·Clinical Research·

Effect of corneal graft diameter on therapeutic penetrating keratoplasty for fungal keratitis

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Abstract

• AIM: To evaluate the effect of corneal graft diameter on therapeutic penetrating keratoplasty(PKP) for fungal keratitis.

• METHODS: A total of 116 patients (116 eyes) suffered from fungal keratitis underwent PKP at the Affiliated Hospital of Medical College Qingdao University from May 2006 to May 2010. They were divided into two groups according to the corneal graft diameter. 64 eyes' corneal graft diameter was 8.00mm or larger and 52 eyes' graft diameter was smaller than 8.00mm. The follow-up time was 2 years. The postoperative visual acuity and complications were documented and compared.

• RESULTS: Sixty-two (96.88%) eyes and fifty (96.15%) eyes preserved eyeballs respectively in two groups. There was no statistical difference in postoperative visual acuity (P = 0.961), corneal graft clear rate (P=0.132) or the incidence of recurred fungal infection (P=0.770) between two groups. But there was a higher incidence of graft rejection (P=0.020) and secondary glaucoma (P=0.039) in group with corneal graft diameter 8.00mm or larger.

• CONCLUSION: PKP is an effective treatment approach for fungal keratitis. There is a higher incidence of complications in large-diameter PKP for fungal keratitis.Effective, preventive and therapeutic measures can improve the prognosis.

• KEYWORDS: keratoplasty; penetrating; eye infection; fungal; corneal graft

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INTRODUCTION

Fungal keratitis is a severe cause of blindness in most developing countries, and it has become the leading cause of the infectious keratitis in most areas of China[1-4]. Most patients have a history of misdiagnosis and extensive application of broad-spectrum antibiotic and glucocorticoid which may result in a prolonged course, when penetrating keratoplasty (PKP) of large size graft is needed to preserve the eyeballs[3]. The diameter of the corneal grafts is decided by the size of ulcerations, and there were no detailed reports on therapeutic effect of patients using different size of corneal grafts. The present study mainly observed the follow-up results of patients with fungal keratitis who underwent PKP and compared the postoperative visual acuity and complications between patients whose corneal graft diameter was 8.00mm or larger and whose graft diameter smaller than 8.00mm[5].

SUBJECTS AND METHODS

Subjects A total of 116 patients (116 eyes) with fungal keratitis who underwent PKP in the Affiliated Hospital of Medical College Qingdao University and had 2 years' follow-up examination were recruited into this study (Table 1). There was no secondary glaucoma or perforation before surgery in patients of present study, and there was no statistical difference in newly corneal vessels areas between the patients of two groups (t=0.359, P=0.720, Table 2). Sixty-four eyes' corneal graft diameter was 8.00mm or larger from patients of 45 males and 19 females with averaged age of (52.14±1.68) years (ranged 12-82 years). Fifty-two eyes' corneal graft diameter was smaller than 8.00mm from patients of 38 males and 14 females with averaged age of (51.42±1.65) years (ranged 14-75 years). There was no statistical difference in gender (P=0.743) or age (P=0.718) between two groups. The following protocol was approved by Hospital's Ethics Committee.

