

Original article

Stroke and the use of Smokeless tobacco- A case-control study

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Abstract

Background: Smokeless tobacco consumption has a high prevalence and acceptance in the Indian community. Although a lot of studies have been done on the ill effects of smoking, there is a dearth in the literature on the cardiovascular effects of smokeless tobacco.

Objectives: This study aimed to see the association between smokeless tobacco and Stroke.

Methods: In a retrospective case control study, information on tobacco habits was collected by the means of an interview schedule. 80 case (adult males who had stroke) and 80 controls (adult males who did not have stroke) were identified from four different hospitals in city of Pune in Maharashtra, India. Each case was matched with one control.

Results: The unadjusted Odds ratio for any form of tobacco were significant [2.98(1.43-6.19)] but were statistically insignificant for smoking [2.08(0.96-4.47)] and smokeless tobacco [1.50(0.80-2.79)]. The adjusted odds ratio was calculated by using a multinomial logistic regression. After adjusting for the known confounding factors of hypertension, alcohol use and diabetes, the Odds ratio was significant for smokeless tobacco at [2.3 (1.1 – 5.1)] and smoking at [3.6 (1.4 – 9.2)].

Conclusions: The results show that consumption of smokeless tobacco and Stroke are associated. There was also a significant relation between consumption of smokeless tobacco and ischemic stroke.

Key Words: Smokeless tobacco, Stroke, Case-control study

Introduction:

Stroke is a global health problem. The global annual incidence of stroke is about 16 million¹ and is responsible for loss of 28 million DALYs². India accounts for nearly 1.4 million of the global incidence of stroke cases and results in loss of 6.4 million DALYs³. Given the current epidemiological transition India is going through, the burden of stroke is expected to increase in coming years. Many studies have incriminated role of smoking in contributing to stroke. More recent data from the Inter-stroke study conducted in 22 countries, including India, confirmed smoking as a major risk factor accounting for large population attributable risk of stroke. Compared to extensive literature on the association between smoking and stroke, little literature is found on relation between smokeless tobacco and stroke. Moreover, there are contradictory evidences about role of smokeless tobacco as an independent risk factor for stroke. One Swedish study found evidence of an increased risk of cerebro-vascular mortality, whereas three others found no increase in risk among snuff users⁴. Snuff is clearly distinct form of tobacco and its use is not being common in India. One American study considered both snuff and chewable form of tobacco and showed increased risk of stroke among smokeless tobacco users⁵. However, the chewable form of tobacco available in USA is qualitatively much different from that in India, the later country likely to have more nicotine in its tobacco products. Prevalence of smokeless tobacco use is high in India and even a smaller relative risk might result in higher population

attributable risk. The present study aimed to explore the association of use of smokeless tobacco and stroke in Indian settings.

Methods and Materials:

Prevalence data for stroke are limited and dependent on studies with small sample size and frequent bias. Analysis of the available data indicates higher prevalence in urban India and among urban India; highest prevalence was reported from cities in state of Maharashtra. The study was conducted in Pune which is a major city in Maharashtra. Even with relatively higher prevalence in the city, stroke is a rare event in population; only about two per 1000. The city has presence of both public and private sector, both well equipped to manage stroke and cases are most likely to get hospitalized. Given this background, hospital based case-control study design was chosen. Four hospitals with facilities to manage stroke cases were purposively selected, two each in public and private sectors.

