











Evaluation of Pre- and Postprocedural Oxidative Stress with TAC-TOS Score in Patients with Atrial Fibrillation Undergoing Atrial Fibrillation Ablation

Atriyal Fibrilasyon Ablasyonu Yapılan Atriyal Fibrilasyonlu Hastalarda Preoperatif ve Postprosedural Oksidatif Stresin TAK-TOD Skoru ile Değerlendirilmesi

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ABSTRACT

Objective: The balance between free oxygen and nitrogen species and physiological antioxidant mechanisms is crucial for maintaining vital tissue functions. Notably, oxidative stress affects the pathophysiology of many diseases, including atrial fibrillation (AF). We investigated the role of oxidative stress in AF and the effects of ablation procedures on oxidative stress.

Methods: A total of 40 patients who underwent cryoballoon or radiofrequency ablation for pulmonary vein isolation were enrolled in the study. Patients with well-known diseases associated with increased oxidative stress were excluded. The total antioxidative capacity and total oxidative status (TOS) values before and six months after the procedure were examined and evaluated according to rhythm status.

Results: After six months, there was a statistically significant difference in TOS compared with the preprocedure values (1880.05 ± 1016.19 vs. 1418.32 ± 1075.11 , $p=0.001$). The postprocedural TOS value was significantly lower in the sinus rhythm group than in the patient group with AF (1237.48 ± 1036.34 vs. 2270.88 ± 870.20 , $p=0.013$). However, there were significant differences between the paroxysmal and persistent AF groups according to preprocedural rhythm status (4.87 ± 5.77 vs. 20.43 ± 23.23 , $p=0.009$). We did not find any association between C-reactive protein levels and the presence of arrhythmia after the procedure (11.29 ± 16.19 vs. 13.70 ± 25.47 , $p=0.662$).

Conclusion: Oxidative stress, as evaluated by TOS values, can be a prognostic parameter for AF recurrence after ablation.

Keywords: Arrhythmia, atrial fibrillation, catheter ablation, oxidative stress

Öz

Amaç: Serbest oksijen ve nitrojen türleri ile fizyolojik antioksidan mekanizmalar arasındaki denge, dokuların yaşamsal fonksiyonlarının devamlılığı için çok önemlidir. Oksidatif stres, atriyal fibrilasyonun (AF) yanı sıra birçok hastalığın patofizyolojisinde önemli rol oynamaktadır. Bu çalışmada oksidatif stresin AF üzerindeki rolü ve ablasyon prosedürlerinin oksidatif stres üzerine etkisi araştırılmıştır.

Gereç ve Yöntem: Pulmoner ven izolasyonu için kriyoballoon veya radyofrekans ablasyon uygulanan toplam 40 hasta çalışmaya dahil edildi. Oksidatif stresi artırdığı bilinen hastalıkları olan hastalar çalışma dışı bırakıldı. İşlem öncesi ve işlemten altı ay sonraki total antioksidan kapasite ve total oksidatif durum (TOD) değerleri incelendi ve ritim durumuna göre değerlendirildi.

Bulgular: Altı ay sonra, işlem öncesi değerlerle karşılaştırıldığında TOD açısından istatistiksel olarak anlamlı bir fark vardı ($1880,05 \pm 1016,19$ vs. $1418,32 \pm 1075,11$, $p=0,001$). İşlem sonrası TOD değeri sinüs ritmindeki hasta grubunda AF ritmindeki hasta grubuna göre istatistiksel olarak anlamlı derecede düşük bulundu ($1237,48 \pm 1036,34$ vs. $2270,88 \pm 870,20$ $p=0,013$). İşlem öncesi ritim durumuna göre tanımlanan paroksizmal ve

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ÖZ

persitan AF grupları arasında anlamlı fark olmasına rağmen ($4,87 \pm 5,77$ vs. $20,43 \pm 23,23$ $p=0,009$). C-reaktif protein ile işlem sonrası aritmi varlığı arasında herhangi bir ilişki bulunamadı ($11,29 \pm 16,19$ vs. $13,70 \pm 25,47$, $p=0,662$).

Sonuç: TOD değerleri ile değerlendirilen oksidatif stres, ablasyon işleminden sonra AF tekrarlamasında prognostik bir parametre olabilir.

