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Effect of basic fibroblast growth factor (bFGF) on the treatment of exposure of the orbital implants

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Abstract: Objective: To evaluate the efficacy and the indication of basic fibroblast growth factor (bFGF) in the treatment of exposure of orbital implants. Design: Retrospective and observational case series. Methods: We reviewed 41 patients (41 eyes) suffering exposure of orbital implants from Jan. 2000 to June 2006. The study group patients with mild exposure received combined treatment with bFGF and antibiotic drops, and while the control group patients with mild exposure were treated with antibiotic drops only. The study group patients with moderate and severe exposure received combined treatment with bFGF and antibiotic drops, and after 2 months they were subjected to amniotic membrane transplantation, while the control group patients with moderate and severe exposure underwent amniotic membrane transplantation after using antibiotic drops. Observation of the growth of conjunctival epithelium and comparison of the healing rate of the two groups. Results: The healing rates of the mild, moderate and severe exposure study group were 100% and 92.3%. The healing rates of the mild, moderate and severe exposure control group were 55.6% and 66.7% respectively. The difference of the healing rates of the mild exposure study group and the control group was significant (P=0.033). And the difference of the healing rates of the moderate and severe exposure study group and the control group was not significant (P=0.167). Conclusion: bFGF may promote obviously the healing of orbital implant exposure, particularly it can be the first choice for the treatment of mild degree exposure. For the moderate and severe cases, it can be administered before surgical repair to enhance neovascularization and will tend to increase the success rate of surgical repair.

Key words: Exposure, Orbital implants, Basic fibroblast growth factor (bFGF)
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INTRODUCTION

Orbital implantation has shown good clinical effect on treatment for hollow socket and malformation after orbital enucleation. However, exposure of the orbital implant is the most notable complication, which may lead to extrusion (Remulla *et al*., 1995). The most important factor which causes orbital implant exposure is delayed fibrovascular ingrowth into the implant (Buettner and Bartley, 1992; Nunery *et al*., 1993). Therefore promoting fibrovascular ingrowth into the implant will reduce the exposure rate of the implant. There have been many reports about trials to promote fibrovascular ingrowth into orbital implants using growth factors (Woo *et al*., 2000; Rubin *et al*., 1997; Soparkar *et al*., 2000). Park *et al*.(2005) demonstrated basic fibroblast growth factor (bFGF) promoted fibrovascular ingrowth in bFGF-soaked and/or bFGF-injected porous polyethylene orbital implants. bFGF is a protein that is deposited in the extracellular matrix. It has the ability to promote proliferation, migration and the angiogenesis of vascular endothelial cells. Moreover, bFGF promotes the growth of conjunctival epithelium cells. The implant exposure can be treated by conservative or/and surgical measures. At present, conservative observation is taken for small scale defect and surgical repair is resorted to large scale defect (more than 5 mm in diameter).

In the recent two years, the patients in our ophthalmologic department with mild exposure received combined treatment with topical bFGF and antibiotic

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drops, while the patients with moderate and severe exposure received the same combined treatment followed by amniotic membrane transplantation in two months. However, the patients with implant exposure did not receive the treatment with bFGF but with antibiotic drops or amniotic membrane transplantation 2 years ago. In order to evaluate the efficacy of bFGF for treatment of exposure of the orbital implants, in this retrospective study we compare the patients who received combined treatment with the patients without the application of bFGF.

