Combinative approach of transzonular triamcinolone-moxifloxacin and perioperative drops to minimize postoperative complications of cataract surgery

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Received: 2023-07-05 Accepted: 2024-02-02

Abstract

● AIM: To investigate the effectiveness of combination therapy with transzonular triamcinolone-moxifloxacin and conventional perioperative drops in reducing postoperative complications of cataract surgery.

● METHODS: Electronic medical records of cataract surgery patients (single surgeon) were reviewed from January 2018 to September 2021. The rate of postoperative complications including prolonged and/or recurrent postoperative inflammation, endophthalmitis, cystoid macular edema (CME), and intraocular pressure (IOP) was compared between the patients receiving combinative therapy and patients receiving drops only.

● RESULTS: Totally 596 patients and 1057 eyes (Combinative-Therapy group 493 and Drop-Only group 564) were included in this study. Using combination therapy reduced the relative risk of postoperative inflammation by 26.9% (16.6% Combinative-Therapy vs 22.7% Drop-Only, P=0.013). The incidence of endophthalmitis was 0 in Combinative-Therapy group vs 0.5% in Drop-Only group (relative risk reduction 100%), although not statistically significant (P=0.10). The incidence of severe IOP spikes was not significantly different between Combinative-Therapy (2.4%) and Drop-Only (1.6%) groups (P=0.33). The relative risk of postoperative CME was 51.4% less in three months follow up visit in Combinative-Therapy group, although not statistically significant (P=0.07). The visual outcome 1-month postop. (best corrected visual acuity) was significantly better in Combinative-Therapy (logMAR 0.10) compared to Drop-Only (logMAR 0.14) groups (P=0.02) while the baseline visual acuity was not significantly different.

● CONCLUSION: The combinative approach of transzonular triamcinolone-moxifloxacin plus perioperative eyedrops is an effective method to minimize postoperative inflammation, with better visual outcomes. It could potentially reduce the risk of postoperative endophthalmitis and CME (near-significant P-values; larger studies could analyze better considering low incidence).

● KEYWORDS: cataract; endophthalmitis; cystoid macular edema; postoperative complications; transzonular injection

INTRODUCTION

Cataract develops in the majority of people with age, and the vision improving treatment, cataract surgery, is one of the most common procedures performed worldwide[1]. Although recent advancements in techniques and technology including clear cornea incision, small incision, and femtosecond laser have improved safety and increased success rate in the majority of the cases, postoperative complications are still a concern[1-3]. The most common vision-threatening complications are postoperative inflammation, cystoid macular edema (CME), and postoperative infection/endophthalmitis[4-6]. Thus, over the years many surgeons and researchers studied the best ways to prevent these potentially devastating complications[7]. The conventional standard method of preventing the aforementioned complications is pre- and postoperative use of eye drops, mainly involving topical corticosteroids, antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs)[1-2]. However, this approach has some disadvantages, including potential ocular surface toxicity if used inappropriately, heavy
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dependency on patient compliance, and unpredictable dose delivery. Hence, during the past years, a drop-free approach using an intraoperative injection of steroids and antibiotics, most commonly triamcinolone acetonide and moxifloxacin (Tri-Moxi), has been suggested as an alternative. But this approach also is controversial. There have been reports of postoperative endophthalmitis as well as high spikes in intraocular pressure (IOP) using 0.2 mL of Tri-Moxi, and a study on animal models suggests this method alone might not provide adequate coverage for some organisms if used alone.

In this study, we present a combinative approach, using an intraoperative injection of 0.1 mL Tri-Moxi (half of the dosage proposed for a drop-free approach to minimize IOP complications) along with pre- and postoperative prophylactic drops (to extend coverage and provide a holistic approach). We aimed to scientifically investigate this approach and compare the outcomes to the traditional approach of topical drops only.

SUBJECTS AND METHODS

Ethical Approval The study was approved by Trinity Health Mid-Atlantic IRB committee (THMA 2021-46E). Electronic medical records were reviewed from January 2018 to September 2021. To minimize bias, all the cataract surgeries included in this study were performed by a single surgeon (Chaudhry IM). The IRB committee waived the need for consent.

