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WHICH TOOL IS THE BEST GUIDE OPTIMIZE THE VORICONAZOLE DOSAGE: THERAPEUTIC DRUG MONITORING OR CYTOCHROME P450 POLYMORPHISM?
HANGİ ARAÇ VORİKONAZOL DOZUNU OPTİMİZE ETMEK İÇİN EN İYİ REHBERDİR: TERAPÖTİK İLAÇ İZLEME Mİ YOKSA SİTOKROM P450 POLİMORFİZMİ Mİ?

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ABSTRACT

Voriconazole (VCZ) is the drug of choice for invasive aspergillosis (IA). However, narraow the rapeuticrange and variable pharmaco kinetics can effect the success of the therapy. VCZ serum concentration is influenced by several factorin cluding CYP450 polymorphisms primarily by CY2C19. The rapeutic drug monitoring (TDM) of VCZ is highly recommended to check adequate serum concentrations. Here in, we investigated the usefulness of detecting CYP450 polymorphism. Patients with hematological malignancies were included in the study. CYP450 polymorphisms which are responsible for metabolism of VCZ were investigated using RT-PCR. TDM of VCZ was peformed using LC/MS/MS.11 patients were included in the study. Frequencies of CYP2C19 geno types are 27% for intermediate metabolizer; 36% rapid metabolizer, 18% for ultra rapid metabolizer, 18% for normal metabolizer. Two patient sexperienced dose related side effects and one of these patient's voriconazole blood concentration was supratherapeutic Although VCZ is the drug of choice for the treatment of IA, the variability of the pharmacokinetics can influence the success of therapy significantly. There fore implementing the pharmacogenetic testing and therapeutic drug monitoring to clinical practice might help clinicians to provide improved care to patients and improve treatment out comes.

Keywords: Antifungal activity, genotyping, voriconazole.

ÖZ

Vorikonazol (VCZ) invazifasperjilloziste (IA) tedavi seçeneklerinden biridir. Bununla birlikte ilacın darterapötik penceresi ve değişken farmakokinetiği tedavi başarısını etkilemektedir. VCZ kan konsantrasyonu kendisini metabolize eden CYP2C19 polimorfizmleri başta olmak üzere bazı faktörler tarafından etkilenmektedir. Terapötik ilaç izlemi (TDM) yeterli kan düzeyine ulaşılmasının kontrolünü sağlamaktadır. Bu çalışma kapsamında CYP450 polimorfizmlerinin saptanmasının faydasını araştırmayı hedefledik. Hematolojik malignitesi olan hastalar çalışmaya dahil edildi. VCZ' nin metabolizmasından sorumlu CYP450 polimorfizmleri RT-PCR ileve TDM ise LC/MS/MS ile yapıldı. 11 hasta çalışmayı tamamlayabildi. CYP2C19 genotiplerinin dağılımı orta dereceli metabolizör için %27, hızlı metabolizör için %36, ultra hızlı metabolizör için %18, normal metabolizör için %18 şeklindeydi. İki hasta dozla ilişkili istenmeyen etkiler yaşadı ve bu hastalardan birinin VCZ kan konsantrasyonu supraterapötik düzeydeydi. VCZ IA' da tedavi seçeneği arasında yer alsa da farmakokinetiğindeki belirgin değişiklik tedavisini etkilemektedir. Bu sebeple VCZ' nin TDM ve RT-PCR gibi metodlar klinikteki hekimin hastalara daha iyi bir bakım sağlamasında yardımcı olabilir, hastanın tedavisi daha iyi hale getirilebilir.

