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RECUPERAÇÃO TARDIA DA TRABECULECTOMIA ATRAVÉS DO AGULHAMENTO COM MITOMICINA C

Orientador: Prof. Dr. Sebastião Cronemberger

Faculdade de Medicina
Universidade Federal de Minas Gerais
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Tese apresentada ao Programa de Pós-Graduação em Ciências Aplicadas à Cirurgia e à Oftalmologia da Faculdade de Medicina da Universidade Federal de Minas Gerais, como requisito parcial para obtenção do título de Doutor em Medicina.

Área de concentração: Oftalmologia

Orientador: Prof. Dr. Sebastião Cronemberger
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Dra. Ana Cláudia Alves Pereira
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“All our science, measured against reality, is primitive and childlike – and yet it is the most precious thing we have.”

Albert Einstein

(1879 – 1955)

LISTA DE ABREVIATURAS

5-FU	5-fluorouracil
CCT	central corneal thickness
DNA	deoxyribonucleic acid
ECC	espessura corneana central
et al.	*et alii* (e outros)
Fig.	Figura
IL	Illinois
Inc.	Incorporation
IOP	intraocular pressure
MD	Medical Doctor
mg	miligrama
ml	mililitro
mm	milímetro
mm^2	milímetro quadrado
mmHg	milímetro de mercúrio
MMC	mitomicina C
µg	micrograma
µm	micrômetro
n	tamanho da amostra
No.	number
P	*p*-valor
PA	Pensilvânia
PhD	Doctor of Philosophy
PIO	pressão intraocular
postop	postoperative
RNA	ribonucleic acid
SD	standard deviation
SPSS	Statistical Package for the Social Sciences
Trab	trabeculectomy
USA	United States of America
vs.	versus
χ^2	Qui-quadrado

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RESUMO

TÍTULO: Recuperação Tardia da Trabeculectomia através do Agulhamento com Mitomicina C.

OBJETIVOS: Avaliar a eficácia e a segurança do agulhamento com mitomicina C (MMC) na recuperação tardia da trabeculectomia, identificar os fatores associados a seu sucesso e estudar seus efeitos sobre o endotélio corneano.

MATERIAL E MÉTODOS: Esta pesquisa consta de três trabalhos prospectivos. Para o primeiro e o segundo trabalho foram selecionados 125 olhos de 98 pacientes portadores de glaucoma sem controle adequado. Todos haviam sido submetidos a pelo menos uma trabeculectomia e apresentavam a bolsa fistulante plana e o óstio interno pérvio à gonioscopia. O agulhamento associado à injeção subconjuntival de 8 µg de mitomicina C foi realizado no bloco cirúrgico, pela mesma cirurgiã, e repetido quando necessário. Para o terceiro trabalho, foram selecionados 42 olhos de 36 pacientes para que tivessem o endotélio corneano estudado e monitorizado antes e depois do agulhamento. A espessura corneana central (ECC) foi avaliada através da paquimetria ultra-sônica antes do agulhamento e após uma semana, 1, 3, 6 e 12 meses. A contagem endotelial foi realizada com microscópio especular de não contato antes do agulhamento e após 1, 6 e 12 meses.

RESULTADOS: Foram realizados 186 agulhamentos nos 125 olhos (média de 1,49 ± 0,64 agulhamentos por olho). Setenta e três olhos (58,4%) foram submetidos a um agulhamento, 44 olhos (35,2%) a dois, sete olhos (5,6%) a três e um olho (0,8%) foi submetido a quatro agulhamentos. O fluxo foi restabelecido em 115 olhos (92%), nos quais obteve-se uma bolsa fistulante elevada. Após um seguimento médio de 20,80 ± 11,96 meses, a pressão intraocular (PIO) média caiu de 20,07 ± 5,20 mmHg no pré-operatório para 13,15 mmHg ± 6,77 mmHg ($p < 0,001$), e o número médio de

medicações hipotensoras por olho caiu de 2,35 ± 1,14 antes do agulhamento para 0,78 ± 1,30 ($p < 0,001$) na última consulta. A taxa global de sucesso (PIO ≤ 16 mmHg) foi de 76% (58,4% sem medicação e 17,6% com o auxílio de medicações hipotensoras). As complicações incluíram hifema discreto (25,8%), câmara anterior rasa (18,3%), descolamento seroso da coróide (15,6%), extravasamento de humor aquoso pelo orifício de entrada da agulha (8,6%) e bolsa encapsulada (7,5%). A maioria das complicações foi leve e transitória, sem necessidade de tratamento. A principal variável associada ao sucesso foi a PIO baixa antes do agulhamento ($p < 0,001$). O sucesso também foi correlacionado a uma PIO baixa no primeiro dia após o agulhamento ($p = 0,005$), um maior intervalo de tempo entre a trabeculectomia e o agulhamento ($p = 0,030$) e à idade ($p = 0,050$; significância limítrofe), sendo que quanto mais idoso o paciente, maior sua chance de sucesso. Observou-se maior tendência ao sucesso também nos pacientes brancos, em olhos pseudofácicos e em olhos com trabeculectomias de base fórnice. Não houve diferença estatisticamente significativa entre as medidas da ECC e da contagem endotelial antes e após o agulhamento, durante todo o primeiro ano de acompanhamento.

CONCLUSÕES: O agulhamento com MMC é eficaz na recuperação de bolsas fistulantes falidas e planas, proporcionando um bom controle da PIO, mesmo quando realizado anos após a trabeculectomia. Com relação às complicações, o procedimento é relativamente seguro e parece não afetar o endotélio corneano. Maiores taxas de sucesso foram alcançadas em olhos com menor PIO pré-operatória, menor PIO no primeiro dia após o agulhamento, maior intervalo de tempo entre a trabeculectomia e o agulhamento e em pacientes mais idosos.

PALAVRAS-CHAVE: Trabeculectomia, Glaucoma, Epitélio Posterior, Mitomicina C/uso terapêutico, Mitomicina C/ administração e dosagem, Reoperação.

ABSTRACT

TITLE: Late Needling of Filtering Blebs with Adjunctive Mitomycin C.

OBJECTIVES: To asses the efficacy and safety of needle revision with mitomycin C (MMC) in reviving failed filtering blebs during the late postoperative period, to identify factors associated with success, and to study its effect on the corneal endothelium.

MATERIAL AND METHODS: This research consists of three prospective studies. The first and second studies investigated 125 eyes from 98 patients with uncontrolled glaucoma. All had at least one failed trabeculectomy, a flat filtering bleb, and a patent internal ostium on gonioscopy. Needle revision with subconjunctival injection of 8 µg of MMC was performed in the operating room, by a single surgeon, and repeated if necessary. The third paper included 42 eyes of 36 patients to study the corneal endothelium before and after needle revision. Central corneal thickness (CCT) was measured by ultrasonic pachymetry preoperatively and 1 week and 1, 3, 6, and 12 months after revision. Corneal endothelial cell density was measured with a non-contact specular microscope preoperatively and after 1, 6, and 12 months.

RESULTS: Overall, 186 needling procedures were performed on 125 eyes (mean 1.49 ± 0.64 procedures per eye). Seventy-three eyes (58.4%) were needled once, 44 (35.2%) were needled twice, seven (5.6%) were needled three times, and one (0.8%) was needled four times. We reestablished aqueous flow and obtained a raised bleb in 115 eyes (92%). After an average follow-up of 20.80 ± 11.96 months, mean IOP decreased from 20.07 ± 5.20 mmHg preoperatively to 13.15 ± 6.77 mmHg ($P < 0.001$), and the mean number of hypotensive medications per eye decreased from 2.35 ± 1.14 at baseline to 0.78 ± 1.30 ($P < 0.001$) at the latest visit. The overall success rate (IOP ≤ 16 mmHg) was 76% (58.4% without medication and 17.6% with hypotensive medications). Complications included mild hyphema (25.8%), shallow

anterior chamber (18.3%), serous choroidal detachment (15.6%), bleb leakage (8.6%), and encapsulated bleb (7.5%). Most complications were minor, transient, and required no treatment. The most important variable associated with success was a lower pre-needling IOP ($P < 0.001$). Successful outcomes also correlated significantly with a lower IOP on the first postoperative day ($P = 0.005$), a longer time between trabeculectomy and needling ($P = 0.030$), and older age ($P = 0.050$; borderline significance). The success rates tended to be greater in whites, pseudophakic eyes, and in eyes with a previous fornix-based trabeculectomy. There was no statistically significant difference between preoperative and postoperative CCT and endothelial cell density during the first year of follow-up.

CONCLUSIONS: Needle revision with adjunctive MMC is effective for reviving flat filtering blebs and controlling IOP, even several years after the original trabeculectomy, and seems to be safe for the corneal endothelium. Complications were minor and transient. Higher success rates were achieved in eyes with lower pre-needling IOP, lower IOP on the first postoperative day, longer interval between trabeculectomy and needling, and in older patients.

KEY-WORDS: Trabeculectomy, Glaucoma, Corneal Endothelium, Mitomycin C/ therapeutic use, Mitomycin C/ administration and dosage, Reoperation.

SUMÁRIO

INTRODUÇÃO

INTRODUÇÃO

A trabeculectomia ainda é a técnica padrão para o tratamento cirúrgico do glaucoma. Apesar de ser altamente eficaz, ela possui elevada taxa de falência, tanto precoce quanto tardia. Estudos mostram taxas de falência em uma primeira trabeculectomia em torno de 20% no primeiro ano e até 52% após 5 anos (The Fluorouracil Filtering Surgery Study Group, 1996). O risco de falência é ainda maior após uma segunda trabeculectomia, podendo variar de 36 a 64%, dependendo do estudo (INABA, 1982; MIETZ; RASCHKA; KRIEGLSTEIN, 1999; YOU et al., 2002).

A resistência ao fluxo do humor aquoso pode ocorrer em qualquer local ao longo da via de filtração, ou seja, no óstio interno, na altura do retalho escleral ou na interface episclera-tenon-conjuntiva. No entanto, na maioria dos casos, a falência está relacionada à excessiva proliferação de fibroblastos e à fibrose subconjuntival (SKUTA; PARRISH II, 1987). Nestes casos, podemos observar dois tipos de bolsa: o primeiro seria a bolsa encapsulada ou cisto de Tenon. O segundo tipo e mais comum é a bolsa plana ou ausente, geralmente com a conjuntiva firmemente aderida à esclera.

O agulhamento é um procedimento eficaz para recuperar a função da trabeculectomia, com taxas de sucesso em torno de 80 a 90% no primeiro ano (GUTIERREZ-ORTIZ; CABARGA; TEUS, 2006; PASSOS et al., 2002), e 75% após 2 anos (GUTIERREZ-ORTIZ; CABARGA; TEUS, 2006; IWACH et al., 2003; NASCIMENTO et al., 2007). Várias técnicas já foram descritas, mas o princípio permanece o mesmo, ou seja, desfazer as aderências episclerais para restabelecer o fluxo do humor aquoso pela fístula.

A eficácia do agulhamento já está bem estabelecida para a recuperação da trabeculectomia no pós-operatório precoce, ou seja, nos primeiros meses (CHANG; HOU, 2002; FAGERLI; LOFORS; ELSAS, 2003; GREENFIELD et al., 1996; GUTIERREZ-ORTIZ; CABARGA; TEUS, 2006; OPHIR; WASSERMAN, 2002; ROTCHFORD; KING, 2008). No entanto, ainda não existe aceitação a respeito de sua eficácia na recuperação das cirurgias falidas há mais tempo (vários meses ou até mesmo anos), nas quais já nem se consegue distinguir o retalho escleral sob a conjuntiva. Portanto, muitos profissionais interpretam estas cirurgias como definitivamente perdidas e reintroduzem o tratamento clínico ou partem para uma nova cirurgia, acreditando não ser possível a recuperação da primeira.

Em 1996, Mardelli et al. foram os primeiros a descrever a recuperação tardia de trabeculectomias através do agulhamento realizado à lâmpada de fenda, associado à injeção subconjuntival de mitomicina C. Outros poucos trabalhos foram publicados sobre o tema (KAPASI; BIRT, 2009; PARIS; ZHAO; SPONSEL, 2004; PASSOS et al., 2002; UNG; VON LANY; CLARIDGE, 2003), porém vemos que este procedimento ainda é pouco aceito e divulgado. Alguns autores chegam até mesmo a acreditar que só são passíveis de recuperação aquelas cirurgias em que existe alguma evidência de funcionamento ou nas quais se pode distinguir o retalho escleral sob a conjuntiva (EWING; STAMPER, 1990).

Alguns fatores de risco já foram identificados para a falência das cirurgias fistulantes, como a pouca idade (AGIS, 2002), a raça negra (AGIS, 2001; BROADWAY; CHANG, 2001; SCOTT et al., 1998), a pressão intraocular (PIO) pré-operatória elevada (AGIS, 2002; STURMER; BROADWAY; HITCHINGS, 1993), o uso prolongado de colírios hipotensores (BROADWAY et al., 1994; BROADWAY; CHANG, 2001), a trabeculoplastia a laser (STURMER; BROADWAY; HITCHINGS,

1993) e a existência de cirurgia conjuntival prévia (BROADWAY; GRIERSON; HITCHINGS, 1998; GREENFIELD et al., 1996; STURMER; BROADWAY; HITCHINGS, 1993), uveíte (MIETZ; RASCHKA; KRIEGLSTEIN, 1994), glaucoma neovascular (MIETZ; RASCHKA; KRIEGLSTEIN, 1999) e afacia (HEUER et al., 1984). Outros fatores, estes já específicos do agulhamento, também já foram associados ao fracasso do procedimento, como o intervalo entre a trabeculectomia e o agulhamento (GUTIERREZ-ORTIZ; CABARGA; TEUS, 2006; MARDELLI et al., 1996; PASSOS et al., 2002; SHETTY; WARTLUFT; MOSTER, 2005), a PIO elevada antes do agulhamento (BROADWAY et al., 2004; GREENFIELD et al., 1996; KAPASI; BIRT, 2009; SHIN et al., 2001), múltiplos agulhamentos (GREENFIELD et al., 1996; NASCIMENTO et al., 2007; ROTCHFORD; KING, 2008) e a obtenção de uma PIO elevada logo após o procedimento (ANAND; KHAN, 2009; BROADWAY et al., 2004; KAPASI; BIRT, 2009; ROTCHFORD; KING, 2008; SHIN et al., 2001).

Antimetabólitos, como o 5-fluorouracil (5-FU) e a mitomicina C (MMC) são essenciais para o sucesso do agulhamento, pois inibem a proliferação de fibroblastos e ajudam a preservar a função da fístula recém recuperada. As taxas de sucesso do agulhamento sem antimetabólitos geralmente são baixas, variando de apenas 7,1% a 31% (COSTA; CORREA; KARA-JOSÉ, 1997; DURAK et al., 2003; MEYER; GUHLMANN; FUNK, 1997). A MMC parece ser mais eficaz do que o 5-FU (ANAND; KHAN, 2008) e, por ser 100 vezes mais potente do que este, pode ser usada como aplicação única durante o agulhamento. O 5-FU, por sua vez, exige uma série de injeções subconjuntivais no pós-operatório, o que torna seu uso mais desconfortável e menos prático. Por outro lado, justamente por ser menos potente, o 5-FU permite uma gradação do efeito antiproliferativo de acordo com o número de aplicações. Ambos são tóxicos para algumas estruturas oculares. Enquanto o 5-FU

é tóxico para a superfície ocular, causando quadros de desepitelizações conjuntivais e corneanas desconfortáveis e de lenta recuperação, a MMC é altamente tóxica para o endotélio corneano (HERNANDEZ-GALILEA et al., 2000; ROH et al., 2008; SILVA; GREGÓRIO, 2009; WU et al.; 1999; WU; WANG; HONG, 2008) e o corpo ciliar (MIETZ et al., 1994; SARI et al., 2005; SCHRAERMEYER et al., 1999), além de já terem sido relatados afilamentos conjuntivais e esclerais após seu uso (SAIFUDDIN; ZAWAWI, 1995; YAMANOUCHI, 1983). Por isso, uma das maiores preocupações quanto ao uso da MMC é quanto a sua segurança, principalmente para o endotélio corneano, devido a sua incapacidade de regeneração. McDermott et al. (1994) realizaram um estudo no qual o endotélio corneano humano foi exposto a duas concentrações de MMC. Na concentração mais baixa (20 µg/ml) não se observaram alterações significativas. No entanto, a exposição a uma concentração 10 vezes maior (200 µg/ml) resultou em imediata destruição do endotélio corneano.

