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Prevalence of Smoking and Its Impact on Treatment Outcomes in Newly Diagnosed Pulmonary Tuberculosis Patients: A Hospital-Based Prospective Study

Vinay Mahishale*, Bhagyashri Patil, Mitchelle Lolly, Ajith Eti and Sujeer Khan

Department of Pulmonary Medicine, KLE University, J N Medical College, Belgaum, Karnataka, India.

There is growing evidence that tobacco smoking is an important risk factor for tuberculosis (TB). India, with a population of 1.26 billion, has the highest number of both TB patients and smokers. The convergence of these two important health hazards is likely severely affecting India's TB control programs. This study was carried out to determine the prevalence of smoking in newly diagnosed pulmonary TB patients and the impact of smoking on disease outcomes in a tertiary care hospital. All patients newly diagnosed with pulmonary TB as per the Revised National Tuberculosis Program of India (RNTCP) 2013 criteria were enrolled in the study. On the basis of their self-reported smoking status, the participants were classified as never smokers, current smokers, and ex-smokers. Patients were started on anti-TB treatment and were followed for 2 years. Among the 2350 subjects (1,758 males and 592 females), 1,593 patients (67.78%) were never smokers. Current and ex-smokers numbered 757 (32.21%), of which 751 (31.95%) were males and 6 (0.26%) were females. Smoking was associated with more extensive lung disease, lung cavitation, and positive sputum smear and culture results at baseline. In both current smokers and ex-smokers, sputum smears and cultures were significantly more likely to remain positive after 2 months of treatment. Ex-smokers and current smokers had significantly high rates of defaults, treatment failures, and relapses. The prevalence of smoking is very high in TB patients. Tobacco smoking is associated with a considerably increased risk of advanced and more severe disease in the form of lung cavitations, positive sputum smear and culture results, and slower smear and culture conversion after initiation of treatment. Smoking has a great negative effect on treatment completion, cure rates, and relapse rates in patients with pulmonary TB.

Key Words: *Smoking; Tuberculosis; Recurrence*

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Corresponding Author:
Vinay Mahishale
Department of Pulmonary Medicine, KLE University, J N Medical College, Belagavi, India
TEL: +91-9448920651
E-mail: pulmovinay@yahoo.com

INTRODUCTION

According to the 2014 World Health Organization (WHO) Global Report, tuberculosis (TB) continues to be the most important infectious disease in terms of incidence and mortality. It is estimated that 9 million new cases and 1.5 million deaths occurred in 2013.[1] India has approximately 2 to 3 million people infected with TB, and this global disease continues to be the largest public health problem in our country. India bears a disproportionately large burden of the world's TB patients, with incidence rates in the range of 160 to 180 per 100,000 population. Risk factors such as overcrowding, alcohol consumption, smoking, drug abuse, poverty, illiteracy, and HIV have all significantly contributed to escalating rates of TB on some level. One of the most important of these risk factors is tobacco smoking, the effect of which on TB was underestimated for several years in India.

Tobacco smoking is an important prevalent risk factor for TB. Nearly one-fifth of the world's population smokes

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tobacco or uses other tobacco products.[2] Most cigarettes are smoked in countries with a high prevalence of TB. Currently, substantially large proportions of tobacco smokers (82%) live in low- and middle-income countries with a high burden of TB as well.[3] Smoking increases the risk of latent TB by a factor of 1.9 [95% confidence interval (CI): 1.6 to 2.3], that of active tuberculosis by 2.0 (95% CI: 1.5 to 2.6), and that of death from TB by 2.6 (95% CI: 1.8 to 3.6), after adjustment for socioeconomic status.[4] Smoking also enhances the risk of treatment failure, the risk of relapse, and the number of defaults. These moderate increases in individual risk of TB due to smoking might translate into a large impact at the population level, because India has a high prevalence of smoking in both urban and rural sections. In India, 38% of deaths from TB among middle-aged men are attributed to smoking, costing the Indian economy three times its TB budget.[5,6]

There are approximately 120 million smokers in India, which is equivalent to 12% of the world's smokers. As reported in 2009, approximately 900,000 people die every year in India as a result of smoking. According to a 2002 WHO estimate, 30% of adult males in India smoke. Among adult females, the figure is much lower at between 3% and 5%. Tobacco is usually consumed in the form of bidis in rural areas. Bidis are smaller than cigarettes and contain only about one-quarter as much raw tobacco, which is wrapped in the leaf of another plant.[7,8]

India, with a population of 1.26 billion, has the highest number of both TB patients and smokers. The convergence of these two important health hazards is likely severely affecting India's TB control programs. Hence, we undertook this study to determine the prevalence of smoking in newly diagnosed pulmonary TB patients and the impact of smoking on disease outcomes in a tertiary care hospital.

MATERIALS AND METHODS

1. Source of data

Data were from the inpatient and outpatient departments of pulmonary medicine and internal medicine and the DOTS center (TB unit) at a tertiary care hospital in the Belgaum district of Karnataka in India.

2. Population

All newly diagnosed pulmonary TB patients registered for treatment in the above hospital were included.

3. Study design

This was a prospective study.

4. Study period

Primary data were collected between January 1, 2012, and December 31, 2013.

5. Inclusion criteria

These were as follows: (1) both male and female patients newly diagnosed with pulmonary TB per the RNTCP (Revised National Tuberculosis Program of India) 2013 criteria and (2) age >15 years.

6. Exclusion criteria

Patients were excluded from the study if they had any of the following conditions: (1) pregnancy, (2) HIV infection, (3) connective tissue disorders, (4) chronic renal failure, (5) chronic liver disease, (6) malignancies with long-term steroid or cytotoxic drug therapy, (7) chronic alcoholism, (8) previous treatment for TB, and (9) unclear smoking status.

7. Procedures

All patients newly diagnosed with pulmonary TB per the RNTCP 2013 criteria were enrolled in the study. Initial baseline details of the patients such as age, sex, sputum smear/culture for *Mycobacterium tuberculosis* status, chest radiography findings, and other relevant details pertaining to TB were recorded. Patients were started on anti-TB treatment. After informed consent was obtained, all patients completed standardized interviewer-administered questionnaires administered by trained resident doctors or nurses. Four questions pertained to smoking: (1) self-reported current smoking status (current cigarette/bidi smoker? Yes/No), (2) self-reported previous smoking status (previous cigarette/bidi smoker? Yes/No), (3) number of cigarettes/bidis smoked per day, and (4) age at which the participant started or quit smoking. An ever-smoker was defined as one who had smoked the equivalent of at least one cigarette per day for a period of 1 year. An ex-smoker was defined as an ever-smoker who had stopped smoking for at least 1 year before the current TB episode, and a current smoker was defined as an ever-smoker who was still smoking or had stopped smoking for less than 1 year. Patients who did not fulfill the criterion of an ever-smoker were classified as never smokers. Relapse was defined as recurrence of TB after successful completion of treatment, either proven by isolation of *Mycobacterium tuberculosis*, or in the absence of bacteriological confirmation, recurrence diagnosed on clinical, radiological, or histological grounds. Participants were followed for 2 years after the initiation of treatment as per RNTCP guidelines for treatment outcome.

8. Statistical analysis

Mean values (±SDs) were calculated for normally distributed numerical outcomes. Mean values (±SD) for demographic characteristics among never smokers, ex-smokers, and current smokers were analyzed by using the Mann Whitney test. The chi-square test was used to compare non-numerical variables. ANOVA was used for numerical variables in the univariable analysis. Logistic regression analysis was used for multivariable analysis of treatment outcome, and Kaplan Meier analysis was used for univariable analysis of relapse with Cox proportional hazards modeling for multivariable analysis. The significance level was kept at a p value ≤ 0.05. The analysis was done after

adjustment for cofounding variables like age, duration of smoking, nutritional status (body mass index, or BMI), socioeconomic status, and diabetes.

RESULTS

A total of 2,504 newly diagnosed pulmonary TB patients were registered for treatment in the hospital during the study period. A total of 154 subjects were excluded from the study because they did not meet the inclusion criteria. Among the 2,350 subjects (1,758 males and 592 females), 1,593 patients (67.78%) were never smokers. Current and ex-smokers numbered 757 (32.21%), of which 751 (31.95%) were males and 6 (0.26%) were females (Table 1). The demographic details of the participants are shown in Table 2. When TB severity and treatment outcome were compared between never smokers, ex-smokers, and current smokers, there was a statistically significant difference in the severity of TB between never smokers and ex-smokers and current smokers. Both ex- and current smokers had more subjects with multiple cavities: 13.5% and 17.4% compared with 8.6% in never smokers ($p < 0.05$). About 73.7% of ex-smokers and 73.9% of current smokers were culture- or smear-positive for *Mycobacterium tuberculosis*, whereas 68.9% of never smokers were smear/culture-positive at the time of diagnosis ($p < 0.05$). At the end of 2 months, 10.2% and 12.4% of ex- and current smokers were smear/culture-positive, respectively ($p < 0.05$).

