Preference of inhalants over pills/injections among pulmonary tuberculosis patients in Western India: A cross-sectional study

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ABSTRACT

Background: Presently, pills and injections are the two modes of therapeutic treatment available for tuberculosis (TB) patients. Many researchers have hypothesized inhalation drug delivery for reducing treatment times and possibly limiting the insurgence of drug resistance. This study was aimed at identifying and assessing the preferences of inhalation therapy over injections/pills among pulmonary TB patients.

Method: Cross-sectional study design was used and a sample of 477 participants were recruited at selected three Directly Observed Treatment Short-Course (DOTS) centers in Bhiwandi city. Data was collected through self-reported questionnaire. Descriptive statistics were reported, and binomial regression models were applied for data analysis.

Results: The preference of inhalants over pills/injections among pulmonary TB patients was significantly associated with clinical characteristics. The patients who underwent treatment for more than 1 year were 1.7 times more likely to prefer inhalants over pills/injections when compared with treatment duration of less than 1 year. Similarly, patients taking five or more pills/day were 1.7 times more likely to prefer inhalants over pills/injections when compared with patients taking 1–4 pills per day.

Conclusion: The study results signify that inhalants could be an acceptable method of drug delivery in this population of TB patients. Diverse drug delivery options for TB patients may greatly contribute towards TB treatment adherence.

1. Introduction

Due to the global advancement in biomedicine and research, the treatment for tuberculosis (TB) is readily available and highly successful [1]. However, considering drug resistance and the long duration of treatment, TB remains a serious global threat to the mankind. India not only shares the highest TB burden in the world accounting for 27% of the global TB cases [2], but also shares over a quarter of global burden of multi-drug resistant TB (MDR-TB) cases [3,4]. In 2014, the first National Anti-Tuberculosis Drug Resistance survey conducted by the Indian Government in collaboration with the World Health Organization (WHO) and the United States Agency for International Development (USAID) showed that, close to 23% of new cases have resistance to any drug with MDR-TB being detected in 3% of the cases [5]. Lengthy treatment duration, high pill burden, and strong side effects of TB medications have been some of the important contributing factors for non-adherence to TB treatment in India [6].

As of today, pills and injections are the two modes of therapeutic treatment available for TB patients. These oral or injectable standard anti-TB drug regimens are well established, relatively inexpensive therapies, and available free of cost under the government of India’s Revised National Tuberculosis Control Program (RNTCP) [4,7]. It is evident from the rise of MDR-TB that, new therapeutic approaches may be an important avenue to improve adherence to TB medications [1,6,8,9].

Inhalation therapy, a treatment by inhaling drugs into the respiratory tract which includes the nose, pharynx, larynx, trachea, bronchi, and alveoli of the lung could potentially be an underexplored avenue to
increase TB treatment adherence [1]. Inhalation therapy for TB was initially investigated in Russia and there has been a rising interest in this new drug delivery technique [10,11]. Inhalation therapy holds promise as an alternative route of administration that limits systemic side effects and delivers high and localized drug concentrations to the site of action [12]. It uses the alveolar-capillary interface to attain satisfactory systemic levels whereas minimizing the risk of systemic toxicity noticed with parentally delivered doses [13]. Over the last five decades, many different formulation approaches for inhalation have been investigated. Micro, nanoparticles, liposomes, propolisomes, and liposphere, with single and combination drugs have all been tried but mostly limited to data collected in vitro or from preclinical studies where for the majority, formulations were found effective in reducing bacterial counts [14-17]. There have been studies which have used aminoglycosides solution administered via nebulization for patients with smear-positive pulmonary TB. This resulted in inhibition of bacillary growth in alveoli, but it failed to affect the bacteria inside the macrophages [11]. However, there are other studies which have similarly attempted the aerosolized drugs like interferon gamma (IFN-g) among smear and culture positive pulmonary MDR-TB patients and have reported negative smears as well as a clear radiological improvement and a reduction in the size of the cavi
tary lesions [18,19]. This signifies that mere aerosolizing drug may not work and for efficient bacteria killing, drugs need to be formulated into suitable delivery systems ensuring their rapid uptake into the macrophages which harbor the tubercle bacilli [11]. Furthermore, the complex host-pathogen relationship and lungs morphology restricts us in achieving sufficiently high drug concentration and targeting drug to alveolar region. Patient’s age, breathing pattern, optimized formulation properties, device performance, and the patient’s understanding/ awareness are key to determine the real fate of aerosol and the final success of inhaled therapy [13]. Inhalation as a drug delivery method could hold to be a key potential new drug delivery mode for millions of TB patients. Many biomedicine and clinical researchers have hypothesized that inhalation drug delivery may reduce treatment times and possibly limit the insurgence of drug resistance [10,11,20]. However, before moving towards this innovative exploration on alternative therapeutic options in the form of inhalants, it is essential to understand patient preferences towards drug delivery mechanisms.

