Aiming for Single Digit Intraocular Pressure and Drop-Free Surgery in Glaucoma: Trabeculectomy with Mitomycin C and Intracamerular Bevacizumab

Pressão Intraocular ≤ 9 mmHg sem Recurso a Medicação: Trabeculectomia com Mitomicina C e Bevacizumab Intracamerular

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ABSTRACT

INTRODUCTION: Our purpose was to assess patients with single digit intraocular pressure (IOP) values and drop-free in primary trabeculectomy after using mitomycin C (MMC augmented with intracamerular bevacizumab).

METHODS: Retrospective, observational and comparative study. Charts from patients who underwent trabeculectomy and with IOP ≤9 mmHg at the last follow-up were included. Subanalysis of patients screened between Oct 2015 and Mar 2019, for inclusion criteria of ≤9 mmHg at last follow-up (24 months).

RESULTS: From 110 eyes screened in the initial study, 30 had the intended IOP target (MMC only: 11; MMC-bevacizumab: 19; 26% *vs* 41%, respectively, odds ratio 1.78, 95% IC (0.80 - 4.89), *p*=0.178). All these low-IOP patients were drop-free in this moment. No systemic adverse events were found and no vision-threatening complications were recorded.

CONCLUSION: Adding intracamerular bevacizumab to MMC in trabeculectomy can be particularly useful in low-target IOP surgeries (such as normal tension glaucoma or very advanced glaucomas) comparing with trabeculectomy with MMC alone.

KEYWORDS: Bevacizumab; Glaucoma; Intraocular Pressure; Mitomycin; Trabeculectomy.

RESUMO

INTRODUÇÃO: O nosso objetivo foi descrever as características dos doentes submetidos a trabeculectomia com mitomicina C (MMC) e bevacizumab intracamerular que obtiveram valores de pressão intraocular de apenas um dígito sem recurso a medicação antihipertensora.

MÉTODOS: Estudo retrospectivo, observacional e comparativo. Subanálise de doentes que realizaram trabeculectomia com MMC e bevacizumab intracamerular entre Outubro de 2015 e Março de 2019, com critério de inclusão de PIO ≤ 9 mmHg no último *follow-up* (24 meses).

RESULTADOS: Dos 110 olhos presentes no primeiro estudo, 30 obtiveram PIO ≤ 9 mmHg aos 24 meses: grupo trabeculectomia com MMC: 11 (26%); grupo trabeculectomia com MCM+bevacizumab: 19 (41%), (*odds ratio* 1,78, 95% IC (0,80 – 4,89), *p*=0,178). Nenhum doente estava a realizar medicação antihipertensora. Não foram detectados efeitos adversos sistémicos e a taxa de complicações foi baixa.

CONCLUSÃO: Adicionar bevacizumab intracamerular à MMC na trabeculectomia pode ser particularmente útil em cirurgias com PIO-alvo baixas (tal como glaucoma normotensional ou muito avançado), comparando com trabeculectomia apenas com MMC.

PALAVRAS-CHAVE: Bevacizumab; Glaucoma; Mitomicina; Pressão Intraocular; Trabeculectomia.

INTRODUCTION

Filtration surgery is the gold-standard procedure for management of advanced glaucoma.[1,2] Fibroblast proliferation and scarring process are the main cause for failure of trabeculectomy. Mitomycin C (MMC), an antifibrotic agent, has been used to control inflammation and scar formation induced by filtration surgery at cost its risk of complications.[3,4] Considering the importance of angiogenesis in the wound healing, antivascular endothelial growth factors (anti-VEGF), such as bevacizumab, seems to have a role slowing this process after trabeculectomy.[5,6] While some literature reported contradictory results,[7–9] other studies demonstrated favorable effects on surgical success.[10–12]

Our analysis described a 24-month follow-up of a two-centre study comparing primary trabeculectomy with MMC with and without intra-operative intracamerular bevacizumab and suggested a greater effectiveness of bevacizumab as an adjunct to MMC on improving the trabeculectomy outcomes.[13] However, one important item in the surgery result is the ability to achieve very low IOP targets (single digits), particularly over a sustained period. Exploring whether this wound healing strategy can provide such ambitious goal would help to personalize surgical outcomes, including in patients with a priori very low targets (very advanced disease at presentation and/or very low IOP at baseline such as normal tension glaucoma).

This sub-analysis aims to describe patients with single digit IOP values and drop-free in primary trabeculectomy using either MMC alone and MMC augmented with intracamerular bevacizumab. An exploratory analysis will be performed to determine which patients characteristics would increase chances of achieving these low target IOP.

MATERIAL AND METHODS

The design and methods of the "Trabeculectomy with mitomycin C alone or coupled with intracamerular bevacizumab? A two year comparative study" were described in detail elsewhere.[13] The study was approved by the Ethics Committee from each centre on December 2019. Informed consent was obtained from all patients before participation. The study adhered to tenets of the Declaration of Helsinki 2013 and was registered on ISRCTN database, prior to any data collection (registration number ISRCTN 93098069, 9 April 2020). The primary outcome was to compare the absolute and qualified surgical success rate (IOP ≤18 mmHg, ≤16 mmHg and ≤14 mmHg with at least 30% reduction, minimum of 6 mmHg with IOP-lowering medication or without) of trabeculectomy with MMC or with MMC plus bevacizumab at 24 months.