As far as treatment outcome, ex-smokers and current smokers had significantly high rates of defaults and treatment failures. Relapse rates were also as high as 10.4% in ex-smokers and 12.9% in current smokers compared with 4.3% in never smokers ($p < 0.05$; Table 3). Univariable and multiple logistic regression analysis of treatment success and relapse in ex- and current smokers after adjustment for confounding variables also demonstrated a significant negative association between smoking and tuberculosis (Table 4).

TABLE 1. Initial screening details of the subjects enrolled

Total no. of subjects registered for TB treatment	2,504
No. of subjects excluded	154
No. of subjects who completed the study	2,350
Males	1,758 (74.8%)
Females	592 (25.2%)
Total number of subjects who were never smokers	1,593 (67.78%)
No. of smokers (current and ex-smokers)	757 (32.21%)
Males	751 (31.95%)
Females	6 (0.26%)
Current smokers	395 (16.8%)
Ex-smokers	362 (15.4%)

TB: tuberculosis.

DISCUSSION

The prevalence of smoking in the current study in newly diagnosed pulmonary TB patients was estimated to be 32.21% in the total study population: 31.95% in males and 0.26% in females. Compared with the prevalence in the general population, this prevalence is very high. The prevalence of smoking in this part of the country (South India) is around 25% to 26% and is negligible in women.[7,8] In a study by Wang et al., the proportion of cigarette smoking was 54.6% in TB cases, which was significantly higher than that in controls (45.1%) in China.[9] Because that study included both pulmonary and extrapulmonary TB cases, our study is unique in that we enrolled subjects with newly diagnosed pulmonary TB only. Also, in the present study, the number of female smokers was very small compared with China, Nepal, and other Western countries.[10,11] In India, the prevalence of smoking among women is negligible because tobacco smoking among women is regarded as socially unacceptable.

Our observations of more extensive lung disease, lung cavitations, and positive sputum smears among current smokers and ex-smokers agreed with many of the results reported in previous studies.[12-14] In this study, a significant proportion of both current smokers and ex-smokers remained smear-positive or culture-positive after 2 months of treatment, closely comparable to the observation in a Brazilian case-control study in which ever-smokers who smoked >20 cigarettes per day were also reported to be two-fold as likely to remain culture-positive after 2 months of treatment.[15] Remarkable evidence from the current study was that smoking was negatively associated with cure or treatment completion, even after control for baseline sociodemographic variables, comorbidities, extent of lung dis-

TABLE 2. Demographic data

No. of subjects	Never smokers	Ex-smokers	Current smokers
Total no. of subjects	1,593	362	395
Males	1,007	359	392
Females	586	3	3
Age (yrs) (Mean±SD)	48±21.7	53±16.8	43±8.2
Duration of smoking (yrs)	-	15±12.8	12±9.8
Subjects from Rural Areas	1,035 (64.9%)	231 (63.8%)	241 (61%)
Subjects from Urban Areas	558 (35.1%)	131 (36.2%)	154 (39%)
Cigarette smokers	-	132 (36.5%)	129 (32.7%)
Bidi smokers	-	230 (63.5%)	266 (67.3%)

TABLE 3. Comparison of severity of pulmonary tuberculosis and treatment outcome

	Never smokers (n=1,593)	Ex-smokers (n=362)	Current smokers (n=395)	p value
Severity of disease (ATS Criteria)				
Minimal	335 (21%)	41 (11.3%)	24 (6%)	0.005
Moderately advanced	860 (53.9%)	208 (57.4%)	229 (57.8%)	0.005
Far advanced	398 (25.1%)	113 (31.3%)	142 (36.2%)	0.005
Patients with multiple cavitatory lesions on chest radiograph	140 (8.6%)	49 (13.5%)	69 (17.4%)	0.004
Smear or culture positive at the initiation of treatment	1,097 (68.9%)	267 (73.7%)	292 (73.9%)	0.002
Smear or culture positive at the end of 2 months	95 (5.9%)	37 (10.2%)	49 (12.4%)	0.001
Smear or culture positive at the end of treatment	58 (3.6%)	42 (11.6%)	56 (14.1%)	0.001
No. of defaulters	64 (4%)	39 (10.7%)	53 (13.4%)	0.001
No. of Relapse	69 (4.33%)	38 (10.4%)	51 (12.9%)	0.001

TABLE 4. Univariable and multiple logistic regression analysis of treatment success and relapse (Cox proportional hazard ratio) in ex- and current smokers after adjustment for confounding variables like age, duration of smoking, nutritional status (BMI), socioeconomic status, and diabetes

