·Clinical Research·

Effects of moxifloxacin exposure on the conjunctival flora and antibiotic resistance profile following repeated intravitreal injections

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Received: 2013-10-23 Accepted: 2013-12-25

Abstract

• AIM: To evaluate the effects of moxifloxacin exposure on the conjunctival flora and antibiotic resistance profile following repeated intravitreal injections.

• METHODS: Seventy-two eyes of 36 patients [36 eyes in control group, 36 eyes in intravitreal injection (IVI) group] were enrolled in the study. All the eyes had at least one IVI and had diabetic macular edema (DME) or age-related macular degeneration (ARMD). Moxifloxacin was prescribed to all the patients four times a day for five days following injection. Conjunctival cultures were obtained from the lower fornix *via* standardized technique with every possible effort made to minimize contamination from the lids, lashes, or skin. Before the application of any ophthalmic medication, conjunctival cultures were obtained from both eyes using sterile cotton culture. An automated microbiology system was used to identify the growing bacteria and determine antibiotic sensitivity.

• RESULTS: The bacterial cultures were isolated from 72 eyes of 36 patients, sixteen of whom patients (44.4%) were male and twenty (55.6%) were female. Average age was 68.4±9.0 (range 50-86). The average number of injections before taking cultures was 3.1+1.0. Forty-eight (66.7%) of 72 eyes had at least one significant organism. There was no bacterial growth in 8 (20.5%) of IVI eyes and in 16 (44.4%) of control eyes (P=0.03). Of the bacteria isolated from culture, 53.8% of coagulase negative staphylococci (CoNS) in IVI eyes and 47.2% CoNS in control eyes. This difference between IVI eyes and control eyes about bacteria isolated from culture was not statistically significant (P=0.2). Eleven of 25 bacteria (44.0%) isolated from IVI eyes and 11 (57.9%) of 19 bacteria isolated from control eyes were resistant to oxacillin. The difference in frequency of moxifloxacine resistance between two groups was not statistically significant (12.0% in IVI eyes and 21.1% in control eyes) (P=0.44). There were no cases of resistance to vancomycin, teicoplanin and linezolid.

• CONCLUSION: There was no difference in species of bacteria isolated from cultures, or in the frequency of resistance to antibiotics between eyes that had recurrent IVI followed by moxifloxacin exposure compared with control eyes. However, the number of eyes that had bacterial growth was higher in IVI group than in the control group.

• KEYWORDS: intravitreal injection; moxifloxacin; endopthalmitis
DOI:10.3980/j.issn.2222-3959.2014.05.21

Ataş M, Başkan B, Özköse A, Mutlu Sarıgüzel F, Demircan S, Pangal E. Effects of moxifloxacin exposure on the conjunctival flora and antibiotic resistance profile following repeated intravitreal injections. *Int J Ophthalmol* 2014;7(5):855-859

INTRODUCTION

The use of intravitreal injection (IVI) has increased in recent years since the effectiveness of anti-vascular endothelial growth factor (anti-VEGF) agents is proved to have played an important role in ophthalmologic diseases such as exudative age-related macular degeneration (ARMD), retinal vein occlusion and diabetic macular edema (DME) [1-3]. Although IVI is an effective and safe method, endophtalmitis is the most imminent complication. The incidence of endopthalmitis after IVI is as low as 0.019%[4-6]. The issue of increased bacterial resistance has attracted recent attention. It is suggested that repeated exposure to antibiotics and povidone iodine 5% after IVI might alter the structure of conjunctival flora, and also facilitate the development of antibiotic-resistant bacterial colonies. The literature contains few studies on the effects of repeated use of antibiotics and povidone iodine with regard to the development of bacterial resistance [7-10]. These prospective studies are conducted with small sample sizes and findings

are subject to change depending on individual and regional factors as well as types of antibiotics used. Of course, conjunctival flora and the frequency of resistance to antibiotics changes along with countries and regions. Therefore such findings should be supported with various multicentric studies, and this is why we conducted this research.

