RESEARCH ARTICLE / *Araştırma Makalesi*

Relationship of Carotid Artery Stenosis Ratio and Perioperative Stent Complications

Karotit Arter Darlık Oranı ile Perioperatif Stent Komplikasyonları İlişkisi

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Abstract

Introduction In this study, we aimed to evaluate the complications of carotid artery stenting in patients with extracranial carotid artery stenosis, retrospectively.

Materials and Methods Complications such as stroke, death, restenosis in the first 30 days and 1 year after the CAS procedure, cerebral hyperperfusion and stent thrombosis/occlusion in the perioperative first 24 hours and first 30 days were evaluated.

Results Of the 205 CAS procedures, complications developed in 12 patients. The complication rate for the first 30 days after the procedure was 4,87%, and at the end of the first year, it was 5,85%. Of the 12 patients with complications, 8 had carotid stenosis of ≥90%. Death occurred in 4 of 195 patients with carotid artery stenosis. The mortality rate within the first 30 days and during the 1-year follow-up period was 1,53% and 2,05%, respectively. Ischemic stroke occurred in 6 of 195 patients with carotid artery stenosis. After the first 30 days and one year follow-up, ischemic stroke had occurred in 3,07% of patients. Stent thrombosis/occlusion rate was 4,87% in 205 CAS procedures, and 7 of them occurred in the perioperative first 24 hours and another 3 occurred within the first 30 days. Restenosis rates were 0,48% and 0,97% at 6 months and the first year, respectively.

Conclusion It has been observed that the incidence of complications in the CAS procedure is higher in symptomatic cases requiring emergency endovascular treatment or in cases with a carotid artery stenosis rate of 90% or more. In addition, the most common CAS complication in our study was found to be carotid artery stent thrombosis/occlusion.

Keywords carotid artery stenting, carotid artery diseases, carotid artery stenosis, stents, stroke.

Öz

Amaç *Biz bu çalışmada ekstrakraniyal karotis arter darlığı olan hastalarda, karotis arter stentleme (KAS) komplikasyonlarını retrospektif olarak değerlendirmeyi amaçladık.*

Yöntem ve Gereçler *KAS işlemi sonrası ilk 30 gün ve 1 yıl içinde inme, ölüm, restenoz; perioperatif ilk 24 saat ve ilk 30 günde serebral hiperperfüzyon ve stent trombozu/oklüzyonu gibi komplikasyonlar değerlendirildi.*

Bulgular *205 KAS işlemde 12 hastada komplikasyon gelişti. 205 KAS işlem sonrası ilk 30 gün için komplikasyon oranı % 4,87 iken, 1. yıl sonunda % 5,85 oranında izlendi. Komplikasyon görülen 12 hastanın 8'inin karotis arterlerinde % 90 ve üzeri darlık mevcuttu. 195 karotis arter hastasının 4' ünde ölüm gelişti. İlk 30 gün içindeki mortalite oranı % 1,53 iken bir yıllık izlem sürecinde toplam mortalite oranı % 2,05 olarak bulundu. 195 karotis arter hastasının 6'sında iskemik inme saptandı. İlk 30 gün ve bir yıllık takip sonrası iskemik inme oranı % 3,07 olarak saptandı. Stent trombozu/oklüzyonu oranı 205 KAS işlemde % 4,87 olup, 7' si perioperatif ilk 24 saatte, 3' ü ise ilk 30 gün içinde meydana gelmişti. Restenoz ilk 6 ay sonunda % 0,48 oranında görülürken, bu oran ilk bir yılsonunda % 0,97 olarak izlendi.*

Sonuç *KAS işleminde komplikasyon görülme sıklığının, acil endovasküler tedavi gerektiren semptomatik veya karotis arter darlık oranı %90 ve üzeri olan vakalarda daha yüksek olduğu gözlenmiştir. Ayrıca çalışmamızda en sık KAS komplikasyonun karotis arter stent trombozu/oklüzyonu olduğu tespit edilmiştir.*

Anahtar Kelimeler *karotis arter stentleme, karotis arter hastalıkları, karotis arter stenozu, stentler, inme*

