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Can postoperative dexamethasone nanoparticle eye drops replace mitomycin C in trabeculectomy?

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ABSTRACT.

Purpose: **Compare (a) nonmitomycin C (MMC) trabeculectomy and 1.5% dexamethasone nanoparticle (DexNP) eye drops postoperatively with (b) trabeculectomy with MMC and Maxidex® eye drops postoperatively.**

Methods: **Randomized prospective single masked clinical trial with 20 patients with primary open-angle glaucoma undergoing primary trabeculectomy. The study group consisted of 10 patients without MMC intraoperatively and postoperative DexNP eye drops, and the control group consisted of 10 patients treated with MMC intraoperatively and postoperative Maxidex®. The drops were tapered out over 8 weeks. The main outcome measures were as follows: rates of complete success, that is intraocular pressure (IOP) within target pressures at different time-points without IOP-lowering medication, or reoperation. Secondary outcome measures included the following: relative success rate (with IOP-lowering medications), number of glaucoma medications and reoperations. Patients were followed for 36 months.**

Results: **Both groups showed similar postoperative course and IOP reduction. Intraocular pressures (IOPs) in the DexNP group and in the control group were 25.6 and 24.4 mmHg, respectively, at baseline. Intraocular pressures (IOPs) were reduced to 13.2 and 14.5 mmHg at 12 months, 11.7 and 12.6 mmHg at 24 months and 11.7 and 12.1 mmHg at 36 months, respectively. There were no statistically significant differences between the groups in absolute ($p = 0.36$) or relative ($p = 1.0$) success rates, number of medications ($p = 0.71$) or reoperations ($p = 1.0$) between the groups at any time-point.**

Conclusions: **DexNP eye drops are effective postoperative treatment following trabeculectomy. The potent anti-inflammatory and antifibrotic effect of DexNP may offer an alternative to mitomycin C in glaucoma surgery.**

Key words: dexamethasone – drug delivery – glaucoma – mitomycin C – nanoparticles – trabeculectomy

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Introduction

Trabeculectomy is the most commonly used method of filtration surgery performed to lower IOP in glaucoma (EGS 2014), and it is still considered by many to be the gold standard in glaucoma surgery (Conlon et al. 2017). The procedure, in which an alternative outflow pathway for aqueous humour is created, sparks a healing reaction in which the body tries to close the pathway through inflammation and scarring, potentially causing the surgery to fail. To counteract this reaction, mitomycin C (MMC) is frequently used intraoperatively. Mitomycin C is a naturally occurring compound with an antiproliferative activity. It acts as an alkylating agent after enzyme activation, resulting in DNA cross-linking (Seibold et al. 2012). Thus, MMC is a potent antifibrotic agent that reduces scar tissue formation and its use in trabeculectomy results in higher success rates (Wilkins et al. 2005; Cabourne et al. 2015).

However, the rate of serious postoperative complications may increase, and the use of MMC in filtering surgery is associated with an increased risk of hypotony maculopathy, thin-walled blebs, blebitis, endophthalmitis, and corneal epithelial toxicity (Hollo 2012). In addition to MMC, and to further diminish the healing reaction and scar tissue formation following filtration surgery, the patients receive

topical steroids postoperatively to treat postsurgical inflammation. The most commonly used steroid is dexamethasone (Maxidex®).

Cyclodextrin nanoparticles have recently been shown to be an effective drug delivery technology to transport lipophilic drugs into the eye. Cyclodextrins are oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. Therefore, they can transport lipophilic drugs in their cavity and thus enhance drug delivery through the tough barriers of the eye surface into the eye (Loftsson et al. 2008).

The steroid dexamethasone has been shown to be a suitable candidate for this nanoparticle technology (Loftsson et al. 2007; Sigurdsson et al. 2007; Loftsson & Stefansson 2007). After instillation of one drop of 1.5% dexamethasone cyclodextrin nanoparticle suspension (DexNP), dexamethasone can be measured in the tear film for at least 6 hr after being instilled in the eye (Johannesson et al. 2014), enabling higher absorption into the eye with potentially enhanced treatment effect. DexNP has been used as topical treatment in humans in both diabetic macular oedema and uveitis with promising results with significant decrease of macular oedema and increase in visual acuity. (Tanito et al. 2011; Krag & Hessellund 2014; Ohira et al. 2015; Shulman et al. 2015) Furthermore, in a study by Saari et al. (2006), postoperative inflammation after cataract surgery was shown to be significantly less with 0.7% dexamethasone in cyclodextrin aqueous solution given once daily than with commercially available 0.1% dexamethasone sodium phosphate three times daily.

