

Sleep Apnea—Predictor of Functional Outcome in Acute Ischemic Stroke

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Background: Sleep apnea is increasingly being recognized as 1 of the important, modifiable risk factors of stroke and cardiovascular diseases. Sleep apnea is thought to impair the functional recovery following stroke. Hence, we evaluated the patients with acute ischemic stroke for prevalence of sleep apnea and compared the functional outcomes of patients with and without sleep apnea, at 3rd month of acute ischemic stroke. *Method:* This study was conducted in Kasturba Medical College (KMC) hospital, Manipal, India, between May 2015 and August 2016. We included 102 consecutive patients of acute ischemic stroke with hemiplegic upper limb power of Medical Research Council (MRC) 3 or less. Sleep apnea was diagnosed in these patients using the sleep disordered Questionnaire, Berlin Questionnaire, and Epworth sleepiness scale. Functional outcome was measured using Barthel score on day 7 and at 3rd month following the onset of stroke. *Result:* Out of 102 patients, sleep apnea was present in 31 (30.6%) patients, more in males (67.7%) and elderly. Hypertension was present in 66.6% of patients with sleep apnea. NIHSS score at admission did not differ between the 2 groups. At 3rd month, the Barthel score calculated was better among patient with no apnea, but this was not statistically significant ($P = .119$). When mean Barthel score at baseline and 3rd month was calculated using repeated measure Analysis of Variance (ANOVA) between the 2 groups, gain in functional independence in no apnea group was statistically significant ($P < .001$). *Conclusion:* Sleep-disordered breathing is an independent risk factor for stroke, and sleep apnea is also associated with other known stroke risk factors like hypertension. In acute ischemic stroke, sleep apnea has a negative impact on functional recovery. Sleep apnea is amenable to treatment and should be considered in patients with acute ischemic stroke to improve the chance of recovery, and to reduce the risk of recurrence.

Key Words: Barthel score—functional dependency—ischemic stroke—sleep apnea
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Introduction

Stroke is currently 1 of the leading cause of neurological disability in adults.¹ Two-thirds of stroke survivors have residual neurological deficits that impair their function, approximately 50% are left with disabilities making them dependent on others for activities of daily living (ADL).² Sleep apnea is common, but usually under-recognized independent risk factor of stroke. Obstructive sleep apnea is also associated with other common known risk factors of stroke, like hypertension, atrial fibrillation, and metabolic syndrome.³

The exact mechanism of sleep apnea causing stroke is not clearly understood. The possible mechanisms considered are, during apneic spells episodes of hypoxemia

develops, which leads to sympathetic activation resulting in sudden rise in blood pressure and release of vasoactive substances like endothelin,⁴ increased inflammation, endothelial dysfunction, increased platelet activation and enhanced coagulation factors leading to hepercoagulable state. enhanced atherosclerosis is also said to enhance the risk of stroke.^{5,6}

Sleep apnea is also associated with cardiac arrhythmias, conduction abnormalities. Cardiac arrhythmias are associated with embolic stroke.⁷ It is noted that there is transient increase in right atrial pressure during apneas, which causes right-to-left shunting through Patent Foramen Ovale (PFO). This may give rise to stroke by means of paradoxical embolism.⁸ It is noticed that patients with sleep apnea have high concentrations of fibrinogen in the morning, high fibrinogen concentrations may be 1 of the mechanisms associated with stroke.⁹

Studies suggest that there is reduction in blood flow velocity of more than 50% in middle cerebral artery of sleep apnea patients, demonstrated by transcranial Doppler.¹⁰ This can result in further neuronal damage in the already damaged brain of stroke patients; this may also affect neuronal plasticity, thus reducing the functional recovery. After the acute stroke care, untreated obstructive sleep apnea can impair cognition, concentration, and excessive daytime sleepiness. These factors impair rehabilitation participation and lead to impaired function recovery. Hence, this study was carried out to look for the prevalence of sleep apnea in newly diagnosed stroke patients and their functional recovery.

Methodology

Aim of the Study

- To analyze the prevalence of sleep apnea in newly diagnosed patients of acute ischemic stroke.
- To compare the functional outcomes of patients with and without sleep apnea, at 3rd month of acute ischemic stroke

Study Population

The prospective observational study was conducted in KMC Hospital Manipal, Karnataka, India. Here we included patients admitted to the Department of Neurology and General Medicine ward between May 2015 and August 2016. The ethical committee clearance obtained from the appropriate authority was appointed by the institution.

