

Preclinical validation of antifibrotic implantables for use in bleb-forming glaucoma surgery

Citation for published version (APA):

van Mechelen, R. J. S. (2023). *Preclinical validation of antifibrotic implantables for use in bleb-forming glaucoma surgery*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20231016rm>

Document status and date:

Published: 01/01/2023

DOI:

[10.26481/dis.20231016rm](https://doi.org/10.26481/dis.20231016rm)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

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Impact

9. Impact

Glaucoma, a degenerative disease of the optic nerve, is the second leading cause of blindness worldwide, and the leading cause of irreversible blindness. Approximately 65 million people suffered from glaucoma in 2020 [1]. Due to the aging population (that continues to grow) and the rise in risk factors such as myopia, diabetes and high blood pressure, it is expected that 112 million people will be affected by 2040 [1]. All current treatments aim to halt visual field loss by lowering intraocular pressure (IOP), the main risk factor for glaucoma, as a causative (neuroprotective) treatment is still unavailable [2]. Usually, a step-up approach is chosen in which is started with medical and/or laser therapy, reserving surgery for advanced cases. However, this may lead to suboptimal treatment as, even in the Western world, 10% of patients' progress to bilateral blindness during their lifetime [3]. Bleb-forming filtering surgeries have the highest IOP reducing potential, but they also require intense follow-up and have known complications. Additionally, substantial surgical skills are needed to obtain satisfactory results. As a result, surgical treatment is often postponed, as both ophthalmologists and patients are reluctant to choose this option.

An important problem with all bleb-forming surgeries is the high postoperative failure rate, which is predominantly caused by the fibrotic response in the filtering bleb. In this dissertation, we have investigated novel methods to reduce the failure rate and searched for more reliable and safer treatment options to further optimize bleb-forming glaucoma surgery. The research presented may not only be beneficial for glaucoma patients, but also for ophthalmologists/physicians, surgeons, scientists, laboratory animals, and the healthcare system.

9.1 Animal models and standardization

Before a drug or a medical device can be introduced into the clinic, it needs to be validated within an animal model. Researchers are both legally and ethically required to test a treatment within an animal model before further use in patients is allowed [4]. Despite the required preclinical validation, high attrition rates are encountered within drug development [5], which are partly accountable to the translational failure from an animal model towards humans [6]. Currently, animal research faces a lot of scrutiny due to changes in society. Ethics related to animal welfare have significantly improved during the last decade, and the process of acquiring approval to conduct a study with animals as test subjects has been intensified and regulated more strictly. In **chapter 2**, animal models that have been used for glaucoma filtration surgery research were reviewed. Throughout the years, a multitude of animals such as rats, mice, hamsters, rabbits, dogs, etc. have been used. Each animal model has its own strengths and limitations which need to be carefully considered before the onset of

an animal study. The systematic review within this thesis will help research groups with setting up their animal study and choosing the appropriate animal model for their specific research question. With a proper selection and set-up of an animal study, less animals will have to be used for research.

Currently, there is a lack of standardization between research groups worldwide regarding *in vivo* research, making it difficult to interpret and compare results between studies. Furthermore, different readout parameters, experimental protocols, and welfare requirements can affect the reproducibility and reliability of results. To reduce variation among research groups, it is paramount to standardize animal research. The results obtained in both **chapter 2** and **chapter 3** support this claim. Further standardization is key to reduce the use of animals and increase reproducibility and reliability across research groups worldwide. Organizations like the National Centre for the Replacement, Refinement & Reduction of animals in Research could offer a reliable means to provide specialized protocols for research groups worldwide.

9.2 Clinical impact

As already mentioned, current bleb-forming surgeries still have high failure rates and intense postoperative follow-up is required after these procedures. Additionally, possibly serious adverse events, such as bleb dysesthesia, hypotony, corneal edema, and blebitis/endophthalmitis may occur. All these risks make current glaucoma surgery burdensome and therefore unpopular for patients as well as surgeons. However, by postponing surgery, glaucomatous field loss may have progressed significantly due to conjunctival irritation/inflammation from long-term use of eye drops. Subsequent increase of growth factors in the aqueous humor (AqH) may further increase the fibrotic response leading to an increased failure rate when bleb-forming glaucoma surgery is finally undertaken [7]. Currently, roughly 10% of all bleb-forming surgeries still fail each year [8], accumulating to a failure rate of 40-50% after 5 years in long term studies [9-11].

Mitomycin C (MMC) is the gold standard treatment to reduce fibrosis after glaucoma filtration surgery. However, due to serious postoperative complications associated with the use of MMC such as endophthalmitis, cystic blebs, and leaking blebs, novel medications are now routinely investigated. Unfortunately, as shown in **chapter 2** and **chapter 6**, novel drugs, although safer, are in most cases less effective in reducing the fibrotic response compared to the gold standard treatment with MMC.

