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Comparative Evaluation of Treatment for Multi drug Resistant Tuberculosis with and without Surgical Resection: A Systematic Review–Meta Analysis of Retrospective Clinical Data

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Abstract

Background: Tuberculosis is still one of the major causes of mortality and morbidity in the world with nearly 1.3 million deaths recorded in 2012. Multi drug resistant tuberculosis has caused high number of deaths and new infections in the same year. The optimal management of MDR TB has been retarded by lack of controlled trials to indicate a fixed drug regimen to be applied universally. Surgical resection, often involving lobectomy and pneumoctomy, is used in patients failing to show improvements with the drug therapy.

Objective: To conduct systematic review meta-analysis on comparative evaluation of treatment for MDR TB with and without surgical resection.

Methods: Eligible studies were identified from databases using key phrases MDR TB, MDR TB treatment, and clinical outcomes for MDR TB therapy. Statistical analysis was performed by Comprehensive meta-analysis (CMA) version 2.2.064 software.

Results: Twenty (20) studies fully met the inclusion criteria. Meta-analysis was performed on 630 MDR patients with and 2149 patients without surgery. The analysis produced success rates of 0.845, 0.520, failure rates of 0.157, 0.100, death rates of 0.172, 0.084 and default rates of 0.184, 0.038 for the non-surgical and surgical groups respectively.

Conclusion: Adjuvant surgical resection results in clinically significant increase in success rates of MDR TB therapy and a reduction in the rates of failure, death and default.

Introduction

Tuberculosis is still one of the major causes of mortality and morbidity in the world population with nearly 1.3 million deaths recorded from 8.6 million in 2012 and 91,729 cases in Ethiopia which makes it the leading infection in HIV positive person and cause of hospital death [1]. The emergence and dissemination of multi drug resistant tuberculosis (MDR TB), a highly toxic, rapidly spreading and main cause of TB related death in developed and developing countries often defined as resistance to at least isoniazid and rifampicin, is a new challenge in TB control [2]. It occurs due to factors related to previous treatments. Genetic factors include accumulation of changes in the genomic content via acquisition of resistant genes. Incomplete (inadequate) treatment, lack of adherence and factors related to previous TB treatments. In addition poor administrative control on purchase and distribution of drugs lacking proper quality control and bioavailability test also contribute to drug resistance [3].

Even though the optimal management of MDR TB has been retarded by lack of controlled trials to indicate a fixed drug regimen to be applied universally, the WHO 2008 and 2011 guidelines for management of MDR TB recommend the use of at least four drugs with certain/almost certain effectiveness selected based on previous treatment history and drug susceptibility test results and use of additional drugs, such as …, increases the probability of intolerance [4,5]. Surgical resection, often involving lobectomy and pneumonectomy, has been revisited for MDR TB management secondary to lack of new drug treatment options that can achieve mycobacteria free sputum [6]. Performance of surgical intervention for MDR TB is often aided by imaging modalities such as radiological imaging, endobronchial ultrasound and mediastinoscopy as a guiding tools, that depends on localization of the infectious sites for complete resection to restore postoperative lung function, persistent positive for acid fast bacilli (AFB), higher risk of relapse and possibility of effective postoperative drug therapy for stump healing [7].

The purpose of surgical resection is to remove damaged lung tissue not to leave grossly diseased lung which contains high bacterial concentration in the cavity (10^7-10^9) and failure of antibiotic penetration to the infectious site [8]. The success or failure of adjuvant surgical resection for MDR TB treatment depends on factors such as duration of pre-surgical drug therapy, patient's age, BMI<18.5, bilateral disease on chest radiograph, being retreatment case, occurrence of

bilateral cavity lesions, reduction of ventilation, total lung capacity, pneumonia and acute respiratory distress syndrome (ARDS) secondary to post-surgical inflammation, surgeon specialty and the availability of equipments [8,9]. The objective of this systematic review meta-analysis is to perform comparative evaluation of treatment outcomes of non- Extensively drug-resistant (XDR) MDR patients with or without surgery to determine the role of surgical resection in increasing the success rates of MDR TB treatment.