Anahtar Kelimeler: Aritmi, atriyal fibrilasyon, kateter ablasyon, oksidatif stress

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. Despite clinical advances in cardiology, the burden of AF remains a concern, especially in the elderly population. Several mechanisms and other clinical conditions are associated with the onset and persistence of AF, including hypertension, coronary artery disease, heart valve disease, and heart failure. AF shares common pathophysiological mechanisms with these pathologies. One of these mechanisms is inflammation and oxidative stress (OS) (1).

The balance between free oxygen and nitrogen species reactive oxygen species/reactive nitrogen species and physiological antioxidant mechanisms is crucial for maintaining the vital functions of tissues (2).

Reactive radicals produced during inflammatory processes, mainly from mitochondria, are the main sources of pro-oxidants generated in neutrophil respiratory bursts (3,4). These species have the potential to damage proteins, polynucleotides, and other tissues (5). Several physiological mechanisms counteract the harmful effects of free oxygen radicals in tissues. An imbalance between free radicals and antioxidant defense mechanisms is referred to as "OS". Although there is no gold standard method for evaluating OS, modalities such as measuring reactive radicals in leukocytes by flow cytometry; measuring modified forms of lipids, proteins and DNA; measuring enzymatic redox proteomics and markers; and measuring the total antioxidant capacity of body fluids are suggested (3). OS has been implicated in many pathophysiological conditions, such as aging, atherosclerosis, carcinogenesis, neurodegenerative diseases, pulmonary diseases, and arthritis (6-10).

The relationship between AF and OS is another research topic in this field. Although the role of OS in the pathophysiology of AF has been investigated, arrhythmia itself has been found to be associated with increased OS (11-15). It has been shown that inflammatory markers begin to increase in the early stages of new-onset AF (16). Moreover, previous studies have shown that the maintenance of sinus rhythm rates is low in patients with high basal inflammatory marker levels (17,18).

The present study aimed to investigate the relationship between AF and OS levels in patients with AF who underwent AF ablation.

METHODS

Study Population

The study included 40 patients with paroxysmal ($n=22$) and persistent ($n=18$) AF in two tertiary hospitals who were symptomatic and underwent AF ablation. Patients were classified into the paroxysmal and persistent AF groups based on the international guidelines (19). Patients underwent cryoablation ($n=24$) and radiofrequency (RF) ($n=16$) ablation according to the clinician's decision. Patients with congestive heart failure, end-stage renal disease, > moderate valvular heart disease, hypertrophic cardiomyopathy, or a history of myocardial infarction that affected the ejection fraction were excluded. Patient demographic data, such as age and sex, and clinical data, including medical treatment, were recorded. The study protocol complied with the ethical standards specified in the 1964 Declaration of Helsinki and was approved by the Clinical Research Ethics Committee (decision no: 2021-20-29, date: 18.10.2021) of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital. Informed consent was obtained from the patients regarding the ablation procedure and their participation in the study.

Biomarker Analysis

Fasting blood samples were collected before and 6 months after the ablation. The samples were centrifuged at 80 °C. The total anti-oxidant capacity (TAC) and total oxidative status (TOS) were evaluated using the method developed by Erel (20). The method's philosophy involves measuring the amount of ferric ions oxidized by oxidants in the medium and measuring the buffering capacity of the serum via the spectrophotometric measurement of O-dianisidine radicals from the Fe^{2+} O-dianisidine complex. This molecule reacts with hydrogen peroxide, releasing free oxygen radicals into the environment. The end product is a yellowbrown-colored dianisidine radical [2,2-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)], which allows spectrophotometric

measurement of color changes according to the buffering capacity of the environment. There was a reverse correlation between color change and antioxidant capacity. The reaction kinetics were calibrated using a standard method called the "Trolox equivalent".

Catheter Ablation

Prior to the procedure, optimal antiarrhythmic and anticoagulant treatment compliance was ensured in the patients. All patients underwent transesophageal echocardiography under pseudoanalgesia to rule out intracardiac thrombi. Two venous lines for the coronary sinus catheter and ablation catheter and one arterial line for the pigtail catheter for guidance to the atrial septostomy were placed. After transeptal puncture, pulmonary vein isolation was achieved using a Medtronic Arctic Front Advance Cardiac Cryoablation System in patients who underwent cryoballoon ablation and a Biosense Webster Thermocool Smarttouch SF Uni-Directional Navigation Catheter in patients who underwent RF ablation. All septostomy procedures were performed under the guidance of transesophageal echocardiography. Procedural success was evaluated by assessing intrinsic and exit blocks via stimulation of the pulmonary veins and coronary sinus. All patients were in sinus rhythm at the end of the procedure.

