4 Quin™ PFS

(1 ml Pre-Filled Moxifloxacin 0.5% Syringe)

A Randomized Control Trial

Safety study of
Intracameral Moxifloxacin
in Indian patients undergoing
uncomplicated cataract
phacoemulsification.

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December 2013.
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Entod Pharmaceuticals Ltd. (INDIA)

ORIGINAL RESEARCH

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Abstract:
Purpose: To assess safety of intracameral moxifloxacin after cataract surgery in Indian patients undergoing uncomplicated cataract phacoemulsification.
Methods: A randomized control trial with assignment of 2/3 to the treated group and 1/3 to the control group was conducted in 272 eyes which underwent phacoemulsification. Blinded observers evaluated eyes treated with an intracameral injection of a Moxifloxacin 0.5% drug preparation (4 QUIN™ PFS, Entod Pharmaceuticals Ltd., India) and controls comparing post op anterior segment inflammation, endothelial toxicity and macular edema in the two arms.
Results: Corneal Pachymetry was done pre op and post op (one month). Two sample T tests did not show any statistical significant difference in two groups (p=.0805). Corneal specular microscopy was done pre op and post op (one month) and cell density noted. Two sample T tests did not show any statistical significant difference in treated and control eyes in the below 65 age group (p=.9768). However patients in the older age group incidentally had lesser loss in the treated group (p=.0001). OCT was done at the end of one month post op. There was no statistical significance in the central macular thickness in the two groups (p=.8088). At the one month follow-up neither group had any inflammatory activity. At the end of one month all patients had a BCVA of 6/12, except one from control group who did not improve beyond 6/36 due to AMD.
Conclusion: There being no statistically significant evidence of ocular toxicity with respect to the parameters of corneal edema, endothelial loss, anterior segment inflammation and macular edema compared to the control group, the drug preparation was considered safe for use.

Keywords: Moxifloxacin, intracameral antibiotics.

Introduction:

Prophylactic Intracameral antibiotics at the end of uneventful phacoemulsification surgery have been advocated with a view to preventing post op endophthalmitis. This has gained more ground amongst phacosurgeons after reports that temporal clear corneal incisions have a higher risk of endophthalmitis[1,2]. Drugs like Cefuroxime and Moxifloxacin have been used for the purpose[3,4]. Safety profile of intracameral drugs not only depend on the molecule but also on formulations such as its pH and osmolarity. This study in Indian patients sought to test the safety of an intracameral injection of a moxifloxacin 0.5% drug preparation designed as a single-use

pre filled syringe. No similar study with adequate sample size had been conducted elsewhere.

Materials and methods:

Ethical committee approval was sought and acquired. Patients undergoing phacoemulsification and fulfilling the inclusion criteria and exclusion criteria underwent clinical assessment, corneal pachymetry and specular microscopy in the eye to be operated.

The inclusion criteria were: (1) Patients with Senile cataract except grade 4/mature/hypermature, (2) Age between 50-75 years, (3) Willing to undergo phacoemulsification and (4) Willing to sign informed consent and follow up for period of study. The exclusion criteria were: (1) Diabetes mellitus, (2) Any other ophthalmic co-morbid conditions and (3) Any systemic inflammatory conditions.

Patients recruited were randomly assigned to the two arms just prior to surgery in a ratio of 2/3 to treated arm and 1/3 to control arm. Randomization was done via a computer program. Patients in the drug arm were injected with a 0.1ml moxifloxacin 0.5% (equivalent to 500µg) intracameral injection at the end of uncomplicated phacoemulsification. 0.1 ml of the drug (4 QUIN™ PFS, Entod Pharmaceuticals Ltd., India) was injected directly from the prefilled 1ml syringe of the manufacturer at the end of cataract surgery following removal of viscoelastic through the side port. The drug was injected under the capsulorhexis rim into the capsular bag and not directly at the corneal endothelial surface. Patients in control group did not receive an injection. Patients with any intraoperative complication were discontinued from the study.

Patients underwent assessment of vision and anterior segment inflammation by Hogan and Kimura score[5] on the second post op day, eighth post op day and one month after surgery, in the operated eye. Corneal pachymetry , specular microscopy and optical coherence topography (OCT) for macular thickness was done after one month. The observer was blinded while the doctor administering drug was different and unblinded, doing away with the need for a placebo injection. In case of any adverse event, it was reported.

Results in both arms were compared. The main outcome variables were the difference between post and pre op Pachymetry before and at one month, difference in percentage Endothelial cell loss and presence of macular edema on OCT at one month. Anterior segment inflammation was graded as per Hogan and Kimura system on the 2nd, 8th day and a month post op. BCVA in both groups at end of one month was recorded. Statistical evaluation was done to compare the outcomes in the two groups with STATA software using the Student T test.