The patients with IOP less or equal to 9 mmHg with no medication at 24 months were selected for this analysis. Background history and ocular-related characteristics including baseline IOP (measured by Goldman applanation tonometry), preoperative visual acuity, glaucoma severity (based on visual field MD) and number of ocular hypotensive medication were retrieved. Data was collected from pre-operative, 1 day, 1 week, 1 month, 3 months, 6 months, 12 months and 24 months consultations. The number of postoperative surgical interventions were also examined.

Demographics and clinical characteristics of patients were described using the mean (standard deviation) or median (inter-quartile range: 25th percentile-75th percentile) for quantitative variables and the frequencies (percentages) for categorical variables. To compare IOP values between baseline and 24-months visits, t- test was used. Group comparisons of quantitative variables were performed using non-parametric Mann-Whitney test and chi-square test or Fischer's exact test were used for categorical variables. A *p*-value of 0.05 or less was considered statistically significant. Statistical analysis was carried out using SPSS (version 25.0, SPSS, Chicago, IL).

RESULTS

Trabeculectomy with MMC was performed in 110 eyes, intracamerular bevacizumab was injected at the end of the procedure in 46% (n=51). Thirty eyes were included in this sub-analysis: 19 eyes in MMC+bevacizumab group and 11 eyes in MMC group had IOP in the single digits range (≤ 9 mmHg) at 24-month visit (odds ratio 1.78, 95% IC (0.80 - 4.89), *p*=0.178). All of the patients with single digits IOP at 24-month visit were drop-free in this moment. Demographic data and overall baseline characteristics of this sample are listed in Table 1, with both groups being similar at baseline in all variables (*p*>0.05).

Table 1. Baseline characteristics of participating patients.

	MMC group (n=11)	MMC + bevacizumab group (n=19)	*p*-value
Age, mean (SD), years	65 (16.6)	71 (6.6)	0.307
Male gender, n (%)	5 (45.5)	11 (57.9)	0.707**
Caucasian, n (%)	11 (100.0)	19 (100.0)	-
IOP, mean (SD), mmHg	24.8 (10.5)	25.0 (6.6)	0.611
Visual acuity, median (P_{25}-P_{75}), logMar	0.3 (0.0-1.0)	0.05 (0.0-0.0)	0.328
Visual field MD, median (P_{25}-P_{75}), dB	-14.0 (11.3-14.75)	-16.5 (7.3-25.3)	0.664
No. of preoperative topical medication, median (P_{25}-P_{75})	3.3 (3.0-4.0)	2.9 (2.0-4.0)	0.328
Oral acetazolamide, n (%)	5 (45.5)	5 (26.3)	0.425**
Previous cataract surgery, n (%)	6 (54.5)	12 (63.2)	0.712**
Time to surgery, median (P_{25}-P_{75}), years of known diagnosis	5.7 (1.0-9.0)	5.4 (2.0-10.0)	1.000
BCVA, logMAR (Mean ± SD)	0.12 ± 0.01	0.11 ± 0.02	0.24

IOP, intraocular pressure; MD, mean deviation; MMC, mitomycin C; P_{25}, 25th percentile; P_{75}, 75th percentile; SD, standard deviation. *Mann–Whitney test for quantitative variables, Chi-squared test for categorical variables; **Fisher's exact test.

Table 2. Intra- and postoperative complications during follow-up.

	MMC (n=11)	MMC + bevacizumab (n=19)	*p*-value*
Intraoperative, n (%)			
Anaesthetic/systemic complications	0 (0)	0 (0)	-
Button hole	0 (0)	1 (5)	0.367**
Subconjunctival haemorrhage	2 (18)	2 (11)	1.000**
Scleral flap problems	0 (0)	0 (0)	-
Vitreous prolapse	0 (0)	0 (0)	-
Postoperative, n (%)			
Choroidal detachment	2 (18)	2 (11)	0.611**
Hypotony > 1 month	3 (27)	3 (16)	0.641**
Positive seidel > 1 month	0 (0)	0 (0)	-
Bleb hemorrhage	0 (0)	1 (5)	1.000**
Blebitis	0 (0)	0 (0)	-
Hyphema	0 (0)	1 (5)	1.000**
Vitreous bleeding	0 (0)	0 (0)	-
Corneal edema	0 (0)	1 (5)	1.000**
Malignant glaucoma	0 (0)	0 (0)	-
Cataract requiring surgery/phakic eyes	0/5 (0)	2/7 (29)	0.520**

MMC, mitomycin C. *Chi-squared test for categorical variables; **Fisher's exact test.

IOP was effectively reduced in both groups at the 24-month visit compared to baseline (MMC: 24.8 (10.5) mmHg *vs* 7.0 (1.1) mmHg; MMC+bevacizumab: 25.0 (6.6) mmHg *vs* 7.1 (1.1) mmHg; $p<0.001$ in both comparisons), with no significant difference between the groups at the final timepoint ($p=0.899$). After week 1, there was a stabilization in IOP values until month 24 in both groups (Fig. 1).