The aim of this study was to assess TB patients’ preferences for inhalation therapy over injections/pills and identify its association with sociodemographic characteristics (age, gender, and socioeconomic class) and clinical characteristics (duration of the treatment, pill burden, experience of side-effects, and medication doses interruption).

2. Materials and methods

2.1. Ethics statement

This study was approved by the Institutional Review Board of the Penn State College of Medicine, Hershey, Pennsylvania, United States (#STUDY00010507).

2.2. Study design and settings, and participants

This cross-sectional study was conducted at three Directly Observed Treatment Short-course (DOTS) centers in Bhiwandi City (15 miles North-east of Mumbai) of Maharashtra state, in Western India. These three DOTS centers were located at Shanti Nagar, Gayatri Nagar, and Nayi Basti slum areas in Bhiwandi City. The DOTS centers selected for this study conduct primary TB prevention activities, including screening and outpatient treatment administration services to TB patients in their respective catchment areas as identified by their names. Only those participants who visited any of the three DOTS centers during the time of data collection were recruited in the study.

2.3. Inclusion and exclusion criteria

Inclusion Criteria

- Ability to give the written consent
- Patients who can understand Hindi Language
- 18 Years and above
- Patients diagnosed with pulmonary TB

Exclusion Criteria

- Patients registered at any other DOTS center in the area except the three selected DOTS centers.
- Patients who have been undergoing TB treatment for less than one month

2.4. Sampling

Using the estimated 50% TB medication non-adherence prevalence rate in India [21], the sample size of 350 was calculated at 80% power and 0.05 level of significance.

2.5. Measurements

A survey instrument was designed and was administered to the respondents to identify the preference of inhalants among pulmonary TB patients. This survey instrument was translated into Hindi.

2.5.1. Demographic information

The sociodemographic information included age, gender, and socioeconomic status. The age was further categorized in three groups (18–35 years, 36–49 years, and 50 years & above). Socioeconomic status was identified using Kuppuswammy Scale [22]. This scale is a validated instrument which uses consumer price index and categorizes the participant’s socioeconomic class into three categories (upper, middle, and lower).

2.5.2. Clinical characteristics

This includes variables such as the duration of TB treatment (up to 1 year and more than 1 year), number of pills consumed per day (1–4 pills per day and 5 or more pills/day), experience of side effects (Yes/No), and medication dose interruption. Medication dose interruption and its frequency during the last month was identified using two questions of the designed survey instrument. The question on medication dose interruption and its frequency was categorized in three groups; zero missed doses, missed 1–5 doses, and missed 6 or more doses in the last one month. The frequency of missing doses was decided based on the patterns of interruption among tuberculosis patients [23].

2.5.3. Inhalant preference

The preference of inhalant over pills/injections was measured using the question, “Would you prefer inhalants over injections/pills”, with a closed response of Yes/No.

