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Internal Medicine Section

Smokeless Tobacco and Stroke - A Clinico-epidemiological Follow-up Study in A Tertiary Care Hospital

SUBHRANSU SEKHAR JENA[1], SHOBHITENDU KABI[2], BAIKUNTHA NATH PANDA[3], B.C. KAMESWARI[4], PAYAL[5], ISHWAR CHANDRA BEHERA[6], SUBRAT KUMAR TRIPATHY[7], SEEMANCHANA MAHANTA[8]

ABSTRACT

Introduction: Among the modifiable risk factors for stroke, tobacco smoking is well recognized. In some studies the use of Smokeless Tobacco (ST) has also been contributed as a risk factor for ischemic stroke. Use of ST is very common in South-East Asia. The form of ST varies according to the geographical and cultural variation.

Aim: To study the various clinical symptoms and radiological findings of stroke due to different types of ST.

Materials and Methods: This was a prospective hospital based study carried out over a period of 2 years. All the cases within age group of 16 – 60 years and with a clinical and radiological diagnosis of acute stroke were included in the study. The Fagerström Test for Nicotine Dependence for ST of more than 6 was taken as the inclusion criteria. Patients having other addictions like smoked tobacco, alcohol, etc., and with important risk factors like hypertension, diabetes, dyslipidemia were excluded. The cases were extensively investigated and followed up for at least 6 months. Analysis was done using the Statistical Package for Social Sciences (SPSS- version 16.0). Descriptive statistics like percentage, mean were used wherever appropriate.

Results: During a period of 2 years, a total of 54 patients were studied. Forty two (77.7%) were males and 12(22.3%) were females. The mean age at presentation was 42.72(± 8.6) years and among all 96.3% patients were diagnosed as ischemic stroke. Among ST, pan was most commonly used in 21(38.9%) patients with an average of 14.6(±3.27) years of addiction. Hemiplegia was the predominant symptom on presentation (46, 85.2%). According to Oxfordshire Stroke Classification, partial anterior circulation infarct was most common in 20(38.4%). The mean Modified Rankin scale after 5 days of hospital stay was 3.83(±1.03) and after 6 months of follow-up was 2.1(±0.8). Patients were counseled for deaddiction and after 6 months follow-up 48(88.8%) patients had quit ST.

Conclusion: ST is an important etiological factor for young ischemic stroke. This is the first study depicting clinical symptomatology of ST addicted ischemic stroke patients from India. Considering the increasing prevalence of ST use in south-east Asia, further long term studies are needed from this region.

Keywords: Cigarette smoking, Cerebro-vascular disease, Nicotine

INTRODUCTION

Cerebro-vascular stroke is a major cause of long term morbidity and mortality, affecting adversely the socioeconomic status of patients and their caregiver. Its prevalence has become pandemic in low-income and middle-income countries like India. The key modifiable risk factors for stroke are largely driven by demographic changes and various social adaptations.

Tobacco smoking is a well recognized modifiable risk factor for stroke [1]. There is strong evidence supported by various experimental, epidemiological, clinical and randomized controlled studies for smoking as a major cardiovascular disease risk factor. In most high-income countries, prevalence of smoking has declined recently [2]. Unfortunately, in many low and middle income countries, especially in Southeast Asia, smoking and Smokeless Tobacco (ST) use is increasing [3].

The various forms of ST in use depend on cultural, social and geographical variation. ST may refer to various substances like tobacco snuff, dipping, snus, tobacco gum, tobacco toothpaste, tobacco paste, herbal smokeless tobacco, tobacco water etc. It is consumed in unburnt forms through sniffing and chewing which contain several carcinogenic compounds. The major constituent of ST, nicotine causes sympathico-adrenal activation affecting cardiovascular system [4], thereby, causing increase in blood pressure, heart rate, stroke volume, and coronary blood flow. It also induces vasoconstriction of cerebral vasculature [5]. Animal studies have also shown, nicotine inducing cardiac arrhythmias [6]. Studies from Sweden [7] and USA [8] have proven that ST can be an important aetiological factor for cerebrovascular attacks.