Table 1 General characteristics of the 116 patients of the study

Patients whose graft diameter 8.00mm or larger

Patients	Gender	Age (a)	Graft size (mm)	Mic. Cul.	His. Exam. (fungal)	Recurred fungal infection	Rej	Sec. Gl.	Final VA	Graft status
CFS	M	43	8.00	Fus.	+		Y		0.08	Translucent
CRL	M	62	8.25	Fus.	+				FC	Translucent
ZJG	F	40	9.50	Fus.	+				0.10	Clear
WZC	M	62	9.00	Fus.	+		Y		0.25	Clear
XSJ	M	39	8.00	Asp.	+				0.25	Clear
MCF	F	40	9.25	Unk.	+				0.06	Clear
ZAZ	M	65	8.50	Fus.	+				0.10	Clear
YWP	F	50	8.00	Unk.			Y		FC	Turbidity
DJJ	M	48	9.50	Fus.	+	Y	Y	Y	HM	Turbidity
LJP	M	12	9.00	Asp.	+		Y		0.10	Clear
SYZ	F	56	8.25		+				0.15	Clear
SKH	M	59	8.25		+		Y	Y	FC	Turbidity
HFZ	M	27	9.00	Fus.	+				0.10	Clear
LCS	M	65	8.50	Unk.	+		Y		0.06	Clear
GZY	M	76	8.50	Unk.	+				0.20	Clear
CJ	F	44	9.50	Unk.	+	Y				Eyeball lose
WJH	M	55	8.00	Fus.	+				0.04	Clear
GZX	M	75	8.25	Fus.	+		Y		0.10	Clear
WYY	M	60	8.25	Can.	+				0.15	Clear
RYH	M	40	9.25	Can.	+		Y		0.06	Translucent
SZX	M	55	8.75	Asp.	+		Y		0.02	Clear
ZBL	M	37	8.00	Fus.	+	Y				Eyeball lose
QYX	M	40	9.50	Fus.	+				0.10	Clear
LRM	F	44	8.75		+			Y	0.08	Clear
LWM	M	60	8.25	Fus.	+	Y	Y	Y	HM	Turbidity
CZX	F	61	9.25		+				0.25	Clear
SQJ	M	17	8.50	Fus.	+				0.02	Clear
FWX	F	46	8.50	Asp.	+		Y		FC	Turbidity
HTX	M	52	8.50	Fus.				Y	FC	Turbidity
MJM	M	40	8.25	Can.	+				0.15	Clear
XB	M	46	8.00	Asp.	+		Y		0.06	Translucent
CXL	M	51	8.50	Fus.	+	Y	Y		HM	Turbidity
HQT	M	44	8.25		+				0.10	Clear
RWG	M	48	8.25	Fus.	+		Y		FC	Clear
ZSJ	M	57	8.50	Fus.	+				0.02	Clear
GQC	M	45	8.25		+		Y		FC	Translucent
LHX	F	61	8.25	Fus.	+				0.25	Clear
SMF	F	53	8.25		+		Y		FC	Turbidity
ZZG	M	56	8.00	Unk.					0.10	Clear
WSY	M	56	8.25	Fus.	+				0.10	Clear
LKT	M	56	8.50	Fus.	+		Y		FC	Clear
WCY	F	39	8.75	Asp.	+		Y		FC	Clear
JZH	M	38	9.00	Fus.	+				FC	Clear
LRA	M	82	8.75		+				0.40	Clear
WMY	F	64	9.50	Asp.	+	Y	Y	Y	HM	Turbidity
WCY	M	71	8.75		+	Y		Y	HM	Turbidity
YXL	F	46	8.50	Fus.	+		Y		FC	Clear
YCF	F	80	8.25	Asp.	+		Y		FC	Clear
FJQ	M	55	8.50	Fus.	+			Y	0.10	Clear
ZJS	M	45	8.50	Fus.	+				0.10	Clear
WCG	F	42	8.75	Unk.	+		Y		FC	Clear
ZSM	M	40	8.25	Fus.					0.15	Clear
WSR	M	57	9.50	Fus.	+				0.08	Clear
JLS	M	55	8.50		+		Y		FC	Translucent
CZX	M	44	8.00	Fus.	+				0.40	Clear
SHS	M	75	8.50	Unk.	+		Y		FC	Translucent
SMF	F	50	9.50		+				0.10	Clear
WRH	F	60	8.25	Fus.	+	Y	Y		HM	Turbidity
WQJ	M	46	8.25	Fus.	+				0.40	Clear
TFX	M	71	9.00	Unk.			Y	Y	FC	Turbidity
ZJB	M	53	9.25	Unk.	+				0.08	Clear
QYZ	M	68	8.00	Fus.	+				0.60	Clear
YZX	F	60	8.50		+		Y		FC	Translucent
CXZ	F	53	8.25	Fus.	+			Y	FC	Clear