Anahtar kelimeler: Antifungal aktivite, genotipleme, vorikonazol

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INTRODUCTION

Voriconazole (VCZ) is a wide spectrum second generationtriazol eagent with potent activity against in vasive fungal infections including aspergillosis and candidiasis. It is the first choice drug of aspergillus infections.[1] These invasive infections are serious health problems for immune suppressed patients such as organ transplant patients and cancer patients.[2] VCZ has narrow therapeutic range and has interpatient variability. There fore, clinicians might fail to obtain an ideal therapeutic blood concentration which can result with treatment failure risk and dose dependent side effects including photo toxicity, hallucinations, neuropathy, periostitis, alopecia, and nail changes.[3,4] It shows non linear pharmacokinetics because of its limited elimination, and the blood concentration of VCZ is dependent on dosage. If VCZ dose is increased, the are aunder plasma concentration time curve will increase super proportionally, requiring dose adjustment to be performed carefully.[5,6] Therapeutic range of VCZ is 1.5-5.5 µg/mL. Checking drug-drug interactions, adjusting dosage according to renal function and body weight are important to achieve adequate VCZ concentrations. Another important factor is CY2C19 enzyme genotype that is responsible for VCZ metabolism and hepatic elimination.[7] Patients who are slow metabolizers might experience dose dependent toxicity such as hallucinations, visual disturbances, liver toxicity, photophobia, renal toxicity, and arrhythmia [QT prolongation) because blood concentrations of these patients are in supra therapeutic range.[8] On the other hand, patients who are fast metabolizers might not benefit VCZ at standard doses because of sub therapeutic serum concentrations.[9] According to our expectations, relation ship between genotype and VCZ serum level relation ship is given in Table1.

Although TDM of VCZ can guide for the optimum dosage, it is only available after several doses which can cause to miss a critical period. CYP450 polymorphism can be detected evenin patients who are at high risk for systemic fungal infections and can enable individualized dosage when VCZ treatment is required. Here in, we investigated the utility of each approach for optimizing VCZ treatment in patients with hematological malignancies. We aimed to see whether there are parallel results between TDM and genotyping results. This study was a replication effort and it is one of the studies to see genetic association with VCZ concentration in Turkish population.

MATERIALS AND METHODS

Patient volunteer selection

Voluntary patient only were included in the study. This study was approved by Erciyes University Clinical Trial Ethical committee, approval number 2015/101 and performed according to favorable clinical practice guide lines.

We conducteda prospective observational study in Erciyes University Hematology and Oncology Hospital. Patients participated in the study after giving written informed consent and the study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Eleven patients who were diagnosed with various hematological malignancies participated in the study (Table 2). Six of the sepatients required VCZ treatment during the course of their hospital stay. Treatment regimen was based on standard weight based dosing. Loading dose at 6 mg/kg/12 hours for the first day was followed by 4 mg/kg/12 hours as the maintenance dose. The treatment regimens were not modified according to pharmoco genetic testing and TDM results because the results of TDM and CYP450 polymorphism were available after their treatments were completed.

DNA Isolation

DNA was collected by whole blood, mouth was hand buccals wab (Table 2). Mouth was hand buccals wab sampling were used in patients who received allogeneic stem cell transplant[11] because the sepatients might have donor's DNA in their blood but not in their mouth epithelial cells. Whole blood sampling was used in non transplant patients. 2 mL blood were with drawned into K_2EDTA tubes ands amples were kept at 4°C until DNA isolation. DNAs were isolated on daily base and kept at -80°C until polymorphism screening. DNA isolation was performed using Roche High Pure Template Prepration kit (11796828001) per kit protocol.

Genotyping

CYP2C19*2 (19154G>A; rs4244285), CYP2C19*3 (17948G>A; rs4986893), CYP2C19*17 (-806C>T; rs12248560) all eles were determined by Roche light SNIP kit using polymerase chain reaction (PCR). This kit uses a hybridizing probe and melting curves were ana-

Table 1. Genotype and voriconazole serum concentration relation[10]

Genotype	Expected phenol type	Voriconazol level	Comment/Possible Solution
Primarily CYP2C19*17	Rapid metabloizer	Prophylactic use: Lower than therapeutic level (0.5 µg/mL) Treatment Lower than therapeutic level (1-2 µg/mL)	No response to treatment and systemic fungal worsening. /Dose should be increased or alternative medication should be considered
Primarily CYP2C19*2 or CYP2C19*3 Secondarily CYP2C9*2 or CYP2C9*3 or CYP3A4*1B or CYP3A5*3A	Slow metabloizer	Proflactic use: Higher than therapeutic level (0.5 µg/mL) Treatment Higher than therapeutic level (1-2 µg/mL); If higher than 4-5 µg/mL ALT and AST increases	Increased response to treatment. Controling fungal infection despiteun tolerable dose dependent side effects /Dose should be decreased or alternative medication should be considered