Methods

Search strategy and selection criteria

Eligible studies were identified by searching PUB MED, HINARI and Google scholar between October and December 2013 using key phrases tuberculosis (TB), MDR TB and MDR TB treatment, surgical resection for MDR TB and clinical outcomes for MDR TB therapy. The studies used in this comparative meta-analysis were selected if they were available fully in English, availability of clinical data confirmed of MDR TB patients taking second-line medications in accordance to individualized or standardized regimens, clear indication of the performance of surgical resection and expression of the clinical outcomes according to WHO classification as success (cure or completion), default, failure (including relapse) and death [10]. Studies failing to present the patient outcomes in accordance to WHO classification, data of XDR TB patients, absence of clear presentation of the number of succeeding, failing, dying and defaulting patients in each group (surgical and non-surgical) were excluded from this meta-analysis.

Data extraction

The initial literature search resulted in the identification of 237 articles. Application of the first selection criterion led to exclusion of 143 irrelevant studies leaving 94 relevant articles. The selection further narrowed the studies to 74 by removing 20 studies which did not use treatment with second line anti-tuberculosis agents, were duplicates and which only showed disease distribution data and lacked treatment outcomes. Further methodological investigation of the 74 studies led to the rejection of 43 studies leaving 31 retrospective studies for additional screening. An additional 6 studies were excluded since they provided qualitative data on factors associated with success in therapy and adverse effects observed on patients. Five more studies were removed due to lack of response from their authors in search of additional data on the outcomes of the surgical and non-surgical groups [11-15].

Among the 20 studies which were found to completely fit the selection criteria, 8 contained outcome data of patients undergoing treatment without adjuvant surgery, 9 used patients to whom surgical resection was performed and 3 studies had complete outcome data of both surgical and non-surgical patients (Table 1). The 20 studies used for this meta-analysis included data of 2829 patients classified under success, failure, death and default categories. Of these patients, 50 patients were excluded (2 were still on treatment, 18 were transferred out and 30 were XDR TB patients). The final data used in this meta-analysis were derived from 2779 patients, 2149 patients without surgery and 630 undergoing surgical resection were used for this meta-analysis.

Author	Study location	Years	Sample size	Regimen	No. of drugs used	Duration of treatment (months)
Treatment without surgical resection						
Anderson et al. [11]	United Kingdom	2004-2007	204	Standardized	-	19
Brust et al. [12]	South Africa	2000-2003	1209	Standardized	5	24
De Siqueira et al. [13]	Brazil	1995-2003	50	Regimen III	2.3	24
Dhingra et al. [14]	India	2002-2004	27	Individualized	6.2	23
Elmahallawy et al. [15]	Egypt	2006-2010	200	Standardized	-	21
Kwan et al. [16]	South Korea	1995-2004	149	Individualized	6	24
Masjedi et al. [17]	Iran	2002-2006	43	Standardized	-	24
Narite et al. [18]	USA	1994-1997	81	Individualized	-	-
Tahoaoglu et al. [19]	Turkey	1992-1999	158	Individualized	5.5	18-24
Thomas et al. [20]	India	1999-2003	67	Individualized	-	18
Yew et al. [21]	Hong Kong	1990-1997	65	Quinolone based	3.6	14
Treatment with adjuvant surgical resection						
Dewen et al. [22]	India	1999-2003	74	-	-	24
Kim et al. [8]	South Korea	1993-2003	79	Individualized	6	32
Kir et al. [23]	Turkey	1993-2005	79	Amikacin/Kanamycin containing	5	12
Mohsen et al. [24]	Egypt	1995- 2005	23	Individualized	4	18-24

Papiashvill et al. [25]	Israel	1998-2011	17	Standardized	-	12.6
Pomerontz et al. [26]	USA	1983- 2000	172	Individualized	-	24
Shiraishi et al. [27]	Japan	2000-2007	56	Individualized	4.6	18
Xie et al. [28]	China	1993-2011	43	Individualized	5.2	5.2
Yalidz et al. [29]	Turkey	2003-2006	13	Standardized	5	24-37

**Table 1:** Characteristics of included studies for the meta-analysis.

The extracted data include the author, study location and period, type and design of study, the sample size (number of MDR patients whose outcome was recorded), the average number of drugs used, type of the resection procedure performed (for those undergoing surgery) and the number of patients in each outcome groups [16-20].