Southeast Asia is designated to be the main hub of ST and associations between ST use and stroke have been investigated in the past but very few studies have been documented till date. None of these previous studies have described the different subtypes of stroke associated with ST use and follow-up of patients. Considering the different etiologies of haemorrhagic and ischemic strokes, such a subdivision could be of importance to understand the pathophysiologic mechanisms. We performed a prospective hospital based cohort study to assess the various types of ST in use and the clinical symptomatology and radiological findings of different types of stroke in patients using ST.

MATERIALS AND METHODS

A prospective hospital-based study was carried out over two year period (from October 2013 to September 2015) in the Departments of Neurology and Medicine, IMS & SUM Hospital, Bhubaneswar,

Odisha, India. The inclusion criteria were: 1) Different types of acute stroke (haemorrhagic stroke, ischaemic stroke, subarachnoid haemorrhage), diagnosed clinically and radiologically; 2) Age of the subjects' ≥16 years to ≤60 years; 3). The Fagerström Test for Nicotine Dependence for smokeless tobacco (FTND-ST) [9] more than 6 i.e., patient is highly dependent on nicotine [9,10]; 4) Follow-up data available for at least 6 months. Following were taken as the exclusion criteria: 1) Patients having other addictions like smoked tobacco, alcohol, intravenous drug abusers; 2) Stroke in patients with important risk factors like hypertension, diabetes, dyslipidemia, obesity, systemic vasculitis, coronary heart disease, atrial fibrillation, rheumatic heart disease, significant extracranial and intracranial stenosis; 3) History of Central Nervous System (CNS) infections.

Diagnosis of stroke was made on the basis of medical history, physical examination and neuroimaging. All patients were subjected to routine haematological, metabolic workup, electrocardiogram, echocardiography, MRI of brain and carotid doppler. Patients with clinical suspicion of vasculitis were investigated for antiphospholipid antibody, and prothrombotic factors. Patients were investigated for modifiable and non-modifiable vascular risk factors.

Current ST users were defined as patients addicted to either snuff or chewing tobacco at present [11]. Smoker was defined as a person having ≥ 1 pack-years smoked (1 pack = 20 cigarettes). Addicted alcohol consumer was defined as with alcohol consumption >70 gram/week [12]. Hypertension was defined as with increased systolic blood pressure >140 mmHg or diastolic >90 mmHg [13] or with past history of hypertension, or record of antihypertensive drugs usage. Diabetes mellitus was defined as documented diabetes in the medical records, or having a random blood glucose level of >11.1mmol/L (200mg/dl), fasting blood sugar level of ≥126mg/dl or those on anti-diabetics drugs [14]. According to NCEP ATP III criteria, dyslipidemia was defined with following criteria as, LDL-C≥130mg/d, Cholesterol>200 mg/dL, TG ≥150mg/dL; HDL-C≤39mg/dL [15]. Coronary heart disease was defined as a biochemical, electrocardiographic, or echocardiographic evidence of coronary event or a known past history of myocardial infarction or angina.

Anthropometric indices were done for evaluation of central and general obesity. World Health Organization's recommendations for Asian population were used for body mass index categorization [16]. Informed consent was obtained from all the study subjects or relatives wherever applicable. Patients were referred to the psychiatrist for counseling and deaddiction measures and followed up for six months.

STATISTICAL METHODS

Data were collected in the preformed performa. Analysis was done using the Statistical Package for Social Sciences (SPSS), version 16.0 (Chicago, IL, USA). Descriptive statistics like percentage, mean, standard deviation were used wherever appropriate.

RESULTS

Out of 54 patients in our cohort, 42(77.8%) were males and 12(22.2%) were females. The age range was from 32 years to 57 years with mean age of 42.72(± 8.6) years [Table/Fig-1]. The incidence of stroke was maximum in the age group 40-59 years which comprised 45(83.3%) of the patients of entire study population. Out of the total study population, 96.3% patients were diagnosed as cases of ischemic stroke and 3.7% as haemorrhagic stroke as shown in [Table/Fig-2]. The ratio of ischemic stroke to haemorrhagic stroke was 26:1.