Postprocedure Follow-up

Patients were discharged with reorganized medical treatment and anticoagulation therapy according to the guidelines. Patients and their concurrent clinical conditions were followed for 6 months. After six months, the rhythm status was evaluated using 12-lead surface electrocardiograms, and biomarker samples were obtained. Patients with symptoms of palpitations without documented arrhythmia were evaluated using Holter monitoring.

Statistical Analysis

The normality of the data was assessed using the Kolmogorov-Smirnov test. Continuous variables are expressed as means and standard deviations, whereas categorical variables are expressed as numbers and percentages. Comparisons between two groups were performed using the independent samples t-test or the Mann-Whitney U test, depending on the distribution of the data. Comparisons of the TAC and TOS before and after ablation were performed using the Wilcoxon signed-rank test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Data

Forty patients with paroxysmal (n=22) or persistent (n=18) AF that were symptomatic under medical treatment at two tertiary hospitals were enrolled in this study. Twenty-two patients were male and 18 were female. Demographic and clinical data are presented in Table 1.

Comparison of Persistent and Paroxysmal AF (PAF) Patients

There were no significant differences in demographic or clinical data, except for thyroid-stimulating hormone and

Table 1. Clinical and demographic characteristics of the study population

Age (years)	55.30±12.04
Gender (n, %)	
Male	22 (55)
Female	18 (45)
Cryoballoon ablation rate (n, %)	27 (67.5)
RF ablation (n, %)	13 (32.5)
Six-month rhythm (n, %)	
Sinus rhythm (n, %)	33 (82.5)
Atrial fibrillation (n, %)	7 (17.5)
Paroxysmal (n, %)	22 (55)
Persistent (n, %)	18 (45)
Beta blocker (n, %)	36 (90)
Amiodarone (n, %)	22 (55)
Propafenone (n, %)	11 (27.5)
Calcium channel blockers (n, %)	4 (10)
Digoxin (n, %)	0
Hypertension (n, %)	21 (52.5)
Cerebrovascular disease (n, %)	2 (5)
Coronary artery disease (n, %)	10 (25)
Diabetes mellitus (n, %)	7 (17.5)
Hemoglobin (g/dL)	12.92±1.78
Glucose (mg/dL)	92.17±8.31
C-reactive protein (mg/dL)	11.66±17.52
Urea (mg/dL)	29.74±8.52
Creatinine (mg/dL)	0.84±0.17
TSH (mIU/L)	2.07±1.82
TOS preprocedural	1880.05±1016.19
TOS postprocedural	1418.32±1075.11
TAC preprocedural	0.44±0.30
TAC postprocedural	0.56±0.39

RF: Radiofrequency, TAC: Total antioxidative capacity, TOS: Total oxidative stress, TSH: Thyroid stimulating hormone

creatinine levels, between the two groups. Compared with PAF, cryoballoon ablation was significantly preferred (19 vs. 8, $p=0.004$), whereas RF ablation was more frequently performed in the persistent AF group (4 vs. 10, $p=0.013$). C-reactive protein (CRP) levels were significantly lower in patients in the PAF group than in patients in the persistent AF group (4.87 ± 5.77 vs. 20.43 ± 23.23 , $p=0.009$).

There were no significant differences in preprocedural TOS (1805.17 ± 1186.31 vs. 1874.26 ± 1040.31 , $p=0.856$), postprocedural TOS (1379.45 ± 1212.38 vs. 1516.56 ± 1146.69 , $p=0.888$), preprocedural TAC (0.076 ± 0.71 vs. -0.214 ± 0.46 , $p=0.153$), or postprocedural TAC between the paroxysmal and persistent AF groups (-0.035 ± 0.79 vs. 0.14 ± 0.57 , $p=0.423$). Table 2 shows the clinical and biochemical features of patients with persistent and PAF.