Patients whose graft diameter smaller than 8.00mm										
Patients	Gender	Age (a)	Graft size (mm)	Mic. Cul.	His. Exam. (fungal)	Recurred fungal infection	Rej	Sec. Gl.	Final VA	Graft status
ZYS	M	57	7.00	Asp.	+				FC	Clear
XBZ	M	31	7.00	Fus.	+		Y	Y	HM	Turbidity
XYX	F	60	7.50	Fus.	+				0.08	Clear
ZRG	M	55	7.75	Fus.	+		Y		0.10	Translucent
TGM	M	38	7.50	Unk.	+				0.40	Clear
ZKY	M	67	7.50		+				FC	Clear
YHC	F	51	6.50	Unk.	+				FC	Clear
CSE	M	14	7.00	Can.	+				0.10	Clear
SZC	F	57	7.50		+	Y		Y		Eyeball lose
ZYQ	M	44	7.25	Fus.	+				0.15	Clear
SXL	F	51	7.50	Unk.	+				0.06	Clear
SKX	M	59	7.75	Fus.	+		Y		FC	Translucent
MYF	M	32	7.25	Fus.	+				0.25	Clear
SXG	M	59	7.25	Fus.	+	Y	Y		HM	Turbidity
ZSR	F	53	7.50	Fus.	+				FC	Clear
WXZ	M	49	7.50	Fus.	+				0.10	Clear
CML	F	51	7.75	Fus.	+				0.10	Clear
CLY	M	60	7.50		+		Y		FC	Translucent
TJG	M	65	7.75	Fus.	+		Y		0.08	Clear
LDJ	M	53	7.75		+				0.30	Clear
LLL	F	36	7.75		+				FC	Clear
HXQ	M	42	7.50	Fus.					FC	Clear
ZAC	F	62	7.75	Unk.	+	Y	Y		HM	Turbidity
WSS	M	39	7.75	Fus.	+				0.08	Clear
YWJ	M	62	7.50	Asp.	+				0.10	Clear
WYL	F	59	7.50	Asp.	+				0.10	Clear
PHJ	M	49	7.50	Unk.	+				FC	Clear
MCL	M	42	7.50	Can.	+				FC	Clear
WSJ	M	52	7.00	Fus.	+				0.08	Clear
WYT	M	61	7.25	Fus.	+		Y		0.02	Clear
YDF	M	51	7.75	Asp.	+				0.50	Clear
LXS	M	35	7.75	Fus.					0.10	Clear
CYL	M	54	7.50	Can.	+				FC	Translucent
GPX	M	50	7.00	Asp.	+				0.08	Clear
TXL	F	45	7.50	Fus.	+				FC	Clear
WXY	F	61	7.75	Fus.	+				0.20	Clear
LXY	M	52	6.75	Fus.	+				0.06	Clear
GQJ	M	35	6.50	Fus.	+				0.02	Clear
WGH	M	60	7.50	Fus.	+		Y		FC	Turbidity
JXX	F	53	6.25		+				0.02	Clear
SMY	F	48	7.75	Unk.	+				FC	Clear
LBJ	M	57	7.75	Fus.	+	Y	Y		FC	Turbidity
ZXS	M	51	7.75	Fus.	+				0.12	Clear
JZJ	M	39	7.50		+				0.08	Clear
WSM	M	56	7.50	Fus.	+				0.06	Clear
YXB	M	59	7.75	Fus.	+				FC	Clear
LAS	M	27	6.50	Fus.	+		Y		FC	Clear
CXL	M	76	7.50		+				0.15	Clear
CBL	M	60	7.75	Fus.	+				0.25	Clear
LMZ	M	65	6.50	Fus.	+		Y		0.02	Translucent
LJ	M	55	7.50	Fus.	+	Y				Eyeball lose
WYZ	F	75	7.75	Fus.	+				0.15	Clear

M: Male; F: Female; Mic. Cul.: Microbiological cultivation; His. Exam.: Histopathological examinations; Rej.: Rejection; VA: Visual acuity; FC: finger counting; HM: Hand movement; Sec. Gl.: Secondary glaucoma; Fus.: Fusarium; Asp.: Aspergillus; Can.: Candida; Unk.: Unknown fungal specie; Y: Yes. And the blank areas stand negative.

Table 2 Area of corneal neovascularization (% total corneal area) of patients in two groups preoperative

Group	Minimum	Area	Maximum
8.00mm or larger	2.13	16.16	8.16±3.61
Smaller than 8.00mm	1.96	16.36	7.93±3.25

Methods

Diagnosis and treatment prior surgery The diagnosis of fungal keratitis was based on the case history, clinical features, identification of fungal elements and cultivation from corneal scraping elements, *etc*. Sensitive antifungal eye drops were administered according to the fungal species and drug sensitivity test.

Surgery indications There was no significant effect to appropriate topical and systematic antifungal medicine

treatment after the usage of 48-72 hours; the size of ulceration was over 6.00mm, and the depth of ulceration reached deep matrix; anterior chamber hypogyny aggravated after medical treatment [6].

Surgery treatment Donor corneas were cry preserved. All operations were performed by one experienced clinical doctor. The lesions of corneas were excised by trephines which were 0.50-1.00mm larger than the diameter of ulcerations. The excised corneal buttons were submitted to microbiological cultivation and histopathological examinations. The fibrous exudative membranes before iris and lens were cleared away and the anterior chamber, the posterior chamber and anterior chamber angle should be carefully washed away. Peripheral iridectomy was given when inflammatory reaction was severe. Corneal grafts were 0.50mm larger than graft bed. The donor cornea was sutured to the graft bed with 10-0 nylon line. Balanced salt solution was injected into the anterior chamber to form sealing status.

Treatment after surgery Tropic amide was used for dilating pupils. Antifungal eye drops were used for about 3 months after surgery. Sutures were dermaled out 6 months after surgery or when suture loosening or new vessels entering.

Diagnosis and treatment of recurred fungal infection Recurred fungal infection can be diagnosed by emerging infiltration of graft bed, corneal graft and emerging of anterior chamber hypopyon. Hypha can be found on recurrence focus. Patients who were diagnosed recurrence were given antifungal eye drops one time every two hours, and severe ones were given subconjunctival injection of antifungal medicine. Secondary PKP or enucleation of eyeball was performed when antifungal treatment could not control recurrence.

Diagnosis, grouping and treatment of graft rejection Graft rejection can be grouped into 3 types: 1) epithelial rejection: the epithelial rejection line appears; 2) stromal rejection: stromal rejection can be represented by stromal infiltrates and vessels; 3) endothelial rejection: cellular infiltrates aggregate on the endothelium which can appear as scattered deposits or a distinct line known as the Khodadoust line appears [7]. Graft rejection happened in two months after surgery was given cyclosporine A eye drops topically, and rejection happened surpass two months after surgery was given glucocorticoid and cyclosporine A eye drops topically. Severe rejection was given subconjunctival injection and oral application of glucocorticoid. The drug dosage was reduced slowly after rejection was controlled.

Diagnosis and treatment of secondary glaucoma The diagnosis of glaucoma after penetrating keratoplasty is based on intraocular pressure (IOP) in the early post-operative period, and IOP, optic disk changes, and progressive visual field changes in the late post-operative period [8,9]. The development of glaucoma was defined as an increase of IOP above 21mmHg and who required the introduction of antiglaucoma therapy (medical or surgical). When medical treatment was not effective, surgical treatments include trabeculectomy and cyclocryosurgery were given.

Statistical Analysis Statistical analysis was performed by using Kruskal-H text for visual acuity and graft transparency data and by using Chi-square text for other data. All tests were performed using software version 11.0 (SPSS Inc, Chicago, Illinois, USA). $P<0.05$ was considered as statistical difference.

RESULTS

Microbiological Cultivation and Histopathological Examinations Out of 116 eyes, 96 eyes (82.76%) were fungal culture-positive ones, and the two most common genera were Fusarium (63.54%) and Aspergillus (13.54%). Additionally, there were 16 culture-positive cases that could not be identified. Fungal was found in 109 eyes (93.97%) in histopathological examinations.

Recurred Fungal Infection There were 8 cases (12.50%) recurred fungal infections in patients whose corneal graft diameter was 8.00mm or larger, and 5 of 8 patients were cured by antifungal medical treatment, and 1 of 8 patient was cured by PKP and anterior chamber washing. A total of 62 (96.88%) out of 64 patients preserved the eyeballs successfully. Only 2 cases underwent enucleation of eyeball due to severe fungal endophthalmitis with no effective antifungal treatment after surgery. There were 5 cases (9.62%) recurred fungal infections in patients whose corneal graft diameter was smaller than 8.00mm, and 3 of 5 patients were cured by antifungal medical treatment, and 2 of 5 cases underwent enucleation of eyeball, so a total of 50 (96.15%) out of 52 patients preserved the eyeballs successfully. There was no statistical difference in the incidence of recurred fungal infection(χ^2=0.038, P=0.770).

Graft Rejection There were 28 (43.75%) out of 62 patients happened allograft rejection in patients whose corneal graft diameter was 8.00mm or larger, and 14 (22.58%) out of 62 patients happened allograft rejection at 2 weeks to 3 months after surgery. Out of 28, 24 patients happened rejection for one time, and the last 4 patients happened for two times (Table 3). After anti-rejection treatment, there were 18 grafts recover clear and 10 grafts became opacity. There were 12 (24.00%) out of 50 patients happened allograft rejection in patients whose corneal graft diameter was under 8.00mm, and 6 (12.00%) out of 50 patients happened allograft rejection at 2 weeks to 3 months after surgery. Out of 12, 11 patients happened rejection for once, and 1 patient happened for twice. After anti-rejection treatment, there were 8 grafts recover clear and 4 grafts became opacity. There was statistical difference in the

Table 3 Immune rejections' types and time distribution

Type	Corneal graft diameter larger than 8.00 mm			Corneal graft diameter smaller than 8.00 mm		
	2weeks-3months	3-6months	6months-2years	2weeks-3months	3-6months	6months-2years
Epithelial immune rejection	6	0	0	2	0	0
Matrix immune rejection	2	3	1	1	1	0
Endothelial immune rejection	6	7	7	3	4	2
Total	14	10	8	6	5	2

Table 4 Visual acuity of two groups %

Group	HM	FC	0.02-0.10	0.12-0.20	0.25-0.30	＞0.30
8.00mm or larger	9.67	30.65	38.71	8.06	6.45	6.45
Smaller than 8.00mm	6.00	34.00	40.00	10.00	6.00	4.00

incidence of graft rejection (χ^2=5.40, P=0.020). The incidence of graft rejection at time of 2 weeks -3 months postoperative between patients whose corneal graft diameter 8.00mm or larger with whose corneal graft diameter under 8.00mm had no statistical difference (χ^2=2.11, P=0.146). Among those allograft rejection cases whose corneal graft diameter were 8.00mm or larger and patients whose corneal graft diameter was smaller than 8.00mm mainly happened endothelial immune rejection (42.86% and 50.00% respectively) and epithelial immune rejection (42.86% and 33.33% respectively) from 2 weeks to 3 months after surgery, and 3 months later mainly happened endothelial immune rejection (77.78% and 80.00% respectively). Majority of implants became transparent following application of glucocorticoid and cyclosporine A.

Secondary Glaucoma There were 10 out of 62 patients happened secondary glaucoma in patients whose corneal graft diameter was 8.00mm or larger, and 2 out of 50 patients happened secondary glaucoma in patients whose corneal graft diameter was under 8.00mm. There was statistical difference in the incidence of secondary glaucoma (χ^2=4.27, P=0.039). IOP was controlled in 8 cases by drug treatment, and 2 cases needed long-term usage of drug treatment. Another 2 cases underwent trabeculectomy due to uncontrolled intraocular pressure and extensive goniosynechia, and one case recovered and one case underwent cyclocryosurgery.

Graft Transparency Out of 62 eyes, 42 eyes whose corneal graft diameter was 8.00mm or larger kept corneal graft clear, and 8 cases were translucent and 12 cases were turbidity. Out of 50 eyes, 40 eyes whose corneal graft diameter was smaller than 8.00mm kept corneal graft clear, and 5 cases were translucent and 5 cases were turbidity. There was no statistical difference in the corneal graft clear rate (Z=-1.508, P=0.132).

Visual Acuity There was no statistical difference in visual acuity between patients whose corneal graft diameter was 8.00mm or larger and patients whose corneal graft diameter was smaller than 8.00mm (Z=-0.049, P=0.961, Table 4).

DISCUSSION

Fungal keratitis is a severe cause of blindness in most developing countries, and its therapies include medical treatment and surgical treatment. Most patients have a history of misdiagnosis and extensive application of broad-spectrum antibiotic and glucocorticoid. When drug treatment has no effect, PKP is needed to preserve the eyeballs [3]. Surgical effects have correlation with the recurrence of fungal infection, allograft rejection and secondary glaucoma.