Table 2. Disease, DNA source and voriconazole use

PatientCode/Age	Disease	Genotyping material
P1/42	Acute myeloid leukemia	Whole blood
P2/23	Acutely mphocytic leukemia	Whole blood
P3/29	Acute myeloid leukemia	Whole blood
P4/39	Acute myeloid leukemia	Allogeneic transplant, buccal epithelial cell or mouth was hepithelial
P5/31	Hodgkin lymphoma	Whole blood
P6/57	Multiple myeloma	Whole blood
P7/57	Acute myeloid leukemia	Whole blood
P8/52	Acute myeloid leukemia	Allogeneic transplant, buccal epithelial cell, mouth was hepithelial
P9/72	Acute lymphocytic leukemia	Whole blood
P10/40	Aplastic anemia	Whole blood
P11/42	Non-hodgkin lymphoma	Very low leucocyte count (leucocyt openia) Buccal epithelial cell or mouth wash epithelial

lysed to determine single nucleotide polymorphisms (SNP). If none of these all eles were detected, patient were accepted as CYP2C19*1 genotype.

Therapeutic drug monitoring of voriconazole

Sampling for TDM was started at second day of VCZ treatment in patients who received intravenous (iv) treatment where as TDM was started at the fourth day in patients who received oral VCZ (Table 3). Samples were collected into K_2EDTA tubes and kept at 4^{o}C until plasma isolation. Plasma samples were kept at -80^{o}C and sent to an externall abnamed Toksilab Medical Diagnositc Labratory (Istanbul) under cold chain storage eusing dryice. VCZ levels were detected with LC/MS/MS. While concentrations lower than 1 µg/mL was accepted as sub therapeutic concentration, the concentrations higher than 5.5 µg/mL were accepted as supra therapeutic concentration.[12-14] Potential drug drug interactions between VCZ and co-administered drugs were checked by using lexicomp drug interactions module in updated database. All the data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Statistical analysis

Eleven patients with ages ranging from 23 to 70 were included in the study. Descriptive analysis was performed using Systat Sigma Plot software ver 12.0 and data normal distribution was tested using Shpirowilk test. Statistical significance was accepted as p> 0.05. Allele frequency was calculated by dividing the numbers of the patients with regarding allele by the number of all the patients and the data was presented as percentage of n value.

RESULTS

Five out of 11 patients were male and all of them were Caucasian. The Mean age of the patients was 43.2±14.76 years. Most common underlying disease was acute leukemia and two patients received allogeneic stem cell transplantation (Table 2). VCZ treatment was administered to six patients diagnosed with invasive pulmonary aspergillosis. All genotyping results regarding CYP2C9, CYP2C19, and CYP3A4 are listed in Table 4. The Patients were hospitalized and on other medications but none of these medications caused drug interactions with VCZ through CYP2C19. In our study, 4 patients (P1,P5, P8,P9) had *1/*17 alleles and they were heterozy-

Table 3. Voriconazole TDM sampling chart

Voriconazole dosing regime and sampling time						
Loading dose (6mg/kg) and maintenance dose (4mg/kg) iv infusion (2x1)						
1st day	2nd day	3rd day	4th day	5th day	6th day	7th day
$t_0$sampling (5mL)	*	*	*	*	*	*
Standard oral dosing 2 x 200 mg or 2 x 4 mg/kg iv						
1st day	2nd day	3rd day	4th day	5th day	6th day	7th day
$t_0$sampling (3mL)	- No sampling	- No sampling	** C_{ss} achieved	** C_{ss}	** C_{ss}	** C_{ss}

* Blood sample could be taken 1 h before dosing for Cssmin sample (5mL), 5 min after dosing for Cssmax sample (3mL)
** Blood sample could be taken 1 h before dosing for Cssmin sample (5mL), 1 h after dosing for Cssmax sample (3mL)

