ABSTRACT

**Background and Objectives:** Almost one third of the world’s population is infected with the tuberculous bacilli. Effective treatment of tuberculosis requires adherence to treatment with multiple drugs for minimum of 6 months. WHO DOTS-strategy was launched in 1993 to improve treatment adherence and cure rates. This study is aimed to compare TB treatment and outcomes before and after the introduction of daily directly observed therapy (DOTS).

**Methods:** The study employed a retrospective record review comparative study design and was conducted at the TB clinic of Pulmonology department of Lady Reading Hospital Peshawar. We compared treatment outcomes among all TB patients treated for pulmonary and extra pulmonary tuberculosis in the TB clinic from 2001 through 2006 with 2001 to 2003 and 2004 to 2006, before and after DOTS implementation respectively.

**Results:** The study included 1235 cases with 867 patients before and 368 after introduction of DOTS. There were 631 (51.1 %) males and 604 (48.9 %) females. Mean age was 34.01 years (+19.717 SD). Before DOTS the cure rate was only 48.61 % which rose to 94.82 % after DOTS. The proportion of treatment completion increased from 75.14 % before DOTS to 99 % after the introduction of DOTS. The default rate which was initially 19.83 %, declined to less than 1 % after daily DOTS. The improvement in treatment outcomes after the implementation of DOTS strategy was statistically significant (p <0.05).

**Conclusion:** Directly Observed Treatment Short course strategy for the treatment of tuberculosis is more effective and have the greatest success in improving tuberculosis treatment outcomes.

**Key words:** Directly observed therapy; Compliance; Pulmonary tuberculosis.

INTRODUCTION:

Tuberculosis (TB) is the second most common cause of death from infectious diseases worldwide, infecting an estimated 8 million people and killing another 2 million people each year. 80% of the TB cases occur among people in the most economically productive age groups, representing a major economic burden for individuals and countries. Twenty-two high-burden countries account for about 80% of the total TB disease burden worldwide. Tuberculosis is endemic disease in Pakistan and the estimated annual incidence and prevalence of 410,000 and 620,000 tuberculosis cases respectively, defines Pakistan as the 4th highest TB burden country worldwide. TB is the diseases of poverty and is the most common disease in rural communities in Khyber Pakhtunkhwa (KP) as the poverty estimate of 34.4 % has persistently remained one of the nation’s highest. The main goals of tuberculosis treatment are to cure the individual with the disease and minimize the transmission of Mycobacterium tuberculosis to others in the community. Treatment of TB is quite challenging for both patients and health care providers because it requirestaking multiple drugs for prolong period of time, 6 months at least.

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The consequences of non-adherence to treatment result in increased rates of acquired drug resistance, treatment failure, relapse, and prolonged infectiousness of patients. The continuous search for improved treatment outcome and improved patient adherence led to the development of the Directly Observed Therapy, Short Course (DOTS) strategy. DOTS strategy has five key elements which are strengthening diagnosis by sputum microscopy, outcome monitoring, uninterrupted drug supplies, direct observation of treatment (DOT) and political commitment. DOT means the patients are actually observed ingesting each dose of anti-tuberculosis medications. Several studies and leading international organizations has shown and recommended DOTS strategy the standard of care for treatment of pulmonary tuberculosis.

DOTS is the cornerstone of a patient-centered approach for the treatment of TB to enhance treatment adherence, likelihood of completion of therapy and cure rate. The current model of treatment recommended by the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease is the DOTS strategy. Most studies evaluating DOTS have showed an average rate of treatment completion of 86%. However, there has been some debate in the literature about how much additional benefit can be derived from the element of directly observing the therapy. A study from Pakistan reported that DOTS was not superior to the self-administered treatment and did not give any additional improvement in cure rates. Another study from Switzerland also found no significant difference in cure rates between direct observation by community health workers and by family members. The early DOTS successes reported, might partly be to some extent on patient selection by health workers as patients who would be able to comply with the DOT regime were more likely to be included, with ‘unsuitable’ patients being excluded from the short-course treatment. In short the effectiveness of direct observation of treatment remains unclear, and further operational research is needed.