Inclusion Criteria

Patients with acute ischemic stroke in the anterior circulation territory, who had a power of MRC grade 3/5 or

less in the hemiplegic upper extremity at presentation were included so that the functional dependency measure using Barthel score calculation has uniform score at the beginning of the study.

Exclusion Criteria

Patients with hemorrhagic stroke and stroke involving the vertebral-basilar circulation were excluded.

A total of 118 patients were included in the study. Out of 118 patients, 16 were lost to follow-up, hence only 102 were included in the study. At the time of admission, NIHSS was administered to each patient for determining the stroke severity. Data on demographic characteristics, sleep, medical history, medication use, and habits were obtained. Detailed neurological examination, routine blood investigation, cardiac evaluation including Electrocardiogram (ECG) and Echocardiogram were done.

Sleep apnea was diagnosed in patients with stroke using 3 clinical instruments, The Sleep Disorders Questionnaire, Berlin Questionnaire, and The Epworth Sleepiness Scale. In nonaphasic patients, the patient themselves and in case of aphasic patients, spouses were asked 3 questions from Sleep Disordered Questionnaire, which are:

- Do you snore?
- Has anyone said or noticed that you stop breathing gasp or choke in your sleep?
- Do you have difficulty staying awake during the day?

If the answer was 'yes' to at least first 2 questions and had observed above said factors on most of the days or every day, spouse/patients were further questioned using Epworth Sleepiness Scale and Berlin Questionnaire. The patients were considered having sleep apnea if they scored >10 points in The Epworth Sleepiness Scale and 2 or more points each in category 1 and category 2 of Berlin Questionnaire. Patients were considered having sleep apnea if they fulfilled criteria of both The Epworth Sleepiness Scale and Berlin Questionnaire, to increase the specificity. The overnight oximetry value even though available for few patients admitted to intensive care unit, was not considered, since there are many reports suggesting presence of sleep disordered breathing following first few days after acute stroke, which usually resolves after few days to weeks.

The functional dependency was measured on day 7 and at 3rd month following acute ischemic stroke using the Barthel score. The Barthel score is a scale that measures disability or dependence in ADL. Barthel score uses 10 variables describing ADL and mobility. A higher score is associated with a greater likelihood of being able to live at home with a degree of independence. A score of 0-20 is taken as a total dependency, 21-60 severe dependency,

61-90 moderate dependency, 91-99 slight dependency, and 100 independence.

Results

Out of 102 patients included, 31 (30.3%) patients had sleep apnea. Sleep apnea was more in males, 21 (67.7%), when compared to females, 10(32%). Mean age of patients in the apnea group was 71.5 years, against 56 years in no apnea group (Tables 1 and 2). Presence of hypertension was significantly more in the apnea group accounting for 64.5% when compared to no apnea group 43.6%. Atrial fibrillation was present in both groups with no significant difference (Table 3 and Fig 1). There was no significant difference in NIHSS at admission between the groups (Table 4 and Fig 2).

Barthel score was calculated at baseline (7th day of onset of ischemic stroke) and at 3rd month following acute ischemic stroke. Patients were divided into different categories depending on the Barthel score, from severe dependency to complete independence. There was no significant difference in the Barthel score between the 2 groups (Table 5 and Fig 3). At 3 months, 2 of 31 patients in sleep apnea and 4 of 71 patients in no sleep apnea group had died, commonest cause being cardiac (Table 6).

Baseline Barthel score and Barthel score at 3rd month was compared between the 2 groups (Table 7), which showed better functional outcome in patients without sleep apnea, especially in the severe dependency group which was much higher in sleep apnea group (24.1% versus 9%), however this was not statistically significant ($P = .119$). When gain in mean barthel score (Table 8) after 3 months was compared between the 2 groups using repeated measures of ANOVA, they showed a statistically significant difference, with an improved functional gain in patients with no sleep apnea group. This suggests that sleep apnea is associated with increased risk of ischemic stroke and also associated with poor functional outcome (Fig 4-6).

Discussion

Our study was a prospective, single-center observational study. In this study, we assessed the prevalence of sleep apnea in acute ischemic stroke and effect of the same on the functional outcome at 3rd month.