Table 4. CYP2C19, CYP2C9,CYP3A4,CYP3A5 genotyping results

Patient-code	CYP2C9*3 A>C rs1799853		CYP2C19*2 G>A rs4244285		CYP2C19*3 G>A rs4986893		CYP2C19*17 C>T rs12248560		CYP3A4*1B A>G rs2740540		CYP3A5*3A A>G rs776746		Genotype	Voriconazole blood concentration (µg/mL)		
	Tm1 A	Tm2 C	Tm1 A	Tm2 G	Tm1 G	Tm2 A	Tm1 T	Tm2 C	Tm1 A	Tm2 G	Tm1 G	Tm2 A		Cssmin	Cssmax	Ctoxic
P1	50.49	-	-	57.38	56.97	-	50.49	60.10	51.81	-	55.65	-	CYP2C19*1/*17. CYP3A5*3A/3A			
P2	50.47	-	-	57.29	57.00	-	50.47	-	51.78	-	55.59	-	CYP2C19*17/ *17.CYP3A5*3A/3A			
P3	60.09	-	-	57.33	57.04	-	-	60.09	51.80	-	60.74	-	CYP3A5*3A/3A			
P4	60.12	-	51.89	57.22	56.96	-	-	60.12	51.82	-	55.60	-	CYP2C19*1/ *2.CYP3A5*3A/3A	1.14	2.12	-
P5	50.32	-	-	57.00	56.65	-	50.32	59.87	51.65	-	55.35	-	CYP2C19*1/ *17.CYP3A5*3A/3A	3.87	4.94	-
P6	50.44	-	51.67	56.94	56.67	-	50.44	60.02	51.54	-	55.25	60.56	CYP2C19*2/ *17.CYP3A5*1/3A	3.75	5.90	-
P7	50.67	-	-	57.36	57.01	-	50.67	-	51.81	-	55.64	-	CYP2C19*17/ *17.CYP3A5*3A/3A	3.29	5.44	-
P8	50.26	-	-	56.93	56.56	-	50.26	59.78	51.75	-	55.31	-	CYP2C19*1/ *17.CYP3A5*3A/3A	-	-	0.94
P9	50.68	-	-	57.39	57.12	-	50.68	60.28	51.35	-	55.63	-	CYP2C19*1/ *17.CYP3A5*3A/3A			
P10	59.49	-	51.40	56.62	56.22	-	-	59.49	51.27	-	54.94	-	CYP2C19*1/ *2.CYP3A5*3A/3A	-	-	11.76
P11	59.49	-	-	56.70	56.44	-	-	59.49	51.03	-	54.90	60.11	CYP3A5*1/3A			

Tm: melting temperature A: Adenine, G:Guanine, C:Cytosine, T: Thymine, $C_{ss:}$Steadystate concentration, C_{toxic}: sample collected when toxicity observed

goticrapid metabolizer (frequency, 36%). 2 patients (P2,P7) had homozygotic *17 allele and they were ultra rapid metabolizers (frequency, 18%), 2 patients (P4,P10) had *1/*2 alleles, one patient (P6) had *2/*14 alleles and they were intermediate metabolizers (frequency, 27%), 2 patients (P3, P11) had *1/*1 alleles and they were normal metabolizers (frequency, 18%).

All patients were normal metabolizers in terms of CYP2C9, CYP3A4, and CYP3A5.

All of TDM, the relation ship between genotyping and side effects is presented in Table 5. 6 of them needed VCZ treatment during their hospital visit. VCZ concentration of P4 and P5 were in normal ranges, and these patients did not experience VCZ related toxicity. These patients' genotype and VCZ levels were not correlated with each other. P6 and P7 blood concentrations were slightly above the therapeutic range and it seems that the genotype of these patients did not affect VCZ serum concentration.

Patient 8's genotype was rapid metabolizer and in parallel with this, VCZ blood concentration level was lower than expected. Despite that low concentration of VCZ, the patients experienced side effect at 3rd day of standard dosing treatment.

