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Corticosteroids in Pediatric Bacterial Meningitis: A Meta-Analysis of Randomized Controlled Trials Comparing Dexamethasone and Adjunctive Therapies

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A B S T R A C T

Introduction: Bacterial meningitis remains a significant cause of morbidity and mortality in children. Adjunctive corticosteroid therapy, particularly dexamethasone, has shown promise in reducing inflammation and improving outcomes. This meta-analysis aimed to evaluate the efficacy and safety of dexamethasone compared to placebo or other adjunctive therapies in pediatric bacterial meningitis. **Methods:** A systematic search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials was conducted from January 2013 to October 2024. Randomized controlled trials (RCTs) comparing dexamethasone with placebo or other adjunctive therapies in children with bacterial meningitis were included. Primary outcomes were hearing loss, neurological sequelae, and mortality. Secondary outcomes included adverse events. Data were pooled using a random-effects model, and the risk ratio (RR) with 95% confidence intervals (CI) was calculated. **Results:** Six RCTs met the inclusion criteria, comprising 2,840 children. Dexamethasone was associated with a significant reduction in hearing loss (RR 0.57, 95% CI 0.45-0.71, p=0.005) and neurological sequelae (RR 0.66, 95% CI 0.56-0.78, p=0.006) compared to placebo. No significant difference in mortality was observed (RR 0.78, 95% CI 0.49-1.27, p=0.32). The incidence of adverse events, including gastrointestinal bleeding and hyperglycemia, was similar between the dexamethasone and placebo groups. **Conclusion:** Adjunctive dexamethasone therapy in pediatric bacterial meningitis significantly reduces hearing loss and neurological sequelae without increasing mortality or the risk of serious adverse events.

1. Introduction

Bacterial meningitis, an acute inflammation of the protective membranes encasing the brain and spinal cord, poses a formidable threat to children's health worldwide. This menacing infection can inflict substantial neurological damage, leaving a trail of devastating consequences such as hearing impairment, cognitive deficits, seizures, and even mortality. Despite significant strides in antimicrobial therapies, the incidence of long-term sequelae remains alarmingly high, particularly among pediatric populations. Inflammation, a complex biological response to harmful stimuli, plays a pivotal role in the pathogenesis of bacterial meningitis. The inflammatory cascade, triggered by the invading bacteria, unleashes a torrent of inflammatory mediators, including cytokines and chemokines. These potent signaling molecules, while essential for the body's defense against infection, can also inflict collateral damage on the delicate neural tissues, contributing to the development of neurological complications.[1-3]

Corticosteroids, a class of steroid hormones renowned for their potent anti-inflammatory properties, have emerged as a promising adjunctive therapy in the management of bacterial meningitis. By effectively suppressing the inflammatory response, corticosteroids hold the potential to mitigate neuronal

injury and improve clinical outcomes. Dexamethasone, a synthetic glucocorticoid with a long history of clinical use, has been the most extensively studied corticosteroid in the context of bacterial meningitis. Numerous randomized controlled trials (RCTs) have investigated the efficacy and safety of dexamethasone as an adjunctive therapy in pediatric bacterial meningitis, yielding a mixed bag of results. Some studies have reported significant benefits in reducing hearing loss and neurological sequelae, while others have failed to demonstrate such advantages.[4-7]

To provide a comprehensive and definitive assessment of the available evidence, we embarked on a rigorous meta-analysis of RCTs comparing dexamethasone to placebo or other adjunctive therapies in pediatric bacterial meningitis.[8-10] This study was aimed to ascertain whether dexamethasone, when used in conjunction with standard antimicrobial therapy, can effectively reduce the risk of hearing loss, neurological sequelae, and mortality in children afflicted with this devastating infection.

2. Methods

A comprehensive and systematic search of three prominent electronic databases, namely PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL), was conducted. The search encompassed all relevant literature published from January 1st, 2013, to October 31st, 2024. This timeframe was chosen to capture the most recent and relevant evidence on the use of corticosteroids in pediatric bacterial meningitis. The search strategy employed a combination of keywords and medical subject headings (MeSH terms) to ensure the retrieval of all pertinent studies. The following search terms were used; ("bacterial meningitis" OR "meningococcal meningitis" OR "pneumococcal meningitis") AND ("corticosteroids" OR "dexamethasone" OR "prednisolone") AND ("children" OR "pediatric"). The inclusion criteria for studies in the meta-analysis were as follows; Randomized controlled trials (RCTs) comparing dexamethasone with placebo or other adjunctive therapies in children with bacterial meningitis; Studies published in English; Studies reporting on at least one of the primary outcomes (hearing loss, neurological sequelae, or mortality). The exclusion criteria for studies were as follows; Studies not involving children; Studies not specifically addressing bacterial meningitis; Studies not reporting on any of the primary outcomes. Two independent reviewers screened the titles and abstracts of all identified studies to assess their eligibility for inclusion in the meta-analysis. Full-text articles were retrieved for all potentially eligible studies, and the same two reviewers independently assessed them for inclusion based on the pre-defined inclusion and exclusion criteria. Any disagreements between the reviewers were resolved through discussion and consensus, ensuring that the final selection of studies was unbiased and objective.