Data analysis

Estimation of the means, proportions and rates in one group at one time point was done to determine event rate with 95% confidence interval using the random model analysis. The heterogeneity analysis among the studies was confirmed by using the Chi square based Q statistics (Q-value and Q-value df, determination of I^2 and heterogeneity P-value which assesses the statistical significance of differences between the effects observed in each study. The existence of publication bias was also determined by using the funnel plot of standard error by Log it event rate. Statistical analysis was performed by Comprehensive meta-analysis (CMA) version 2.2.064 software [21-25].

Results

Figure 1 shows the overall success rate value with 95% CI and the observed result was higher for the surgical group (0.845, p=0.000) than the overall success rate of patients without surgery (0.520, p=0.031).
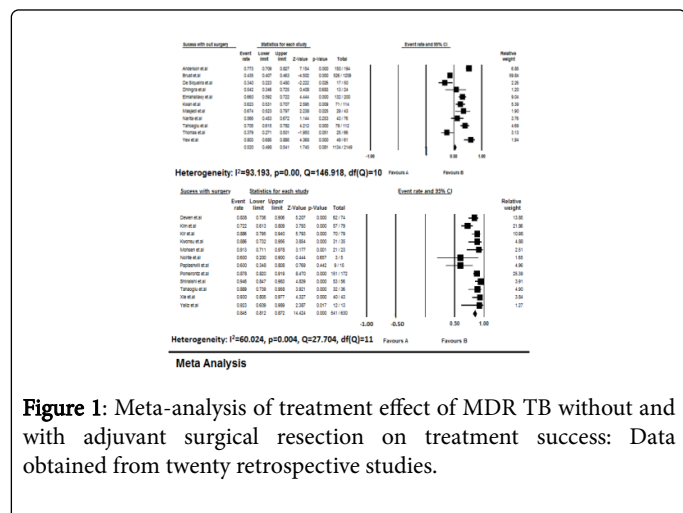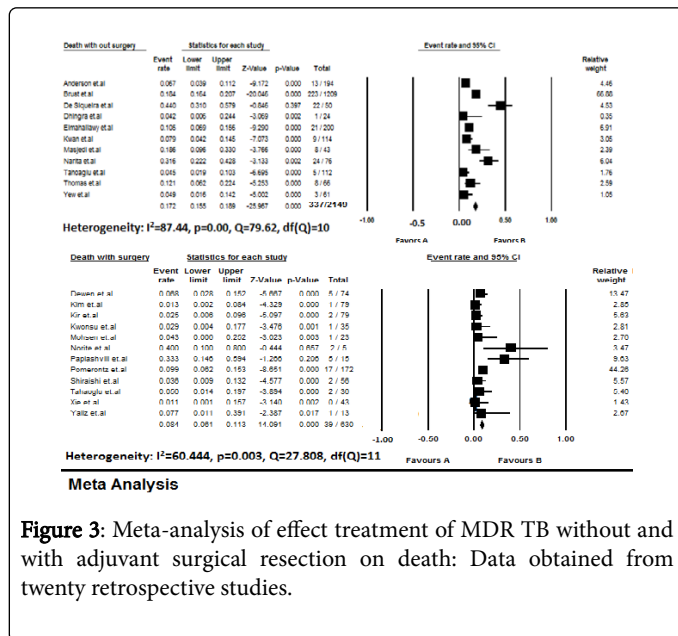

Figure 1: Meta-analysis of treatment effect of MDR TB without and with adjuvant surgical resection on treatment success: Data obtained from twenty retrospective studies.