Our investigation indicated that there was no statistical difference in the incidence of recurred fungal infection between patients whose corneal graft diameter were 8.00mm or larger and patients whose corneal graft diameter were smaller than 8.00mm. PKP is effective to cure fungal keratitis. It is important to clear away the lesions including pseudopodium, satellite focus, immune ring, fibrous exudative membrane on the iris and the anterior capsule of lens and to wash away fungi in the anterior chamber angle and the anterior chamber for preventing the recurrence of fungal infection. When the fungal culture before surgery was negative, a postoperative culture and drug sensitivity test should be given. The antifungal treatments should be used before and after surgery. Once the manifestation of fungal recurrence is found, antifungal drug should be given immediately. During the study, we also observed that patients who underwent the recurrence of fungal infection accompanied with severe anterior chamber reaction had a high incidence of allograft rejection and secondary glaucoma. This may be related to anterior chamber-associated immune deviation destroyed by inflammatory reaction followed recurrence of fungal infection and trabeculae blocked by pigment particle freed by inflammation. The prevention and controlling of recurrence fungal infection play an important role after PKP for fungal keratitis.

Allograft rejection is an important case of graft failure[10,11]. Rejection reaction can be resulted by severe inflammatory reaction and not promptly used glucocorticoid, thereby

increasing the risk of graft rejection. Our investigation indicates that there was statistical difference in the incidence of graft rejection between patients whose corneal graft diameter was 8.00mm or larger and patients whose corneal graft diameter smaller than 8.00mm (P=0.029). This was in agreement with Xie L and Shi W 's research results [5,12]. Patients who underwent PKP with big implant usually had long time severe inflammation reaction which can drawn cells of the innate immune system from the vascular compartment into the cornea and destroy the blood aqueous barrier and anterior chamber-associated immune viation (ACAID). All these can induce allograft rejection. We observed that the incidence of graft rejection at early of 2 weeks -3 months in patients whose corneal graft diameter was 8.00mm or larger was higher than patients whose corneal graft diameter was under 8.00mm though there was no statistical difference, and graft rejection types were mainly epithelial rejection and endothelial rejection. Once the recipient epithelium replaced the donor epithelium, epithelial rejection did not tend to occur. This was correlated with Hori *et al* [13] report that donor corneal epithelium can lead to rapid early rejection. Rejection type was mainly endothelial rejection after operation 3-6 months which may be related with the strong antigenicity of endothelial cells that can induce delayed endothelial rejection. The epithelial and stromal type of rejection is easy to control, and the endothelial rejection has poor prognosis. Claerhout *et al* [14] reported that graft rejection treatment and endothelial cell protection had effective window period, a delay of 1 day can cause serious consequences. In present study, we avoided long-term epithelial coloboma which may cause non-specific corneal inflammation and neovascularization. Patients and their relatives paid attention to the follow-up and were educated about the prompted rejection symptoms. Timely diagnosis and timely anti-rejection therapy reduced the adverse consequences of rejection and improved the postoperative curative effect.

Glaucoma after penetrating keratoplasty is a frequently observed postoperative complication and is a risk factor for graft failure. PKP performed for inflammatory conditions are more likely to cause postoperative glaucoma [11], which may be related to inflammation preoperation, washing away of anterior chamber angle and high rate of graft rejection. In present study, we observed that there was a higher incidence of secondary glaucoma in patients whose corneal graft diameter was 8.00mm or larger than patients whose corneal graft diameter smaller than 8.00mm. Patients who underwent PKP of big implant usually had long-term severe inflammation reaction even with hypopyon which can plug the trabecular meshwork and long-term response to inflammatory stimuli closely related to trabecular meshwork edema. Operation with large diameter graft costs a longer time, and operations near the chamber angle structure have much more angular perturbation. In the research, we observed inflammatory response can promote peripheral iris adhesion, leading to secondary glaucoma and large diameter PKP had a high incidence of rejection, especially matrix and endothelial rejection with anterior chamber inflammation can cause secondary glaucoma. This may be related with rejection inflammatory cells, fibroblasts and iritis release of pigment particles blocking the trabecular meshwork and drainage channel[10].

PKP is an effective approach to preservation of eyeballs and restoration of visual function in patients with fungal keratitis, who cannot be treated by conservative therapy. PKP of big implant has a higher incidence of rejection reaction and secondary glaucoma, and those complications can influence each other. Inflammation reaction is the main cause of adverse reaction. Effective perioperative treatment can reduce the incidence and influence of complications.

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