Prevalence of sleep apnea in our study was 30%, which is comparable to other studies where they demonstrated the frequency of about 30%-80% of sleep-disordered breathing in patients with acute ischemic stroke.^{5,11}

Prevalence of hypertension was more in apnea group (64.5% versus 43.6 % in no apnea group); this is comparable with other studies, which demonstrated frequency of hypertension to be 30%-70% in sleep apnea and increases as the severity of the disease.¹² Sleep apnea is found to have the greatest association with resistant hypertension.¹³

In our study, association of sleep apnea with other risk factors like diabetes, hyperlipidemia, atrial fibrillation, and ischemic heart disease did not differ between the 2 groups. There are studies which suggested a strong association of obstructive sleep apnea and diabetes, and there are few studies which demonstrated no significant association between these 2 as well.^{14,15} There are many studies which showed increased prevalence of atrial fibrillation and dysrhythmias in patients with obstructive sleep apnea.^{16,17}

NIHSS and baseline Barthel Index at admission did not differ significantly between the groups. At the end of the 3rd month, the mean Barthel score calculated between the groups showed a statistically significant difference between the sleep apnea and no sleep apnea groups ($P < .001$) suggesting that sleep apnea is associated with poor functional outcome.

This study is comparable with other studies, done by Yaggi et al *In Obstructive Sleep Apnea as a Risk Factor for Stroke and Death*.¹⁸ In this study among 1022 enrolled patients, 697 (68%) had the obstructive sleep apnea syndrome, after adjustment for age, sex, race, smoking status,

Table 1. Age distribution of patients

	No sleep apnea (N = 71)	Sleep apnea present (N = 31)	P value*
Age in years mean (SD)	56 (13.8)	71.5 (8.8)	<.001

*Unpaired *t* test.

Table 2. Demographic variability of patients

Patient characteristics	No sleep apnea (N = 71)	Sleep apnea present (N = 31)	P value*
Gender			
Male	50 (70.4)	21 (67.7)	.302
Female	21 (29.6)	10 (32.3)	

*Chi square test, column percentage.

Table 3. Medical history

	No sleep apnea	Sleep apnea present	P value*
Hypertension	31 (43.6)	20 (64.5)	.052
Diabetes	19 (26.8)	10 (32.3)	.571
Atrial fibrillation	6 (8.5)	2 (6.5)	.723
Ischemic heart disease	7 (9.9)	4 (12.9)	.648

*Chi square test, column percentage.

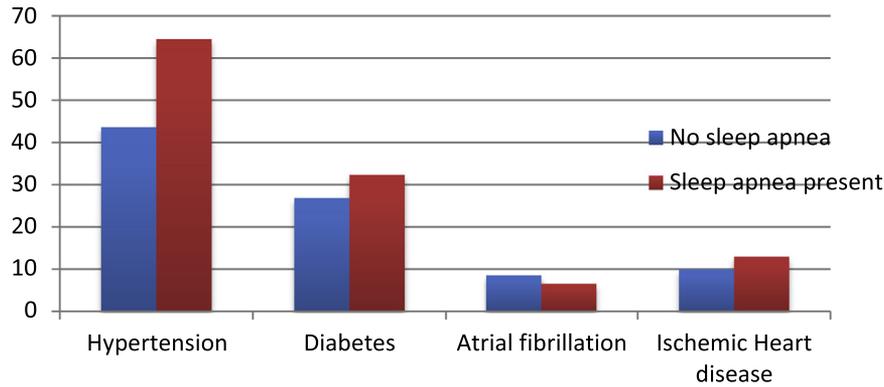


Figure 1. Multiple bar diagram showing percentage of hypertension, diabetes mellitus, atrial fibrillation and ischemic heart disease between no sleep apnea and sleep apnea group. (X-axis: percentage of patients, Y-axis: medical illness). (Color version of figure is available online.)

Table 4. Comparison of NIHSS score between 2 groups

NIHSS score	No sleep apnea (N = 71)	Sleep apnea present (N = 31)	P value*
Minor stroke	3 (4.2)	(0.0)	.680
Moderate stroke	47 (66.2)	21 (67.7)	
Moderate to severe stroke	16 (22.5)	7 (22.6)	
Severe stroke	5 (7.0)	3 (9.7)	
Total	71 (100.0)	31 (100.0)	

*Chi square test, column percentage.

