Intravitreal Infliximab Injection to Treat Experimental Endophthalmitis

Deneysel Endoftalmi Tedavisinde İntravitreal İnfliksimab

Osman Ondas[1], Orhan Ates[1], Sadullah Keles[1], Kenan Yildirim[2], Orhan Baykal[1], Selina Aksak Karamese[3], Murat Karamese[4], Hakan Uslu[5], Mustafa Yildirim[6], Muhammet Emin Naldan[7], Irem Ates[8]

ABSTRACT

Objective: The purpose of this study was to compare the use of an intravitreal injection of infliximab and of dexamethasone combined with vancomycin to treat experimental endophthalmitis induced by *Staphylococcus epidermidis*.

Materials and Methods: The study was conducted between March 25 and April 13, 2012. Twenty-five six-month-old healthy rabbits were used, each weighing 2.5-3 kg. The rabbits were randomized into five groups with five animals per group. Endophthalmitis was induced by 0.1 mL (103 colony-forming units) *S. epidermidis* in all groups. In group 1, injection was not implemented after the occurrence of endophthalmitis. In groups 2, 3, and 4, the following intravitreal injections were given 24 h after the occurrence of endophthalmitis: group 2, 0.1 mg/0.1 mL vancomycin; group 3, 1 mg/0.1 mL vancomycin and 1 mg/0.1 mL dexamethasone; and group 4, 1 mg/0.1 mL vancomycin and 2 mg/0.1 mL infliximab. Group 5 was the control/uninfected group. The rabbits were clinically assessed each day for seven days. On day 9, a histopathologic evaluation was performed after enucleation.

Results: After a clinical evaluation, no statistically significant difference was found between the vancomycin+infliximab and vancomycin+dexamethasone groups (p>0.05). The difference was significant when both groups were compared with the vancomycin group (p<0.001). After the histopathologic evaluation, no statistically significant difference was found among the three groups (p>0.05).

Conclusion: An intravitreal injection of infliximab and of dexamethasone combined with vancomycin have similar clinical and histopathologic effects. To supplement the antibiotic treatment of endophthalmitis, infliximab in a safe dose range can be used as an alternative to dexamethasone to suppress inflammation and prevent ocular damage.

Keywords: Infliximab, dexamethasone, vancomycin, *staphylococcus epidermidis*, endophthalmitis

ÖZ

Amaç: Bu çalışmada tavşanlarda *Stafilokok epidermidis* ile oluşturulan deneysel endoftalmilerde vankomisin ile kombine; intravitreal infliksimab ile intravitreal deksametazonun etkinliklerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışma 25 Mart 2012-13 Nisan 2012 tarihleri arasında uygulandı. Çalışmada; 6 aylık, 2,5-3 kg ağırlığında, 25 adet sağlıklı tavşan kullanıldı. Denekler herbiri 5 tavşandan oluşan 5 gruba ayrıldı. Grup 1'e; 0,1mL (103 Colony Forming Units) *Stafilokok epidermidis* ile endoftalmi oluşturulduktan sonra herhangi bir tedavi uygulanmadı. Grup 2, 3 ve 4'e endoftalmi oluşturulduktan 24 saat sonra sırasıyla; 1mg/0,1mL vankomisin, 1mg/0,1mL vankomisin ve 1mg/0,1mL deksametazon, 1mg/0,1mL vankomisin ve 2mg/0,1mL infliksimab intravitreal olarak enjekte edildi. Grup 5 ise kontrol/nonenfekte grup olarak çalışmaya alındı. Denekler 1, 2, 3, 4, 5, 6 ve 7. günlerde klinik olarak değerlendirildi. 9. gün enükleasyon uygulanarak histopatolojik inceleme yapıldı.

Bulgular: Klinik değerlendirmede; vankomisin + infliksimab verilen grup ile vankomisin + deksametazon verilen grup kendi arasında karşılaştırıldığında istatistiksel olarak anlamlı farkın olmadığı (p>0,05), her iki grup sadece vankomisin verilen grup ile karşılaştırıldığında istatistiksel olarak anlamlı farkın olduğu görüldü (p<0,001). Histopatolojik olarak gruplar arasında yapılan karşılaştırmada; vankomisin + infliksimab, vankomisin + deksametazon ve vankomisin grupları arasında istatistiksel olarak anlamlı farkın olmadığı görüldü (p>0,05).

Sonuç: Endoftalmide intravitreal infliksimab ile intravitreal deksametazon uygulamasının klinik ve histopatolojik olarak benzer etkinlikte olduğu görülmüştür. İntravitreal uygulamada infliksimab deksametazona alternatif olabilir.

Anahtar Kelimeler: İnfliksimab, deksametazon, vankomisin, *stafilokok epidermidis*, endoftalm

Introduction

Endophthalmitis is an inflammatory condition that develops most often due to infection in the intraocular cavities. It is the postoperative complication of greatest concern following ocular surgery. In an endophthalmitis prophylaxis study, the European Society of Cataract and Refractive Surgeons found the rate of endophthalmitis to be 0.025% [1]. Coagulase-negative micrococci

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were found in 70% of culture-positive cases, followed by *Staphylococcus aureus* in 10%, other *Streptococcus* species in 9%, *Enterococcus* species in 2%, other gram-positive bacteria in 3%, and gram-negative bacteria in 6% [2].

The first intravitreal drug considered in treating endophthalmitis is vancomycin because of its low toxicity risk and wide antimicrobial spectrum [3]. In infectious endophthalmitis, in addition to bacterial destruction, the negative consequences of inflammation are of great concern. Killing microbiological agents is not synonymous with healing inflammation as dead microbiological agents and their residues continue to act as pro-inflammatory antigens. As a result, cell debris, toxic residues, and proteolytic enzymes begin to appear in the vitreous humour. Intravitreal corticosteroids can be used in conjunction with antibiotic treatment to reduce inflammation and its damage to the retina [4].

As in other inflammatory processes, TNF-α plays a central role in endophthalmitis [5]. In a study on experimental endophthalmitis induced by *S. epidermidis*, elevated levels of cytokines, such as TNF-α, IL-1 β, and IFN-γ, were found [6]. Infliximab is a TNF-α-specific monoclonal antibody and causes the death of cells which programmed with TNF-α [7, 8]. Infliximab can be used to treat endophthalmitis because it has a similar effect as steroids in treating inflammation. Recently, the speed and efficacy of infliximab in the treatment of many autoimmune diseases, including ocular involvement in Behçet's disease, has led to its increasing popularity. The use of intravitreal infliximab has gained attention because it is an effective and fast-acting treatment. In a study on seven groups with four rabbits per group, infliximab that was intravitreally applied at a dose of 2 mg/0.1 mL was shown to be safe [9]. In our study, we compared the efficacy of an intravitreal injection of infliximab and of dexamethasone combined with vancomycin in rabbits with experimental endophthalmitis induced by *S. epidermidis*.

Materials and Methods

The study was conducted at between March 25 and April 13, 2012. Twenty-five rabbits that were six-months old and weighed 2.5-3 kg were used in the study. The rabbits were housed in equivalent environmental conditions and were given the same food. The same preoperative preparation, anesthesia, and surgical technique were employed for each group. No complications, such as cataracts, vitreous hemorrhages, or retinal detachment, were observed during the clinical follow-up period.

The *S. epidermidis* strain used in this study was acquired from clinical isolates. The isolate was obtained from a medical microbiology laboratory and was derived from the blood culture of a patient with a primary diagnosis of sepsis. The proliferating strain was purified within 24 h in an automated blood culture system, after which bacteria were identified by traditional methods and with an automatic bacterial isolation system. The antibiotic disc sensitivity profile of the isolate showed susceptibility to methicillin and vancomycin. The isolate was incubated in 5% sheep blood agar for 24 h to obtain 2.5 mL × 4-10^3 colony-forming units (CFU) and was adjusted according to the McFarland scale to prepare bacterial suspensions for inoculation [10]. The rabbits were anesthetized by an intramuscular injection of 50 mg/kg ketamine hydrochloride. Following anesthetization, 0.1 mL (10^3 CFU) of the prepared *S. epidermidis* suspension was injected through a pars plana incision 2 mm from the corneal limbus to the middle vitreous of the rabbit's right eyes with a 30-gauge injector to induce experimental endophthalmitis. Intraocular pressure was immediately normalized with a different sterile 30-gauge injector that was made to enter the anterior chamber and when paracentesis was performed.