Comparing group characteristics on the sub-analysis of patients with single-digits IOP, a higher rate of non-clinical hypotony existed in the MMC+bevacizumab group. Nevertheless, this higher rate of numerical events did not incur into clinical hypotony, nor did there was a need for any surgical correction in this group.

Table 3. Postoperative interventions.

	MMC (n=11)	MMC + bevacizumab (n=19)	*p*-value*
Standard care, n (%)			
Suture lysis	9 (81)	18 (95)	0.537**
Surgical intervention, n (%)			
Needlings	1 (9)	0 (0)	0.367**
Bleb revision	0 (0)	0 (0)	-
Vitrectomy due to choroidal detachment	0 (0)	0 (0)	-
Additional glaucoma surgery	0 (0)	0 (0)	-

MMC, mitomycin C. *Chi-squared test for categorical variables; **Fisher's exact test.

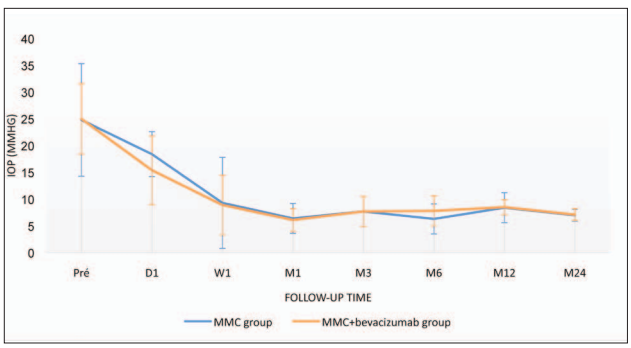

Figure 1. Intraocular pressure throughout the study visits.

IOP, intraocular pressure; MMC, mitomycin C.

No significant differences in rates of intra- or early postoperative complications were detected (Table 2). A similar rate of suture lysis was performed in the groups (MMC: 81% vs MMC+bevacizumab: 95%, *p*=0.537). Despite one needling in MMC group, no further interventions were required (Table 3).

DISCUSSION

Our study describes the role of intracamerular bevacizumab as an adjunct to MMC in primary trabeculectomy. With a follow-up of 24 months, this group revealed a higher number of patients with IOP in single digits comparing with trabeculectomy with MMC alone (46% *vs* 21%). Of note, no patient needed IOP-lowering medication after the first week to achieve these lower IOP values.

One rationale behind this study is that these results may be applied in normal tension glaucoma (NTG), a type of glaucoma that are a challenge to treat. The Collaborative Normal Tension Glaucoma Study revealed that reduction 30% of IOP influences the course of normal tension glaucoma with slower progression of visual field.[14] Patients with NTG have a baseline IOP in the statistically normal range, that is, it may be difficult to achieve single digits with medication. This factor is relevant in issues associated with compliance, ocular surface changes, poor tolerance, ophthalmic and systemic adverse effects. The Early Manifest Glaucoma Trail (EMGT) demonstrated the limited role of argon laser trabeculoplasty in NTG in patients with baseline IOP of 15 mmHg or less.[15] So, with our study results the trabeculectomy with MMC and intracamerular bevacizumab may have a role in this type of glaucoma where the IOP target is lower. Being an aggressive IOP lowering procedure, the associated adverse effects (such as hypotony maculopathy) need to be considered carefully. Interestingly, our sub-analysis did show that adding bevacizumab does increase the chance of hypotony. This however seems to be sub-clinical, as it was not associated with either loss of vision or any increase in the need for surgical correction. Indeed, it is a subject of debate on whether setting an artificial lower threshold makes sense to labelling an intervention as a failure. A significant number of subjects in clinical trials (as with our clinical practice) have lower IOP values than 6 mmHg while depicting no negative signs of that hypotony. Nevertheless, this needs to be balanced with the possible sight-threatening complications associated with hypotony (macular hypotony, choroidal swelling, flat anterior chamber, cataract formation). As no risk profile exists to identify beforehand those where extreme low IOP can have these deleterious consequences, this balance between promoting and preventing wound healing needs to remain in the surgeons' mind. However, in our study, no major complications were described, which makes the case for this combination of antifibrotic agents (mitomycin C and bevacizumab) can be of clinical value with a rather acceptable safety profile.

The current study has some drawbacks. First, our study has a relatively small sample, which could not allow to detect significant factors associated with lower IOP values. Secondly, our findings are based on retrospective data selected from a larger cohort study performed by the same

team. Thirdly, the study findings may not be applicable for other types of glaucoma, such as secondary glaucoma.

To conclude, trabeculectomy with MMC coupled with intracamerular bevacizumab had a steady IOP profile over 24 months in patients with single digit IOP at week 1 with no influence on the safety profile.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

PJ: Data collection and analysis, conceptualization and original draft creation
RB: Data collection and analysis
AB: Methodology
CMN, JPS: investigation, manuscript revision
LAP: conceptualization, supervision, manuscript revision

RESPONSABILIDADES ÉTICAS

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

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ETHICAL DISCLOSURES

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

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