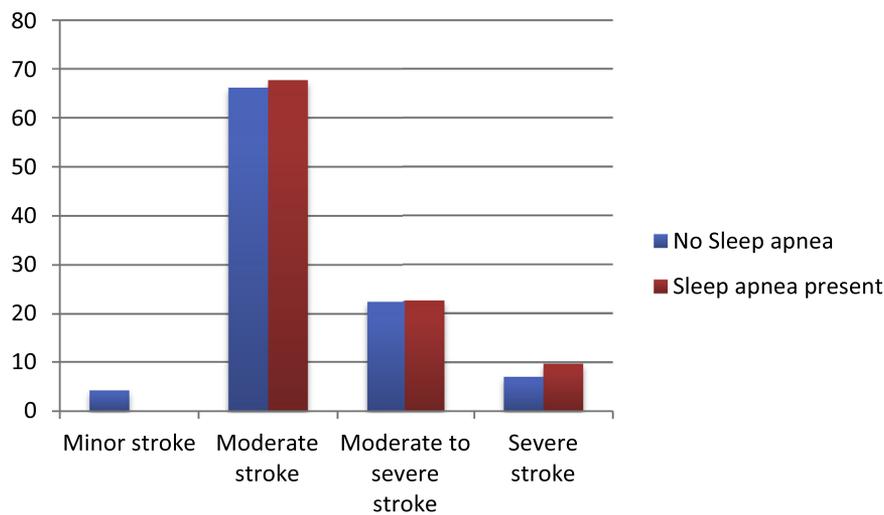


Figure 2. Multiple bar diagram showing comparison of stroke severity by NIHSS between the 2 groups. (Color version of figure is available online.)

Table 5. Comparison of Barthel score at baseline between no sleep apnea and sleep apnea group

Barthel index at baseline	No sleep apnea (N = 71)	Sleep apnea present (N = 31)
Total dependency	16 (22.5)	11 (35.5)
Severe dependency	51 (71.8)	18 (58.1)
Moderate dependency	4 (5.6)	2 (6.5)
Total	71 (100.0)	31 (100.0)

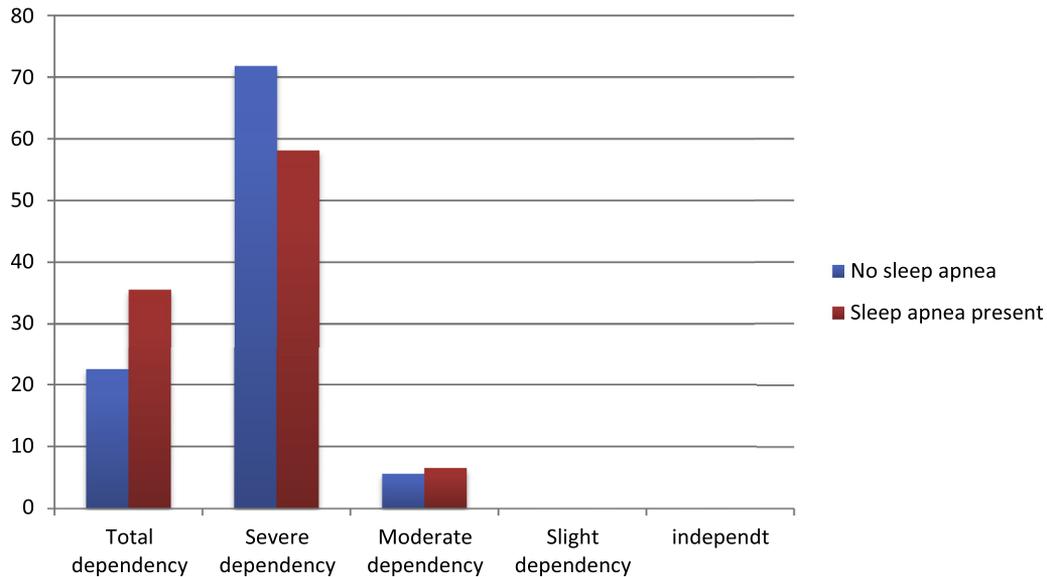


Figure 3. Multiple bar diagram showing the Barthel score of the individuals in no sleep apnea and sleep apnea group baseline. (X-axis: percentage of patients, Y-axis: Barthel score categories). (Color version of figure is available online.)

alcohol-consumption status, body-mass index, and the presence or absence of diabetes mellitus, hyperlipidemia, atrial fibrillation, and hypertension, the obstructive sleep apnea syndrome retained a statistically significant association with stroke or death.

Table 6. Comparison of death

Death	No sleep apnea (N = 71)	Sleep apnea present (N = 31)	P value*
No	67 (94.4)	29 (93.5)	.872
Yes	4 (5.6)	2 (6.5)	

In another study, *One Year Outcome of Acute Stroke Patients with Sleep Apnea*,¹⁹ by Kojic et al, 1 year after stroke, significantly more patients survived without (94.5%) than with apnea (82.7%) ($P = .01$). A study was done by Good et al, *Sleep-Disordered Breathing and Poor Functional Outcome After Stroke*,²⁰ showed sleep-disordered breathing was common in patients undergoing rehabilitation after stroke and is associated with higher mortality at 1 year and lower Barthel index scores at discharge and at 3 and 12 months after stroke.

In a study by Bassetti et al²¹ "Sleep-Disordered Breathing And Acute Ischemic Stroke: Diagnosis, Risk Factors, Treatment, Evolution, And Long-Term Clinical Outcome" concluded that sleep-disordered breathing is common in

Table 7. Comparison of Barthel index at 3rd month between no sleep apnea and sleep apnea group

Barthel index at 3 mo	No sleep apnea (N = 67)	Sleep apnea present (N = 29)	P value*
Severe dependency	6 (9.0)	7 (24.1)	.119
Moderate dependency	44 (65.7)	19 (65.5)	
Slight dependency	14 (20.9)	2 (6.9)	
Independent	3 (4.5)	1 (3.4)	
Total	67 (100.0)	29 (100.0)	

*Chi square test, column percentage.

Table 8. Comparison of mean Barthel index at baseline and at 3rd month (N = 96) between no sleep apnea and sleep apnea group

Barthel index score	No sleep apnea (N = 67)	Sleep apnea (N = 29)	P value*
Baseline Mean (SD)	35.4 (18.1)	30.9 (17.5)	<.001
3 mo Mean (SD)	81.3 (13.4)	75.0 (14.0)	

*Repeated measures of ANOVA.

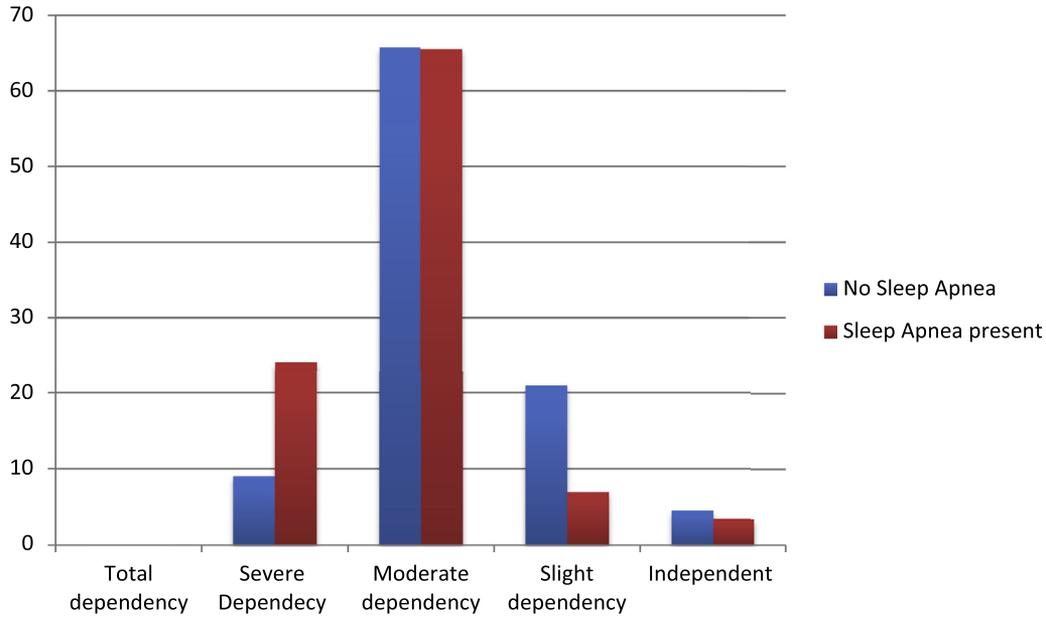


Figure 4. Multiple bar diagram showing comparison of percentage of Barthel score between the 2 groups at 3rd month. (X-axis: percentage of patients, Y-axis: Barthel score). (Color version of figure is available online.)

elderly stroke male patients, diabetes, night time stroke onset as cause of stroke; it improves after the acute phase and associated with an increased post-stroke mortality which can be treated with Continuous Positive Airway Pressure (CPAP) in a small percentage of patients.