2.6. Data collection

The study was conducted in two phases. The first phase was conducted in September–October 2018 and 212 surveys were completed during the first phase. A total of 265 surveys were completed in the second phase which was conducted in September–October 2019. In all a total of 477 participants were surveyed. The collected data were self-reported and only those participants who visited the three DOTS centers at the point of data collection were recruited in the study. The study respondents received a peanut and dry fruits nutrition bar package, irrespective of their decision to participate in the study. Pilot testing of the study procedures and the survey were conducted at the different
DOTS centers in Bhiwandi city.

2.7. Statistical analysis

The data were analyzed using Statistical Package for the Social Sciences (SPSS) version 26, 2018 software [24]. The following analytical strategies were employed to examine the preference of inhalants over injections/pills. First, descriptive statistics were used to present the basic sample characteristics. Second, multivariable logistic regression models were applied to identify the association between the preference of inhalants over injection/pills and other sociodemographic and clinical variables. The Wald test was used to determine potential associations at a significance level of $p \leq 0.05$.

3. Results

Out of 477 study participants, women comprised more than half (58%) of the study population. More than two thirds (66%) of the respondents 18–35 years of age. Close to 74% of the study participants belonged to the lower socioeconomic class. The majority (62%) of patients reported a treatment duration of less than one year. More than two thirds (72%) of the respondents took 1–5 pills per day and 68% of the patients experienced side-effects of their TB medication. Among all study participants, 23% missed their doses in the last month. During this group more than 61% patients missed their doses 1–5 times, and the remaining 39% patients missed their doses $\geq 6$ times in the last month. When asked about the preference of inhalants over pill/injections, 77% of the total 477 patients responded, and among them, 23% revealed that they would prefer inhalants over injections/pills (Table 1).

Among the participants who preferred inhalants over injections/pills, the majority (53%) of them were women. More than two thirds (66%) of the respondents who preferred inhalants were in the age group of 18–35 years. Around 78% of the respondents who preferred inhalants belonged to the low socioeconomic class. The duration of treatment among 63% of the patients who preferred inhalants was one year or less. The majority (66%) of the patients who preferred inhalants consumed 1–4 pills per day compared to the remaining patients who consumed 5 or more pills per day. Around 76% of the patients who preferred inhalants revealed that they have experienced side-effects from taking TB medications. Finally, about 20% of the patients who preferred inhalants had had missed at least one dose of TB medication in the last month. Among them, 12% patients had missed their doses 1–5 times and 8% had missed their doses more than 6 times in the last month (Table 2).

After adjusting for age, gender, and socioeconomic class, the preference of inhalants over pills/injections among pulmonary TB patients were significantly associated with duration of TB treatment, number of pills taken per day, and reported experience of side-effects from TB medications. The TB patients who underwent treatment for more than one year were 1.7 times more likely to prefer inhalants over pills/injections (Adjusted OR = 1.684 [95% CI: 1.006–2.818]). Further, patients taking five or more pills per day were 1.7 times more likely to prefer inhalants over injections/pills when compared with patients taking 1–4 pills per day (Adjusted OR = 1.681 [95% CI: 1.022–2.763]). Patients who had experienced side-effects were two times more likely to prefer inhalants over pills/injections (Adjusted OR = 2.006 [95% CI: 1.185–3.403]) (Table 3).

### Table 1

Socio-demographic and clinical characteristics pulmonary tuberculosis patients ($n = 477$).

