Dexamethasone Administration and Mortality in Patients with Brain Abscess: A Systematic Review and Meta-Analysis

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Key words
- Brain abscess
- Dexamethasone
- Meta-analysis
- Pyrogenic brain abscess

Abbreviations and Acronyms
CI: Confidence interval
FE: Fixed effects
IV: Intravenous
RE: Random effects
RR: Risk ratio
SOC: Standard of care

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BACKGROUND: **Dexamethasone has been used to treat cerebral edema associated with brain abscess. Whereas some argue that dexamethasone might aid antibiotic treatment, others believe that because of its immunosuppressive characteristics, it might have a negative impact on outcomes. How corticosteroid use affects overall mortality of brain abscess patients remains unclear.**

METHODS: **A systematic search of the literature was conducted in accordance with PRISMA guidelines. PubMed, Embase, and Cochrane databases were utilized to identify all studies related to patients diagnosed with a brain abscess treated with dexamethasone. The main outcome of interest was mortality. Pooled effect estimates were calculated using fixed-effects (FE) and random-effects (RE) models.**

RESULTS: **After removal of duplicates, 1681 articles were extracted from the literature of which 11 were included. These included 7 cohort studies and 4 case series. Indications to administer dexamethasone were either hospital brain abscess protocol or clinical presentation of cerebral edema. The 7 cohort studies involving 571 patients with brain abscesses comprised of 330 patients treated with standard of care (SOC) plus dexamethasone and 241 patients treated with SOC alone, after aspiration or surgical management of the abscess in either group. Pooling results from all seven cohort studies demonstrated a nonsignificant mortality benefit comparing SOC and dexamethasone patients to SOC patients (FE: risk ratio [RR], 0.94; 95% confidence interval [CI], 0.64–1.37; RE: RR, 0.95; 95% CI, 049–1.82; I^2 = 53.9%; *P* for heterogeneity = 0.04).**

CONCLUSIONS: **In patients with a brain abscess treated with antibiotics, the use of dexamethasone was not associated with increased mortality.**

INTRODUCTION

The incidence of brain abscesses has been estimated at 0.3–1.3 per 100,000 people per year but can be considerably higher in certain risk groups, for example, patients with human immunodeficiency virus/AIDS.[1] Mortality and morbidity remain high despite recent decades of advancements in diagnosis and treatment modalities.[2] For example, especially in patients with poor clinical presentation on admission, severe sequelae, such as seizures and hemiparesis, have been noted at follow-up after treatment for brain abscess.[3] The mainstay of brain abscess treatment is drainage of the abscess followed by long term antibiotic treatment. Glucocorticoids, most commonly in the form of dexamethasone, are sometimes added to the treatment regimen to reduce edema associated with the abscess.[2] However, the use of supplemental dexamethasone remains controversial due to fear of its immunosuppressive and potential negative effects on antibiotic penetration.[4] Despite these effects, some clinical studies have also demonstrated that simultaneous administration of low-dose dexamethasone with antibiotics resulted in decreased mortality from brain abscesses and did not affect antibiotic penetration.[5] Thus, how the properties of dexamethasone may influence overall mortality in patients with brain abscess remains unclear. The main purpose of this study was to assess the relationship between the use of dexamethasone in the treatment of brain abscess and mortality.

MATERIALS AND METHODS

Literature Search

A meta-analysis for the influence of dexamethasone on outcomes of brain abbesses was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A literature search for relevant articles was conducted using PubMed, EMBASE, and Cochrane Library from their date of establishment through

November 2016. Studies evaluating the use of dexamethasone in brain abscess therapy were queried. The search strategy combined various search terms for dexamethasone (e.g., glucocorticoid, corticosteroid, decadron), brain (e.g., intracerebral, parenchymal, intracranial), and abscess (e.g., bacterial abscess, pyogenic brain abscess, infectious abscess) using multiple versions of relevant medical subheading (MeSH) terms, Emtree, terms, and text words. The detailed search items are included in **Supplementary Table 1**.

Study Eligibility

Studies were considered for inclusion in the current meta-analysis if they met the following criteria: describing patients with brain abscess receiving dexamethasone and reporting the following outcomes: morbidity, mortality, or volume/size of abscess. Two levels of screening were conducted: level one, in which titles and abstracts were screened and potentially relevant articles were selected, and level two, the full-text evaluation, which was performed independently in duplicate by 3 investigators (T. Simjian, I. V. Muskens, and R. Veronneau). Discrepancies were resolved by consulting the clinical expert (M. L. D. Broekman).

