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Pattern of FDCs and Polytherapy in the Tuberculosis patients receiving treatment at Delhi and NCR

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Abstract

Tuberculosis (TB) remains a significant global health challenge, with substantial morbidity and mortality rates. Effective TB management relies on prolonged, consistent treatment with multiple antibiotics, posing challenges for patient adherence and the emergence of drug resistance. Fixed drug combinations (FDCs) have emerged as a promising approach to streamline TB treatment regimens. This study aimed to evaluate the pattern of FDC and polytherapy prescriptions in TB patients in Delhi and the National Capital Region (NCR).

A prospective observational study was conducted over two years and six months at a tertiary care facility in Haryana. Data were collected from 107 TB patients prescribed FDCs.

Results showed that the majority of patients were aged between 19 to 40 years (42.99%), with a relatively equal distribution between males (52.34%) and females (47.66%). Among the participants, 38.32% were prescribed two sets of FDC drugs, while 22.43% received three sets. Notably, 56.66% of patients were on polytherapy.

In conclusion, while FDCs hold promise for improving TB treatment adherence and outcomes, ongoing research and concerted efforts are essential to address challenges related to pharmacokinetic interactions, global implementation, and polytherapy. Collaborative action among stakeholders is imperative to optimize FDC utilization and effectively manage TB on a global scale.

Keywords: Fixed drug combinations, polytherapy, tuberculosis patients, prescribing pattern

Introduction:

Tuberculosis (TB) caused by Mycobacterium tuberculosis, remains a major global health challenge, with significant morbidity and mortality. The World Health Organization (WHO) reported an estimated 10 million cases of TB worldwide in 2019, underlining the ongoing burden of this infectious disease (WHO, 2020). Effective management of TB relies on prolonged and consistent treatment with multiple antibiotics, which often leads to issues with patient adherence and the emergence of drug resistance. Fixed drug combinations (FDCs) have been developed and are increasingly utilized in TB treatment regimens.

FDCs combine two or more anti-TB drugs in a single formulation, which simplifies the treatment regimen, potentially enhancing patient compliance. The standardized FDC regimens typically include first-line anti-TB drugs such as isoniazid, rifampicin, ethambutol, and pyrazinamide. The primary rationale for using FDCs lies in their ability to reduce the pill burden on patients, thereby improving adherence to the treatment protocol and reducing the likelihood of incomplete drug intake, which is a significant factor in the development of drug-resistant TB strains (Blomberg et al., 2001).

Moreover, FDCs ensure the simultaneous ingestion of multiple drugs, which can be particularly advantageous in ensuring that patients do not selectively omit one or more components of the regimen. Studies have demonstrated that FDCs can lead to better treatment outcomes and a lower incidence of drug resistance compared to separate drug formulations (Nijland et al., 2006).

Polytherapy, or multidrug therapy, is the cornerstone of TB treatment. The rationale behind this approach is to use multiple drugs that target different aspects of the bacterial life cycle, thereby enhancing the likelihood of killing the bacteria and preventing the emergence of drug-resistant strains. The use of multiple drugs reduces the bacterial load quickly and decreases the probability of selecting for resistant mutants. If only one drug is used (monotherapy), resistant strains can emerge rapidly, rendering the treatment ineffective. The synergistic effect of polytherapy is therefore essential for both killing the bacteria and curbing the development of resistance.

However, the use of FDCs and polytherapy is not without challenges. The pharmacokinetics and pharmacodynamics of the combined drugs must be carefully balanced to ensure efficacy and minimize adverse effects. Drug-drug interactions within FDCs can affect absorption,

metabolism, and excretion, potentially altering the therapeutic efficacy and safety profile of the treatment. There are also concerns regarding the stability of multi-drug formulations and the potential for adverse drug interactions within the combination. Ensuring quality control in the manufacturing of FDCs is critical to prevent subtherapeutic dosing or drug degradation, which could compromise treatment efficacy and safety (Zhang et al., 2015).

The research was conducted to study the pattern of FDCs and polytherapy in the tuberculosis patients to address the challenges associated with FDCs and to optimize their role in TB management.

Aim and Objective:

To study the pattern of prescribing fixed drug combinations and polytherapy in tuberculosis patients in Delhi and NCR

Materials and Methods:

The Study was a prospective observational study conducted for 2 years and 6 months in a tuberculosis clinic of a tertiary care facility located in Haryana.

Study setting: The study was conducted in the tuberculosis clinic of a tertiary care facility.

Study design: The study design was prospective observational study.

Study Duration: Two years and 6 months from January 2021.

Sample Size: The study utilized convenience sampling and collected 107 patients' data.