MATERIALS AND METHODS

Patients

From Jan. 2000 to June 2006, we reviewed 41 patients (41 eyes) who suffering exposure of orbital implants in our eye center. Conjunctival defects for a scale of less than 5 mm, 5~10 mm (including 10 mm) and more than 10 mm in diameter are defined as mild, moderate and severe levels respectively. The cases are divided into study and control groups. The patients with mild exposure in study group received the combined treatment with topical bFGF and antibiotic drops and the patients with moderate and severe exposure in study group were given amniotic membrane transplantation after using topical bFGF and antibiotic drops for 2 months in recent 2 years. While the patients with mild exposure in control group were just treated with antibiotic drops and the patients with moderate and severe exposure in control group were subjected to amniotic membrane transplantation after using antibiotic drops 2 years ago. The study group with 15 males and 8 females aged 32~67 years, including 10, 9 and 4 eyes at mild, moderate and severe (Fig.1) levels respectively, which occurred from 2 weeks to 5 months after implantation and were composed of 9 hydroxyapatite (HA) implants (integrated orbital implants, San Diego, California, USA), 12 Medpor implants (Proex, USA) and 2 bioceramic implants (Guangze Corporation, Shanghai, China); the control group with 11 males and 7 females aged 16~63 years, included 9, 6 and 3 eyes at mild, moderate and severe level respectively, which occurred from 2 to 4 months after implantation and were composed of 7 HA implants and 11 Medpor implants (Tables 1 and 2).

Table 1 The demographic data of patients

		Study group	Control group
Total number		23	18
Gender	Female	8	7
	Male	15	11
Age	<20 years	0	1
	20~50 years	19	15
	>50 years	4	2
Enucleation indication			
Painful blind eye		6	7
Ruptured globe		14	9
Endophthalmitis		2	1
Malignant tumor		1	1
Implant material			
HA		9	7
Medpor		12	11
Bioceramic		2	0
Implant size			
18 mm		2	1
20 mm		5	2
22 mm		16	15

Table 2 The occurring time and degree of the implant exposure

	Study group	Control group
Exposure time after implantation		
2~4 weeks	3	1
1~2 months	12	11
2~4 months	7	6
>4 months	1	0
Exposure degree		
Mild	10	9
Moderate	9	6
Severe	4	3

Materials

The bFGF drops (12000 AU/5 ml) were manufactured by Dongda Biologic Pharmacy Company, Zhuhai, China.

Preparation and preservation of human amniotic membrane: informed consent was obtained and the donor was screened to exclude risk of transmissible infections such as human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus, chlamydia, cytomegalovirus and Treponema pallidum infections. The placenta was dipped in a 1600 U/ml solution of

gentamicin for 15 min after being washed with normal saline. Then amniotic membrane was separated with chorion and dipped in balance solution for 5 min. With the epithelial surface up, the amniotic membrane was pruned into 4 cm×5 cm and 3 cm×4 cm pieces without folds or tears, and then dehydrated in pure glycerol for 24 h. Later the amniotic membrane was transferred for storage in another bottle of pure glycerol at 4 °C. At the time of transplantation, the amniotic membrane was washed by normal saline and kept in a 300 U/ml solution of gentamicin for 30 min for reversion.

Methods

Topical antibiotic drops were administered for all cases in the same way. For the study group, we added topical bFGF drops 6 times per day, one drop at a time. For the moderate and severe cases in study group, we performed operations to repair the exposure of orbital implants with prepared amniotic membrane 2 months later. For the control group, mild cases received topical antibiotic drops only and moderate and severe cases received the same amniotic membrane transplantation after using topical antibiotic drops for 1 week.

After topical infiltration anesthesia, the conjunctiva was undermined circumferentially from the Tenon's layer around the area of the exposure. An amniotic membrane graft measuring 20% more than the conjunctiva defect area was fashioned to overlap the Tenon's layer. The graft was placed onto the surface of the implant and the edges of the graft were inserted between the Tenon's capsule and conjunctiva. The epithelial surface of the amnion was positioned toward the conjunctiva. The amniotic membrane was sutured to the Tenon's layer with 10-0 nylon sutures. The conjunctiva was then closed over the amniotic membrane with 10-0 nylon sutures (Fig.2). After removing residual air and fluid, antibiotic ointment was applied, followed by an eye patch.

All patients in both groups received the same postoperative medication regimen, beginning with systemic antibiotics, dexamethasone and a sterile dressing for 3 d. Later, all patients received topical antibiotic drops 4 times per day. A follow-up examination with slit lamp microscope and fluorescein dyeing to observe conjunctival epithelium once a week for 12 weeks was made.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 software (SPSS Inc., Chicago, USA). Age and scale of exposure variables were compared through the *t*-test. The constituent ratio of different types of implants between the study group and control group were compared through the chi square test. The healing rate of the two groups was compared by the Fisher exact test.

