Effects of Varenicline on Cardiovascular Parameters and Oxidative Stress

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Abstract

Objective: Pharmacotheraphy is recommended for smoking cessation in clinical practice. However, the cardiovascular safety of smoking cessation drugs has been questioned. Our goal is to evaluate the effects of the smoking cessation drug varenicline on some cardiovascular parameters and oxidative stress in subjects.

Methods: Twenty-six smokers without cardiovascular diseases and 25 healthy subjects were enrolled in the study. Total oxidant status (TOS), total antioxidant status (TAS), and urotensin II levels were determined in blood samples. Echocardiography was performed in all individuals. Smokers were assessed with the measurements mentioned above at the beginning of the treatment (V0 group) and at the end (third month, V3 group). The same measurements were performed once in the control group (C).

Results: Aortic strain and distensibility measurements in the V0 group were found to be significantly lower than those in the C group. No significant changes were observed after varenicline treatment. TOS values in the V0 group were found to be higher than those in the V3 and C groups, but these differences were not statistically significant. However, TAS values of the V3 group were found to be significantly lower than those of the V0 group. There were no differences between the groups in terms of diastolic dysfunction and urotensin II levels.

Conclusion: Our study revealed that varenicline may decrease TAS in smokers thanks to smoking cessation. Varenicline does not seem to have negative effects on aortic stiffness. Further studies are needed to confirm these results.

Keywords: Antioxidant status, aortic stiffness, oxidant status, smoking cessation, varenicline

INTRODUCTION

Cigarette smoking is one of the preventable causes of premature death (1). Cardiovascular diseases are important causes of mortality and morbidity among tobacco users. Smoking cessation provides cardiovascular benefit in smokers (2, 3). Varenicline, one of the effective drugs for smoking cessation, is a partial agonist at the α4β2 nicotinic acetylcholine receptor (nAChR) and a full agonist at α7 nAChR (4, 5). In the literature, the risk of serious cardiovascular events related to varenicline remains controversial (6). Some authors have reported that cardiovascular events increased after using varenicline for smoking cessation (7-10). However, others have reported that varenicline does not appear to be associated with an increased risk of documented cardiovascular events (11, 12).

Free radicals are molecules with unstable structures that can generate oxidative stress. Increased free radical formation which cannot be compensated by antioxidant defense mechanism is called oxidative stress (13). Previous studies have shown the relationship between oxidative stress and circulatory system disorders (14, 15). However, only one study has investigated the effects of varenicline on oxidative stress (16). Nevertheless, to the best of our knowledge, no study has investigated the effects of varenicline on both oxidative stress and antioxidant defense.

Received Date: 03.07.2016
Accepted Date: 29.09.2016
Available Online Date: 13.12.2016

DOI: 10.5152/ejp.2016.73644

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• Available online at www.eurasianjpulmonol.com

Oxidative stress is believed to be closely associated with arterial stiffness (17). A recent study suggested that one possible mechanism for arterial stiffness is the imbalance between oxidative stress and total antioxidant status (TAS) (18).

Aortic distensibility is a measurement of vascular elasticity, which reflects the stiffness of the aorta (19). Furthermore, aortic distensibility was shown to be the most sensitive and specific marker of arterial stiffness in younger individuals (20). Aortic stiffness increased as aortic distensibility decreased (19, 20).

Urotensin II is one of the most potent vasoconstrictor peptide and its high-affinity G-protein-coupled receptor GPR14. In addition, this peptide may contribute to the physiological regulation of cardiovascular homeostasis in humans (21, 22). It was suggested that urotensin II can be used as a marker of myocardial and ischemia reperfusion injuries (23, 24). Previously, it was shown that plasma urotensin II levels increased in smokers (25).

In this study, we aim to investigate the effects of varenicline on aortic stiffness parameters (aortic distensibility and strain), oxidative balance, and urotensin II levels in patients undergoing smoking cessation treatment.