O tratamento do glaucoma é um grande desafio médico e social. A falência de uma trabeculectomia é extremamente frustrante tanto para o médico quanto para o paciente. A reintrodução do tratamento clínico ou a realização de uma nova cirurgia trazem custos para o paciente e para o sistema de saúde. O agulhamento é um método simples, barato e eficaz, porém subutilizado na recuperação de fístulas antiglaucomatosas. A determinação de sua eficácia e segurança em fases tardias do pós-operatório pode trazer uma grande redução dos custos financeiros e sociais do glaucoma, razão que justifica a realização do presente estudo.

OBJETIVOS DA TESE

A presente pesquisa foi idealizada e planejada para responder às seguintes perguntas:

1) O agulhamento é eficaz para recuperar bolsas fistulantes falidas em uma fase tardia do pós-operatório, ou seja, meses ou anos após a trabeculectomia?
2) O agulhamento é eficaz no caso de bolsas totalmente planas, ou seja, na ausência de bolsa fistulante?
3) Quais são os fatores que podem influenciar a taxa de sucesso do agulhamento com MMC?
4) O agulhamento com MMC é seguro no que diz respeito a suas complicações?
5) O agulhamento com MMC é seguro para o endotélio corneano?

Para responder a essas perguntas foram conduzidos os seguintes trabalhos:

1) Agulhamento tardio de bolsas fistulantes planas com mitomicina C: estudo prospectivo;
2) Fatores preditivos para o sucesso do agulhamento com mitomicina C: estudo prospectivo;
3) Espessura corneana e densidade endotelial antes e depois do agulhamento com mitomicina C: estudo prospectivo.

Como os três trabalhos foram enviados para publicação em periódicos estrangeiros, são apresentados na presente tese em sua versão original, na língua inglesa.

ANÁLISE DOS TRABALHOS

PRIMEIRO TRABALHO

“Late Needling of Flat Filtering Blebs with Adjunctive Mitomycin C: A Prospective Study”

“Agulhamento Tardio de Bolsas Fistulantes Planas com Mitomicina C: Estudo Prospectivo”

OBJETIVOS DO PRIMEIRO TRABALHO

Os objetivos principais do primeiro trabalho foram:

1) Determinar a eficácia do agulhamento episcleral com MMC na recuperação de fístulas antiglaucomatosas falidas, quando realizado no pós-operatório tardio (mínimo de 6 meses após a trabeculectomia).
2) Avaliar especificamente sua eficácia no caso de bolsas planas (ausência de bolsa fistulante).
3) Avaliar a segurança do agulhamento com MMC através do estudo de suas complicações.

Os resultados desta pesquisa foram enviados para a revista “Ophthalmology”.

RESUMO DO PRIMEIRO TRABALHO

OBJETIVO: Avaliar a eficácia e a segurança do agulhamento com mitomicina C (MMC) na recuperação tardia de trabeculectomias com bolsas fistulantes planas.

MÉTODO: Neste estudo prospectivo, foram selecionados 125 olhos de 98 pacientes portadores de glaucoma sem controle adequado. Todos haviam sido submetidos a pelo menos uma trabeculectomia e apresentavam a bolsa fistulante plana e o óstio interno pérvio à gonioscopia. O intervalo de tempo médio entre a trabeculectomia e o agulhamento foi de 5,31 ± 5,29 anos (mínimo de 6 meses e máximo de 30 anos). O agulhamento associado à injeção subconjuntival de 8 µg de mitomicina C foi realizado no bloco cirúrgico, pela mesma cirurgiã e repetido, quando necessário.

RESULTADOS: Foram realizados 186 agulhamentos nos 125 olhos (média de 1,49 ± 0,64 agulhamentos por olho). Setenta e três olhos (58,4%) foram submetidos a um agulhamento, 44 olhos (35,2%) a dois, sete olhos (5,6%) a três e um olho (0,8%) foi submetido a quatro agulhamentos. O fluxo foi restabelecido em 115 olhos (92%), nos quais se obteve uma bolsa fistulante elevada. Após um seguimento médio de 20,80 ± 11,96 meses, a pressão intraocular (PIO) média caiu de 20,07 ± 5,20 mmHg no pré-operatório para 13,15 mmHg ± 6,77 mmHg ($p < 0,001$), e o número médio de medicações hipotensoras por olho caiu de 2,35 ± 1,14 antes do agulhamento para 0,78 ± 1,30 ($p < 0,001$) na última consulta. A taxa global de sucesso (PIO ≤ 16 mmHg) foi de 76% (58,4% sem medicação e 17,6% com o auxílio de medicações hipotensoras). As complicações incluíram hifema discreto (25,8%), câmara anterior rasa (18,3%), descolamento seroso da coróide (15,6%), extravasamento de humor aquoso pelo orifício de entrada da agulha (8,6%) e bolsa encapsulada (7,5%). A maioria das complicações foi leve e transitória, sem necessidade de tratamento.

CONCLUSÕES: O agulhamento com mitomicina C é relativamente seguro e altamente eficaz na recuperação de bolsas fistulantes falidas e planas, proporcionando um bom controle da PIO, mesmo quando realizado anos após a trabeculectomia.

Late Needling of Flat Filtering Blebs with Adjunctive Mitomycin C: A Prospective Study.

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ABSTRACT

Purpose: To assess the efficacy and safety of needle revision using mitomycin C (MMC) to revive failed filtering blebs during the late postoperative period.

Design: Prospective interventional case series.

Participants: We recruited 125 eyes from 98 patients with uncontrolled glaucoma. All had at least one failed trabeculectomy, a flat filtering bleb, and a patent internal ostium on gonioscopy. The average time between the last trabeculectomy and needle revision was 5.31 ± 5.29 years (range, 6 months−30 years).

Intervention: Needle revision with a subconjunctival injection of 8 μg of MMC, performed in an operating room by a single surgeon.

Main Outcome Measures: Intraocular pressure (IOP) and number of hypotensive medications at the latest visit, intra and postoperative complications.

Results: Overall, 186 needling procedures were performed on 125 eyes (mean 1.49 ± 0.64 procedures per eye). Seventy-three eyes (58.4%) were needled once, 44 (35.2%) were needled twice, seven (5.6%) were needled three times, and one (0.8%) was needled four times. We reestablished aqueous flow and obtained a raised bleb in 115 eyes (92%). After an average follow-up of 20.80 ± 11.96 months, mean IOP decreased from 20.07 ± 5.20 mmHg preoperatively to 13.15 ± 6.77 mmHg ($P < 0.001$), and the mean number of hypotensive medications per eye decreased from 2.35 ± 1.14 at baseline to 0.78 ± 1.30 ($P < 0.001$) at the latest visit. The overall success rate (IOP ≤ 16 mmHg) was 76% (58.4% without medication and 17.6% with hypotensive medications). Complications included mild hyphema (25.8%), shallow anterior chamber (18.3%), serous choroidal detachment (15.6%), bleb leakage (8.6%), and encapsulated bleb (7.5%). Most complications were minor, transient, and required no treatment.

Conclusions: Needle revision with adjunctive MMC is relatively safe and highly effective for reviving flat filtering blebs and controlling IOP, even several years after the original trabeculectomy.

INTRODUCTION

Trabeculectomy is still the standard surgical treatment for glaucoma patients. It is highly effective, but has significant early and late failure rates, usually due to subconjunctival fibrosis.[1] Failure leaves the physician with limited options to control intraocular pressure (IOP). Reinstitution of medical therapy can result in an increase in morbidity and cost, and may be ineffective for lowering IOP to a sufficient level. A second trabeculectomy may have a similar outcome to the first, with further sacrifice of virgin conjunctiva. Surgical revision and drainage device implant are generally more time consuming, and subsequent failure rates are usually higher than for primary surgery. Cyclodestructive procedures are unpredictable and carry a risk of visual loss and ocular atrophy.

Bleb needling provides a relatively simple approach to the problem. A variety of methods have been described, but the principle remains the same, which is to disrupt subconjunctival scar tissue and restore bleb function. Although it was reported as early as 1941, by Ferrer,[2] needle revision did not become widespread until the advent of antifibrotic agents. In 1990, Ewing and Stamper[3] first reported the use of 5-fluorouracil (5-FU) and, in 1996, Mardelli et al.[4] first described the use of mitomycin C (MMC) as an adjunctive therapy for needle revision. Five-fluorouracil has some side effects, such as persistent corneal and conjunctival defects and requires repeated subconjunctival injections. Mitomycin C has several advantages over 5-FU, including less corneal epithelial toxicity, higher potency, and the need for only a single intraoperative application. The inhibitory effect of 5-FU can be regulated by varying the number of postoperative injections, but a single-dose injection of MMC does not allow for this modulation.

Most studies in the literature have focused on needle revisions performed early during the postoperative period,[5-10] but there are few reports confirming its efficacy during the late postoperative period.[11-14] Some authors believe that success is only possible when a bleb is present preoperatively, or when the scleral flap is visible under the conjunctiva. When faced with a flat bleb months or years after the original surgery they prefer a second trabeculectomy, believing that needle revision cannot be used to revive it.

The purpose of this prospective study was to determine the efficacy and safety of needling with adjunctive MMC to revive flat filtering blebs during the late postoperative period.

METHODS

Patient Selection

The study protocol was approved by the Ethics Committee of the Federal University of Minas Gerais, Brazil. Each patient provided written informed consent.

In this prospective case series, we recruited 125 eyes from 98 patients, with an average age of 61.64 years [standard deviation (SD), 18.81; range, 5−91; median, 66 years] and uncontrolled glaucoma, defined as an IOP above target-pressure or visual field progression. We measured IOP in the morning (between 8:00 am and 11:00 am), on three different days preoperatively, and the mean value was calculated for the baseline IOP. The average vertical cup-to-disk ratio was 0.83 (SD, 0.22; range, 0.2−1). All eyes had at least one previous failed trabeculectomy (performed with or without antifibrotic agents), a patent internal ostium on gonioscopy, a completely flat filtering bleb, and a minimum of 6 months from the filtering surgery. The average time between the last failed trabeculectomy and needle revision was

5.31 years (SD, 5.29 years; range, 6 months−30 years). We excluded eyes with encapsulated blebs.

Information regarding gender, race, type of glaucoma, lens status and previous surgery is shown in Table 1.

TABLE 1. Demographics and characteristics of the study population

	No. of eyes	%
Gender		
Male	61	48.8
Female	64	51.2
Race		
White	41	32.8
Black	84	67.2
Type of glaucoma		
Open-angle	97	77.6
Angle-closure	10	8.0
Congenital	6	4.8
Inflammatory	4	3.2
Cortisonic	3	2.4
Aphakic	3	2.4
Neovascular	1	0.8
Cogan Reese Syndrome	1	0.8
Lens status		
Phakic	69	55.2
Pseudophakic	53	42.4
Aphakic	3	2.4
Previous surgery		
1 trab	55	44
2 trabs	9	7.2
3 trabs	1	0.8
Cataract + 1 trab	47	37.6
Cataract + 2 trabs	9	7.2
Trabeculotomy + 1 trab	3	2.4
Trabeculotomy + 2 trabs	1	0.8

Trab = Trabeculectomy

Surgical Technique

The same surgeon (HAM) performed all needling procedures in an operating room under sterile conditions, between November 2002 and April 2007, using a standardized technique. After topical anesthesia with 5% proparacaine, eyelids and

surrounding skin were prepared with a 10% povidone-iodine solution, and a drop of the 5% povidone-iodine solution was applied to the conjunctiva. A lid speculum was placed, and the patient was asked to look down. The surgeon drew up 0.2 ml of 2% lidocaine with epinephrine and 0.1 ml of a 0.25 mg/ml MMC solution into a 1.0 ml syringe, for a final MMC concentration of 0.08 mg/ml. The needle was changed to a 26-gauge, and it was bent bevel up at the hub to an angle of 45º. Only 0.1 ml from the lidocaine-MMC mixture was injected into the subconjunctival space (MMC dose of 8 µg), 10 mm away from the posterior lip of the scleral flap (or from the place it was expected to be). The lid speculum was withdrawn and a gentle massage was applied to the superior eyelid for 5 minutes. The speculum was inserted again, and the needle was introduced superiorly as far as possible from the bleb; the needle was carefully advanced, using a side-to-side motion, beneath the Tenon's space, breaking episcleral adhesions around the bleb and over the scleral flap until the bleb was reformed. We never introduced the needle under the scleral flap or into the anterior chamber. We verified reestablishment of flow by one of the following signs: softening of the eyeball, release of aqueous humor into the subconjunctival space, which created a raised conjunctival bleb, and, occasionally, a small reflux of blood into the anterior chamber. The conjunctival wound was not sutured, because of the oblique nature of the needle entry. One drop of a broad-spectrum topical antibiotic was applied after the procedure.

A combination of tobramicin or ciprofloxacin and dexamethasone 0.1% was administered six times daily for 1 week and gradually tapered as ocular inflammation subsided. Cycloplegic agents were administered only if the anterior chamber was shallow or choroidal detachment was present. Patients were seen on the first

postoperative day and after 1 week, and 1, 3, 6, 12, 18, and 24 months, or more often as necessary, and complications were documented.

Needling was repeated using the same technique if the initial revision was not successful for controlling IOP. We permitted as many needling procedures as were necessary, but did not perform more than four needlings per eye. Some eyes received additional slit-lamp subconjunctival injections of antimetabolites during follow-up based on bleb morphology (elevation and extent) and signs of scarring (vascularization and increasing IOP). Moderately vascularized blebs received 5 mg of 5-FU (0.2 ml at a concentration of 25 mg/ml) and severely vascularized blebs received 8 µg of MMC (0.1 ml at a concentration of 0.08 mg/ ml).

Statistical Analysis

Reestablishment of aqueous flow with a resultant raised bleb was classified as an *immediate success*. At the last visit we defined an *absolute success* as an IOP ≤ 16 mmHg without medication, a *qualified success* as an IOP ≤ 16 mmHg with the aid of hypotensive agents, and a *failure* as an IOP > 16 mmHg despite medication, or if further conventional surgery was required to lower IOP.

We used SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA) for statistical analyses. We used Levene's test to confirm homogeneity of variance and the two-tailed Wilcoxon signed rank test with continuity correction to compare preoperative and postoperative IOP and the number of hypotensive agents (non-parametric data). Two Kaplan-Meier survival curves were produced to compare the results of the first needling versus all needlings. A P value < 0.05 was deemed to be statistically significant.

RESULTS

We performed 186 needling procedures on 125 eyes (a mean of 1.49 needlings per eye; SD, 0.64; range, 1−4). Seventy-three eyes (58.4%) were needled once, 44 (35.2%) were needled twice, seven (5.6%) were needled three times, and one (0.8%) was needled four times. When we performed more than one needling, the mean interval between the first and second needling was 5.12 months (SD, 7.26; range, 4 days−33.57 months). The average follow-up from the first needling was 20.80 months (SD, 11.96; range, 1−57). Thirty-one eyes (24.8%) received 5-FU injections during the postoperative period, with an average of 4.10 applications per eye (SD, 2.80; range, 1−14). Four eyes (3.2%) received additional slit-lamp MMC injections during the postoperative period, with an average of 1.25 applications per eye (SD, 0.50; range, 1−2).

We reestablished aqueous flow and obtained a raised bleb in 115 eyes (92%), which were classified as *immediate successes*.