RESULTS

The average age of the study group and control group was (41.83±7.96) and (39.39±10.56) years respectively without statistical difference (t=2.02, P=0.40). The average scale of exposure before intervention in the two groups was (7.83±4.44) and (7.50±4.58) mm in diameter respectively without statistical difference (t=2.02, P=0.62). The constituent ratio of different types of implants between the two groups showed no statistical difference (χ^2=1.709, P=0.425).

The renascent conjunctival epithelium in the mild cases was observed on the edge of the defect one week after treatment in the study group. It grew centripetally at about 0.5~1.5 mm per week and all 10 mild cases healed completely during the period of follow-up observation. While 4 cases of mild exposure in the control group appeared as rolling inside growth of the renascent conjunctival epithelium and enlargement of the defect, which was repaired by surgery at last. The healing rate of the study group and control group for mild cases (Table 3) was 100% and 55.6% respectively with statistical difference (P=0.033).

The centripetal growth of the renascent conjunctival epithelium of about 0.5~3 mm was observed 2 weeks after treatment with bFGF (Fig.3) and renascent granulation tissue was observed on the surface of implants at 7~8 weeks after treatment for the moderate and severe cases in the study group. After the amniotic membrane repair surgery, only a case of dissolving transplanted amniotic membrane and failure of the conjunctival epithelium healing occurred. The area over the exposed implant was completely conjunctivalised in the other cases (Fig.4). While 3 of the 9 moderate and severe cases in the control group

showed dissolvation of the transplanted amniotic membrane and enlargement of the defect during 12 weeks. The healing rate of the study and control group for moderate and severe cases (Table 3) was 92.3% and 66.7% respectively with no statistical difference (P=0.167).

Table 3 The comparison of healing rate (%) between the study group and the control group

Exposure degree	Study group	Control group	P
Mild	100 (10/10)	55.6 (5/9)	0.033
Moderate and severe	92.3 (12/13)	66.7 (6/9)	0.167

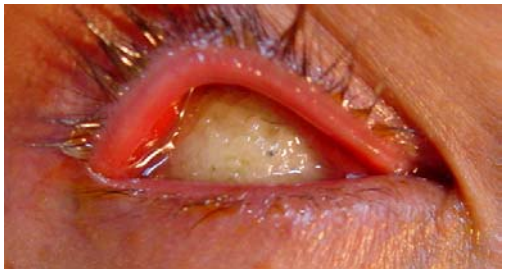

Fig.1 The pre-treated figure of severe implant exposure

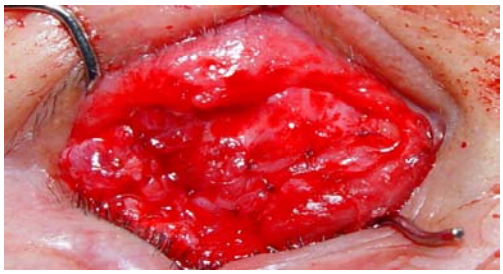

Fig.2 The graft was placed onto the surface of the implant and the edges of the graft was inserted between the Tenon's capsule and conjunctiva. The epithelial surface of the amnion was positioned toward the conjunctiva. The amniotic membrane was sutured to the Tenon's layer with 10-0 nylon sutures

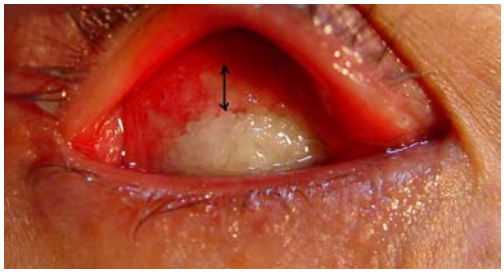

Fig.3 The growth distance of the conjunctival epithelium 2 weeks after the treatment with bFGF

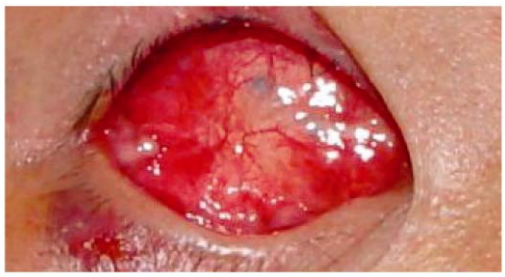

Fig.4 Healed postoperative appearance of the same patient with longer follow-up of Fig.3. The area over the exposed Medpor was completely conjunctivalised

DISCUSSION AND CONCLUSION

Porous orbital implants have advantages of excellent motility and biocompatibility, low incidence of exposure, displacement and foreign body reaction. Fibrovascular ingrowth of the implant offers excellent movement and prevents infection, exposure and displacement. Recently, porous orbital implants are the most commonly used orbital implant material. In spite of improvement in surgical technic and implant material, exposure of the implants is still the most notable complication at incidence rate of 1%~21.6% (Oestreicher *et al*., 1997; Shields *et al*., 1994). Exposure is initially treated conservatively. If exposure persists and the defect diameter is more than 5 mm, surgical treatment is indicated, including use of different materials, such as scleral patch grafts, bucca or lip mucosa, or dermis fat grafts (Tawfik *et al*., 2005; Sagoo and Olver, 2004). However, the problems of secondary contraction and survival exist. Lee-Wing (2003) reported amniotic membrane may be useful for the treatment of HA orbital implant exposures. Our previous research confirmed that preserved amniotic membrane transplantation for reconstruction of conjunctival sac combined with orbital implantation is safe and effective in degree I and degree II conjunctival sac constriction (Cui *et al*., 2005). The basement membrane of amniotic membrane, which contains almost the same components and structure as the conjunctiva, can promote the migration of the epithelial cell centripetally around the defect, differentiate, and then cover the surface completely. Despite its peculiar advantage, repair of exposure using amniotic membrane may fail sometimes, as a result of incomplete fibrovascular ingrowth of the implants. Yang and Wang (2005) reported that the success rate

of amniotic membrane transplantation for implant exposure is 82.6%.

Many factors are thought to cause orbital implant exposure (Custer and Trinkaus, 2007), but much evidence supports that delayed fibrovascular ingrowth into the porous orbital implant is the most important factor. Goldberg and Holds (1992) found that there was no fibrovascular ingrowth at the anterior pole when the anterior pole of the implant was exposed, and concluded that more fibrovascular ingrowth into implants will lead to less exposure of the implants. bFGF composed of 146 amino acids is a kind of multifunctional cytokine, which can enhance the differentiation, proliferation, migration and chemotaxis of vascular endothelial cells. Yang *et al*.(1997) confirmed bFGF can induce the neovascularization of cornea and Li *et al*.(1998) confirmed bFGF can promote the reparation of the epithelium of the alkali-injured cornea. Nicaeus *et al*.(1996) reported that bFGF can accelerate the growth of endothelial cells into HA orbital implants. In our research, renascent conjunctival tissue was observed on the edge of the defect at a week after combined treatment with topical bFGF and continued to grow centripetally. The mild cases in the study group finished healing completely during the follow-up 12 weeks observation, which showed statistical difference from the control group. It can be concluded that bFGF can promote the repair of implant exposure through enhancing the growth of conjunctival epithelium. The rolling inside growth of conjunctival epithelium in the control group may be attributed to inhibition at the contact side of the conjunctival epithelium, or insufficient fibrovascular ingrowth of the implants. Although there is no statistical difference for healing rate of moderate and severe cases in the two groups, the study group showed relatively higher healing rate than the control group. In addition, we can observe that neovascularization emerged centripetally on the surface of implants after combined treatment with topical bFGF before the surgical repair in the study group. It suggests that bFGF can enhance the neovascularization of the implants, and provide a good basis for the growth of conjunctival epithelium and improve the conditions for surgical repair.

In conclusion, bFGF can promote obviously the healing of exposure of the orbital implants. Especially for the mild cases, it can be the first choice. For the moderate and severe cases, it can be administered before surgical repair to enhance neovascularization and increase success rate of surgical repair.

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