

## Chronic Smoking, a Cause for Development of Peripheral Neuropathy in Chronic Obstructive Pulmonary Disease

Aparna Garg\*, Suresh kumar Goyal\*, D.A. Biswas\*\*

\*Assistant Professor, Department of Physiology, Mahatma Gandhi Medical College & Hospital Jaipur Rajasthan 302022

\*\* Professor and Vice Dean, Department of Physiology, Jawaharlal Nehru Medical College, Sawangi (Meghe) Wardha, (Maharashtra).444204

**Abstracts: Background:** Cigarette smoking is the most commonly encountered risk factor for COPD, and causes COPD by its noxious particles and or gases. Cigarette smoke contains some neurotoxin substances that might be important in the pathogenesis of peripheral neuropathy. **Objective:** To determine whether the effect of the duration of smoking leads to development of peripheral neuropathy in different groups of the COPD patients as measured by nerve conduction studies of upper extremities **Material and Methods:** The nerve conduction test, of the median and ulnar nerves of the upper extremities, was performed on the subjects (study and control group), who were assessed for their anthropometric measurements, history regarding pack years, the pulmonary function tests, SpO<sub>2</sub> levels. **Results:** Significant difference was found between smoking history in pack years and in the values of Nerve Conduction Velocity of the nerves of upper extremities in different groups of COPD patients, which was found to be statistically significant at  $p < 0.001$ . **Conclusion:** A decrease in nerve conduction velocity was observed in the nerves of upper extremities as duration of smoking in pack years increased in the different groups of COPD patients. [Garg A NJIRM 2014; 5(6):1-6]

**Key Words:** chronic obstructive pulmonary disease, cigarette smoking, duration of smoking history, peripheral neuropathy.

**Author for correspondence:** Dr. Aparna Garg; Assistant Professor Department of Physiology, Mahatma Gandhi Medical College & Hospital, Jaipur Rajasthan 302022 **Mo:** 8504092472 **Email:** gargaparna@ymail.com

**Introduction:** "Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity of the disease in the individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. This airflow limitation is usually both progressive and associated with abnormal inflammatory responses of the lung to the noxious particles or gases"<sup>1</sup>.

Worldwide cigarette smoking is the most commonly encountered risk factor for COPD, due to its noxious particles and or gases, thus making it the most important risk factor for the development of COPD<sup>2</sup>. The other known environmental factors are passive tobacco smoke, heavy exposure to occupational dusts and chemical (vapors, irritants and fumes).

Understanding that COPD is more than a lung disease, potentially relevant systemic effects of COPD are also seen, one of it is seen as alterations of the nervous systems<sup>3</sup>. Although, the clinical manifestation of polyneuropathy in COPD is generally masked by the features of severe pulmonary disease, thus the asymptomatic or

mildly symptomatic peripheral nerve disease in patients of COPD remains undiagnosed frequently<sup>4</sup>. There are few studies reported in context to COPD and peripheral neuropathy, but the available knowledge which highlights this aspect of the complications in the patients of COPD is not enough. Hence the study was undertaken with the aim to understand the presence of the peripheral neuropathy in COPD patients based on the duration of smoking history in pack years. Our objective was to study the nerve conduction velocities of the median and ulnar nerves in the different groups of COPD patients in relation to their duration of smoking in pack years.

**Material and Methods:** The study was conducted in Department of Physiology, Jawaharlal Nehru Medical College (J.N.M.C.) and Department of TB & Chest, Acharya Vinoba Bhave Rural Hospital (A.V.B.R.H.), Sawangi (Meghe), Wardha, after obtaining the approval from the Institutional Ethical Committee of the college.

A case control study, sample size of 78 in which the study group (39) were diagnosed cases of COPD according to GOLD guidelines, and were recruited from Department of TB & Chest. The control group

(39) were of healthy volunteer selected from medical, paramedical staff of the institute; some healthy attendants of the patients also volunteered. The written consent was obtained from all the recruited subjects at the onset of the study. The subjects were recruited with the following criteria.

**Inclusion Criteria:** Diagnosed male patients of COPD, between ages 40-60 yrs, chronic smokers under treatment and willing to participate in the study

**Exclusion criteria:**

1. Unstable ,unwilling ,uncooperative patients of COPD
2. Patients with parenchymal lung pathology
3. Patients suffering from cardiovascular, endocrinal (Diabetes mellitus), hepatic or renal dysfunctions.
4. Chronic alcoholics, malnourished, anaemic and leprosy patients
5. Patients with history of drugs causing neuropathy.

The study group recruited from the chest OPD of the AVBRH were assessed for their anthropometric measurements. A detailed history, pertaining to their personal, occupational and any other relevant medical problem was obtained. The smoking history was reported as in the unit of "pack-year" which is defined as smoking of a pack of cigarettes (20 pieces) per day for one year. The number of pack years is calculated as: the number of cigarettes smoked per day/20 × the number of years smoked<sup>5</sup>.

They were further evaluated for respiratory symptoms, by Chest X- Ray, Oxygen saturation, and Spirometry. The other tests done, were Haemogram (Hb%), fasting blood glucose, renal parameters to exclude other concurrent risk factors for peripheral neuropathy. They were then subjected for the electrophysiological evaluation by the nerve conduction test for the median and ulnar nerves of the upper extremities, both for their motor and sensory components by the methodology adopted by Mishra Kalita<sup>6</sup>.The healthy volunteers were also evaluated for all the above mentioned parameters.

The subjects of the study group were in a stable and ambulatory condition. The mild group of COPD based on the GOLD guidelines could not be included in this study as the patients visited the OPD only when they were symptomatic. Mannino et al 2000<sup>7</sup> has mentioned that by the time the patient report on the appearance of the clinical signs, COPD is often in a moderate to advance stage. Thus in this study, the severity of the disease ranged from the moderate COPD to the severe COPD.

- Moderate COPD (where FEV<sub>1</sub> ranged 50%-79%) and n=14
- Severe COPD: (where FEV<sub>1</sub> ranged 30%- 49%) and n = 13
- Very Severe COPD (where FEV<sub>1</sub> < 30%) and n = 12

**Statistics:** ANOVA, unpaired "t" test were applied to the data to test the significant difference in the various study groups (defined according to the FEV<sub>1</sub>) for the motor and sensory component of the peripheral nerves of both the upper extremities namely the median and ulnar. Trial version of SPSS 13.0 was used for the statistical analysis.

**Observation and Results:**

**Table 1: This Table Shows the Comparison between the Features of COPD Patients and Healthy Volunteers/ Control Group.**

	Study group	Control group	p-value
Age	53.90±7.79	46.24±5.75	0.00*
Smoking	33.87±8.50	Nil	-
Saturation of oxygen.(SpO <sub>2</sub> )	94.71±1.50	97.94±0.29	0.00*
forced expiratory volume in 1 sec (FEV <sub>1</sub> %)	49.15±18.32	98.56±11.98	0.00*

The table shows\* statistical significance with p value < 0.001 for SpO<sub>2</sub> ,FEV<sub>1</sub> % & age, when compared between the two groups.

**Table 2: Mean Values for Age, SpO<sub>2</sub>, Smoking History In Years, And FEV<sub>1</sub>% In The Different Study Groups Formed According To FEV<sub>1</sub>% (% Predicted Values)**

COPD groups	Age in years	Smoking history in pack years	SpO <sub>2</sub>	FEV <sub>1</sub> % (%predicted values)
Moderate	54.07±7.73	23.93±1.94	95.21±1.19	67.79±9.65
Severe	56.46±6.35	35.31±2.10	95.15±0.99	47.76±11.38
Very severe	59.92±2.87	43.92±1.51	94.67±1.23	28.83±8.82
p values	0.06	0.00*	0.43	0.00*

\*Statistically significant (p<0.001) is observed in the different groups in relation to smoking History in pack years and the FEV<sub>1</sub>%.

**Table 3: The Relationship between the Smoking Histories in Years, Various Groups of COPD and the Nerve Conduction Velocities of Different Nerves**

COPD Groups	N	Smoking history in pack years	Median Motor NCV m/sec	Median Sensory NCV m/sec	Ulnar Motor NCV m/sec	Ulnar Sensory NCV m/sec
Moderate	14	23.93±1.94	52.15±3.97	53.64±6.66	56.83±4.31	48.85±7.13
Severe	13	35.31±2.10	48.68±3.33	51.50±5.45	52.91±4.18	42.83±10.35
Very Severe	12	43.92±1.51	45.38±4.56	39.58±9.14	47.85±4.39	32.0±7.42
p values		0.0000**	0.00**	0.00**	0.00**	0.00**

n= no. of male COPD patients in the various COPD groups

\*\* statistically significant at p<0.001 is observed by one way ANNOVA

It is observed that as the smoking history in pack years is increasing, there is the severity of the COPD disease and there is decrease in the values of NCV of the different nerves.

**Discussion:** In this study the majority of patients experienced a stable course of COPD and it was of practical interest to study the development of peripheral neuropathy. **Table 1** shows the comparison between the two groups (study and the control). The age was between 40-60 years of the subjects and controls, showing a highly statistically significant value at p < 0.001 which was

also observed in the study conducted by Agrawal et al 2007<sup>8</sup>. Studies have also shown that there is a reduction in the nerve conduction values from the age of 30-40 years but the changes in values are seen only at the sixth decade or still later<sup>6</sup>.