All these studies demonstrate DexNP as being potent and effective for treatment of intraocular inflammation. Corticosteroids are also known to have antifibrotic effect (Armstrong et al. 2019). Therefore, we hypothesize that postoperative treatment with DexNP after trabeculectomy will suppress inflammation and fibrosis so effectively that intraoperative use of MMC is not necessary.

Materials and Methods

This was a prospective, randomized, single masked, single-centre study performed at the Eye Clinic, Department of Ophthalmology, University of Iceland. The study was performed in accordance with the Declaration of Helsinki and approved by the Icelandic Medicines Agency and the Icelandic Biomedical Ethics board. The study was registered at the European Clinical Trials Database (EudraCT no: 2013-001093-16). Patients scheduled for primary trabeculectomy between September 2013 and January 2014 were asked to participate. Inclusion criteria included the following: patients with the diagnosis of primary open-angle glaucoma (POAG), age >18 years and ability to sign informed consent form. Exclusion criteria included the following: any active ocular disease or infection, allergy to the study medication, pregnant and breastfeeding women, those unable to understand informed consent and those who had participated in any clinical study during the previous 6 months.

The study drug, 1.5% dexamethasone γ-cyclodextrin nanoparticle (DexNP) eye drops were manufactured at Fresenius Kabi in Austria in 10-mL glass vials. The eye drops which contain a preservative were transferred to eye drop bottles with drop counter at the hospital pharmacy production unit at Landspitali – The National University Hospital of Iceland where the eye drops were dispensed to the patients. The eye drops were self-administered by the patients. Patients did receive training from a study nurse on the use of the eye drops. They also received written instruction on how to self-administer the eye drops and were instructed to shake the eye drop bottle before use as the formulation is a suspension.

Prior to the inclusion, five subjects took part in an open-label pilot study performed as a safety measure to evaluate the risk for serious adverse effects in the first weeks following surgery. Those subjects were allocated to the trabeculectomy without MMC but with DexNP drops four times daily. No serious adverse effects occurred in those five patients between surgery and when the randomized study was started. According to study protocol, the results of the first five subjects were not included in the analysis as they were neither randomized nor masked.

Subjects included in the second part of the study were randomized to either: (a), the study group, with trabeculectomy without MMC and postoperative treatment with DexNP drops four times daily or (b), the control group, with trabeculectomy with intraoperative application of MMC (0.3 mg/ml for 2 min) and postoperative treatment with commercially available Maxidex® drops six times daily. The postoperative eye drops were tapered down during eight weeks (w) as follows: subjects in the non-MMC arm used DexNP drops four times daily for four weeks, then three times daily for two weeks, then two times daily for 1 week and finally once daily for 1 week. Subjects in the MMC arm used Maxidex® eye drops six times daily for four weeks, then four times daily for two weeks and finally two times daily for 2 weeks.

All surgeries were performed by one surgeon (MSG). After topical and subtenon anaesthesia, a fornix-based conjunctival flap was made superiorly. Sponges soaked in either 0.3 mg/ml MMC or balanced salt solution (BSS), depending on which group the subject

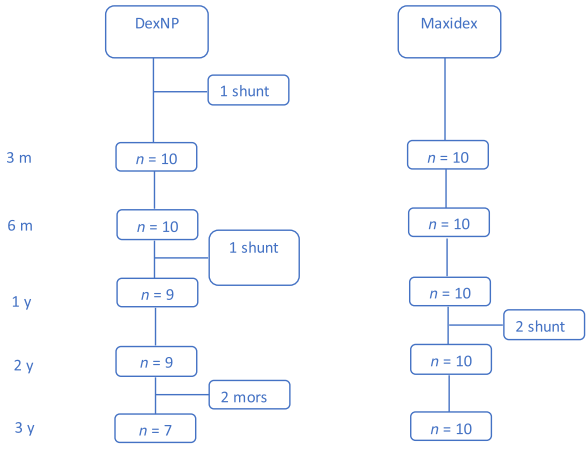

Fig. 1. Flow chart. Mors = deceased subject, m = month, y = year.

was randomized to, were instilled under the conjunctiva for two minutes. Then, the subconjunctival space was irrigated thoroughly with BSS. A partial thickness sclera flap was created and a fistula was made underneath the flap and iridectomy was performed. The scleral flap was then sutured with four 10.0 nylon single sutures. Finally, the conjunctiva was closed with a running 8/0 vicryl suture. The surgeon and the subject were masked to whether the subject got sponges with MMC or BSS. The surgeon continued to be masked throughout the trial but the subjects received unmasked bottles with either Maxidex® or DexNP. Thus, it was possible for the subjects to know which group they belonged. Intraocular pressure measurement was performed once with Goldmann Applanation Tonometry at every postoperative control by the surgeon.