Data Extraction

For each identified article, the following information was extracted: study characteristics (authors, title of the study, journal name, publication year, country of origin, sample size, study design), participant characteristics (sex, mean age, inclusion/exclusion criteria, abscess size), operation characteristics (surgical type), intervention characteristics (indication for steroid administration, dose of steroid, duration of steroid), and outcome results (morbidity, mortality). The quality of the cohort studies was evaluated using the Newcastle–Ottawa Scale,[6] which assesses for 3 areas, including the selection of the 2 groups being compared, the comparability between them, and the outcome assessment. For case series, the same Newcastle–Ottawa Scale was used while dropping the comparability component. Data extraction was conducted independently in duplicate and double-checked by three investigators (T. Simjian, K. Wong, and R. Veronneau). Discrepancies were resolved by consulting the clinical experts (I. V. Muskens and M. L. D. Broekman).

Statistical Analysis

Data analysis was performed using Comprehensive Meta-Analysis version 3. The fixed-effects (FE) model was used to obtain the overall relative risk (RR) estimates. A random-effects (RE) model according to the method of DerSimonian and Laird that accounted for variation between studies in addition to within-study variance was evaluated for comparison.[7] Forest plots were used to visualize the individual and summary estimates. Heterogeneity among studies was evaluated using the Cochran Q test ($P < 0.10$) and I^2 values to measure the proportion of total variation due to that heterogeneity. An I^2 value ranging from 50% to 90% was considered substantial, and a value >90% was considerable.[8] A meta-regression analysis on different trial-level covariates (i.e., mean age, mean abscess diameter, number of aspirations, number of resections, percentage of patients with multiple abscesses, publication year, study duration, study quality, impact factor, and continent) was conducted to explore sources of heterogeneity. Potential publication bias was assessed using funnel plots, the Egger linear regression test, and the Begg and Mazumdar rank correlation test at a level of significance of $P < 0.05$. If publication bias was indicated, the number of missing studies in a meta-analysis was evaluated by the trim and fill method. A P value <0.05 was considered to indicate significance except where specified otherwise.

RESULTS

Study Selection

The search strategy yielded 1681 unique articles after duplicates were removed. Fifty-one full-text articles were assessed for eligibility after screening for title and abstracts, and 11 articles met the inclusion criteria (**Figure 1**). Four of the 11 studies were case series,[5,9-11] and the remaining 7 were cohort design studies and were used for a final quantitative synthesis.[3,12-17] These studies described a total of 571 patients, including 330 patients with brain abscess who received dexamethasone and 241 who did not (**Table 1**).

Study Characteristics

The mean age of participants ranged from 22 to 49 years, and the median of means was 38.5 years. Five studies were conducted in Europe, 3 in Asia, 2 in North America, and 1 in Africa. Study duration varied across studies (2–17 years). The study publication year ranged from as early as 1981 to as recent as 2015. Only 2 studies reported on the dose of dexamethasone used; Dyste et al.[10] reported a course of intravenous (IV) dexamethasone of 6–10 mg/6 hours, whereas Aras et al.[13] reported use of a 16-mg IV bolus of dexamethasone followed by 4 × 4 mg IV/day for 7 days. Another 2 studies reported dexamethasone was administered preoperatively[11] or perioperatively.[3] The indication to administer dexamethasone was generally either at the clinician's discretion to treat brain edema[3,13-15,17] or incorporated in the hospital protocol as a standard of care for brain abscess.[5,9-11] Four case series collectively reported on 106 unique patients with a brain abscess, of whom all were treated with dexamethasone and 9 had experienced death. Seven cohort[3,12-17] design studies collectively reported 57 deaths out of 330 patients that received dexamethasone and 45 deaths out of 241 patients that did not receive dexamethasone.

Meta-Analysis Outcomes

Of the 7 studies included in the meta-analysis, only 1 study demonstrated a statistically significant mortality benefit in the dexamethasone group versus the no dexamethasone group; while the remaining 6 studies reported non–statistically significant results. Pooling results from all 7 studies demonstrated a non–statistically significant mortality benefit of dexamethasone over placebo (**Figure 2**). Using the FE model, the overall pooled RR of mortality was 0.94 (95% CI, 0.64–1.37), which was similar to the overall RR from the RE model (0.95; 95% CI, 0.49–1.82). However, considerable heterogeneity was observed (I^2 = 53.9%; P for heterogeneity = 0.04). On exploring the sources of heterogeneity using FE meta-regression (**Table 2**), mean diameter (slope, 3.10; 95% CI, 0.42–5.78; new I^2 = 0%; R^2 = 100%); number of aspirations (slope, 0.01; 95% CI, 0.01–0.03; new I^2, 28.8%; R^2 = 63%) and