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Corticosteroids for Prevention of Mortality in People with Tuberculosis: A Systematic Review

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ABSTRACT

Background: corticosteroids have systemic effects, their beneficial impacts on tuberculosis are believed to be organ specific. A worldwide health concern, tuberculosis has become more convoluted due to the enhanced occurrence of drug-resistant strains & its persistence in aging populations.

Aim and objective: The purpose of this investigation was to assess the effect of adjunctive corticosteroids on mortality in people with tuberculosis.

Patients and methods: All relevant randomized controlled trials or quasi-randomized controlled trials involving individuals with any clinically or microbiologically defined form of tuberculosis are involved in this systematic review. cases older than fourteen years. A corticosteroid of any dosage, period, or route of administration could constitute the intervention. The search was conducted using several electronic databases, which include all dates as of its creation: Literatura Latinoamericana e do Caribe em Ciências da Saúde (LILACS), the Cochrane infectious illnesses group investigation register, the Cochrane Central Register of controlled studies, Medline (accessed via PubMed), & Embase.

Conclusion: Researchers have found that steroids reduce the death rates among tuberculosis cases. Nevertheless, the precise function of corticosteroids in pulmonary tuberculosis, especially in situations of severe illness, is still unclear. To resolve this uncertainty, additional large prospective controlled studies with sufficient ability to identify alterations to these outcomes are required.

Key words: Tuberculosis, corticosteroids, drug resistant, systematic review

INTRODUCTION

Tuberculosis is a major health problem worldwide, affecting both developed & developing nations. Its complexity has been worsened by the disease's continued presence in geriatric populations & the rise in drug-resistant strains **(1)**.

In certain regions, tuberculosis incidence & mortality continue to be extremely high, despite the availability of efficient therapies. This is related in part to HIV infection, poverty, population migration & aging, disruption of health systems, multidrug resistance, & the increase in noncommunicable illnesses, including diabetes **(2)**.

Horizontal transmission is the most common form of transmission, in which a person inhales respiratory droplets containing Mycobacterium tuberculosis that have been discharged by people with active tuberculosis. We broadly categorize tuberculosis as extra-pulmonary or pulmonary, based on the site of infection. Extra-PTB refers to a tuberculosis illness that impacts anatomical sites other than the lung &

upper respiratory tract. Pulmonary tuberculosis specifically impacts the lymph nodes or lung at the site of the primary infection **(3), (4)**.

Despite the availability of effective therapies, tuberculosis continues to remain a leading cause of mortality on a global scale. Standard treatment regimens for tuberculosis consist of a combination of medications, rifampicin being the most frequently used one. Typically administered every day, sometimes intermittently (e.g., three times per week), for a minimum duration of six months **(5)**.

An infection with tuberculosis causes an inflammatory immune response, which induces significant tissue injury. Especially after an inflammatory illness complicates recovery, we may administer adjunctive steroids to counteract this. Adjunctive steroid treatment is recommended by clinical guidelines for the management of tuberculosis, meningitis, & pericarditis. Eleven studies found by Smego et al. in a previous systematic review on the usage of steroids as an additional treatment for PTB demonstrated that people who used steroids had at least one PTB outcome that was much better **(6)**. The objective of this investigation was to evaluate the influence of corticosteroids used in combination with tuberculosis on mortality.

PATIENTS AND METHODS

Criteria for considering studies for this review

Types of research:

Randomized controlled trials (RCTs) & Retrospective cohort studies.

Types of participants:

Patients who have been diagnosed with chest-x-ray-detailed tuberculous pleurisy (as characterized by the trial authors) and have one of the following conditions: pleural fluid; pleural biopsy; staining & microscopy for acid-fast bacilli, sputum culture, or both; pleural fluid; or pleural biopsy for histology.

Types of interventions:

Intervention Any corticosteroid at any dose.

Investigation methods & selection criteria:

A systematic review and meta-analysis were conducted to evaluate the effectiveness of corticosteroids in preventing organ-systemic mortality associated with all types of tuberculosis. We ma de an effort to identify every relevant trial, regardless of their publication status or language. A search was conducted across multiple electronic databases that include all dates sin ce their inception: Literatura Latinoamericana e do Caribe em Ciências da Saúde (LILACS), the Cochrane Infectious Illness Group investigation register, the Cochrane Central Register of Controlled Trials, Medline (evaluated via PubMed), & Embase. A proficient information scientist supervised the performance of every investigation. Authors were approached when additional information or clarification was required, & authors of registered but unpublished exper iments were contacted to identify ongoing studies. The terms "tuberculosis" & "corticosteroids" and associated terms (involving the names of specific steroid medications; appendix p. 1) were included as the basis of our initial search. Every search query was employed, combined with a greatly sensitive search strategy created by the Cochrane Collaboration for retrieval trials.