Comparison of Patients with Sinus Rhythm and AF

At the 6-month follow-up, sinus rhythm was sustained in 33 patients, and 7 patients had AF. The mean age of patients with an AF rhythm was significantly greater than that of

patients with a sinus rhythm (66.57 ± 9.07 vs. 52.91 ± 11.30 years, $p=0.005$). Patients with sinus rhythm had lower blood urea levels than those with AF did (27.86 ± 7.67 vs. 38.59 ± 6.87 , $p=0.002$).

Postprocedural TOS was significantly lower in the sinus rhythm group than in the patient group with AF rhythm (1237.48 ± 1036.34 vs. 2270.88 ± 870.20 $p=0.013$).

In both groups, preprocedural TOS (1779.94 ± 1036.08 vs. 2352.02 ± 819.78 , $p=0.179$), preprocedural TAC (0.41 ± 0.32 vs. 0.57 ± 0.15 , $p=0.167$), postprocedural TAC (0.56 ± 0.41 vs. 0.55 ± 0.34 , $p=0.986$), and CRP (11.29 ± 16.19 vs. 13.70 ± 25.47 , $p=0.662$) values were similar (Table 3).

Comparison of Patients by the Type of Ablation Procedure

Preprocedural TOS (1611.19 ± 968.14 vs. 2379.37 ± 939.34 $p=0.021$) and postprocedural TOS (1093.13 ± 888.31 vs. 2022.25 ± 1160.09 $p=0.014$) were significantly lower in patients who underwent cryoballoon ablation than in those who underwent RF ablation (Table 4).

Table 2. Demographical and clinical data of the paroxysmal and persistent AF groups

	Paroxysmal AF (n=22)	Persistent AF (n=18)	p-value
Age (years)	55.14±12.47	55.50±11.86	0.926
Gender (n, %)			
Male	9 (40.9)	13 (72.2)	
Female	13 (59.1)	5 (27.8)	
Cryoballoon ablation (n, %)	19 (86.4)	8 (44.4)	0.004
RF ablation (n, %)	4 (18.2)	10 (55.6)	0.013
Beta blocker (n, %)	21 (95.5)	15 (83.3)	0.204
Amiodarone (n, %)	9 (40.9)	13 (72.2)	0.045
Propafenone(n, %)	9 (40.9)	2 (11.1)	0.036
Calcium channel blockers (n, %)	1 (4.5)	3 (16.7)	0.204
Hypertension (n, %)	11 (50)	10 (55.6)	0.736
Cerebrovascular disease (n, %)	2 (9.1)	0	0.492
Coronary artery disease (n, %)	5 (22.7)	5 (27.8)	0.731
Diabetes mellitus (n, %)	3 (13.6)	4 (22.2)	0.680
Hemoglobin (g/dL)	13.20±1.72	12.57±1.86	0.279
Urea (mg/dL)	28.04±8.39	31.38±8.43	0.168
Creatinine (mg/dL)	0.78±0.15	0.89±0.15	0.038
TSH mIU/L	1.74±1.85	2.51±1.72	0.038
C-reactive protein (mg/dL)	4.87±5.77	20.43±23.23	0.009
TOS preprocedural	1805.17±1186.31	1874.26±1040.31	0.856
TOS postprocedural	1379.45±1212.38	1516.56±1146.69	0.888
TAC preprocedural	0.076±0.71	-0.214±0.46	0.153
TAC postprocedural	-0.035±0.79	0.14±0.57	0.423

RF: Radiofrequency, TAC: Total antioxidative capacity, TOS: Total oxidative stress, TSH: Thyroid stimulating hormone, AF: Atrial fibrillation

Table 3. Demographic and clinical data, oxidative status, and antioxidant capacity according to rhythm status