INTRODUCTION

Stroke is an important cause of mortality and morbidity. One of the causes of ischemic stroke is carotid artery stenosis. The recurrence rate is high in strokes due to symptomatic carotid artery stenosis followed by medical treatment. In carotid artery stenosis, the possibility of stroke increases as the stenosis rate increases. Therefore, revascularization is an effective and safe method of preventing stroke in patients with severe carotid stenosis presenting due to stroke and transient ischemic attack or those who are asymptomatic.[1,2] Medical, interventional, and surgical treatments (endarterectomy) are performed to treat carotid artery stenosis effectively. In studies utilizing embolic protective devices, it was demonstrated that carotid artery stenting (CAS) treatment was similar to carotid artery endarterectomy (CAE) in terms of preventing recurrent ischemic strokes, and these two methods were found to have similar complication rates.[3,4]

In this study, we aimed to examine the complications of CAS, the causes of these complications, their frequency, and their relationship with pre-procedural carotid artery stenosis.

MATERIAL and METHODS

In this study, patients with symptomatic and asymptomatic carotid artery stenosis who underwent CAS in Bezmialem Vakıf University Neurology Clinic between 2011 and 2016 were analyzed retrospectively after obtaining the approval of the Bezmialem University Ethics Committee (10.09.2019/16-318). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. All participants gave their written informed consent to participate in the study. Internal carotid artery (ICA) stenosis was detected by computed tomography angiography, magnetic resonance angiography (MRA) and/or digital subtraction angiography (DSA). For CAS, symptomatic patients older than 18 years with stenosis of ≥50% and asymptomatic patients with stenosis ≥70% were selected based on the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.[5] Symptomatic stroke criteria were ipsilateral transient ischemic attack or stroke in the previous 6 months. Patients with a recent history of hemorrhage, total occlusion in the target vessel, bleeding coagulation disorder, who could not receive antiaggregant treatment or allergic to antiaggregant and contrast agents, who had a life expectancy of <1 year, and who could not undergo CAS due to these reasons were excluded. The study included 195 patients who underwent 205 procedures. The patients were divided into symptomatic and asymptomatic groups. Four groups were formed based on carotid artery stenosis rates: 50%–70%, 70%–90%, 90%–98%, and 98%–99%. In addition, the contralateral carotid artery of the CAS site was classified according to the same stenosis rates. Complications, such as cerebral hyperperfusion, bleeding due to hyperperfusion, stroke, death, stent thrombosis/occlusion, and restenosis were evaluated on the 30th day after CAS and at the end of 1 year.

The demographic data of the patients, risk factors, the symptomatic and asymptomatic presentation of stroke events, rates of carotid stenosis, the side (left/right) receiving CAS treatment, and complications in the perioperative first 24 hours, first 30 days, first year were recorded.

Statistical Analysis

PASW Statistics 22 for Windows statistical package program was used for transferring the data to the computer and statistical analysis. Descriptive statistics (frequency, percentage) were used in the presentation of data. Variables are expressed as mean, standard deviation, frequency and percentage. All other features/properties were assessed by an expert observer.

Revascularization Procedure

Aspirin (100 mg/day) and clopidogrel (75 mg/day) were administered at least 2 days before CAS after routine imaging of the patients with brain computed tomography (CT). On the day of the procedure, the patients were regularly administered with antihypertensive drugs, except ß block-

ers. CAS was performed under local anesthesia through the femoral approach. An 8F introducer sheath was placed, and unfractionated heparin (100 IU/kg) was administered to extend the anticoagulation time to 250–300 seconds. Arterial pressure and echocardiography (ECG) of the patients were monitored continuously during the procedure. An 8F guiding catheter (Cordis,USA) was placed proximal to the target lesion. Distal embolic protection was applied with a vascular filter (Filter wire EZ, Boston, USA) in all patients during CAS. After the protection devices were placed, the procedures were performed as follows: predilation (2–3 mm), stent placement, and post-dilatation (4–6 mm).

Predilation was performed to facilitate the passage of the stent to the lesion in cases with critical stenosis (>85%) or when severe calcifications were seen during fluoroscopy. Self-expanding stents (Wallstent, Boston Scientific, Natick, MA, USA) were placed in the stenotic carotid arteries. When necessary, residual stenosis of <30% was obtained after the stent was placed by post-dilating the lesion.