Study Population: The patients diagnosed with tuberculosis either pulmonary or extra-pulmonary and prescribed with fixed drug combinations were enrolled in study. The patients unwilling to participate in the study were excluded from the study.

Sources of Data: Clinicians notes, Past medical history of the patient.

Data Collection: The tubercular patients prescribed with fixed drug combinations and eligible as per selection criteria were included in study. The informed consent was received from the enrolled patients. Patients demographic details, medical and the prescribed medication details were noted.

Statistical Analysis: Descriptive statistics were used to calculate Frequency and Average using MicroSoft Excel.

Results:

The Study enrolled 107 tubercular patients where they were classified based on age and sex as shown in figure 1. and figure 2. respectively.

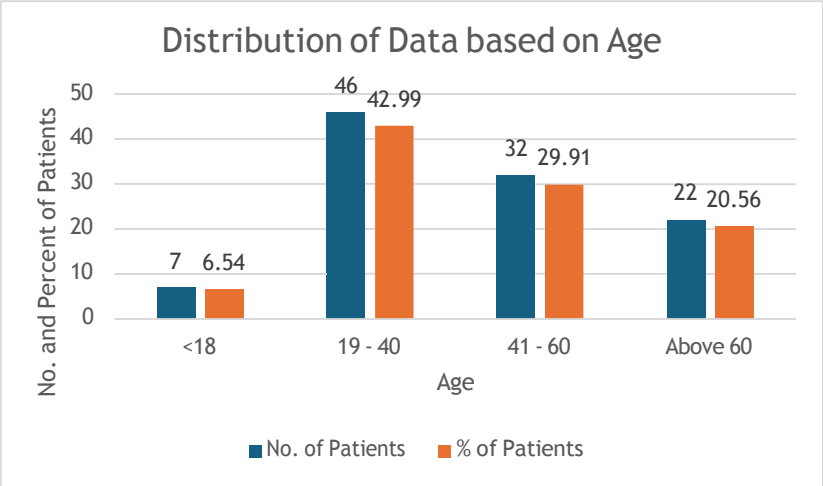

Figure 1. Distribution of Data based on Age

The age distribution of patients revealed that the majority were within the 19 to 40 years age group, comprising 46 individuals (42.99%). This was followed by the 41 to 60 years age group, which included 32 patients (29.91%). Patients over 60 years of age accounted for 22 individuals (20.56%), while those under 18 years of age constituted 7 patients (6.54%), as illustrated in Figure 1.

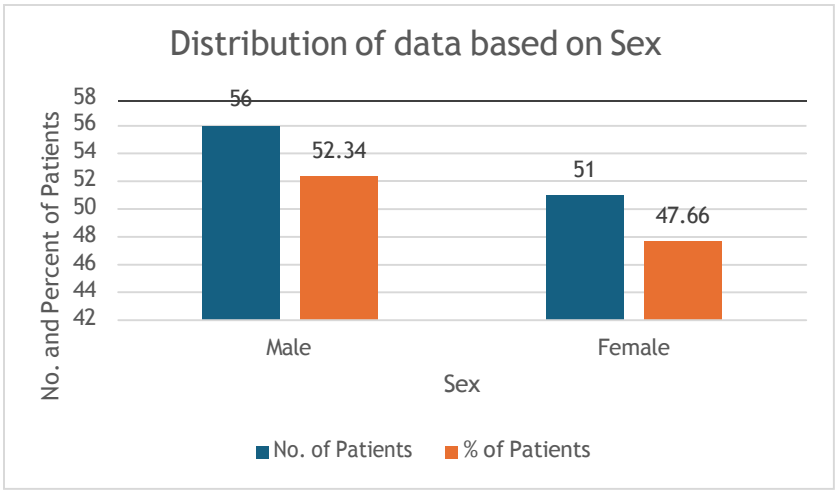

Figure 2. Distribution of data based on Sex

Figure 2 shows the distribution of data by sex, showing that male patients accounted for 56 individuals (52.34%), while female patients comprised 51 individuals (47.66%).