For estimating sample size, following formula on sample size determination was used⁶.

$$N = \{z_{1-\alpha/2} \sqrt{[2 P_2^* (1-P_2^*)]} + z_{1-\beta} \sqrt{[P_1^* (1-P_1^*)]} + 1 / [P_2^* (1-P_2^*)]\}^2 / (P_1^* - P_2^*)^2$$

Where, P_1^* is anticipated probability of exposure for people with disease, P_2^* is anticipated probability of exposure without the disease, $100\alpha\%$ is the level of significance, $100(1-\beta)\%$ is power of the test. A recent Indian study estimated odds ratio of 3.92 for stroke among smokers compared to non-smokers⁷. Review of western studies revealed that smokeless tobacco use was associated with increased risk of stroke (RR = 1.42)⁸. We assumed an odds ratio of 2.5 for calculating sample size. For anticipated probability of 'exposure' for people without the disease, we used nationally available prevalence data on smokeless tobacco use. National Family Health Survey (NFHS) round III found that prevalence of smokeless tobacco use was 36.2% among men and

8.4% among women in India⁹. Given the time and other constraints, it was decided to limit the study to men only. The sample size was estimated to be 73 cases (α error 5% and β error 20%) and equal number of controls.

Male inpatients diagnosed with stroke at the selected four hospitals during study period were explained the purpose of study and were invited to participate. Ethical aspects were explained and informed consent was obtained before enrolling them in the study. Patients with neurological deficit similar to stroke but of different origins like head injury and history of infantile hemiplegia were excluded from the study. Those eligible patients who were willing to participate were recruited in the 'case' group. The control group consisted of adult males who had never suffered a stroke. They were selected from in-patient departments mainly orthopaedics and surgery wards of same hospitals. Patients with any kind of neurological deficit were excluded from the control group as well. While selecting controls, matching was done with cases with respect to age, gender and family income. Informed consent was administered to all the participants prior to data collection. Study participants were interviewed using a structured interview schedule, which had three main sections. The first section included information on demographic and socio-economic variables. Second section was related to exposure variables, smokeless tobacco use as well as confounding factors including hypertension, alcohol use and diabetes. It was not possible to collect past data on obesity, cholesterol levels, and only their present value could be collected, wherever possible. The third section was about present medical condition, including type of stroke and extent of neurological deficit. Data was entered in SPSS version 15.0. Unadjusted odds ratio was computed for stroke in smokeless tobacco users compared with men who never used tobacco. Since matching was not possible

for factors like hypertension, diabetes and alcohol use; logistic regression was used to estimate adjusted odds ratio. Odds ratio was also calculated for those who suffered from ischemic stroke as the later was the main sub-group.

Results:

Sample consisted of 80 cases and 80 controls. The average age of the sample was 61.7 years. The mean age of the cases was 61.8 years and of the controls was 61.7 years. The cases and controls were matched for age (+/- 2 years) and monthly income range of the family. 75(93.7%) cases had Ischemic stroke and 5(6.3%) had Hemorrhagic stroke. The prevalence of various forms of tobacco use among the cases and controls is presented in Table 1. The average duration of time for which cigarettes/ bidis were consumed was 30 years and the average age of initiation for smoking was 25 years. The average duration for which smokeless tobacco was consumed was 37.2 years and the average age of initiation for the same was 19.2 years.

Data regarding confounding factors was also collected. 15 (18.7%) cases and 16 (20%) controls had diabetes whereas 41 (51.3%) cases and 37 (46.3%) controls reported alcohol use. The distribution of these confounding factors among the cases and controls was not statistically different. However, hypertension was significantly more common among cases (42.5%) compared to controls (28.7%). Other risk factors were also considered and included obesity, level of physical activity, cholesterol levels and diet. The tool attempted to measure obesity by means of waist hip ratio. However the same data could not be collected for all respondents, either due to the condition of the patient or due to lack of permission (from hospital or respondent) for taking measurements. Thus the data could not be used for analysis. In certain situations, the patients had external devices like catheters or drains the hip circumference measurement may have been flawed. The waist and hip

circumference measurement data was taken for fifty six respondents from the control group and thirty seven respondents from the group of controls. The average waist hip ratio for the respondents was 0.91. The average waist hip ratio for cases was 0.93 and was 0.88 for controls.