To prevent bradycardia and hypotension, 0,5–1 mg intravenous atropine was routinely administered before balloon inflation. Intravenous (IV) atropine was re-administered in patients who had a >20 beats/min decrease in heart rate during balloon dilation and stent placement. In case of severe hypotension (systolic blood pressure <80 mmHg), infusion of inotropic agents (dopamine 5–15 μg/kg/min) and additional IV fluids were used. On the other hand, nitroprusside infusion was administered in cases where hypertension developed. Before removal of the protection device, two angle angiograms and intracranial images of the stent implantation area were obtained. The procedure was considered successful when the stenotic segment of the carotid artery was effectively dilated (residual stenosis <30% with adequate blood flow). After the procedure, antiplatelet therapy was continued (dual antiaggregant therapy for at least 3 months and aspirin continued indefinitely). All patients were followed up in the intensive care unit during the first 3 hours after the procedure. In addition,neurological examinations were continued regularly until discharge, and magnetic resonance imaging (MRI) or CT was performed in patients demonstrating neurological changes after the procedure. Strict blood pressure control was achieved to maintain the systolic blood pressure between 100 and 130 mmHg or maintain a decrease of 10%–20% from baseline.

RESULTS

This study retrospectively analyzed 205 CAS procedures performed on 195 patients with symptomatic (n = 133) and asymptomatic (n = 62) carotid artery stenosis. Of the patients with a mean age of 68,45 ± 9,05 years, 143 were males and 52 were females. CAS procedures were right-sided in 93 patients, left-sided in 92 patients and bilateral in 10 patients. The patients were divided into four groups according to the degree of carotid artery stenosis (stenosis rate): 50%–70%, 70%–90%, 90%–98%, and 98%–99%.

In patients with right ICA stenting, 8, 35, 51, and 9 patients had carotid artery stenosis rates of 50%–70%, 70%–90%, 90%–98%, and 98%–99%, respectively. In patients with left ICA stenting, 9, 29, 50, and 14 patients had carotid artery stenosis rates of 50%–70%, 70%–90%, 90%–98%, and 98%–99%, respectively. Additionally, the carotid artery stenosis rates of the contralateral side (relative to the CAS application site) were examined. Regarding the contralateral carotid artery stenosis rates in patients with stenting to the right ICA, 18, 12, 8, and 4 patients had carotid artery stenosis rates of 50%–70%, 70%–90%, 90%–98%, 98%–99%, respectively, and 10 patients had contralateral carotid total occlusion; whereas the remaining 51 patients had <50% stenosis. Regarding the contralateral carotid artery stenosis rates in patients with stenting to the left ICA, 16, 8, 7, and 1 patient(s) had carotid artery stenosis rates of 50%–70%, 70%–90%, 90%–98%, 98%–99%, respectively. Also, 17 patients had contralateral carotid total occlusion and the remaining 54 patients had <50% stenosis.

Considering the risk factors of patients who underwent carotid stent; 86,66% hypertension, 63,58% hyperlipidemia, 44,10% coronary artery disease, 38,97% diabetes mellitus, 19,48% smoking and 5,12% atrial fibrillation were observed.

Complications developed in 10 patients within the first 30 days and in 2 patients at the end of 1 year. The complication rate was 4,87% for the first 30 days after CAS and 5,85% at the end of the first year. Of the 12 patients with complications, 8 had ≥90% stenosis in their carotid arteries. Stent thrombosis/ occlusion developed in 10 of the 12 patients, and 8 of these patients were symptomatic cases with emergency. The rate of stent thrombosis/occlusion was 4,87%, with 8 of them occurring in the perioperative first 24 h and 2 within the first 30 days. Neurological deficit development was prevented by performing CAS again in one of the two patients who developed stent thrombosis/occlusion, while CAE was utilized in the other patient. Due to stent thrombosis/occlusion, two patients died during the procedure; one patient died in the first month due to a large infarction after the procedure, and one patient died at the end of 1 year. The mortality rate during the 30 day and 1-year follow-up periods were 1,53% and 2,05%, respectively. Furthermore, 6 patients had ischemic strokes in the first 30 days. No new strokes were observed during the 1-year follow-up; thus, ischemic stroke rate was 3,07% for both follow-up periods. Restenosis occurred in 2 patients, 1 at the end of the 6th month and 1 at the end of 1 year; thus, restenosis rate was 0,48% at 6 months and 0,97% at the end of the first year (Table 1).