Inclusion criteria were cataract surgery performed by Chaudhry IM, attendance of follow-up visits (1d, 1wk, 1mo, and 3mo postop.), and age above 18 years old and below 89 years old. Exclusion criteria were no or incomplete follow-up after surgery, having pars plana vitrectomy or other major intraocular procedures at the same time as cataract surgery, and age below 18 years old or above 89 years old. The complications of focus for this study included prolonged and/or recurrent postoperative inflammation (defined as inflammation needing new steroid use after 6wk postoperatively or need for continuous steroid use for more than 6wk postoperatively), infection/endophthalmitis, severe IOP elevation (defined as spikes of more than 15 mm Hg from baseline, excluding day one postop.), and CME.

The variables included age, sex, use of intraoperative Tri-Moxi, preoperative and/or postoperative inflammation (diagnosed by the ophthalmologist examining the patient), CME (presence of CME identified by the ophthalmologist examining the patient), central macular thickness on optical coherence tomography (OCT - number recorded in test report sheet), intraocular pressure (IOP measured by technicians and double-checked by an ophthalmologist), endophthalmitis (diagnosed by an ophthalmologist), and best-corrected visual acuity (BCVA), measured by the technicians and double-checked by the ophthalmologist). Risk factors status was also collected including diabetes, hypertension, hyperlipidemia, glaucoma, and diabetic retinopathy. Data for preoperative exams and up to 4 postoperative exams were documented, up to 3mo after the surgery (1d, 1wk, 1, and 3mo).

Patients were categorized based on receiving intraoperative Tri-Moxi plus perioperative eyedrops (Combinative Therapy group) or only perioperative eyedrops (Drop Only group). Both groups received conventional prophylactic eyedrops pre- and postoperatively, including prednisone acetate 1% three times a day (TID), ofloxacin 0.3% TID, and ketorolac tromethamine 0.5% TID for three days before and 1wk after the surgery, then stopped ofloxacin 0.3% and ketorolac tromethamine 0.5% and gradually tapered prednisone acetate 1% as two times a day (BID) for the second week, one time a day (QD) for the third week, then stopped. The patients in the Combinative Therapy group received a transzonal injection of 0.1 mL of Tri-Moxi (half of the usual dose) during the cataract surgery, after viscosurgical device removal, supertemporal or infratemporal into the anterior vitreous with a transzonular approach using a blunt 27-gauge cannula. Total drug delivery is 1.5 mg of triamcinolone acetonide and 0.1 mg of moxifloxacin for this amount.

Each variable between groups was compared with Wilcoxon matched pairs test, t-test and/or Chi-square test, and one-way ANOVA where appropriate. Comparisons were done between treatment groups for preoperative, and postoperative follow-up visits to evaluate the postoperative complications and response to treatment. To account for confounders (risk factors for postop. complications including diabetes, hypertension, hyperlipidemia, glaucoma, and diabetic retinopathy), data were stratified based on each risk factor and the Mantel-Haenszel test was performed. The level of significance was set at P<0.05.

RESULTS

In total, 596 patients and 1057 eyes were included in this study. Of these, 493 eyes received intraoperative Tri-Moxi alongside pre- and postoperative eye drops (Combinative Therapy group) and 564 received only pre- and postoperative eye drops (Drop Only group; Figure 1, Table 1).

The incidence of prolonged and/or recurrent postoperative inflammation was significantly lower in patients receiving combinative therapy compared to those receiving drops only with a relative risk reduction of 26.9% (16.6% vs 22.7% respectively, P=0.013). This difference remained significant after accounting for confounding risk factors, including diabetes (P=0.018), hypertension (P=0.031), hyperlipidemia (P=0.028), glaucoma (P=0.014), and diabetic retinopathy (P=0.014).
The specific indications for steroid use for more than 6wk to manage postoperative inflammation are listed in Table 2. Endophthalmitis incidence was 0 in patients receiving combinative therapy, compared to 0.5% in patients who received drops only (relative risk reduction 100%), although this comparison was not statistically significant (P=0.10). This could be due to the fact that this specific complication is very rare (no case in 493 eyes receiving combinative therapy and 3 cases in 564 eyes receiving drops only).

The incidence of IOP spikes (IOP reading more than 15 mm Hg compared to preoperative baseline, excluding day 1 postop.) was not significantly different between the patients receiving combinative therapy (2.4%) compared to those receiving drops only (1.6%, P=0.33). Mean IOPs of preop. and postop. visits are shown in Figure 2.