Table 1. Demographics

Patient characteristics	DexNP	MMC/ Maxidex®
Age (mean years ± SD)	77 (11)	75 (8)
Sex (female/ total)	6/10	5/10
No. of glaucoma medications (mean ± SD)	2.6 ± 0.8	2.6 ± 1.2
Baseline IOP (mean mm Hg ± SD)	25.6 ± 7.0	24.4 ± 8.4
Mean defect (dB)	11.2 ± 6.1	12.1 ± 7.0
Visual acuity logMAR (mean (range))	0.20 (0.05–0.7)	0.2 (0.05–1.0)

The main outcome measure was IOP change after trabeculectomy and the rate of complete success defined as IOP ≥6 mmHg and ≤18 mmHg without IOP-lowering medication or an additional IOP-lowering operation. According to the World Glaucoma Association's guidelines on designing glaucoma trials, the definition of IOP success ought to include an upper and lower limit, include more than one upper limit or a combination of an upper limit and a percentage reduction (Shaarawy 2009). Thus, the results in this study are reported with a lower limit and several upper limits.

Secondary outcome measures included the following: relative success defined as IOP ≥6 mmHg and ≤18 mmHg with or without additional IOP-lowering medication. Secondary outcome measures included incidence of medical and surgical interventions (need of postoperative medications, needling, laser suture lysis and bleb needling) and safety.

Treatment could be stopped in cases suggesting drug intolerance.

End-point of the study was the occurrence of reoperation due to failure of the previous glaucoma operation. The decision of performing reoperation was made by the surgeon when target IOP was not fulfilled despite suture lysis and/or IOP-lowering topical medication. The patients were followed for 36 months.

Statistical analysis

Summary statistics are presented with means and range. The Wilcox signed-rank test was used in paired samples and Mann–Whitney *U*-test for nonpaired samples for IOP measures. A generalized mixed-effect model with fixed effect for time after operation and a random subject effect was used. Another model with fixed effect for treatment and random subject effect for patients was fitted against the number of medications used. A Poisson likelihood was assumed in these two models. A two-sample test for equality was used to test proportions. A mixed-effect model with fixed effect for time after operation, treatment and interaction between time and treatment, and random subject effect was fitted to test the association with IOP. A general estimating equation was used to test the association of treatment with rate of success. Statistical significance was set at p = 0.05.

Results

The study included a total of 20 patients with POAG undergoing primary trabeculectomy because of poorly controlled IOP and/or intolerance to topical eye drops. All patients had glaucomatous optic nerve head damage and corresponding visual field defects. None of the patients in either group had previously undergone filtering surgery. One patient in the DexNP group had performed argon laser trabeculoplasty eight months prior to surgery. The study group included 10 subjects treated with DexNP without MMC, and the control group included 10 subjects treated with MMC and Maxidex® (Fig. 1). Three patients in the DexNP arm died during the study time, two before the 2-year control and one before the 3-year

Table 2. Results of IOP, number of glaucoma medications and reoperations in the two treatment arms. IOP is with or without glaucoma medication and data are given as mean IOP (range) and number of subjects at each time point. Medicines refers to number of medications at each time point and data are given as mean (range). Re-operation shows the number of subjects that had gone through re-operation/total subjects.

