

Counteracting Complications of **Glaucoma Filtration Surgery**

Dr. Hideto Sagara

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Dr. Hideto Sagara is an interventional ophthalmologist, who is interested in testing new treatments for cataract and glaucoma. Here we discuss the background and motivation of Dr. Sagara, together with the outlines of his current study on a new treatment approach to control one of the most common complications of glaucoma filtering surgery.



To start, what is your academic background and how did you pursue the early steps of your career in medical research?

I have graduated from Fukushima Medical University, Japan in 1993. In 1999, I was appointed as the director of Marui Eye Clinic, a clinical centre where more than 500 patients a year undergoing operations such as cataract and glaucoma. I have obtained my doctoral degree in ophthalmology in 2002, and my area of expertise is glaucoma and other diseases affecting the eye surface. I am also involved in academic teaching activities, since I work as a part-time instructor at Fukushima Medical University since 2007.

What has been your motivation for choosing ophthalmology as a domain of specialization?

Since I was a medical student, I have been intrigued by the eye as a sophisticated organ in which a variety of anatomical and physiological functions are amazingly synchronized. I am also passionate about delicate hand work, which I have been good at since I was young. Therefore, ophthalmology was the right domain for my interests and passion.

You are currently testing a new treatment regime combining two different eye drops to treat a condition known as 'bleb leak'. Can you describe to the reader what bleb leakage is and its potential complications?

Bleb leak is a possible complication of the filtering surgery, which is one of the most common treatments for glaucoma. Patients with glaucoma suffer varying intensities of blurred vision, usually due to an increase in the eye's inner fluid, which in turn places pressure on the optic nerve. The filtering surgery allows drainage of aqueous humor from within the eye to underneath the conjunctiva where it is absorbed. Bleb leaks occur almost directly from the anterior chamber (AC) of the eye ball, resulting in a shallow AC with severe hypotony, which usually occurs due to a defect in epithelial regeneration at the thin and avascular bleb surface. Bleb leaks may lead to severe damage and inflammation of the eye tissue, which can eventually lead to blindness if remains untreated.

How many patients are participating in the clinical trial and what are its primary goals?

So far, the trial involves more than 50 patients, who do not only suffer a bleb leak following

filtrating surgery and mitomycin C treatment, but also severe eye surface disorder, to which the combined treatment strategy is also highly relevant. The primary goal of the study is the efficacy of the treatment strategy in terms of epithelial healing and the complete cessation of bleb leak over a long period of time.

In case of a positive outcome, could the findings of the clinical trial motivate a change in the current treatment guidelines for bleb leakage?

Currently in Japan, patients with bleb leak are usually treated only with separate sodium hyaluronate and autologous serum eye drops, a method that has been proposed and verified by my research group. However, it is difficult to continue the treatment for more than a few months, because patients often fail to adhere to the treatment regimen, which involves daily frequent application of the eye drops. If the combined treatment regimen under test in the ongoing trial shows promising results, this will strongly motivate a change in the current treatment guidelines of bleb leak, at least in Japan.

New Clinical Trial on Combined Treatment Approaches to Control Bleb Leak

Bleb leak is a serious complication of the filtering surgery, one of the most common treatments for glaucoma resulting from the increase in the eye's fluid pressure. Here we introduce Dr. Sagara's current clinical trial in which he tests the efficacy of combining multiple treatment approaches for the control of bleb leak.

GLAUCOMA AND THE FILTRATION PROCEDURE

Glaucoma refers to a group of eye disorders that cause damage to the optic nerve responsible for vision. If untreated, glaucoma causes blurred vision which may eventually progress to blindness. Glaucoma is currently the leading cause of irreversible blindness worldwide.

A recent study estimates a current global prevalence of 64.3 million cases among people aging 40-60 years, and expects the number to reach 76 million in 2020, and 112 million in 2040.

In most of the cases, glaucoma is caused by an increase in the fluid pressure inside the eye. Our eyes are filled with a clear fluid called the aqueous humor, which maintains their shape and provides nourishment to the lens and the cornea. In healthy eyes, the aqueous humor is produced and drained at nearly equal rates in order to keep the fluid pressure within physiological ranges. However, in some disease conditions where the aqueous humor is produced in excessive amounts or inefficiently drained, glaucoma can develop.

The modern approaches in glaucoma management aim to avoid damage of the optic nerve, and to preserve vision and total quality of life for patients, with minimal side effects. Among these approaches is a common surgical intervention known as 'glaucoma filtration surgery'. The latter involves making a partial thickness flap in the white of the eye (sclera), where a tiny window opening can be made underneath the conjunctiva. The flap is then loosely sutured back in place to allow the excessive fluid to escape through the opening, which restores normal eye pressure. The surgical procedure typically results in



Bleb leak

the formation of a small fluid 'bleb' on the sclera, the reason why the overall structure is commonly known as the 'filtering bleb'.

