



Earliest Administration of Dexamethasone in a Case Diagnosed With Bacterial Meningitis Along With Antibiotics Leading to Full Recovery in the Shortest Period

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Abstract

Acute bacterial meningitis has high mortality and morbidity rate. Use of Dexamethasone prior to antibiotics improves outcome in most of the patients with bacterial meningitis. Early use of Dexamethasone leads to accelerated overall recovery with no or minimal neurological sequelae depending on patient's condition at the time of arrival to the hospital or initiation of treatment. Dexamethasone limits the increase of CSF lactate, leukocyte concentration and reverses development of brain edema, hence reduces intra cranial pressure. Administration of antibiotics leads to cytokine storm which adds to brain edema and can be successfully managed with early use of Dexamethasone. We report a patient who received Dexamethasone for severe pain in the large joints for 72 hours prior to progressing to coma and diagnosed as *Neisseria meningitis*. On admission to the hospital patient was comatose. The patient was continued on dexamethasone and antibiotics were also initiated and discharged from ICU within 13 hours of admission. She was awake, alert, and fully oriented without any neurological deficits. Long term follow up, a year later, the patient showed no residual neurological sequelae. We believe this case represents the earliest use of dexamethasone in bacterial meningitis with dramatic recovery and positive outcome on the short and long term. Although, it is hard to foresee, as in this case, immune mediate oligoarticular arthritis as the prodromal signs of *Neisseria Meningitis*, this case may make physicians more aware of the possibility. We also recommend Dexamethasone be considered earlier upon suspicion of meningitis much prior to culture and sensitivity reports and much before administration of antibiotics.

Keywords

Bacterial Meningitis, Dexamethasone, *Neisseria meningitis*, Cerebral spinal fluid

Introduction

Bacterial meningitis is usually preceded by colonization of nasopharynx and bacteremia [1]. The pathogens translocate into the Cerebral Spinal Fluid CSF either intracellularly [2], through the blood brain barrier by disruption of intercellular tight junctions and endothelial cell death [3], or through the choroid plexus [4]. It is the host with secondary inflammatory response that leads to entry of micro-organisms into the subarachnoid space, producing the neuronal damage. Once entered into the subarachnoid space, the bacteria multiply and release pro-inflammatory and toxic compounds by autolysis or secretion. Antibiotics cause rapid killing of the bacteria in the CSF that effectively sterilize the meningeal infection but, in the process, enhance the release of proinflammatory and toxic compounds that precipitate the cytokine-mediated inflammatory response to the development of cerebral edema (cytotoxic, interstitial, and vasogenic cerebral edema). Marked increases in intracranial pressure (ICP) can be deleterious in patients with bacterial meningitis by causing cerebral herniation or decreasing cerebral perfusion and can ultimately lead to irreversible brain injury (neuronal damage an apoptosis) and death.

According to Glasgow coma scale (GCS) a score of 1 indicates death, 2 a vegetative state, 3 severe disability, 4 moderate disability, and 5 minimal or no disability. An

Article Information

DOI: 10.31021/ijcmc.20203165
Article Type: Case Report
Journal Type: Open Access
Volume: 3 Issue: 8
Manuscript ID: IJCMC-3-165
Publisher: Boffin Access Limited
Received Date: 26 October 2020
Accepted Date: 04 November 2020
Published Date: 06 November 2020

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Citation: Mehandru SK, Kaur S, Sen S, Asif A, Vaccharajani T. Earliest Administration of Dexamethasone in a Case Diagnosed With Bacterial Meningitis Along With Antibiotics Leading to Full Recovery in the Shortest Period. Int J Clin Med Cases. 2020 Nov;3(8):165.

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unfavorable outcome was defined as a score of 1 to 4 [5]. Poor outcome was also defined as mortality, hearing loss, focal neurological sequelae, coma, ataxia, hemiparesis, and cranial nerve palsy. For patients with meningitis, initial presentation of convulsions and focal neurological abnormalities invariably carry unfavorable outcome including neurological sequelae. To that end, the triad of neck stiffness, fever, and altered mental status have shown strong association with neurological and audiological sequelae. Worse outcomes and sequelae are associated with C-reactive protein (CRP) in blood of more than 200 mg/L at admission positive, hyponatremia (PNa less than 130 mmol/L) in the first 72 hours after admission or transfer from another hospital [5].

From diagnostic point of view, patients with bacterial meningitis have poor prognosis if CSF cell count is below 1000, glucose is less than 20 and lactate is over 10 [5], or the presence of cloudy CSF is noted.

A study in New England Journal of Medicine has shown percentage of patients with unfavorable outcomes was significantly smaller in dexamethasone group than in placebo group (15 percent versus 25 percent) [6]. The proportion of patients who died was significantly smaller in the dexamethasone group than the placebo group (7 percent vs 15 percent) [6].