The rate of occurrence of failure with 95% CI shown in Figure 2 and the analysis result shows higher overall rate of failure (0.157, p=0.00) for the same number of non-surgical patients and lower rate of failure for the surgical group, (0.100, p=0.00) [25-29].
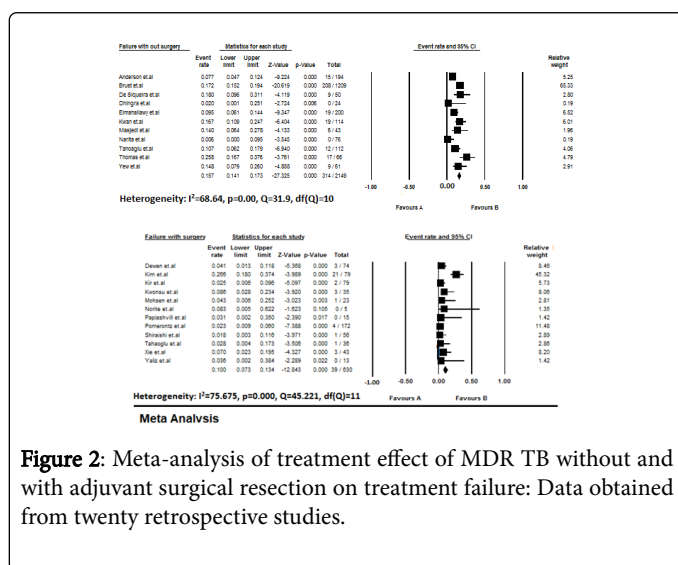
Figure 2: Meta-analysis of treatment effect of MDR TB without and with adjuvant surgical resection on treatment failure: Data obtained from twenty retrospective studies.
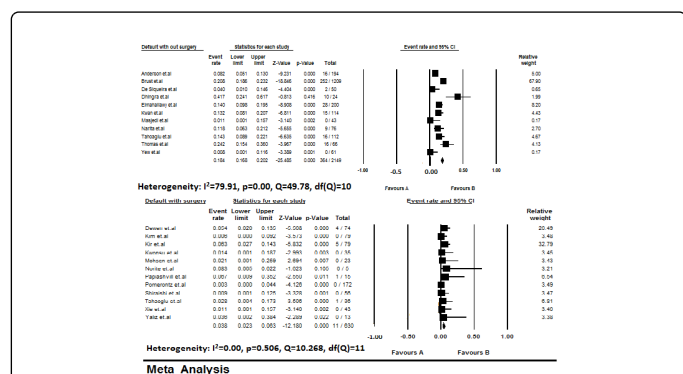

Figure 3: Meta-analysis of effect treatment of MDR TB without and with adjuvant surgical resection on death: Data obtained from twenty retrospective studies.

Regarding to the rate of death, the overall value of death rate was 0.172, p=0.00, with heterogeneity values, I^2=87.44 (p=0.00) and Chi squared based Q value of 79.62 with 10 df was observed in non-surgical group. This value is higher than the value observed in the 630 patients with adjuvant surgery and the values of death rate is 0.084,

$p=0.00$ and having heterogeneity values of, $I^2= 60.444$ ($p=0.003$) and Q-value of 27.808 with 11 df (Figure 3).

As Figure 4 shows the default rate among 630 surgical patients indicates an overall value of 0.038, $p=0.00$ with a heterogeneity I^2 of 0.00 ($p=0.506$) and Chi squared based Q value of 10.268 with 11 df. The non-surgical groups (2149 patients) had higher default rate, 0.184, $p=0.00$, with $I^2=79.91$ ($p=0.000$) and Q-value=49.78 under 10 df heterogeneity.

Figure 4: Meta-analysis of effect treatment of MDR TB without and with adjuvant surgical resection on default rate of patients: data obtained from twenty retrospective studies.
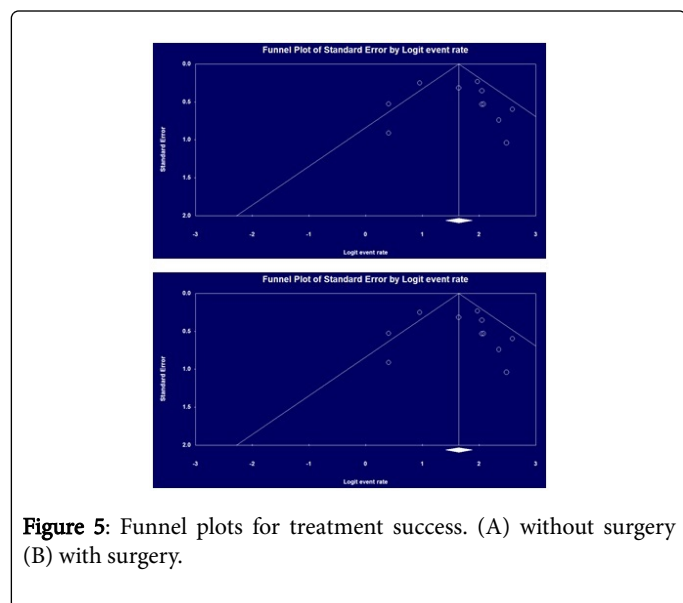
Figure 5: Funnel plots for treatment success. (A) without surgery (B) with surgery.

Funnel plot for publication bias is symmetrical for the non-surgical group while the plot for surgical group is skewed to the right (Figure 5).

