

TB Treatment with DOT: RCT vs. Effective Program Management

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Abstract

In the area of Directly-Observed Treatment (DOT), one of 5 essential elements of Directly-Observed Treatment, Short-course (DOTS)- the internationally accepted strategy to combat tuberculosis (TB) promoted by the World Health Organization (WHO) - its usefulness has been continuously debated. Many researchers have tried to conduct randomized controlled trials (RCT) to explore its effectiveness. The results have always led to the conclusion that DOT and self-administration (SA) could produce the same treatment outcomes. However, RCT should be conducted under ideal conditions to develop the efficacy of TB drug regimens, and it may not be necessary for it to be conducted in the field under routine circumstances to find out the effectiveness. Instead of RCT, effective management is needed in the fields, both at program level and at individual level, to produce TB treatment outcomes that come close to the efficacy of TB drug regimens.

Keywords: Tuberculosis, DOT, RCT

Introduction

Tuberculosis (TB) re-emerged as a major health problem affecting the world population over 2 decades ago. The World Health Organization (WHO) declared TB as a global emergency in 1993 [1]. Directly-Observed Treatment, Short-course (DOTS), the internationally accepted strategy to combat TB promoted by WHO, has been adopted in many countries around the world [2]. Even though Directly-Observed Treatment (DOT) is one of the 5 essential elements of DOTS [3], its usefulness has been continuously debated. Researchers in many countries have tried to conduct randomized controlled trials (RCTs) to explore the effectiveness of DOT, usually comparing between DOT and self-administration (SA), and frequently comparing also among different types of DOT observers. The results have always led to the conclusion that DOT and SA could produce the same treatment outcomes. Does this mean that DOT should no longer be conducted for TB patients, and that all TB patients should keep administering their TB drugs by themselves as usual, without DOT observers? The objective of this review is to find out whether we really need RCTs of DOT for TB treatment, or whether we actually need effective program management to conduct DOT.

Methods

The exact definitions of "efficacy" and "effectiveness" were reviewed. Articles on RCT of DOT for TB treatment were searched for on-line, using the "search online database" of the Center for Library Resources and Educational Media of Walailak University. Nine original articles of randomized controlled trials on DOT for TB treatment were found and reviewed to conclude the overall results. Finally, a conclusion was drawn for a solution of DOT.

Results and discussion

The terms “efficacy” and “effectiveness” have been used confusedly, which may result in improper practices on TB treatment, and also in conducting research on DOT in unfavorable ways. These 2 terms have been defined in “A Dictionary of Epidemiology” of John M Last [4] as follows:

Efficacy

In CLINICAL EPIDEMIOLOGY, the extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions; the benefit or utility to the individual or the population of the service, treatment regimen or intervention. Ideally the determination of efficacy is based on the results of a RANDOMIZED CONTROLLED TRIAL.

Effectiveness

In the usage made standard among epidemiologists by A. L. Cochrane (1909 - 1988), effectiveness is a measure of the extent to which a specific intervention, procedure, regimen, or service, when deployed in the field in routine circumstances, does what it is intended to do for a specified population [5].

In other words, in TB treatment, the “efficacy” of TB drug regimens results from RCT under ideal conditions, when sound-good drug regimens are used to treat TB patients in the real practice of the fields under routine circumstances, produces TB treatment outcomes which are classifiable as “effectiveness”. Effective TB case management is needed to make “effectiveness” come as close as possible to “efficacy”. Therefore, RCT is essential to develop TB drug regimens with high efficacy. But this poses the question whether more RCT should be further conducted to test the effectiveness of DOT, or not? It can be misleading to ignore some important and necessary issues affecting the benefit of TB patients and their community as a whole.

Rifampicin-containing short-course TB chemotherapy was developed and has shown high efficacy [6], even in a recent study that attained a favorable outcome as high as 93 % [7]. It has become the standard TB treatment regimen for new TB patients, recommended by WHO, particularly the daily drug regimen 2HRZE/4HR (the initial intensive phase of 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol, following by the continuation phase of 4 months of isoniazid and rifampicin). In addition, DOT was developed concomitantly to prevent the emergence of TB drug resistance, especially of rifampicin [8], the single most important drug in short-course treatment [6]. DOT means the observation of patients actually swallowing or ingesting their medication [8]. Actually, DOT should be an important tool to make sure that the TB patient really administers all the TB drugs, which increases the chances of being truly cured, with the lowest chance of the emergence of drug resistance. Therefore, DOT can make “effectiveness” in the routine field practice come close to the “efficacy” of TB drug regimens. However, many researchers around the world have conducted RCT to confirm “whether DOT is good and necessary or not” since 1998 (see **Table 1**) [9-17]. Most of the results have concluded that DOT produced TB treatment outcomes with no difference compared to SA, or no difference among the various options of DOT observer. The Cochrane systematic review also concluded likewise [18] and could be debatable that DOT might be unnecessary to be conducted for treating TB patients.