METHODS

Patients and Study Design

We conducted an observational study for 3 months on 27 patients receiving smoking cessation treatment and 25 controls at our clinic. Control subjects (ages 20–65) were included in the study if they were nonsmokers, had no health problems, and did not take regular medications. Patients (ages 20–65) who smoked an average of 10 cigarettes daily for a year before the study were enrolled. Patients were excluded if they had any documented cardiovascular disease, uncontrolled concomitant disease, cancer, clinically diagnosed depression, or were taking antidepressant drugs in the past year. Patients with a history of bipolar disorder, psychosis, dependence on drug in the past year, or use of smoking cessation medication in the past month were also excluded.

Patients were started on varenicline treatment. The targeted smoking cessation date was planned to be within 8 days after the initiation of varenicline. Varenicline was administered for 12 weeks. The primary outcome was carbon monoxide (CO)-confirmed self-reported two-week abstinence at the end of the treatment. Patients with a CO level of ≥6 ppm were still considered to be smokers (26). One of the patients was excluded from the study due to severe withdrawal symptoms and continued smoking.

Echocardiography (ECO), electrocardiography (ECG), spirometric tests, CO level measurement, and routine blood analysis were performed at the beginning (V0 group) and the end of the treatment (third month, V3 group). CO levels in expired gas were measured using a piCO Smokerlyzer (Bedfont, Kent, UK). Participants were evaluated in terms of self-reported smoking status before (V0) and after (V3) varenicline-assisted smoking cessation.

CO level measurement, blood sampling for biochemical analyses and complete blood count, ECO and ECG, and spirometric analyses were performed only once in the control group.

All patients were informed of the study procedure and written informed consent was obtained. The study protocol was approved by the Institutional Ethics Committee.

At the end of the study, plasma level of urotensin II in the serum sample, stored at −20°C, was determined using a commercial kit (USCN life Science, Inc., Wuhan, China).

Measurement of Plasma Total Oxidant and Antioxidant Status

The total oxidant status (TOS) and total antioxidant status (TAS) were measured using automated colorimetric measurement method for TOS and TAS developed by Erel (27, 28).

Calculation of Oxidative Stress Index

The ratio of TOS to TAS is referred to as the oxidative stress index (OSI). OSI is calculated using the following formula:
OSI (arbitrary unit) = TOS (μmol H2O2 Equiv./L)/TAS (mmol Trolox Equiv./L) × 100 (29).

Transthoracic Echocardiography

Standard echocardiographic examination was performed using a Vingmed Vivid System 6 device (General Electric, Milwaukee, WI) with a 2.5-MHz transducer.

Measurement of Aortic Stiffness Parameters with Echocardiography

Assendan aorta records were obtained 3 cm above aortic valves using M mode Doppler ultrasonography in the supine position. Aortic diameter was calculated as the distance between the inner edges of front and back walls in systole and diastole. Systolic diameter was obtained at the full opening of the aortic valve. Diastolic diameter was simultaneously obtained at the peak of the QRS complex in ECG records. Three measurements were made and the mean value was calculated. For local carotid and femoral distensibility, normal and reference values were recently published but reference values for aortic stiffness were not available (30, 31). Generally, these parameters used in clinical studies were compared with those in the controls.

Aortic strain and distensibility were calculated using the following formula (32).
(1) Aortic strain (%) = (systolic aortic diameter – diastolic aortic diameter)×100/diastolic aortic diameter.
(2) Distensibility (cm^2/dyn)=2×(aortic strain)/(systolic blood pressure−diastolic blood pressure).

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences 20.0 (SPSS Inc.; Chicago, IL, USA). Results are presented as means ± standard deviation. Differences in the frequencies for both groups were tested using chi-square and Fisher's exact tests. Differences between related groups (V0 and V3 groups) were compared using paired t-test. To compare the diferences between independent groups, the independent samples t-test was used. P-value of <0.05 was considered statistically significant.