We consider it highly important to repeat such studies periodically in order to evaluate the potential flora changes and antibiotic sensitivities. The purpose of this study is to investigate the effects of repeated use of moxifloxacin after IVI on conjunctival flora as well as the development of bacterial resistance compared with control eyes.

SUBJECTS AND METHODS

This single center, cross-sectional, case-control trial was conducted between June 1, 2013 and August 30, 2013 in Kayseri Education and Research Hospital, Turkey. All the patients examined agreed to participate in the present study, and a written informed consent form was obtained from each patient. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Erciyes University Ethics Committee (No.2013/423)

Patients received IVI of ranibizumab (Lucentis; NovartisPharma AG, Basel, Switzerland; and Genentech Inc, South San Francisco, CA, USA) injection at least once for wet type ARMD or clinically significant DME enrolled in the study. All the patients were aged over 20. The eyes that had IVI were classified as IVI group, and the other eyes of the same patients, which had not previously had injection, were classified as control group. Exclusion criteria were signs and symptoms of conjunctivitis, keratitis, blepharitis, glaucoma, history of ocular surgery, using contact lense, seborrhea of meiboiman gland, obstruction of nasolacrimal duct and chronic dacriosistitis. Also the patients who had used oral antibiotic or steroid for the last two months were not included in the study.

Conjunctival cultures were obtained from the lower fornix via standardized method with every effort made to minimize the contamination from the lids, lashes, or skin. Before the application of any ophthalmic medication, conjunctival cultures of both eyes were obtained using sterile cotton culture swab moistened with brain-hearth infusion broth agar (BHIB) and was inoculated into 2 mL BHIB. The BHIB were incubated at 37℃ for 2-4h. Then three samples from BHIB were incubated separately in 5% sheep blood agar, eosin methylene blue agar and chocolate agar. The first two were incubated at 37℃ for 24-48h and the latter was incubated in a wax-sealed jar in a medium that contained 5% to 10% carbon dioxide. The one sample for the presence of fungi from BHIB was incubated Sabouraud dextrose agar at 25℃ and 37℃ for 3wk. Culture results were evaluated through classical methods. Colony morphology, hemolysis, Gram's stain, catalase, oxidase and coagulase tests were performed. Fungal cultures were explored via colony, lactophenol cotton blue preparation, germ tube experiments, and hyphae, blastospore and chlamydospore formation in cournmeal agar. All bacterial isolates were identified and antibiotics susceptibilities were tested for each of 14 antibiotics by Vitek 2 compact automated microbiology system (Biomerieux, France)**.** Minimal inhibition concentration was interpreted as susceptible, intermediate or resistant in accordance with the Clinical Laboratory Standards Institute guidelines. A quality control strain, *S.aureus* ATCC 25923, was used to validate and monitor results.

After conjunctival cultures were obtained, patients underwent complete ocular preparation for IVI according to our clinical protocol.

Statistical Analysis Statistical analyses were carried out with SPSS statistical software (version 21.0 for Windows; IBM). Continuous variables were presented as mean ± standard deviation and (min-max). Categorical variables were summarized as frequencies and percentages. Chi-square test or Fisher exact test was used to determine the associations between categorical variables. A P value of 0.05 was considered significant.

RESULTS

The bacterial cultures were isolated from 72 eyes of 36 patients sixteen of whom were male (44.4%) and twenty were female (55.6%). The average age of the patients was 68.4 ±9 (50-86). Table 1 summarizes the baseline demographics of the study population. The indication for IVI is ARMD in 18 (50%) of the patients and DME in 18 (50%) of the patients. Patients had an average of 3.1±1.0 previous injections. Forty-eight (66.6%) of 72 eyes had at least one significant organism isolated from conjunctiva; of these eyes, 3 had two significant organisms. No cases of endophthalmitis were observed during the study. The microorganisms isolated from IVI eyes and control eyes were shown at Table 2.

The bacteria isolated from conjunctival cultures didn't differ in the means of species and colony counts (P=0.2). There was no statistically significant difference in growth ratio of *S. epidermidis*and *S. aureus*between two groups (P=0.24, P=0.24, respectively). There was no statistically significant difference in species of bacteria isolated from cultures between DME and ARMD. But control eyes had lower bacterial growth in 16 eyes (44.4%) compared with IVI eyes in 8 eyes (20.5%), which is statistically significant (P =0.03). Coagulase negative staphylococci (CoNS) was the most frequently isolated organism in both groups of eyes (53.8% in IVI eyes and 47.2% in control eyes).

There was no statistically significant difference in antibiotic resistance between control eyes and IVI eyes. Eleven of 25 bacteria (44%) isolated from IVI eyes and 11 of 19 bacteria (57.9%) isolated from control eyes had oxacillin resistance (P=0.543). Resistance to moxifloxacine was observed in seven colonies four of which were composed of *S.*

Table 1 Baseline characteristics and indications for IVI in patients undergoing culture of conjunctiva and control patients

Parameters	Average±standard deviation
Age a (mix-max)	68.4±9.0 (50-86)
No. of previous injections (mix-max)	3.1±1.0 (2-6)
Gender *n* (%)	
M	16 (44.4)
F	20 (55.6)
Indication	
Diabetes mellitus	18 (50.0)
ARMD	18 (50.0)
Eyes undergoing culture	
IVI eyes	36 (50.0)
Control eyes	36 (50.0)

ARMD: Age-related macular degeneration; IVI: Intravitreal injection.

Table 2 Organisms isolated from the conjunctiva in patients undergoing IVI and control patients *n* (%)

Parameters	IVI group (*n*=39)	Control group (*n*=36)
S. epidermidis	9 (23.1)	12 (33.3)
S. hominis	6 (15.4)	4 (11.1)
S. aerus	6 (15.4)	2 (5.6)
S. haemolyticus	2 (5.1)	1 (2.8)
S. warneri	1 (2.6)	-
S. lugdunensis	1 (2.6)	-
Kocuria cristinae	1 (2.6)	-
Kocuria rosea	1 (2.6)	-
Kocuria varians	0 (0.0)	1 (2.8)
C. albicans	1 (2.6)	-
CoNS	21 (53.8)	17 (47.2)
None	8 (20.5)	16 (44.4)

CoNS: Coagulase negative staphylococci.

Table 3 Antimicrobial resistance of organims isolated in the conjunctiva of patients undergoing IVI and control patients *n* (%)

Parameters	IVI group (*n*=25)			Control group (*n*=19)			*P*
	Sensitivity	Intermed	Resistance	Sensitivity	Intermed	Resistance	
Oxacillin	14 (56.0)	-	11 (44.0)	8 (42.1)	-	11 (57.9)	0.543
Penicillin	7 (28.0)	-	18 (72.0)	5 (26.3)	-	14 (73.7)	1.000
Imipenem	17 (68.0)	-	8 (32.0)	9 (47.4)	-	10 (52.6)	0.285
Gentamicin	24 (96.0)	-	1 (4.0)	18 (94.7)	-	1 (5.3)	1.000
Ciprofloxacin	16 (64.0)	2 (8.0)	7 (28.0)	9 (47.4)	3 (15.8)	7 (36.8)	0.505
Moxifloxacin	22 (88.0)	-	3 (12.0)	15 (78.9)	-	4 (21.1)	0.443
Erythromycin	16 (64.0)	-	9 (36.0)	12 (63.2)	-	7 (36.8)	1.000
Clindamycin	21 (84.0)	-	4 (16.0)	17 (89.5)	-	2 (10.5)	0.684
Linezolid	25 (100.0)	-	-	19 (100.0)	-	-	-
Teikoplanin	25 (100.0)	-	-	19 (100.0)	-	-	-
Vankomicin	25 (100.0)	-	-	19 (100.0)	-	-	-
Tetracycline	11 (44.0)	-	14 (56.0)	10 (52.6)	-	9 (47.4)	0.792
Tigecyclin	24 (96.0)	1 (4.0)		19 (100.0)	-	-	1.000
Fusidic acid	14 (56.0)	9 (36.0)	2 (8.0)	9 (47.4)	7 (36.8)	3 (15.8)	0.695
Sulfamethaxozol	25 (100.0)	-	-	17 (89.5)	-	2 (10.5)	0.181

epidermidis, one of *S. aureus*, one of *S. haemolyticus* and one of *S. hominis*. Eight of 14 colonies resistant to ciprofloxacin were *S. epidermidis*. Resistance to vancomycin, teicoplanin and linezolid was observed in none of the cases. Antibiotic resistance patterns were shown in Table 3.

DISCUSSION

Conjunctival flora is composed after the birth and could change with age, inflammatory disease of eyelids, use of contact lenses, ocular surgery, antibiotics, immunosuppression and such systemic diseases as diabetes[11-13]. Normal conjunctival flora is composed mainly of gram positives similar to upper respiratory tract and skin flora. The most common bacteria in conjunctiva are *staphylococcus* species, *corynebacterium* species, and anaerobic *propionibacterium* species. It is postulated that these members of normal conjunctival flora play protective role against pathogenic bacteria by preventing the growth of them. Specifically, *S. epidermidis* prevents colonization from more pathogenic *S. aureus via* probiotic function[14-16].

Despite the protective role of *S. epidermidis*, it is also the most frequent organism isolated in conjunctivitis, keratitis and endophtalmitis. Resistant colonies of *S. epidermidis* appear immediately after exposure to antibiotics and they also gain resistance to other classes of antibiotics such as gentamycin, trimethoprim/sulfamethoxazol and doxycycline. Resistant *S. epidermidis* colonies cause more virulent and serious intraocular inflammation and also the eradication of resistant colonies becomes more difficult [17,18]. Schimel *et al*[18] reported *S. epidermidis* as the most frequent isolated bacteria (30.1%) from culture positive endophalmitis cases in their study prolong for ten years.

Dave *et al* [8] established recurrent exposure to fluoroquinolones and azithromycin change the conjunctival flora and increase growth of *S. epidermidis*. They found out that conjunctival flora was composed of 45.7% *S. epidermidis* before IVI and 63.4% after IVI. Conversely, Milder *et al* [9] found no difference in the mean of culture positivity or the species of bacteria isolated from cultures

between IVI eyes and control eyes.

In our study, 28 species of bacteria were isolated from IVI eyes and 20 from control eyes. This difference is not statistically significant. Also, the two groups showed no significant difference in the growth ratio of *S.epidermidis* and *S.aureus*. The species of bacteria isolated from two groups are not different. This similarity between the two groups might be due to the small number of specimens and the low rate of bacterial growth.

Some preoperative and postoperative prophylactic cautions are necessary to reduce the risk of post-IVI endophthalmitis. Aiello *et al* [19] emphasized the importance of use of povidone iodine, sterile eyelid speculum, proper and sufficient anesthesias to lower the risk of postoperative endophthalmitis in their guideline. It is advised to avoid exaggerated manipulations and paracentesis after IVI[19]. Preoperative and postoperative antibiotic prophylaxis is used in a number of clinics. Recently there have been different thoughts about advantages of antibiotic prophylaxis [7,20-22]. In our clinic, we use prophylactic antibiotic immediately before IVI and for 5d after injection.

Although topical antibiotics are used commonly in a line with the hypothesis of that antibiotics decrease risk of infection after IVI, Halachmi-Eyal *et al* [23] showed that there was no decrease in bacterial colonization with the use of moxifloxacin 0.5% together with povidone iodine 5% after cataract operation. In summary, the effect of topical fluoroquinolones on conjunctival flora is not so clear.

Speaker and Menikoff [20] reported that bacteria isolated from vitreous of eyes with endophthalmitis are similar to bacteria isolated from conjunctiva and nares of the same patients. The only proven method in prophlaxis of endophthalmitis is the sterilization of ocular surfaces with povidone iodine.

In a large case series, Cheung *et al*[6] found that the frequency of endophthalmitis after IVI was lower among patients who did not use antibiotics after the injection than among those who used antibiotics.

Bhatt *et al* [24] found no significant difference in the incidence of endophthalmitis between patients who used antibiotics and those who did not. Storey *et al* [25] reported using postinjection topical antibiotic drops does not reduce the risk of endophthalmitis developing and is associated with a trend toward higher incidence of endophthalmitis. Lyall *et al*[26] reported measures to minimise the risk of post-intravitreal anti-VEGF endophthalmitis include treatment of blepharitis before injection, avoidance of subconjunctival anaesthesia, topical antibiotic administration immediately after injection with consideration to administering topical antibiotics before injection.

There are different techniques and cautions advised to lower the risk of endophthalmitis. Previous studies reported no significant difference in the prevalence of endophthalmitis between these techniques and precautions[27,28].

It was hoped that there would be lower resistance and lower frequency of postoperative endophthalmitis when the new fourth-generation quinolones become available, due to their wide spectrum of antibacterial effect, good ocular penetrance and inhibitor effect to both DNA gyrase and topoisomerase IV. Despite the use of these antibiotics, postoperative endopthalmitis continued to develop[29-31] .

Schimel *et al* [18] reported reduction of sensitivity to quinolones from 100% to 40% in CoNS endopthalmitis cases during 15y from 1990 to 2005. Of course, the frequency of resistance to quinolones changes along with countries and regions. In our study, the low incidence moxifloxacin resistance might be due to its limited use, because until one year prior to our study its use was limited to inpatients.

In our study, there is no statistically significant difference in antibiotic resistance between IVI and control eyes. The frequency of resistance (21.1%) before exposure to fluoroquinolones in control eyes is similar to that reported in other studies (32%-34%)[7,9,21]. Kim *et al* [7] and Milder *et al* [9] reported widespread resistance (63%-77%) after quinolone exposure, whereas only 12% of our patients showed resistance. Alabiad *et al* [10] found high prevalence (45%) of resistance to fluoroquinolones in bacteria isolated from conjunctiva and nares of IVI eyes, but found no relationshipbetween the prevalence of resistance and the number of injections. They reported moxifloxacine resistance as 32%. They concluded that recurrent IVI and subsequent exposure to fourth-generation quinolones did not increase the prevalence of resistant microorganisms. However, the use of quinolones as the first choice for prophylaxis should be reviewed, due to the high prevalence of resistant microorganisms present in conjunctiva and nares. Moss *et al*[21] showed that three days exposure to fluoroquinolones significantly inhibited bacterial growth in conjunctiva. They also found a significant decrease in conjunctival flora after topical povidone iodine. Povidone iodine acts by increasing the permeability of antimicrobial agents from bacterial wall.

The limitations of this study include the small sample size, and that it was conducted in only one center. In addition, the average of 3.1 injections might also be a limitation. A study designed with a higher number of injections might produce different results to the present study. Although moxifloxacin has been available in Turkey since 2008, it has only been used for outpatients since the second half of 2011. This could explain the low prevalence of resistance to moxifloxacin in our country. These results derive from a limited number of patients, and show the situation only in our region; it is therefore not possible to generalize our results.

In conclusion, no differences in bacterial isolate counts or the frequency of resistance were observed between control eyes and IVI eyes exposed to moxifloxacin following repeated intravitreal injection. Also, there was not an increase in moxifloxacin resistance after repeated IVI eyes and control

eyes. However, the number of eyes which had bacterial growth was higher in the IVI group than the control group.

All of the bacterial isolates were not eradicated by moxifloxacin which is used after IVI treatment; so the use of quinolones as the first choice for endophthalmitis prophylaxis should be reviewed.

ACKNOWLEDGEMENTS

Conflicts of Interest: Atas M, None; **Baskan B,** None; **Özköse A,** None**; Mutul Sarıgüzel F,** None; **Demircan S,** None; **Pangal E,** None.

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