In TB clinic at LRH DOTS has been used in a substantial number of patients since 2001 with particular attention to patients with substance abuse, psychiatric illness, children and teenagers, and those who are at increased risk for treatment non-adherence. Therefore this study is aimed to assess the rates of treatment completion, cure, failure and death due to tuberculosis among patients with tuberculosis reported in over a 6-year period in an effort to determine any differences between patients treated by DOTS compared with those treated by self-administered therapy.

**METHODOLOGY:**

TB control program at Lady Reading Hospital was started in 1992 and run initially by the pulmonology department and later on with collaboration of provincial TB control program. The TB clinic at Lady Reading Hospital is a diagnostic center and receives patients from the whole province, FATA and patients from Afghanistan. This TB clinic is also a TB treatment center for the locality surrounding the hospital with population of about 50000. DOTS was first implemented by TB control program at TB clinic in 2003. The DOTS strategy has been shown to increase the cure rate and may help reverse the TB epidemic if implemented in its true spirit. So this study was designed to see the effectiveness of DOTS at our TB clinic. This was a retrospective comparative record review study that was conducted at the Pulmonology department post graduate medical institute lady reading hospital Peshawar from 2001 to 2006. From the TB clinic record we identified all those patients who had been treated for pulmonary and extra pulmonary TB during the 6 year study period from 2001 to 2006. The record from 2001 to 2003 consisted of patients who were treated for TB before the DOTS introduction while the record from 2004 to 2006 contained those patients who...
received TB treatment after DOTS implementation. In this study DOTS was referred to as the ingestion of anti-tuberculosis medications that was directly supervised by a healthcare worker only and took place at tuberculosis clinic. Daily supervision along with checking of treatment cards and pill counts continued for the first 2 months. Patient was called telephonically or the health care worker visited the patient's home himself if a patient missed the daily dose of medication. Self-administered therapy referred to as unsupervised self-administration of anti-tuberculosis medications by patients as prescribed by their health care provider. One month drug supply was given at diagnosis and after each follow-up visit with no treatment supervision between visits. All participants received the same drug regimen including isoniazid, rifampicin, pyrazinamide and Ethambutol for 2 months followed by isoniazid, rifampicin and / or Ethambutol for next 4 to 6 months. All the patients treated by DOTS strategy received their intensive phase treatment daily for the first 2 months and then for the continuation phase daily doses were self-administered by the patient. Anti-tuberculous medications taken by patients were provided by the Department of Public Health and dispensed at the Tuberculosis Clinic. Patients treated by DOTS were monitored according to the protocol recommended by national TB control program for symptoms, adherence, drug toxicity and sputum conversion. Patient's records were reviewed for the following data like dates of treatment, age, sex, sputum smear status, presence of pulmonary or extra-pulmonary disease. The main outcomes, assessed were the rates of completion, cure, treatment failure, default rate and death. Cure was defined as a person who completes all prescribed doses, does not have treatment failure, and was documented to have negative sputum sample at the end of treatment. Completion of treatment was defined as completion of all prescribed doses but lacking bacteriologic proof of cure because of inability to produce sputum. Death during tuberculosis treatment was defined as death during the treatment period of tuberculosis after receiving at least 1 week of anti-tuberculosis medications, irrespective of the cause of death. Treatment failure was defined as a TB patient who, while on treatment, remained smear-positive at the fifth month or later during the course of treatment, or one who was initially smear-negative before starting treatment and became smear-positive after the second month of treatment. Return after interruption (default) was defined as patient who completed at least one month of treatment and returned after at least two months' interruption of treatment. Data were analyzed by using SPSS version 17.0. Frequencies / Percentages were calculated for qualitative variables, while Mean± standard deviation was calculated for quantitative variables. Where applicable, Chi-squared and Fisher's exact tests were used for statistical analysis. P-value less than 0.05 was considered significant.