RESULTS

The study included 26 smokers (mean age of 34.26±9.38 years; 19 males and 7 females) and 25 control subjects (mean age of 34.62±12.64 years, 17 males and 8 females). Mean smoking pack/year was 18.36±12.61 and mean dependence level was 6±2.26 in

Table 1. Comparison of clinical and functional characteristics between V0 and control group (C)

	V0	C	p
Age (years)	34.26±9.38	34.62±12.64	0.761
Sex (n) (M/F)	19/7	17/8	0.084
Smoking (pack/year)	18.36±12.61		
Fagerström score	6±2.26		
SBP (mmHg)	126.86±11.60	120.57±9.24	0.059
DBP (mmHg)	80.71±11.15	76.10±10.47	0.174
Aortic strain (%)	7.69±5.89	11.88±5.88	0.030
Distensibility (cm^2/dyn)	0.34±0.27	0.56±0.29	0.017
Urotensin II (pg/mL)	0.39±0.16	0.40±0.18	0.246
CO	21.95±12.56	1.76±0.77	<0.001
Urea	24.63±6.18	25.95±5.53	0.059
Creatine	0.84±0.15	0.92±0.22	0.264
Uric acid	4.79±1.16	5.54±1.66	0.124
Hgb	15.27±1.23	13.72±1.47	0.001
Hct	44.88±3.44	41.25±4.23	0.005
WBC	9.12±2.60	6.77±1.30	0.001
MPV	8.13±0.59	8.32±0.83	0.470
PLT	238.53±37.96	244.38±62.62	0.658
RBC	5.06±0.39	4.93±0.51	0.352

Values are presented as means±standard deviation
CO: carbon monoxide; SBP: systolic blood pressure; DBP: diastolic blood pressure; Hgb: Hemoglobin; Hct: hematocrite; WBC: white cell count; MPV: mean platelet volume; PLT: platelet; RBC: red blood count

Table 2. Comparison of clinical and functional characteristics of smokers before (V0) and after smoking (V3) cessation

	V0	V3	p
Age (years)	34.26±9.38		
Sex (n) (M/F)	19/7		
Smoking (pack/year)	18.36±12.61		
Fagerström score	6±2.26		
SBP (mmHg)	126.86±11.60	124.38±13.35	0.314
DBP (mmHg)	80.71±11.15	78.10±11.06	0.407
Aortic strain (%)	7.69±5.89	9.72±6.81	0.082
Distensibility (cm^2/dyn)	0.34±0.27	0.42±0.29	0.231
Urotensin II (pg/mL)	0.39±0.16	0.43±0.18	0.979
CO	21.95±12.56	2.95±3.01	<0.001
Urea	24.63±6.18	26.53±5.46	0.110
Creatine	0.84±0.15	0.95±0.23	0.031
Uric acid	4.79±1.16	5.61±1.36	0.001
Hgb	15.27±1.23	14.83±1.06	0.010
Hct	44.88±3.44	43.72±3.07	0.012
WBC	9.12±2.60	8.19±1.94	0.023
MPV	8.13±0.59	8.03±0.63	0.154
PLT	238.53±37.96	250.11±34.07	0.025
RBC	5.06±0.39	4.99±0.39	0.063

Values are presented as means ± standard deviation
CO: carbon monoxide; SBP: systolic blood pressure; DBP: diastolic blood pressure; Hgb: Hemoglobin; Hct: hematocrite; WBC: white cell count; MPV: mean platelet volume; PLT: platelet; RBC: red blood count

the smoker group. The demographic and clinical characteristics and complete blood analysis of smoker and controls are given in Table 1. In addition, clinical parameters and blood count results of smokers before and after varenicline-assisted smoking cessation are shown in Table 2.