Actually, DOT is a measure in the stage of effectiveness, not the efficacy. DOT is only a tool to improve adherence to TB treatment. If all necessary resources are mobilized and many key activities are conducted - such as training, closed supervision and monitoring, and several other necessary activities in the field - to conduct the real DOT, TB treatment outcomes, or so-called effectiveness, can come close to the efficacy of the regimens. In other words, effective management is needed in the fields, both at the program level and the individual level. Therefore, DOT should not be ignored or refused, even though all RCTs produced poor outcomes of DOT. In addition, DOT does not need RCT, because it is in the stage of effectiveness, not efficacy.

Table 1 Nine original articles of randomized controlled trials (RCTs) of directly-observed treatment (DOT) for TB patients.

No.	Ref.	Country	Results	Conclusions
1	[9] 1998	South Africa	Successful treatment: Self-supervised patients (n = 105) = 60 % Direct observation (DO) (n = 111) = 54 % Difference between groups 6 % [90 % CI - 5.1 to 17.0]	At high rates of treatment interruption, self-supervision achieved equivalent outcomes to clinic DO at lower cost.
2	[10] 1999	Thailand	Cure: The directly observed treatment (DOT) cohort (n = 414) = 76 % Self-supervised (SS) (n = 422) = 67 %	No significant differences in outcomes could be observed between patient groups receiving DOT under the various options for treatment supervisors.
3	[11] 2000	South Africa	Cured: Supervision by clinic nurse (clinic DOT) (n = 58) = 41 % Supervision by lay health worker (LHW) (n = 54) = 57 % Self supervision (n = 44) = 41 % All group (n = 156) achieved similar outcomes (LHW vs. clinic nurse: risk difference 17.2 %, 95 % CI - 0.1 - 34.5; LHW vs. self supervision 15 %, 95 % CI - 3.7 - 33.6)	LHW supervision approaches statistically significant superiority, but fails to reach it, most likely due to the study's limitation, the small sample size.
4	[12] 2001	Pakistan	Cure rates: Direct observation of treatment by health worker (n = 170) = 64 % Direct observation of treatment by family member (n = 165) = 55 % Self-administered treatment (n = 162) = 62 %	None of the 3 strategies tested was shown to be superior to the others, and direct observation of treatment did not give any additional improvement in cure rates.
5	[13] 2003	Tanzania	Community-based DOT (CBDOT, n = 221) vs. institutional-based DOT (IBDOT, n = 301): Conversion and cure rates: M-H pooled odds ratio (OR) 0.62; 95 % confidence interval (CI) 0.23, 1.71 and OR = 1.58; 95 % CI 0.32, 7.88, respectively	Overall, there was no significant difference in conversion and cure rates between the two strategies.
6	[14] 2003	Australia	The rate of non-compliance was 24 % (41/173): DOT observed by a family member (FDOT) = 22/87 Standard supervised but non-observed therapy (ST) = 19/86	No significant difference between FDOT and ST
7	[15] 2004	Swaziland	Cured or completed treatment: Community health worker or CHWs (n = 664) = 68 % Family member (n = 662) = 66 % The cure and completion rate between direct observation of treatment by CHWs and family members = 2 % difference (95 % CI - 3 % to 7 %)	No significant difference in the cure and completion rate
8	[16] 2004	Tanzania	Treatment success rate: Community-based DOT* (n = 260) = 85 % Health facility-based DOT (n = 327) = 83 % (OR 1.17, 95 % CI 0.75 - 1.83) *using guardians and former TB patients	Community-based DOT is as effective as health facility-based DOT and can achieve good treatment outcomes.
9	[17] 2006	Nepal	Success rates: Community DOTS (n = 549) = 85 % Family-member DOTS (n = 358) = 89 % OR = 0.67 [95 % CI 0.41 - 1.10]	The family-member DOTS and community DOTS strategies can both attain international targets for treatment success under program conditions.

Following the recommendations of the CDC (Centers for Disease Control and Prevention, USA) [19] and a document of WHO [20], a non-family DOT model was developed in Thailand in 1999 [21]. It could produce a very high TB treatment outcome close to WHO's global targets. Nowadays, the model is applied in many areas of the country, as is shown especially in one of the best models in the Thasala community hospital of Nakhon Si Thammarat Province.

Conclusions

Effective TB program management should be focused intensively, instead of conducting RCTs for DOT, to improve TB treatment outcomes, and will hopefully result in controlling TB.

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