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Biocompatibility of Implantable Sensor for Real-time Monitoring of Intraocular Pressure

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Biocompatibility of Implantable Sensor for Real-time Monitoring of Intraocular Pressure

by

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Abstract

Biocompatibility of Implantable Sensor for Real-time Monitoring of Intraocular Pressure

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Purpose: To evaluate the rabbit-eye biocompatibility of a new implantable intraocular pressure (IOP) sensor for real-time continuous monitoring of IOP.

Methods: The novel IOP sensor is a prototype rectangular (5 mm long by 3.5 mm wide) implantable device that allows radiofrequency-based (wireless) real-time IOP measurement. The sensor was implanted into the eyes of two New Zealand white rabbits (one eye per rabbit). The rabbits were observed and examined by microscopy and external ophthalmic photography at two, four, and eight weeks post-implantation. Then, still at eight weeks post-implantation, the two eyes were enucleated. Following the gross pathologic evaluation, the IOP sensors were explanted and subjected to histological

analysis.

Results: The new IOP sensor was well tolerated in both rabbit eyes. The sequential microscopic in vivo evaluations performed up to eight weeks post-implantation showed no evidence of significant inflammation or scar formation. And according to the histopathologic findings, there were no significant inflammatory reactions or deformities of the ocular-tissue structures.

Conclusions: The prototype IOP sensor showed favorable rabbit-eye biocompatibility, there being no significant evidence of toxicity or foreign-body reaction.

Keywords: Biocompatibility, Continuous monitoring, Glaucoma, Intraocular pressure, Implantable sensor.

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Introduction

Glaucoma causes progressive damage of optic nerves and subsequent visual field defect, and is also a common cause of blindness. Among the several risk factors related to the development and progression of glaucoma, intraocular pressure (IOP) remains the only proven therapeutic target. The normal IOP range is 10 – 21 mmHg.[1, 2] However, even healthy eyes show daily diurnal fluctuation within the 1 – 5 mmHg range.[3-5] IOP as measured during periodic office visits might not accurately represent this phenomenon,[6-8] even though large IOP fluctuation is a major risk factor for progression of glaucoma.[9-11] Continuous monitoring of IOP for the detection of progression and proper management of glaucoma, therefore, is of paramount importance.

Unfortunately, with current IOP measurement methods such as Goldmann applanation tonometry (GAT), continuous, real-time monitoring is difficult. Therefore most patients visit clinics to measure their IOP, but these episodic measurements at office hours cannot represent the precise IOP states of the patients. Further, GAT is affected by corneal biomechanics, specifically corneal thickness, corneal curvature, and the corneal tear film, among other aspects.[12-14]

Therefore, various types of sensors have been developed.[15-24] The most widely known continuous IOP sensor is that which is incorporated into a soft contact lens to measure changes in corneal IOP-related biomechanics.[17, 24-26] However,

like GAT, the contact-lens-type sensor is affected by corneal biomechanics,[27] which means that measurements in patients with corneal abnormalities will be skewed. Moreover, this type of sensor can lead to complications associated with long-term contact lens use.

To overcome these limitations, we have been developing a new IOP sensor that can be implanted inside the eye. With this new sensor and its external reader, IOP can be measured wirelessly, continuously, and precisely: "true" IOP monitoring free of the distortional influence of corneal biomechanics is enabled. This continuous real-time IOP monitoring system, accordingly, facilitates early detection of risk and more effective treatment of glaucoma. We already reported about this novel IOP sensor on researching (Gunawan A, Chae MS, Kang JY, Lee SH, "Fabrication and Characterization of Implantable Wireless Pressure Sensor for Biomedical Applications", The 12th World Congress on Biosensors (Biosensors 2012), Cancun, Mexico, (2012)).

One of the most important prerequisites for an implantable sensor, and also one of the unresolved issues, is long-term biocompatibility. To that end, in the present study, we evaluated the biocompatibility of a novel IOP sensor.

Material & Methods

(1) Telemetric Implantable IOP sensor

This sensor was made by the Korea Institute of Science and Technology (KIST). An IOP sensor system consists of two components: the implantable IOP sensor, and the portable external telemetry-based IOP reader. The implantable IOP sensor has top and bottom layers. The top layer is composed of an inductor (L) and capacitor (C) cross-linked in parallel, which combination generates a resonant frequency. The bottom layer is a silicon wafer, the backside of which is etched, the grooves filled with copper or ferrite. The two layers are bonded with a biocompatible adhesive.

The fabrication processes of top layer and bottom layer are summarized as follows.

A. Fabrication process of Top layer

a) Biocompatible polyamide was spin-coated over the surface of a silicon wafer.

b) Thermal curing was done by convention oven under 200℃.

c) A copper layer was electroplated.

d) Processes a) to c) were repeated.

e) Bionate® (Thermoplastic Polycarbonate Urethane) was spin-coated.

f) The backside of the silicon wafer was etched.

B. Fabrication process of Bottom layer

a) Silicon rubber was spin-coated over the surface of the silicon wafer.

b) The backside of the silicon wafer was etched.

c) Copper or ferrite was bonded in the grooves.

When the IOP changes, it effects a mechanical indentation or deflection of the bottom layer, which changes the distance between the inductor (coil) of the top layer and the ferrite or copper of the bottom layer, which change, in turn, alters the magnitude of inductance, which alteration is measured digitally and transmitted externally by radiofrequency. The external IOP reader then detects the resonant frequency and converts it to an IOP value. This prototype IOP sensor was designed to a 5 mm (length) × 3.5 mm (width) size (Figure 1) suitable for implantation into the eyeball of a rabbit.