Medical records were reviewed for blood lipid levels; they were available for 42 respondents of which 27 belonged to the group of cases and 15 to the group of controls. Among the cases, average total serum cholesterol level was 155mg/dl, high density lipoprotein (HDL) was 36.8 mg/dl, low density lipoprotein (LDL) was 79.7 mg/dl and very low density lipoprotein (VLDL) was 20.2 mg/dl. Among controls, average cholesterol was 132.6 mg/dl; HDL was 42.4 mg/dl, LDL 63.3 mg/dl and VLDL 23.1 mg/dl. Few (21.9%) respondents reported of self imposed restriction of either salt or excess sugar in their diet with no significant difference between the two groups.

Odds ratio was calculated for all forms of tobacco and then separately for smoking and smokeless tobacco (Table-2). The unadjusted odds ratio for any form of tobacco was significant [2.98(1.43-6.19)] but were statistically insignificant for smoking [2.08(0.96-4.47)] and smokeless tobacco [1.50(0.80-2.79)]. The odds of suffering from stroke are three times more in tobacco consumers as compared to non users of tobacco in the sample. The number of respondents who consumed both forms of tobacco (smokeless and smoked) was very less. Most of the tobacco using respondents either used smokeless tobacco or smoked form of tobacco exclusively. Hypertension, an important risk factor was unequally distributed in the two groups. The adjusted odds ratio was calculated by using a multinomial logistic regression. After adjusting for the known confounding factors of hypertension, alcohol use, diabetes and smoking, the odds ratio was significant for smokeless tobacco (Table-3). Of the different types of stroke, 95% of

the cases had ischemic stroke and 5% had hemorrhagic stroke. A multivariate analysis was done to see the association of smokeless tobacco with ischemic stroke in the presence of other confounding factors. (Table- 4)

Discussion:

The present study showed increased risk of stroke among tobacco users. When adjusted for hypertension, diabetes, alcohol use and smoking, the odds of having stroke, in smokeless tobacco users, was 2.3 times that among non users of tobacco. However, the bi-variate analysis did not show increased risk of stroke among smokeless tobacco users compared with non users of smokeless tobacco. Similar finding was observed for smokers. The reason for the difference in the bi-variate and multivariate analysis may be due to the distribution of the tobacco habits among the respondents. Of the tobacco users, only 5.2% (6/115) used both forms of tobacco namely smokeless and smoked form. Thus, most smokers did not use smokeless form of tobacco. Similar to this, only 6 of the 84 smokeless tobacco users smoked. Since smoking is a known confounding factor for stroke, it might have affected the bivariate analysis. Although some confounding factors were considered in multi-variate analysis, other confounders like diet, obesity and blood lipid levels could not be adequately adjusted for in the study. This could have affected the study findings.

As far as risk of stroke among smokeless tobacco use are concerned, a Swedish study concluded that smokeless tobacco users (moist snuff) are not at a higher risk of stroke as compared to non tobacco users.⁴ However, this Swedish study considered only one type of smokeless tobacco (moist snuff). Moreover the study population was of Sweden whereas the present study was conducted in Maharashtra, India. The types of smokeless tobacco used, the environmental factors and socio

economical factors in both countries vary and this could be the reason of difference in the findings.

A meta-analysis pooled data of five studies in western societies (including the one discussed in above paragraph) estimated the relative risk of developing stroke to be 1.19 for smokeless tobacco users¹⁰. However, this finding was not statistically significant as it considered both current and former users. Relative risk was higher among the current users of tobacco. Present study also considered current users only. Studies have shown that smokeless tobacco has mainly short term effects on cardiovascular system. This suggests that the risk may wane after discontinuation of smokeless tobacco. However, to prove the effect of discontinuation of smokeless tobacco on risk of stroke, a cohort study would be needed. In the present study, testing for dose-response relationship was not attempted because the patients in the study used a variety of products differing from each other not only in nicotine but also other contents. The meta-analysis study showed that data on dose-response did not suggest a strong relation between risk of dying from stroke and frequency or duration of use of smokeless tobacco products.

