Anti-Oxidant Treatment in Obstructive Sleep Apnoea Syndrome

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ABSTRACT

Purpose. To investigate whether oral intake of N-acetylcysteine (NAC) is a treatment option in patients with obstructive sleep apnoea syndrome (OSAS).

Methods. Twenty patients with OSAS were enrolled in the study. After polysomnography (PSG), they were randomly assigned to receive a placebo (n=10) and NAC (n=10). A repeat PSG was done after the treatment period of 30 days. Fasting venous samples were collected for various biochemical analysis.

Results. In the patients of NAC group, compared to their baseline values, slow wave sleep as sleep percent time (27.9±2.7 vs 42.3±4.2; p<0.01) and sleep efficiency (90.8±1.3 vs 94.4±1.5; p<0.05) improved considerably. The apnoea-hypopnoea index (61.2±8.5 vs 43.1±8.6; p<0.05), apnoea related arousals (22.2±7.6 vs 11.6±4.7; p<0.05), longest apnoic episode duration (seconds) (54.9±7.1 vs 37.8±5.6; p<0.01), oxygen desaturation events per hour (51.8±7.7 vs 37±7.8; p<0.01) and epworth sleepiness score (16.6±0.8 vs 9.2±0.9; p<0.001) decreased significantly. The relative snore time (%) (10.2±2.9 vs 4.9±1.9; p<0.01), number of snore episodes (63.8±23.9 vs 28.2±9.9; p<0.05) and duration of longest snore episode (min) (2.5±0.7 vs 0.6±0.1; p<0.05) also decreased significantly. Such responses were not evident in the placebo group. N-acetylcysteine produced significant decrease in lipid peroxidation and increase in total reduced glutathione.

Conclusions. Oral NAC administration appears to have a therapeutic potential in the treatment of OSAS. It is proposed that long-term treatment with NAC in patients with OSAS may reduce their dependency on continuous positive airway pressure therapy. [Indian J Chest Dis Allied Sci 2011;53:153-162]

Key words: Anti-oxidant, N-acetylcysteine, Oxidative stress, Sleep apnoea.

INTRODUCTION

Obstructive sleep apnoea syndrome (OSAS) is a common form of sleep-disordered breathing (SDB) characterised by repeated episodes of upper airway occlusion during sleep and excessive day-time sleepiness (EDS). The most common symptom of OSAS is EDS, which has a profound negative effect on the quality of life of these patients. The SDB refers to an abnormal breathing pattern during sleep that is often quantified as the apnoea-hypopnoea index (AHI). In general population, SDB is estimated to occur in 9% of middle-aged women and 24% of middle-aged men. However, only 2% of women and 4% of men complain of EDS, and therefore, meet the strict criteria for OSAS. Thus, OSAS is very often an underdiagnosed entity. In patients diagnosed to have OSAS, nasal continuous positive airway pressure (CPAP) remains the usual first-line of treatment. However, poor adherence to CPAP treatment is common, first because of its prohibitive cost and second because of the discomfort associated with its usage. The failure rate with CPAP treatment is more than 50% and has remained so in the last one decade. Thus, there is urgent need for an alternative line of treatment for patients with OSAS.

It has been increasingly recognised that there is an association between oxidative stress and occurrence of various cardiovascular diseases, such as hypertension, coronary artery disease and heart failure. An increased cardiovascular morbidity has been reported in patients with OSAS. Since there is repetitive nocturnal hypoxia-reoxygenation in OSAS, several studies have proposed that oxidative stress may be an underlying mechanism for the association between OSAS and cardiovascular disease.

In a recent investigation, we provided direct evidence that in patients with OSAS, there was a derangement in the oxidant-anti-oxidant balance with a shift towards oxidative stress. More importantly, it was noted that after treatment with the anti-oxidants vitamin E and vitamin C, there was not only a reduction in oxidative stress but also an improvement in the SDB and EDS. This preliminary investigation prompted us to look for other anti-oxidants which prove to be equally or more beneficial...
MATERIAL AND METHODS

The study was conducted in the Department of Physiology, in conjunction with Department of Respiratory Medicine, at Vallabh Bai Patel Chest Institute (VPCLI), Delhi in accordance with the ethical guidelines for biomedical research on human subjects by Central Ethics Committee on Human Research (CECHR), Indian Council of Medical Research (ICMR)-2000 and those as contained in “Declaration of Helsinki”.