(2) Animal

This study's animal-experimentation protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Seoul National University Hospital (Seoul, Korea), and the experimentation was conducted in an Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC)-approved animal laboratory. Two adult male New Zealand white rabbits (weight: 2.0 ~ 2.5 kg) were purchased from Yonam Laboratory Animals, Cheonan, Korea. Prior to the beginning of the study, both of the animals were subjected to a complete ophthalmologic exam.

(3) Surgical implantation of IOP sensor

The IOP sensors, sterilized preoperatively with ethylene oxide gas, were implanted in a dedicated animal operating room under surgical microscopy.

The rabbits were anesthetized using Tiletamine Hydrochloride with Zolazepam Hydrochloride (Zoletil®, 10 mg/kg of body weight) and Xylazine hydrochlorid (Rompun®, 6.8 mg/kg of bodyweight) by intramuscular injection.

The surgical procedure began with formation of a fornix-based conjunctival flap by dissection of the superotemporal quadrant. This was followed by formation of a limbus-based, rectangular partial-thickness scleral flap (approximately 33% ~ 50% depth) using a beaver blade. A sensing part of the IOP sensor was inserted into the anterior chamber via scleral incision site beneath the scleral flap, and an anchoring part of the IOP sensor was fixed to sclera with 10-0 nylon (Ethicon®). The scleral flap and conjunctival peritomy sites were then sutured with 10-0 nylon (Ethicon) (Figure 2).

Oxytetracycline/PolymyxinB ointment (Terramycin®) was applied during the night of the surgery. Topical antibiotics (Tobramycin [Tobra eye soln®]) and steroid (Prednisolone acetate 1% ophthalmic suspension [PredForte1%®]) were administered once daily from postoperative day one to postoperative one month.

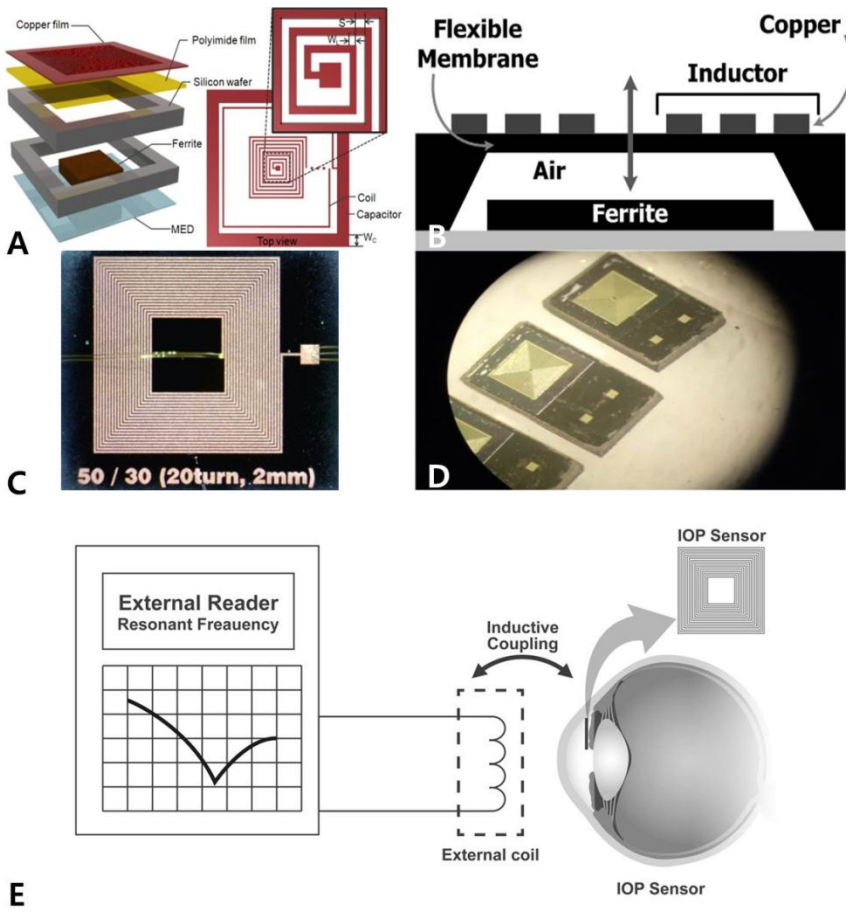
(4) Follow-up

Slit-lamp evaluation and external ophthalmic photography were performed at two, four, and eight weeks post-implantation. We evaluated the cornea, iris, lens, anterior-chamber depth and reaction, wound healing, and the position and structural stability of the implant.

(5) Histology

Two eyes of two rabbits (Rabbit No. 1 and 2) were enucleated at eight weeks post-implantation. The specimens were placed in 4% formaldehyde in phosphate-buffered solution. Rabbit No. 1 was paraffin embedded and Rabbit No. 2 was cryopreserved, respectively, preparatory to histologic sectioning. Subsequently, the histologic sections were stained with hematoxylin and eosin.