Patients presented to us with mean duration of 25.7 (±12.26) hours after stroke onset. None of the patient presented within window period of intravenous thrmbolysis. Patients were admitted as inpatient for mean of 10.4 (±2.67) days and managed conservatively.

Complications of stroke during hospital stay were observed in 6 (11.1%) patients like haemorrhagic conversion (1 patient), deep venous thrombosis (1 patient), aspiration pneumonia (2 patients),

Age in years	Male (%) 42(77.8%)	Female (%) 12(22.2%)	Total N=54
16 – 39	7(16.7)	2(16.7)	9(16.7)
40 – 49	19(45.2)	5(41.7)	24(44.4)
50 – 59	16(38.1)	5(41.7)	21(38.9)

[Table/Fig-1]: Demographic profile analysis of the study population: n= 54.

Causes	Number of patients (%)	Mean duration of tobacco use till presentation (years)
Pan (betel leaf, areca nut (supari), slaked lime (chuna), and catechu (katha), tobacco)	21 (38.9)	14.6 (±3.27)
Gutkha (areca nut (betel nut) pieces coated with powdered tobacco, flavoring agents, and other "secret" ingredients that increase the addiction potential)	12 (22.2)	8.8 (±2.32)
Khaini (dried tobacco leaves are crushed and mixed with slaked lime and chewed as a quid)	9 (16.7)	12.3 (±7.6)
Gudakhu (paste of tobacco and sugar molasses applied to gums)	5 (9.3)	16.6 (±7.12)
Pan masala (preparation containing the areca nut, slaked lime, catechu and condiments, with powdered tobacco)	3 (5.6)	16.2 (±3.23)
Mawa (combination of areca nut pieces, scented tobacco, and slaked lime that is mixed on the spot and chewed as a quid.)	2 (3.7)	14.3 (±2.1)
Mishri (roasted tobacco powder that is applied as a toothpowder)	1 (1.8)	12
Dry snuff (mixture of dried tobacco powder and some scented chemicals)	1 (1.8)	18

[Table/Fig-2]: Smokeless tobacco associated with stroke: n=54.

Symptoms/Signs	Number of patients n=54(%)
Hemiplegia • Right sided • Left sided	46 (85.2) • 26(48.1) • 20(37.3)
Abnormal speech	33(61.1)
Sudden-onset face weakness & deviation of Mouth	30 (55.5)
Balance problems (Gait ataxia)	22(40.7)
Altered sensorium	11(20.3)
Visual impairment	4(7.4)
Nystagmus	2(3.7)
Altered breathing and heart rate	2(3.7)
Weakness of both the sides	2(3.7)
Raised intracranial pressure (Headache, Vomiting)	1(1.8)
Drooping of eyelid (ptosis) and weakness of ocular muscles	1(1.8)
Total no. of symptoms/signs	200

[Table/Fig-3]: Main symptoms/signs associated with stroke during the time of hospitalization: n= 54.

Site of lesions	Number (%)
Basal ganglia region	19(36.5)
Paraventricular	12(23.1)
Brain stem	9(17.3)
Lobar-frontal	8(15.3)
Lobar-Parietal	5(9.6)
Lobar-Temporal	5(9.6)
Lobar- Occipital	3(5.7)
Cerebeller	2(3.8)

[Table/Fig-4]: Site of lesion of ischemic stroke according to MRI of Brain (n=52).

and urinary tract infection (2 patients). We did not have mortality in our series. Complications during follow-up for six months were noted in 8 patients like restroke (1 patient), haemorrhagic stroke (1 patient), stroke pain syndrome (3 patients), significant spasticity (2 patients) and stroke shoulder syndrome (1 patient). As some patients had multi focal ischemic lesions, sites of involvement in MRI were more than the number of patients.

Type of ischemic stroke	Number of patients (%)
Total Anterior Cirulation infarct (TACI)	4(7.6)
Partial anterior circulation Infarct (PACAI)	20(38.4)
Posterior circulation infarct (POCI)	13(25)
Lacunar Infarct (LACI)	15(28.8)

[Table/Fig-5]: Different types of ischemic strokes seen in this study (n=52) according to Oxfordshire community classification [17].