	Sinus rhythm (n=33)	Atrial fibrillation (n=7)	p-value
Age (years)	52.91±11.30	66.57±9.07	0.005
Gender (n, %)			0.122
Male	20 (60.6)	2 (28.6)	
Female	13 (39.4)	5 (71.4)	
Cryoballoon ablation (n, %)	22 (69.7)	4 (57.1)	0.519
RF ablation (n, %)	11 (33.3)	3 (42.9)	0.631
Hypertension (n, %)	16 (48.5)	5 (71.4)	0.270
Cerebrovascular disease (n, %)	1 (3)	1 (14.3)	0.215
Coronary artery disease (n, %)	7 (21.2)	3 (42.9)	0.230
Diabetes mellitus (n, %)	6 (18.2)	1 (14.3)	0.805
Hemoglobin (g/dL)	13.14±1.74	11.87±1.74	0.049
C-reactive protein (mg/dL)	11.29±16.19	13.70±25.47	0.662
Urea (mg/dL)	27.86±7.67	38.59±6.87	0.002
Creatinine (mg/dL)	0.82±0.16	0.93±0.18	0.127
TSH mIU/L	2.18±1.88	1.31±1.25	0.288
TOS preprocedural	1779.94±1036.08	2352.02±819.78	0.179
TOS postprocedural	1237.48±1036.34	2270.88±870.20	0.013
TAC preprocedural	0.41±0.32	0.57±0.15	0.167
TAC postprocedural	0.56±0.41	0.55±0.34	0.986

RF: Radiofrequency, TAC: Total antioxidative capacity, TOS: Total oxidative stress, TSH: Thyroid stimulating hormone

Table 4. Oxidative parameters of patients according to the type of ablation procedure

	Cryoballoon ablation (n=26)	RF ablation (n=14)	p-value
TOS preprocedural	1611.19±968.14	2379.37±939.34	0.021
TOS postprocedural	1093.13±888.31	2022.25±1160.09	0.014
TAC preprocedural	0.39±0.30	0.53±0.28	0.164
TAC postprocedural	0.55±0.39	0.57±0.42	0.919

TAC: total anti-oxidant capacity, TOS: Total oxidative stress, RF: Radiofrequency

When all patients were compared before the ablation procedure and at six months, there was a statistically significant difference in TOS compared with preprocedure values (1880.05±1016.19 vs. 1418.32±1075.11, $p<0.001$). Pre- and postoperative TAC did not change in the entire study population (0.44±0.30 vs. 0.56±0.39 $p=0.098$).

DISCUSSION

The relationship between AF and OS is complex. There is increasing evidence that AF is associated with high systemic

and cardiac OS. However, whether OS causes AF or whether AF increases OS remains to be determined. Although existing studies suggest that OS plays an important role in the development of AF, there is limited evidence that OS decreases after ablation.

In our study, we found lower OS levels according to TOS after ablation than before the procedure. Subgroup analyses could not be performed due to the sample size and the transition between groups at the end of the 6th month due to the rhythm status. However, when postprocedure TOS values were evaluated according to rhythm status, OS seemed to be associated with the presence of arrhythmia.

Neuman et al. (12) reported a positive correlation between the presence of AF and the levels of oxidative and inflammatory markers in their 2007 study. In a study investigating the effects of AF recurrence after ablation, Shimano et al. (14) reported that AF recurrence was correlated with serum reactive oxidative metabolites. According to a study conducted by Henningsen et al. (13), high sensitivity-C-reactive protein (hs-CRP) and IL-6 may have predictive value for the recurrence of AF after successful catheter ablation. In contrast, the antioxidant capacity evaluated by TAC was not directly associated with the presence of arrhythmia. These findings related to anti-oxidant capacity were consistent with the data of our

study. In contrast, there was no relationship between AF recurrence and CRP levels.

Tascanov et al. (21) investigated the relationships among TOS, DNA damage, and PAF. A series of 56 patients with PAF were compared with healthy controls. They reported that hs-CRP, TOS, and 8-hydroxy-2-deoxyguanosine levels were greater in the PAF group. They also suggested that TOS and DNA damage could be used to identify patients at greater risk for AF. A similar study conducted by Neuman et al. (12) in patients with persistent AF revealed that the levels of reactive oxygen metabolites were greater in patients with AF than in controls. In both studies, it was not clear whether OS caused AF or increased OS. In our study, although TOS decreased significantly in patients in sinus rhythm at the end of the 6-month period compared with before the procedure, no significant change was observed in patients who developed AF. These findings suggest that AF increases OS.