Subjects

Of the 2163 new patients presenting to the out-patient department (unit) of the co-investigator in a period of 15 months, 52 male and 36 female (post-menopausal) patients were screened on the basis of obesity (body mass index, [BMI]>25), short neck, history of snoring or EDS. Excessive day-time sleepiness was assessed as a supplement for treatment of diseases associated with systemic inflammation. N-acetylcysteine is often prescribed as evidence of EDS.10 Thus, out of 88 patients screened, 25 patients with features of obesity, loud snoring and EDS were given a detailed questionnaire. The remaining 63 patients were having either one or any two of the symptoms, and hence, were not followed-up further. Among the 25 patients, only 20 agreed to undergo a polysomnography (PSG) study. None of them was a smoker or alcoholic.

Study Design

Patients were acclimatised in the sleep laboratory one night prior to sleep study following which a split night sleep study (diagnostic and CPAP titration done on the same night due to the constraints on availability of sleep laboratory) was done and the diagnosis of OSAS was confirmed based on standard polysomnography (PSG) (Remlogic™ version 1.1, Embla N7000, Medcare, Netherland). Polysomnography included recording of electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), oronasal thermistor and pressure transducer, thoracoabdominal movements, electrocardiogram, limb movements, body position and arterial oxygen saturation. Airflow was registered with an oronasal thermistor and pressure transducer, respiratory efforts with strain strips and transcutaneous saturation (SaO₂) monitored continuously using a pulse oximeter. Apnoea was defined as a drop in the peak thermal sensor by more than or equal to 90% of baseline or complete cessation of airflow for at least 10 seconds and was classified either as obstructive, central or mixed, based on the presence or absence of the respiratory efforts. Hypopnoea was defined as a nasal pressure signal drop by more than or equal to 30% of baseline for at least 10 seconds with ≥ 4% desaturation from pre-event baseline or a drop by more than or equal to 50% of baseline for at least 10 seconds with 3% or more desaturation from pre-event baseline or the event associated with arousal. At least 90% of the duration of events met the amplitude reduction criteria for hypopnoea. Oxygen desaturation events were defined as drop in oxygen by 3% or more or ≥ 4%. Arousal was defined as an abrupt shift in EEG frequency including alpha, theta and/or frequencies greater than 16 hertz (not including spindles) that lasted at least for three seconds with at least 10 seconds of stable sleep preceding it. Scoring of arousal during rapid eye movement (REM) sleep was associated with a concurrent increase in submental EMG lasting for at least one second. Continuous positive airway pressure titration was done according to the American Academy of Sleep Medicine (AASM) guidelines. Optimal pressure was obtained when the patient slept in supine position with stable REM sleep, saturation maintained, snoring vanished, no heart rate variability and no arousals. Snoring period was detected when a minimum of three snores were present. Snoring periods were merged into one when the interval between them was less than 10 seconds.11-13 Apnoea-hypopnoea index was calculated for each patient using the formula given below:

$$\text{AHI} = \frac{\text{Number of apnoeas} + \text{Number of hypopnoeas}}{\text{Total sleep time}}$$

Titration of CPAP was done using a mask and apparatus (Respironics, PA). These patients were then put either on NAC (Mucinac, Cipla) 600 mg thrice daily or placebo for 30 days. After 30 days, the patients were again assessed by the same sleep questionnaire and ESS. A repeat split night sleep study was performed. Venous blood samples were collected in diamine ethylene diatetraacetic acid (EDTA) vials and plain vials early in the morning. Plasma was separated for estimation of lipid peroxidation. Whole blood was lysed for estimation of total reduced GSH. Two collections of venous
blood samples were done totally—one before sleep study (Baseline) and second after treatment with NAC or placebo. All the samples collected were stored at -80 °C before subjecting them to biochemical analysis. The measurements were done in triplicate for concordance in values. Along with PSG, the following routine investigations were done: haemoglobin, total leucocyte count (TLC), differential leucocyte count (DLC), fasting blood sugar (FBS), chest radiograph (postero-anterior view), electrocardiogram (ECG), pulmonary function tests including forced expiratory volume at the end of first second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio, thyroid function tests (when indicated), arterial blood gases (ABG) analysis, and computed tomography (CT) of the paranasal sinuses (when required). The BMI was calculated in all subjects using the following formula:

$$\text{BMI} = \frac{\text{Weight in kg}}{\text{Height in m}^2}$$

Systemic arterial blood pressure was measured from the brachial artery in the morning before the patient got out of bed using a sphygmomanometer. Each measurement was done twice and the average was taken into consideration. The circumference of the neck was measured at the cricothyroid membrane level. All the measurements were performed by the same observer. The nasal septum, nasal mucosa, soft palate, uvula, tonsils, tongue, and chin abnormalities were assessed semi quantitatively. All subjects were examined by the same observer.

Biochemical Estimation

Total GSH concentration was estimated in venous blood samples by the method of Griffith using Ellman’s reagent. Whole blood was lysed by the addition of 6% acetic acid and total GSH was immediately precipitated by the addition of 10% 5-sulphosalicylic acid. After centrifugation at 4 °C, the supernatant was kept at –80 °C. The standard assay mixture contained 700mL of 0.3 mM/L nicotinamide adenine dinucleotide phosphate (NADPH), 100mL of 6mM/L 5,5’-Dithio-bis (2-nitrobenzoic acid) (DTNB), 5mL sample, and 95mL sodium-EDTA buffer (100mM/L, pH 7.5). All the reagents were made in sodium phosphate (125 mM/L)-EDTA buffer (6.3mM/L) buffer (pH 7.5). To start the reaction, 100mL of GSH reductase (15U/mL) was added and the A412 was monitored for three minutes. Lipid peroxide levels in the plasma were estimated in venous blood samples. The thiobarbituric acid reactive substance (TBARS) assay was carried out by the precipitation of lipid peroxides in phosphotungstic acid-sulfuric acid system, and malondialdehyde levels were determined by the reaction with thiobarbituric acid (TBA).

The assay mixture contained 200mL of distilled water, 200mL of plasma, 50mL of butylated hydroxytoluene (BHT) (11mg/10mL ethanol) and 400mL of orthophosphoric acid (OPA) (1.115 OPA in upto 50mL distilled water). To the assay mixture, 50mL of TBA (160 mg/10mL) of 0.1M sodium hydroxide was added and incubated in boiling water bath for 45 minutes. The eppendorfs were ice cooled and colour was extracted with 1000mL of butanol. After centrifugation at 10000 rpm for five minutes, absorption of the supernatant was read at 535 nm.

Statistical Analysis

All the data were expressed as mean±SEM (standard error of mean). 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 placebo and NAC groups. The tests were considered significant if they yielded p<0.05.

RESULTS

The 20 patients who stayed for the full length of the study were divided equally into (a) the placebo group and (b) the NAC group randomly. The anthropometric measurements, blood pressure, and pulse rate in OSAS patients are presented in table 1. The mean age, mean body weight, mean BMI, mean haemoglobin of the patients in NAC group were 53.1±2.3 years, 84.8±4.7kg, 34.8±2.4kg/m² and 14.4±1.3mg/dL, respectively; while in the placebo group these were 56.2±3.1 years, 82.8±5.0kg, 15.1±1.2mg/dL, respectively (Table 1). In the NAC group alone systolic blood pressure decreased significantly after treatment (Table 1). Though it did not reach statistically significant levels, there was a decrease in the diastolic blood pressure also after treatment with NAC.

Within the NAC group, one patient had systemic hypertension with diabetes mellitus (type 2) and one patient had hypothyroidism. Both the patients were on medications and their diseases were under control. Three patients were having deviated nasal septum and mild to moderate nasal obstruction on computed tomography (CT) of the para-nasal sinus (PNS). In the placebo group also, two patients had systemic hypertension and one patient had hypothyroidism. Both these patients were on medications and their diseases were under control. Two patients were having deviated nasal septum and mild to moderate nasal obstruction on CT of the PNS. The chest radiograph and pulmonary function test showed no abnormality.
Polysomnography Parameters

The various PSG parameters, namely sleep parameters, respiratory parameters, the titrated CPAP pressure and ESS are shown in Table 2.

Epworth Sleepiness Score

Epworth sleepiness score decreased significantly in the NAC group compared to baseline (p<0.001, Table 2). All patients treated with NAC reported back saying that their quality of life (QOL) had improved. The weekly assessment of ESS using the questionnaire revealed that the improvement occurred within the first week itself. However, there was no change in ESS in the placebo group (p>0.05, Table 2).

Sleep Parameters

Stage 3 of Non-rapid eye movement (NREM) as Sleep Percentage Time

The time that the patients spent in stage 3 of non-rapid eye movement (NREM) sleep increased significantly in the NAC group (p<0.01, Figure 1, Table 2). Two patients who were suffering from morning headache and seven patients who complained of day-time fatigue, found them to be relieved after treatment with NAC. All patients reported saying that they had a more refreshing sleep. In the placebo group, there was no significant change in the time spent in stage 3 of NREM sleep (p>0.05, Table 2).

### Table 1. Anthropometric measurements, blood pressure and pulse rate in patients with OSAS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo Group (n=10)</th>
<th>NAC Group (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After Baseline</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>82.8±5.0</td>
<td>82.8±5.0</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>32.9±2.3</td>
<td>32.9±2.3</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>39.1±1.2</td>
<td>39.1±1.2</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>130.2±4.8</td>
<td>130.0±4.0</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>86.4±2.5</td>
<td>85.2±3.5</td>
</tr>
<tr>
<td>Pulse rate (per minute)</td>
<td>70.5±3.0</td>
<td>71.4±3.0</td>
</tr>
</tbody>
</table>

All data are shown as mean±SEM; *=p<0.05, compared to corresponding baseline values.

OSAS=Obstructive sleep apnoea syndrome; NAC=N-acetylcysteine; CPAP=Continuous positive airway pressure

### Table 2. Polysomnography parameters in patients with OSAS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo Group (n=10)</th>
<th>NAC Group (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>After placebo</td>
</tr>
<tr>
<td>Stage 3 of NREM as SPT (%)</td>
<td>23.7±1.2</td>
<td>20.5±1.7</td>
</tr>
<tr>
<td>REM as SPT (%)</td>
<td>10.1±3.1</td>
<td>7.0±2.5</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>92.5±1.9</td>
<td>90.0±1.9</td>
</tr>
<tr>
<td>Epworth sleepiness score</td>
<td>17.5±1.4</td>
<td>17.9±1.3</td>
</tr>
<tr>
<td>Apnoea-hypopnoea index (per hour)</td>
<td>44.0±9.9</td>
<td>47.2±8.9</td>
</tr>
<tr>
<td>Obstructive apnoeas (per hour)</td>
<td>39.5±10.5</td>
<td>50.4±12.4</td>
</tr>
<tr>
<td>Apnoea related arousals</td>
<td>13.4±5.9</td>
<td>22.5±10.4</td>
</tr>
<tr>
<td>Hypopneas (per hour)</td>
<td>2.7±1.0</td>
<td>5.2±1.7</td>
</tr>
<tr>
<td>Longest apnoeic episode duration (seconds)</td>
<td>32.7±6.2</td>
<td>33.4±5.1</td>
</tr>
<tr>
<td>Average minimum oxygen saturation</td>
<td>92.5±1.9</td>
<td>90.0±1.9</td>
</tr>
<tr>
<td>Number of desaturation episodes below 90%</td>
<td>26.2±10.4</td>
<td>29.3±11.0</td>
</tr>
<tr>
<td>Oxygen desaturation events (per hour)</td>
<td>41.7±9.1</td>
<td>47.5±10.1</td>
</tr>
<tr>
<td>CPAP (cmH₂O)</td>
<td>7.1±1.1</td>
<td>7.4±1.1</td>
</tr>
</tbody>
</table>

All data are shown as mean±SEM; *=p<0.01, †=p<0.05, ‡=p<0.001 vs corresponding baseline values;

OSAS=Obstructive sleep apnoea syndrome; NAC=N-acetylcysteine; NREM=Non-rapid eye movement; SPT=Sleep percentage time; REM=Rapid eye movement; CPAP=Continuous positive airway pressure
Rapid Eye Movement as Sleep Percentage Time
In patients treated with NAC and those treated with placebo, there was no significant change in the time spent in REM sleep (p>0.05, Table 2). However, there was a tendency for an increase in the time spent in REM sleep in the NAC group.

Sleep Efficiency
There was a significant improvement in sleep efficiency in the NAC group (p<0.05, Table 2). Such a change in sleep efficiency was not seen in the placebo group (p>0.05, Table 2).

Respiratory Parameters
Apnoea-Hypopnoea Index
The AHI decreased significantly in the NAC group (p<0.05, Table 2). Such a change in AHI was not seen in the placebo group (p>0.05, Table 2).

Apnoea
The number of apnoeic episodes decreased significantly in the NAC group (p<0.05, Figures 2 and 3, Table 2). In the placebo group, there was no such significant change (p>0.05, Table 2).

Apnoea Related Arousals
The apnoea related arousals decreased significantly in the NAC group (p<0.05, Table 2). In the placebo group, there was no such significant change (p>0.05, Table 2).

Average Minimum Oxygen Saturation
The average minimum oxygen saturation increased significantly in the NAC group (p<0.001, Table 2). Such a response was not evident in the placebo group (p>0.05, Table 2).

Number of Desaturation Episodes Below 90 Percent
The number of desaturation episodes below 90% decreased significantly in the NAC group (p<0.05, Table 2). In the placebo group, there was no such significant change (p>0.05, Table 2).

Oxygen Desaturation Events
The number of oxygen desaturation events per hour decreased significantly in the NAC group (p<0.01, Table 2). In the placebo group, there was no such significant change (p>0.05, Table 2).

Continuous Positive Airway Pressure
There was a significant drop in the pressure required to keep the upper airways patent by CPAP in the NAC group (p<0.01). Indeed, as shown in figure 4, a pressure which was sub-optimal before became optimal after treatment with NAC. The results of all
the patients studied are presented in table 2. Three patients who required CPAP did not require it after treatment with NAC. In the placebo group, there was no such significant change (p>0.05, Table 2).

**Snore Parameters**

The snore characteristics are shown in table 3.

**Relative Snore Time**

The relative snore time decreased significantly in the NAC group (p<0.01, Figure 3, Table 3). In the placebo group, there was no such significant change (p>0.05, Table 3).

**Snore Episodes**

The number of snore episodes decreased significantly in the NAC group (p<0.05, Figure 3, Table 3). In the placebo group, there was no such significant change (p>0.05, Table 3).

**Lipid Peroxidation**

In the NAC group, after the treatment period, the lipid peroxidation (LPO) levels decreased significantly compared to their baseline (p<0.001, Table 4). There was no significant change in the LPO levels of placebo group after the treatment period (p>0.05, Table 4).

Table 3. Snore parameters in patients with OSAS

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group (n=10)</th>
<th>NAC Group (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>After placebo</td>
</tr>
<tr>
<td>Relative snore time (%)</td>
<td>11.7±2.9</td>
<td>11.9±2.7</td>
</tr>
<tr>
<td>Snore episodes</td>
<td>43.6±9.7</td>
<td>45.1±9.3</td>
</tr>
<tr>
<td>Longest snoring episode (minute)</td>
<td>2.9±0.9</td>
<td>3.6±0.8</td>
</tr>
</tbody>
</table>

All data are shown as mean±SEM; *=p<0.01, †=p<0.05 vs corresponding baseline values.

OSAS=Obstructive sleep apnoea syndrome; NAC=N-acetylcysteine
Total Reduced Glutathione

In the NAC group, after the treatment period, the total reduced glutathione (GSH) levels increased significantly compared to their baseline (p<0.001, Table 4). There was no significant change in the total reduced GSH levels of placebo group after the treatment period (p>0.05, Table 4).

**Measure of Anti-Oxidant Capacity**

**Total Reduced Glutathione**

In the NAC group, after the treatment period, the total reduced glutathione (GSH) levels increased significantly compared to their baseline (p<0.001, Table 4). There was no significant change in the total reduced GSH levels of placebo group after the treatment period (p>0.05, Table 4).

**DISCUSSION**

The major findings of the present study are that in patients with OSAS who were treated with the anti-oxidant NAC, there were significant improvements in the sleep parameters, respiratory parameters and snore characteristics. Their overall QOL improved as evident from the significant decrease in ESS.

In the NAC group, the day-time sleepiness decreased significantly. The mechanism for the EDS in these patients (before treatment) has been speculated to be due to increased production of pro-inflammatory mediators. Indeed there are reports that, inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1β and IL-6 are involved in physiology of sleep regulation. Exogeneous administration of these cytokines induces sleepiness even in normal subjects. In obese individuals and in diabetic patients, the excessive sleepiness and fatigue are considered to be due to these cytokines. Vgontzas et al reported that in patients with obstructive sleep apnoea, TNF-α and IL-6 were significantly elevated.

It is recognised that when there is oxidative stress, there is an increase in the production of the inflammatory cytokines which in turn would
produce further free radicals, thus forming a vicious cycle and worsening the disease condition. Veasey et al.21 showed that long-term intermittent hypoxia increased NADPH-oxidase gene and protein responses in wake-active brain regions in rats. The resultant lipid peroxidation injury and the subsequent inflammatory cytokine release from these cells were considered responsible for the hypersomnolence observed in them. The results obtained from our study support this observation. In our OSAS patients also, there was oxidative stress as evidenced by an increase in LPO products. It is likely that the oxidative stress causes damage to the wake promoting cells and reduces their activity. We propose that, NAC intake will maintain the activity of wake promoting cells by reducing the oxidative stress, and thus, inflammatory cytokines. Further experiments are in progress to assess the role of inflammatory cytokines in influencing sleep pattern in these patients.

In our study we found that after NAC intake, the sleep efficiency of these patients increased. They spent more time in stage 3 of NREM sleep instead of stages 1 and 2 of NREM sleep which were more frequent before treatment. There was a tendency for an increase in the time spent in REM sleep also. Additionally there was an improvement in the respiratory parameters, especially the AHI. These findings are in agreement with our previous investigation in which the anti-oxidants administered were vitamin E and vitamin C. A noteworthy feature of the present study was the general decrease in the number of oxygen desaturation events in the NAC group suggesting an overall improvement in their ventilation. All these improvements are possible only if the tone of upper airway muscles is maintained and prevented from falling during sleep. The tone of these muscles can be affected by several mechanisms including production of reactive oxygen species (ROS). Reactive oxygen species produced in the hypoglossal region of the medulla during long term intermittent hypoxia reduces the hypoglossal neural output and promotes airway collapsibility.23 Additionally, ROS produced in the upper airway respiratory muscles impairs their endurance during hypoxia/intermittent hypoxia. This effect is reduced considerably by anti-oxidant treatment or enhanced further by inhibition of the anti-oxidants.24,25 Further, oxidative stress can cause contractile dysfunction, diminishing the force developed per muscle cross-sectional area in skeletal muscles.26 The fatigue in skeletal muscles is reversed to a large extent by endogenous anti-oxidants including thiol compounds such as GSH and cysteine.27 We propose that an increase in ROS production and a decrease in anti-oxidant capacity would lead to a fall in the tone of the upper airway dilator muscles. In that case, it would be reversed by anti-oxidant treatment. Support for this proposition is obtained in the present study. There was not only an increase in LPO but also a decrease in reduced GSH which got reversed after treatment with NAC. That the endurance of the upper airway dilator muscles is enhanced is supported indirectly by the improvement in oxygen desaturation events which must be due to an increase in the patency of the airway. As glutathione crosses the blood-brain barrier,28 it may have produced its effects centrally and peripherally.

All the patients who participated in the present study exhibited loud snoring. It is known that in patients with OSAS, there is a decrease in the patency of the upper airway29 which may be due to oxidative stress. As discussed above, oxidative stress may decrease the tone of the upper airway dilator muscles by inhibiting hypoglossal nerve activity 23 or produce soft tissue oedema in the upper airway by promoting inflammatory mediator release. Both these factors cause airway narrowing. Due to this narrowing, there will be turbulence to the airflow which may promote snoring. In that event, it should be possible to reduce snoring by decreasing oxidative stress and increasing the anti-oxidant capacity. Indeed, in the NAC group, there was not only a decrease in the number of snoring episodes and snore duration but also a reduction in the snore intensity. To the best of our knowledge, this is the first study in which a significant reduction in snoring was observed in patients with OSAS using a drug which is in use in medical practice for the last several years. The improvement was dramatic in some of them. In fact, the bed partners of all these patients reported back saying that the snoring of their spouses no longer bothered them. Coupled with the improvements in respiratory parameters, a reduction in snore episodes adds to the QOL in these patients.

The titrated CPAP pressures to keep the upper airway patent before and after the treatment period were 7.1±1.1 and 7.4±1.1cmH2O, respectively in the placebo group. These values were not significantly different from each other. The results from our investigation suggest that CPAP measurements are reproducible when repeated within a period of 30 days.

In contrast to the observations in the placebo group, the titrated CPAP pressures before and after the treatment period were 8.7±0.5 and 5.0±1.2cmH2O, respectively in the NAC group. The pressure drop was significant. While the application of sub-optimal pressure still produced apnoeic periods, a similar pressure did not produce them in the same patient after treatment with NAC. Indeed, three patients who needed CPAP before did not require them after NAC. These results are in agreement with our previous
observations\textsuperscript{5} using the anti-oxidants vitamins E and C and support the contention that long-term treatment with anti-oxidants may reduce the dependency on CPAP machine.

An imbalance in the oxidant-anti-oxidant status has been implicated in the development of cardiovascular abnormalities in patients with OSAS.\textsuperscript{31} There is not only an increase in pro-oxidants but also a decrease in anti-oxidants.\textsuperscript{32,33} The results from the present study are in agreement with these findings—there was an increase in LPO and a decrease in total reduced GSH. Compared to our previous investigation\textsuperscript{7} in which the anti-oxidants used were vitamins E and C, there was a greater increase in total reduced GSH level in the NAC used were vitamins E and C, there was a greater increase in total reduced GSH level in the NAC group. It is understandable as NAC being a GSH prodrug, has the ability to increase as well as replenish the intracellular GSH that is utilised for scavenging ROS.\textsuperscript{34} Additionally, GSH helps in the regeneration and maintenance of the free radical neutralising activity of endogenous vitamins E and C,\textsuperscript{35,36} which will indirectly facilitate the total reduced GSH.

CONCLUSIONS

The present study establishes that there is oxidative stress in patients with OSAS. Oral intake of the anti-oxidant NAC for a period of one month not only improves the sleep parameters but also produces beneficial effects on oxygen saturation and snore characteristics. There is a significant reduction in the CPAP pressure requirement also. These results suggest that long-term treatment of OSAS patients with anti-oxidants may gradually reduce their dependency on CPAP therapy. However, clinical trials involving a larger number of patients are required before making the recommendation that anti-oxidant intake is a primary therapy for patients with OSAS.

REFERENCES