Figure 1. Novel implantable IOP sensor



A. Structure map of implantable IOP sensor.

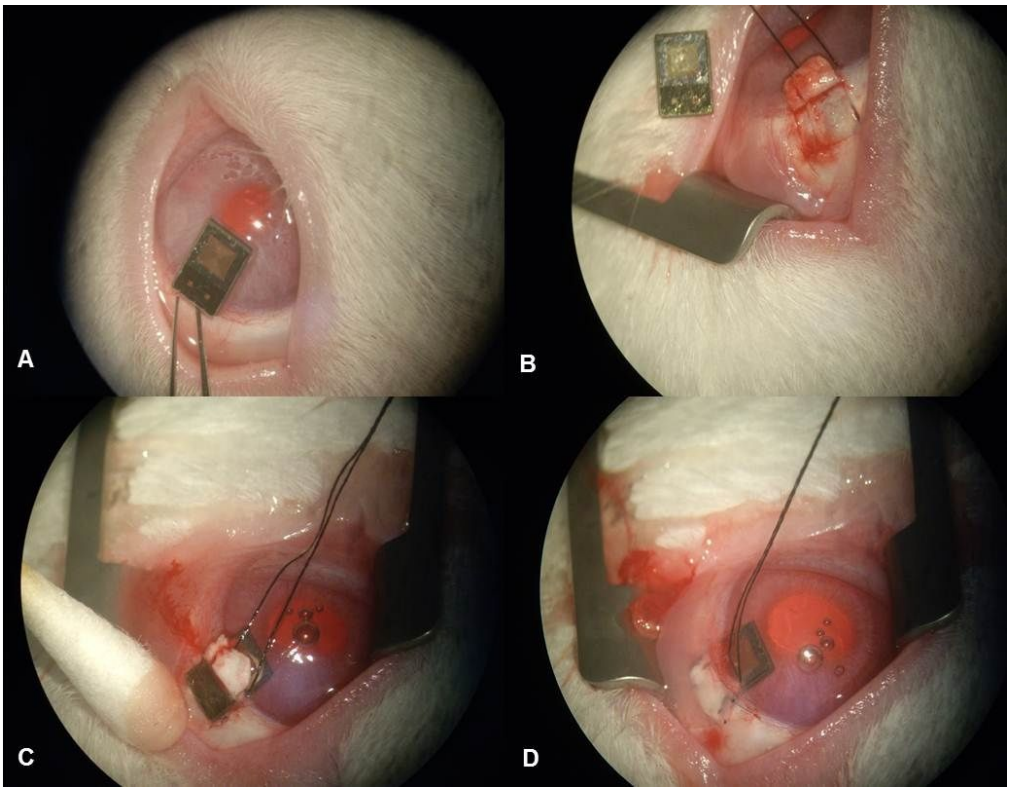
B. Cross-sectional view of implantable IOP sensor: metal of bottom layer is Ferrite.

C. Top layer of implantable IOP sensor.

D. Prototype implantable 5 mm long × 3.5 mm wide IOP sensor.

E. The schematic diagram of wireless IOP monitoring system.

Figure 2. IOP sensor implantation procedure



A. Positioning for location of IOP sensor.

B. Formation of partial-thickness limbus-based scleral flaps.

C. Insertion of measuring component into anterior chamber via sclera incision site and scleral fixation of anchoring component.

D. Repair of conjunctival peritomy sites and partial scleral flap.

Results

Clinical examination by portable slit-lamp evaluation and surgical microscopy showed that in the immediate-postoperative period, conjunctival chemosis, conjunctival injection, corneal edema and transient anterior-chamber reactions consistent with the implantation procedure were common to the two rabbits. However, in both cases, these manifestations regressed within four weeks. There were no significant complications such as fibrinous reaction, membrane formation, iris atrophy, cataract formation or chronic uveitis (Figure 3).

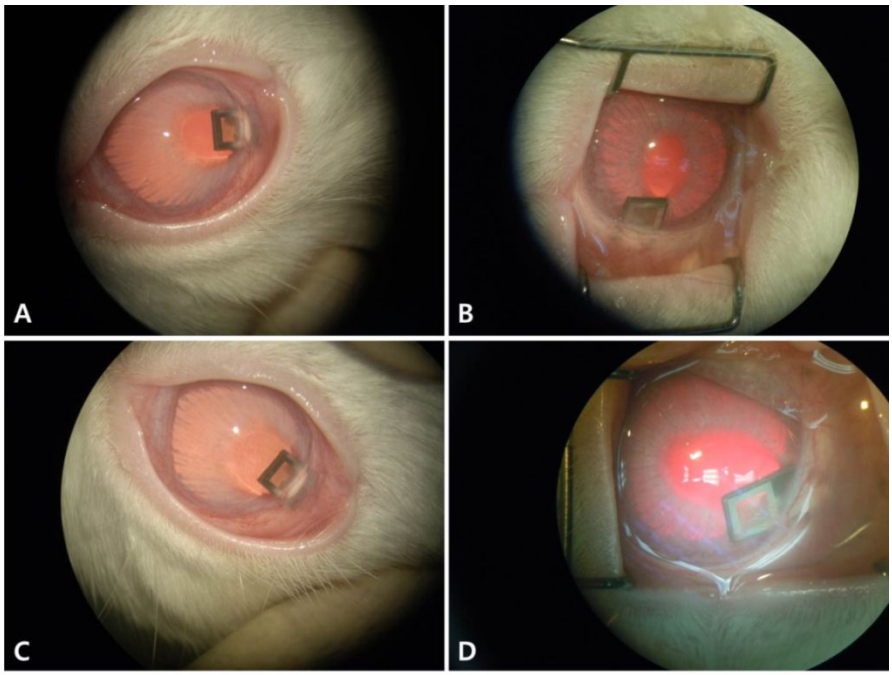
Eight weeks post-implantation, the gross pathologies of the eyes, now enucleated, were evaluated. There was no fibrinous adhesion, gross inflammation or encapsulation around the implant, and the globe integrity had been preserved (Figure 4).