Patient 11 was geno typed as a normal metabolizer and VCZ level was above therapeutic range. Despite this high concentration, no hepatoxicity was detected. This patient experienced side effects on the 2nd day of treatment 1 hr after maintenance dose was given, and there fore blood sample was collected when the toxicity was recognized. This patient was on amphotericin B before VCZ treatment. Genotype and VCZ level was not compatible with achother. Interestingly these two patients did nothave dose related toxicities such as hepatoxicity, high bilirubin, AST, ALT level, etc. The treatment protocol of patient 8 is presented in Table 6. According to drug interaction data there is no interaction with VCZ. Despite the low blood concentration of VCZ, the patient experienced hallucination on the 3rdday of standard dosing regimen. Instantaneous blood sample VCZ level was low although the patient experienced hallucination. According to patient's treatment protocol no drug interactions were detected. Another reason for psychiatric side effects seen in patients might be acyclovir. According to the product information sheet, hallucination occurs very rarely after acyclo viruse at therapeutic doses.[15] There fore, patients might experience this side effect because of acyclovir instead of VCZ. Renal function plays an important role in terms of acyclovir toxicity and it is reported that dose should be adjusted carefully if renal function is impaired[16]. In our case, the patient's renal function was normal and acyclovir was being dosed accordingly but acyclovir concentration was not measured. Patient 11 was genotyped as normal metabolism and blood VCZ level was above the rapeutic window. Despite this high concentration, no hepatoxicity was detected. This patient experienced side effects on the 2nd day of treatment 1 hr after maintenance dose was given and blood sample was collected when the toxicity was recognized. This patient was using fluconazole against Candida infection. After resistance was observed, antifungal treatment was replaced by VCZ. It is

Table 5. CYP2C19 Genotyping results TDM and side effect relation

Patientcode	Disease	Expected Genotype of CYP2C19[10]	Voriconazole level (1-4 µg/mL)			Voriconazole dosings cheme	Side effects probably related to voriconazole
			Cssmin	Cssmax	Ctoxic		
P4	Acute myeloid leukemia Allogenic transplant	CYP2C19*1/*2 (Intermediate metabolizer)	1.14	2.12	-	iv 2 x 6 mg/kg loading and 2 x 4 mg/kg maintenance dose	None
P5	Hodgkin's lymphoma	CYP2C19*1/*17 (Rapid metabolizer)	3.87	4.94	-	iv 2 x 6 mg/kg loading and 2 x 4 mg/kg maintenance dose	None
P6	Multiple slyphoma/ Autologous Transplant	CYP2C19*2/*17 (Intermediate metabolizer)	3.75	5.90	-	iv 2 x 6 mg/kg loading and 2 x 4 mg/kg maintenance dose	None
P7	Acute myeloid leukemia	CYP2C19*17/*17 (Ultra rapid metabolizer)	3.29	5.44	-	iv 2 x 6 mg/kg loading and 2 x 4 mg/kg maintenance dose	None
P8	Acute myeloid leukemia. Allogenic transplant	CYP2C19*1/*17 (Rapid metabolizer)	-	-	0.94	2x200 mg standard dosing	Hallucination and nightmare that continue whole night
P11	Non-Hodgkin's lymphoma Autologous Transplant	CYP2C19*1/*1 (Normal metabolizer)	-	-	11.76	iv 2 x 6 mg/kg loading and 2 x 4 mg/kg maintenance dose	Visual disturbances. photophobia

Clinical Pharmaco genetics Implementation Consortium guide line supplement S1 for diplo types is used for determining genotype.

known that VCZ's in vitro efficacy is higher than fluconazole against Candida spp.[17] There fore, antifungal treatment choice was right in this case but supratherapeutic levels of VCZ might have caused visual side effects. According Table 6, there is not anyother medication that causes this type of effect in patient's treatment plan.

tients who experienced VZ toxicity were P8 and P11.P11's expected phenotype was normal metabolizer and despitehat serum VCZ level was at supra therapeutic level. P8 was rapid metabolizer and VCZ blood level was sub therapeutic. According to these two patient's results genotype is not always a good tool to predict

Table 6. P8 and P11 treatmen tprotocols

Initials	Patient code	Sampling type	Medications being used at that week	Dosing regime	Active ingredient	Toxicity
S.F	P8	Potential toxicity	Duphalac 670 mg	3x1	Lactulose	Hallucination andnightmare thatlastswhol enight
			Aklovir 200 mg	2x1	Acyclovir	
			Antepsin	4x1	Sucralfate	
			Leucostim 45 MIU	1x1	Filgrastim	
			Desferal 0.5g	1x1	Deferoxamine	
			Nevofam 20 mg	2x1	Famotidine	
			Methylprednisolone 250 mg	1x1	Methylprednisolone	
			Urikoliz	1x1	Allopurinol	
Initials	**Patient code**	**Sampling type**	**Medications being used at that week**	**Dosing regime**	**Active ingredient**	**Toxicity**
H.K	P11	Potential toxicity	Asirax 250 mg	2x1	Acyclovir	
			Leucostim 30 MIU	1x1	Filgrastim	
			Maxipen 1 g	3x1	Meropenem	
			Metronidazole 500 mg	4x1	Metronidazol	Photophobia, visualdisturbances
			Protaz 400 mg	1x1	Pantoprazole	
			Setrex 3 mg	2x1	Granisetron	
			Vancomax 500 mg	2x1	Vancomycin	