The meta-analysis found that the relative risk estimated was higher (1.4) for fatal stroke, which did not seem to be explained by chance. Although, the present study considered all types of stroke, it might have missed fatal strokes where the patient died before reaching the hospital or soon after hospitalization and thus, were not available for interview at the time of study. To comment on fatality in short term, a follow up of about a month is needed. This study being a cross-sectional one, follow up could not be done and no comments can be made about risk of fatal stroke.

Majority of strokes in the study were of ischemic type which evolves with atherosclerosis and very few were of

hemorrhagic type which is associated more with hypertension. Recent study on ultrasonographic investigation of carotid intima media thickness showed that smokeless tobacco user has tendencies for atherosclerosis but without definite statistical significance¹¹. This study concluded that occurrence of atherosclerosis in smokers is caused by other components of tobacco smoke than nicotine. In India, smokeless tobacco has

Table 1: Prevalence of tobacco consumption in cases and controls

Tobacco consumption	Cases (n=80) N (%)	Controls (n=80) N (%)	Total (N=160) N (%)
Any tobacco	66(82.5)	49(61.2)	115 (71.8)
Smoking	23(28.7)	13(16.3)	36 (22.5)
Smokeless	46(57.5)	38(47.5)	84 (52.5)
Both	4(5)	2(2.5)	6 (3.7)
No tobacco	14 (17.5)	31 (38.7)	45(28.1)
Gutka	41(51.2)	32(40)	73(45.6)
Misheri	11(13.7)	8(10)	19(11.8)
Pan	5(6.2)	3(3.7)	8(3.5)
Other smokeless	1(1.2)	0	1 (0.06)
Cigarettes	15(18.7)	8(10)	23(14.4)
Bidis	8(10)	10(12.5)	18(11.2)

Table 2: Unadjusted odds ratio of stroke associated with tobacco use among men

Factor	Odds ratio (CI)	p value
Smokeless tobacco	2.6(1.1 – 5.6)	0.016
Smoking	3.4 (1.3 – 8.9)	0.009
Hypertension	2.2 (1.1-4.3)	0.028
Diabetes	1.1 (0.4 – 2.7)	0.447
Alcohol use	0.7 (0.4 – 1.5)	0.579

various forms with various ingredients and the effects seen in present study could be possibly due to these other components but no conclusion can be made about this from the study findings.

To conclude, smokeless tobacco leads to increased risk of stroke especially ischemic stroke independent of smoking, alcohol use or presence of hypertension or diabetes.

Table 3 Adjusted odds ratio of stroke associated with smokeless tobacco use and other confounders among men

Tobacco consumption	Cases (n= 80) N (%)	Controls (n= 80) N (%)	OR (C. I.)
Any tobacco	66(82.5)	49(61.25)	2.98 (1.43-6.19)
Smoking	23(28.7)	13(16.30)	2.08 (0.96-4.47)
Smokeless	46(57.5)	38(47.50)	1.50 (0.80-2.79)

Table 4 Adjusted odds ratio of ischemic stroke associated with smokeless tobacco use

Factor	Odds ratio (CI)	p value
Smokeless tobacco	2.3 (1.1 – 5.1)	0.025
Smoking	3.6 (1.4 – 9.2)	0.007
Hypertension	2.05 (1.1-1.4)	0.043
Diabetes	0.9 (0.4 – 2.3)	0.959
Alcohol use	0.8 (0.4 – 1.6)	0.579

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“The aim of medicine is to prevent disease and prolong life, the ideal of medicine is to eliminate the need of a physician. “

William James Mayo

“Medicine, is the only profession that labours incessantly to destroy the reason for its own existence.”

James Bryce

“He who cures a disease may be the “skillfullest”, but he who prevents it is the safest physician”

Thomas Fuller

"Take care of your body. It's the only place you have to live in."

Jim Rohn