Immediately following the gross pathologic evaluation, the IOP sensors were explanted, and the enucleated eyes were subjected to a histopathologic evaluation. In the section specimens for rabbit No. 1, a comparison with the opposite side (the control region) of the same eye revealed that inflammatory cells had infiltrated into the limbal area. Moreover, inflammatory infiltrates were found throughout the subepithelium and anterior stroma of the cornea. However, the stromal layer generally maintained its normal configuration, and there were no significant deformities of tissue structures in the sclera, limbus, cornea, or anterior-chamber-angle region. The non-pigmented iris and ciliary

body stroma were both anatomically intact (Figure 5).

The specimens for rabbit No. 2 also showed infiltration of inflammatory cells into the limbal area, mostly the subepithelial and anterior stromal layers. Under high magnification (Figure 6D), the inflammatory cells were found to be composed mainly of polymorphonuclear neutrophils (PMNs). There was no definite deformity of tissue structures; the sclera, cornea, iris, ciliary body and lens showed their normal configurations (Figure 6).

Figure 3. Follow-up external photography of Rabbit No. 1 (A, C) and Rabbit No. 2 (B, D)



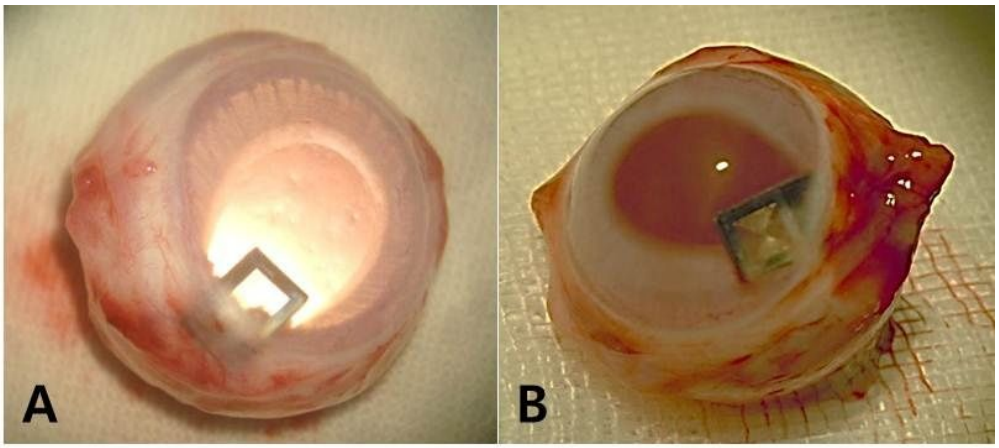
A. Four weeks post-implantation: ciliary injection around insertion site can be seen.

B. Four weeks post-implantation: ciliary injection and mild corneal neovascularization with haziness around insertion site is apparent.

C. Eight weeks post-implantation: ciliary injection much decreased; transparency of cornea within normal range.

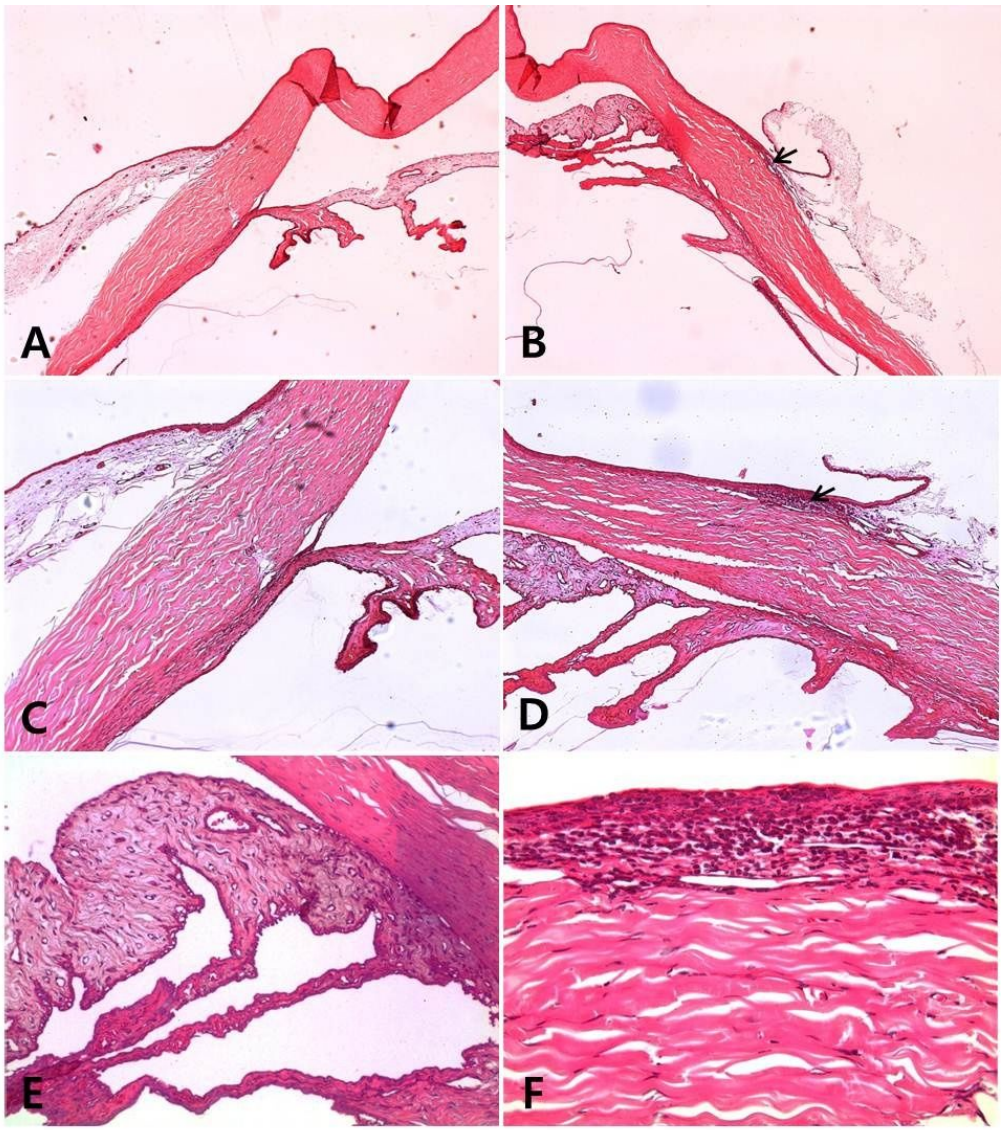
D. Eight weeks post-implantation: ciliary injection much decreased; corneal neovascularization with haziness nearly regressed.

