Society (POS)/Ophthalmological Society of the Philippines (OSP) – Philippine Society of Ophthalmology (PSO) – Philippine Academy of Ophthalmology (PAO)
- 1959: Philippine Society for the Prevention of Blindness (Severino Lopez)¹³
- 1971: National Council on Blindness (Salvador Salceda)¹⁴
- 1989: Department of Health (DOH) Blindness Prevention Committee¹⁵
- 1995: Philippine Academy of Ophthalmology (PAO) Prevention of Blindness Committee
- 1999: National Committee for Sight Preservation (NCSP) (Evangeline Olivar-Santos)¹⁶

The eye society, civic groups, and nongovernment organizations (NGOs) provided service to the blind Filipino through outreach missions, but these were insufficient to significantly reduce blindness prevalence.

The National Council on Blindness (NCB) composed of professional groups, civic organizations, government agencies, educational institutions and commercial corporations envisioned to bring together those involved in the prevention and elimination of blindness to a common program of action. One of its major accomplishments was the formulation of the National Sight Plan (NSP). Implementation, however, proved difficult.

In 1989, the DOH reformulated the National Sight Plan into the DOH Prevention of Blindness Program. By 1995, the Second National Blindness Survey showed a reduction in blindness prevalence from 1.07% to 0.7%.

In 1992, health services were devolved to local government units and a new organizational structure had to be established. The NCSP composed of key players in the Philippine blindness prevention program was established to take the lead in achieving the goals of Vision 2020.

We have implemented various intervention programs

- 1966: POS operation sight saver¹⁷
- 1970: PSO rural eye clinic¹⁸
- 1973: A rural eye clinic in Ilocos Norte (Olivar EO)¹⁹
- 1974: Christoffel Blindness Mission (CBM) prevention of blindness partners
- 1978: National Sight Plan²⁰
- 1983: Rotary Club Outreach Cataract Clinic (Dr. Edgardo Caparas)
- 1983: Helen Keller International (HKI) Bicol prevention of blindness program²¹
- 1989: DOH Prevention of blindness program¹⁵
- 1990s: Project Sight Restoration²²
- 1995: Lion's Sight First project
- 2000: Vision 2020 Philippines²³

Finding that 75% of eye problems are primary care cases and 50% of the secondary eye cases required surgery, the POS operation sight saver provided eye consultation and surgery for patients and training for local primary physicians. The society's slogan was "Join the rural eye clinic and see the Philippines."

The National Sight Plan formulated by the NCB envisioned 4 operational programs, namely: eye-health education, first contact vision screening and treatment, early diagnosis and treatment, and rehabilitation.

The HKI prevention of blindness program in Bicol was the first attempt to test the National Sight Plan. The project consisted of enhancing the ophthalmic capability of the Bicol Regional Hospital, the training of primary health care workers, vitamin A supplementation, and cataract surgeries.

The DOH blindness prevention program was prompted by the results of the first national blindness survey, which showed blindness prevalence of 1.07%, and the WHO declaration that blindness prevalence higher than 1.0% constituted a public-health problem. The National Sight Plan and the Bicol experience served as models for the 1989 DOH Prevention of Blindness program.¹⁵ It had 4 objectives:

- reduce the cataract backlog,
- reduce the prevalence of vitamin A deficiency,
- integrate primary eye care with primary health care,
- develop the country's capability for eye-care services.

Vision 2020²³ had three strategies:

- disease control program
- human resource needs and development
- infrastructure/technology needs and development

Vision 2020 eyes the reduction of blindness prevalence to 0.5% with no community (province) having a rate greater than 1.0%.

We have increased the ophthalmologic manpower and brought eye care to almost all the provinces

- 1970: Philippine Board of Ophthalmology (PBO) was established (Almeda E)²⁴
- 1973: Common basic course for residents in ophthalmology (Fajardo RV)²⁵
- 1977: Requirements for hospital accreditation of ophthalmology residency training²⁶
- 1977: For more ophthalmology residency positions (Fajardo RV)²⁷
- 1988: Outreach ophthalmology residency program (Fajardo RV)^{28, 29}
- 1982: Ophthalmological manpower development plan in the Philippines (Fajardo RV)³⁰
- 1985: Modified Residency Training Program (Olivar-Santos EO)³¹

In the late 1970s, we had one ophthalmologist for every 170,000 Filipinos and 10-15 graduates of ophthalmology per year. The Philippine Board of Ophthalmology took the challenge and set out to increase the residency graduate to 40 per year and improve the ophthalmologist-population ratio to 1:100,000.

Today, we have 44 accredited residency training programs producing 60 to 70 graduates per year and an ophthalmologist for every 63,000 people. We have improved the ratio almost threefold.

In 1979, 60% of the provinces were without an ophthalmologist; today only 20% don't have the services of one. These are provinces that are either economically deprived or where the population is too small to warrant an ophthalmologist, or the terrain is too inhospitable, or the peace and order situation is bad.

We have collaborated with various government agencies and nongovernment organizations

Government agencies

- DOH: Vitamin A Supplementation, Measles Immunization, Primary Eye Care, Modified Residency Training Program, Ophthalmologic Services, National Blindness Survey
- Department of Education: School for the Deaf and Blind, Special Education, Munting Doktor
- Department of Social Welfare and Development: Rehabilitation of the Blind
- Commission Concerning Disabled Persons

International organizations and civic groups

- Helen Keller International: Vitamin A Supplementation
- Christoffel-Blindenmission and partners: Cataract Program
- Lions
- Rotary Professional groups and NGOs
- Optometric associations: School vision screening, error of refraction
- EPHPHETA: rehabilitation of the blind
- Resources for the Blind: rehabilitation of the blind
- Sukob
- Cataract Foundation
- Eye Health and Safety Foundation

Before 1979, groups concerned with helping the blind worked independently of each other. The National Council on Blindness and the National Sight Plan were envisioned to provide the mechanism for a collaborative and coordinated program of action but their effectiveness was reduced by lack of a political mandate. The DOH provided the political authority for the Prevention of Blindness program. It highlighted the critical role of the ophthalmologist and the necessary support from nongovernment organizations. With the devolution, the political authority of the DOH has been weakened. As a result, continuity of the program has shifted to the National Committee for Sight Preservation under the PAO leadership.

We have provided low vision services in collaboration with other groups

- EPHPHETA
- Resources for the Blind
- School for the Deaf and Blind
- Department of Social Welfare and Development (DSWD) Bureau of Rehabilitation
- 1968: Philippine Eye Research Institute (PERI) low vision clinic³²
- 1991: Philippine General Hospital (PGH) low vision clinic
- 2001: St Luke's low vision clinic

The number of Filipinos with irreversible blindness and low vision has been increasing because of diabetic retinopathy, age-related macular degeneration, and glaucoma. In the past, this group of patients was served by nonophthalmologists. However, ophthalmologists are sub-specializing in the rehabilitation of the visually impaired and providing services for low vision.

We have documented the eye care and prevention of blindness movement in the Philippines.

- 1978: Eye Health Care Movement in the Philippines³³
- 1997: A Century of Ophthalmology in the Philippines³⁴
- 2000: The Work on the Prevention of Blindness in the Philippines: Its Evolution³⁵

10 LESSONS LEARNED

1. Eye health education has not been successful. Urine is still used for red eyes, iridology is popular, patients consult late, and many misconceptions still persist.

2. Cataract remains the major cause of blindness.

3. The ophthalmologist is crucial in the elimination of avoidable blindness but they cannot achieve it alone.

4. We are producing enough ophthalmologists, but maldistribution remains a problem.

5. Cataract surgical services are available, accessible, and acceptable but not affordable for many. Misconceptions about cataract and cataract surgery persist.

6. Cataract surgery rate (CSR) has to increase to reduce the cataract backlog and meet the incidence of new cases associated with an ageing population.

7. The emerging problems of glaucoma, diabetic retinopathy, and age-related macular degeneration have to be confronted.

8. New and innovative operational approaches have to be developed.

9. The needs of the economically deprived blind population have to be met.

10. We don't have enough resources to finance the program to eliminate avoidable blindness.

Table 1. Causes of visual impairment in the Philippines

Population	1987 ³ 60M		1995 ¹² 68M		2002 ^{**} 79.5M	
	Prevalence % (Rank)	Number	Prevalence % (Rank)	Number	Prevalence % (Rank)	Number
Cataract	1.24 (1)	744,000	2.97 (1)	2,032,193	1.83 (2)	1,455,049
Error of refraction			1.09 (2)	745,822	2.06 (1)	1,638,592
Amblyopia/strabismus	0.11 (3)	66,000			0.04 (8)	34,581
Glaucoma	0.07 (6)	42,000	0.16 (3)	109,478	0.09 (6)	71,821
Corneal opacity/staphyloma	0.04 (7)	24,000	0.14 (4)	95,794	0.09 (6)	69,161
Disorganized eyeball/enucleated	0.08 (5)	48,000	0.12 (5)	82,109	0.10 (5)	82,461
Uncorrected aphakia			0.11 (6)	75,266	0.04 (8)	34,581
Retinal/macular disease	0.13 (2)	78,000				
Chorioretinitis			0.04 (9)	27,370		
Vascular retinopathy			0.02 (10)	13,684		
Retinopathy Macular degeneration			0.07 (7)	47,897	0.11 (4)	85,121
Optic atrophy	0.10 (4)	60,000	0.05 (8)	34,212	0.16 (3)	127,682
Anterior uveitis			0.01 (11)	6,842	0.06 (7)	47,880
Others			0.09	61,582	0.01 (9)	5,320
Total	1.77	1,062,000	4.87	3,332,249	4.65	3,696,920

*Causes of binocular and monocular blindness only
 **Olivar-Santos EO, Third National Survey of Blindness Philippines, 2002

Table 2. Cataract blindness in the Philippines

Population	1987 ³ 60M		1995 ¹³ 68M		2002 ⁴ 79.5M	
	Prevalence %	Number	Prevalence %	Number	Prevalence %	Number
Blind, bilateral	0.93	558,540	0.54	369,490	0.36	287,285
Blind, mono.	0.31	186,000	0.28	191,587	0.51	
Blind, Low vision			0.33	225,115		
Low vision, bilateral			1.29	882,670	0.64	
Low vision, monocular			0.52	358,542	0.32	252,704
Total cataract cases		744,540	2.97	2,032,193	1.83	
Cataract cases/million				29,885		18,030
Estimated incidence				403,920	0.37	
Estimated CSR/million				440		630

CSR: Cataract surgery rate

WHAT NEEDS TO BE DONE?

Worldwide, the leading causes of blindness are trachoma (146 million cases), vitamin-A deficiency (75 million), cataract (16-20 million), onchocerciasis (17 million), and glaucoma (5 million).²³ In the Philippines, cataract remains the major cause of blindness.

Other emerging causes are corneal scar, diabetic retinopathy, age-related macular degeneration, childhood blindness other than xerophthalmia, error of refraction and presbyopia, and rehabilitation of the low-vision and blind patients. The Third National Survey on Blindness showed: error of refraction, glaucoma, retinopathy/maculopathy, and corneal scars as major targets of concern.

Causes of visual impairment

While the three national blindness surveys are not comparable, they show a trend in the causes of visual impairment: cataract is decreasing, error of refraction now ranks first, macular and retinal problems have dislodged glaucoma and corneal opacity in the third and fourth spot, and optic atrophy remains a concern (Table 1).

Cataract blindness

The prevalence of operable cataract was reduced by 22.88% and the cataract cases per million by 35.75%. The estimated cataract surgery rate per million has increased by 43.18% (Table 2).

Ophthalmic services

The ophthalmologist-population ratio has improved over the years, but ophthalmologists are unevenly distributed, resulting in an oversupply of eye doctors in some areas (Table 3). On the other hand, many provinces still have no ophthalmologist, although the population of some of these provinces is too small to support even one ophthalmologist.

Stages of eye care programs

Dr. Kazuichi Konyama³⁶ identified 4 stages in the development of blindness prevention programs:

- Preplanning Stage where domestic capability is minimal and international NGOs provide humanitarian services;
- Primary Health Care/Primary Eye Care/Prevention of Blindness stage where primary eye care is integrated with primary health care and disease-oriented vertical programs are developed;
- Eye Health-Care System Stage where eye care is integrated into the health-care system; and
- Noncommunicable Disease-Control Scheme Stage where the challenge is how to deal with noncurable blindness like glaucoma, diabetic retinopathy, age-related macular degeneration.

Table 3. Ophthalmic services in the Philippines

Population	1978 ²⁰		1987 ¹⁵		1995 ³⁷		2002 ³⁸	
	36.5M		60M		68M		79.5M	
	Number	Ratio	Number	Ratio	Number	Ratio	Number	Ratio
No. eye MDs	213		350		884		1267	
No. training programs	5		27		44		44	
No. graduated/yr	10		34		66		70	
Prov. w/o eyeMD	45/75	60.0%	32/75	42.7%	17/75	22.7%	16/78	20.5%
Eye MD:pop ratio	213	1:170,000	350	1:170,000	884	1:78,000	1267	1:63,000
Region I	2	1:1,493,000	18	1:197,000	36	1:106,000	51	1:82,000
Region II	4	1:419,000	9	1:260,000	22	1:115,000	20	1:141,000
Region III	20	1:185,000	17	1:365,000	79	1:88,000	76	1:106,000
Region IV	4	1:831,000	23	1:359,000	82	1:121,000	131	1:90,000
Region V	6	1:494,000	10	1:391,000	22	1:197,000	21	1:223,000
Region VI	14	1:257,000	15	1:359,000	39	1:148,000	53	1:117,000
Region VII	2	1:1,190,000	21	1:219,000	55	1:91,000	57	1:100,000
Region VIII	10	1:303,000	7	1:436,000	9	1:374,000	22	1:300,000
Region IX	6	1:328,000	5	1:492,000	21	1:133,000	14	1:221,000
Region X	10	1:221,000	10	1:220,000	26	1:96,000	20	1:137,000
Region XI	6	1:1,024,000	17	1:240,000	31	1:148,000	53	1:98,000
Region XII	1	1:805,000	3	1:678,000	11	1:214,000	9	1:289,000
CAR			8	1:143,000	12	1:104,000	14	1:97,000
NCR	128	1:39,000	185	1:43,000	388	1:24,000	452	1:22,000
CARAGA			1	1:1,764,000	6	1:324,000	8	1:262,000
ARRM			1	1:1,837,000	6	1:337,000	8	1:302,000

Table 4. Overall strategies of Vision 2020

Strategy	Specific	Vision 2020 WHO	Vision 2020 Philippines
Overall objective		• Eliminate avoidable blindness	• Reduce blindness prevalence to 0.5%, then 0.2%
Control of major causes of blindness	Cataract	• 0% prev. rate	• Less than 0.50%
	Trachoma	• CSR = 4000/M	• CSR=3000/M
	Onchocerciasis	• 0 cases of TF	• Not applicable
	Vit A deficiency	• 5% TF rate	
Human resource development	Blind children	• No new cases	• Not applicable
	Primary health care worker	• Nil incidence	• Nil incidence
	Ophthalmic/medical assistants/nurses	• 0.4/1000	• 0.4/1000
	Refractionists	• PEC integrated with PHC	• PEC integrated with PHC
Infrastructure and appropriate technology development	Ophthalmologists	• 1: 50 000	• P MEC trained
	Primary level (RHU/BHS)	• 1: 50 000	• Not available
	Subdistrict (District Hosp)	• 1: 50 000	• 1: 50 000
	District (Province)	• screening/case referral	• screening/case referral
Technology		• health education	• primary treatment
		• outreach cataract surgery	• primary medical eye care
		• refraction services	• refraction services
		• cataract surgery	• outreach cataract surgery
		• training	• eye center
		• refraction	• outreach activities
		• outreach activities	• integration and coordination
		• coordination	
		• cost effectiveness	• cost effectiveness
			• equity

TF: Trachoma
 PEC: primary eye care
 PHC: primary health care

PMEC: primary medical eye care
 RHU: rural health unit
 BHS: barangay health station

Operational paradigm

How then can we achieve the objectives of Vision 2020 (Table 4)?

First, prevention of blindness (PBL) planners must take heed of the ten lessons we have learned.

Second, PBL planners must review the 1978 National Sight Plan and the DOH 1989 Prevention of Blindness Program. In these documents unimplemented ideas such as eye health education, primary medical eye care, screening and referral system, support and research program can be reassessed.

Third, use the systems paradigm for detailing the operational projects. The essential components of the system are:

1. define the desired output (year-round public eye health education)

2. define the demand subcomponent system:

- identify the target demand groups (C, D, and E economic brackets, particularly mothers)
- identify the process (radio and television)
- identify the input messages

3. define the core system process (for example, pattern after the *Kapwa Ko Mahal Ko* or *Damayyan* radio-TV program)

4. define the core system inputs:

- radio-TV carrier
- ophthalmologist who will provide the service and the educational messages
- program host
- program venue (studio or on site or both)
- program sponsors

5. define the management subsystem component (professional producer)

Fourth, I endorse the PAO-Prevention of Blindness Committee strategy of “my community, my responsibility.”

I believe that:

1. The goal of this strategy is “people empowerment and universal access to eye care.”

2. People empowerment means an educated populace who take responsibility for their eye health. Activities to achieve this include:

- Year-round public eye health education
- Eye-health education in the elementary and secondary level
- Eye safety program
- Eye health education on the web

3. Universal access to eye care means availability of quality services when needed, where needed. It means having an integrated eye care delivery system. It means equity for all irrespective of financial capacity.

4. An integrated eye care delivery system shall consist of:

- Integration of primary eye care (PEC) with primary health care (PHC);
 - PEC screening/treatment and referral at the rural health unit (RHU) level;
 - Station eye clinic at the district level providing primary medical eye care (PMEC), with refraction, and regular, scheduled ophthalmic services; and
 - Comprehensive eye care service at the provincial level with subspecialty ophthalmic group practice
5. Equity for all can be achieved through:
- Advocacy for the implementation of the government’s universal health insurance program;
 - Advocacy for community-based health maintenance scheme; and
 - Foundation and donations

Fifth, geographically individualized programs (region or province) may be the better option for some compo-

nents and a common national program for other components. For example: The cataract program and the development of the eye-care system may be a local concern, but eye-health education and universal health insurance must be a national concern.

CONCLUSION

We have succeeded in reducing the prevalence of blindness from 1.07% to 0.58%. We achieved this by focusing on the problem of cataract, increasing and distributing the ophthalmologic manpower, and enhancing the cost-effectiveness of eye-care service delivery.

Dr. Gemiliano Ocampo's vision of no Filipino becoming blind given the benefits that ophthalmic care offers remains a dream. The prevalence of blindness has to be reduced not to 0.5% but to less than 0.2%. The program must address not only the cataract problem but also the emerging causes of blindness. The program must also have an implementing organizational structure.

Here's what I think should characterize a dream prevention of blindness program (Cadiz M., A profile of the practice of ophthalmology in the Philippines, 2003):

- *To have an educated population responsible for sight conservation and blindness prevention.* Eye-health education must start with elementary education and be continually reinforced throughout life.
- *To have ophthalmologists in every community who are part of the solution.* They hold the key to the establishment of an eye-care delivery system.
- *To have a complete range of eye services available and accessible.* Data have shown that the expertise of an ophthalmologist is required in only 25% of eye conditions.²¹ Trained primary eye-care workers, midlevel eye-care workers, and nonophthalmic physicians can adequately handle the rest. The eye care delivery system will consist of various levels of facilities and expertise linked by a referral system.
- *To make eye-care services affordable and acceptable.* Nonconventional methods of continuing education and referral should be explored, particularly the use of information technology. Cost effectiveness should be included as a criterion in the formulation of practice guidelines. Innovative payment schemes, not dependent on government subsidy or donations, need to be explored.
- *To have an eye-care system that is effective, efficient and equitable.* This system will be fine-tuned at each operational level.

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Provide a structured abstract of 300 words or less with the following four headings:

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Journal Article (If five or more authors, list only the first three and add et al):

Vail A, Gore SM, Bradley BA, et al. Clinical and surgical factors influencing corneal graft survival, visual acuity, and astigmatism. *Br J Ophthalmol* 1996; 103: 41-49.

Chapter in a Book

Parks MM, Mitchell PR. Cranial nerve palsies. In: Tasman W, Jaeger EA, eds. *Duane's Clinical Ophthalmology*, revised ed. Philadelphia: JB Lippincott, 1993; v. 1, chap. 19.

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World Health Organization. Hospital infection control guidelines for severe acute respiratory syndrome. April 16, 2003: <http://www.who.int/csr/sars/infectioncontrol/en> (accessed April 24, 2003).

TABLES

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