RESULTS:
This study was conducted at the Pulmonology Department of Post Graduate Medical Institute, Lady Reading Hospital, Peshawar. The study population consisted of 1235 cases including 867 patients before and 368 after implementation of DOTS. There were 631 (51.1 %) males and 604(48.9 %) females, with male to female ratio of 1.04. The age of patients ranged from 10-90 years with a mean age of 34.01 years and standard deviation of ±19.717. Most common age group was from 15-24 years (37 %). Of the total 867 patients before DOTS 568 were diagnosed with pulmonary TB while 299 patients were having extra pulmonary TB. After the implementation of DOTS, out of the 368 cases 191 patients were having Pulmonary TB either smears positive or negative, while 177 patients were carrying the diagnosis of extra pulmonary TB (Table I). Most of the patients with extra pulmonary TB were having tuberculous lymphadenopathy followed by pleural effusions, TB lymphadenitis
was diagnosed either on fine needle aspiration cytology or excision lymph node biopsy. Tuberculous pleuritis was diagnosed on basis of histopathology of Abram’s needle blind pleural biopsy and / or history and clinical examination, excluding other causes of lymphocytic exudative pleural effusion and a satisfactory response to anti tuberculosis treatment. Total number of smear positive pulmonary TB patients before and after DOTS was 360 and 116 respectively. Similarly 208 and 75 patients were sputum smear negative before and after DOTS respectively (Table I).

TABLE I: TYPE OF TUBERCULOSIS AND SPUTUM SMEAR STATUS OF PATIENTS BEFORE AND AFTER DOTS

<table>
<thead>
<tr>
<th>Type</th>
<th>Before DOTS</th>
<th>After DOTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2001</td>
<td>2002</td>
</tr>
<tr>
<td>Smear + ve</td>
<td>166</td>
<td>183</td>
</tr>
<tr>
<td>Smear - ve</td>
<td>92</td>
<td>99</td>
</tr>
<tr>
<td>Extra Pulmonary</td>
<td>133</td>
<td>146</td>
</tr>
<tr>
<td>Total</td>
<td>391</td>
<td>428</td>
</tr>
</tbody>
</table>

The rates of treatment completion, cure, treatment failure, default and death are the main outcomes that were assessed in the study. Before DOTS the cure rate was only 48.61 % which rose to 94.82 % after the implementation of DOTS. The proportion of patients who completed their treatment also increased from 75.14 % before DOTS to 99 % after the introduction of DOTS. The most noticeable significant parameter after the implementation of DOTS, was the default rate which was initially 19.83 %, declined to less than 1 % after daily DOTS. The increase in the cure rate, treatment completion and decline in default rate after the implementation of DOTS strategy were all statistically significant with p value of less than 0.05 (Table II).