There was no significant difference in IOP changes on postoperative day 1 between the two groups. The IOP change for the Combinative Therapy group was slightly higher compared to the Drop Only group in postoperative week 1 and month 1, but on 3mo postoperative visit, the mean difference in IOPs was not significantly different between the two groups (Table 3).

The incidence of postoperative CME was 4.5% in patients receiving combinative therapy and 6.7% in those receiving drops only (relative risk reduction of 32.8%), although this comparison was not statistically significant (P=0.1). The most noticeable relative risk reduction (51.4%) was found in CME three months postop. visit (1.7% in the Combinative Therapy group vs 3.5% in Drop Only group) and the P-value although close to significance level (0.07), was not statistically significant (Table 4).

### Table 1 Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Combinative Therapy (271 patients, 493 eyes)</th>
<th>Drop Only (325 patients, 564 eyes)</th>
<th>Total (596 patients, 1057 eyes)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.6480</td>
</tr>
<tr>
<td>Female</td>
<td>166 (61.3)</td>
<td>192 (59.1)</td>
<td>358 (60.1)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>105 (38.7)</td>
<td>133 (40.9)</td>
<td>238 (39.9)</td>
<td></td>
</tr>
<tr>
<td>Age, mean±SD</td>
<td>70.5±7.7y</td>
<td>67.2±9.0y</td>
<td>68.7±8.6y</td>
<td></td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>71 (39-88)y</td>
<td>68 (33-87)y</td>
<td>69 (33-88)y</td>
<td></td>
</tr>
<tr>
<td>Eyes laterality, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.9903</td>
</tr>
<tr>
<td>OD</td>
<td>245 (49.7)</td>
<td>279 (49.5)</td>
<td>524 (49.6)</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>248 (50.3)</td>
<td>285 (50.5)</td>
<td>533 (50.4)</td>
<td></td>
</tr>
</tbody>
</table>

Tri-Moxi: Triamcinolone acetonide and moxifloxacin ophthalmic preparation; OD: Right eye; OS: Left eye.

**Table 2 Indications for steroid use past 6wk postoperatively**

<table>
<thead>
<tr>
<th>Indication for steroid use</th>
<th>Combinative Therapy</th>
<th>Drop Only</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged and/or recurrent AC inflammation</td>
<td>65 (13.1)</td>
<td>101 (17.9)</td>
<td>0.04&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Retained lens fragments</td>
<td>1 (0.2)</td>
<td>0</td>
<td>0.99</td>
</tr>
<tr>
<td>CME</td>
<td>14 (2.8)</td>
<td>24 (4.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Neurotrophic ulcer</td>
<td>1 (0.2)</td>
<td>0</td>
<td>0.99</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>0</td>
<td>3 (0.5)</td>
<td>0.10</td>
</tr>
<tr>
<td>Total</td>
<td>82 (16.6)</td>
<td>128 (22.7)</td>
<td>0.013&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

AC: Anterior chamber; CME: Cystoid macular edema. <sup>a</sup>Statistically significant.
The BCVA of the patients pre-operatively and on a 1-month follow-up visit is shown in Figure 3. The visual outcome (BCVA) of the surgery was significantly better in the Combinative Therapy group (logMAR 0.10±0.24) compared to the Drop Only group (logMAR 0.14±0.34, \( P = 0.02 \)), while the baseline BCVA was not significantly different in the two groups (logMAR 0.51±0.40 vs 0.54±0.49, respectively, \( P = 0.18 \)).

**DISCUSSION**

In this large-scale study, we assessed the efficacy of our proposed combinative approach of intraoperative transzonular Tri-Moxi plus conventional perioperative eyedrops in comparison with conventional perioperative eyedrops only in terms of postoperative complications. Different methods of intraocular drug delivery have been suggested for controlling postoperative infection and inflammation. Intracameral injection has shown promising results in controlling inflammation and preventing endophthalmitis in several studies\(^{[1,16-17]}\). Intracameral injection of moxifloxacin after cataract surgery, as well as intracameral cefuroxime injection, were reported to reduce the incidence of postoperative endophthalmitis\(^{[11,16-19]}\). Additionally, intracameral injection of dexamethasone and triamcinolone acetonide has shown success in limiting postoperative inflammation and infection following cataract surgery\(^{[20]}\). On the other hand, posterior segment drug delivery methods such as transzonal injection provide more sustainable and effective intraocular transfer\(^{[12]}\). Specifically, it has been shown that transzonal injection of Tri-Moxi-vancomycin is non-inferior in controlling postoperative inflammation and infection compared to conventional perioperative drop therapy after cataract surgery\(^{[2]}\).