There was no significant difference between the groups with respect to age, sex, and blood pressure (Table 1). Aortic strain and distensibility measurements in the V0 group were found to be significantly lower than those in the control group (p=0.030, p=0.017, respectively) (Table 1). The measurements increased after the treatment (V3) compared with those at baseline (V0), but this increase was not statistically significant (Table 2). In smokers (V0), CO levels, hemoglobin, hematocrit, and leukocyte (WBC) were found to be significantly higher than those in controls (p<0.05). As expected, CO levels measured at the end of the treatment (third month) in the V3 group were lower than those at baseline in the V0 group (2.85±3.01, 21.95±12.56, p<0.001, respectively) (Table 2). In smoking cessation (V3) group, hemoglobin, hematocrit, and WBC values decreased, but platelets, creatinine, and uric acid increased compared with those in the V0 group (p<0.05) (Table 2).

In the echocardiographic assessment for diastolic dysfunction, in two subjects in the control group, five subjects in the V0 group and six subjects in the V3 group, grade I diastolic dysfunction was determined, whereas in three subjects in the V0 group and two subjects in the V3 group, grade II diastolic dysfunction was determined. However, there was no significant alteration among the groups in terms of diastolic dysfunction. In addition, there were no significant changes in urotensin II levels.

TOS, TAS, and OSI results are shown in Figures 1, 2, and 3, respectively. TOS values in the V0 group were found to be higher than those in the V3 and control groups, but these differences were not statistically significant (Figure 1). There were also no significant changes in terms of OSI values between the groups (Figure 3). However, TAS values in the V3) group were found to be significantly lower than those in the V0 group (1.42±0.13 mmol/L, 0.91±0.22 mmol/L, p=0.035, respectively) (Figure 2).

DISCUSSION

Our results suggest that use of varenicline during smoking cessation has no negative effect on aortic stiffness. Although some studies have reported on the effects of smoking cessation on arterial stiffness, the effects of varenicline on arterial stiffness are unclear. Takami and Saito reported that arterial stiffness parameters significantly decreased in smokers treated with varenicline a year after treatment (33). This result indicates that smoking cessation could have positive effects on endothelial dysfunction. Our study is different from

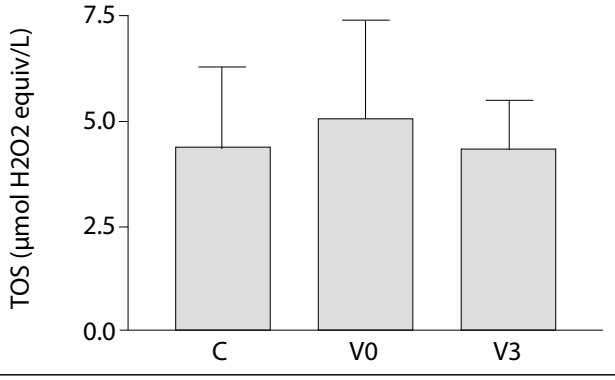

Figure 1. Serum total oxidant status levels. Values are presented as means ± standard deviation

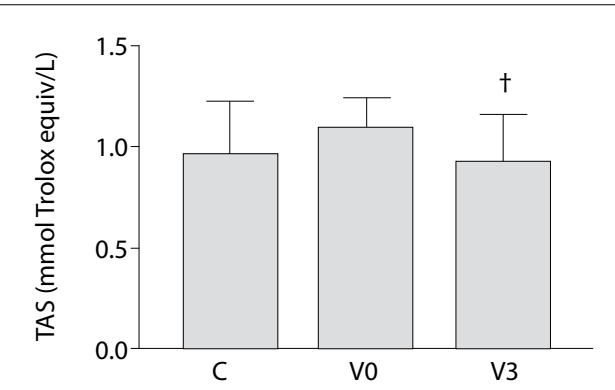

Figure 2. Serum total antioxidant status levels. Values are presented as means ± standard deviation
†: Different from V0, (p=0.035)