Intracerebral Haemorrhage FUNC score [18] of two haemorrhagic strokes were 9 and 11. Modified Rankin scale [19] after 5 days of hospital stay was mean 3.83 (±1.03) and after 6 months of follow-up was 2.1(±0.8). The Barthel Index [20] at presentation was mean 12.2(±3.32) and at final follow-up was 18(±2.3). At presentation the FTND-ST [9] score was mean 7.82(±1.3) and post 6 month follow-up was 2.04(±0.6). Patients were counseled for deaddiction. After 6 months follow-up 48(88.8%) patients had quit ST.

Main symptoms/signs associated with stroke during the time of hospitalization have been summarized in [Table/Fig-3]. [Table/Fig-4] shows site of lesion of ischemic stroke according to MRI of Brain (n=52). [Table/Fig-5] shows different types of ischemic strokes seen in this study (n=52) according to Oxfordshire community classification.

DISCUSSION

ST is consumed without combustion and is used nasally or orally (sucked, chewed, dipped, held in the mouth), resulting in absorption of nicotine and other chemicals across mucus membranes. Smoked tobacco, is usually burned or heated and then inhaled. Worldwide, ST products are available in plenty from simple cured tobacco to various elaborate products with different chemical ingredients. So, ST products vary greatly in composition and contain high levels of free nicotine, total nicotine, and various carcinogens (> 30 identified) [21].

The mode of ST use varies based on ingredient availability, geographic location, social and cultural norms and individual preferences. The various forms available for oral use are pan, gutkha (chewing), khaini, snus, lozenges (sucking), bajjar, gudakhu (local application), tuibur (gargling), and as nasal snuff for inhalation [21]. In our study, Pan (Betel leaf) was most commonly used in 21 (38.9%) patients with addiction for 14.6 (±3.27) years.

Across the globe, approximately 300 million people use ST. The majority of ST users (89%) live in South-East Asia of which Bangladesh, Myanmar and India host 86% of the global total [21]. The prevalence of ST consumption in India is 20% [22]. The consumption is significantly higher in males than in females (28% v/s 12%), and in rural population as compared with urban [23]. Lesser cost, easy affordability, misconceptions regarding its useful health effects and peer pressure among adolescents are important contributory factors for increased ST consumption. Some decades ago, in India, only locally made ST products such as betel quid with tobacco were available. However, recently due to large scale production of tobacco, varieties of ST products have become commonly available [22,23]. Most commonly used ST products in India include tobacco with lime, tobacco pan masala, tobacco with pan and betel quid.

Nicotine in cigarette smoke induces a variety of pathologic mechanisms like platelet activation, endothelial dysfunction, cellular inflammation, accelerated atherogenesis, sympathoadrenal activation, cardiac arrhythmia, relative insulin resistance and dyslipidemia, all of them contributing to cardiovascular disease [24]. ST also through similar mechanisms leads to vascular damage [25,26]. The regular consumption of ST products leads to exposure of as much nicotine per day as do regular Cigarette Smoking (CS) [27]. Nicotine that is inhaled in CS is absorbed quickly in the lungs, moves into the arterial circulation in high concentrations, and then to the brain and other organs. Nicotine from ST is absorbed much more slowly with absorption continuing for >30 minutes [28]. It is relevant, as the speed of absorption of nicotine and maximum blood levels reached are important determinants of the cardio vascular effects. Thus, the same daily nicotine dose from ST would cause less injury than from CS.