Table 1. Characteristics of patients with complications related to carotid artery stenting

Patient Number	Age	Gender	Risk Factors	Carotid Artery Stenosis Rate	Symptomatic / Asymptomatic	Stent Thrombosis/ Occlusion In The Perioperative	Stent Thrombosis/ Oclusion In The First 30	Stroke	Death	Restenosis	1st Month mRS
1	48	M		50%	symptomatic	+	-	+	-	-	3
2	70	M	CAD, DM, HT	99%	asymptomatic	+	-	-	+	-	6
3	70	F	CAD, DM, HT	90%	symptomatic	+	-	+	-	-	1
4	81	F	CAD, HT, HL	70%	symptomatic	+	-	-	-	-	0
5	60	M	CAD, HT, DM, HL	95%	symptomatic	-	+	+	+	-	6
6	82	F	HT, HL	95 %	symptomatic	+		-	-	-	0
7	86	F	HT	70%	asymptomatic	-	+	+	-	-	1
8	81	M	HL	90%	asymptomatic	+	-	+	*	-	5
9	58	M	HT, DM, HL	90%	symptomatic	+	-	-	+	-	6
10	56	F	HT, DM, HL	90%	symptomatic	+	-	+	-	-	5
11	64	M	CAD, HL	95%	symptomatic	-	-	-	-	**	0
12	57	F	HT,HL, Smoking	70%	symptomatic	-	-	-	-	***	0

*The patient died after 1 year, **Restenosis developed in the 6th month, ***Restenosis developed in the 1st year
HT hypertension, HL hyperlipidemia, CAD coronary artery disease, DM diabetes mellitus, mRS; Modified Rankin Score

DISCUSSION

Approximately 75% of ischemic strokes are caused by the anterior system, and the cause for one-third of them is carotid artery stenosis. In carotid artery stenosis, the risk of stroke recurrence is high in the first 7 days. In patients with stroke due to symptomatic carotid artery stenosis, recurrence rate in the first 2 years reaches up to 26% in those treated medically after the first event.[6] In asymptomatic patients with carotid artery stenosis (comprising >60% of patients) the annual incidence of stroke has been reported to be 2,5%, even under medical treatment.[7] Therefore, surgical and interventional treatments have gained considerable importance as effective alternatives to medical treatment.

After carotid artery stenosis is diagnosed, the indication(s) and method of treatment should be evaluated. The degree of stenosis is important in this evaluation. Medical treatment is usually sufficient in cases with a stenosis of <50% in the vascular lumen.[8] The superiority of surgical treatment over medical treatment in patients with significant stenosis in the carotid arteries (≥70%) has been demonstrated by large-scale studies, such as the NASCET study, the European Carotid Surgery Trial (ECST), and the Asymptomatic Carotid Atherosclerosis Study (ACAS).[5,7,9]

The reliability and efficacy of CAS has been demonstrated in studies conducted with comparisons to surgical treatments. The Carotid and Vertebral Artery Transluminal Angioplasty (CAVATAS) study, published in 2002, was the first randomized study including symptomatic and asymptomatic patients, and the rates of stroke with periprocedural sequela, death, and long-term stroke were found to be similar.[10,11] In the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy study (SAPPHIRE) study, conducted in 2004, wherein only high-risk patients were included from symptomatic and asymptomatic patients, the rates of stroke, death and myocardial infarction (MI) within 30 days; and ipsilateral stroke and death rates between 31 days and 1 year (12,2% vs 20,1%) were in favor of CAS. By contrast, no difference was found in periprocedural stroke, death and MI rates between 31 days and 3 years, and ipsilateral stroke and death rates between 31 days and 3 years.[4,12] In 2006, the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis study (EVA 3S), wherein only symptomatic patients were included, was terminated early due to periprocedural stroke on the CAS side and high mortality rate. The 5-year periprocedural stroke, death and non-procedural ipsilateral stroke rates were similarly high on the CAS side, and no difference was found in the 10-year follow-up.[13,14] In the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study in 2006, which included symptomatic patients, no significant difference was observed between the groups in terms of periprocedural death and ipsilateral stroke (6,84% vs 6,34%). In the 2-year period, ipsilateral stroke, periprocedural stroke and death rates were similar.[15,16] In the largest study concerning this topic, the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) which included 2502 symptomatic and asymptomatic patients, the rates of periprocedural stroke, death and MI were again found to be similar (5,2% vs 4,5%). Although periprocedural stroke was more common in the CAS arm of the study, MI was more common on the endarterectomy side. No significant difference was found in stroke, MI and mortality rates at the 10-year follow-up. Stroke, death and ipsilateral stroke were more common in the CAS group in the 10-year period. The long-term results of postprocedural ipsilateral stroke were similar.[3,17]