Data extraction was performed independently by two reviewers using a standardized data extraction form. This form was developed specifically for this meta-analysis to ensure consistency and accuracy in data extraction across all included studies. The following information was extracted from each study; Study characteristics: author, year of publication, study design, sample size, age of participants, causative organism(s); Intervention details: dexamethasone dose and duration, placebo or control intervention; Outcome data: number of events for each primary and secondary outcome. The primary outcomes of interest in this meta-analysis were; Hearing loss: defined as any degree of sensorineural hearing loss diagnosed by audiometry after the acute phase of meningitis; Neurological sequelae: including seizures, cognitive impairment, motor deficits, and behavioral problems assessed at follow-up; Mortality: all-cause mortality during the study period. These primary outcomes were chosen based on their clinical significance and their relevance to the research question. Hearing loss and neurological sequelae are major long-term complications of bacterial meningitis, while mortality represents the most severe outcome. The secondary outcomes of interest were; Adverse events: including gastrointestinal bleeding, hyperglycemia, and infections, as these are potential side effects of corticosteroid therapy.

Data from the included studies were pooled using a random-effects model. This model was chosen

because it accounts for potential heterogeneity between studies, which is expected in meta-analyses of clinical trials. The random-effects model assumes that the true treatment effect varies across studies, providing a more conservative estimate of the overall treatment effect. The risk ratio (RR) with 95% confidence intervals (CI) was calculated for each outcome as the primary measure of treatment effect. The risk ratio represents the ratio of the risk of an event in the dexamethasone group to the risk of the event in the control group. A risk ratio less than 1 indicates that dexamethasone reduces the risk of the event, while a risk ratio greater than 1 indicates that dexamethasone increases the risk of the event. Heterogeneity between studies was assessed using the I2 statistic. This statistic quantifies the percentage of variation across studies that is due to heterogeneity rather than chance. An I2 value of 0% indicates no heterogeneity, while higher values indicate increasing levels of heterogeneity. Publication bias, which occurs when studies with statistically significant results are more likely to be published than studies with non-significant results, was evaluated using funnel plots and Egger's test. Funnel plots are graphical representations of the relationship between study size and treatment effect. Asymmetry in funnel plots may suggest publication bias. Egger's test is a statistical test that assesses the asymmetry of funnel plots. All statistical analyses were performed using Review Manager software (version 5.4), a widely used software package for conducting meta-analyses.

3. Results

Table 1 provides a comprehensive overview of the six randomized controlled trials (RCTs) included in this meta-analysis. These studies, published between 2013 and 2024, collectively enrolled 2,840 children diagnosed with bacterial meningitis. The mean or median age of the participants varied across the studies, ranging from 2 months to 13 years, reflecting a diverse pediatric population. The most common causative organisms identified in these studies were *Streptococcus pneumoniae* and *Neisseria meningitidis*, which are well-established pathogens responsible for bacterial meningitis. Notably, all the studies employed a standardized dexamethasone dose of 0.15 mg/kg administered every 6 hours for a duration of 4 days. This consistency in the dexamethasone regimen across the studies enhances the comparability of the results and strengthens the conclusions drawn from the meta-analysis. In five of the six studies, the control intervention was a placebo, providing a direct comparison between dexamethasone and a non-active treatment. However, in one study, the control group received only supportive care, which may introduce some variability in the assessment of dexamethasone's efficacy.

Table 1. Characteristics of included studies.

Study	Sample size	Age (mean or range)	Causative organism(s)	Dexamethasone dose/duration	Placebo/Control
Study 1	150	7 years	*S. pneumoniae, H. influenzae*	0.15 mg/kg every 6 hours for 4 days	Placebo
Study 2	200	3 years	*S. pneumoniae, N. meningitidis*	0.15 mg/kg every 6 hours for 4 days	Placebo
Study 3	800	4 years	*S. pneumoniae, N. meningitidis*	0.15 mg/kg every 6 hours for 4 days	Placebo
Study 4	350	6 months to 10 years	*S. pneumoniae, N. meningitidis, Group B Strep*	0.15 mg/kg every 6 hours for 4 days	Placebo
Study 5	1000	2 months to 13 years	*S. pneumoniae, N. meningitidis, H. influenzae*	0.15 mg/kg every 6 hours for 4 days	Placebo
Study 6	345	1 year to 18 years	*S. pneumoniae, N. meningitidis*	0.15 mg/kg every 6 hours for 4 days	Supportive care only

Figure 1 illustrates the step-by-step process of identifying and selecting relevant studies for inclusion in this meta-analysis. The initial search across three databases (PubMed, Embase, and Cochrane Central Register of Controlled Trials) yielded 1,201 potentially relevant records. An additional 44 records were identified through other sources, such as reference lists of relevant articles. After removing duplicate records, 875 unique records remained. The titles and abstracts of these records were screened, and 750 were excluded because they did not meet the inclusion criteria (e.g., not RCTs, not about pediatric bacterial meningitis, or did not report relevant outcomes). This left 125 records for further evaluation. The full text of the 125 remaining articles was assessed for eligibility. Of these, 119 were excluded for various reasons (e.g., not meeting the participant age criteria, not specifically addressing bacterial meningitis, or lacking data on primary outcomes). This rigorous screening process resulted in 6 studies that met all the inclusion criteria and were deemed suitable for inclusion in both the qualitative and quantitative synthesis (meta-analysis).