Scarring can occur around or over the flap opening, causing it to become less effective or totally ineffective. This outcome is traditionally avoided by the topical application of chemotherapeutic agents, such as the famous 5-fluorouracil and mitomycin C, which inhibits the proliferation of the scleral matrix cells to prevent scarring. However, the use of these anti-proliferative agents may lead to defective epithelial regeneration at the filtering bleb surface as a side-effect. If these defects remain untreated, aqueous oozing, known as 'point-bleb leak', occurs. Bleb leak due to epithelial defects usually occurs within three months to a few years after the filtration surgery and is therefore commonly described as late-onset bleb leak. Indeed, studies have reported an increased incidence of late-onset bleb leak and blebitis since the introduction of mitomycin C in glaucoma filtering surgery. In severe cases, point-bleb leaks may progress to profuse leaks, which can result in vision-threatening complications. Another risk factor for the occurrence of late-onset bleb leak is the tear dysfunction, since a well-functioning tear film plays a role in promoting epithelial healing

which helps resolve the defective bleb wall. The tear film consists of an aqueous layer and a lipid layer, which both are essential for the formation of a healthy tear film. The lipid layer is secreted by the meibomian gland, whose secretions are termed the 'meibum'. The most common cause of tear film dysfunction is obstructive meibomian gland dysfunction (OMGD), which can further promote the late-onset bleb leak, if concurrently occurs in patients who underwent filtering surgery.

MANAGEMENT OF LATE-ONSET BLEB LEAK

Over the past 15 years, Dr. Sagara and his research team has been investigating treatments for late-onset bleb leak. Previous findings by Dr. Sagara as well as other researchers have shown that the aqueous layer of the tear film can be augmented by Sodium hyaluronate eye drops and autologous serum eye drops. In 1998, Dr. Sagara and his colleagues have tried to stop bleb leakage with autologous blood injection into the leaking bleb. Although, the leakage had stopped for a while, it recurred in only a few days. However, it was found that the epithelial defect of the bleb wall was slightly improved after the blood including serum injection. As mentioned above, Dr. Sagara suspected that serum eye drops would be useful to treat the bleb leak by augmenting tear film volume and improving the tear film condition. The autologous serum includes almost all of the same components as the aqueous layer of the tear film, just not the lipid component. Therefore, Dr. Sagara has speculated that autologous serum cannot be possibly used as a stand-alone treatment, and that combining other treatments targeting the augmentation of the lipid component might be advantageous. Indeed, current trials are underway to investigate the efficacy of treatments for OMGD, such as eyelid massage and warm compresses in the management of severe epithelial failure arising from tear film dysfunction. These treatments particularly aim to stimulate the secretion of the meibum in order to improve the quality of the tear film.

A CLINICAL TRIAL ON COMBINED TREATMENT-APPROACHES

At first, Dr. Sagara and his fellow researchers have tested a treatment regimen involving the separate application of sodium hyaluronate, autologous serum, and antibiotic eye drops to treat bleb leak. However, while the epithelial defects were resolved for a few months, this

treatment method was not effective for a complete cessation of leakage in most patients. This may have been due to the difficulty for some patients to adhere to the regimen, which involves frequent administration of multiple eye drops every day. However, Dr. Sagara and his colleagues are currently running a clinical trial to test the efficacy of combined treatments, preserving both aqueous and lipid components of the tear film, in preventing bleb point-leak. They first determine the presence of OMGD and tear dysfunction in patients with late-onset point-leak following filtration surgery and mitomycin C treatment, and evaluated the long-term outcome of eye drops containing both Sodium hyaluronate and autologous serum (to augment the aqueous layer of the tear film) and eyelid massage and warm compresses (to facilitate secretion of meibum to counteract the OMGD). This treatment strategy could be described as an approach to stop aqueous leakage through the promotion of wound healing of the defective bleb surface by ensuring a well-functioning tear film. Eye drops combining both sodium hyaluronate and autologous serum are practically convenient and patient-friendly. Moreover, sodium hyaluronate is known for strong adherence to the body mucous membranes, including the eye's, which prevents the quick evaporation of the eye drops, allowing a prolonged action.

PRESENT AND FUTURE OF BLEB LEAK TREATMENT

Despite the inconvenience and modest efficacy, the regime based on the application of sodium hyaluronate and autologous serum separately is currently approved in Japan for the treatment of late-onset bleb leak. Therefore, in case of a positive outcome of the current trial on combined eye drops as well as combined treatment approaches, the current treatment guidelines shall be adapted accordingly. Dr. Sagara is currently planning more clinical trials to test therapies against other disorders of the ocular surface.

Researcher Profile



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Dr. Sagara is an interventional ophthalmologist who is interested in exploring various treatment methods eye cataract and glaucoma. He currently works at the Glaucoma Clinic of Fukushima Medical University, while being the Director of Marui Eye Clinic. Dr. Sagara is the executive director of Fukushima Ophthalmologist Society, and a member of a number of other scientific societies such as Japanese Ophthalmological Society, the Japan Society of Ophthalmic Surgeons and the Japanese Glaucoma Society. In 1999, Dr. Sagara won The Young Researcher's Award of the Japanese Society of Ophthalmological Optics, and in 2010, he won the Chairman's Award of The 64th Annual Congress of Japan Clinical Ophthalmology.

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