In our study, although the mortality rate in the first 30 days in CAS recipients was 1,53%, the total mortality rate was 2,05% during the 1-year follow-up period. The ipsilateral ischemic stroke rate was 3,07% after the first 30 days and 1-year follow-up, which was compatible with the mortality (0%–2%) and stroke (2,9%–8,3%) rates of CAS in various series conducted since June 1997.[18,19] Although more than half of the patients were symptomatic, stroke rates in our study were low and consistent with the literature. Similar

to previous studies, this may be related to appropriate pre- and post-dilatation and the use of an embolism protective device and a closed-cell stent. Emboli-preventive filters reduce the frequency of embolism associated with CAS therapy. In addition, these vascular filters allow stenting while blood flow continues, making it possible to treat patients with occluded contralateral ICA.[20] Although the benefit of emboli protective devices is still not clearly demonstrated, in a large-scale study involving 11243 patients, periprocedural stroke and mortality rates were lower among patients in which emboli-protective devices were used.[21]

In our study, 101 of the patients who underwent CAS had >90% carotid stenosis. The mortality rate was 3,96% in these patients who represented a group with a high risk of stroke. Because this rate is within the acceptable range, CAS has been suggested to be a reliable treatment method in patients with severe stenosis (≥90%).

Apart from ischemic stroke that may occur during carotid revascularization, another major neurological complication is cerebral hyperperfusion. The mortality and morbidity rates of hemorrhage due to hyperperfusion after CAS was 1%.[22] In one study, to prevent postoperative hyperperfusion, percutaneous transluminal angioplasty (PTA) was recommended (followed by CAS) with the use of a PTA balloon with a diameter of ≤3.0 mm in the first session, leaving an appropriate interval (such as 1–3 weeks) between PTA and CAS, and measurement of cerebral blood flow.[23] None of our patients developed hemorrhage associated with cerebral hyperperfusion, which may be due to the use of a PTA balloon with a diameter of ≤3,0 mm in the first session and strict blood pressure regulation.

Although stent thrombosis, another complication, is uncommon, it is a complication with serious mortality and morbidity.[24] In stent thrombosis, the first 30 days have been classified as the early stage, and after 30 days (usually to 12 months) as late stage.[25] For the early period, the first 24 hours is defined as the acute period, while the period between 1 and 30 days is classified as subacute.[26] Stroke following stent thrombosis is thought to occur either as a direct result of thrombosis or as a complication of indirect distal embolism.[27] In the data, acute stent thrombosis rate was observed between 0,04% and 2%.[28] The literature on this topic mostly includes case-by-case evaluations, instead of large, randomized studies on stent thrombosis. In another study, the incidence of acute stent thrombosis was 0,5%–0,8%.[29] However, in the follow-up of acute carotid stent thrombosis (ACST) using serial CT angiography, the stent thrombosis rate in the early period was 43,5% in 23 cases.[30] Some studies include only emergency and symptomatic patients for stent thrombosis in CAS, while other studies also include asymptomatic patients. In elective cases, the frequency of thrombosis ranged from 0,36% to 2,1%.[31] In emergency situations, this rate demonstrates and increase, with frequencies ranging from 5,6% to 33%.[32-34] In some series, especially in tandem occlusions associated with intracranial thrombectomy, higher than expected ACST rates up to 45% were observed.[32] In our study, the stent thrombosis/ occlusion rate was 4,87%, and the relatively high rate may be due to CAS being performed on mostly emergency and symptomatic patients in this retrospective study. Actually, among the eight patients who developed stent thrombosis/occlusion six were emergency cases, and most of them were symptomatic and had multiple risk factors. In addition, seven of the patients who developed stent thrombosis/occlusion had a carotid artery stenosis of ≥90%, and these patients were included in the high-risk patient group.