Mean IOP decreased from 20.07 mmHg (SD, 5.20; range, 11.3−38.7; median, 19 mmHg) preoperatively to 13.15 mmHg (SD, 6.77; range, 1−38; median, 12 mmHg) at the last follow-up (Wilcoxon signed rank test; $P < 0.001$). The change in IOP after needling is shown in Figure 1. The mean number of hypotensive agents per eye decreased from 2.35 (SD, 1.14; range, 0−5; median, 3) at baseline to 0.78 (SD, 1.30; range, 0−4; median, 0) at last follow-up (Wilcoxon signed rank test; $P < 0.001$).

At the latest visit, 95 eyes (76%) achieved an IOP ≤ 16 mmHg. Overall, 73 eyes (58.4%) achieved an *absolute success*, 22 eyes (17.6%) a *qualified success*, and 30 eyes (24%) were classified as *failures*. Data regarding IOP and number of hypotensive medications in each group are listed in Table 2. The mean IOP during the postoperative period is shown in Figure 2. Of the 30 eyes that failed, 13

subsequently restarted the medical therapy, 14 underwent another trabeculectomy, and three a Molteno implantation.

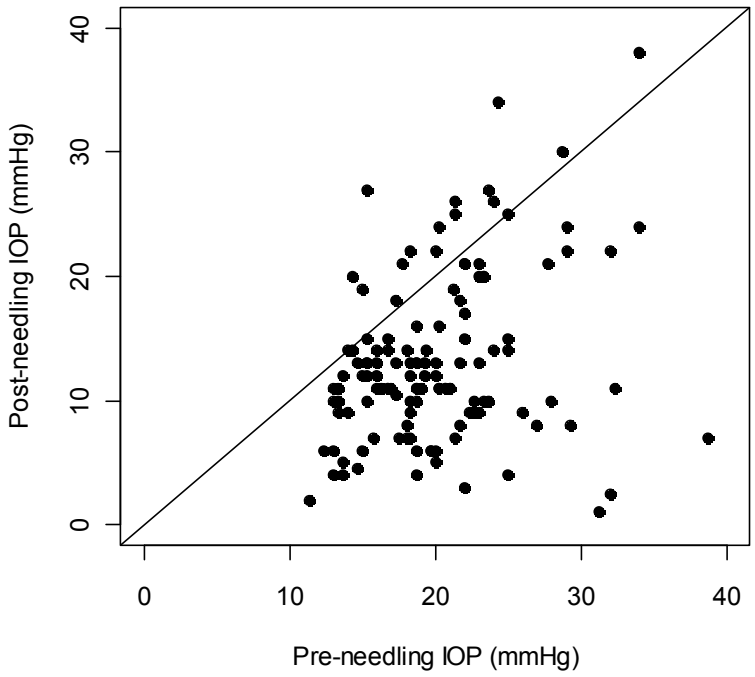

FIGURE 1. Change in intraocular pressure (IOP) after all bleb needle revisions. Points to the right of the equality line indicate pressures improved.

TABLE 2. Data regarding IOP and number of hypotensive medications

	Pre-needling		Post-needling		P
	Mean (±SD)	**Median**	**Mean (**±SD)	**Median**	**value***
Absolute success group (73 eyes; 58.4%)					
IOP (mmHg)	19.74 (±5.14)	18.7	9.22 (±3.50)	10	**< 0.001**
No. of medications	2.26 (±1.09)	2	0	0	**< 0.001**
Qualified success group (22 eyes; 17.6%)					
IOP (mmHg)	17.01 (±3.02)	16.4	12.57 (±1.50)	13	**< 0.001**
No. of medications	2.32 (±1.21)	3	2.36 (±1.09)	3	0.949
Failure group (30 eyes; 24.0%)					
IOP (mmHg)	23.13 (±5.15)	22.5	23.13 (±4.67)	22	0.940
No. of medications	2.60 (±1.19)	3	1.50 (±1.55)	1	**0.001**

*Two-tailed Wilcoxon signed rank test with continuity correction. Bold P values are statistically significant. IOP = intraocular pressure. SD = standard deviation.

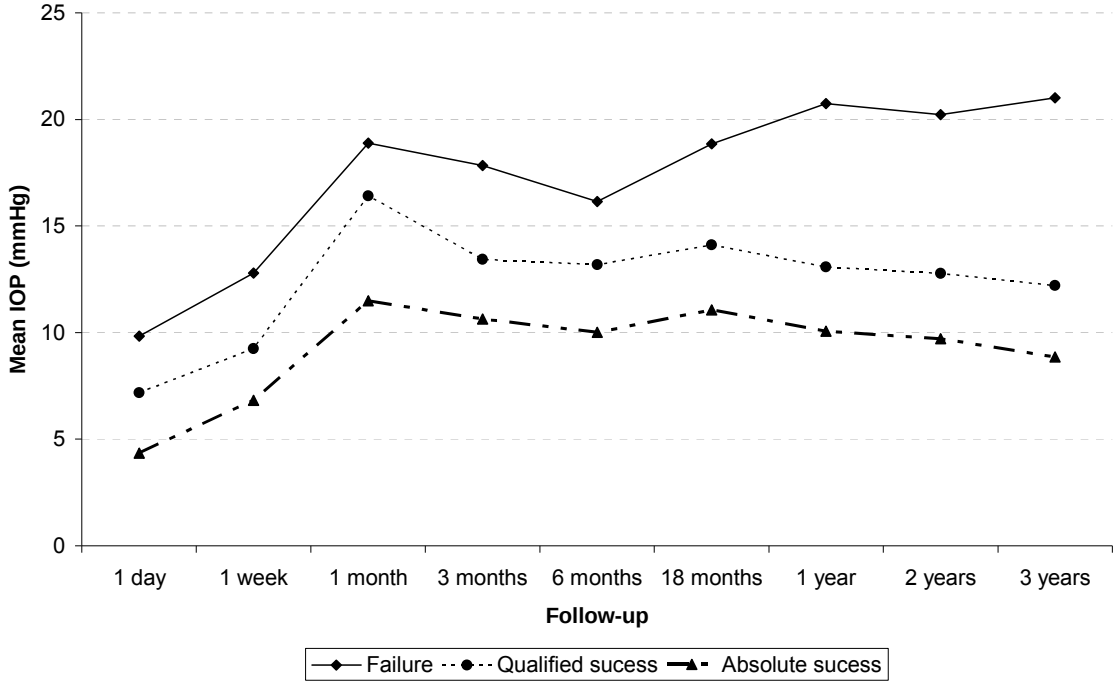

FIGURE 2. Mean intraocular pressure (IOP) during postoperative period.

Complications developed in 92 (49.46%) of the 186 needling procedures. The main intraoperative occurrences were conjunctival hemorrhage (186 procedures, 100%) and a mild hyphema (48 procedures, 25.81%). The conjunctiva overlying the scleral flap was accidentally perforated during three procedures (1.61%). The area was Seidel-positive after the procedure, but healed within a few days in all cases. Postoperative complications are listed in Table 3. Most were mild and resolved spontaneously in a few days. Two atalamic eyes required anterior chamber reformation with air during the first postoperative day. Encapsulated blebs received topical treatment with hypotensive eyedrops and massage or another needling procedure. Eleven of the 125 eyes (8.8%) developed late hypotony, defined as an IOP < 6 mmHg after 6 months. One required a scleral patch graft 6 months after the

needling procedure. Eleven eyes (8.8%) gradually developed cataracts some months after needling. There was no correlation between the number of needling procedures and late hypotony (Fisher's exact test; P = 0.152) or cataract formation (Fisher's exact test; P = 0.896). None of the eyes developed corneal decompensation, suprachoroidal hemorrhage, blebitis, or endophthalmitis.

TABLE 3. Postoperative complications

Complication	No. of needling procedures (total 186)	%
Mild hyphema	48	25.81
Shallow anterior chamber	34	18.28
Serous choroidal detachment	29	15.59
Bleb leakage	16	8.60
Encapsulated bleb	14	7.53
Mild vitreous haemorrage	5	2.69
Punctate keratopathy	4	2.15
Transitory corneal edema	1	0.54

Kaplan-Meier cumulative survival curves for the first needling and for all needlings are shown in Figure 3. Survival rates were higher when multiple needlings were performed. When we compared a single needling versus all needlings, success rates were 65.6% versus 91.2% at the one month follow-up, 49.5% versus 84.5% at 6 months, 46.2% versus 81.0% at 1 year, 37.0% versus 74.6% at 2 years, and 25.2% versus 66.3% at 3 years.

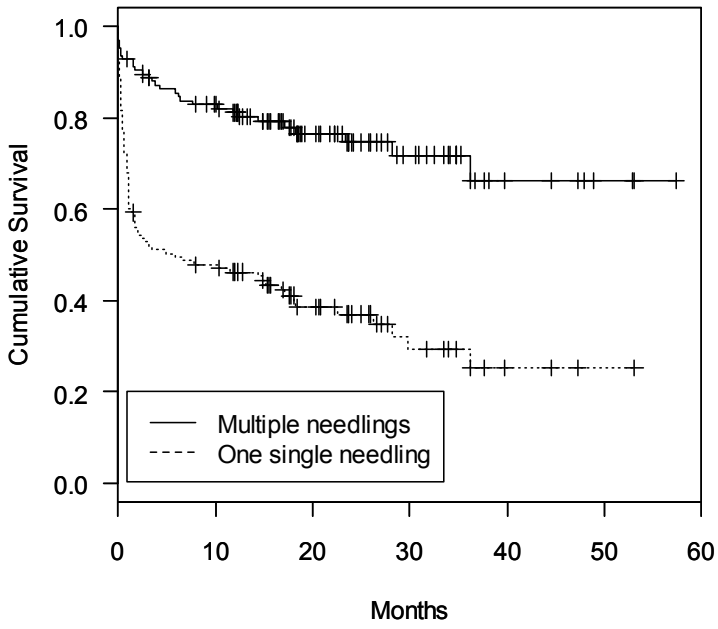

FIGURE 3. Kaplan-Meier cumulative survival curves for all needlings vs. the first needling (125 eyes). Success criteria: IOP ≤ 16 mmHg.

DISCUSSION

Failure of filtration surgery is a very common problem. In the 5-fluorouracil filtration study,[15] the early success rate was 80%, but after a follow-up period of 5 years, it dropped to 48%. The probability of success is even lower after repeat trabeculectomies, ranging from only 36 to 64%, depending on the study.[16-18]

Trabeculectomies fail because of aqueous resistance at one of three levels: (1) at the internal sclerostomy, (2) at the scleral flap, or (3) at the level of the subconjunctival space. Most failures are caused by fibrosis involving the subconjunctival space,[1] and needle revision is intended to act exactly at this level. The adjunctive use of antifibrotic agents, such as MMC or 5-FU, is essential to inhibit the postoperative scarring process and preserve bleb function. Success rates for needling revisions without antiproliferative agents are usually low, ranging from 7.1 to

31%.[19-21] Subconjunctival MMC seems to be more effective than 5-FU for needle revision[22] and offers the advantage of a single intraoperative application. However, 5-FU allows for a gentle modulation of the healing response during the postoperative period.[23] In 1997, Apostolov and Siarov[24] proposed the use of subconjunctival MMC injections during the early postoperative period in some cases of failing trabeculectomies. In our study, 31 eyes (24.8%) received postoperative 5-FU injections and four eyes (3.2%) received additional slit-lamp MMC injections based on bleb morphology and signs of scarring. We believe that these additional antifibrotic injections are a useful tool for reducing the healing response in high risk eyes.

There are many studies reporting that bleb needling can rectify a failing bleb during the early postoperative phase,[5-10] but few reports confirm its effect during the late postoperative period.[11-14] In the present study, the average time between the last failed trabeculectomy and needle revision was 5.31 years, ranging from 6 months to 30 years, which means that all needle revisions were performed in a late postoperative period.

We chose to use an operating room rather than a slit-lamp because of increased patient comfort, a lower risk of infection, and better control of the surgical technique allowed by a two-handed procedure. We performed all needle revisions at an episcleral level and never introduced the needle under the scleral flap or into the anterior chamber, because the scleral flap is seldom outlined under the conjunctiva during the late postoperative period. We believe that elevating the scleral flap is not only unnecessary and technically difficult during the late postoperative period, but also risky. All cases of suprachoroidal hemorrhage[4,5,10,22,25,26] and endophthalmitis[5] were described by authors who performed needle revisions with flap elevation.

Our criteria for success were more stringent than those reported by previous studies.[4,6,8,9,25-30] We chose an IOP level of 16 mmHg as a cutoff point for success because most of the patients involved in this study had advanced glaucoma and required low IOP levels to prevent further damage to the optic nerve.

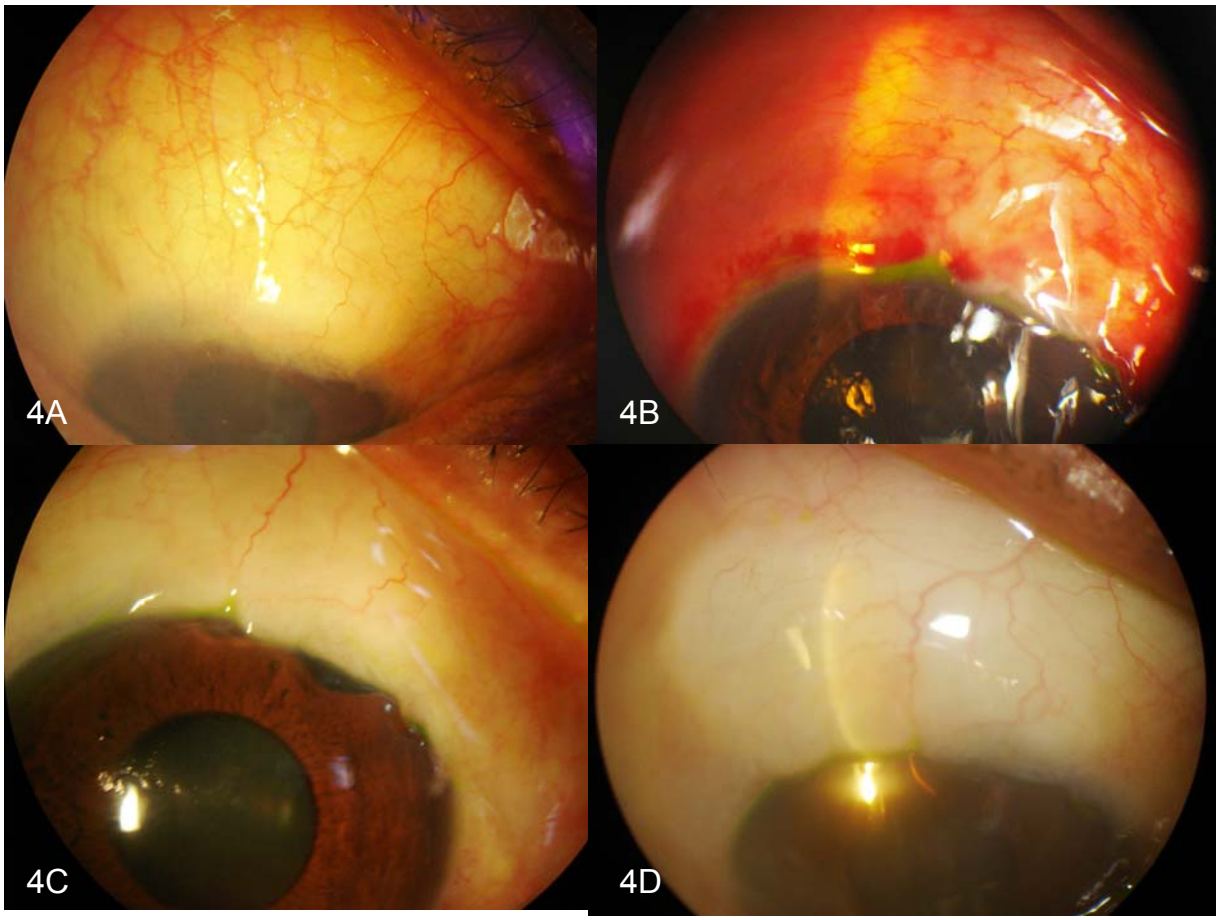

FIGURE 4. Bleb appearance before and after bleb needling with MMC. 4A: Preoperative aspect (flat bleb, IOP 20 mmHg). 4B: First postoperative day (raised bleb, IOP 6 mmHg). 4C: Six months after needling (diffuse bleb, IOP 12 mmHg). 4D: Two years after needling (diffuse bleb, IOP 10 mmHg).