Figure 4. Gross photography of enucleated rabbit eyes at eight weeks post-implantation of the IOP sensor.



A. Rabbit No. 1 B. Rabbit No 2: no evidence of gross inflammation, membrane formation, or encapsulation of IOP sensor; globe integrity appears normal.

Figure 5. Histologic sections of Rabbit No. 1, enucleated at eight weeks post-implantation of the IOP sensor (Hematoxylin-eosin stain)



A. Histologic section of limbal area on side opposite to insertion site (control region) (original magnification: × 40)

B. Histologic section of limbal area near insertion site: compared with control region (Fig. 5A), there is no definite deformity of tissue structures, though there is infiltration of inflammatory cells into limbal area (black arrow) (original magnification: × 40)

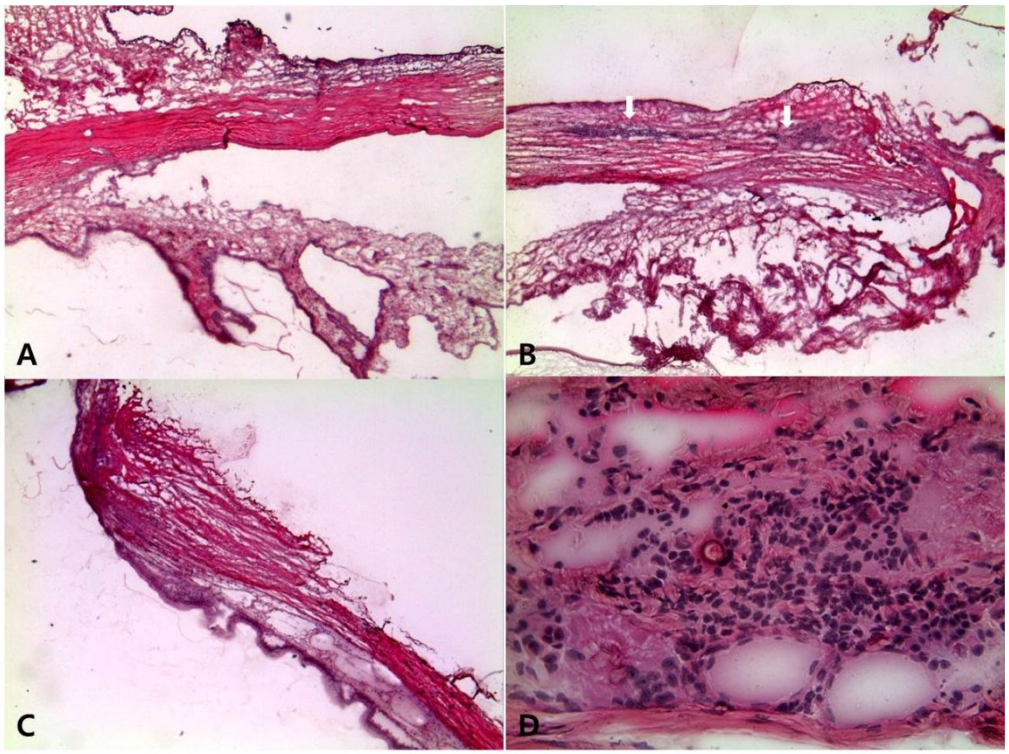
C. Histologic section of limbal area on side opposite to insertion site (original magnification: × 100)

D. Histologic section of limbal area near insertion site: black arrow denotes infiltration of inflammatory cells into limbal area (original magnification: × 100)

E. Histologic section of ciliary body and iris near insertion site: non-pigmented iris and ciliary body stroma are anatomically intact (original magnification: × 200)

F. Histologic section of limbal area near insertion site: inflammatory infiltrates were commonly found subepithelially. normal configuration of stromal layer maintained (original magnification: × 400)

Figure 6. Histologic sections of rabbit No. 2, enucleated at eight weeks post-implantation of the IOP sensor (Hematoxylin-eosin stain)



A. Histologic section of limbus and anterior-chamber angle on side opposite to insertion site (control region) (original magnification: × 100)

B. Histologic section of limbal area near insertion site: compared with control region (Fig. 6A), there is infiltration of inflammatory cells into limbal area, mostly subconjunctival area (white arrows) (original magnification: × 100)

C. Histologic section of sclera near insertion site (original magnification: × 100)

D. Histologic section of limbal area near insertion site: infiltration of inflammatory cells, mainly polymorphonuclear neutrophils (PMNs), is evident in subepithelial and anterior stromal layers.