The carotid artery stenosis rates of patients who died were ≥90%. In 7 of the 10 patients who developed stent thrombosis/occlusion, and in 4 of the 6 patients who had a stroke, the carotid stenosis rate was also ≥90%. No complications were observed in patients with bilateral carotid stenosis, who had undergone treatment for each carotid at different times. Thus, current evidence shows that the incidence of complications for CAS does not increase in those with bilateral carotid stenosis, but in those with high

stenosis rate (≥90%) those with emergency and patients who are symptomatic.

Another complication associated with CAS is restenosis. In studies, the restenosis rate after CAS was 5%–11% with different follow-up periods.[35,36] Barros et al. reported a restenosis rate of 6% within 2 years.[35] In the CAVATAS, carotid revascularization using endarterectomy or stenting systems (CaRESS), and SPACE studies, a higher rate of post-CAS restenosis was reported compared to post-CAE restenosis rate.[10,15,37] However, EVA3S and Mannheim and Karmeli advocated the opposite in their studies including a 1-year follow-up.[38,39]

Many factors, such as smoking, hyperlipidemia, hypertension and diabetes mellitus, can, increase the incidence of restenosis after CAS.[40,41] In addition, the role of sex and age was also mentioned.[36,38] The CAVATAS study reported that smoking contributed to the progression of restenosis.[42] In other studies, recurrent carotid artery stenosis increased in patients with residual stenosis after CAS, history of cardiovascular and cerebrovascular disease, high-grade carotid artery stenosis, and contralateral carotid stenosis.[43-45] One particular study also reported that the presence of calcified plaque was associated with restenosis.[46] From these data, it is evident that improving risk factors can reduce the incidence of restenosis. In our study, restenosis rate in our patients who underwent CAS was 0,48% at the end of the first 6 months and 0,97% at the end of 1 year. While looking at antiaggregant resistance and genetic polymorphisms for effective antiaggregant treatment in our patients, we tried to control various risk factors with frequent polyclinic controls throughout the first 6 months. This situation may be associated with the low rate of restenosis in our patients.

In our study, no complications were observed in high-risk patients with bilateral stenosis after bilateral CAS procedures had been performed at separate times. In a multicenter, prospective study on bilateral carotid stenosis, which included 747 patients at high risk for CAE47, two separate CAS procedures were performed with a >30-day interval in 78 of these patients (10,4%), while procedures were bilateral in other patients. No significant differences were found between the two groups with respect to any of the endpoints, at neither 30 days nor 1 year. Thus, both approaches are effective in the CAE treatment of high-risk patients without any increase in morbidity and mortality.[47] Our study also supports this finding, and it may be feasible to note that CAS may be an alternative in this group of patients wherein CAE could be considered risky due to bilateral stenosis.

CONCLUSION

Unilateral and bilateral CAS is a procedure with low mortality rate and is an effective treatment method that can prevent recurrent ischemic stroke. The incidence of possible complications is associated with presence of emergency, the symptomatic nature of the patient and degree of stenosis rate (≥90%), rather than the presence of bilateral carotid stenosis. In addition, although the incidence of stent thrombosis/occlusion was not observed as a clear rate in the literature, it was the most common carotid stent complication in our study.

Limitations

It can be said that the most important limitation of this study was the small number of patients, its single centered nature and retrospective design. Anatomical features such as aortic arch type, target lesion length, calcification of the target area, ICA/CCA angle/tortuosity were not evaluated for perioperative risk. In addition, the type of stent used in our study was only closed cell stent and only distal vascular filter type as embolic protective device. All these can be considered as limitations of our study.

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Credit Authorship Contribution Statement

Conceptualization; CD,VG,GH,OG Data curation; CD,VG,MN,GH Formal analysis; CD,OG,VG,MN Investigation; CD,MN,OG,GH. Methodology; TA,GH,VG Project administration; CD,OG,TA,VG Resources; CD,VG,OG. Supervision; TA,GH,OG Validation; CD,TA. Roles/Writing-original draft; CD, TA. Writing-review & editing; CD

Conflict of interest statement

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Ethics Approval

Approval was obtained from the ethics committee of Bezmialem Vakıf University (10.09.2019/16-318). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. All participants gave their written informed consent to participate in the study

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