Based on these findings, we chose the transzonular approach to ensure more sustained and effective intraocular drug delivery, while covering the ocular surface and wound site with topical medications to achieve a holistic coverage. Furthermore, by reducing the dose of transzonal injection by half of the common method (0.1 vs 0.2 mL), we sought to reduce the controversial side effects of this method such as IOP spikes. We observed promising results, showing that the combinative approach was associated with a significant decrease in postoperative inflammation, resulting in better visual outcomes. It could also potentially reduce the risk of postoperative endophthalmitis and CME (our \( P \) value was close to significant; due to low incidence of these complications a larger study could better analyze these findings).

One of the main concerns following cataract surgery is prolonged and/or recurrent postoperative inflammation. The
The incidence of this complication has been reported to be from 8% to 21%, based on the criteria of the studies[1,21-22]. Recurrent uveitis in high risk patients has been reported to be as high as 51%[23-24]. We used a very strict criteria in our study by including minimal anterior chamber cells and flare to include all types of inflammation. This postop. inflammation could also lead to CME via inflammatory factors such as leukotrienes and prostaglandins[11]. Even in patients without major risk factors for CME such as diabetes and operative complications, the rate of pseudophakic CME is reported as high as 1.17%[25-26]. This rate is much higher in patients with major risk factors, although modern phacoemulsification techniques have helped reduce the adverse events[25-27]. Treatment and prevention of CME are achieved by anti-inflammatory agents targeting the aforementioned inflammatory mediators such as NSAIDs and corticosteroids[28-29]. Using a combination of NSAIDs and corticosteroids has shown to be superior to single-agent therapy in reducing the risk of clinically significant macular edema[30]. Furthermore, CME can develop several weeks after the surgery, and patients would benefit from a longer follow-up period to address this condition in a timely manner[1,25]. Based on these, we hypothesized that the combinative approach of intraoperative transzonal Tri-Moxi plus conventional perioperative eyedrops would be potentially a more holistic approach to control the risk of CME compared with the conventional drop only regimen, as well as drop-free regimen which does not include NSAIDs. Our results showed a significant decrease in prolonged and/or recurrent postoperative inflammation with the combinative therapy, with a relative risk reduction of 27% compared to drops only. This risk reduction remained significant after stratified analysis based on major confounding risk factors, including diabetes, hypertension, hyperlipidemia, glaucoma, and diabetic retinopathy. This showed that this combinative approach is potentially superior to controlling inflammation, by covering intraocular space, wound site, and ocular surface. We also found a decrease in the risk of CME during the follow-up period (up to 3mo) by 33% in our proposed combinative approach compared to drop-only treatment, although this was not statistically significant (P=0.1). The most noticeable risk reduction was for the three months follow-up visit, where patients receiving the combinative treatment had a 51% relative risk reduction compared to drop-only treatment (P=0.07). The P-value was very close to a significant level and this could be due to the fact that the rate of this complication is very low and larger sample size would increase the power of the study to enable better judgment regarding the significance.