We revived 92% of all needled blebs (immediate success), which is excellent effectiveness for a relatively simple procedure. The appearance of resultant blebs after needling varied, but the most common type was large, diffuse, and discretely vascularized (Fig. 4). Our results are similar to those of Nascimento et al.,[31] who obtained an elevated bleb in 90.3% of 84 eyes after needle revision with MMC.

Interestingly, in their study, they found that success was positively associated with the absence of an elevated bleb preoperatively. Our results also show that a completely flat bleb can provide excellent filtration, even several years after the original surgery.

It is difficult to compare studies because of differences in surgical techniques, success criteria, antimetabolite type and dose, timing of the needling procedure, and follow-up period, but our overall success rate of 76% at the latest visit agrees with previous reports[4,27,28,31] that ranged between 71.6 and 76%. Needling proved to be highly effective. We achieved a significant reduction in mean IOP (from 20.07 mmHg preoperatively to 13.15 mmHg at the latest visit) and in the mean number of hypotensive agents (from 2.35 per eye preoperatively to 0.78 at last follow-up). In 58% of our patients (absolute success group), we obtained more than a 50% reduction in mean IOP. In 17.6% of our patients (qualified success group), even if the number of hypotensive medications remained the same, mean IOP dropped by 26%. In the failure group, although the mean IOP remained the same, there was a significant reduction in the mean number of medications. For most of the patients the procedure provided the chance to reduce the cost and morbidity associated with medical therapy and contributed to a better quality of life.

Multiple needlings have been reported by several authors.[4-6,8-10,14,22,25,26,29-31] In our study, 41.6% of the eyes underwent more than one needling procedure. The mean number of 1.49 needling procedures per eye also confirms that more than one revision may be needed to achieve good IOP control. The Kaplan-Meier survival curves (Fig. 3) showed that success rates after all needlings were higher than after a single needle revision. Some single needle failures became successes when a repeat needling was performed. The survival curve for the first needling also shows

that most failures occurred within the first month and caused a slight elevation in mean postoperative IOP at the 1 month follow-up (Fig. 2). After that, a significant proportion of the eyes were needled again, which reduced mean IOP.

Bleb needle revision with MMC was first reported by Mardelli et al.[4] who injected 4 µg of MMC at a concentration of 0.13 mg/ml and performed an average of 1.9 revisions per eye. In our study, we used a higher dose (8 µg of MMC at a concentration of 0.08 mg/ml) and performed 1.49 revisions per eye. Shetty et al.[30] used a much higher MMC dose (40 µg of MMC at a concentration of 0.20 mg/ml), and required even fewer needle revisions (1.05 per eye). It is possible that fewer repeat procedures would have been required in our study if a higher MMC dose had been used.

Complications were similar to those seen after a trabeculectomy. They included small hyphemas, transient choroidal effusion, temporary conjunctival wound leaks, and shallowing of the anterior chamber. Most were minor, tolerable, and transient and required no treatment. However, the potential for more serious complications should not be underestimated. “Kissing” choroidal detachment that required surgical drainage,[14,26] suprachoroidal hemorrhage,[4,5,10,22,25,26,32] malignant glaucoma[22,33,34] and endophthalmitis[5] have been reported after bleb needling. None of the eyes in our study developed blebitis or endophthalmitis. In fact, the incidence of infectious events related to needling is very low. Pasternack et al.,[26] Nascimento et al.,[31] and Anand et al.[22] reported a few cases of successfully treated blebitis, and Greenfield et al.[5] reported the only case of endophthalmitis after bleb needling in the literature.

It is possible that a small amount of MMC may enter the eye during the needling procedure. However, the risk for direct inoculation of the anterior chamber

can be minimized by careful technique; the MMC solution must be injected slowly and some millimeters away from the bleb, to avoid a pressure gradient from the subconjunctival space to the anterior chamber, and some minutes should elapse between injection and needling. Even if the entire amount of MMC used in our study inadvertently entered the anterior chamber, it would be insufficient to cause endothelial toxicity.[35] In the present study, only one eye experienced transient and mild corneal edema, which subsided within 1 week, but its preoperative endothelial cell density was very low (869 cells/mm^2) and remained similar during the postoperative period (814 cells/mm^2 after 6 months). MMC may also be toxic to the ciliary body epithelium and lead to persistent ocular hypotony.[36-38] In our study, bleb formation was essential for reduction of IOP, which suggests that subconjunctival injection of MMC may not in itself lower IOP. Eleven eyes developed late hypotony, but all were related to large, avascular, and clearly overfiltering blebs. Only one required surgical treatment: a scleral patch graft 6 months after the needling procedure. The others were asymptomatic. There was no case of hypotonous maculopathy. Moreover, none of the eyes in our study had any evidence of scleral or conjunctival necrosis.

We believe that when the internal ostium is patent on gonioscopy, needle revision should be considered before a repeat trabeculectomy. Needling has the potential to be equally effective as a trabeculectomy, with a lower cost and a smaller degree of surgical trauma. It is relatively simple, safe, and fast compared with a major surgical procedure and has a relatively high success rate, even in complicated glaucomas. It probably induces less postoperative fibrosis than conventional surgery, and if it does fail, the surgical field is still preserved for another filtering procedure.

In conclusion, needling revision with adjunctive MMC is relatively safe and highly effective for reviving flat filtering blebs and controlling IOP, even several years after the original trabeculectomy.

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CONCLUSÃO DO PRIMEIRO TRABALHO, FORMULAÇÃO DE NOVAS HIPÓTESES E OBJETIVOS DO SEGUNDO TRABALHO

O primeiro trabalho demonstrou, portanto, que o agulhamento com mitomicina C, realizado em uma fase tardia do pós-operatório, é eficaz na recuperação de fístulas antiglaucomatosas falidas, mesmo após muitos anos da realização da trabeculectomia e perante a ausência total de bolsa fistulante. Quando realizado em nível apenas episcleral, é relativamente seguro, pois suas complicações geralmente são transitórias e têm resolução espontânea. O presente trabalho demonstrou, também, a necessidade de, muitas vezes, se repetir o agulhamento para a obtenção de adequado controle da pressão intraocular. A sobrevivência de apenas um agulhamento mostrou-se bem menor quando comparada à sobrevivência de múltiplos agulhamentos.

Diante dos resultados obtidos, foram feitas então novas formulações. Gostaríamos de saber quais seriam os fatores que poderiam influenciar a taxa de sucesso do agulhamento. Já se conhecem vários fatores que interferem no resultado da trabeculectomia. Gostaríamos de saber se eles também influenciariam a taxa de sucesso do agulhamento e se haveria outras variáveis, estas já específicas do agulhamento, que também poderiam afetar seu sucesso ou seu fracasso.

O objetivo principal do segundo trabalho foi, portanto, identificar os fatores pré e pós-operatórios que pudessem estar associados ao sucesso do agulhamento com MMC na recuperação tardia de fístulas antiglaucomatosas falidas.

Os resultados desta pesquisa foram enviados para a revista “Journal of Glaucoma”.

SEGUNDO TRABALHO

“Predictors of Success in Needle Revision of Filtering Blebs with Mitomycin C: A Prospective Study”

“Fatores Preditivos para o Sucesso do Agulhamento com Mitomicina C: Estudo Prospectivo”

RESUMO DO SEGUNDO TRABALHO

OBJETIVO: Identificar os fatores associados ao sucesso do agulhamento com mitomicina C (MMC) na recuperação tardia de bolsas fistulantes falidas.

MÉTODO: Foram submetidos ao agulhamento com MMC 125 olhos de 98 pacientes portadores de glaucoma sem controle adequado. Todos tinham pelo menos uma trabeculectomia prévia, a bolsa fistulante estava totalmente plana e o óstio interno estava pérvio à gonioscopia. O agulhamento associado à injeção subconjuntival de 8 µg de MMC foi realizado no bloco cirúrgico, pela mesma cirurgiã e repetido, se necessário.

RESULTADOS: Após um seguimento médio de 20,8 ± 11,96 meses, a pressão intraocular (PIO) média caiu de 20,07 ± 5,20 mmHg no pré-operatório para 13,15 ± 6,77 mmHg no pós-operatório ($p < 0,001$) e o número médio de colírios hipotensores por olho caiu de 2,35 ± 1,14 para 0,78 ± 1,30 na última consulta ($p < 0,001$). Noventa e cinco olhos (76%) foram classificados como sucesso (PIO ≤ 16 mmHg) na última consulta. A principal variável associada ao sucesso foi a PIO baixa antes do agulhamento ($p < 0,001$). O sucesso também foi correlacionado a uma PIO baixa no primeiro dia após o agulhamento ($p = 0,005$), um maior intervalo de tempo entre a trabeculectomia e o agulhamento ($p = 0,030$) e à idade ($p = 0,050$; significância limítrofe), sendo que quanto mais idoso o paciente, maior sua chance de sucesso. As taxas de sucesso também foram maiores em pacientes brancos, em olhos pseudofácicos e em olhos com trabeculectomias de base fórnice, mas não em um grau que atingisse significância estatística.

CONCLUSÕES: O agulhamento com mitomicina C é um método eficaz para recuperar bolsas fistulantes falidas. Maiores taxas de sucesso foram alcançadas em

olhos com menor PIO pré-operatória, menor PIO no primeiro dia após o agulhamento, maior intervalo de tempo entre a trabeculectomia e o agulhamento e em pacientes mais idosos.

Predictors of Success in Needle Revision of Filtering Blebs with Mitomycin C: A Prospective Study

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ABSTRACT

Purpose: To identify factors associated with success of needle revision of failed filtering blebs with adjunctive mitomycin C.

Patients and Methods: We investigated 125 eyes in 98 patients with uncontrolled glaucoma. All had at least one failed trabeculectomy, a flat filtering bleb, and a patent internal ostium on gonioscopy. Needle revision with subconjunctival injection of 8 μg mitomycin C was performed in the operating room. Needling was repeated if necessary.

Results: After an average follow-up of 20.80 ± 11.96 months, mean intraocular pressure (IOP) decreased from 20.07 ± 5.20 mmHg preoperatively to 13.15 ± 6.77 mmHg ($P < 0.001$), and the mean number of hypotensive agents per eye decreased from 2.35 ± 1.14 at baseline to 0.78 ± 1.30 ($P < 0.001$) at the latest visit. Overall, 95 eyes (76%) qualified as successes (IOP ≤ 16 mmHg) at the latest visit. The most important variable associated with success was a lower pre-needling IOP ($P < 0.001$). Successful outcomes also correlated significantly with a lower IOP on the first postoperative day ($P = 0.005$), a longer time between trabeculectomy and needling ($P = 0.030$), and older age ($P = 0.050$; borderline significance). The success rates tended to be greater in whites, pseudophakic eyes, and in eyes with a previous fornix-based conjunctival flap, but not to a degree that was statistically significant.

Conclusions: Needle revision with mitomycin C is effective to revive failed filtering blebs. Higher success rates were achieved in eyes with lower pre-needling IOP, lower IOP on the first postoperative day, longer interval between trabeculectomy and needling, and in older patients.

Key words: needle revision, mitomycin C, trabeculectomy, glaucoma, treatment failure.

INTRODUCTION

Failure of trabeculectomy is a common problem and is usually the result of subconjunctival fibrosis.[1] As the process of wound healing continues to occur indefinitely after initial surgery, trabeculectomy may fail at any time in the postoperative period. Needle revision is a simple and effective procedure to revive failing and failed filtering blebs,[2-4] even several years after the original filtration surgery.[5-7] Antimetabolites, such as 5-flurouracil (5-FU) and mitomycin C (MMC), are usually used as adjunctive therapy to inhibit fibroblast proliferation and preserve bleb function. MMC seems to be more effective than 5-FU[8] and offers the advantage of a single intraoperative application, instead of a series of postoperative injections for 5-FU.

Risk factors such as young age,[9] black race,[10,11] high preoperative intraocular pressure (IOP),[9] previous conjunctival surgery,[12] uveitis,[13] neovascular glaucoma[13] and aphakia[14] have been reported to reduce the success of any filtration procedure. The objective of this prospective study was to identify preoperative and postoperative factors associated with success or failure of needle revision of filtering blebs with adjunctive subconjunctival MMC.

PATIENTS AND METHODS

Patients

In this prospective study, we investigated 125 eyes in 98 patients with inadequate IOP control or visual field progression. All eyes had a flat filtering bleb, a patent internal ostium on gonioscopy, and a minimum interval of 6 months after trabeculectomy. Eyes with encapsulated blebs were excluded. IOP was measured on three different days preoperatively and the mean value was used for baseline IOP.

TABLE 1. Demographics and characteristics of the study population

	No. of eyes	%
Gender		
Male	61	48.8
Female	64	51.2
Race		
White	41	32.8
Black	84	67.2
Type of glaucoma		
Open-angle	97	77.6
Angle-closure	10	8.0
Congenital	6	4.8
Inflammatory	4	3.2
Cortisonic	3	2.4
Aphakic	3	2.4
Neovascular	1	0.8
Cogan Reese Syndrome	1	0.8
Lens status		
Phakic	69	55.2
Pseudophakic	53	42.4
Aphakic	3	2.4

TABLE 2. Previous surgery and antimetabolite exposure

	No. of eyes	%
Previous surgery		
1 trab	55	44
2 trabs	9	7.2
3 trabs	1	0.8
Cataract + 1 trab	47	37.6
Cataract + 2 trabs	9	7.2
Trabeculotomy + 1 trab	3	2.4
Trabeculotomy + 2 trabs	1	0.8
Previous conjunctival flap		
Limbus-based	59	47.2
Fornix-based	52	41.6
Unknown	14	11.2
Previous antimetabolite use		
None	49	39.2
MMC	31	24.8
5-FU	2	1.6
MMC + 5-FU	9	7.2
Unknown	34	27.2

Trab = Trabeculectomy. MMC = Mitomycin-C. 5-FU = 5-fluorouracil.

Information regarding gender, race, type of glaucoma, and lens status is shown in Table 1. Data from previous surgery are listed in Table 2. The average age of the study population was 61.64 years [standard deviation (SD), 18.81; range, 5−91; median, 66 years]. The average time interval between the original filtration surgery and the needling revision was 5.31 years (SD, 5.29 years; range, 6 months−30 years).

The study protocol was approved by the Federal University of Minas Gerais, Brazil, and all patients provided written informed consent.

Surgical Technique

All needling procedures were performed in the operating room, under sterile conditions, by the same surgeon (HAM) between November 2002 and April 2007. One drop of 5% proparacaine and one of 5% povidone–iodine were instilled into the conjunctival sac, and the eyelids and surrounding skin were prepared with 10% povidone–iodine. The surgeon prepared a solution as follows: 0.2 ml of 2% lidocaine with epinephrine and 0.1 ml of a 0.25 mg/ml MMC solution were drawn into the same insulin syringe, for a final MMC concentration of 0.08 mg/ml. A lid speculum was placed and the patient was asked to look down. From the lidocaine–MMC mixture, only 0.1 ml (8 μg MMC) was injected into the superior subconjunctival space, approximately 10 mm from the site of the failed filtering bleb, using a 26-gauge needle, bent bevel up at the hub, to an angle of 45°. The lid speculum was withdrawn and a gentle massage was applied to the superior eyelid. After 5 minutes, the speculum was reinserted and the needle was introduced in the same needle track and advanced beneath the Tenon's space, with side-to-side motions, disrupting episcleral adhesions around the bleb, and finally over the scleral flap. Attention was

given to avoiding inadvertent perforation of the overlying conjunctiva. The needle was never introduced under the scleral flap or into the anterior chamber. Reestablishment of aqueous flow was verified by one of the following signs: release of aqueous humor into the subconjuntival space, which created a raised bleb, softening of the eyeball and, occasionally, a small influx of blood into the anterior chamber. The conjunctival wound was not sutured. One drop of ciprofloxacin was applied immediately after the procedure.