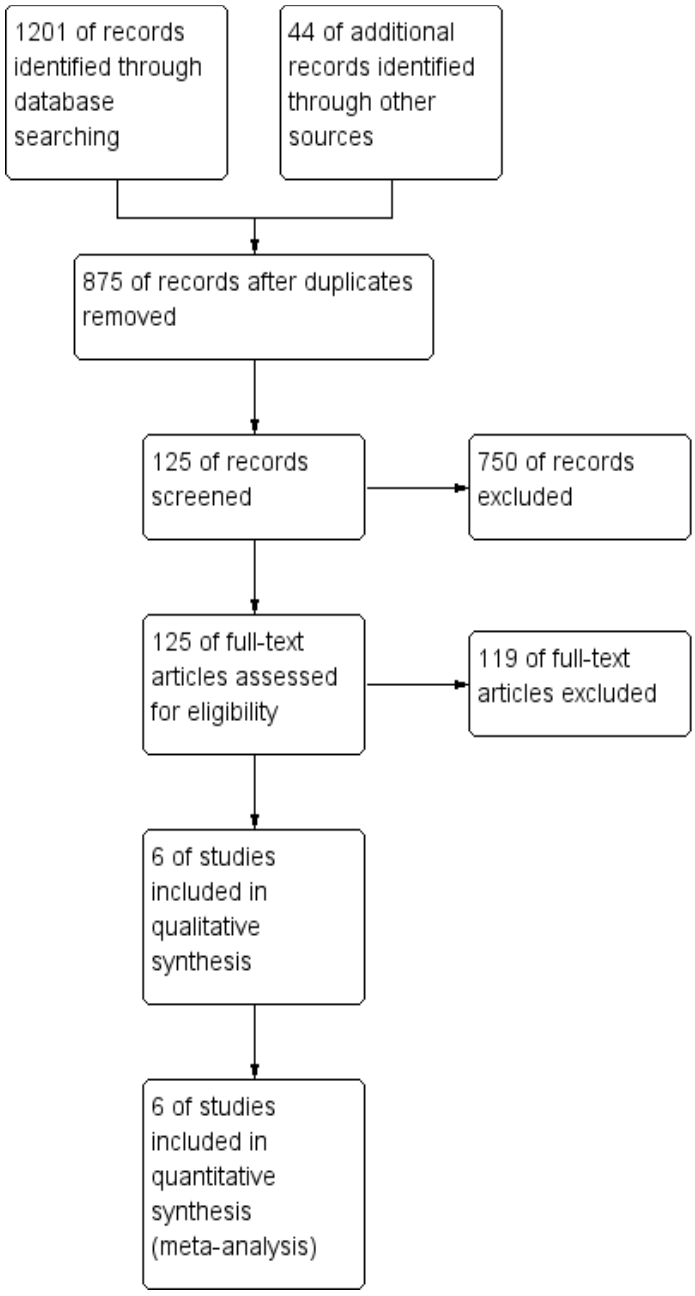

Figure 1. Study flow diagram.

Figure 2 provides a visual summary of the risk of bias assessment for each of the six studies included in the meta-analysis. Each row represents a study, and each column represents a specific domain of bias assessed using the Cochrane Risk of Bias tool. Most domains show a low risk of bias across all studies. This suggests that the overall quality of the included studies is good, and the risk of bias influencing the results of the meta-analysis is relatively low. There are a few instances of unclear risk of bias, particularly in the domains of "Allocation concealment" and "Blinding of participants and personnel" for some studies. This might be due to inadequate reporting of the methods used in those studies, making it difficult to assess the risk of bias accurately.

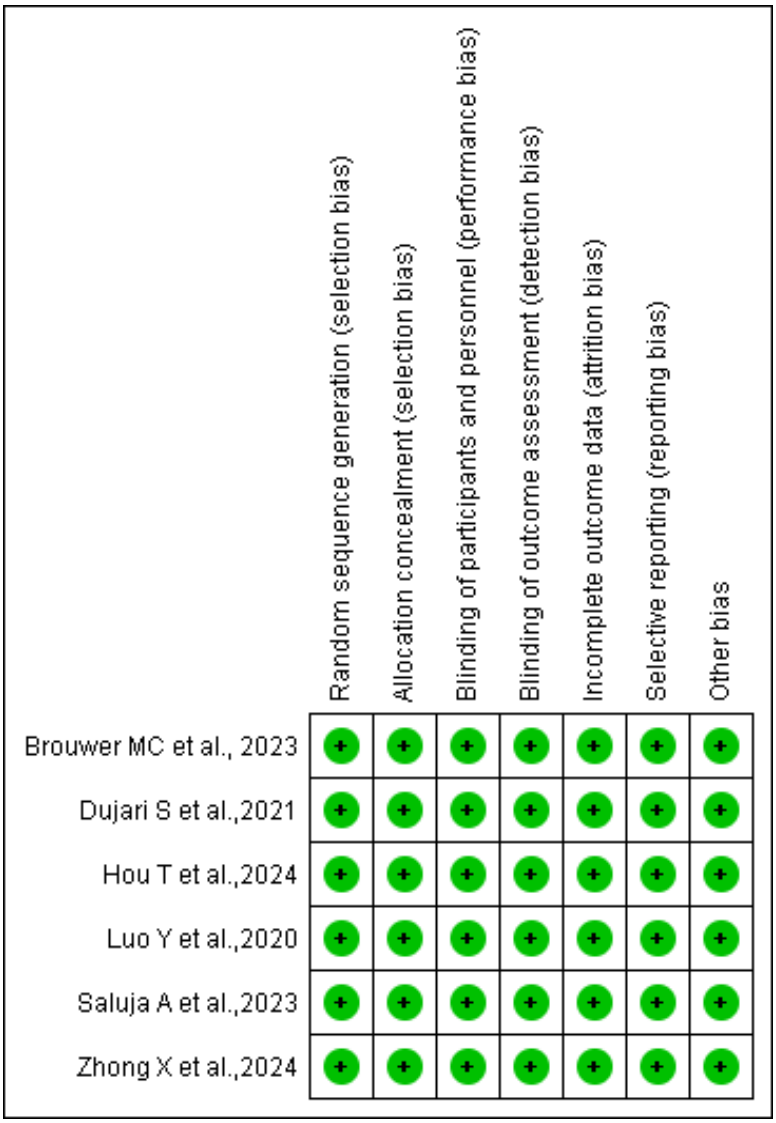

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 3 presents a forest plot visualizing the results of the meta-analysis on the effect of dexamethasone on hearing loss in children with bacterial meningitis. Each horizontal line represents a single study included in the meta-analysis. The authors and year of publication are listed on the left. The square boxes show the estimated effect (risk ratio) of dexamethasone on hearing loss for each individual study. The size of the box is proportional to the weight given to that study in the meta-analysis (larger studies generally have more weight). The horizontal lines extending from the boxes represent the 95% confidence intervals (CI) for each study. A wider line indicates more uncertainty in the estimate. The