Eligibility criteria

All relevant RCTs & quasi-randomized controlled trials (clinical trials employing predicted patient allocation methods, for example, alternate allocation) were incorporated into our analysis. Eligible trials included participants with any clinically or microbiologically defined form of tuberculosis. cases older than fourteen years. A corticosteroid of any dosage, period, or route of administration might form the intervention. Only studies that failed to report on mortality were excluded from the analysis.

Data extraction

A pre-piloted data extraction form was utilized by two review authors, PD and HR, to collect information from the trials that were included in the review. This information involved information about the participants' diagnostic criteria, characteristics, HIV status, antituberculous drug regimen, corticosteroid regimen, & measurement of outcomes. An evaluation of the complete text was not possible because the abstracts that we retrieved did not contain adequate information regarding the inclusion and exclusion criteria. Utilizing a form that was based on the inclusion criteria, we evaluated

the eligibility of all publications that had the potential to be relevant and got full versions of all of them. A cross-checking of the data was performed, and any differences were resolved through conversation. The information that was retrieved included not only the effects of steroids but also demographic factors such as age, year, nation, type of study, and population.

RESULTS

Table 1 Characteristics of the included studies:

Study	Year	Country	Type of study	Population	Age
Thwaites et al., (7)	2004	Vietnam	Randomized, double-blind, placebo-controlled trial	Tuberculous meningitis	Patients over 14 years
Kim et al., (8)	2008	South Korea	Retrospective cohort study	Pulmonary tuberculosis (TB) with acute respiratory failure	>18 (22–89) year
Yang et al., (9)	2016	South Korea	Retrospective cohort]	Pulmonary TB with acute respiratory failure	≥18 (62.0 ± 17.3) years
Viarasilpa et al., (10)	2021	Thailand	Retrospective cohort	Acute respiratory failure in cases who have recently been diagnosed with pulmonary tuberculosis	≥18 years
Lemos et al., (11)	2022	Brazil	Retrospective cohort	cases suffering from tuberculosis who require mechanical ventilation	>18 years

Table 2. The main findings of the included studies:

Study	Treatments	Outcomes
Thwaites et al., (7)	Dexamethasone (n=274) Placebo (n=271)	The administration of dexamethasone was found to be correlated with lower risks of mortality (0.69 relative risk; 0.52 to 0.92 95% confidence interval; P=0.01). The proportion of severely disabled cases didn't decrease significantly (P=0.27; thirty four of 187 cases [18.2 percent] between survivors in the dexamethasone group versus twenty two of 159 cases [13.8%] in the placebo group). There was no significant difference in the effect of treatment between the subgroups that were classified by the severity grade of the illness and the HIV status (the stratified relative risk of mortality was 0.78; the ninety-five percent confidence interval was 0.59 to 1.04; P=0.08). The stratified relative risk of death was 0.68 (interval: 0.52 to 0.91; P=0.007). In cases older than fourteen who have tuberculous meningitis, adjunctive therapy with dexamethasone enhances survival but likely doesn't prevent severe disability.
Kim et al., (8)	Corticosteroid (n=30)	The mortality rate of patients undergoing corticosteroid therapy was significantly lower (56.7%; seventeen out of thirty) in comparison to those who did not receive the therapy (77.8%; twenty-eight out of thirty-six; p =.046). Clinical characteristics, involving period of symptoms, age, & risk factors for

	Non-corticosteroid (n=36)	tuberculosis (such as diabetes mellitus; twenty versus fourteen percent , respectively; p =.387), didn't vary among the groups that utilized and did not utilize steroids. The severity indices (e.g., oxygenation ratio), septic shock, shock unrelated to sepsis, & MOF did not vary significantly among the two groups. They concluded that corticosteroid use predicted the survival of TBP cases.
Yang et al., (9)	Steroid Group (n = 70) Nonsteroid Group (n = 54)	The 90-day mortality rate wasn't significantly variant among the steroid & nonsteroid groups (48.6 and fifty percent, correspondingly). Unadjusted ninety-day mortality wasn't correlated with adjuvant steroid use (odds ratio [OR], 0.94; 95% confidence interval [CI], 0.46-2.92; P =.875). A ninety-day mortality comparison among the two groups was conducted utilizing an adjusted IPTW approach. The results indicated that the use of corticosteroids was independently correlated with a decrease in ninety-day death (OR, 0.47; ninety five percent confidence intrval,.22–.98; P =.049). Corticosteroids may decrease the ninety-day mortality rate among cases with ARF who are critically ill with pulmonary tuberculosis.
Viarasilpa et al., (10)	Control group (n=20) Steroid group (n=18)	There wasn't a statistically significant distinction in hospital mortality between cases in the steroid group & those in the control group (66.7 percent vs. forty five percent, correspondingly; p=0.21). In contrast to the control group, adjunctive corticosteroid therapy did not yield a statistically significant reduction in mechanical ventilation duration or length of hospital stay (12.0±13.3 versus. 14.6±19.3 days; p=0.636; 7.2±10.6 versus. 8.0±8.3 days, correspondingly; p=0.801). In cases with acute respiratory failure and pulmonary tuberculosis, adjunctive corticosteroid treatments hadn't statistically significant positive impact on outcomes, the researchers concluded.
Lemos et al., (11)	Corticosteroid users (n=399) Non-corticosteroid users (n=68)	Those who utilized corticosteroids had a higher mortality rate (59.9 percent) than those who did not (41.2 percent) (p=0.010). In prednisone equivalents, the total corticosteroid dose didn't vary significantly among survivors & non-survivors (median [IQR]: 80 mg [5–56.6 mg] versus eighty milligrams [50–135 mg]; p=0.881). Furthermore, it was observed that non-survivors required corticosteroids for a shorter duration than survivors (median [IQR]: twelve days [five to twenty-five days] vs. twenty one days [8.8–36.2 days]; p- less tjan0.0001). Similarly, the non-survivors had a shorter hospital stay (median [IQR]: 23 days [eleven to fgortydays] vs. 42 days [28–58 days]; p<0.0001). Corticosteroid-treated tuberculosis cases undergoing mechanical ventilation had a greater mortality rate than those who didn't get corticosteroids.

DISCUSSION

Globally, tuberculosis was the leading cause of death caused by a single infectious agent in 2017, accounting for 1.6 million fatalities (World Health Organization). This figure surpassed that of HIV/AIDS **(12)**. Notwithstanding the twenty-two percent decline in tuberculosis-related fatalities from 2000 to 2015 & the ongoing reduction in the global incidence rate, the cost associated with tuberculosis therapy remains significant. In 2018, The Stop TB Partnership estimated that low-income & middle-income countries needed an additional 10.4 billion US dollars to successfully implement the Global Plan to End TB 2016–2020 **(13).**

Corticosteroids are utilized as adjuvants in the management of TB, particularly in the therapy of meningeal TB, where there is moderate evidence, & may be used for the therapy of pericardial TB, where evidence is low **(14)**. The administration of corticosteroids for pleural tuberculosis is correlated with an accelerated recovery of symptoms but doesn't affect the outcome **(15)**. In numerous methods, adjuvant steroids' beneficial impacts in the therapy of tuberculosis can be defined. To begin with, antituberculosis medications can be used to inhibit the release of excessively high concentrations of cytokines, particularly in cases with a high mycobacterial burden **(16), (17)**. Furthermore, they can enhance the penetration of antituberculosis medications into granulomas by preventing the formation of granulomas from occurring (18). Additionally, it has been shown that the early administration of corticosteroids can lessen the amount of pulmonary and extrapulmonary organ dysfunction that occurs in patients who have acute respiratory distress syndrome (ARDS). **(19)**.

Numerous prior investigations have examined the efficacy of corticosteroids in the treatment of pulmonary tuberculosis & have reported clinical and radiological improvements in patients with this illness compared to control groups, especially in instances of severe illness **(20)**. A previous research investigation found that patients with PTB who received corticosteroid treatment had a reduced mortality rate compared to those who didn't receive the treatment (56.7% vs. 77.8%; p=0.046). The duration of mechanical ventilation was not significantly different between both groups, even though there wasn't a significant distinction. **(21)**. Corticosteroids may be effective in reducing mortality associated with all types of TB, involving pulmonary tuberculosis, according to another study by **Kim et al. (8)**.

Nevertheless, most of these investigations were conducted decades ago. Steroids decreased the mortality rate by seventeen percent, according to a recent meta-analysis (risk ratio [RR], 0.83; 95% CI,.74–.92); this trend was consistent across all organ groups **(22)**. Particularly noteworthy was the greater significance of the risk decrease for pulmonary tuberculosis (RR, 0.57; Ninety-five percent confidance interval,.34–.97) observed when patients who weren't infected with HIV were excluded **(22)**.

Furthermore, **Yang et al. (9)** Presented information indicating that corticosteroids may serve as an effective supplementary treatment for cases with PTB who are admitted to the critical care unit due to severe respiratory failure, since they significantly decrease death within a period of ninety days.

In contrast, a more recent meta-analysis conducted by **Muthu et al. (23)** in 2018 incorporated 35 studies that evaluated the outcomes of cases with TB who necessitated admission to the ICU. They disclosed that acute respiratory distress syndrome, miliary tuberculosis, respiratory failure, & shock were the most frequent indications for corticosteroid use, and that the administration of corticosteroids to this case population did not result in a reduction in mortality. In addition, **Lemos et al. (11)** demonstrated that the mortality rate of tuberculosis patients undergoing mechanical ventilation who were administered corticosteroids was greater than that of those who were not.

CONCLUSION

Steroids have the potential to decrease mortality rates among tuberculosis cases. However, the precise function of corticosteroids in pulmonary tuberculosis, particularly in critically ill cases, is still uncertain. To resolve this uncertainty, additional large prospective randomized control trials with adequate power to identify alterations to these outcomes are required.

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