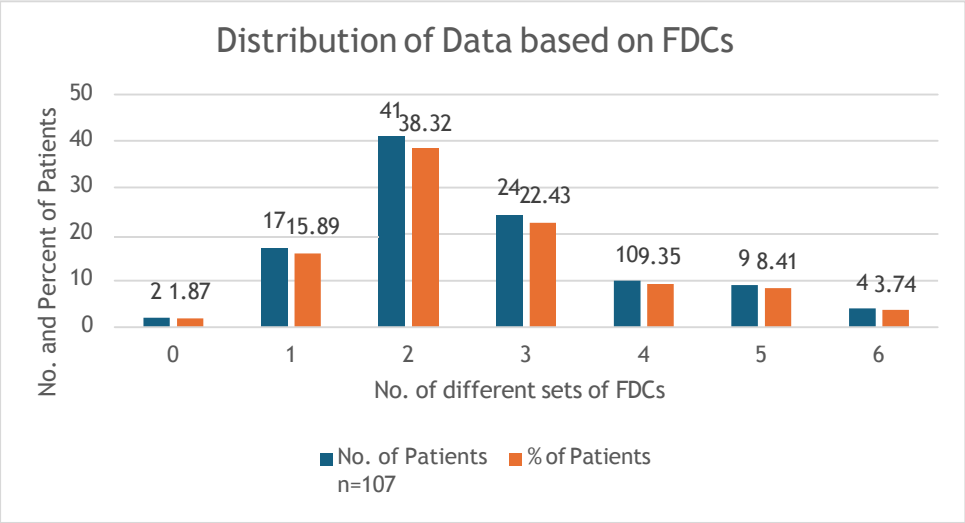

Figure 3. Distribution of data based on FDCs

Among the 107 subjects involved in the study who were administered multiple Fixed-Dose Combination (FDC) medications, there was a notable diversity in prescription patterns. Specifically, 41 individuals (38.32%) were prescribed two distinct sets of FDC drugs, while 24 participants (22.43%) received three different sets. A smaller group, consisting of 17 individuals (15.89%), was prescribed only one set of FDC medication. Additionally, 10 participants (9.35%), 9 participants (8.41%), and 4 participants (3.74%) were prescribed four, five, and six different sets of FDC drugs, respectively. Remarkably, only 2 individuals (1.87%) were not prescribed any FDC regimen. The distribution of participants based on their FDC medication prescriptions is depicted in Figure 3.

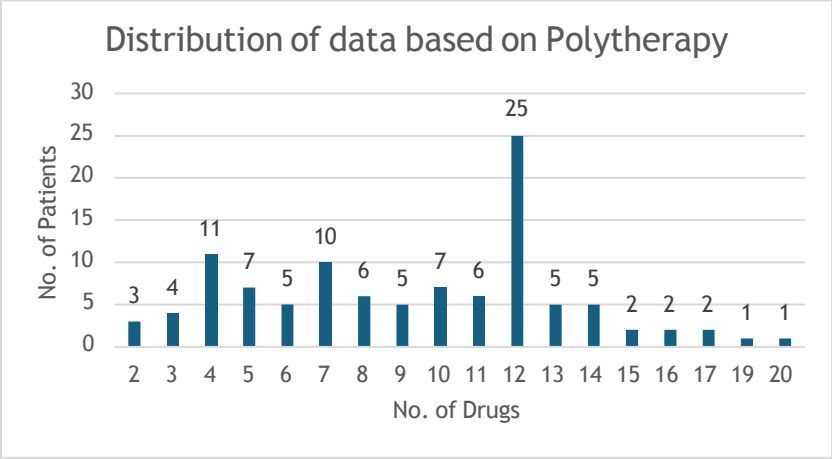

Figure 4. Distribution of data based on Polytherapy

The prescriptions of the participants were analyzed to determine patterns of polytherapy. It was found that 25 prescriptions (23%) contained twelve different medications, 11 prescriptions (10%) included four medications, and 10 prescriptions (9%) consisted of seven medications. Figure 4 provides a detailed representation of the data regarding patients who were administered polytherapy.

Discussion:

Combination drugs, or fixed drug combinations (FDCs), are recognized as advantageous when they exhibit clear benefits, such as:

a) Enhancing Therapeutic Efficacy: Several studies have shown that FDCs can improve treatment outcomes by ensuring that patients receive a consistent, balanced dose of multiple drugs. For instance, research has demonstrated that FDCs in tuberculosis treatment lead to better patient outcomes compared to monotherapy, as the combined drugs work synergistically to combat the infection more effectively (Blomberg et al., 2001; Mitchison, 2004).

b) **Lowering the Occurrence of Adverse Drug Effects**: Evidence suggests that FDCs can reduce the incidence of side effects by enabling lower doses of individual drugs, thus mitigating their toxicities. For example, the combination of antihypertensive medications in FDCs has been found to lower the occurrence of adverse effects compared to higher doses of single agents (Gandhi et al., 2010).

c) **Providing Pharmacokinetic Benefits**: FDCs can offer improved pharmacokinetic profiles, including more stable plasma drug concentrations and reduced fluctuations, which enhance the overall therapeutic effect. Studies on antiretroviral FDCs for HIV treatment have shown more consistent drug levels and better viral suppression compared to separate drug regimens (Boyd et al., 2012).