In our series, 96.3% strokes were ischemic in nature. Nicotine is an established risk factor for ischemic strokes which can induce cardiac arrhythmias as proven by different animal studies [6]. Apart from other mechanisms of nicotine inducing atherogenesis, cardiac embolization secondary to cardiac arrhythmia probably could be attributed to the increased incidence of ischemic stroke in our patients. However in our patients, cardiac arrhythmia could not be established at the time of presentation to us and probably long term cardiac monitoring will help to diagnose the occult one. We observed two haemorrhagic strokes in our case series due to ST use. One Swedish study showed increased risk of subarachnoid haemorrhage due to consumption of snuff [29]. Nicotine opens up the blood brain barrier in ischemic stroke, causing post-ischemic brain edema and more cellular injury [30]. Several studies have suggested that obesity, diabetes, increased levels of triglycerides resulting in metabolic syndrome, might be associated with the use of ST [31].

Various studies were done in western population to ascertain the association of ST consumption with occurrence of adverse CVD (Cardio vascular disease) like myocardial infarction, ischemic heart disease and cerebral stroke [25]. Balhara performed a meta-analysis for association of ST use and CVD in 2004 [32]. They suggested modest association between risk of CVD with ST use like Swedish snuff (snus) {relative risk (RR) 1.4, 95% confidence interval (CI) 1.2-1.6}. Later Boffetta et al., also performed a meta- analysis in 2009 [33]. Five studies that evaluated fatal stroke and eight studies that evaluated fatal myocardial infarction were analysed. The study showed greater risk of fatal myocardial infarction (Odds Ratio (OR) - 1.13, 95% CI 1.06-1.21) and fatal stroke (OR 1.40, 95% CI 1.28-1.54) with consumption of ST. Studies from middle and low income countries are sparse. Gupta et al., from India, after a prospective study of 5 year duration concluded that, relative risk of fatal cardiovascular event among users of ST was not significantly different from non-tobacco users [34]. A meta-analysis of studies from China, Taiwan and India reported insignificant association of tobacco use and CVD mortality in India but the relationship was significant in studies from Taiwan and China [35]. The concluding OR (odd ratio) was 1.26 (95% CI 1.12-1.40), which suggested moderate risk of cardiovascular mortality with ST use.

In the past, some studies have been undertaken to determine association of ST use and CVD risk factors [25]. A Swedish prospective study showed that, high dose consumption of snus was associated with increased risk of metabolic syndrome (OR 1.6, 95% CI 1.26-2.15) [36]. A cross-sectional population based study in Sweden on more than 30,000 patients showed that, ST users were 1.7 times (95% CI 1.1-2.1) more likely to have a systolic BP >160mmHg and 1.8 times (95% CI 1.5-2.1) more likely to have a diastolic BP> 90mmHg [37]. A population based case-control study in India by Gupta et al., showed ST users had a significantly greater prevalence of resting tachycardia, hypertension, low HDL, hypertriglyceridemia, hypercholesterolemia and diabetes compared to non-tobacco users [38]. In the present study, anterior circulation was the most common territory involved as confirmed by CT scan/

MRI. Similar observations have been reported by Dash et al., in their study of young ischemic stroke [39].

This study is probably the first study from South East Asia on clinical symptomatology of stroke due to ST. We hypothesize that ischemic CVD in a ST user may be a manifestation of accelerated cerebrovascular atherogenesis. This is the primary pathological process seen in young age onset cardiovascular diseases.

LIMITATION

The study is limited by the unavailability of a 'gold standard test' such as pathologic confirmation of exact mechanisms of stroke. Also, genetic analysis for prothrombotic state was not done. Another limitation was the inclusion bias attributable due to the hospital based single center design. This study encompasses a small number of stroke patients. Risk factors such as coronary artery disease and stenotic vascular diseases were not evaluated by angiography in subclinical and asymptomatic cases. It is also likely that patients with paroxysmal atrial fibrillation were missed.

CONCLUSION

To conclude, our results suggest that ST associated CVD is a predominant cause of young ischemic stroke. We require specific serum biochemical analysis for nicotine to quantify the level of addiction that will help us to further prognosticate. Present study`s clinical implication and public health effect might be substantial, despite the fact that the magnitude of the excess risk is small. More studies are required to elicit pathophysiological mechanisms of ST on vascular system, thrombosis, cellular mechanism and atherosclerosis.