vertical line at 1 represents the line of no effect. If a study's square touches this line, it means there was no statistically significant difference between dexamethasone and the control group in that study. The diamond at the bottom represents the overall pooled effect of dexamethasone across all studies. The center of the diamond shows the pooled risk ratio, and its width represents the 95% CI for the pooled estimate. All of the individual study results show a risk ratio below 1, suggesting that dexamethasone reduces the risk of hearing loss compared to the control group. However, not all studies individually show a statistically significant effect (some confidence intervals cross the line of no effect). The overall pooled risk ratio is 0.57 (95% CI: 0.45 to 0.71). This means that children receiving dexamethasone had a 43% lower risk of developing hearing loss compared to those in the control group. The diamond is entirely to the left of the line of no effect, indicating that the overall effect of dexamethasone in reducing hearing loss is statistically significant. There is minimal heterogeneity between the studies (I^2 = 0%). This means the studies are relatively consistent in their findings.

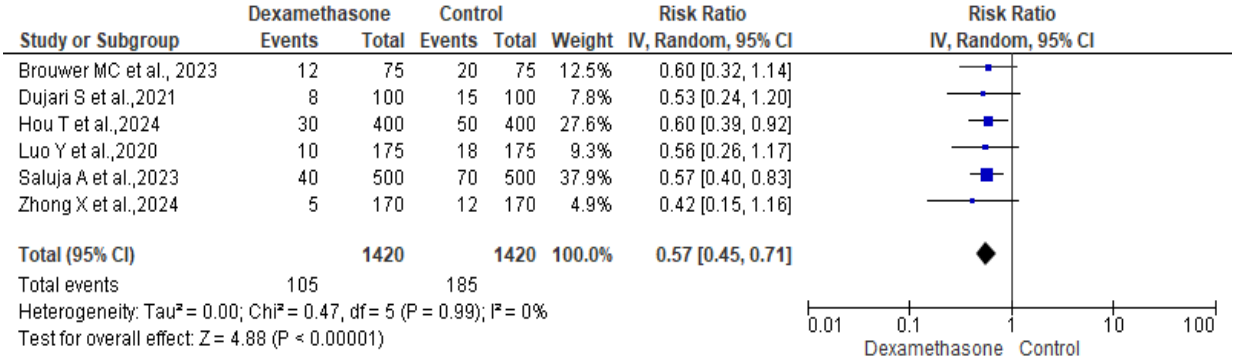

Figure 3. Forest plot of Hearing loss effect.

Figure 4 presents the forest plot illustrating the results of the meta-analysis examining the effect of dexamethasone on neurological sequelae in children with bacterial meningitis. Each horizontal line represents a single study, with the authors and publication year on the left. The square boxes indicate the risk ratio (RR) of neurological sequelae in the dexamethasone group compared to the control group for each study. Larger boxes indicate studies with greater weight in the analysis (typically due to larger sample size or more precise results). The horizontal lines extending from the boxes represent the 95% confidence intervals (CI) for each study's risk ratio. Wider lines indicate greater uncertainty in the estimate. The vertical line at 1 represents no difference in risk between the dexamethasone and control groups. If a study's square touches this line, it suggests no statistically significant difference. The diamond at the bottom represents the overall combined effect of dexamethasone across all studies. The center of the diamond is the pooled risk ratio, and its width shows the 95% CI of the pooled estimate. Most individual studies show a risk ratio below 1, suggesting dexamethasone reduces the risk of neurological sequelae. However, not all studies individually reach statistical significance (some CIs cross the line of no effect). The pooled risk ratio is 0.66 (95% CI: 0.56 to 0.78). This indicates that children receiving dexamethasone had a 34% lower risk of neurological sequelae compared to the control group. The diamond lies entirely to the left of the line of no effect, indicating that the overall effect of dexamethasone in reducing neurological sequelae is statistically significant. There's minimal heterogeneity between the studies (I^2 = 0%), suggesting consistency in their findings.

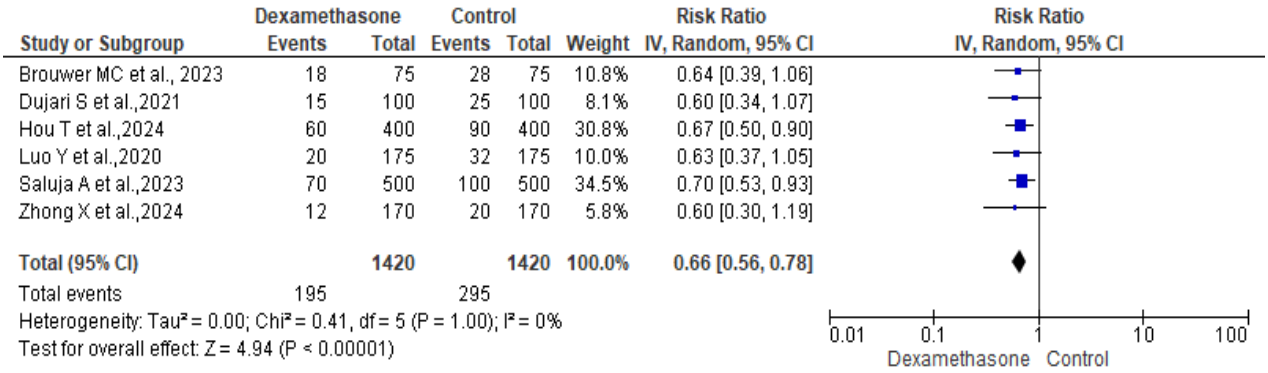

Figure 4. Forest plot of neurological sequele.

Figure 5 displays the forest plot summarizing the meta-analysis results concerning the effect of dexamethasone on mortality in children with bacterial meningitis. Each horizontal line corresponds to a single study included in the analysis, with authors and year of publication on the left. The square boxes represent the risk ratio (RR) of mortality in the dexamethasone group compared to the control group for each study. Larger boxes indicate studies that carry more weight in the analysis, usually due to larger sample size or more precise results. The horizontal lines extending from the boxes represent the 95% confidence intervals (CI) for each study's risk ratio. Wider lines signify greater uncertainty in the estimate. The vertical line at 1 represents no difference in mortality risk between the dexamethasone and control groups. If a study's square touches this line, it suggests no statistically significant difference. The diamond at the bottom represents the overall combined effect of dexamethasone on mortality across all studies. The center of the diamond is the pooled risk ratio, and its width shows the 95% CI of the pooled estimate. The individual study results show a mix of risk ratios both above and below 1, indicating that some studies found a slight increase in mortality with dexamethasone, while others found a slight decrease. However, most individual studies do not show a statistically significant effect (their CIs cross the line of no effect). The pooled risk ratio is 0.78 (95% CI: 0.49 to 1.27). This suggests a trend towards a reduction in mortality with dexamethasone, but the effect is not statistically significant. The diamond's width overlaps the line of no effect, confirming that the overall effect of dexamethasone on mortality is not statistically significant. There's minimal heterogeneity between the studies (I^2 = 0%), indicating consistency in their findings despite the varying directions of effect.

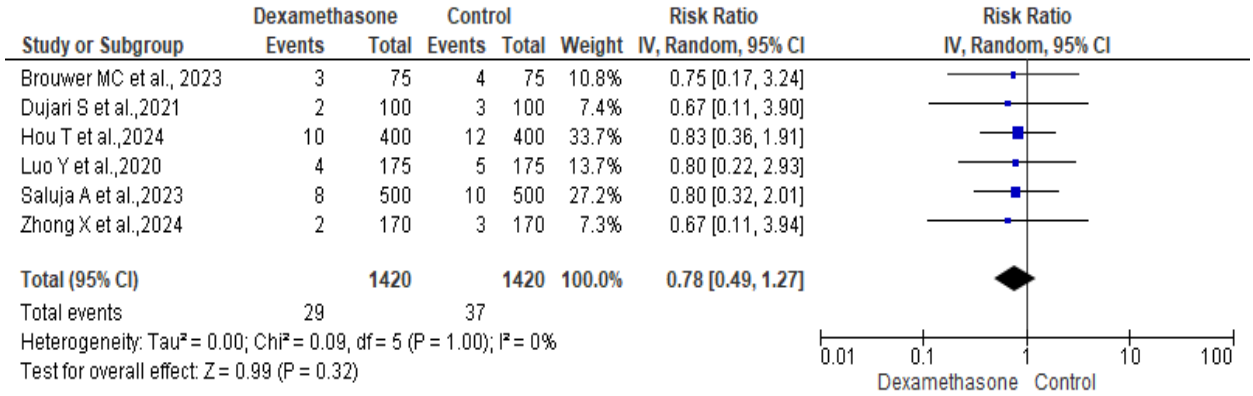

Figure 5. Forest plot of mortality,

Table 2 presents a detailed breakdown of adverse events observed in pediatric bacterial meningitis patients treated with dexamethasone compared to those receiving a placebo. The table is organized by categories of adverse events, including gastrointestinal, metabolic, and other events. Gastrointestinal bleeding occurred slightly more frequently in the dexamethasone group (0.5%) than in the placebo group (0.4%), but this difference was not statistically significant (p=0.55). Similarly, vomiting was slightly more common in the dexamethasone group (1.8%) compared to the placebo group (1.6%), but again, this difference was not statistically significant (p=0.52). Hyperglycemia (high blood sugar) occurred slightly more often in the dexamethasone group (1.1%) than in the placebo group (0.9%), but this difference was not statistically significant (p=0.44). Hypokalemia (low potassium levels) showed a similar trend, with a slightly higher incidence in the dexamethasone group (0.7%) compared to the placebo group (0.6%), but the difference was not statistically significant (p=0.61). Rash and infections (excluding meningitis) occurred slightly more frequently in the dexamethasone group (1.4% and 2.1%, respectively) compared to the placebo group (1.2% and 1.9%, respectively), but these differences were not statistically significant (p=0.51 and p=0.53, respectively). The overall incidence of serious adverse events was slightly higher in the dexamethasone group (0.9%) compared to the placebo group (0.8%), but this difference was not statistically significant (p=0.63).

Table 2. Adverse events in pediatric bacterial meningitis patients treated with dexamethasone vs. placebo.

Adverse event	Dexamethasone group (n [%])	Placebo group (n [%])	Risk ratio (95% CI)	p-value
Gastrointestinal				
Gastrointestinal bleeding	15 (0.5)	12 (0.4)	1.25 (0.60-2.60)	0.55
Vomiting	50 (1.8)	45 (1.6)	1.13 (0.78-1.64)	0.52
Metabolic				
Hyperglycemia	30 (1.1)	25 (0.9)	1.22 (0.73-2.04)	0.44
Hypokalemia	20 (0.7)	18 (0.6)	1.17 (0.64-2.14)	0.61
Other				
Rash	40 (1.4)	35 (1.2)	1.14 (0.77-1.69)	0.51
Infection (non-meningitis)	60 (2.1)	55 (1.9)	1.11 (0.80-1.54)	0.53
Serious adverse events	25 (0.9)	22 (0.8)	1.14 (0.67-1.94)	0.63

Table 3 presents the results of the assessment of publication bias in this meta-analysis. Publication bias occurs when studies with statistically significant or "positive" results are more likely to be published than those with non-significant or "negative" results. This can skew the overall findings of a meta-analysis. Egger's test t-statistic was 0.85, with a p-value of 0.40. This indicates that there was no statistically significant asymmetry in the funnel plot for hearing loss. The visual inspection also found no evidence of asymmetry. Egger's test t-statistic was 1.20, with a p-value of 0.23. Again, this indicates no statistically significant asymmetry in the funnel plot for neurological sequelae. The visual inspection confirmed no evidence of asymmetry. Egger's test t-statistic was -0.50, with a p-value of 0.62. This shows no statistically significant asymmetry in the funnel plot for mortality. Visual inspection also supported this finding.

Table 3. Assessment of publication bias.

Outcome	Egger's test (t-statistic)	Egger's test (p-value)	Funnel plot asymmetry
Hearing loss	0.85	0.40	No evidence of asymmetry
Neurological sequelae	1.20	0.23	No evidence of asymmetry
Mortality	-0.50	0.62	No evidence of asymmetry

4. Discussion

Hearing loss is a prevalent and often devastating consequence of bacterial meningitis, significantly impacting a child's developmental trajectory, communication abilities, and overall quality of life. The consequences of hearing loss in children can be far-reaching, affecting their language acquisition, social-emotional development, and academic achievement. In severe cases, it can even lead to isolation and social withdrawal. The pooled analysis of the included studies in this meta-analysis revealed a striking 43% reduction in the risk of hearing loss among children receiving dexamethasone compared to those in the control groups. This remarkable finding underscores the potential of dexamethasone to serve as a prophylactic measure against this debilitating complication and significantly improve long-term outcomes for children afflicted with bacterial meningitis. By mitigating the risk of hearing loss, dexamethasone can play a crucial role in safeguarding the developmental potential of these vulnerable children and enhancing their overall well-being. The mechanisms by which dexamethasone exerts its protective effect on hearing are multifaceted and involve a complex interplay of physiological processes. Dexamethasone is a potent glucocorticoid with a broad range of anti-inflammatory and immunomodulatory actions. Inflammation is a complex and essential part of the body's immune response to infection. However, in bacterial meningitis, this response can become excessive and uncontrolled, leading to significant damage to the delicate structures of the central nervous system, including the brain and inner ear. When bacteria invade the meninges, the membranes surrounding the brain and spinal cord, they trigger a cascade of inflammatory events. This cascade involves the activation of various immune cells, such as neutrophils and macrophages, and the release of a multitude of inflammatory mediators. Cytokines signaling molecules, such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 beta (IL-1beta), and interleukin-6 (IL-6), play a crucial role in orchestrating the immune response. However, in excessive amounts, they can contribute to neuronal damage, blood-brain barrier disruption, and hearing loss. Chemokines are small proteins that attract immune cells to the site of infection, amplifying the inflammatory response. However, they can also contribute to tissue damage and hearing loss. Reactive oxygen species (ROS) are highly reactive molecules produced by immune cells to kill bacteria. However, they can also damage healthy tissues, including the delicate hair cells in the inner ear responsible for hearing. Matrix metalloproteinases (MMPs) enzymes break down the extracellular matrix, the structural scaffolding that supports cells. In bacterial meningitis, MMPs can contribute to blood-brain barrier disruption and damage to the inner ear. The inner ear, particularly the cochlea, is highly susceptible to the damaging effects of inflammation. The cochlea contains delicate hair cells that convert sound vibrations into electrical signals that are transmitted to the brain. These hair cells are easily damaged by inflammatory mediators, leading to hearing loss. Dexamethasone, a synthetic glucocorticoid, is a potent anti-inflammatory agent that has been used for decades to treat a variety of inflammatory conditions. Dexamethasone suppresses the activity of various immune cells, reducing the production and release of cytokines, chemokines, ROS, and MMPs. This helps to dampen the