d) **Improving Compliance by Reducing Pill Count**: By decreasing the number of pills a patient needs to take daily, FDCs significantly enhance adherence to treatment protocols. This is particularly important in chronic diseases like TB and HIV, where long-term medication adherence is critical. Research has consistently indicated higher compliance rates among patients on FDC regimens (Harries et al., 2002).

e) **Lowering Individual Drug Dosages**: FDCs can allow for lower doses of each component drug, which reduces the likelihood of dose-dependent side effects. This has been observed in

treatments for diseases such as hypertension and diabetes, where combination therapies can effectively control symptoms with fewer side effects (Bakris et al., 2000).

f) **Decreasing Resistance Development**: The simultaneous use of multiple drugs in FDCs can reduce the risk of developing drug resistance, as the pathogen must simultaneously adapt to several active agents. This has been particularly noted in the management of TB and HIV, where FDCs help prevent the emergence of resistant strains (Zhang & Yew, 2009).

g) **Offering Cost Savings**: FDCs can be more cost-effective than individual drugs, due to savings in manufacturing, packaging, and distribution. Studies have shown that FDCs can lower healthcare costs by simplifying supply chains and reducing the need for separate packaging (Garrison et al., 2014).

However, the development and use of FDCs without thorough research can present significant challenges:

a) **Pharmacodynamic Discrepancies**: Inadequate research may lead to combinations where the drugs have additive or antagonistic effects, potentially reducing overall efficacy or increasing toxicity. Studies have highlighted the importance of thorough preclinical and clinical testing to ensure synergistic effects of combined drugs (Bauman, 2003).

b) **Pharmacokinetic Discrepancies:** Variations in the absorption, distribution, metabolism, and excretion of the combined drugs can result in peak efficacy occurring at different times, which can diminish therapeutic outcomes. Research underscores the necessity of aligning pharmacokinetic profiles to ensure concurrent efficacy (Levy, 1998).

c) **Chemical Incompatibility**: FDCs can face issues related to chemical stability, leading to decreased shelf life. Studies on various FDCs have shown that without proper formulation, chemical incompatibility can significantly impact drug stability and efficacy (Blomberg et al., 2001).

d) **Potential Drug Interactions**: Shared metabolic pathways can lead to drug interactions, which can alter the effectiveness and safety of the FDC. Research has documented cases where interactions in FDCs have led to altered drug metabolism, requiring careful consideration during development (Gupta et al., 2013).

e) **Challenges in Fine-Tuning Dosages**: Ensuring optimal dosages for individual components in an FDC can be difficult, particularly when patient needs vary. Studies emphasize the

importance of flexible dosing options to accommodate individual patient requirements (Mitchison, 2004).

Addressing the concerns surrounding FDCs requires a multi-faceted approach involving regulatory bodies, academic institutions, industry stakeholders, healthcare professionals, and the public. Comprehensive strategies should include rigorous clinical trials, robust regulatory oversight, and ongoing monitoring to ensure safety and efficacy.

Moreover, a significant percentage of patients (56.66%) are found to be on polytherapy, highlighting the need for well-researched and effectively formulated FDCs to optimize treatment outcomes and minimize risks (Harries et al., 2002).

Conclusion

In conclusion, the use of fixed drug combinations (FDCs) in tuberculosis (TB) treatment offers promising possibilities for improving patient adherence and treatment outcomes. While studies have highlighted the benefits of FDCs in simplifying treatment regimens and potentially reducing the risk of treatment failure, concerns regarding pharmacokinetic interactions and global implementation challenges persist.

Addressing these concerns requires ongoing research into the pharmacodynamics and pharmacokinetics of FDCs, particularly in diverse populations. Moreover, concerted efforts are needed to ensure the quality and availability of FDCs, especially in resource-limited settings where TB prevalence is highest.

It is also imperative to prioritize the safe and effective management of TB globally. This necessitates collaborative efforts among researchers, healthcare providers, policymakers, and international organizations to optimize the use of FDCs and improve TB treatment outcomes worldwide. Only through such collective action can we hope to effectively combat this persistent public health threat.

Future Scope of Study:

This research may serve as a comparative study assessing the efficacy and safety of fixed drug combinations (FDCs) versus individual drugs in tuberculosis (TB) patients. Such investigations contribute to understanding the optimal treatment approaches, aiding in the advancement of TB management strategies and patient outcomes assessment.

Ethical disclosure: The Institutional Ethics Committee - SGT Dental College, Hospital and Research Institute (IEC-SGTDCHRI) approved the study.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations:

TB Tuberculosis

FDC Fixed Drug Combinations

NCR National Capital Region

WHO World Health Organization

HIV Human Immunodeficiency Virus

IEC Institutional Ethics Committee

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