Results:

A randomised control Safety study of intracameral moxifloxacin in Indian patients undergoing uncomplicated cataract phacoemulsification was conducted at HV Desai Hospital after ethical committee clearance. 330 patients were randomized into injection and non injection groups in a ratio of 2/3 to 1/3. 160 injected patients and 112 non injected patients completed the study period of one month.

Being a safety study, the emphasis was on finding out whether there was any difference in the treated and control group with respect to corneal edema, endothelial cell loss and macular edema, which was objectively assessed using pachmetry, specular microscopy and OCT. Anterior segment inflammation was graded subjectively using the Hogan and Kimura score. BCVA was recorded at 4 weeks.

Corneal Pachymetry was done pre op and post op (one month). The mean difference in pachymetry was 11.85 microns with median 5 and standard deviation of 14.49 in the treated group against 9 microns with median of 4 and

standard deviation of 11.04 in control group. Two sample T tests did not show any statistical significant difference in two groups(p=.0805).

Corneal specular microscopy was done pre op and post op (one month) and cell density noted. The mean endothelial cell loss was 9.547% with median 9.235% and standard deviation of 5.54% in the treated group, against 13.63% with median of 13.36% and standard deviation of 5.15% in control group. The percentage of endothelial cell loss after surgery was studied in the two groups- those under 65 years of age (136 eyes) and those 65 years and above(136). Two sample T tests did not show any statistical significant difference in the treated and control eyes in the below 65 years age group(p=.9768). However in the patients in the older age group incidentally had lesser loss in the treated group (p=.0001).

OCT was done at the end of one month post op. There was no statistical significant in the central macular thickness in the two groups (p=.8088). The mean CMT was 200.7 microns with median 178.5 and standard deviation of 64.90 in the treated group against mean CMT 202.43 microns with median of 195 and standard deviation of 46.13 in the control group.

On the 2nd follow up visit at 8 days, 10% eyes had grade 2 cells and 5% had grade 2 flare as compared to none in control group. At the one month follow up neither group had any inflammatory activity. At the end of one month all patients had a BCVA of 6/12, except one from control group who did not improve beyond 6/36 due to AMD. There were no adverse events.

Discussion:

Endophthalmitis as a complication of cataract surgery is extremely difficult to explain to an affected patient in today's era of flawless surgical technique and near perfect visual recovery.

The clear corneal cataract phacoemulsification with the "no injection no pad" technique was found to have a higher percentage of post operative endophthalmitis. The clear cornea incision is thought to have contributed to the increase in the number of endophthalmitis cases following phacoemulsification surgery[1,2,6].

Taban (2005) performed a meta-analysis of 215 studies that addressed post-cataract surgical endophthalmitis which met his selection criteria. A total of 3,140,650 cataract extractions were pooled from ECCE and phacoemulsification surgery giving an overall incidence of 0.128 per cent for post-operative endophthalmitis. He found this incidence varied with time from 0.265 per cent in 2000/2003, 0.087 per cent in the 1990s, 0.158 per cent in the 1980s to 0.327 per cent in the 1970s. He found the clear corneal incision of phacoemulsification to be a risk factor between 1992 and 2003 with an increased rate of 0.189 per cent compared to 0.074 per cent for scleral tunnel incision. However Taban reviewed the limitations of his meta-analysis study depending mostly on retrospective studies with limited statistical power of intracameral antibiotics during surgery being advocated during those times.[7] The ESCRS study found that the risk for contracting postoperative endophthalmitis was significantly reduced, approximately 5-fold, by an intracameral injection of 1mg cefuroxime at the close of surgery (p=0.001 for presumed endophthalmitis; p=0.005 for proven endophthalmitis).

Drugs like Cefuroxime and Moxifloxacin have been used for the purpose.[8,9] Safety profile of intracameral drugs not only depend on the molecule but also on formulations such as its pH and osmolarity. Safety studies look at absence of drug toxicity or tissue damage finally affecting visual function rather than the efficacy of the antibiotic molecule. This is even more important when the drug is being used prophylactically rather than therapeutically.

Importance of using the right dose (volume)

intraocularly and directing the jet away from endothelium are important practices to be followed.

Few other studies done elsewhere (with other preparation) had the similar results but were limited with smaller sample sizes and incomplete evaluation.[10,11,12]

Our inclusion and exclusion criteria ensured decreased effect of confounders and bias. Patients with any intra operative complication such as capsular rent , vitreous loss, nucleus drop prior to instillation of the drug were discontinued from the study.

Pachymetry is a very sensitive indicator of the corneal endothelial pump function while specular microscopy is an accurate documentation of the anatomical integrity of the endothelium. No significant difference in these was present in the two arms.

Macular OCT was done only one at the end of one month to rule out development of cystoid macular edema. Some safety studies additionally do an ERG , but this is mainly used in drugs used intra vitreally.

Conclusion:

There being no statistically significant evidence of ocular toxicity with respect to the parameters of corneal edema, endothelial loss, anterior segment inflammation and macular edema compared to the control group, the drug was considered safe for use.

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