The levels of inflammatory markers are increased in patients with AF. This result was due to the presence of cytokines. Many inflammatory cytokines increase fibrosis by promoting the proliferation of cardiac fibroblasts, promoting their differentiation into myofibroblast, and increasing collagen deposition (22). In our study, we also measured and compared the levels of CRP, a well-known inflammatory marker. Although there were significant differences between the paroxysmal and persistent AF groups according to preprocedural rhythm status, no association was noted between CRP levels and ARF after the procedure. Similarly, a study by Neuman et al. (12) involving 40 male subjects with or without permanent or permanent AF revealed that OS was significantly associated with AF, whereas inflammatory markers were not. Conway et al. (23) reported that CRP predicted initial but not long-term cardioversion success. The fact that AF is associated with OS but not inflammatory markers indicates that OS plays a more prominent role than inflammation in the maintenance of AF rather than its initiation.

Catheter ablation techniques play an increasingly important role in the clinical management of AF. Currently, two main catheter ablation methods are used for the treatment of AF. RF ablation provides pulmonary vein potential for isolation. The second approach is cryoablation, a frozen balloon atrial isolation technique that provides bidirectional isolation of the atrial pulmonary venous potential by freezing the balloon into the pulmonary vein. Both techniques have been shown to have similar clinical efficacy (24). On the other hand, postprocedural inflammatory responses and therefore OS responses may differ. Schmidt et al. (25) compared myocardial

enzymes and inflammation markers using different catheter ablation methods and reported a more significant increase in hs-CRP levels after RF ablation than after cryoablation. However, the authors did not find a significant difference in the duration of postoperative inflammation between the two methods. Rienstra et al. (26) followed >900 patients for 5 years and reported that recurrence was greater in patients with higher inflammation parameters, but there are no conclusive results on whether there are differences in the inflammation indices after different catheter ablation methods and whether inflammation is associated with postoperative AF recurrence. In our study, we did not find any differences between the two ablation techniques in terms of long-term OS parameters. Although our sample size was small, we did not find any significant difference between the two techniques in terms of AF recurrence.

Other findings from our study also deserve further investigation. Patients who failed ablation were older and had higher urea levels. Although these patients also had higher creatinine levels, the difference from patients who underwent successful ablation did not reach statistical significance. Similarly, patients with persistent AF had higher creatinine levels, highlighting the importance of traditional risk factors for AF occurrence and treatment.

Study Limitations

There are several limitations in our study. There was essentially no control group because the characteristics of the study population necessitated further treatment. Ethically, a control group could not be recruited because the research was conducted on a patient population in need of advanced treatment. Second, because of the sample size, we could not evaluate the data in fixed cohorts. According to the rhythm status, there were transitions between the groups; therefore, we evaluated the data cross-sectionally. Although the patients were followed closely, their rhythm status at the 6-month follow-up was evaluated according to the rhythm holter performed according to the patient's complaints and control electrocardiography. Rhythm holders were not used for any of the patients. Additionally, the treatment modality (cryoballoon ablation vs. RF ablation) was selected according to the clinician's recommendation.

CONCLUSION

Oxidative markers are associated with sinus rhythm restoration after ablation therapy. Current AF treatment is primarily based on stroke prevention, rate, and rhythm control. A better understanding of AF pathogenesis may also reveal new treatment options that may help delay or ideally suppress AF progression. However, increasing

pathophysiological and clinical knowledge can guide more rational choices regarding patient selection and treatment options. Future research should focus on translating our basic understanding of the role of OS in AF pathophysiology into more focused preventive strategies and more effective treatment options, for which the possible causal relationship between OS and AF still needs to be clarified; hence, studies with larger patient populations are needed to investigate the association between OS and AF recurrence.

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ETHICS

Ethics Committee Approval: The study protocol was in accordance with the ethical standards stated in the 1964 Helsinki Declaration and was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2021-20-29, date: 18.10.2021).

Informed Consent: Informed consent was obtained from the patients regarding the ablation procedure and their participation in the study.

Authorship Contributions

Concept: E.O., A.S.E., A.K., N.I., V.S.Ş., Design: E.O., A.S.E., M.E.A., A.K., F.N.T.Ç., Data Collection or Processing: E.O., A.S.E., M.E.A., C.Y., N.I., V.S.Ş., F.N.T.Ç., Analysis or Interpretation: E.O., A.S.E., M.E.A., C.Y., A.K., N.I., V.S.Ş., F.N.T.Ç., Literature Search: A.S.E., M.E.A., A.K., F.N.T.Ç., Writing: E.O., A.S.E., A.K.

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