Discussion

Drug therapy for MDR TB is toxic and causes interruption from psychiatric, GIT, dermatologic and other ADRs [30]. Failure of MDR TB treatment also increases the risk for occurrence of XDR TB [31].

The proportion of treatment success (favourable outcomes) is significantly higher in the surgical group than those which didn't undergo surgical resection, 0.845 ($p=0.000$) and 0.520 ($p=0.061$)

respectively. This indicates that adjuvant surgical resection increases the treatment success of MDR TB patients. According to the definition by Cochrane Collaboration, statistically significant refers to result that is unlikely to have happened by chance. The usual threshold for this judgment is that the results, or more extreme results, would occur by chance with a probability of less than 0.05 if the null hypothesis was true [32]. However the success rates of the three studies mutually using both surgical and non-surgical groups did not have a large difference, 0.792 ($p=0.002$) and 0.631 ($p=0.001$) respectively, which indicates that variation in the settings of the studies contributing to the increased positive outcomes for the surgical group.

Higher number of success rates in the surgical group is associated with the use of higher proportion of individualized regimens (10/12) than the non-surgical group (6/10). But a systematic review meta-analysis by Orenstein et al. indicates that though the individualized treatment regimen increases the success rates of MDR TB treatment, the difference is not clinically significant. Hence, the use of individualized /standardized regimen has an insignificant impact on the success rates, which eliminates one reason for heterogeneity [33].

Similarly the rates of occurrence of treatment failure, death and default is lower in the surgical resection group than patients treated without adjuvant surgical resection which indicates the role of surgery in reducing unfavourable outcomes associated with the treatment of MDR TB. This finding is supported by the meta-analysis conducted by Xu Hong-Bin et al. [34]. In the present study, this can be supported by the statistically significant reduction of unfavourable outcomes with adjuvant surgery, 0.141 ($p=0.000$) in patients who had surgery and 0.472 ($p=0.022$) in their non-surgical counterparts. Analysis of heterogeneity among the studies indicates large values of I2 and Q values for the majority of them except for the rates of occurrence of default with surgery. These values indicate that there is high level of heterogeneity among the studies which made it difficult to obtain clinically significant outcomes. The higher variability among the population groups which creates a difference in the response to drug therapy, the difference in the duration of chemotherapy before surgery and the total duration are the most likely contributing factors. Therefore further meta-analysis should be done using randomized trials using both surgical and non-surgical groups to reach a better correlation.

The funnel plots (A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect, usually resembles asymmetrical inverted funnel in the absence of bias (publication bias and selection process bias) for this meta- analysis were all asymmetrical for the 630 surgical resection group patients and lesser asymmetry was observed for the 2149 patients without adjuvant surgery. Asymmetry observed in the plots (Figure 5) is an indication of the occurrence of bias [32]. The possible reasons for asymmetric plots are language bias (the preferential publication of studies with significant findings in languages other than English) due to language barrier, true heterogeneity which occurs due to differences in the intensity of interventions or differences in underlying risk between studies of different sizes and chance. The number of studies and methodology did not contribute to bias since 20 studies were selected carefully with the planned criteria that were discussed above in the Methods section. This can be seen by the narrowing spread of effect estimates that occurs among the studies that had a larger number of patients.

Conclusion

From 237 articles searched electronically, 20 studies fully fitted with the inclusion criteria of this meta-analysis. The results indicate that adjuvant surgical resection results in statistically significant increase in success rates of MDR TB therapy and a reduction in the rates of failure, death and default for those patients to whom the procedure is indicated. However, it is also associated with a number of limitations that include; the reduction of ventilation and total lung capacity and occurrence of early or late surgery related complications like pneumonia and acute respiratory distress syndrome (ARDS) in the post-surgical period. In addition, the requirements of specialized personnel and equipment increase the cost of MDR therapy making it unaffordable for many patients in developing countries.

Recommendations

The Longer duration of chemotherapy with second line anti TB agents in the pre-surgical resection period and continuation of the therapy after surgery increases the success rates. But it is recommended to determine the optimal duration before and after surgery. Additional studies should also be done with studies of less heterogeneity that include both a large sample of both surgical and non-surgical patients in the same study. This would help to discern a clearer determination of the influence of surgical resection on treatment outcomes of MDR TB.

Acknowledgements

Authors' contributions

All authors contributed equally to this work.

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