All antiglaucoma medications were discontinued and the patient was placed on a topical combination of 0.1% dexamethasone and ciprofloxacin six times daily for 1 week. Thereafter, the dose was tapered according to the appearance (especially vascularization) of the bleb. Patients were examined on the first postoperative day and after 1 week, and 1, 3, 6, 12, and 24 months, or more often, as necessary, and complications were documented.

If the initial revision was not successful in controlling IOP, needling was repeated, using the same technique. Based on bleb morphology and signs of scarring, some eyes received subconjunctival injections of 5-FU (0.2 ml, at a concentration of 25 mg/ml).

Outcomes

At the latest visit, bleb needle revision was considered an *absolute success* if IOP ≤ 16 mmHg was achieved without medication. A *qualified success* was defined as IOP ≤ 16 mmHg with the aid of hypotensive agents, and *failure* if IOP was > 16 mmHg despite medication, or if further conventional surgery was required to lower IOP.

We analyzed several variables that might affect the success rate: age, race, type of glaucoma, lens status, pre-needling number of hypotensive agents, previous conjunctival flap (limbus or fornix-based), number and type of previous operations, use of antimetabolites in previous trabeculectomy, time elapsed between trabeculectomy and needling, pre-needling IOP, number of needling procedures, occurrence of complications, IOP on the first postoperative day, and use of 5-FU in the postoperative period.

Statistical analysis

We used SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA) for statistical analyses. To compare preoperative and postoperative IOP and number of hypotensive agents (non-parametric data), we used Levene's test (to confirm variance homogeneity) and the Wilcoxon signed rank test with continuity correction. To test the association between success and variables measured in the study, we used the Pearson χ^2 test with Yates' continuity correction and the Fisher's exact test for categorical variables, and the Mann-Whitney *U*-test for continuous variables; all tests were two-tailed. Finally, we performed a stepwise multiple logistic regression analysis. Because it requires a dichotomous response, absolute success and qualified success were categorized as success. P values < 0.05 were deemed to indicate statistical significance.

RESULTS

Seventy-three eyes (58.4%) were needled once, 44 (35.2%) were needled twice, seven (5.6%) were needled three times, and one (0.8%) was needled four

times. Thirty-one eyes (24.8%) received 5-FU injections in the postoperative period, with an average of 4.10 applications per eye (SD, 2.80; range, 1−14).

There was a statistically significant reduction in the mean IOP and the mean number of hypotensive agents after bleb needle revision. The mean IOP decreased from 20.07 mmHg (SD, 5.20; range, 11.3−38.7; median, 19 mmHg) preoperatively to 13.15 mmHg (SD, 6.77; range, 1−38; median, 12 mmHg) at last follow-up (Wilcoxon signed rank test; $P < 0.001$). The mean number of hypotensive agents per eye decreased from 2.35 (SD, 1.14; range, 0−5; median, 3) at baseline to 0.78 (SD, 1.30; range, 0−4; median, 0) at last follow-up (Wilcoxon signed rank test; $P < 0.001$).

After an average follow-up from the first needling of 20.80 months (SD, 11.96; range, 1−57 months), 95 eyes (76%) were classified as successes (IOP ≤ 16 mmHg) at the latest visit. Overall, 73 eyes (58.4%) achieved an absolute success, 22 (17.6%) a qualified success, and 30 (24%) were classified as failures.

In univariate analysis, successful outcomes correlated significantly with a lower pre-needling IOP ($P < 0.001$), a lower IOP on the first postoperative day ($P = 0.005$), a longer time between trabeculectomy and needling ($P = 0.030$), and older age (borderline significance; $P = 0.050$). Analyses are shown in Table 3. The success rates tended to be greater in whites, pseudophakic eyes, and in eyes with a previous fornix-based conjunctival flap, but not to a statistically significant degree (Table 4). Pseudophakic patients were significantly older than phakic patients (mean age, 72.7 vs. 52.9 years; median, 74 vs. 55 years; Mann-Whitney *U*-test; $P < 0.001$). Because of the possibility of interaction among the various independent variables, we performed a multiple stepwise logistic regression analysis, which confirmed only pre-needling IOP ($P = 0.017$) and the IOP on the first postoperative day ($P = 0.010$) as being statistically significant.

TABLE 3. Continuous variables in success and failure groups

Variable	Success group		Failure group		P-value*
	Mean (±SD)	Median	Mean (±SD)	Median	
Age (years)	63.31 (±18.35)	68	56.41 (±19.58)	53	**0.050**
Pre-needling no. of medications	2.27 (±1.12)	2	2.60 (±1.19)	3	0.174
No. of previous surgeries	1.48 (±0.68)	1	1.53 (±0.86)	1	0.895
Time trab-needling (years)	5.70 (±5.49)	4.17	4.01 (±4.75)	2.42	**0.030**
Pre-needling IOP (mmHg)	19.11 (±4.86)	18.7	23.13 (±5.15)	22.5	**< 0.001**
No. of needling procedures	1.49 (±0.67)	1	1.47 (±0.57)	1	0.971
IOP first postop. day (mmHg)	5.02 (±6.55)	3	9.83 (±9.43)	6	**0.005**

*Two-tailed Mann-Whitney U test with continuity correction. Bold P-values are statistically significant. SD = Standard Deviation. Trab = Trabeculectomy. Postop. = postoperative.

TABLE 4. Categorical variables and success rates

Variable		Success rate n (%)	P-value
Race	White (n=41)	35 (85.37)	0.136*
	Black (n=84)	60 (71.43)	
Type of glaucoma	Open-angle (n=97)	75 (77.32)	0.520*
	Other types (n=28)	20 (71.43)	
Lens status	Pseudophakic (n=53)	45 (84.91)	0.086**
	Phakic (n=69)	48 (69.57)	
	Aphakic (n=3)	2 (66.67)	
Previous trabeculectomy conjunctival flap	Fornix-based (n=52)	43 (82.69)	0.163*
	Limbus-based (n=59)	41 (69.49)	
Previous use of antimetabolites	Yes (n=42)	33 (78.57)	0.589*
	No (n=49)	35 (71.43)	
Post-needling complications	Yes (n=62)	48 (77.42)	0.874*
	No (n=63)	47 (74.60)	
Post-needling use of 5-FU	Yes (n=31)	24 (77.42)	0.977*
	No (n=94)	71 (75.53)	

*Two-tailed Pearson χ^2 test with Yates' continuity correction. **Two-tailed Fisher's exact test.

No significant correlation was observed between success and type of glaucoma, pre-needling number of hypotensive agents, number and type of previous operations, use of antimetabolites in previous trabeculectomy, number of needling procedures, and post-needling use of 5-FU (Tables 3 and 4).

Complications did not affect the success rate (Table 4), and included mild hyphema (25.8%), shallow anterior chamber (18.3%), serous choroidal detachment (15.6%), bleb leakage (8.6%), and encapsulated bleb (7.5%). Most were minor, transient, and required no treatment.

DISCUSSION

Factors associated with the success or failure of needling have been evaluated in previous studies, with variable findings.[3,4,12,15-23] This variability may be explained by differences in surgical techniques, success criteria, antimetabolite type and dose, specific factors evaluated, differences in study design, and methods of data collection and statistical analyses. Some studies have been based on retrospective analyses,[3,12,15,16,18-20] which is subject to various limitations, while others have evaluated risk factors prospectively,[4,17,21,22] which provides stronger results. Some risk factors have been recognized for the failure of trabeculectomy, such as young age, black race,[3,19] previous conjunctival incisions,[12] and aphakia,[18] whereas, others are more specific to needling revision, such as the interval between filtration surgery and needling,[3,4,17,20] high pre-needling IOP,[6,12,15,21] multiple needlings,[12,22,23] and high IOP immediately after the procedure.[6,8,15,21,23]

In the present prospective study, the most important variable associated with success was pre-needling IOP. The lower the IOP, the better the needling result ($P < 0.001$). Our results are consistent with those of Kapasi and Birt,[6] Broadway et al.,[21] Greenfield et al.,[12] and Shin et al.,[15] who found that failure correlated directly with higher pre-needling IOP.

A low IOP on the first postoperative day was also a predictor for success ($P = 0.005$). Broadway et al.[21] found that the most significant factor to have an effect on

success was the immediate attainment of an IOP < 11 mmHg, a finding also reported by Shin et al.,[15] who found that, if needle revision produced an IOP ≤ 10 mmHg, the procedure could be judged a preliminary success, and could predict future success. Rotchford et al.,[23] Kapasi and Birt[6] and Anand and Khan[8] also found that immediate reduction in IOP was a good prognostic sign. We think that a low immediate IOP reflects a good aqueous flow and the reestablishment of a well-functioning filtering bleb.

Many studies have analyzed the influence on the success rate of time between initial filtration surgery and needling revision; the issue is controversial. We found that a longer interval was associated with success (P = 0.030). We suggest that the inflammatory response from the original trabeculectomy, which starts soon after surgery and continues for several months, leads to failure if bleb needling is performed too early. As time passes, the healing response diminishes and fewer fibroblasts are present, which increases the chance of success. Our results are consistent with those of Mardelli et al.,[3] who found that trabeculectomy performed more than 4 years previously was a success factor for MMC needling revision. Passos et al.[4] found that the longer this interval, the higher the success rate, and that this was the only significant variable associated with success. Shetty et al.[20] found a higher chance of success in eyes that were needled at least 12 months after the original surgery, and Shin et al.[18] also observed that success rate was correlated with an increased interval between filtration surgery and needling intervention. On the other hand, Gutierrez-Ortis et al.[17] found that a short interval (< 4 months) between initial surgery and needling was associated with success, and Kapetansky & Kapetansky[24] suggested that early bleb needling affords the best opportunity to successfully restore the function of a failing bleb. However, Hawkins et al.,[16] Ewing

and Stamper,[2] Pasternack et al.,[19] Kapasi and Birt,[6] Greenfield et al.,[12] Broadway et al.[21] and Nascimento et al.[22] reported that this interval did not affect the success rate.

Older age was also positively related with success in our study, although this tendency was of borderline significance (P = 0.050). Higher success rates in older patients have been attributed to a weaker healing response.[1] Our results also tended to be better in pseudophakic eyes, but this perhaps reflected only the fact that these patients were older than the phakic ones. Shetty et al.[20] also found a higher chance of success in pseudophakic eyes and postulated that needling was safer and better tolerated in pseudophakic eyes with a deeper chamber than in phakic eyes. On the other hand, in 1993, Shin et al.[18] reported that needling tended to be more successful in phakic than aphakic and pseudophakic eyes, but, at that time, most cataract surgery was performed by extracapsular extraction, which necessitated a large conjunctival incision. In 1996, Greenfield et al.[12] found unsuccessful outcomes in needle revisions performed in eyes with prior surgery that involved conjunctival incisions. In our study, the number and type of prior operations did not influence the chance of success.

Needling tended to be more successful in whites versus blacks, although this tendency was not statistically significant, a finding also reported by Broadway et al.[21] Mardelli et al.[3] obtained a higher success rate in whites than blacks, and Pasternack et al.[19] found that African-American race was the only significant risk factor for needle revision failure. Blacks have been shown to have a lower success rate in any filtration surgery because of a more exuberant healing response.[1]

A further factor of potential importance is pre-needling bleb morphology. Rotchford et al.[23] and Kapetansky & Kapetansky[24] reported that bleb needling was more effective when an elevated bleb was still present preoperatively. On the other

hand, Nascimento et al.[22] found that success was positively related with the absence of an elevated bleb preoperatively. Fagerli et al.[25] found no difference in success between eyes with a flattened bleb and those with a cystic bleb. Hawkins et al.[16] and Broadway et al.[21] also showed that pre-needling bleb characteristics had no effect on outcome. In the present study, we could not analyze this variable, because all blebs were completely flat before needle revision, but our results show that a flat bleb can provide excellent filtration, even several years after the original trabeculectomy.

In the present study, needling revision of fornix-based blebs tended to be more successful, although not to a statistically significant degree. It is easier, technically, to perform a needle revision in these blebs, and resultant post-needling blebs are also more diffuse, because there are no restrictive scarred lines in the conjunctiva, like those seen in limbus-based blebs. However, Hawkins et al.,[16] in a retrospective study, found that fornix-based blebs were more likely to fail needle revision, compared with limbus-based blebs.

In previous studies, greater success has been achieved in eyes that required only one needle revision, compared with those that required multiple revisions.[12,22,23] In the present study, the number of needling procedures did not affect the success rate.

In the present study, as shown in most previous studies,[3,4,16,19,20] the use of antifibrotic agents during the original trabeculectomy did not affect the success rate. Shin et al.[15] were the only authors to report that lack of MMC during previous filtration surgery is a significant risk factor for failure. Additionally, we did not find any difference in the success rate of eyes that received 5-FU after the needling procedure compared with those that did not. We used postoperative injections of 5-FU in eyes considered to be at a greater risk of failure, based on bleb morphology

and signs of scarring, especially bleb vascularization, elevation, and extent. We think that these additional antifibrotic injections are a safe and useful tool to reduce the healing response in these eyes, and perhaps some of them could have failed without this aid.

The role of antiglaucoma medication is also interesting. Kapasi and Birt[6] observed that patients in their success group had used a lower number of hypotensive agents before needling, compared with the failure group. Chang and Hou[26] found that the only risk factor associated with failure of needling of filtering blebs with 5-FU was the number of antiglaucoma drugs used before the filtering surgery. The use of more topical agents could result in a greater inflammatory reaction in the conjunctiva, leading to failure of the procedure.[27] In the present study, however, we found no significant correlation between success and the number of pre-needling hypotensive agents.

Complications were not associated with poorer outcome and were similar to those seen after trabeculectomy. They included small hyphemas, transient choroidal effusion, temporary conjunctival wound leaks, and shallowing of the anterior chamber. Most of these were minor, tolerable, transient, and required no treatment. Finally, no significant correlation was observed between success and type of glaucoma or gender.

Needling proved to be highly effective, although sometimes two or more revisions per eye were needed to achieve good IOP control. A significant reduction in the mean IOP (from 20.07 to 13.15 mmHg) and mean number of antiglaucoma agents per eye (from 2.35 to 0.78) were achieved at the latest visit. The overall success rate of 76% at the latest visit agrees with other studies,[3,22,28,29] where the rate ranged from 71.6 to 76%.

Our study has some limitations. First, the postoperative use of 5-FU was based on clinical judgment. Patients were not assigned randomly to groups in which they would receive 5-FU injections or not. Although its use did not apparently affect the success rate, the results may have been biased by the influence of this antimetabolite. Second, post-needling follow-up was highly variable, ranging from 1 to 57 months. The short follow-up period on some eyes may have biased the analysis.

In conclusion, needle revision with adjunctive MMC is effective to revive failed filtering blebs, even several years after the original trabeculectomy. The main predictors of success were a low pre-needling IOP, a low IOP on the first postoperative day, a longer time interval between trabeculectomy and needle revision, and older age. The success tended to be greater in whites, pseudophakic eyes, and in eyes with a previous fornix-based conjunctival flap.

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CONCLUSÃO DO SEGUNDO TRABALHO, FORMULAÇÃO DE NOVAS HIPÓTESES E OBJETIVOS DO TERCEIRO TRABALHO

O segundo trabalho demonstrou a existência de alguns fatores que têm o potencial de influenciar a taxa de sucesso do agulhamento com MMC. A principal variável associada ao sucesso do procedimento foi a pressão intraocular baixa antes do agulhamento. O segundo fator ligado ao sucesso foi a obtenção de uma pressão intraocular baixa logo no primeiro dia de pós-operatório, refletindo o restabelecimento de um bom fluxo de humor aquoso pela fístula antiglaucomatosa. O terceiro fator para o sucesso foi o intervalo de tempo entre a trabeculectomia e o agulhamento, sendo que quanto maior este tempo, maiores as chances de sucesso. Por fim, o quarto fator associado ao sucesso do procedimento foi a idade do paciente. Quanto mais idoso o paciente, maior a taxa de sucesso. Pudemos observar também melhores resultados nos pacientes brancos, nos olhos pseudofácicos e nos olhos cuja trabeculectomia prévia havia sido realizada com um retalho conjuntival de base fórnice.

Já se conhecendo a eficácia do agulhamento, os fatores relacionados a seu sucesso, e a segurança do procedimento quanto a suas complicações, decidimos aprofundar a investigação a respeito de sua segurança, desta vez, especificamente para o endotélio corneano. Sabe-se que a MMC é potencialmente tóxica para o endotélio da córnea. Durante o agulhamento, a MMC pode ter acesso à câmara anterior tanto através de difusão pelos tecidos, quanto através da entrada direta após a reabertura da fístula antiglaucomatosa. Interessava-nos saber se a dose de MMC utilizada no agulhamento seria lesiva para o endotélio corneano.

Para responder a este questionamento, foi idealizado o terceiro trabalho, para o qual foram selecionados 42 olhos de 36 pacientes, para terem seu endotélio corneano estudado e acompanhado durante um ano após o agulhamento.

Os objetivos principais do terceiro trabalho foram:

1) Avaliar os efeitos do agulhamento com MMC para o endotélio corneano do ponto de vista funcional, através da espessura corneana central. Foram comparadas as medidas pré-operatórias com as pós-operatórias em diversos momentos do primeiro ano de seguimento.
2) Avaliar os efeitos do agulhamento com MMC para o endotélio corneano do ponto de vista anatômico, através da contagem endotelial. Também para esta variável, foram comparadas as medidas pré-operatórias com as pós-operatórias em diferentes momentos do primeiro ano de seguimento.

Os resultados desta pesquisa foram enviados para a revista “Ophthalmology”.

TERCEIRO TRABALHO

“Corneal Thickness and Endothelial Density before and after Needling with Mitomycin C: A Prospective Study”

“Espessura Corneana e Densidade Endotelial antes e depois do Agulhamento com Mitomicina C: Estudo Prospectivo”

RESUMO DO TERCEIRO TRABALHO

OBJETIVO: Avaliar a segurança do agulhamento com mitomicina C (MMC) para o endotélio corneano na recuperação tardia de bolsas fistulantes falidas.

MÉTODO: Foram selecionados 42 olhos de 36 pacientes portadores de glaucoma sem controle adequado e que seriam submetidos ao agulhamento com MMC. Todos tinham pelo menos uma trabeculectomia prévia, a bolsa fistulante estava totalmente plana e o óstio interno estava pérvio à gonioscopia. O agulhamento associado à injeção subconjuntival de 8µg de MMC foi realizado no bloco cirúrgico, pela mesma cirurgiã. Quando necessário, o procedimento foi repetido. A espessura corneana central (ECC) foi avaliada através da paquimetria ultra-sônica antes do agulhamento e após uma semana, 1, 3, 6 e 12 meses. A contagem endotelial foi realizada com microscópio especular de não contato antes do agulhamento e pós 1, 6 e 12 meses.

RESULTADOS: Não houve diferença estatisticamente significativa entre as medidas da ECC e da contagem endotelial antes e após o agulhamento, durante um ano de acompanhamento. A ECC média antes do agulhamento foi de 520 ± 38 µm. Os valores médios da ECC após o agulhamento foram 523 ± 40 µm após uma semana ($p = 0,628$), 513 ± 35 µm após um mês ($p = 0,100$), 513 ± 38 µm após 3 meses ($p = 0,467$), 521 ± 36 µm após 6 meses ($p = 0,353$) e 521 ± 39 µm após um ano ($p = 0,684$). A média da contagem de células endoteliais antes do agulhamento foi de 1991 ± 513 cels/mm^2. No pós-operatório, os valores médios foram 2054 ± 555 cels/mm^2 após um mês ($p = 0,584$), 1966 ± 613 cels/mm^2 após 6 meses ($p = 0,679$) e 1966 ± 585 cels/mm^2 após um ano ($p = 0,432$). Foram realizados 60 agulhamentos nos 42 olhos. Vinte e cinco olhos (59,52%) foram submetidos a um agulhamento, 16 olhos (38,10%) a dois agulhamentos e um olho (2,38%) a três. Após um seguimento

médio de 19,15 ± 8,38 meses, a pressão intraocular média caiu de 21,81 ± 4,87 mmHg no pré-operatório para 13,57 ± 6,59 mmHg (p < 0,001) e o número médio de medicações hipotensoras por olho caiu de 2,55 ± 0,89 para 0,98 ± 1,52 (p < 0,001) na última consulta.

CONCLUSÃO: O agulhamento com uma dose baixa de MMC subconjuntival parece ser seguro para o endotélio corneano.

Corneal Thickness and Endothelial Density before and after Needling with Mitomycin C: A Prospective Study.

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Running head: Corneal Endothelium after Needling with MMC

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ABSTRACT

Purpose: To assess the safety of needling revision of filtering blebs with mitomycin C (MMC) for the corneal endothelium.

Design: Prospective interventional case series.

Participants: We investigated 42 eyes in 36 patients with uncontrolled glaucoma, who were scheduled to undergo needling revision of a filtering bleb, with adjunctive MMC. All had at least one failed trabeculectomy, a flat filtering bleb, and a patent internal ostium on gonioscopy.

Intervention: Needling revision with subconjunctival injection of 8 μg of MMC, performed in the operating room by a single surgeon.

Main Outcome Measures: Central corneal thickness (CCT) measured by ultrasonic pachymetry preoperatively and 1 week and 1, 3, 6, and 12 months after revision. Corneal endothelial cell density measured with a non-contact specular microscope preoperatively and after 1, 6, and 12 months.

Results: There was no statistically significant difference between preoperative and postoperative CCT or endothelial density. Mean preoperative CCT was 520 ± 38 μm. Mean postoperative values were 523 ± 40 μm at 1 week (P = 0.628), 513 ± 35 μm at 1 month (P = 0.100), 513 ± 38 μm at 3 months (P = 0.467), 521 ± 36 μm at 6 months (P = 0.353), and 521 ± 39 μm at 1 year (P = 0.684). Mean preoperative endothelial cell density was 1991 ± 513 cells/mm^2. Mean postoperative values were 2054 ± 555 cells/mm^2 at 1 month (P = 0.584), 1966 ± 613 cells/mm^2 at 6 months (P = 0.679), and 1966 ± 585 cells/mm^2 at 1 year (P = 0.432). Sixty needling procedures were performed on 42 eyes. Twenty-five eyes (59.52%) were needled once, 16 (38.10%) were needled twice, and one (2.38%) was needled three times. After an average follow-up of 19.15 ± 8.38 months, the mean intraocular pressure decreased from

21.81 ± 4.87 mmHg preoperatively to 13.57 ± 6.59 mmHg (P < 0.001), and the mean number of hypotensive agents per eye decreased from 2.55 ± 0.89 at baseline to 0.98 ± 1.52 (P < 0.001) at the latest visit.

Conclusions: Needling revision with a low dose of adjunctive subconjunctival MMC seems to be safe for the corneal endothelium.

INTRODUCTION

Trabeculectomy is still the most common anti-glaucoma surgery worldwide. It is a very effective technique for controlling intraocular pressure (IOP), but failure of the filtering bleb occurs frequently. When failure occurs after initial success, it is almost always caused by episcleral fibrosis overlying the filtration area.[1] Many methods for dealing with failed blebs have been described, including digital massage, suture lysis, topical and oral medication, needling, and surgical revision.

Needling is an effective procedure for reviving failing or failed filtering blebs, with success rates of 80−90% after 1 year[2,3] and 75% after 2 years.[3–5] Usually, 5-fluorouracil (5-FU) is used as an adjunctive anti-fibrotic therapy during and after needling. However, 5-FU is toxic to the corneal epithelium, and its administration as a series of subconjunctival injections is inconvenient and uncomfortable.

Since Mardelli et al.[6] reported the use of subconjunctival mitomycin C (MMC) during slit-lamp needle revision in 1996, MMC has been used increasingly as an adjunctive anti-fibrotic agent to enhance needling,[2–4,7,8] because it is very potent and has the advantage of a single application. However, MMC is highly toxic to some ocular tissues, especially the corneal endothelium. MacDermott et al.[9] demonstrated that exposure of human corneal endothelium to MMC at a dose of 200 µg/ml resulted in prompt destruction of the endothelium.

Endothelial cell density and central corneal thickness (CCT) are widely used parameters for assessing the status of the corneal endothelium. Deturgescence of the cornea is controlled by the pumping action of the endothelium and can be monitored by measuring CCT. Damage to endothelial cells initially leads to an increase in corneal thickness and ultimately to corneal decompensation and loss of vision.

This prospective study analyzed CCT and endothelial cell density before and after needle revision with adjunctive subconjunctival MMC, to assess the safety of the procedure with regard to the corneal endothelium.

METHODS

Patient Selection

All patients scheduled to undergo a needle revision with adjunctive MMC, between March 2005 and April 2007, at the Federal University of Minas Gerais, Brazil, were enrolled in this case series and studied prospectively. Each patient provided written informed consent. The study protocol was approved by the Ethics Committee of the Federal University of Minas Gerais. Forty-two eyes of 36 patients were selected. All had undergone at least one previous trabeculectomy, and at the time of bleb needling, had an IOP above the target pressure, or showed evidence of visual field progression. All were considered late failures; the average interval between the last failed filtration surgery and needle revision was 5.8 years (SD, 6.2 years; range, 7 months−30 years). All subjects had a flat filtering bleb and a patent internal ostium on gonioscopy. Eyes with encapsulated blebs were excluded.

The average age of the study population was 58.5 years (SD, 17.28; range, 17−88; median, 59 years). Information regarding gender, race, type of glaucoma, lens status, and previous surgery is shown in Table 1.

TABLE 1. Demographics and characteristics of the study population

	No. of eyes	%
Gender		
Male	20	47.62
Female	22	52.38
Race		
White	9	21.43
Black	33	78.57
Type of glaucoma		
Open-angle	32	76.19
Angle-closure	3	7.14
Congenital	3	7.14
Inflammatory	2	4.76
Cortisonic	1	2.38
Cogan Reese Syndrome	1	2.38
Lens status		
Phakic	34	80.95
Pseudophakic	8	19.05
Previous surgery		
1 trab	26	61.90
2 trabs	5	11.91
Cataract + 1 trab	5	11.91
Cataract + 2 trabs	3	7.14
Trabeculotomy + 1 trab	2	4.76
Trabeculotomy + 2 trabs	1	2.38
Previous antimetabolite use		
None	19	45.24
MMC	13	30.95
MMC + 5FU	1	2.38
Unknown	9	21.43

Trab = Trabeculectomy. MMC = Mitomycin C. 5-FU = 5-fluorouracil.

Surgical Technique

Bleb needling was performed in the operating room by one surgeon (HAM), using a standardized sterile technique. Eyelids and surrounding skin were prepared with a 10% povidone–iodine solution, and the eye received one drop of 5% proparacaine and one of 5% povidone–iodine solution. A mixture of lidocaine and MMC was prepared by drawing 0.2 ml of 2% lidocaine with epinephrine and 0.1 ml of 0.25 mg/ml MMC solution into the same insulin syringe, for a final MMC concentration of 0.08 mg/ml. A lid speculum was placed, the patient was asked to

look down, and the subconjunctival space was entered with a 26-gauge needle, bent bevel up at the hub, 10 mm away from the failed bleb. Only 0.1 ml of the lidocaine-MMC mixture (8 μg of MMC) was injected. After 5 minutes, needling was performed with sweeping movements, to break episcleral adhesions around and over the scleral flap. The re-establishment of aqueous flow was indicated by an immediate increase in the size of the bleb, softening of the eyeball, and occasionally, a small reflux of blood into the anterior chamber. All revisions were performed at an episcleral level, and the needle was never introduced under the scleral flap or into the anterior chamber. Conjunctival wounds were never sutured. One drop of ciprofloxacin was applied at the end of the procedure.

A combination of ciprofloxacin and 0.1% dexamethasone was administered six times daily for 1 week and was gradually tapered as the bleb inflammation subsided. Cycloplegic agents were administered only when the anterior chamber was shallow or choroidal detachment was present. Patients were seen on the first postoperative day, after 1 week, and after 1, 3, 6, 12, 18, and 24 months, or more often, if necessary. Complications were documented.

For cases in which the initial revision was unsuccessful in controlling IOP, needle revision was repeated using the same technique. We permitted as many needling procedures as were necessary, and performed a maximum of three needlings in one eye.

Central corneal thickness was measured by ultrasonic pachymetry (DGH-5100e; DGH Technology, Exton, PA, USA) preoperatively and at 1 week and 1, 3, 6, and 12 months postoperatively; the mean value of three measurements was used. Corneal endothelial cell density at the center of the cornea was measured with a non-

contact specular microscope (SP-9000; Konan, Hyogo, Japan) preoperatively and at 1, 6, and 12 months postoperatively.

Statistical Analysis

We used SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA) for the statistical analysis. To compare preoperative and postoperative IOP, number of medications, and corneal endothelial cell density (non-parametric data), we used the two-tailed Wilcoxon signed rank test with continuity correction. To compare preoperative and postoperative measures of CCT, we used the two-tailed, paired Student's *t*-test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Sixty needling procedures were performed on 42 eyes, with a mean of 1.43 needlings per eye (SD, 0.55; range, 1−3). Twenty-five eyes (59.52%) were needled once, 16 (38.10%) were needled twice, and one (2.38%) was needled three times. The average follow-up from the first needling was 19.15 months (SD, 8.38; range, 3−36 months).

There was no statistically significant difference between preoperative and postoperative CCT or endothelial cell density (Tables 2 and 3, Figures 1 and 2). One eye experienced mild and transient corneal edema, which subsided clinically within 1 week; however, its preoperative endothelial cell density was very low (869 cells/mm^2), remained stable until the sixth postoperative month (814 cells/mm^2), and dropped to 763 cells/mm^2 after 1 year. Its CCT increased from 452 μm preoperatively to 627 μm at 1 week, but gradually returned to 501 μm after 1 year. Another eye with a diagnosis of congenital glaucoma showed a significant reduction in endothelial cell

density after 1 year (from 1265 to 686 cells/mm^2), but because of the presence of Haab striae, incorrect measurements might have been a source of considerable variation. Its CCT remained stable during the entire follow-up period.

TABLE 2. Central corneal thickness over time (µm) (n=42)

Time	Mean (±SD)	Median	Range	P Value*
Pre-needling	520.31 (±38.19)	521	424 – 595	-
1 week	522.64 (±39.79)	516	447 – 627	0.628
1 month	512.55 (±34.96)	510	433 – 584	0.100
3 months	513.48 (±37.54)	510	435 – 577	0.467
6 months	520.81 (±35.67)	516	452 – 592	0.353
1 year	520.54 (±38.71)	520	449 - 588	0.684

SD = Standard deviation. * Two-tailed paired Student's *t* test.

TABLE 3. Central corneal endothelial cell density over time (cells/mm^2) (n=42)

Time	Mean (±SD)	Median	Range	P Value*
Pre-needling	1990.71 (±513.31)	2185	869 – 3058	-
1 month	2054.15 (±554.79)	2220	808 – 2994	0.584
6 months	1966.30 (±612.55)	2105	814 – 2865	0.679
1 year	1966.03 (±584.66)	2087	686 - 2840	0.432

SD = Standard deviation. * Two-tailed Wilcoxon signed rank test with continuity correction.

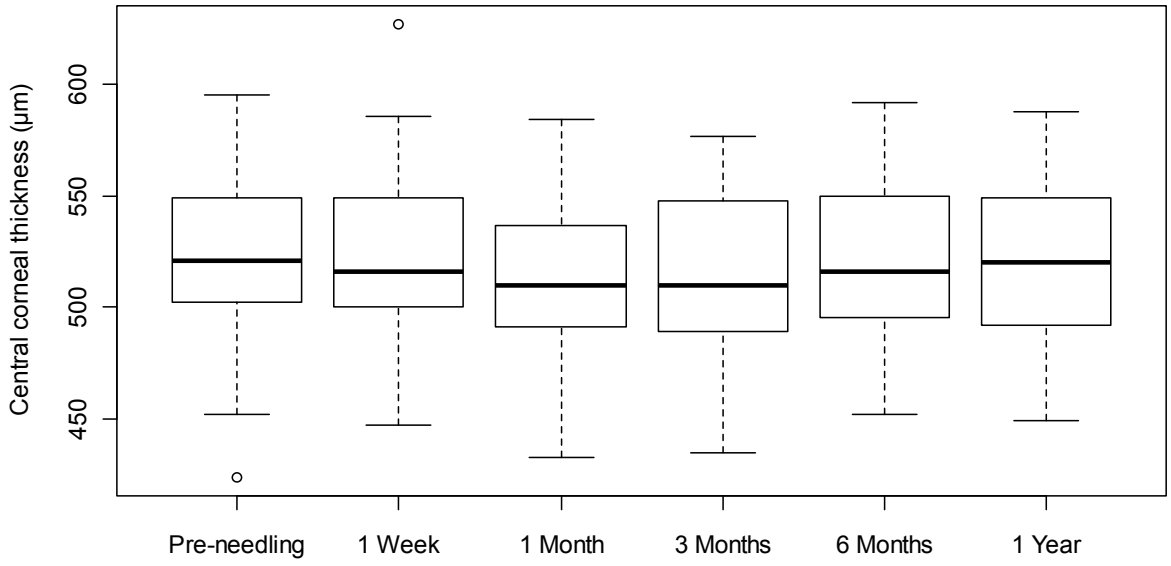

FIGURE 1. Central corneal thickness over time

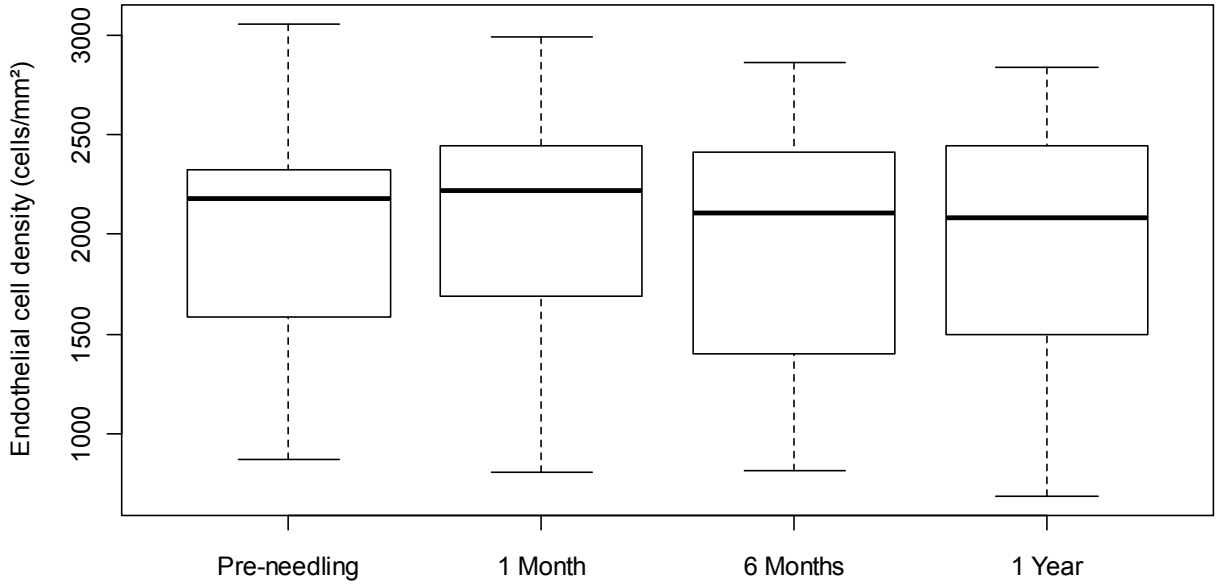

FIGURE 2. Central corneal endothelial cell density over time

There was a statistically significant reduction in mean IOP and number of hypotensive agents after bleb needle revision. Mean IOP decreased from 21.81 mmHg (SD, 4.87; range, 14.3−38.7; median, 21 mmHg) preoperatively to 13.57 mmHg (SD, 6.59; range, 1−26; median, 13 mmHg) at last follow-up (two-tailed Wilcoxon signed rank test; $P < 0.001$). The mean number of hypotensive agents per eye decreased from 2.55 (SD, 0.89; range, 1−4; median, 3) at baseline to 0.98 (SD, 1.52; range, 0−4; median, 0) at last follow-up (two-tailed Wilcoxon signed rank test; $P < 0.001$).

Complications developed in 18 eyes (42.86%), or 30 needling procedures (50%), and are listed in Table 4. All were mild and resolved spontaneously within a few days. One eye (2.38%) developed an encapsulated bleb, which was treated successfully with another needling procedure. Four eyes (9.52%) developed late

hypotony, defined as IOP < 6 mmHg after 6 months, but were asymptomatic. There were no cases of hypotonous maculopathy. Eyes with postoperative complications also did not show statistically significant changes in CCT (paired Student's *t*-test; P = 0.044 at 1 week, P = 0.782 at 3 months, P = 1.000 at 6 months, and P = 0.240 at 1 year) or endothelial cell density (Wilcoxon signed rank test; P = 0.485 at 1 month, P = 0.830 at 6 months and P = 0.999 at 1 year) after bleb needling. None of the eyes developed corneal decompensation.

TABLE 4. Postoperative complications

Complication	No. of needling procedures (total 60)	%
Shallow anterior chamber	15	25.0
Mild hyphema	13	21.67
Serous choroidal detachment	10	16.67
Bleb leakage	8	13.33
Encapsulated bleb	1	1.67
Transitory corneal edema	1	1.67

DISCUSSION

Mitomycin C is an antineoplastic and antibiotic agent produced by the fungus *Streptomyces caespitosus*. It inhibits the synthesis of DNA, RNA, and protein, and damages cells by cross-linking DNA.[10] This effect results in long-term inhibition of subconjunctival fibroblast proliferation. In ophthalmology, it has been used topically to prevent recurrence after pterygium surgery, to enhance glaucoma filtration surgery, to treat ocular surface neoplasia, and to modulate corneal wound healing after excimer photorefractive surgery.

One of the major concerns with the use of MMC remains its safety because it is potentially toxic in some ocular tissues. Scleral and corneal ulceration and perforation, scleromalacia, necrotizing scleritis, uveitis, symblepharon, and scleral

calcification have been reported following the topical use of MMC in pterygium surgery.[11–13] MMC also may be toxic to the ciliary body epithelium, which may lead to decreased production of aqueous humor and persistent hypotony. Some studies have reported severe histopathological damage to the ciliary epithelium in rabbits[14–16] and humans[17] after strict extraocular application of MMC. The degree of cell destruction was closely related to the MMC concentration.

Experimental work has also demonstrated the toxicity of MMC in corneal endothelial cells. Roh et al.[10] have shown that exposure to MMC produces cross-linking of corneal endothelial DNA, persistent DNA damage, and endothelial death via apoptosis. Wu et al.[18] have reported that MMC induces corneal endothelial cell apoptosis in a time- and dose-dependent manner. McDermott et al.[9] exposed human corneal endothelium to MMC at concentrations of 20 and 200 µg/ml; no changes were attributed to the low dose of 20 µg/ml, but exposure to 200 µg/ml resulted in prompt corneal swelling and destruction of the endothelium. Wu et al.[19] have demonstrated toxic effects of MMC in cultured porcine keratocytes and endothelial cells, and Silva and Gregorio[20] and Hernandez-Galilea et al.[21] have reported lethal effects in rabbit corneal endothelium exposed to different concentrations of MMC.

Some clinical studies in humans have reported the effect of MMC on corneal endothelial cells. A study by Sihota et al.[22] on the effect of intraoperative single-use MMC during trabeculectomy revealed an endothelial cell loss of 14.5%, compared with preoperative values. Storr-Paulsen et al.[23] found significant endothelial cell loss (9.5%) immediately after MMC-augmented trabeculectomy, but could not estimate the extent of cell loss as a result of surgical trauma or MMC toxicity. The authors found no progressive cell loss after the third postoperative month, which suggests that MMC has no prolonged toxic effect on the corneal endothelium. Avisar et al.[24]

and Bahar et al.[25] have reported significant endothelial cell loss (6 to 21%) after pterygium surgery with the application of MMC. Morales et al.[26] and Nassiri et al.[27] found endothelial cell loss of around 14% after photorefractive keratectomy with MMC. Cardozo and Passos[28] have reported a case of corneal decompensation after needling with adjunctive subconjunctival injection of MMC. However, they could not be sure of the relationship of this complication to MMC, because the injected solution also contained bupivacaine, adrenaline, and preservatives that were potentially toxic to the endothelium. On the other hand, deBenito-Llopis et al.,[29] Goldsberry et al.,[30] and Zhao et al.[31] have shown that the application of 0.02% MMC after excimer laser ablation did not change corneal endothelial cell density. This has also been reported by Panda et al.,[32] who have demonstrated that the use of topical 0.04% MMC drops to treat ocular surface squamous neoplasia did not significantly affect corneal pachymetry or endothelial cell count.

In the present study, we subconjunctivally injected a small dose (8 μg) of MMC (0.1 ml at a concentration of 0.08 mg/ml) 5 minutes before the needling procedure. With this technique, it is possible that a small amount of MMC might have entered the eye by two routes. The first is via diffusion through the ocular tissues. Kawase et al.[33] have measured MMC concentrations in aqueous humor after a single subconjunctival injection in rabbits and detected a peak after 30 minutes, followed by a rapid disappearance within 3 hours. Seah et al.[34] have detected MMC in human aqueous humor within minutes of external application to the episclera or the scleral bed during trabeculectomy. Silva and Gregorio[20] have reported corneal endothelium changes in rabbits after applying MMC under a scleral flap. The second possible route of MMC entry is direct inoculation into the anterior chamber after reopening of the fistula. The risk for this can be minimized by careful technique, especially slow subconjunctival

injection of the MMC solution to avoid a pressure gradient from the subconjunctival space to the anterior chamber, allowing an appropriate time to elapse between injection and needling, and injecting at a site several millimeters away from the bleb. Even if the entire amount of MMC used in our study were to have inadvertently entered the anterior chamber, the concentration of 32 μg/ml (based on an anterior chamber volume of 0.25 ml) would be well below the level known to cause endothelial toxicity (approximately 200 μg/ml), as demonstrated by McDermott et al.[9]

Needling with adjunctive subconjunctival MMC at the concentration used in the present study appears to be safe for the corneal endothelium. In our study, there was no statistically significant difference between preoperative and postoperative corneal thickness or endothelial cell density during 1 year of follow-up, even in those eyes needled more than once and in those with postoperative complications. Only one eye with a very low preoperative cell density (869 cells/mm^2) experienced mild and transient corneal edema, without significant postoperative endothelial cell loss. Another eye, with a diagnosis of congenital glaucoma, showed a reduction in cell density (from 1265 cells/mm^2 preoperatively to 686 cells/mm^2 after 1 year), without any evidence of corneal edema, as its CCT remained stable during the entire follow-up period. We think that the presence of Haab striae might have been a source of incorrect measurements and considerable variation in this case.

Even though more than one needle revision was needed in some cases to achieve good IOP control, needling with adjunctive MMC proved to be highly effective. Significant reductions in mean IOP (from 21.81 to 13.57 mmHg) and number of hypotensive medications per eye (from 2.55 to 0.98) were achieved at the latest visit. Needling was also relatively safe. Complications were similar to those seen after trabeculectomy, but were mild and transient. None of the eyes required

specific treatment for any complication. Four eyes were hypotonous (IOP < 6 mmHg) at the end of the study, but were asymptomatic. Complications also did not seem to affect the status of the corneal endothelium, because they were not related to any changes in endothelial cell density or CCT.

Previous studies have reported significant endothelial cell loss after trabeculectomy,[22,23,35–38] ranging from 6.35% without MMC[36] to 14.5% with adjunctive MMC.[22] Needling revision seems to be safer for the corneal endothelium, probably because it is an essentially extraocular procedure. We performed all needling revisions at an episcleral level and never introduced the needle under the scleral flap or into the anterior chamber. Moreover, the MMC concentration and dose used in the present study proved to be non-toxic to endothelial cells.

We believe that needle revision should be considered before repeat trabeculectomy, even in flat filtering blebs and several years after the original surgery. In the present study, only flat blebs were revised, and the average time between the failed filtration surgery and needle revision was 5.8 years, which means that all needle revisions were performed in a late postoperative period. Needling has the potential to be as effective as trabeculectomy, with a smaller degree of surgical trauma, especially to the corneal endothelium. It is simple, repeatable and, if it does fail, it preserves precious conjunctiva and endothelial cells for further filtration surgery.

To our knowledge, this is the first study to assess the safety, with regard to the corneal endothelium, of bleb needle revision with adjunctive MMC. In conclusion, this study suggests that needle revision of failed filtering blebs with adjunctive subconjunctival MMC is safe for the corneal endothelium.

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CONCLUSÃO DO TERCEIRO TRABALHO

Este terceiro trabalho demonstrou que o agulhamento com MMC parece ser seguro para o endotélio corneano. Este não foi afetado nem do ponto de vista funcional nem anatômico. No geral, os valores pré-operatórios e pós-operatórios da espessura corneana central e da contagem endotelial foram semelhantes e permaneceram estáveis durante todo o primeiro ano de seguimento após o agulhamento.

Vale aqui ressaltar que tais conclusões são válidas apenas para olhos com contagem endotelial normal, quando se leva em consideração a dosagem de MMC utilizada no presente estudo e quando se tomam os devidos cuidados técnicos para se evitar a penetração direta da MMC na câmara anterior durante o agulhamento. Em olhos com o endotélio previamente doente, o agulhamento com MMC, assim como qualquer procedimento cirúrgico, pode desestabilizar o precário equilíbrio da função endotelial, ainda que temporariamente.

DISCUSSÃO

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O tratamento cirúrgico do glaucoma é um grande desafio, pois, ao contrário de todas as outras cirurgias, o sucesso de uma cirurgia antiglaucomatosa depende da prevenção da cicatrização para que a fístula entre a câmara anterior e o espaço subconjuntival permaneça patente. O processo natural de cicatrização é, portanto, o grande responsável pelas altas taxas de falência da trabeculectomia. O agulhamento é uma técnica rápida, de baixo custo e eficaz para resgatar o funcionamento de fístulas antiglaucomatosas recém falidas ou falidas há muitos meses ou anos. O uso de antimetabólitos é essencial para seu sucesso, pois reduz a resposta cicatricial e ajuda a manter a fístula patente. A mitomicina C, devido a sua alta potência e praticidade, vem sendo cada vez mais utilizada como terapia adjuvante nos agulhamentos (BEN-SIMON; GLOVINSKY, 2003; GUTIERREZ-ORTIZ; CABARGA; TEUS, 2006; IWACH et al., 2003; MARDELLI et al.,1996; PASSOS et al., 2002; SHETTY; WARTLUFT; MOSTER, 2005).

No presente estudo, através do agulhamento, foi possível restabelecer o fluxo de humor aquoso pela fístula antiglaucomatosa em 92% dos olhos, o que representa um excepcional resultado para um procedimento tão simples, rápido e pouco invasivo. A taxa final de sucesso, de 76%, foi semelhante à relatada em estudos anteriores (BEN-SIMON; GLOVINSKY, 2003; IWACH et al., 2003; MARDELLI et al., 1996; NASCIMENTO et al., 2007). Obteve-se uma importante redução da PIO e do número de medicações hipotensoras, o que confirma a alta eficácia do procedimento. Para a maioria dos pacientes do estudo, o agulhamento trouxe uma importante redução dos custos do tratamento e de seus efeitos colaterais, contribuindo, assim, para uma melhor qualidade de vida.