The average SpO<sub>2</sub> and average FEV<sub>1</sub>% of COPD group in comparison to the control group was found to be statistically significant at p value <0.001. The SpO<sub>2</sub> and the FEV<sub>1</sub>% values in both the groups was as expected, which was also seen in Agrawal et al 2007<sup>8</sup>.

**Table 2** shows the formation of the different group on the basis of the FEV<sub>1</sub> %. It was found that there was progression of the COPD in relation to smoking history and FEV<sub>1</sub> %. Study done by K.M. Padmavathy 2008<sup>9</sup> had mentioned that any type of smoking whether cigarette or beedi affects the pulmonary variables. David Stav<sup>10</sup>, in his study had established a correlation among smokers aged 45 years who had history of at least 20 pack years and severity of COPD, which is also found in this study. The non significance of SpO<sub>2</sub> between the different groups of the COPD patients implies that the patients were in a stable condition as also mentioned by Agrawal et al<sup>8</sup>.

**Table 3** gives the information about the nerve conduction velocity of the median (motor and sensory) nerves and ulnar (motor and sensory) nerves of both the extremities in the various groups of COPD. It shows there is decrease in the nerve conduction velocities in the nerves of the upper extremities of COPD patients with the increasing severity of the disease, in relation to the increase in the duration of smoking history in pack years at statistically significant at p value < 0.001.

Similar studies done by A. Ozge<sup>4</sup> who observed that patients had neuropathy in the COPD group of FEV<sub>1</sub> % < 50% and a statistical correlation was found between the severity of expiratory airflow obstruction and neuropathy (p=0.001). Alan Faden et al<sup>11</sup> mentioned the moderate to severe COPD patients (COPD classification based on ATS guidelines) had abnormal findings of the nerve conduction studies both of the sensory nerves as well as the motor nerves. On the contrary, the study done by Gokhan Asal 2003<sup>12</sup> showed no significant difference with the NCV values of the median and ulnar nerves of different groups of COPD when based on the FEV<sub>1</sub> parameter.

In COPD, changes occur in the peripheral nerves that are chronically subjected to hypoxemia as a result of reduced airflow to the small airways, resulting in the less O<sub>2</sub> concentration in blood than normal. Hypoxemia seems to be the most important cause of neuropathy in the cases of COPD. Hypoxic neuropathy is associated with nerve capillary endothelial cell hyperplasia and hypertrophy, predisposing to luminal occlusion.

When combined with the thickening of the nerve perineurium, this phenomenon may impede the transport of nutrients and oxygen. This mechanism seems to be applicable to peripheral nerve dysfunctions, seen as decreased in the NCV, which results from impaired axonal transport (an energy-requiring process)<sup>13</sup>.

Cigarette smoke contains neurotoxin substances mainly nicotine that might be important in the pathogenesis of peripheral neuropathy. Nicotine receptors are found on the axons and motor nerve fibers and terminals of many sensory and motor nerve fibers. Nicotine in high doses affect sensory and neuromuscular transmission by causing damage to the nerves resulting in the nerve dysfunction<sup>11</sup>.

Cigarette smokers do have a significant concentration of Carbon Mono-oxide, which leads to the 5 % to 10% carboxyhaemoglobin levels in the blood leading to the slowing of the nerve conduction velocity. This action is believed to have a direct effect on the nerve conduction in addition to the existing hypoxemia. Slowing of nerve conduction with increased carboxyhemoglobin levels<sup>14</sup> is another common observation in smokers. Hydrocyanic acid found, is another neurotoxin agent in the cigarettes which has an adverse effect on the nerve conduction studies<sup>15</sup>. In the study done, by Ozge and co workers<sup>4</sup> on COPD patients who had a history of smoking for 40±23.57 of pack years had neuropathy. Faden et al<sup>11</sup> have also put forth in their study that cigarette smoking did correlate with sensory nerve impairment to a remarkable degree. He further mentioned that for patients whose smoking history exceeds 60 pack years suggests cigarette smoking as a toxic factor in the pathogenesis of COPD associated neuropathy. Our findings are consistent with the above mentioned studies.

**Conclusion:** Cigarette smoking can thus be mentioned as another causative factor for polyneuropathy in COPD patients along with hypoxemia. As smoking and COPD are themselves closely related, the smoking neuropathy association reflects a more complex interaction between cigarette neurotoxins and metabolic

changes secondary to pulmonary disease. It was seen that as duration of smoking in pack years increased, there was deterioration in conduction velocity and this correlation was statistically significant. To conclude COPD related Peripheral neuropathy is frequent with the severity of the disease, due to reduction in the expiratory flow rates, increase duration of smoking history in pack years in the stable COPD patients.

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**Limitations of the Study:** Although there is difference in nerve conduction velocities of case and control group but study with exact match case and control need to be carried out to remove confounding factors i.e. age.

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