The rabbits were randomized into five groups with five animals per group. Except for the control group, a single dose of a specific treatment was injected with a 30-gauge injector into the middle vitreous of the rabbits' right eyes 2 mm from the corneal limbus. On day 3 after endophthalmitis induction, injections were administered to the groups as follows: group 1 (sham), enfected but no injection was given; group 2 (VAN), intravitreal injection of 1 mg/0.1 mL vancomycin; group 3 (VAN+DEX), intravitreal

injection of 1 mg/0.1 mL vancomycin and 1 mg/0.1 mL dexamethasone; group 4 (VAN+INF), intravitreal injection of 1 mg/0.1 mL vancomycin and a reportedly safe dose of 2 mg/0.1 mL infliximab [9]. Group 5 was the control/uninfected group and received no injection.

Starting on the first day after endophthalmitis induction, examinations of the anterior segment and fundus were performed daily by indirect ophthalmoscopy and biomicroscopy for seven days. On day 9, all rabbits were euthanized by an intraperitoneal injection of 100 mg/kg thiopental sodium, after which the rabbits' right eyes were enucleated for a histopathologic evaluation.

All eyes were fixed in 4% formaldehyde for 48-72 h in the histopathology laboratory and were then processed. Tissue samples were embedded in paraffin wax blocks for sectioning. Five-micrometer sections were obtained using a microtome and were mounted on slides for staining with hematoxylin and eosin. The stained slides were examined, and images were captured for all groups using an Olympus BH 40 light microscope with an attached camera. The level of inflammation and the presence of fibrin, exudation, and neutrophils were evaluated in the cornea and limbus, anterior chamber, ciliary body, vitreous, and choroid in the sections. Separate scores were given for each variable and were then totaled. The severity of endophthalmitis was then determined for each rabbit. A clinical evaluation and endophthalmitis scoring were conducted as described by Player et al. [11] (Table 1). The histopathologic evaluation results were scored as described by Meredith et al. [12] (Table 2).

Table 1. Clinical grading and scoring of endophthalmitis

| Score | Conjunctiva | Clinical grading | | |
		Cornea	Iris	Vitreous
0	Normal	Clear	Normal	Clear
1	Mild edema	Focal edema	Mild hyperemia	Cloudy
2	Edema and hyperemia	Diffuse edema	Distinct hyperemia	Fundus detail (-)
3	Severe reaction	Opaque	Synechia and irregularity	Fundus reflex (-)

Table 2. Histopathological scoring scale

Score	Cornea and limbus	Anterior chamber	Ciliary body	Vitreous	Choroid	Retina
0	Normal	Normal	Normal	Normal	Normal	No detachment
1	Mild inflammation	Fibrin, exudate, mild inflammation	Minimal inflammation	Fibrin and exudate only	Mild inflammation	Partial detachment
2	Moderate inflammation	Fibrin, exudate, moderate inflammation	Moderate inflammation	Some cellular infiltration	Moderate inflammation	Segmental detachment
3	Severe inflammation	Severe inflammation	Severe inflammation	Extreme cellular infiltration	Severe inflammation	Total detachment

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Table 3. Average clinical and histopathologic scores

Group	Average clinical score	Average histopathologic score
1	12	18
2	7.6	12
3	6	7
4	5.8	6
5	0	0

Table 4. Statistical comparison of the clinical scores between groups

		Sum of squares	df	Mean square	F	Sig.
		ANOVA				
Conjunctiva	Between groups	14.400	4	3.600	.	.
	Within groups	.000	10	.000		
	Total	14.400	14			
Cornea	Between groups	14.667	4	3.667	55.000	.000
	Within groups	.667	10	.067		
	Total	15.333	14			
Iris	Between groups	14.400	4	3.600	27.000	.000
	Within groups	1.333	10	.133		
	Total	15.733	14			
Vitreous	Between groups	18.400	4	4.600	8.625	.003
	Within groups	5.333	10	.533		
	Total	23.733	14			

Table 5. Statistical comparison of the histopathological scores between groups

		Sum of squares	df	Mean square	F	Sig.
		ANOVA				
Cornea and limbus	Between groups	15.600	4	3.900	.	.
	Within groups	.000	10	.000		
	Total	15.600	14			
Anterior chamber	Between groups	27.600	4	6.900	.	.
	Within groups	.000	10	.000		
	Total	27.600	14			
Ciliary body	Between groups	15.600	4	3.900	.	.
	Within groups	.000	10	.000		
	Total	15.600	14			
Vitreous	Between groups	14.400	4	3.600	.	.
	Within groups	.000	10	.000		
	Total	14.400	14			
Choroid	Between groups	18.000	4	4.500	.	.
	Within groups	.000	10	.000		
	Total	18.000	14			

Approval was obtained from the Local Animal Experiments Ethics Committee (27.01.2012-1/2) and the Local Surgeons Ethics Committee (09.03.2012-292/03). Animal rights were maintained in accordance with the "Guide for the Care and Use of Laboratory Animals."

Statistical analysis
Statistical analysis were performed using the Statistical Package for Social Sciences version 17.0 software (SPSS Inc.; Chicago, IL, USA). Differences among the groups and significance levels were determined using one-way analysis of variance, and $p < 0.05$ was considered to be significant. For multiple comparisons, Duncan's multiple range test was used.

Results
On day 1 after *S. epidermidis* inoculation, biomicroscopic examination revealed corneal edema and conjunctival edema and hyperemia in the rabbits' right eyes. On day 2, eyelid edema, conjunctival hyperemia, corneal edema, distinct hyperemia of the iris, and vitreous opacity were seen in the right eyes of all the rabbits except those in the control group, indicating the development of experimental endophthalmitis. On day 3, treatments were administered to the rabbits' right eyes according to group. On days 4-7, examinations of the anterior segment and fundus were performed by indirect ophthalmoscopy and biomicroscopy. Following euthanasia on day 9, the rabbits' right eyes were enucleated for histopathologic inspection. Average clinical and histopathologic scores were calculated for each group (Table 3).

In the clinical evaluation, there were no statistically significant differences found in conjunctival scores among groups ($p > 0.05$). In the cornea score comparison, there was no significant difference between the VAN+DEX and VAN+INF groups ($p > 0.05$), although both groups differed significantly from the VAN group ($p < 0.001$). Among the VAN, VAN+DEX, and VAN+INF groups, there were statistically significant differences in iris scores ($p < 0.001$) but not in vitreous scores ($p > 0.05$). When total scores and averages from the clinical evaluation were analyzed, there was no statistically significant difference between the VAN+DEX and VAN+INF groups ($p > 0.05$), although each group differed significantly from the VAN group ($p < 0.001$; Table 4).

In the analysis of the histopathology data, there were no statistically significant differences found between groups in cornea and limbus scores ($p > 0.05$), anterior chamber scores ($p > 0.05$), ciliary body scores ($p > 0.05$), vitreous scores ($p > 0.05$), or choroid scores ($p > 0.05$). There were also no significant differences in total scores and averages from the histopathologic evaluation among the VAN, VAN+DEX, and VAN+INF groups ($p > 0.05$; Table 5).

Discussion
Endophthalmitis is a serious and destructive complication that can arise following intraocular surgery, perforating injuries, or endogenic infection. The postoperative incidence of endophthalmitis has significantly decreased due to several factors, including the development of effective antibiotics, the use of aseptic/antiseptic

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practices, the improvement of surgical devices, and the shortened duration of operations. Recent advances in vitreoretinal surgery and the increased use of intravitreal antibiotics have resulted in better endophthalmitis prognosis. Factors that influence endophthalmitis prognosis are the virulence of the infecting organism, severity of inflammation, time elapsed between the onset of infection and initial treatment, and accompanying conditions [13]. Endophthalmitis can be caused by bacteria, fungi, or, more rarely, parasites. In general, although the frequency changes according to the type of endophthalmitis, the microorganisms encountered most often are *S. epidermidis, S. aureus, Propionibacterium acnes, Pseudomonas aeruginosa*, and *Haemophilus influenza* [14]. Coagulase-negative staphylococci are the most common cause, at a rate of 70%, in the etiology of postoperative bacterial endophthalmitis [2]. In our study, we induced experimental endophthalmitis by injecting 0.1 mL (10^3 CFU) *S. epidermidis* intravitreally into rabbit eyes [10].