	Pre op	3 months	p*	6 months	p*	12 months	p*	24 months	p*	36 months	p*
IOP (mm Hg)											
DexNP	25.6 (16-38) 10	14.6 (10-30) 9	0.012	14.9 (10-30) 9	0.021	13.2 (10-18) 8	0.014	11.7 (7-16) 7	0.022	11.7 (9-17) 6	0.035
Maxidex	24.4 (16-42) 10	12.7 (8-18) 10	0.006	13.1 (9-17) 10	0.002	14.5 (9-28) 10	0.006	12.6 (8-25) 8	0.025	12.1 (9-16) 7	0.016
p	0.57	0.68		0.65		0.929		0.769		0.768	
Medicine											
DexNP	2.7 (1-4)	0 (0-0)	NA**	0.2 (0-2)	0.001	0.5 (0-2)	0.002	0.7 (0-2)	0.008	0.8 (0-2)	0.018
Maxidex	2.6 (0-4)	0 (0-0)	NA**	0.2 (0-1)	0.001	0.6 (0-4)	0.001	0.2 (0-2)	0.002	0.7 (0-2)	0.017
p	0.929	1		0.949		0.888		0.21		0.807	
Reoperation											
DexNP		1/10		1/10		2/10		1/8		1/7	
Maxidex		0/10		0/10		0/10		2/10		3/10	
p										0.864	

DexNP = 1.5% dexamethasone cyclodextrin nanoparticles suspension, IOP = intraocular pressure, Maxidex = commercially available dexamethasone, NA = not applicable, p = p-value for difference between DexNP and Maxidex, p* = p-value for difference at given time-point compared with baseline (pre-op).

control. The demographics of the study population can be seen in Table 1.

The IOP was reduced in both treatment arms at all time–points, and there was no statistically significant difference between the treatment arms at any time-point (Table 2, Fig. 2). The portion of subjects reaching absolute and relative success is shown in Table 3.

Figure 2A–C shows the individual relationships between pre- and postoperative IOP and whether the IOP reduction was more than 25% as compared with the preoperative IOP level. There was no difference between the treatment arms in terms of number of glaucoma medications or surgical failures, in which case the patients needed to undergo additional surgical intervention, that is shunt operation with an Ahmed valve (Table 2). Suture lysis was performed in eight subjects in the DexNP arm and in nine subjects in the MMC/Maxidex arm. No needlings or 5-FU injections were performed postoperatively on subjects in either group.

Baseline visual acuity is presented in Table 1. Visual acuity was significantly decreased compared to baseline at three, six and 24 months in the DexNP group by 0.05 ± 0.04, 0.05 ± 0.06 and 0.06 ± 0.06 logMAR, respectively. For the MMC/Maxidex group, visual acuity was significantly decreased at 3, 6 and 10 months by 0.05 ± 0.04, 0.04 ± 0.04 and 0.04 ± 0.04 logMAR, respectively. There was no significant difference in visual acuity change between the groups at any time-point.

Discussion

The results of this prospective, randomized study show no difference between trabeculectomy performed with adjuvant MMC and regular topical dexamethasone (Maxidex®) postoperatively as compared with trabeculectomy without MMC and with topical DexNP postoperatively. This indicates that the anti-inflammatory and antifibrotic effect of DexNP is noninferior compared with the antifibrotic effect of MMC in trabeculectomy.

Antimetabolites such as MMC and 5-FU are widely used to prevent scarring of the bleb in trabeculectomy. Studies have shown MMC to have superior antifibrotic effects compared with 5-FU (Cabourne et al. 2015), and thus, MMC has become a standard procedure in trabeculectomy. In a