Contrariando a idéia, muitas vezes vigente, de que é necessária a presença de bolsa fistulante ou de algum funcionamento da fístula antes do agulhamento para que ele funcione, nossos resultados comprovaram sua eficácia em bolsas totalmente planas. Em um estudo publicado por Nascimento et al. (2007), maiores taxas de sucesso foram obtidas justamente nos olhos com bolsas planas. Em nenhum de nossos pacientes o retalho escleral era visível sob a conjuntiva, o que não impediu a realização do procedimento, que foi, quase sempre, guiado pela posição da iridectomia.

Nossos resultados mostraram, também, a necessidade de, muitas vezes, se repetir o agulhamento para a obtenção um bom controle da PIO. Pode-se concluir, então, que a falência de um primeiro agulhamento não deve desestimular o cirurgião. Este deve estar ciente das características do procedimento, prontificando-se a repeti-lo sempre que necessário. Casos de falência após o primeiro agulhamento frequentemente se transformam em sucessos duradouros após o segundo ou o terceiro procedimento.

O conhecimento dos fatores que influenciam a taxa de sucesso do agulhamento, tais como a PIO pré-operatória, a PIO logo após o agulhamento, a idade e a raça do paciente e o tempo decorrido entre a trabeculectomia e o agulhamento, é útil na preparação do cirurgião para seus resultados. Diante de fatores que aumentem o risco de falência, tanto cirurgião quanto paciente deverão estar preparados para a eventual necessidade de uma nova trabeculectomia ou de um implante valvular.

O agulhamento mostrou-se bastante seguro no que diz respeito a suas complicações, que foram, em sua maioria, leves e transitórias. Deve-se ressaltar, no entanto, que o procedimento foi essencialmente extra-ocular, sempre realizado em

nível episcleral. Em nenhum momento o retalho escleral foi levantado ou a agulha foi introduzida na câmara anterior. Deve-se estar ciente de potenciais complicações mais sérias relatadas em estudos pregressos, tais como grandes descolamentos serosos da coróide (PASSOS et al., 2002; PASTERNACK et al., 2005), hemorragia supracoroideana (ANAND; KHAN, 2009; GREENFIELD et al., 1996; HAWKINS; FLANAGAN; BROWN, 2002; MARDELLI et al., 1996), glaucoma maligno (ANAND; KHAN, 2009; MATHUR; GAZZARD; OEN, 2002; RAMANATHAN et al., 2003), e endoftalmite (GREENFIELD et al., 1996).

O terceiro trabalho demonstrou que o agulhamento com MMC não provocou alterações funcionais nem estruturais no endotélio corneano, comprovando, assim, sua segurança. Possivelmente, em face da baixa dose utilizada no presente estudo, a MMC não chegou a entrar em contato com o endotélio ou não foi suficiente para danificá-lo.

Acreditamos que, se o óstio interno de uma trabeculectomia falida está pérvio à gonioscopia, deve-se considerar o agulhamento com MMC antes de se indicar uma nova trabeculectomia. A ausência de bolsa fistulante, a impossibilidade de se visualizar o retalho escleral sob a conjuntiva ou o fato de a trabeculectomia ter sido realizada há muitos anos não devem ser considerados fatores impeditivos para sua realização. O agulhamento com MMC é um procedimento relativamente seguro, fácil, rápido e de baixo custo quando comparado a uma cirurgia convencional. Seu potencial de sucesso é semelhante ou superior ao de uma segunda trabeculectomia, com a vantagem de provocar menor trauma cirúrgico. Por fim, caso o agulhamento não seja eficaz, ele não interfere na realização de futuras cirurgias antiglaucomatosas.

Futuros estudos poderão indicar novos caminhos para a cirurgia antiglaucomatosa, com o desenvolvimento de técnicas que sejam menos dependentes da conjuntiva e menos afetadas por seu processo cicatricial. Novas drogas têm sido testadas como adjuvantes nas cirurgias fistulizantes e no agulhamento, tais como as drogas inibidoras de fatores angiogênicos. Talvez se consiga encontrar uma droga ideal para o agulhamento, sem os efeitos adversos da MMC. Até que os resultados destes estudos possam mudar o cenário atual, acreditamos que o agulhamento com MMC é uma técnica útil, que deve fazer parte do arsenal terapêutico de todos os oftalmologistas que se disponham a enfrentar os desafios do tratamento cirúrgico do glaucoma.

CONCLUSÕES

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Os resultados desta pesquisa permitiram concluir que:

1) O agulhamento com MMC realizado em uma fase tardia do pós-operatório é eficaz na recuperação de fístulas antiglaucomatosas falidas, mesmo após muitos anos da realização da trabeculectomia.
2) O agulhamento tardio com MMC é eficaz no caso de bolsas totalmente planas, ou seja, perante a ausência de bolsa fistulante.
3) Os principais fatores associados ao sucesso do agulhamento com MMC foram a PIO baixa antes do procedimento, a PIO baixa no primeiro dia após o agulhamento, um maior intervalo de tempo entre a trabeculectomia e o agulhamento, e a idade, sendo que quanto mais idoso o paciente, maior a chance de sucesso. As taxas de sucesso também foram maiores em pacientes brancos, em olhos pseudofácicos e em olhos com trabeculectomias de base fórnice.
4) No que diz respeito às complicações, o agulhamento com MMC mostrou-se relativamente seguro, pois a maioria das complicações foi leve e transitória, não exigindo tratamento.
5) O agulhamento com MMC parece ser seguro para o endotélio corneano.

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APÊNDICES

APÊNDICE A – Carta de submissão do primeiro trabalho

TRANSMITTAL LETTER

To the Ophthalmology, Journal of The American Academy of Ophthalmology

Dear Editor-in-Chief,

We are submitting for publication the paper entitled **"Late Needling of Flat Filtering Blebs with Adjunctive Mitomycin C: A Prospective Study".** The present study is part of a PhD thesis developed in the Department of Ophthalmology, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil, under the orientation of Prof. Sebastião Cronemberger, MD, PhD.

No author has any conflict of interest.

Yours faithfully,

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APÊNDICE B – Carta de submissão do segundo trabalho

TRANSMITTAL LETTER

To the Journal of Glaucoma

Dear Editor-in-Chief,

We are submitting for publication the paper entitled **"Predictors of Success in Needle Revision of Filtering Blebs with Mitomycin C: A Prospective Study".** The present study is part of a PhD thesis developed in the Department of Ophthalmology, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil, under the orientation of Prof. Sebastião Cronemberger, MD, PhD.

The study protocol was approved by the Ethics Committee of the Federal University of Minas Gerais, Brazil. Each patient provided written informed consent.

Each author made a significant intellectual contribution to the research project. No author has any conflict of interest.

Yours faithfully,

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APÊNDICE C – Carta de submissão do terceiro trabalho

TRANSMITTAL LETTER

To the Ophthalmology, Journal of The American Academy of Ophthalmology

Dear Editor-in-Chief,

We are submitting for publication the paper entitled **"Corneal Thickness and Endothelial Density before and after Needling with Mitomycin C: A Prospective Study".** The present study is part of a PhD thesis developed in the Department of Ophthalmology, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil, under the orientation of Prof. Sebastião Cronemberger, MD, PhD.

No author has any conflict of interest.

Yours faithfully,

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APÊNDICE D – Termo de Consentimento Livre e Esclarecido

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

PROJETO: "RECUPERAÇÃO TARDIA DA TRABECULECTOMIA ATRAVÉS DO AGULHAMENTO EPISCLERAL ASSOCIADO À INJEÇÃO DE MITOMICINA C".

O procedimento cirúrgico realizado neste estudo é chamado de AGULHAMENTO. Ele tem como **objetivo** fazer com que uma cirurgia antiga de glaucoma volte a funcionar. O agulhamento é realizado no bloco cirúrgico, com anestesia tópica (apenas colírios) e tem uma duração média de 5 a 20 minutos. Com o auxílio de uma pequena agulha introduzida sob a conjuntiva, rompem-se as aderências e cicatrizes subconjuntivais, restabelecendo-se, assim, a drenagem do líquido interno do olho (humor aquoso) no local da antiga cirurgia. Durante o procedimento é injetada na conjuntiva uma pequena quantidade da substância chamada mitomicina C, que serve para impedir a formação de novas aderências e cicatrizes.

O agulhamento normalmente é indolor, mas pode gerar um pequeno desconforto durante o procedimento e nos primeiros dias de pós-operatório. É comum que a visão fique embaçada no primeiro mês. As **possíveis complicações** desta técnica são:

- Hemorragia conjuntival (presença de sangue superficial no branco do olho). Muito comum.
- Hifema (presença de sangue dentro do olho). Comum.
- Extravasamento de humor aquoso pelo orifício de entrada da agulha durante os primeiros dias de pós-operatório. Raro.
- Descolamento da coróide. Raro.
- Funcionamento excessivo da cirurgia, fazendo com que a pressão do olho fique muito baixa. Raro.
- Piora transitória (comum) ou permanente (muito rara) da visão.
- Desenvolvimento de catarata. Muito raro.

Todas estas complicações normalmente são transitórias e sem conseqüências importantes. Muito raramente podem ocorrer complicações **mais graves**, tais como processos infecciosos, lesão permanente com perda da transparência da córnea e piora grave e irreversível da visão.

O principal **benefício** desta técnica é a possibilidade de se conseguir controlar a pressão intra-ocular sem a necessidade do uso de colírios a longo prazo, ou, pelo menos, com uma quantidade menor de colírios. Desta forma, o controle do glaucoma pode se tornar mais eficaz, fácil e principalmente mais barato.

Caso o agulhamento não funcione, poderá ser realizada posteriormente a cirurgia convencional para o glaucoma (trabeculectomia), sem que haja prejuízos em seus resultados, ou o controle da pressão intra-ocular poderá voltar a ser realizado através do uso de colírios.

O **pós-operatório** será realizado no Serviço de Glaucoma do Hospital São Geraldo, onde também serão realizados os exames complementares. O seguimento pós-operatório é tão importante quanto a cirurgia e deverá ser feito no dia seguinte ao do agulhamento, no 7º dia, com 30 dias, com 3 meses, 6 meses e 1 ano. Se necessário serão agendados outros retornos. Na ocorrência de eventuais complicações, todos os pacientes poderão contar com a infra-estrutura do Hospital São Geraldo para seu tratamento.

Os **exames complementares** serão os seguintes:

- Biomicroscopia ultra-sônica (BUS): É um ultra-som do olho, que serve para estudar a região onde é feita a cirurgia. Será feita antes da cirurgia e repetida após 1 mês, 6 meses e 1 ano.
- Microscopia especular da córnea: Serve para estudar a saúde da córnea. Será feita antes da cirurgia e repetida após 1 mês, 6 meses e 1 ano.

- Paquimetria corneana: Serve para medir a espessura da córnea. Será feita antes da cirurgia e repetida após 1 semana, 1 mês, 3 meses e 6 meses.

Não haverá despesas para os pacientes com a cirurgia nem com os exames complementares.

Assim como em qualquer cirurgia, **não é possível garantir** o sucesso do resultado do agulhamento. Da mesma forma, não há previsão de ressarcimentos ou indenizações no caso de insucesso da técnica ou para eventuais complicações dela decorrentes.

Todos os dados coletados durante este estudo serão mantidos em **sigilo**, sendo garantida a cada paciente sua **privacidade** e a proteção de sua identidade. Os dados serão analisados e utilizados exclusivamente em publicações científicas apenas para esta pesquisa.

Os pesquisadores estarão disponíveis para **esclarecimentos** quanto ao estudo antes e durante toda a pesquisa.

Cada paciente terá a **liberdade** de recusar ou retirar seu consentimento em qualquer momento do estudo, ou seja, poderá se desligar do projeto, se isto lhe convier, sem qualquer penalização.

Pesquisadores responsáveis:

Assinatura:_____
Dr. Sebastião Cronemberger Sobrinho
Endereço: Rua Martim de Carvalho 410, apto 501. Belo Horizonte.
Telefones: 3248-9583 (Serviço de Glaucoma) e 3335-6218 (residência).

Assinatura:_____
Dra. Heloisa Andrade Maestrini
Endereço: Rua Laranjal 201, apto 302. Belo Horizonte.
Telefones: 3248-9583 (Serviço de Glaucoma) e 3284-4070 (residência).

Eu, _____ confirmo que entendi este termo de consentimento que assino em baixo e do qual recebo uma cópia. Meu médico explicou-me todos os procedimentos requeridos e as possíveis formas de tratamento que eu poderia realizar. Perguntei e fui esclarecido sobre todos os detalhes do estudo. Portanto dou o meu consentimento para minha inclusão neste estudo.

Belo Horizonte, _____ de _____ de 20_____.

Assinatura do paciente
ou responsável: _____

OBS: Este termo de consentimento livre e esclarecido foi analisado e aprovado pelo Comitê de Ética em Pesquisa (COEP) da UFMG.
Endereço: Campus da Pampulha, Prédio da Reitoria, 7º andar, sala 7018.
Telefones: 3499-4592 e 3499-4516.

APÊNDICE E – Formulário de coleta de dados

Nº DO PACIENTE NO ESTUDO:_____

PLANO DE COLETA DE DADOS: RECUPERAÇÃO TARDIA DA TRABECULECTOMIA PELO AGULHAMENTO EPISCLERAL

NOME:	TEL:

DATA NASCIMENTO: / /	REGISTRO:
IDADE: SEXO:	RAÇA:

DIAGNÓSTICO:	**OLHO:**

DADOS DAS CIRURGIAS PRÉVIAS:

	DATA	Po PRÉ-OP	CIRURGIA	BASE	USOU MMC?	INTERCORRÊNCIAS
1						
2						
3						
4						

DADOS CLÍNICOS PRÉ-AGULHAMENTO:

1) ACUIDADE VISUAL COM MELHOR CORREÇÃO:
2) PRESSÃO INTRA-OCULAR (3 ÚLTIMAS MEDIDAS): / /
3) ESCAVAÇÃO DO NERVO ÓPTICO:
4) GONIOSCOPIA: ☐ Estreito ☐ Intermediário ☐ Amplo
5) ☐ FÁCICO ☐ PSEUDOFÁCICO ☐ AFÁCICO
6) CÂMARA ANTERIOR: ☐ Rasa ☐ Média ☐ Profunda
7) MEDICAÇÃO HIPOTENSORA:

AGULHAMENTO:

DATA: _____/_____/_____ Tempo entre a última TREC e o agulhamento (meses):_____
INTERCORRÊNCIAS INTRA-OPERATÓRIAS:

PÓS-OPERATÓRIO:

	1º DPO	1 semana	1 mês	3 meses	6 meses	1 ano
Po (mmHg):						
COLÍRIOS:						
AV CORRIGIDA:	___	___				
INTERCORRÊNCIAS E COMPLICAÇÕES:						

Nº DO PACIENTE NO ESTUDO:

RE-AGULHAMENTOS E APLICAÇÕES DE ANTI-MITÓTICOS:				
DATA	REAGULHOU?	Lâmpada de fenda ou bloco cirúrgico?	5-FU?	MMC?
1)				
2)				
3)				
4)				
5)				
6)				
7)				
8)				
9)				
10)				

EXAMES COMPLEMENTARES:

PAQUIMETRIA:						
	PRÉ-OP	1 semana	1 mês	3 meses	6 meses	1 ano
1ª medida:						
2ª medida:						
3ªmedida:						
Média:						

MICROSCOPIA ESPECULAR:				
DADOS:	**PRÉ-OP**	**1 mês**	**6 meses**	**1 ano**
AVE:				
MAX:				
MIN:				
NUM:				
CD:				
SD:				
CV:				
GA:				
PACHY:				
Outros:				

BIOMICROSCOPIA ULTRA-SÔNICA (BUS)			
PRÉ-OP	1 mês	6 meses	1 ano