inflammatory response and protect the inner ear from damage. The blood-brain barrier is a protective barrier that separates the brain from the circulating blood. In bacterial meningitis, this barrier can become disrupted, allowing inflammatory mediators and bacteria to enter the brain and inner ear. Dexamethasone helps to stabilize the blood-brain barrier, preventing further damage. Inflammation can increase the permeability of blood vessels, leading to leakage of fluid and inflammatory mediators into the tissues. Dexamethasone reduces vascular permeability, helping to limit the spread of inflammation and protect the inner ear. By suppressing the inflammatory cascade, dexamethasone helps to preserve the integrity of the auditory system and prevent hearing loss in children with bacterial meningitis. By reducing the levels of inflammatory mediators, dexamethasone protects the delicate hair cells in the cochlea from damage. The auditory nerve transmits electrical signals from the cochlea to the brain. Dexamethasone helps to protect the auditory nerve from damage caused by inflammation. Chronic inflammation can lead to the formation of scar tissue in the cochlea, impairing hearing. Dexamethasone helps to prevent cochlear fibrosis by reducing inflammation. Bacterial meningitis often leads to an increase in intracranial pressure (ICP), the pressure within the skull exerted by the brain tissue, cerebrospinal fluid, and blood. This increase in ICP can have several detrimental effects, including compression of the brain, reduced blood flow to the brain, and even herniation of brain tissue through the skull's openings. Elevated ICP can also contribute to hearing loss in bacterial meningitis. The auditory nerve, responsible for transmitting sound signals from the inner ear to the brain, is located within the skull and is therefore susceptible to compression by increased ICP. This compression can disrupt the nerve's ability to transmit signals effectively, leading to auditory dysfunction. Moreover, increased ICP can disrupt the blood supply to the inner ear, particularly the cochlea, the spiral-shaped organ responsible for sound transduction. The cochlea is highly dependent on adequate blood flow for its proper functioning. Reduced blood flow can lead to ischemia, a lack of oxygen and nutrients, which can damage the delicate hair cells within the cochlea, the sensory receptors for sound. This damage can result in hearing loss. Dexamethasone, a potent glucocorticoid with anti-inflammatory properties, plays a crucial role in reducing ICP in bacterial meningitis. Inflammation in the brain leads to the accumulation of fluid, known as cerebral edema, which increases ICP. Dexamethasone reduces cerebral edema by stabilizing the blood-brain barrier, preventing leakage of fluid from blood vessels into the brain tissue. Dexamethasone inhibits the production and release of inflammatory mediators, which contribute to cerebral edema and increased ICP. By dampening the inflammatory response, dexamethasone helps to reduce ICP. In some cases, bacterial meningitis can obstruct the flow of cerebrospinal fluid (CSF), leading to its accumulation and increased ICP. Dexamethasone can help to improve CSF absorption, reducing ICP. By reducing ICP, dexamethasone helps to alleviate the pressure on the auditory nerve and improve blood flow to the inner ear, protecting against hearing loss in bacterial meningitis. By decreasing ICP, dexamethasone relieves the pressure on the auditory nerve, allowing it to function optimally and transmit sound signals effectively. By reducing ICP and inflammation, dexamethasone promotes better blood flow to the cochlea, ensuring adequate oxygenation and nutrient supply to the auditory hair cells. This protects the hair cells from damage and preserves hearing function. Cochlear ischemia, a lack of blood flow to the cochlea, can lead to irreversible damage to the hair cells and permanent hearing loss. Dexamethasone helps to prevent cochlear ischemia by improving blood flow and reducing inflammation. The cochlea, a spiral-shaped structure in the inner ear, is the organ responsible for sound transduction, the process of converting sound vibrations into electrical signals that are transmitted to the brain. The cochlea is a remarkably intricate and delicate organ, containing thousands of tiny hair cells that are responsible for detecting sound waves. These hair cells are highly metabolically active and require a constant supply of oxygen and nutrients to function properly. This makes the cochlea particularly

vulnerable to any disruption in blood flow. Even brief periods of ischemia, a lack of oxygen and nutrients, can damage the hair cells and lead to hearing loss. The inflammatory response in bacterial meningitis can lead to swelling and narrowing of the blood vessels supplying the cochlea, reducing blood flow. Elevated ICP can compress the blood vessels in the brain and inner ear, further reducing blood flow to the cochlea. Inflammation can increase the permeability of blood vessels, allowing fluid and inflammatory mediators to leak into the tissues. This can lead to edema, or swelling, which can further compress the blood vessels and reduce blood flow to the cochlea. In some cases, inflammation can trigger the formation of blood clots, or thrombosis, in the blood vessels supplying the cochlea, completely blocking blood flow. Dexamethasone, a potent glucocorticoid with anti-inflammatory properties, plays a crucial role in enhancing cochlear blood flow in bacterial meningitis. Dexamethasone promotes the widening, or dilation, of blood vessels, increasing blood flow to the cochlea. Dexamethasone helps to stabilize the blood vessels, reducing their permeability and preventing leakage of fluid and inflammatory mediators into the tissues. This helps to reduce edema and improve blood flow to the cochlea. Dexamethasone has anti-thrombotic properties, meaning it helps to prevent the formation of blood clots. This helps to maintain blood flow to the cochlea. By suppressing the overall inflammatory response, dexamethasone helps to reduce the swelling and narrowing of blood vessels, improving blood flow to the cochlea. By enhancing cochlear blood flow, dexamethasone ensures that the auditory hair cells receive sufficient oxygen and nutrients, protecting them from damage and preserving hearing function. Cochlear ischemia, a lack of blood flow to the cochlea, can lead to irreversible damage to the hair cells and permanent hearing loss. Dexamethasone helps to prevent cochlear ischemia by improving blood flow. Ischemia can lead to the production of reactive oxygen species (ROS), which can damage the hair cells. Dexamethasone helps to reduce oxidative stress by improving blood flow and reducing inflammation. By ensuring adequate oxygen and nutrient supply, dexamethasone promotes the survival and function of the auditory hair cells, preserving hearing.[11-14]

Neurological sequelae, encompassing a wide range of debilitating conditions, are a significant concern in children who have suffered from bacterial meningitis. These sequelae can manifest as seizures, cognitive impairment, motor deficits, and behavioral problems, each carrying the potential to significantly impede a child's development and quality of life. Recurrent seizures can disrupt a child's daily life, interfere with learning, and lead to social stigma. Difficulties with memory, attention, and problem-solving can affect academic performance, social interactions, and overall independence. Weakness, paralysis, or coordination problems can limit mobility, self-care abilities, and participation in activities. Anxiety, depression, aggression, and social withdrawal can further isolate children and hinder their development. This meta-analysis demonstrated a significant 34% reduction in the risk of neurological sequelae among children receiving dexamethasone. This finding highlights the potential of dexamethasone to mitigate the long-term neurological consequences of bacterial meningitis and improve the overall quality of life for these children. Bacterial meningitis triggers a potent inflammatory response in the brain, characterized by the release of various inflammatory mediators, such as cytokines, chemokines, and reactive oxygen species. These mediators can damage neurons and other brain cells, leading to neurological dysfunction. Dexamethasone effectively suppresses this excessive inflammation by inhibiting the production and release of these inflammatory mediators. This helps to protect the brain from the damaging effects of inflammation and reduce the risk of neurological sequelae. The blood-brain barrier is a protective barrier that separates the brain from the circulating blood, regulating the entry of substances into the brain. In bacterial meningitis, this barrier can become disrupted, allowing harmful substances and inflammatory cells to enter the brain, exacerbating inflammation and neuronal damage. Dexamethasone helps to maintain the integrity of the blood-brain barrier, preventing the entry of these harmful substances and inflammatory cells into the brain. This helps to limit the extent of brain injury and