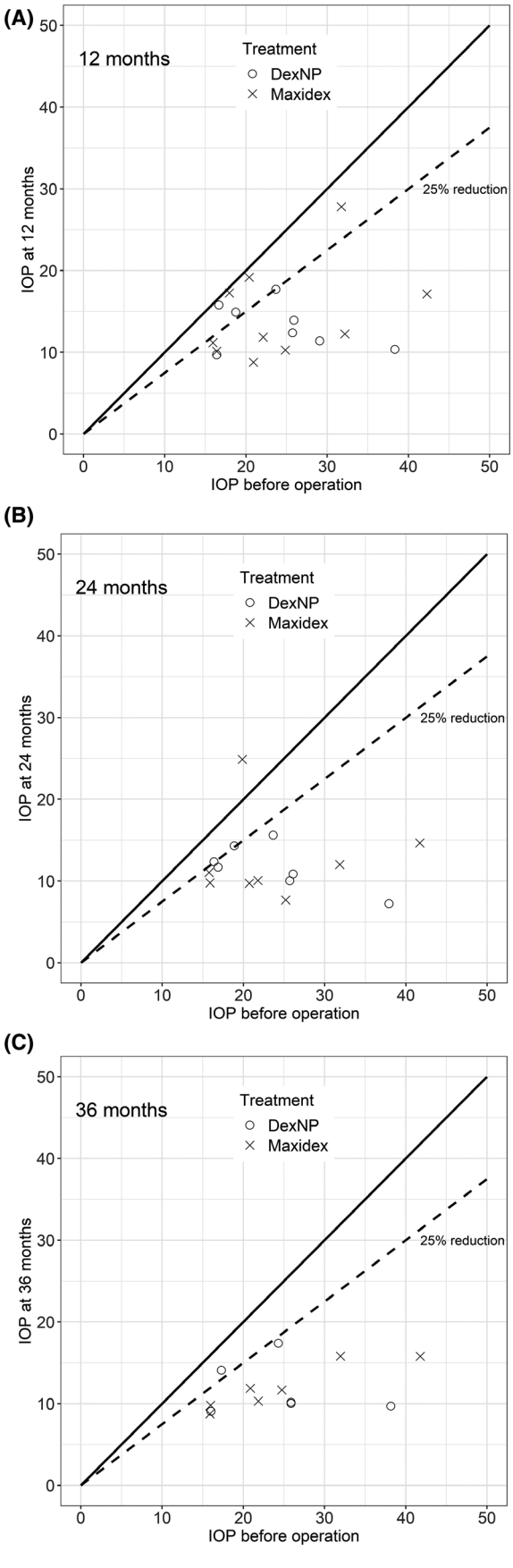

Fig. 2. Scatterplot showing preoperative intraocular pressure (IOP) plotted against postoperative IOP at (A) 12 months, (B) 24 months and (C) 36 months in the two treatment arms. All symbols below the black line represent eyes where IOP was lower postoperatively than preoperatively. The dashed line represents eyes with IOP reduction more than 25%.

Table 3. (a) Portion of subjects reaching absolute success (IOP ≥ 6 mmHg and ≤18 mm Hg) without IOP-lowering medications. (b) Portion of subjects reaching relative success (IOP ≥ 6 mmHg and ≤18 mmHg) with or without IOP-lowering medications.

	3 months	6 months	12 months	24 months	36 months
(a)					
DexNP	80% (8/10)	70% (7/10)	50% (5/10)	37.5% (3/8)	28.6% (2/7)
Maxidex	100% (10/10)	80% (8/10)	70% (7/10)	60% (6/10)	40% (4/10)
All	90% (18/20)	75% (15/20)	60% (12/20)	50% (9/18)	35.3% (6/17)
p	0.46	1	0.65	0.64	1
(b)					
DexNP	80% (8/10)	80% (8/10)	80% (8/10)	87.5% (7/8)	85.7% (6/7)
Maxidex	100% (10/10)	100% (10/10)	80% (8/10)	70% (7/10)	70% (7/10)
All	90% (18/20)	90% (18/20)	80% (16/20)	77.8% (14/18)	76.5% (13/17)
p	0.46	0.46	1	0.75	0.86

Data are given as % success and as no. of subjects out of total no. of subjects.

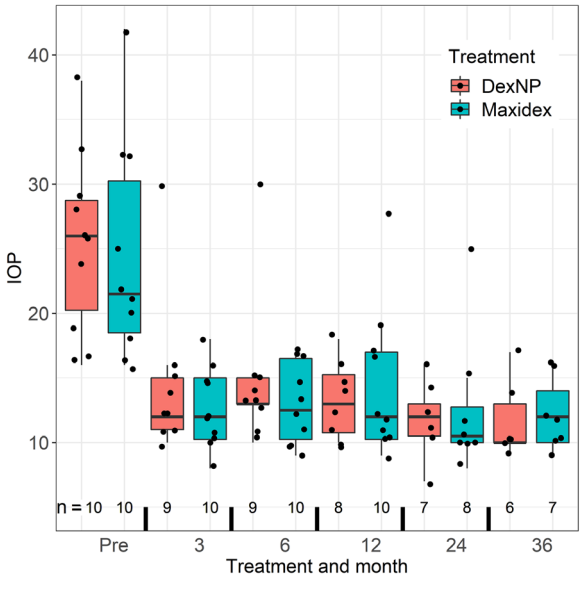

Fig. 3. Boxplot with absolute IOP values at baseline and at postoperative controls. Number of subjects is indicated above the x-axis. Boxes show 25% percentile and 75% percentile with a horizontal line representing the median value.