TABLE II: TREATMENT OUTCOME OF PATIENTS WITH TUBERCULOSIS BEFORE AND AFTER DOTS

<table>
<thead>
<tr>
<th>Treatment Outcome</th>
<th>Before DOTS</th>
<th>After DOTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PERIOD</strong></td>
<td>2001</td>
<td>2002</td>
</tr>
<tr>
<td>CURED</td>
<td>99</td>
<td>71</td>
</tr>
<tr>
<td>COMPLETED</td>
<td>203</td>
<td>287</td>
</tr>
<tr>
<td>DEFAULTED</td>
<td>89</td>
<td>70</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>391</td>
<td>428</td>
</tr>
</tbody>
</table>
DISCUSSION:
The current situation of tuberculosis in Pakistan is quite alarming and the high incidence and prevalence of tuberculosis defines Pakistan as the 4th highest TB burden country worldwide. Although the World Health Organization (WHO) Directly Observed Treatment Short-course (DOTS) strategy for TB was adopted and piloted in Pakistan from 1995 onwards, but major efforts for the TB control was made only after the revival of the NTP in 2001 when TB had been declared a national public health emergency through the “Islamabad Declaration.”
The main goals of tuberculosis treatment are to cure the patients and minimize the spread of disease to others people. Treatment can be challenging for both patients and doctors because it requires taking multiple medications for a minimum of 6 months which is exhausting and lead to noncompliance. To overcome the problem of non adherence to treatment, DOTS is recommended as the standard of care for patients with TB. This DOTS strategy has been shown to increase the cure rate and reverse the TB epidemic in many countries.
This study has assessed the potential treatment outcome of patients taking anti tuberculous treatment under DOT. Of these the most noticeable significant parameter after the implementation of DOTS, was the default rate which declined to less than 1 % after daily DOTS. Although some studies have reported a high default rate with DOTS. The main reason for this high default rate and noncompliance in these studies was due to homelessness and alcoholism and these two conditions were uncommon in our study population. Another reasons for this improvement in the treatment outcomes and decrease default rate in our study was the fact that DOT was supervised only by a healthcare worker and took place at tuberculosis clinic. Patients were called telephonically or the health care worker visited the patient’s home himself if a patient missed the daily dose of medication. To improve compliance and make it more cost effective, only those patients were recruited who were living around the vicinity of lady reading hospital. As the TB clinic for most these patients were at walking distance, DOT was feasible and cost effective both for patients and healthcare worker supervising the treatment and led to improved treatment outcomes.
In this study the total number of TB cases registration before DOTS was quite huge but it has reduced after implementation of DOTS. The reason for this decrease in the case registration was due to restriction of the catchment area for proper DOTS implementation. Initially before DOTS we were registering patients from all over the province including patients from even Federally Administered Trial Areas and Afghanistan. After the DOTS we registered patients only from around the vicinity of lady reading hospital with the population of about 50,000.
Our results showed significant increase in the rates of cure and treatment completion and decrease in default rates after the implementation of DOTS as compared to before to DOTS. These findings are in agreement with several studies. However the results of some studies regarding DOTS are conflicting. A study from South Africa found that treatment of tuberculosis had significantly higher completion and cure rates among self-supervised patients than among those on direct observation of treatment. Another study from Pakistan showed similar completion and cure rates among patients randomized to direct observation of treatment by a healthcare worker, direct observation of treatment by a family member, or self-administered treatment. The apparent disparity in treatment outcomes among studies might be due to a number of limitations in these studies. The lack of randomization, differences in the outcome with a first episode of tuberculosis as compared to relapse TB, differences in the model of DOTS, number of patients, lack of proper training and motivation of health care workers, high burden of TB and overcrowded TB clinics. Due to these facts
relation between DOT and treatment outcome is complex and the factors affecting its usefulness in various settings require further research. For example whether DOT efficacy differs in people receiving tuberculosis treatment for the first time compared with those requiring retreatment, and in men compared with women.

There were several limitations to our study, first it was a retrospective record review study where we could not randomly assign patients to DOTS. Therefore, it is possible that patients who were treated under DOT were more likely to benefit from this intervention than those treated before DOTS. Second; the DOTS model we applied was rigid and the treatment was supervised only by healthcare worker and the patients had to come to the TB clinic daily. Although due to walking distance from TB clinic, DOT was cost effective for most patients and led to improved outcomes in our study; it may be very expensive for patients elsewhere and even may not be applicable in some settings. Third; our study population with TB was mixed including patients with new and retreatment tuberculosis and the treatment outcomes might be different in different groups.

In summary this study shows that tuberculosis patients treated by DOTS had significantly higher treatment outcomes compared with those treated by self-administered strategy and we conclude that DOTS strategy should be the standard of care for patients with tuberculosis. Cure of TB patients is the only way to stop the spread of disease to healthy people and DOTS strategy is the best solution at present and the improved treatment outcomes can reverse the epidemic of tuberculosis especially in this country with very high incidence and prevalence of tuberculosis.

REFERENCES:


