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Original Research Article

Oxidative Stress Markers & Effect of Grape Seed Extract in Obstructive Sleep Apnoea

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Abstract

Introduction: Obstructive sleep apnoea is characterized by recurrent nocturnal obstruction of the upper, repeated changes of oxygen saturation could be considered analogous to recurrent episodes of ischemia-reperfusion injury, which causes damage after the restoration of blood flow to ischemic or hypoxic tissues. Although several mechanisms are involved, such damage is mainly attributed to the production of reactive oxygen species (ROS) during reoxygenation.

Material & Methods: The study was conducted at VPCI Delhi. 20 subjects agreed to undergo a detailed polysomnography study. Epworth sleepiness scale was conducted on these subjects. Biochemical parameters Glutathione Assay, Nitric Oxide assay, Lipid Peroxide Assay & Total Antioxidant capacity of plasma was estimated.

Statistical Analysis: Paired t-test with two tail significance was used to compare the changes in study parameters in the same patient before and after the treatment. Unpaired t-test was used to compare the baseline data in the control subjects and the patients. The tests were considered significant if they yielded $p<0.05$.

Results: Epworth Sleepiness Score decreased significantly in the group treated with GSE as compared to the baseline. Nitric oxide levels increased after one night of CPAP therapy, given prior to start of treatment, in both GSE and placebo treated groups. In the GSE as well as placebo treated group, prior to the beginning of treatment, CPAP therapy for one night, increased the total reduced glutathione levels significantly. Though a decrease in plasma Ox-LDL levels was observed in both groups after one-night CPAP therapy, it was not statistically significant.

Conclusion: The present study establishes that there is indeed oxidative stress in patients with OSAS. Oral intake of the antioxidant Grape Seed Extract (GSE) for a period of one month appears to have therapeutic potential.

Keywords: GSE (Grape seed extract), LPO (Lipid peroxidase).

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Introduction

The past decade has seen a rapid increase in the number of patients being referred for obstructive sleep apnoea syndrome (OSAS). Indeed, in many centres, possible OSAS is now among the most common respiratory referrals and is a common outpatient respiratory diagnosis [1].

A recent study on mildly obese but otherwise healthy men (mean body mass index [BMI] = 30 kg/m^2) reported 60% prevalence of SDB and 27% prevalence of OSAS[2]. The risk factors and prevalence of OSAS in India appear to be similar to those in the west. The prevalence rate of OSAS in Delhi has been reported to be 13.7% and 3.6% for habitual and Non habitual snorers' respectively[3]. In another study, the prevalence of OSAS in rural Delhi was estimated to be 11%[4]. This prevalence is similar in magnitude to the prevalence of some diseases considered to be major public health issues such as diabetes mellitus and asthma [5].

The basis of this association between OSAS and cardiovascular disease seems to be the triggering of various inflammatory pathways in OSAS[6,7]. Studies have shown that oxidative stress occurring in OSAS as an underlying cause of inflammation. Various studies using different antioxidants such as vitamin-C, vitamin-E and N-Acetyl Cysteine (NAC) have been done at our institute and they report measurable improvements in symptoms of

OSAS[8,9]. It is likely that these antioxidants may also be affecting the level of inflammatory mediators. Previous studies did not examine the effect of antioxidants on inflammatory mediators. Hence it was decided to investigate the same as it will not only confirm the previous studies but also prove a basis for the pathways involved in the improvement in the measured parameters. A different antioxidant, namely grape Seed Extract (GSE), was used. The effect of GSE on various polysomnography (PSG) parameters, oxidative stress parameters and inflammatory mediators was studied. Grape seed extract, which is a potent antioxidant, can be used to combat the oxidative stress in OSAS and may hold therapeutic potential for treating OSAS[10].

In chemical terms, oxidative stress is a large increase (becoming less negative) in the cellular reduction potential, or a large decrease in the reducing capacity of the cellular redox couples, such as glutathione[11,12].

several mechanisms are involved, damage in OSA is mainly attributed to the production of reactive oxygen species (ROS) during reoxygenation [13.14]. Studies have provided evidence that supports an increase of oxidative stress in OSA. Schulz et al (2000) [15]and Dyugovskaya et al (2002) [16] detected an increase in the production of ROS in OSA, while Barcelo et al (2000)[17] demonstrated an increase of plasma lipid peroxides. In addition, Christou et al (2003)[18]and Singh et al (2009) [19] proved that patients with severe OSA have a reduced antioxidant capacity. Furthermore, Carpagnano et al (2003)[20]found an increase of the 8-isoprostane level in the exhaled breath condensate in OSA patients. It is well known that the prevalence of asymptomatic SDB is several times higher than that of recognized SDB[21]. Thus, oxidative stress in persons with SDB may also be a public health issue. The gold standard for OSAS diagnosis is overnight polysomnography in a sleep laboratory. Obstructive hypopneas and apneas are seen as reduction or absence of airflow with persistent respiratory effort, i.e., chest or abdominal wall movement [22].

To grade the severity of sleep apnea, the number of events per hour is reported as the apnea-hypopnea index (AHI). An AHI of less than 5 is considered normal. An AHI of 5-15 is mild; 15-30 is moderate and more than 30 events per hour is characterized as severe sleep apnea[23-25].

Material & Methods

The study was conducted in the Department of Physiology, in conjunction with Department of Respiratory Medicine, at Vallabhbhai Patel Chest Institute (VPCI), Delhi.

Subjects: In a period of fifteen months, 48 male and 33 female (post-menopausal) subjects were screened on the basis of obesity (BMI>25), short neck, history of snoring or excessive day time sleepiness. Loud snoring was assessed from the questionnaire (Appendix-1) and excessive day time sleepiness assessed by Epworth sleepiness score (ESS). A score >10 on ESS was taken as significant day time sleepiness. Out of 81 subjects, 35 subjects with features of obesity, loud snoring and excessive day time sleepiness, were given a detailed questionnaire (Appendix-2). The remaining 46 subjects were having either obesity or loud snoring or excessive day time sleepiness alone, and hence not followed further. Out of these 35 subjects, having features suggestive of OSAS as assessed by questionnaire, 26 subjects agreed to undergo a detailed polysomnography study.

The study protocol was approved by the institutional Committee on Ethics in Medical Research. Patients were included in the study according to the following criteria

1. Adult males and postmenopausal females having symptoms suggestive of OSAS like loud snoring, excessive day time sleepiness and easy fatigability.
2. Apnoea hypopnea index >5. Apneic event being defined as cessation of oro-nasal airflow for at least 10 sec. Hypopnea being defined as reduction in oronasal airflow by 50% or below for atleast 10 sec.

Patients with FEV_1>50% of predicted value and ABG within normal limits were included in the study. 25 subjects underwent polysomnography in this study. 20 patients remained for the full length of the study.

Venous blood samples were collected early in the morning before the patient got out of the bed and during the day time for various biochemical estimations. It was also done three times-one before sleep study, one after 1 night of CPAP and one after treatment with GSE.

Height and weight were measured using standard methods, and the body mass index (BMI) was calculated using the following formula- weight in kg/(height in m)[2]. The circumference of the neck was measured at the cricothyroid membrane level.

A questionnaire prepared at VPCI was completed by the subjects and EPWORTH SLEEPINESS SCALE was completed with the help of the subjects.

Estimation of nirtic oxide (NO) assay was carried out according to the method developed by Tracey et al Results were expressed in µM/L[26-29]. The levels of plasma oxLDL was measured by commercially available ELISA kits. This assay used a polyclonal anti-ox-LDL antibody and an oxLDL-HRP conjugate. The assay sample and buffer were incubated together with oxLDL-HRP

conjugate in pre-coated plate for one hour. After the incubation the wells were washed and incubated with a substrate for HRP enzyme. The product of the enzyme-substrate reaction formed a blue colored complex. finally, a stop solution was added, which change the color to yellow. The intensity of the color was measured at 450 nm.

Statistical Analysis

All the data were expressed as mean ± SEM. Paired t-test with two tail significance was used to compare the changes in study parameters in the same patient before and after the treatment.

Unpaired t-test was used to compare the baseline data in the control subjects and the patients. The tests were considered significant if they yielded $p<0.05$.

Results

The results presented here are the data collected from 20 patients with OSAS. These patients were divided into two groups of 10 each randomly. Each patient of one group was given Grape Seed Extract (GSE) and each patient of the other group was given placebo. These 20 patients stayed for the full length of the study.

The mean age was 41.1 ± 3.3 years, mean body weight, mean BMI ,84.6 ± 5.0 kg, 32.9 ± 2.3 kg/m2 as shown in Table-1 & mean hemoglobin of the patients in GSE group were and 12.6 ± 1.7 mg/dL respectively.

The mean age, mean body weight, mean BMI, of the patients in the placebo group were 45.6 ± 3.7 years, 87.2 ± 4.8 kg, 31.5 ± 2.7 kg/m2 as mentioned in Table-1 and mean hemoglobin was 14.1 ± 1.8 mg/dL respectively. Within the GSE group, five patients had systemic hypertension, two patients had type 2 diabetes and one patient had hypothyroidism as shown in Table-1.

Table 1:

Parameters	GSE group (n=10)			Placebo group (n=10)		
	Baseline	CPAP	GSE	Baseline	CPAP	Placebo
Body weight (kg)	84.6±5.0	84.7±5.0	85.8±5.0	87.2±4.8	87.6±4.7	87.6±4.6
Body mass index (kg/m^2)	32.9±2.3	32.9±2.3	32.9±2.3	31.5±2.7	31.5±2.7	31.5±2.7
Neck circumference (cm)	40.1±1.6	40.1±1.6	40.1±1.6	41.7±1.2	41.7±1.2	41.7±1.2
Systolic blood pressure (mmHg)	130.2±4.1	129.3±3.9	131.0±3.8	135.8±2.7	134.2±2.9	131.5±2.3
Diastolic blood pressure (mmHg)	86.6±2.5	85.4±2.9	84.2±3.2	89.4±2.7	89.8±2.4	88.8±2.9
Pulse rate (/min)	74.6±3.6	75.2±3.2	73.4±3.0	75.6±2.3	77.5±2.7	74.2±2.5

All patients were on medications and their diseases were under control. Any chest disease in all the 20 patients was ruled out by auscultation of the chest, chest X-ray, pulmonary function test, ABG, TLC, DLC and if needed CT-scan. Cardiac disease was ruled out by history, auscultation, ECG, and chest X-ray.

Epworth Sleepiness Score (ESS): ESS decreased significantly in the group treated with GSE as compared to the baseline ($p<0.001$, Table 2). Thus, the overall quality of life improved after treatment with GSE. There was no change in ESS in placebo treated group.

Apnea-Hypopnea Index (AHI): AHI decreased significantly in the group treated with GSE ($p<0.05$, Table 2) as compared to the baseline values. There was no significant decrease in AHI in the group treated with placebo.

REM as SPT: There was no significant change in the time spent in REM in the group treated with GSE ($p>0.05$, Table 2). Though there was a decrease in the time spent in REM in the group treated with placebo, it was not statistically significant ($p>0.05$,Table 2).

Mean O_2 Saturation: Though mean O_2 saturation decreased slightly in GSE group, there was no significant change in mean O_2 saturation in either group ($p>0.05$, Table 2).

Continuous Positive Airway Pressure (CPAP) : The pressure required to keep the airway patent during sleep decreased significantly in GSE treated group ($p < 0.005$,Table 2). There was a small and insignificant increase in CPAP in placebo treated group

Table 2:

	GSE (n=10)		Placebo (n=10)	
	Basal	**After treatment**	**Basal**	**After treatment**
REM as SPT (%)	4.0±1.3	3.9±1.3	4.5±2.6	2.7±2.2
Apnea-hypopnea index (AHI)	66.4±9.6	60.6±9.7*	94.3±9.2	95.6±8.8
Longest apneic episode duration (s)	45.2±3.7	40.6±3.3	41.8±4.3	45.8±5.3
Mean O_2 saturation	88.6±2.1	86.0±3.2	87.2±2.1	87.6±2.0
Snore time (min)	10.8±3.5	5.1±1.2	8.4±2.8	10.9±2.8
Snore episodes	37.7±9.1	38.8±12.0	32.4±9.2	35.8±6.4
CPAP (cm H_2O)	10.2 ± 0.7	8.3 ± 1.1**	9.4 ±0.6	9.5 ± 0.7
ESS	13.9 ± 1.2	8.9 ± 1.6**	13.5 ± 1.1	13.3 ± 1.1

Plasma Nitric Oxide (NO_X) levels: Nitric oxide levels increased after one night of CPAP therapy, given prior to start of treatment, in both GSE and placebo treated groups ($p<0.001$, Table 3). After treatment with GSE, NO levels increased significantly ($p<0.01$, Table 3), whereas there was no significant change in NO levels after treatment with placebo.

Total Plasma Ox-LDL levels: Though a decrease in plasma Ox-LDL levels was observed in both groups after one night CPAP therapy, it was not statistically significant ($p>0.05$,Table 3). GSE group also showed insignificant decrease in Ox-LDL levels after 5 weeks of treatment. No such change was seen in placebo group.

Table 3:

	GSE group (n=10)			Placebo group (n=10)		
	Baseline	**CPAP**	**GSE**	**Baseline**	**CPAP**	**Placebo**
Nitiric Oxide (nM/ml) (NOx)	30.3±1.0	33.3±1.0***	36.8±1.0**	30.5± 1.9	33.5 ± 1.3***	30.8 ± 1.8
Plasma Ox-LDL	20.5±4.3	18.0±2.8	16.6±2.3	22.1±4.3	20.5±3.9	22.8±4.4

Discussion

Hypoxic conditions, such as OSAS may result in transient depletion of cellular reductants, such as glutathione, which constitute a main line of antioxidant defence. Both apneas and hypopneas usually end in arousal, where reoxygenation causes the production of ROS. Also microsomal radical generation is maximal under hypoxic conditions, which may also be associated with loss of cellular energy metabolites, and hence reductants that defend against radical fluxes[30].Studies have shown that patients with severe OSA syndrome had reduced antioxidant capacity, suggesting the role of hypoxia-reoxygenation occurring in OSA patients to be responsible for reducing the antioxidant capacity[31].

Several studies report abnormal Lipid peroxidation profile in OSAS patients, Barcelo et al (2000) [32] have found that thiobarbituric acid reactive substance (TBARS) formation was higher in OSAS patients and CPAP treatment improves the abnormal lipid peroxidation events in these patients. Similarly Lavie et al (2004) [33] have reported that morning levels of TBARS and peroxides were significantly higher in OSAS patients, with or without cardiovascular disease, than in controls; and the CPAP treatment decreases this nocturnal rise. Increased lipid peroxidation in OSAS patients may be because of hypoxia/reoxygenation. Chronic intermittent hypoxia (CIH) is characterized by periodic reoxygenations, which are absent with continuous hypoxia. It is possible that ROS may be generated during the reoxygenation phase of CIH, similar to that seen in ischaemia–reperfusion[34]. Recent studies have reported that CIH indeed results in increased generation of ROS in the carotid body , adrenal medullaand brainstem. Application of CPAP improves the oxygenation status throughout the night by reducing the apneic episodes, diminishing the hypoxia/ reoxygenation phenomenon and minimizing the oxidative stress [35-37]. Similar to the above studies and our previous observations, in the present study also we found increased levels of lipid peroxidation (OxLDL) in OSAS patients (Table 3). After one night of CPAP, lipid peroxidation decreased significantly (Table 3). This observation is in contrast to the finding of Wali et al (1998), who reported that CPAP therapy of one night did not have immediate effects on lipid peroxidation in severe OSA patients [38].We further found that lipid peroxidation in OSAS patients decreased after treatment with GSE (Table 3). This finding is also explained by the antioxidant properties of GSE which scavenge the ROS and lead to decreased lipid peroxidation.

In our study we found that plasma nitric oxide levels increased after one night of CPAP therapy

(Table 3). This finding is similar to that of Schulz et alwho reported an increase in plasma nitate concentrations after two nights of CPAP therapy [39]. NO is the main vasodilating substance released from endothelium. Deficiency of NO has been implicated in the pathogenesis of cardiovascular disease[40,41]. Studies have also suggested reduced endothelium dependent vasodilation in OSAS [42,43]. Thus the increase in NO levels by CPAP therapy may be one of the mechanisms by which it exerts a favorable influence on progression of cardiovascular disease[44]. Levels of NO derivatives (nitrate and nitrite (NOX)) increased after intake of GSE also (Table 3). This finding is supported by another recent study which shows that GSE upregulates eNOS in human umbilical vein endothelial cells. This upregulation of eNOS is mediated by the activation of the PI3 kinase/Akt signaling pathway, resulting in the phosphorylation of eNOS. This directly leads to increased NO production by vascular endothelium[45]. The quality of life of patients (as reported by patients themselves and assessed by the sleep questionnaire (Appendix-2) and ESS) treated with GSE improved markedly. However, unlike our previous studies there was only modest improvements in various PSG parameters. Some of the parameters such as apnea related arousals, sleep efficiency, REM as SPT, stage 3 of NREM as SPT, oxygen desaturation events and mean oxygen saturation did not show significant change after GSE treatment (Table 2). This is in contrast to previous study done at our institute using NAC [9]. In that study, all the PSG parameters except REM as SPT had shown significant improvements. In another study done in our department using vit.C and vit.E, similar changes in ESS and patients' quality of life were found without corresponding improvements in all the PSG parameters. The role of antioxidants in OSA has been reported in many studies, though opinions may differ. Several studies reported decreased levels of vitamins A and E in OSA patients compared with healthy individuals [46,47]. In contrast, Saruhan et al. found that concentrations of vitaminA are increased in OSA patients and are positively correlated with Apnoea, Hypopnea per hour AHI [48]. The GSPE treatment markedly decreased interleukin (IL)-4, IL-13, and vascular endothelial growth factor (VEGF) levels in BALF in addition to the total serum IgE levels. A histological examination demonstrated that GSE significantly ameliorated allergen-induced lung eosinophilic inflammation and decreased PAS-positive epithelial cells in the airway. The elevated hydroxyproline contents, lung α-SMA contents, and TGF-β1 protein expression that were observed in the OVA mice were also inhibited by GSE [49]. The mean age of the patients was 45.6±3.7 years in placebo group and 41.1±3.3 years in GSE group. There was no change in body weight in patients of both groups after one night of CPAP and after treatment with GSE or placebo for 5 weeks. There was no change in BMI in patients of both groups after one night of CPAP and after treatment with GSE or placebo for 5 weeks. In patients with OSAS there are recurrent cycles of hypoxia/reoxygenation. These events lead to generation of ROS resulting in oxidative stress which in turn causes tissue damage and inflammation. The tissue injury in the respiratory and wakeness promoting centres of brain further accentuates the severity of OSAS thus perpetuating a vicious cycle. Oral intake of GSE will decrease the oxidative stress by decreasing lipid peroxidation products and increasing antioxidant capacity.

Conclusions

The present study establishes that there is indeed oxidative stress in patients with OSAS. Oral intake of the antioxidant Grape Seed Extract (GSE) for a period of one month appears to have therapeutic potential. By removing oxidative stress and increasing antioxidant capacity, it not only improves the sleep parameters but also produces beneficial effects on levels of inflammatory mediators. There is a significant reduction in the CPAP pressure also. These results suggest that with long term treatment of OSAS patients with antioxidants (GSE)may prove to be beneficial in improving sleep parameters and may gradually reduce their dependency on CPAP therapy.

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