| Socio-demographic and Clinical variables | N (%) |
|-----------------------------------------|-------|
| Gender                                  |       |
| Male                                    | 199 (41.7) |
| Female                                  | 278 (58.3) |
| Age in years                            |       |
| 18–35                                   | 330 (69.2) |
| 36–49                                   | 77 (16.1)  |
| $\geq 50$                                | 70 (14.7)  |
| Socioeconomic Class                     |       |
| Lower                                   | 361 (75.7) |
| Middle                                  | 86 (18.0)  |
| Upper                                   | 30 (6.3)   |
| Duration of the TB Treatment            |       |
| Up to 1 year                            | 295 (61.8) |
| More than 1 year                        | 140 (29.4) |
| Number of Pills Taken Per Day           |       |
| 1–4                                     | 344 (72.1) |
| $\geq 5$                                 | 133 (27.9) |
| Have Experienced Side Effects of TB Medications |       |
| Yes                                     | 325 (68.1) |
| No                                      | 146 (30.6) |
| Inhaling Preference over pills/injections |       |
| Yes                                     | 109 (22.9) |
| No                                      | 259 (54.3) |
| Number of TB Medication Doses Missed in Last One Month |       |
| Never Missed                            | 368 (77.1) |
| 1–5 times                               | 66 (13.8)  |
| $\geq 6$ times                          | 43 (9.0)   |

### Table 2

Sociodemographic and clinical characteristics based on drug delivery preferences among pulmonary tuberculosis patients ($n = 477$).

| Socio-demographics/Clinical Characteristics | Inhaling Preference overPills/Injections (N = 477) |
|---------------------------------------------|--------------------------------------------------|
|                                             | Yes (%)  | Non (%)  |
| Total                                       | 109 (23) | 259 (54) |
| Gender                                      |         |         |
| Male                                        | 51 (61.7) | 105 (22) |
| Female                                      | 48 (49.5) | 104 (21) |
| Age in years                                |         |         |
| 18–35                                       | 79 (27.2) | 180 (68) |
| 36–49                                       | 12 (4.2)  | 44 (17.0) |
| $\geq 50$                                   | 18 (6.1)  | 35 (13.5) |
| Socioeconomic Class                         |         |         |
| Lower                                       | 85 (78)  | 191 (37) |
| Middle                                      | 21 (19)  | 47 (45.9) |
| Upper                                       | 3 (3.4)  | 21 (21.7) |
| Duration of the TB Treatment                |         |         |
| Up to 1 year                                | 60 (22.5) | 175 (69) |
| $\geq 5$                                    | 37 (15)  | 62 (27.4) |
| Number of Pills Taken Per Day               |         |         |
| 1–4                                         | 72 (29)  | 197 (71) |
| $\geq 5$                                    | 37 (15)  | 62 (27.4) |
| Have Experienced Side Effects of TB Medications |       |         |
| Yes                                         | 80 (26.5) | 161 (54) |
| No                                          | 25 (8.3)  | 99 (31)  |
| Number of TB Medication Doses Missed in Last One Month |       |         |
| Never Missed                                | 87 (28)  | 194 (62) |
| 1–5 times                                   | 13 (4.2)  | 42 (14.7) |
| $\geq 6$ times                              | 9 (3)    | 23 (8.3)  |

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4. Discussion

Several studies examining preferences among various routes of drug delivery for chronic diseases typically yielded findings in the expected direction with easier or more convenient routes of administration preferred over more difficult routes of administration [25-31]. There have been studies conducted among patients with osteoporosis, diabetes and multiple sclerosis where respondents were found to prefer oral over injectable administration [26-28], and inhaled medication over injections [29,30]. Some studies have also shown preference for pills over inhaled medication and injections [30,31]. However, there is a scarcity of literature on the treatment preferences for the various routes of administration of TB treatment. The present study focused on largely unexplored issue, that is, the TB patient’s preference of the use of inhalants over injections/pills as a choice of drug delivery method. Many of the patients have the experience of using pills and injections for TB treatment, however this study gave an opportunity for the TB patients to give their hypothetic preference without direct experience of using inhalants for their TB treatment. The study results revealed that, inhalant preference over pills/injections had a significant association with clinical variables like long treatment duration, high pill burden, and reported side-effects of TB medications.