Discussion

Intraocular pressure (IOP) is among the most important risk factors for development and progression of glaucoma, and, as of now, it remains the only modifiable one.[28-30] Therefore, in glaucoma-management regimes, effective control of IOP is mandatory.[28,29] Nonetheless, IOP is not a static but rather a dynamic physiologic parameter showing a normal circadian pattern of variation, along with occasional random short- and long-term fluctuations[3, 4] that represent a significant risk factor for progression of glaucoma.[9-11] Thus, one-time "snapshot" IOP measurement cannot safely be considered to provide a complete IOP profile.[6-8, 31] Therefore, in glaucoma patients, continuous IOP monitoring is necessary to evaluate the proper state of IOP and to determine the effective management plan for the fluctuating IOP. Furthermore it may help the early diagnosis and proper treatment of glaucoma.

However, continuous real-time monitoring of IOP is not possible with the current standard applanation tonometry (Goldmann applanation tonometry: GAT). Instead, most patients visit clinics for IOP measurement once every few weeks or months. But again, such an intermittent measurement of the IOP cannot provide physicians with anything approaching a complete IOP profile of a patient. Besides, IOP GAT-measured in the sitting position does not reflect the positional changes that occur during the sleep. Indeed, recent studies have reported that nocturnal IOP in the supine or lateral decubitus

position does not correlate with daytime sitting-position IOP.[32, 33]

Microelectronic technology advancements in recent decades have enabled the development of various types of telemetric (wireless) sensors for continuous monitoring of IOP.[15-27] These devices can be classified into invasive (implantable) and non-invasive categories. The representative non-invasive IOP sensor is that which is incorporated into a soft contact lens to measure changes in corneal IOP-related biomechanics.[17, 24-26] One such example is Leonardi et al.'s microstrain gauge sensor, which measures changes of corneal curvature.[17] However, like GAT, the contact-lens-type sensor is affected by corneal biomechanics,[27] which means that measurements in patients with corneal abnormalities will be skewed. Moreover, this type of sensor can lead to complications associated with long-term contact lens use.

On the other hand, an invasive implantable IOP sensor enables continuous IOP monitoring that, unlike the cases with GAT and the contact-lens-type IOP sensor, is unaffected by corneal biomechanics. And because it is implanted inside the eye, it can provide the "true internal IOP," again unlike GAT or the contact-lens-type sensor, both of which can measure the IOP only indirectly as based on the relationship between the measured parameter and the true IOP. Thus the implantation option enables precise IOP measurement in patients for whom, due to corneal problems or a history of refractive surgery, it would be impossible by GAT or contact-lens-type sensor. The implantable IOP sensor also has several other advantages over standard GAT. It can help to reduce the

number of clinic visits a patient is obliged to make for IOP monitoring, and can improve treatment compliance. Furthermore, with developments in information and communications technology, it could also contribute to the advance of telemedicine. Certainly, the ability to transmit IOP data to a central server using the portable digital external IOP reader would be a great help for patients living in secluded regions or areas otherwise distant from clinics.

For all the above-noted reasons, many groups have been conducting research into the development of continuous-IOP-sensing implantable devices. Collins et al. (1967)[34] were the first to achieve such a sensor. Their "capacitive pressure sensor" measured the change of resonant frequency induced by the change of distance between the two parallel coaxial coils of an inductor (L)- and capacitor (C)-resonant circuit, which change was itself induced by IOP. This capacitive pressure sensor offers the advantages of low power consumption, low noise, high sensitivity, low temperature drift, and good long-term stability.[35] Additionally, with the recent progress made in micro electro mechanical systems (MEMS) and microfabrication technologies, miniaturization of the telemetric IOP sensor by incorporation of LC-resonant-circuit technology has been proceeding apace.[15, 18, 19, 36, 37] Our IOP sensor system, also of the capacitive type, has gone through various improvement processes including polymerization, the results for which have shown good elasticity and biocompatibility. Our system has the extra merit of not requiring any external power supply: thereby, device lifetime is extended, and battery-

related biocompatibility problems are avoided.

Indeed, one of the most fundamental requirements of an implantable device is to ensure long-term biocompatibility. However, there have been relatively few reports on the biocompatibility of implantable IOP sensors.[38, 39] The data from the present in vivo experiments, sequential clinical evaluation and histopathologic examination showed our IOP sensor to have achieved comparatively high biocompatibility in rabbit eyes. Of course, on clinical evaluation, both rabbit eyes immediate-postoperatively presented with conjunctival hyperemia, corneal edema and anterior-chamber inflammation. These, however, gradually subsided within four weeks post-implantation, and by eight weeks postoperatively, there were no definite sequelae in the conjunctiva, cornea or lens, excepting mild degrees of conjunctival hyperemia. In both rabbits moreover, the anterior-chamber depths and angles were patent throughout the follow-up.

On gross pathologic evaluation of the enucleated eyes, there was no definite membrane formation or encapsulation around the implant. This finding also suggested that there was and had been no definite foreign-body reaction to the implant.

On histopathologic examination of the enucleated eyes at eight weeks postoperatively, and comparing with the control region in each eye, there were no significant deformities of ocular-tissue structures. As for the cornea, there

was no definite abnormality in the endothelial cell lining or in the arrangement of the stromal layers, excepting the inflammatory infiltrations in the limbus. Neither were there any significant inflammatory infiltrations or structural deformations in the iridocorneal angle or the lens. Taking all of these findings into account, we considered the inflammatory or foreign-body reactions to the implantable IOP sensor to be slight. This suggested that our IOP sensor had achieved a favorable degree of biocompatibility with the rabbit eye.