Another major concern after cataract surgery is endophthalmitis. The incidence of acute postoperative endophthalmitis after cataract surgery has been reported 0.1% to 0.7%[31-33]. Researchers and clinicians have been trying to find the best approach to prevent this potentially devastating complication for decades. The common approaches to prevent postoperative endophthalmitis are drop free with an intraoperative injection of steroids and antibiotics or traditional perioperative eyedrops (corticosteroids, antibiotics, and NSAIDs). Each of these methods has its advantages and disadvantages. Conventional drop therapy rise concerns for proper use, compliance, and potential ocular surface toxicity if used inappropriately[8-9]. The drop-free approach was developed to minimize the effect of compliance and potential ocular surface toxicity and showed to be non-inferior to conventional drop therapy[10-12]. But this approach showed to cause high IOP spikes in 0.2 mL dose of Tri-Moxi (usual dose) in some patients, and there have been concerns of postoperative endophthalmitis as well[13]. Moreover, a study on animal models suggests that using this method alone might not provide adequate antimicrobial coverage[14]. Considering these, we hypothesized that the proposed method of combining half of the regular dose of Tri-Moxi (0.1 mL) in combination with traditional perioperative drop therapy will provide intraocular, wound site, and ocular surface coverage of antibiotics and maximize the efficacy and minimize the risk of endophthalmitis, while reducing the potential side effects of full-dose Tri-Moxi such as IOP spikes. Our results showed a noticeable 100% decrease in the relative risk of postoperative endophthalmitis using the combinative therapy (0) compared to conventional perioperative drops only (3 cases in 564 patients, 0.5%), however, this was not statistically significant (P=0.10). Two of these three endophthalmitis cases disclosed that they have not been compliant with their postoperative drop therapy. This highlights the importance of complementing this method with an intraocular injection even more. It is noteworthy that this complication is incredibly rare (0 in 493 in the combination therapy group and 3 in 564 in drop only group), and a very large sample size is required to provide adequate power to compare the efficacy properly. Hence our results suggest that the combinative therapy could potentially reduce the risk of postoperative endophthalmitis by covering more aspects of the eye involved in the process.

Postoperative ocular hypertension is a major concern with the full dose dropless method[16-17]. In our study, there was no significant difference in postoperative IOP and incidence of IOP spikes in both groups, showing that the combinative therapy with half the dose (0.1 mL Tri-Moxi; 1.5 mg of triamcinolone acetonide and 0.1 mg of moxifloxacin) alongside perioperative drop did not increase the risk of IOP rise and spikes. Intravitreal injection of high dose triamcinolone acetonide (20 mg) has shown to cause a significant increase in IOP[26], but injection of low dose triamcinolone acetonide
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(<3 mg) has actually been associated with lower IOP spikes compared to postoperative drops\(^{[2,37]}\). In line with these, our results showed that our proposed combinative approach with low-dose triamcinolone acetone does not pose the risk of significant postoperative IOP rise and spikes. Interestingly, the combinative therapy group showed a significantly better visual outcome in postoperative month 1 of follow-up. This could be attributed to better control of inflammation and corneal edema, as well as better control and prevention of CME, leading to a better visual outcome which represents the function of the eye as a whole system.

The main limitation of this study was the retrospective nature of the study. However, these results could be a foundation for a potential large-scale prospective clinical trial to investigate this further. Although our study had a relatively large sample size compared to similar studies on the subject, a very large sample size study in the future could better evaluate the difference in rare complications such as endophthalmitis with a greater study power. Another point was the different antibiotics used for topical (ofloxacin) and intraocular (moxifloxacin) treatments. The routine drops in our area of practice are ofloxacin for topical, and moxifloxacin for injection. We did not intend to define a protocol for an intervention clinical trial in this study. Furthermore, please note that ofloxacin and moxifloxacin are from the same class of antibiotics and their actions and coverages are very similar based on many published studies. Some surgeons consider longer course of post-operative steroid therapy to hypothetically prevent later onset complications such as CME; in our practice 3wk is deemed sufficient to prevent IOP spikes.

In conclusion, our study showed that the combinative approach of intraoperative transzonular Tri-Moxi injection plus conventional perioperative eyedrops is an effective method to significantly reduce prolonged and/or recurrent postoperative inflammation, resulting in better visual outcomes. This method could also potentially reduce the risk of postoperative endophthalmitis and CME (the \(P\) values were close to significant, and larger studies could better analyze the difference due to very low incidence of these side effects).

ACKNOWLEDGEMENTS

Authors’ contributions: Rabiee B helped design the study, and was the major contributor to data gathering, analyzing the data, and writing the manuscript. Festok M, Gaspari M, Haseeb A, Chaudhry A, Kamoun L, Chaudhry I, and Chaudhry IM helped with patient follow-up, data gathering, and scientific discussion. Chaudhry IM designed the study, performed all the surgeries, and helped revise the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest: Rabiee B, None; Festok M, None; Gaspari M, None; Haseeb A, None; Chaudhry A, None; Kamoun L, None; Chaudhry I, None; Chaudhry IM, None.

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