Cochrane review of the use of MMC in glaucoma surgery, Wilkins et al. (2005) concluded that intraoperative MMC reduces the risk of surgical failure in primary trabeculectomy, and compared with placebo, MMC reduces the mean IOP of all reviewed participants at 12 months.

The disadvantage of using MMC in filtrating surgery is the risk of complications associated with antimetabolites. Reports on vision-threatening complications such as scleral melting (Coutinho et al. 2017), avascular and atrophic conjunctiva (Siggel & Dietlein 2018), wound leaks (Membrey et al. 2000; Soltau et al. 2000) and bleb-related infections (Luebke et al. 2019), hypotony (Suner et al. 1997) and cataract formation (Wilkins et al. 2005) have been linked to the use of MMC. The risk of complications is greater with longer duration of intraoperative MMC exposure and higher concentrations of MMC (Robin et al. 1997; Kim et al. 1998; Wilkins et al. 2005). Thus, it is important to limit duration and exposure to MMC in order to minimize the risk of complications, and in this study, MMC applications were within the limits proposed by The Moorfields Safer Surgery recommendations (Dhingra & Khaw 2009).

However, it is important to point out that these feared complications are rare (Luebke et al. 2019) and that surgeons have developed techniques to reduce the incidence of these complications (Wilkins et al. 2005). Furthermore, a limitation of many studies of filtration surgery is too short follow-up time as many of the potential MMC complications are late-onset (Soltau et al. 2000; Wilkins et al. 2005). Luebke et al. (2019) report results from more than 1800 trabeculectomies in which they identified MMC as a significant risk factor for bleb-related infection. However, and in contrast, in another recent retrospective review of trabeculectomy-related complications, which spans a period of 25 years, the authors could not see an increase of complications that could be linked to the use of MMC (Olayanju et al. 2015). In this present prospective study, we had a follow-up period of three years and did not see any serious complications in either arm of the study.

Harju et al. showed in a randomized controlled trial on deep sclerectomy with either MMC or not, that although the group with MMC had higher success rates, a statistical difference was not reached at the end of follow-up. Success with low IOP in the non-MMC group was maintained with higher frequencies of postoperative interventions of goniopunctures and needling procedures (Harju et al. 2018). No difference in postoperative suture lysis was seen in that study.

The nanotechnology-based drug delivery technology used in DexNP has been investigated in several human clinical trials with good results. In two studies on subjects with diabetic macular oedema, treatment with topical DexNP significantly reduced central macular thickness and increased visual acuity (Tanito et al. 2011; Ohira et al. 2015). Furthermore, topical DexNP has been used to treat patients with intermediate uveitis and cystoid macular oedema with significantly improved clinical status (Krag & Hessellund 2014; Shulman et al. 2015). Thus, DexNP has been proven effective to treat conditions deep in the eye, which is unusual for topical eye drops due to the immense barriers to drug penetrance in the eye (Loftsson et al. 2008). Encouraged by these results, the current study was undertaken with the hypothesis that the enhanced uptake of dexamethasone would be comparable to MMC. Although small, the study confirmed the hypothesis that trabeculectomy without MMC and with DexNP was noninferior to trabeculectomy with MMC and conventional dexamethasone postoperative treatment. This indicates that the strong penetrance of DexNP might be an alternative to MMC in filtration surgery.

There are limitations in this study that need to be acknowledged. Firstly, the study is a pilot study with a small sample size. Thus, it cannot be excluded that a larger sample might have produced a significant difference between the treatment arms. Secondly, the surgeon was masked to whether the patients received MMC or not intraoperatively, but the patients were not masked to whether they received DexNP or Maxidex® during their initial postoperative period which could theoretically have affected the subjects' compliance. Ideally, the drugs would have been repackaged into similar bottles but that was not possible in this study. Finally, it is notable that several subjects needed to undergo reoperation with shunt and thus were classified as failures. However, these were more frequent in the MMC/Maxidex® arm and can therefore not be due to the absence of MMC.

In conclusion, this study showed that there was no statistical difference between using postoperative treatment with DexNP eye drops in trabeculectomies without MMC compared with postoperative treatment using conventional steroid drops (Maxidex®) in trabeculectomies with MMC. This suggests that the use of DexNP, with its large anti-inflammatory and antifibrotic effect, could reduce or even in some cases replace the use of MMC perioperatively.

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