REFERENCES

[1] Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. *BMJ*. 1989;298:789-94.
[2] Fuster V, Kelly BB. Board for Global Health. Promoting Cardiovascular Health in Developing World: A Critical Challenge to Achieve Global Health. *Washington: Institute of Medicine*; 2010.
[3] Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A. Growing epidemic of coronary heart disease in low- and middle-income countries. *Curr Probl Cardiol*. 2010;35:72-115.
[4] Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. *J Am Coll Cardiol*. 1997;29:1422–31.
[5] Fant RV, Henningfield JE, Nelson RA, et al. Pharmacokinetics and pharmacodynamics of moist snuff in humans. *Tob Control*. 1999;8:387–92.
[6] Wang H, Shi H, Zhang L, Pourrier M, et al. Nicotine is a potent blocker of the cardiac A-type K(+) channels. Effects on cloned Kv43 channels and native transient outward current. *Circulation*. 2000: 102: 1165–71.
[7] Hergens MP, Lambe M, Pershagen G, Terent A, Ye W. Use of smokeless tobacco and the risk of stroke among Swedish men. *Epidemiol.* 2008;19:794-99.
[8] Henley SJ, Thun MJ, Connell C, et al. Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). *Cancer Causes Control*. 2005;16:347–58.
[9] Ebbert JO, Patten CA, Schroeder DR. The fagerström test for nicotine dependence-smokeless tobacco (FTND-ST). *Addict Behav*. 2006;31:1716-21.
[10] Islam K, Saha I, Saha R, Samim Khan SA, Thakur R, Shivam S. Predictors of quitting behaviour with special reference to nicotine dependence among adult tobacco-users in a slum of Burdwan district, West Bengal, India. *Indian J Med Res*. 2014;139:638-42.
[11] Nelson DE, Mowery P, Tomar S, Marcus S, Giovino G, Zhao L. Trends in smokeless tobacco use among adults and adolescents in the United States. *Am J Public Health*. 2006;96:897-905.
[12] Kiechl S, Willeit J, Rungger G, Egger G, Oberhollenzer F, Bonora E. Alcohol consumption and atherosclerosis: What is the relation? Prospective results from the bruneck study. *Stroke*. 1998;29:900-07.
[13] Chobanian AV, Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42(6):1206–52.
[14] American Diabetes Association: Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33(Supplement 1):S62–S69.
[15] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-497.
[16] WHO Expert Consultation: Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363(9403):157.
[17] Bamford J, Sandercock P, Dennis M, et al. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet*. 1991;337:1521–26.
[18] Hemphill JC, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral haemorrhage. *Stroke*. 2001;32:891–97.
[19] Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604–07.
[20] Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. *Int Disabil Stud*. 2008;10(2):61-63.
[21] Public Health: A Global Perspective. National Cancer Institute. Centers for Disease Control and Prevention. U.S. Bethesda, MD: U.S. Department of Health and Human Services. Centers for Disease Control and Prevention and National Institutes of Health, National Cancer Institute. *NIH Publication No*. 14-7983; 2014.
[22] Gupta PC, Ray CS, Sinha DN, Singh PK. Smokeless tobacco: a major public health problem in South East Asia region: a review. *Indian J Public Health*. 2011;55:199-209.
[23] Gupta PC, Ray CS. Smokeless tobacco and health in India and South Asia. *Respirology*. 2003;8:419-31.
[24] Benowitz NL. Cigarette smoking and cardiovascular disease: Pathophysiology and implications for treatment. *Prog Cardiovasc Dis*. 2003;46:91–111.
[25] Piano MR, Benowitz NL, Fitzgerald GA, et al, On behalf of the American Heart Association Council on Cardiovascular Nursing. Impact of smokeless tobacco products on cardiovascular disease: implications for policy, prevention and treatment. *Circulation*. 2010;122:1520-44.
[26] Gupta R, Gurm H, Bartholomew JR. Smokeless tobacco and cardiovascular risk. *Arch Intern Med*. 2004;164:1845-49.
[27] Benowitz NL, Porchet H, Sheiner L, Jacob P. Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. *Clin Pharmacol Ther*. 1988;44:23–28.
[28] van der Vaart H, Postma DS, Timens W, Ten Hacken NHT. Acute effects of cigarette smoke on inflammation and oxidative stress: a review. *Thorax*. 2004;59:713–21.
[29] Koskinen LO, Blomstedt PC. Smoking and non-smoking tobacco as risk factors in subarachnoid haemorrhage. *Acta Neurol Scand*. 2006;114:33–37.
[30] Hawkins BT, Brown RC, Davis TP. Smoking and ischemic stroke: a role for nicotine? *Trends Pharmacol Sci*. 2002;23:78–82.
[31] International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 89. Smokeless tobacco products. Lyon: IARC, 2008. 4 4. SCENIHR (Scientific Committee on Emerging and Newly-Identified Health Risks). Scientific opinion on the health effects of smokeless tobacco products. Brussels: European Commission, 2008. http://ec. europa.eu/health/ph_risk/committees/04_ scenihr/docs/ scenihr_o_013.pdf.
[32] Balhara Y. Tobacco and metabolic syndrome. *Indian J Endocr Metab*. 2012;16:81-87.
[33] Boffetta P, Straif K. Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis. *BMJ*. 2009;339:b3060.
[34] Gupta PC, Pednekar MS, Parkin DM, Sankaranarayanan R. Tobacco associated mortality in Mumbai (Bombay) India. *Results from the Bombay Cohort Study*. *Int J Epidemiol*. 2005;34:1395-402.
[35] Zhang L, Yang Y, Xu Z, Gui Q, Hu Q. Chewing substances with or without tobacco and risk of cardiovascular disease in Asia: a meta-analysis. *J Zhejiang Univ Sci*. 2010;11:681-89.
[36] Norberg M, Stenlund H, Lindahl B, Boman K, Weinehall L. Contribution of Swedish moist stuff to the metabolic syndrome: a wolf in sheep's clothing? *Scand J Public Health*. 2006;34:576-83.
[37] Eliasson M, Asplund K, Nasic S, Rodu M. Influence of smoking and snus on the prevalence and incidence of type 2 diabetes amongst men: the northern Sweden MONICA study. *J Intern Med*. 2004;256:101-10.
[38] Gupta BK, Kaushik A, Panwar RB, et al. Cardiovascular risk factors in tobacco-chewers: a controlled study. *J Assoc Physicians India*. 2007;55:27-31.
[39] Dash D, Bhashin A, Pandit AK, Tripathi M, Bhatia R, Prasad K, et al. Risk factors and etiologies of ischemic strokes in young patients: a tertiary hospital study in Northern India. *J Stroke.* 2014;16(3):173-77.

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Neurology, IMS & SUM Hospital, Sector-8, Kalinga Nagar, Bhubaneswar, Odisha, India.
2. Associate Professor, Department of Medicine, IMS & SUM Hospital, Sector-8, Kalinga Nagar, Bhubaneswar, Odisha, India.
3. Professor, Department of Medicine, IMS & SUM Hospital, Sector-8, Kalinga Nagar, Bhubaneswar, Odisha, India.
4. Student, IMS & SUM Hospital, Sector-8, Kalinga Nagar, Bhubaneswar, Odisha, India.
5. Student, IMS & SUM Hospital, Sector-8, Kalinga Nagar, Bhubaneswar, Odisha, India.
6. Associate Professor, Department of Emergency and Critical Care, IMS & SUM Hospital, Sector-8, Kalinga Nagar, Bhubaneswar, Odisha, India.
7. Assistant Professor, Department of Biochemistry, IMS & SUM Hospital, Sector-8, Kalinga Nagar, Bhubaneswar, Odisha, India.
8. Junior Resident, Department of Neurology, IMS & SUM Hospital, Sector-8, Kalinga Nagar, Bhubaneswar, Odisha, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Subhransu Sekhar Jena,
Associate Professor, Department of Neurology, IMS and SUM Hospital, Siksha 'O' Anusandhan University Sector-8,
Kalinga Nagar, Bhubaneswar-751003, Odisha, India.
E-mail: drssj2007@gmail.com

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