DISCUSSION

Personalized medicine has two key factors, which are choosing the right drug and adjusting the dosage for the patient appropriately. Drugs like VCZ which have irreversible organ toxicity, non liear kinetics and narrow therapeutic range, metabolized by CYP450 enzymes need additional approaches like therapeutic drug monitoring and pharmacogenomic analysis for correct dosead justing. These two tools might be used together to fully individualize the treatment especially for CYP450 polymrophisms. Although adjusting the dosage using only pharmacogenomic data might be considered but blood concentration should also be checked to see whether or not the drug is at therapeutic range. Besides blood sample can be drawn instantly when a suspicious reaction occurs to determine whether the drug in question is the real cause of this suspicious reaction. We conducted our study according to this logic and we collected momentary blood samples when a suspicious reaction occurred during the standard therapeutic drug monitoring process. Although genotyping is not always correlated with TDM, we observed itin our study. Padrug concentration because it should be remembered that when a genotyping analysis is performed, it only gives an idea about the patient's expected phenoyte, not real life results. In addition analyzing the phenotype is harder than TDM and genotyping because samples should be taken when patient is not receiving any treatment, and phenotype is affected by environmental factors so much. In addition, P4,P5,P6,P7 did not experience any VCZ toxicity and their VCZ concentrations were in therapeutic ranges. It seems that genotype did not affect VCZ concentration.

The limitation of our study was the number of the patients. It was because systemic fungal infections and concomitant chronic diseases might be a cause of death in hematological malignancy patients and during the study we genotyped nearly 50 patients but most of them were deceased and thus the frequency of the patients who suffered from fungal infections were low. For these reasons the number of the patients was limited in our study.

In general, clinicians observe toxicities in the patients who have hematological malignancies. Medications in

the treatment plan should be monitored carefully in terms of toxicities, blood concentration and inter individual variances. In patients who have malignancies and use multiple drugs side effect monitoring sholud be performed regularly. TDM is such a nice tool that it can be used to show whether the reactions in patients are actually caused by the drug concerned or other factors. The rapeutic drug monitoring might help monitor patients because in one of our cases hallucination was probably caused by acyclovir instead of VCZ, because the VCZ was at sub therapeutic concentration[18]. In another case therapeutic drug monitoring revealed that VCZ is the cause of hallucination. In addition, at supra therapeutic VCZ level, these patients are potentially at risk for other dose dependent side effects such as hepatoxicity. Although health authorities do not force to test for CYP2C19 polymorphisms for VCZ, pharmacogenomics might be a good tool to check potential side effects that might be experienced. It is clear that the patients with homozygotic CYP2C19 slow metabolizer will highly experience dose dependent side effects of VCZ and other medications which are inactivated by this CYP2C19. If patient's pharmacogenomic data is available at clinician's hand, this data should be used when other CYP2C19 substrates are prescribed as well. Consequently, one time genotyping is good for adjusting or having a clue for potential dose related side effects of all medications. Additionally, therapeutic drug monitorin gshould be added to support polymorphisms which change pharmacokinetics of a drug.

CONCLUSION

Therapeutic drug monitoring might help in monitoring patients because in one of our case hallucination is probably caused by acyclovir instead of VCZ, because the VCZ was at sub therapeutic concentration. In general pharmacogenomic analyses are performed to predict the treatment out come but therapeutic drug monitoring should support genomic data and it is another important tool to monitor patient's response.

The survival expectancy of the patient population included in the study was low, only 11 patients completed the study. Nearly 40 patients were screened but most of them were deceased during the study because of disease progression. No statistical report was generated because of this.

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Ethics Committee Approval: This study was approved by Erciyes University Clinical Trial Ethical committee, approval number 2015/101 and performed according to favorable clinical practice guidelines.

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