Smoking status	Subjects (n)	Treatment success (%)	OR (95% CI)	p value	Adjusted OR (95%CI)	p value	Relapse (%)	Adjusted HR (95%CI)	p value
Never smokers	1,593	92.4	Reference		Reference		4.33	Reference	
Ex-smokers	362	77.7	0.61 (0.58-0.64)	<0.001	0.71 (0.68-0.81)	<0.001	10.4	1.43 (1.06-1.61)	<0.001
Current smokers	395	72.5	0.82 (0.76-0.84)		0.69 (0.63-0.80)		12.9	1.68 (1.46-1.98)	

ease, lung cavitations, and bacteriology. These findings are consistent with many previous studies.[16,17] These observations in our study were despite the use of standard four-drug short course regimens for drug-susceptible TB in a fully functioning treatment program setting that also allowed individualized regimen modification and treatment prolongation. Relapse rates were as high as 10.4% in ex-smokers and 12.9% in current smokers compared with 4.3% in never smokers. This finding further substantiates the significant association between smoking and treatment default as reported in previous studies.[18,19]

The effects of smoking on clinical parameters (lung cavitations, positive sputum smear and culture results) and slower smear and culture conversion after initiation of treatment highlight a serious need for prevention of community-level transmission. Even for patients with initially drug-sensitive TB, the treatment completion rates fell substantially below the WHO target of 85% among both current and ex-smokers in this study. The high proportion of smokers who default treatment also raises concern over the emergence of drug resistance and secondary spread within the community. The emerging results from our study as well as the many studies discussed above have demonstrated that a large number of smoking TB patients, despite successful treatment, run a substantially higher risk for redeveloping active TB compared with the overall TB risk in the general population. The unfavorable outcome in these TB patients with prolonged smoking behavior poses a risk of a prolonged period of contagiousness. These patients may transmit mycobacteria to their contacts for a longer period than nonsmokers, both before the diagnosis and after the initiation of treatment.

Smoking is expected to postpone the millennium development goals of the WHO. The Global Strategy to Stop TB: 2006-2015, established by the Stop TB Partnership, set a global target for complete elimination of TB by 2050. The WHO TB report 2013 highlighted that progress is too slow, and globally we are off target with only a 2% drop in prevalence per year.[20] These discouraging reports highlight the urgent need for smoking cessation programs at all levels of health care services. It is essential to note that interventions to decrease the prevalence of smoking among patients with TB (or in the general population) may have an important impact on the incidence of TB and treatment outcome as well. Therefore, the WHO, the International Union Against Tuberculosis and Lung Disease (IUATLD), and the European Respiratory Society (ERS) insist that the issue of smoking be addressed within the framework of TB management and care and that efforts be undertaken to help TB patients who smoke to stop.[21] Interventions including counseling and pharmacological treatment for cessation of smoking in TB patients are still far from being implemented in routine clinical practice. This is particularly true in countries like India where the national TB control programs are overburdened with TB cases, many of whom are smokers, especially in rural settings.

Smoking continues to be the most major cause of preventable disease and death worldwide. Strengthening

measures for the control of smoking may have a supplementary and welcome impact on our progress toward TB elimination. The profound negative impact of smoking on the outcome and transmission of TB should be addressed at all levels of TB control programs. It is a clear duty of all health care workers managing TB patients to bring up this critical issue with their patients with special emphasis on the potential gain associated with smoking cessation.

A major strength of our study was the prospective design, which avoided the problems of control selection in case-control studies and obscured temporality in cross-sectional studies. Availability of thorough smoking details of all subjects made it possible to demonstrate a clear relationship between smoking and TB treatment outcome. The detailed information on demographic, socioeconomic, and behavioral factors allowed us to eliminate major potential confounders because a specific group at risk was targeted (pulmonary TB cases only). The study was limited by the fact that it was a single-center study, the results of which cannot be generalized. However, this provides a window of opportunity for clinicians and researchers to carry out further studies with involvement of different geographical areas across India. Also, studies can be performed to assess the impact of smoking cessation programs on TB treatment outcome in these high-risk subjects. Passive smoking is another field of interest. A randomized controlled trial assessing the effect of smoking cessation on TB treatment outcome under a program setting would be worth exploring.

CONCLUSIONS

The prevalence of smoking is very high in TB patients. Tobacco smoking is associated with a considerably increased risk of advanced and more severe disease in the form of lung cavitations, positive sputum smear and culture results, and slower smear and culture conversion after initiation of treatment. Smoking has a profound negative effect on treatment completion, cure, and relapse rates in patients with pulmonary TB.

CONFLICT OF INTEREST STATEMENT

None declared.

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