This is in contrast with the study done by Low et al,²² "Obstructive Sleep Apnea is Associated with Improved Ischemic Stroke Outcomes" showed obstructive sleep apnea was associated with lower odds of death and poor discharge status and concluded that ischemic preconditioning could

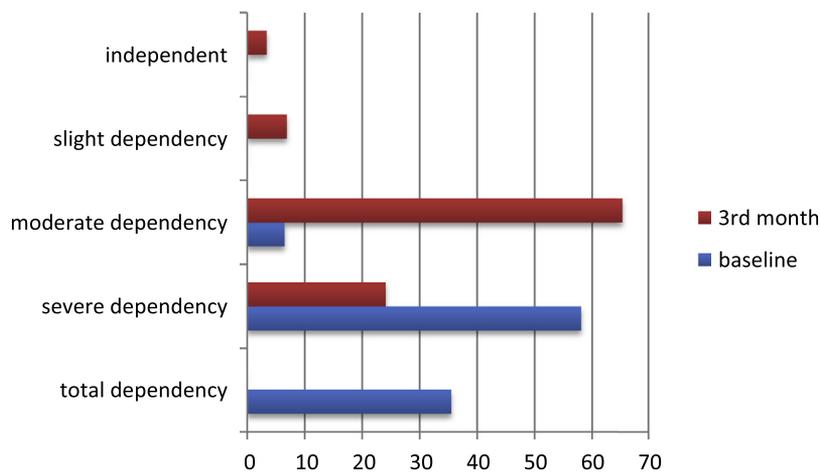


Figure 5. Barthel score in patients with sleep apnea at baseline and 3rd month. (Color version of figure is available online.)

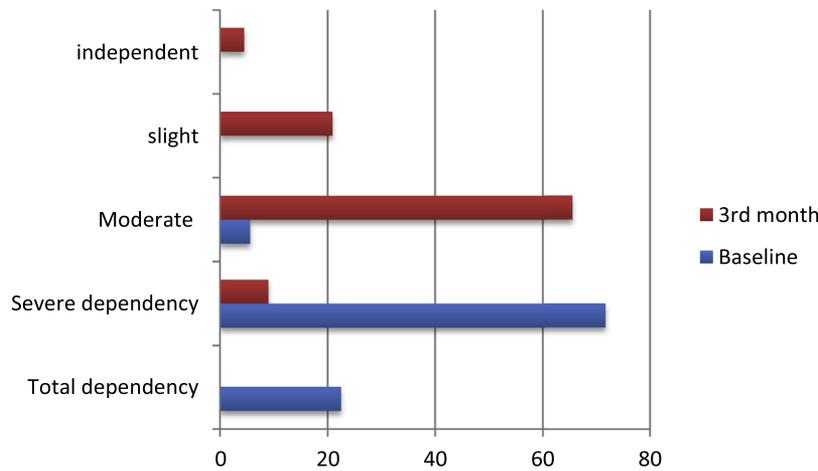


Figure 6. Barthel score in patients without sleep apnea at baseline and 3rd month. (Color version of figure is available online.)

be a mechanism by which obstructive sleep apnea leads to better outcomes after stroke in humans.

In a study by Festic et al “*Sleep Apnea in Patients Hospitalized With Acute Ischemic Stroke: Under Recognition and Associated Clinical Outcomes*”²³ prevalence of sleep apnea was low in the study, stroke and sleep apnea patients had a less severe neurological injury.

Conclusion

Sleep apnea is not only associated with stroke, but also with another independent major risk factor of stroke-like hypertension. The functional outcome following an acute ischemic stroke depends on multiple factors; sleep apnea is 1 of the most important and modifiable risk factors. Hence timely diagnosis and treatment in the form of CPAP may improve the functional outcome in these patients and prevent recurrence of stroke.

Limitation of the Study

Sleep apnea was considered using the Epworth sleepiness scale, Berlin’s Questionnaire, and Sleep Disorders Questionnaire. Polysomnography was not done to establish the diagnosis, as it was difficult to get overnight polysomnography in acute stroke patients.

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