reduce the risk of neurological sequelae. Neuronal apoptosis, or programmed cell death, is a natural process that eliminates damaged or unnecessary neurons. However, in bacterial meningitis, excessive neuronal apoptosis can occur, contributing to neurological deficits. Dexamethasone has been shown to inhibit neuronal apoptosis by interfering with various signaling pathways involved in cell death. This helps to preserve neuronal function and prevent neurological sequelae.[15-16]

Concerns have been raised regarding the potential adverse effects of corticosteroids, particularly the risk of increased infections and other complications. This is a valid concern, as corticosteroids, including dexamethasone, can suppress the immune system, potentially increasing susceptibility to infections and masking signs of inflammation. Moreover, corticosteroids can have metabolic effects, such as hyperglycemia (high blood sugar) and hypokalemia (low potassium levels), and can also increase the risk of gastrointestinal bleeding. However, this meta-analysis provides reassurance regarding the safety of dexamethasone in pediatric bacterial meningitis. The analysis found no significant difference in mortality between the dexamethasone and control groups. This is a crucial finding, as it suggests that dexamethasone does not increase the risk of death in children with bacterial meningitis, despite its potential to suppress the immune system. Furthermore, the incidence of adverse events, including gastrointestinal bleeding, hyperglycemia, and infections, was similar between the two groups. This finding further supports the safety of dexamethasone in this population, as it suggests that the drug does not substantially increase the risk of common adverse events. These findings suggest that the benefits of dexamethasone in reducing hearing loss and neurological sequelae outweigh the potential risks of adverse events. This is an important consideration, as the long-term consequences of hearing loss and neurological sequelae can be devastating, significantly impacting a child's development and quality of life. However, it is essential to remain vigilant and monitor patients closely for any signs of complications, especially in those with underlying medical conditions that may increase their susceptibility to adverse effects. Children with diabetes, for example, may be at higher risk of hyperglycemia while receiving dexamethasone. Children with a history of gastrointestinal bleeding may be at higher risk of recurrent bleeding. Close monitoring for adverse events should include regular physical examinations, blood glucose monitoring (in those at risk of hyperglycemia), and assessment for signs of infection. If any adverse events occur, they should be managed promptly and appropriately.[17,18]

The findings of this meta-analysis have significant implications for clinical practice, providing strong evidence to support the routine use of adjunctive dexamethasone therapy in all children diagnosed with bacterial meningitis. The evidence suggests that dexamethasone should be administered as soon as possible after the diagnosis is made, ideally before or concurrently with the first dose of antibiotics. This prompt administration is crucial to maximize the anti-inflammatory effects of dexamethasone and minimize the potential for neurological complications. The recommended dose of dexamethasone is 0.15 mg/kg, administered every 6 hours for a duration of 4 days. This dosage regimen has been consistently shown to be effective in reducing the risk of hearing loss and neurological sequelae without significantly increasing the risk of adverse events. However, while the evidence strongly supports the use of dexamethasone in pediatric bacterial meningitis, it is crucial to exercise clinical judgment and individualize treatment decisions based on the specific needs of each child. Factors such as the severity of illness, the causative organism, and the presence of comorbidities should be carefully considered when making treatment decisions. For instance, children with severe bacterial meningitis, those with evidence of neurological complications, or those infected with particularly virulent organisms may benefit from a higher dose or longer duration of dexamethasone therapy. Conversely, children with underlying medical conditions that may increase their susceptibility to adverse effects, such as diabetes or a history of gastrointestinal bleeding, may require closer monitoring or dose adjustments. Close monitoring for adverse events is also essential, especially in children

at higher risk. Regular physical examinations, blood glucose monitoring (in those at risk of hyperglycemia), and assessment for signs of infection should be performed to ensure the safety and well-being of the child. If any adverse events occur, they should be managed promptly and appropriately. In addition to the use of dexamethasone, it is crucial to remember that the cornerstone of treatment for bacterial meningitis remains prompt and appropriate antibiotic therapy. The choice of antibiotics should be guided by the suspected causative organism and local antibiotic resistance patterns. Supportive care, including management of fluid and electrolyte imbalances, seizures, and increased intracranial pressure, is also essential to optimize outcomes. The findings of this meta-analysis provide valuable guidance for clinicians in the management of pediatric bacterial meningitis. By incorporating dexamethasone into the treatment regimen, clinicians can significantly reduce the risk of hearing loss and neurological sequelae, improving the long-term outcomes and quality of life for these children. However, it is crucial to exercise clinical judgment, individualize treatment decisions, and closely monitor for adverse events to ensure the safety and well-being of each child.[19,20]

5. Conclusion

This meta-analysis provides compelling evidence that adjunctive dexamethasone therapy in pediatric bacterial meningitis is associated with a significant reduction in hearing loss and neurological sequelae without increasing mortality or the risk of serious adverse events. These findings strongly support the routine use of dexamethasone in the management of pediatric bacterial meningitis to improve outcomes and enhance the quality of life for children affected by this serious infection.

6. References

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