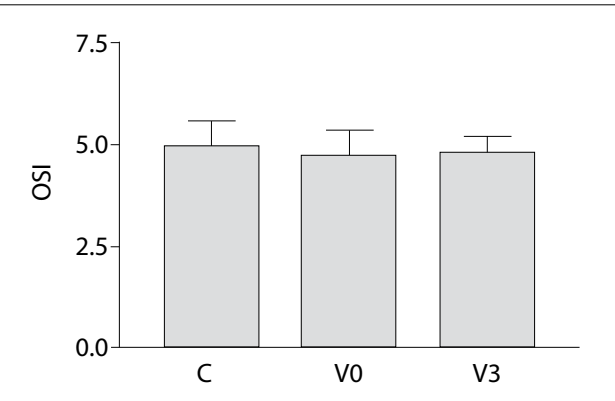

Figure 3. Oxidative stress index values. Values are presented as means ± standard deviation

the previous study in terms of having control group of nonsmokers. Furthermore, the indicators of arterial stiffness were measured at the end of the treatment to determine the short term side effects of varenicline. In our study, aortic strain and distensibility values of the V0 group were found to be significantly lower than those of the control group. It means that arterial stiffness was higher in smokers than in nonsmokers. This finding is consistent with those of previous studies, and it may be explained by an increase in sympathetic activation based on smoking (34). Aortic strain and distensibility were found to be increased in the V3 group compared with those in the V0 group, but this increase was not statistically significant. This result shows that varenicline has no negative effect on arterial stiffness. On the contrary, it seems to have positive effects on arterial stiffness by helping the subjects to quit smoking.

Urotensin II has been used as a marker of myocardial injury and ischemia reperfusion injury (23, 24). In a previous study, urotensin II levels were found to be increased in smokers but the relationship between this marker and varenicline has not been considered so far (25). In this study, there were no significant differences among the three groups in terms of urotensin II levels. This result may be related to the small sample size.

Previous studies have reported that smoking increases oxidative stress (35, 36). In our study, this increase did not reach a statistical significance. The cause of this result might be associated with the fact that many of the participants were middle-aged (34.26±9.38 year) and had smoked less than 20 packs/year.

Our study suggested that TAS measured in the V3 group was found to be significantly lower than that in the V0 group. Likewise, TOS were also found to be decreased. TAS is a compensatory mechanism against increase in oxidative stress. Therefore, we can assume that the decrease in TAS levels is a parallel reaction to the decrease of serum TOS levels.

Previously, Kato et al. (17) studied the effect of varenicline on oxidative stress and showed that it decreased oxidant stress. They used reactive oxygen metabolites to determine the oxidant status; however, we used TOS for this purpose. Different from the previous study, we studied antioxidant status in addition to the oxidant status.

In the present study, we also observed differences in some parameters in complete blood count and biochemical tests between V0 and V3 groups. These findings are consistent with Kato et al. (17) results and these alterations can be explained by the effect of nicotine on these parameters.

Although success rate on smoking cessation with varenicline was high in the first 3 months, relapse was observed in five persons who were monitored for a year.

The present study has several limitations. First of all, smokers in the study were of the middle-age group; as a result, cardiac side effects related with varenicline may have been minimized. Therefore, studies involving aged smokers should be conducted. Another limitation is that the heterogeneity of addiction levels of smoking individuals might have affected the study results.

CONCLUSION

Our study reveals that varenicline treatment may decrease in TAS in smokers in connection with smoking cessation. It was demonstrated that varenicline has no negative effect on arterial stiffness during smoking cessation. Further studies are needed to confirm the results.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Balıkesir University Clinical Research.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.S., G.E., E.A., Ö.K.; Design - N.S., G.E., Ö.K.; Supervision - F.E., Ö.Y.; Resources - G.E., Ö.K., T.G.; Materials - G.E., E.A., T.G.; Data Collection and/or Processing - N.S., T.G.; Analysis and/or Interpretation - N.S., G.E., Ö.Y.; Literature Search - F.E., E.A.; Writing Manuscript - N.S., G.E.; Critical Review - Ö.Y., F.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was supported by Balıkesir University Research Funds (Project number: "BAP-2012/100 and BAP 2013/104").

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