The first line of treatment for intravitreal infection is the polypeptide antibiotic vancomycin. According to the results obtained by the Endophthalmitis Vitrectomy Working Group, a 1 mg/0.1 mL dose of vancomycin was found to be 100% effective against gram-positive bacteria [15]. We also used a dose of 1 mg/0.1 mL vancomycin that was intravitreally injected after the development of experimental endophthalmitis. In endophthalmitis, even after an antibiotic has rendered the infective agent inactive, inflammation causes most of the damage. Killing microbiological agents is not synonymous with healing inflammation as the dead microbiologic agents and their residues continue to act as pro-inflammatory antigens. As a result, cell debris, toxic residues, and proteolytic enzymes begin to appear in the vitreous. To minimize damage to the tissues near the retina caused by cell debris and the host response, administering anti-inflammatory treatment in combination with antibiotics is of utmost importance. Corticosteroids may be administered with antibiotics to reduce inflammation and the associated retinal damage [4]. TNF-α is a pro-inflammatory cytokine released from various cell types that is central to the immune system; it plays a role in immune development and hemostasis and in regulating cell activation, differentiation, and cell death. As in other inflammatory processes, TNF-α plays a central role in endophthalmitis [5]. Studies on *S. epidermidis*-induced experimental endophthalmitis have demonstrated elevated intravitreal levels of cytokines, such as TNF-α, IL-1 β, and IFN-γ [6].

Infliximab is a TNF-α-specific monoclonal antibody that neutralizes the effect of TNF-α by binding to its extracellular and transmembrane forms and that inhibits its binding to intracellular receptors; it prevents TNF-α-mediated programmed cell death [7, 8]. TNF-α is the key mediator in the pathogenesis of sepsis. Infliximab has been tested in the treatment of sepsis [16]. Because it has a similar effect in inflammation, infliximab, like steroids, can be used in the treatment endophthalmitis. An intravenous injection of infliximab can be used to treat refractory uveitis, panuveitis related to Behçet's disease, rheumatoid arthritis, psoriasis, systemic vasculitis, sarcoidosis, and Crohn's disease. In a study including five patients with ocular manifestations of Behçet's disease, systemic infliximab treatment resulted in a marked regression of symptoms, including retinal infiltrates and vasculitis, within 24 h and the complete remission of these symptoms within seven days [17]. In another study, 10 eyes of seven patients with chronic noninfectious uveitis were treated with an injection of 1.5 mg/0.15 mL intravitreal infliximab. In patients with noninfectious uveitis and significant macular edema and vision loss, the central retinal thickness may be reduced with infliximab treatment, which may lead to improvements in visual acuity [18].

Patients with neovascular age-related macular degeneration unresponsive to antivascular endothelial growth factor medications have shown improvement with repeated intravitreal infliximab injections [19]. In one elderly patient with peripheral ulcerative keratitis unresponsive to high doses of systemic steroids, ulcer healing was reported after repeated intravenous infliximab injections. Another patient with Mooren's ulcer and corneal perforation unresponsive to conventional immunosuppressant therapies was successfully treated with an intravenous infliximab injection [7]. In a study on seven groups with four rabbits per group, an intravitreal dose of 2 mg/0.1 mL infliximab was shown to be safe, and this dose was used in our study for the intravitreal injection [9]. In another study on 33 rabbits, an experimental uveitis model was induced, and the efficacy of infliximab at an intravitreal dose of 1 mg/0.1 mL was demonstrated [20].

There are no documented reports of using intravitreal infliximab injections to treat endophthalmitis. In this study, we compared the effects of an intravitreal injection of infliximab and of dexamethasone combined with vancomycin in a model of *S. epidermidis*-induced experimental endophthalmitis in rabbits. We would also like to mention that this was a non-blinded study, which could have generated observer bias.

Our results indicated that an intravitreal injection of infliximab and of dexamethasone combined with vancomycin have similar clinical and histopathologic effects. Steroids have well-known side effects such as glaucoma and cataracts [21, 22]. Although the cost is high to supplement antibiotic treatment of endophthalmitis, infliximab in a safe dose range can be used as an alternative to dexamethasone to suppress inflammation and prevent ocular damage.

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