However, this study has several limitations. First, there were only a small number of cases (two rabbit eyes) and a relatively short-term (eight-week) follow-up period. For confirmation of the long-term biosafety of sensors, a long-term study with a large number of cases will be required. Second, the ocular tissue and structures were evaluated on the basis only of the gross and microscopic findings. For thorough and accurate evaluation of the biochemical or ultrastructural changes of tissue structures, immunohistochemical stains or electron microscopic observations might be necessary. Third, this study is relatively lacking in IOP data. Sequential evaluation of IOP is essential to any evaluation of the influence of device-implantation procedures on IOP. For the compensate such a limitation, we are planning to conduct a long-term follow up study at least over 3 months, with a large number of subjects. And in this next experiment, we are going to perform various methods of tissue analysis including the

immunohistochemical stains or electron microscopic observations.

In conclusion, we designed and developed a prototype implantable IOP sensor that enables continuous telemetry (wireless communications)-based monitoring of IOP. In this preliminary report, we demonstrate the favorable rabbit-eye biocompatibility of this sensor, with respect to which no significant evidence of toxicity or foreign-body reaction except mild inflammatory infiltrations in the limbus was evident in our investigation.

However, this is the short term results with a small number of cases. Thus, in the future, long-term animal studies involving a large number of subjects are required.

References

1. Leske MC, Connell AM, Wu SY, Hyman L, Schachat AP. Distribution of intraocular pressure. The Barbados Eye Study. Arch Ophthalmol. 1997;115:1051-1057.

2. Hashemi H, Kashi AH, Fotouhi A, Mohammad K. Distribution of intraocular pressure in healthy Iranian individuals: the Tehran Eye Study. Br J Ophthalmol. 2005;89:652-657.

3. Sihota R, Saxena R, Gogoi M, Sood A, Gulati V, Pandey RM. A comparison of the circadian rhythm of intraocular pressure in primary phronic angle closure glaucoma, primary open angle glaucoma and normal eyes. Indian J Ophthalmol. 2005;53:243-247.

4. Fogagnolo P, Rossetti L, Mazzolani F, Orzalesi N. Circadian variations in central corneal thickness and intraocular pressure in patients with glaucoma. Br J Ophthalmol. 2006;90:24-28.

5. Drance SM. The significance of the diurnal tension variations in normal and glaucomatous eyes. Arch Ophthalmol. 1960;64:494-501.

6. Hughes E, Spry P, Diamond J. 24-hour monitoring of intraocular pressure in glaucoma management: a retrospective review. J Glaucoma. 2003;12:232-236.

7. Barkana Y, Anis S, Liebmann J, Tello C, Ritch R. Clinical utility of intraocular pressure monitoring outside of normal office hours in patients with

glaucoma. Arch Ophthalmol. 2006;124:793-797.

8. Fogagnolo P, Orzalesi N, Ferreras A, Rossetti L. The circadian curve of intraocular pressure: can we estimate its characteristics during office hours? Invest Ophthalmol Vis Sci. 2009;50:2209-2215.

9. Asrani S, Zeimer R, Wilensky J, Gieser D, Vitale S, Lindenmuth K. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. J Glaucoma. 2000;9:134-142.

10. Caprioli J, Coleman AL. Intraocular pressure fluctuation a risk factor for visual field progression at low intraocular pressures in the advanced glaucoma intervention study. Ophthalmology. 2008;115:1123-1129.

11. Nouri-Mahdavi K, Hoffman D, Coleman AL, Liu G, Li G, Gaasterland D, et al. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. Ophthalmology. 2004;111:1627-1635.

12. Brandt JD, Beiser JA, Kass MA, Gordon MO. Central corneal thickness in the Ocular Hypertension Treatment Study (OHTS). Ophthalmology. 2001;108:1779-1788.

13. Phillips LJ, Cakanac CJ, Eger MW, Lilly ME. Central corneal thickness and measured IOP: a clinical study. Optometry. 2003;74:218-225.

14. Zhang Y, Zhao JL, Bian AL, Liu XL, Jin YM. [Effects of central corneal thickness and corneal curvature on measurement of intraocular pressure with Goldmann applanation tonometer and non-contact tonometer]. Zhonghua Yan Ke Za Zhi. 2009;45:713-718.

15. Chen PJ, Saati S, Varma R, Humayun MS, Tai YC. Wireless intraocular pressure sensing using microfabricated minimally invasive flexible-coiled LC sensor implant. Journal of Microelectromechanical Systems. 2010;19:721-734.

16. Eggers T, Draeger J, Hille K, Marschner C, Stegmaier P, Binder J, et al., editors. Wireless intra-ocular pressure monitoring system integrated into an artificial lens. 2000: IEEE.

17. Leonardi M, Leuenberger P, Bertrand D, Bertsch A, Renaud P, editors. A soft contact lens with a MEMS strain gage embedded for intraocular pressure monitoring. 2003: IEEE.

18. Stangel K, Kolnsberg S, Hammerschmidt D, Hosticka B, Trieu H, Mokwa W. A programmable intraocular CMOS pressure sensor system implant. Solid-State Circuits, IEEE Journal of. 2001;36:1094-1100.

19. Chitnis G, Maleki T, Samuels B, Cantor L, Ziaie B. A Minimally Invasive Implantable Wireless Pressure Sensor for Continuous IOP Monitoring. IEEE Trans Biomed Eng. 2012;19:19.

20. Rizq RN, Choi WH, Eilers D, Wright MM, Ziaie B. Intraocular pressure measurement at the choroid surface: a feasibility study with implications for implantable microsystems. British journal of ophthalmology. 2001;85:868-871.

21. Kakaday T, Hewitt AW, Voelcker NH, Li JS, Craig JE. Advances in telemetric continuous intraocular pressure assessment. Br J Ophthalmol. 2009;93:992-996.

22. Downs JC, Burgoyne CF, Seigfreid WP, Reynaud JF, Strouthidis NG, Sallee V. 24-hour IOP telemetry in the nonhuman primate: implant system performance and initial characterization of IOP at multiple timescales. Invest Ophthalmol Vis Sci. 2011;52:7365-7375.

23. Chen PJ, Rodger DC, Meng E, Humayun MS, Tai YC, editors. Implantable Unpowered Parylene MEMS Intraocular Pressure Sensor. 2006: IEEE.

24. Greene ME, Gilman BG. Intraocular pressure measurement with instrumented contact lenses. Invest Ophthalmol. 1974;13:299-302.

25. Faschinger C, Mossbock G. [Continuous 24 h monitoring of changes in intraocular pressure with the wireless contact lens sensor Triggerfish. First results in patients]. Ophthalmologe. 2010;107:918-922.

26. Hediger A, Kniestedt C, Zweifel S, Knecht P, Funk J, Kanngiesser H. [Continuous intraocular pressure measurement: First results with a pressure-sensitive contact lens]. Ophthalmologe. 2009;106:1111-1115.

27. Mansouri K, Medeiros FA, Tafreshi A, Weinreb RN. Continuous 24-Hour Monitoring of Intraocular Pressure Patterns With a Contact Lens Sensor: Safety, Tolerability, and Reproducibility in Patients With Glaucoma. Arch Ophthalmol. 2012;13:1-6.

28. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration.The AGIS Investigators. Am J Ophthalmol. 2000;130:429-440.

29. Musch DC, Gillespie BW, Niziol LM, Lichter PR, Varma R.

Intraocular pressure control and long-term visual field loss in the Collaborative Initial Glaucoma Treatment Study. Ophthalmology. 2011;118:1766-1773.

30. Sommer A, Tielsch JM. Risk factors for open-angle glaucoma: the Barbados Eye Study. Arch Ophthalmol. 1996;114:235.

31. Sit AJ. Continuous monitoring of intraocular pressure: rationale and progress toward a clinical device. J Glaucoma. 2009;18:272-279.

32. Liu JH, Kripke DF, Hoffman RE, Twa MD, Loving RT, Rex KM, et al. Nocturnal elevation of intraocular pressure in young adults. Invest Ophthalmol Vis Sci. 1998;39:2707-2712.

33. Liu JH, Kripke DF, Twa MD, Hoffman RE, Mansberger SL, Rex KM, et al. Twenty-four-hour pattern of intraocular pressure in the aging population. Invest Ophthalmol Vis Sci. 1999;40:2912-2917.

34. Collins CC. Miniature passive pressure transensor for implanting in the eye. IEEE Trans Biomed Eng. 1967;14:74-83.

35. Puers R. Capacitive sensors: when and how to use them. Sensors and Actuators A: Physical. 1993;37:93-105.

36. Ullerich S, Mokwa W, Vom Bogel G, Schnakenberg U, editors. Micro coils for an advanced system for measuring intraocular pressure. 2000: IEEE.

37. Simons RN, Hall DG, Miranda FA, editors. RF telemetry system for an implantable bio-MEMS sensor. 2004: IEEE.

38. Todani A, Behlau I, Fava MA, Cade F, Cherfan DG, Zakka FR, et al.

Intraocular pressure measurement by radio wave telemetry. Invest Ophthalmol Vis Sci. 2011;52:9573-80.

39. Chen PJ, Rodger DC, Saati S, Humayun MS, Tai YC. Microfabricated implantable parylene-based wireless passive intraocular pressure sensors. Journal of Microelectromechanical Systems, 2008;17:1342-1351.

초 록

목적: 본 연구는 실시간 지속적 안압 측정을 위해 새롭게 개발한 삽입형 안압센서의 토끼 안구에서의 생체적합성을 알아보고자 하였다.

방법: 공진주파수 변화 측정을 통한 무선방식의 실시간 안압측정이 가능한 5mm x 3.5mm크기의 직사각형 형태의 삽입형 안압센서를 개발하였다. 뉴질랜드 흰색 토끼 2마리 2안을 대상으로 안압센서를 삽입 후 2주, 4주, 8주에 현미경 관찰과 외안부 사진촬영을 시행하였다. 삽입 8주 후 안구를 적출하여 육안 병리 소견을 관찰하였으며 삽입된 안압센서를 제거 후 조직학적인 소견을 관찰하였다.

결과: 안압센서를 토끼 안구 내에 삽입 후 8주까지 지속적 현미경 관찰 결과 유의한 염증반응이나 반흔형성 없이 비교적 안정된 임상양상을 보였다. 조직학적 검사상 심한 염증반응이나 이물질 반응, 안구 조직구조의 변화는 관찰되지 않았다.

결론: 새롭게 개발된 원형 안압센서는 토끼 안구 내에 삽입 시 유의한 독성 반응이나 이물질 반응 없이 비교적 우수한 생체적합성을 보였다.

주요어: 생체적합성, 지속적 안압측정, 녹내장, 안압, 삽입형 센서

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