A fundamental problem that hinders more effective TB control is the ability of TB bacteria to persist in the host and to develop drug resistance, often because of poor adherence to lengthy therapy [32]. While there are several clinical trials which are looking at shorter drug regimens, most of the new agents identified as anti-TB drug candidates are still in the preclinical phases [32]. Rather than focusing on treatment agents, this study guides us towards inhalants as a potential preference of drug delivery method among some pulmonary TB patients. Patients with a longer treatment duration (more than 1 year) have shown more interest towards inhalation therapy in this study. Hence, while it is important to focus on new anti-TB drug candidates, it becomes equally imperative to think simultaneously towards utilizing alternative methods of drug delivery. These drug delivery methods could potentially improve TB medication adherence for the patients with MDR-TB in India where the standardized treatment regimen is a 6-drug regimen, with an intensive phase of 6–9 months and a continuation phase of 18 months; for a total treatment duration of about 24–27 months [33].

Another important barrier to TB-medications adherence for TB patients is pill burden. A MDR-TB patient swallows about 14,600 pills in two years of treatment and undergoes 8 months of painful injections [34]. Burden of such a huge number of pills also affects patient adherence and influences health seeking behavior, with adherence rates dropping to as low as 20% among patients who must take thirteen or more pills each day [35]. In our study, the preference for inhalants was found to be more common among the patients who consumed five or more pills per day. Hence, innovative drug delivery methods which could reduce their pill burden and contribute towards effective compliance.

In addition to the pill burden, side-effects are another cause of concern associated with TB treatment. Harsh side effects contribute towards non-adherence and are potential reasons towards the development of MDR-TB [6,8,36]. Injectable agents on the other hand, have been found to be among the most problematic medications in use, cause a great deal of pain and distress for patients, and are associated with frequent, serious adverse effects [37]. This study further strengthens this argument as patients experiencing some form of side effects from TB medications were found to be more likely to prefer inhalants over pills/injections.

Overall, duration of treatment, pill burden and painful side effects of TB medications/injections leads to intentional nonadherence where patients might skip their doses or cut their number of pills without informing their provider [38]. Considering these challenges associated with pills and injections, it becomes imperative to think of future research strategies regarding the development and design of new drug delivery methods for TB patients. Inhalation therapy could be one such method which needs further exploration.

A major therapeutic advance took place in 1997, when tobramycin designed for inhalation was approved by the U.S. Food and Drug Administration (FDA) for use in patients with cystic fibrosis (CF) with chronic Pseudomonas aeruginosa infection [14]. Attracted by the clinical benefits observed in CF, there has been a growing interest in the use of inhaled antibiotics in other lower respiratory tract infections, such as TB [1]. However, there are also existing practical barriers associated with the usage of inhalers. These barriers include forgetfulness and poor routines, inadequate inhaler technique, organizational difficulties (such as repeat prescriptions), and families not understanding or accepting the use of an inhaler [39]. There are families and people in India who believe that that inhalers could stigmatize individuals and also potentially become a habit among patients with chronic conditions [40,41]. Additionally, other challenges remain: for instance, the use of specialized delivery devices could, perhaps, make this therapeutic avenue more expensive than oral delivery, resulting in a disadvantage for implementing this therapy on a large scale, especially in developing countries like India [1]. Hence, pills and injections should remain available alongside inhalants.

5. Study limitations

The sample size was small, and data were collected from just three DOTS centers in Mumbai, therefore the results may not be generalized to all pulmonary tuberculosis patients. The other limitation of the study is that the main outcome question about inhalant preference does not differentiate between injections and pill taking preferences. In addition, the study had participants with a treatment duration ranging from 6 months to 2 years and did not distinguish between resistant and non-

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Table 3

| Characteristics | Inhalant Preference over Pills/Injections (n = 368) | Unadjusted OR (95% CI) | p-value | Adjusted OR (95% CI) | p-value |
|-----------------|-------------------------------------------------|------------------------|---------|-----------------------|---------|
| **Duration of the TB Treatment** | | | | | |
| Up to 1 year | Referent | 1.908 (1.40-3.194) | 0.01 | 1.268 (1.104-1.452) | 0.04 |
| More than 1 year | Referent | 2.008 (1.853-2.294) | 0.01 | | |
| **Number of Pills Taken Per Day** | | | | | |
| 1-4 | Referent | 1.233 (1.002-1.661) | 0.04 | 1.681 (1.222-2.763) | 0.01 |
| ≥5 | Referent | | | | |
| **Have Experienced Side Effects of TB Medications** | | | | | |
| Yes | Referent | 0.992 (0.992-1.002) | 0.74 | 1.003 (0.992-1.002) | 0.98 |
| No | Referent | 1.000 (0.992-1.001) | 0.45 | | |
| **Number of TB Medication Doses missed in the last month** | | | | | |
| Never | Referent | | | | |
| 1-5 times | Referent | 1.090 (1.035-1.145) | 0.04 | 1.069 (1.035-1.101) | 0.01 |
| ≥6 times | Referent | 0.938 (0.873-1.001) | 0.78 | 0.999 (0.936-1.063) | 0.98 |

OR, Odds ratio; CI, confidence interval; variables- gender, age in years, and socioeconomic class were adjusted in determining the association of inhalant preference with each of the clinical variables (duration of TB treatment, number of pills taken per day, experiencing side-effects and number of TB medication doses missed in last one month); p ≤ 0.05 statistically significant.
resistant patients. Hence, the results cannot be generalized to a particular group of TB patients or to a particular preference for injections or pills. Future research with specific groups of patients and one with differentiating injections and pill taking preferences might be useful. Another limitation of the study was, the inhalant preference question was given as yes/no question but only 77% of patients responded to that question and 23% of them did not answer the main outcome question. There might be a possibility where they did not know the answer, however the question did not give them the liberty of an option to say that they did not know. Future studies must consider incorporating the did not know response so that it can help identify the reasons for missing cases. Lastly, the study relied on self-report during interviews given by field staff, and we were not able to map it with the e-nikshay system for confirmation. This could result in recall or respondent bias.

6. Conclusion

The study results signify that inhalants could be an acceptable method of drug delivery in this population of TB patients. In this study, the preference of inhalants was significantly associated with clinical factors like treatment duration, pill burden and experience of side effects from TB medication. While the world remains committed to tackling TB through early detection and limiting the exposure among non-infected individuals; there is still a need to invest more in research, including basic and applied TB research and the development of shorter innovative therapies and new modes of drug delivery methods which could potentially improve adherence. Although the study results reported participants preferring inhalants over pills/injections, future research should examine the reasons associated with these choices along with other alternatives like syrups or a combination of all these choices (pills, injections, inhalants, and syrups) of drug delivery methods could be considered. Furthermore, in the future, it would be worthy to explore and compare the inhalation preferences among diverse group of TB patients such as 1) pediatric cases, 2) pulmonary TB patients, 3) extrapulmonary cases, 4) MDR-TB patients, 5) Pre-XDR TB patients, and 6) XDR-TB patients. In addition, it would also be beneficial to explore the distinction in preferences of inhalants between drug resistant and non-drug resistant TB patients. Overall, these studies may eventually contribute towards understanding the generalization of inhalant preferences among diverse group of TB patients.

Finally, considering the complexities of TB treatment including treatment duration, pill burden, multi-drug resistance, side-effects and other socioeconomic determinants around TB, there cannot be a one size fits all solution for the treatment delivery options of a complex disease like TB. Diverse drug delivery options for TB patients may greatly increase TB-medication adherence.

CRediT authorship contribution statement

Ahuja Nirmal: Conceptualization, Methodology, Formal analysis, Writing - original draft. Kristin Snazdjer: Conceptualization, Methodology, Formal analysis. Rajendra Patil: Resources, Project administration. Bushra Shaikh: Resources, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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