In this dissertation, several methods to reduce the fibrotic response after glaucoma filtration surgery were assessed. Firstly, the use of surface topographies in conjunction with a glaucoma drainage device to enhance forming of a robust well-functioning filtering bleb (**chapter 5**) and secondly, a degradable continuous-release

drug delivery system (DDS) filled with MMC (**chapter 7**) were evaluated. *In vitro* research has shown that surface topographies can alter the reaction of cells, e.g., more, or fewer alternatively activated (M2) macrophages upon a surface [12]. The research presented in this thesis showed that surface topographies can modify the cellular response *in vivo*. However, we found an increased capsule thickness and presence of inflammatory cells after topographies were used. With further optimization, selection, and research for viable surface topographies, a reduced failure rate of bleb-forming surgeries with glaucoma drainage devices may be found. Surface topographies can be easily engineered onto a biomedical device, making it a viable method to implement with glaucoma drainage devices. However, further refinement and selection of surface topographies with SIBS is necessary.

The already mentioned gold-standard MMC is regularly used in the clinic as an antifibrotic drug during bleb-forming glaucoma surgery. MMC can either be applied intraoperatively with sponges, or injected postoperatively into the bleb (e.g., in a bleb needling procedure). However, the use of MMC in Europe is off-label, resulting in unstandardized protocols, which may lead to unreliable and highly variable results between patients and clinics [13, 14]. The implementation of a DDS, loaded with MMC, during bleb-forming glaucoma surgery will help with standardizing the surgery and minimizing the risk for adverse events. In **chapter 7** two DDS designs were evaluated *in vivo*. Some adverse effects were found to be associated with the use of a DDS *in vivo* (e.g., thin-walled cystic blebs). However, larger fluid-filled bleb cavities were seen during follow-up after using a DDS when compared to the gold standard, one-time intraoperative application of MMC. Although further optimization is required (e.g., slower release of MMC or lower total dosage of MMC), the use of a DDS seems promising towards obtaining safer and more reliable methods to reduce fibrosis after bleb-forming glaucoma surgery.

The research presented within this thesis is another step forward towards safer and more successful bleb-forming glaucoma surgery, making early surgery more acceptable for patients and surgeons in the near future, and hopefully reducing the number of patients becoming severely visually impaired or getting blind from glaucoma.

9.3 Economic impact

It is problematic that healthcare professionals as well as patients tend to postpone surgical intervention until other options such as eye drops or laser surgery have failed, because of the aforementioned fear of considerable postoperative care and vision threatening complications [15]. Besides the large burden glaucoma has on

patients, the management of glaucoma puts a large strain on the current health care system. The medical costs (including office visits, glaucoma exams, visual field tests, medication, glaucoma surgeries, and cataract extraction), amount to approximately 400 to 1000 euros per person per year depending on disease severity [16, 17]. In 2020, it was estimated that approximately 65 million people suffered from glaucoma worldwide, which would account for medical costs of around 26 to 65 billion euros, which could even increase up to 45 to 112 billion euros by 2040 worldwide [1]. If the disease is not managed properly, costs can increase even more due to the need of home care for visually impaired patients. In the Netherlands, roughly 357.000 patients were diagnosed with glaucoma in 2021, an increase of approximately 5,5% compared to 2020 [18]. When considering medical costs of 400-1000 euros per patient per year, glaucoma treatment costs can yearly amount up to 357 million euros in the Netherlands alone.

Currently, topical medication is the first line of treatment in the management of glaucoma, accounting for roughly 55 to 61% of all health care costs [19]. Unfortunately, eye drops can be troublesome to instill and may cause side effects, which may lead to poor adherence [20]. It is estimated that 50% of patients will have stopped adhering to their treatment within the first year [21]. Nonadherence with medication and/or not reaching a target pressure that is sufficiently low causes further progression of visual field loss. When the disease progresses, additional medication is often prescribed, increasing both the costs and side effects caused by long-term use [19, 22]. Every 1 mmHg of reduction can save annually 10 million euros [23]. Therefore, with proper management of glaucoma, the total health care costs can be decreased by approximately 30-50% [17].

A shift in treatment paradigm would be required to reduce the healthcare costs for the management of glaucoma. In 2020, topical medication had a gross revenue of 4.8 billion dollars, while surgical glaucoma devices only had a gross revenue of 575 million dollars [21, 24]. In an ideal world, surgical intervention for glaucoma will be performed only once throughout a patient's life with no further need of additional medication or surgery to adjust IOP. Further implementation of safe and effective surgical methods may therefore be very cost effective. The implementation of the methods researched in this thesis, like surface topographies or using a DDS, may be helpful to reach this goal.

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