The overall benefit of dexamethasone remains substantial. Similarly, it has been shown that among patients with pneumococcal meningitis 26 percent in the Dexamethasone group had an unfavorable outcome as compared with 52 percent in the placebo group [6].

Among patients with meningitis due to *Neisseria meningitidis*, however, adjuvant treatment with Dexamethasone did not provide significant benefit [7]. However, as shown in our case report, Dexamethasone is beneficial in *Neisseria meningitidis* if given early resulting in full recovery within a very short period of time with no neurological sequelae.

Dexamethasone reduces morbidity and mortality in bacterial meningitis by blunting the inflammatory response secondary to bacterial lysis, which frequently causes detrimental physiological effects. Dexamethasone interferes with suppression of inflammatory substances TNF- α and IL-1, and limits the increase in CSF lactate and leukocyte concentration [5]. It also reverses development of brain oedema and hence reduces the increase in ICP [8,9].

Administration of oral glycerol instead of dexamethasone prior to antibiotics in bacterial meningitis may be as effective as dexamethasone in preventing neurological complications of bacterial meningitis. Glycerol has been widely used as an osmotic dehydrating agent and has been applied as a safe drug for children and adults in treatment of cerebral edema. In this study, the comparison of glycerol to glycerol + dexamethasone as well as dexamethasone with glycerol + dexamethasone was performed, and no significant difference was observed between the two groups. Till date, no clinical trial has been conducted in this field that could be compared to our results [10]. The osmotic property of glycerol decreases the intracranial pressure during meningitis [11] and reduces the risk of neurological sequelae.

A meta-analysis of randomized controlled trials performed since 1988 showed a beneficial effect of adjunctive dexamethasone therapy in terms of severe hearing loss in children with *Haemophilus influenzae* type b meningitis and suggested a protective effect in those with *pneumococcal meningitis* if the drug was given before or with parenteral antibiotics [6]. According to several protocols implemented, administration of the dexamethasone IV 20 minutes prior to antibiotic initiation

in patients with acute bacterial meningitis improves patient's morbidity and mortality.

Anti-inflammatory effect of dexamethasone is approximately 30 times more than that of cortisol. Anti-inflammatory effects are complex, but primarily *via* inhibition of inflammatory cells and suppression of expression of inflammatory mediators. NEJM, 2002 several protocols are being followed with administration of the dexamethasone IV 15-20 minutes prior to antibiotic initiation in patients with acute bacterial meningitis [6]. This improves patient's morbidity and mortality. However the case being presented receives dexamethasone oral for three days prior to manifestation of high fever, 101.5 degrees and coma. Patient was transported to the emergency department ED IV antibiotics were initiated within one hour of mental changes and spiked temperature. Patient had miraculous recovery and was awake, alert and fully oriented within 13 hours of arrival in ED. Oral dexamethasone was given for fleeting large joint pain and swelling possibly related to sepsis culminating into meningitis and coma. This case shows earliest use of dexamethasone in a patient with acute meningitis with earliest recovery within 13 hours. Dexamethasone, before or within one hour of the first dose of antibiotics is likely to be one of the most significant practice changes that will benefit many adults and children in common types of acute bacterial meningitis and has great value in the developed world.

Level of consciousness was stated using Glasgow coma scale (GCS) which ranges from score of 3 to 15. Patients with a score of 15 were considered as fairly conscious, 9 to 14 as impaired consciousness and a coma was designated for severe score between 3 and 8. Hearing impairments is the most common complication of bacterial meningitis [12-14].

Case Report

70 year old Asian female while travelling to India, presented to the ED in coma. She had past medical history of well controlled essential hypertension, no history of seizures. She was in perfect health six days prior when she traveled by air for three hours. Three days after the flight the patient started complaining of chills with a temperature of 98.7 and left knee pain of moderate degree with no swelling. With a preliminary diagnosis of viral syndrome and acute arthritis, she was started on NSAIDs with mild relief. Oral dexamethasone 4 mg three times a day was started with significant pain relief. Next day left knee pain subsided however right knee developed severe pain which was relieved by NSAID and continuation of dexamethasone. Patient had low grade fever during this time period. On the 4th day, morning of hospital admission, patient developed severe pain in the right wrist joint, again relieved with NSAID and dexamethasone. Patient was seen by an internist with no physical findings. Vitals: BP 110/72, temperature 97.5 F, pulse rate 86/regular rate and rhythm, respirations 18/min. There was no pain or tenderness of joints. Once home, patient developed temperature of 101.5 F and became progressively lethargic. Patient became comatose at home that evening and was taken to hospital within an hour with Glasgow coma scale of 4.

In the emergency Department vitals were BP 112/70, pulse rate 80, respirations 19/min, and temperature 97.5 Fahrenheit. Patient was unresponsive on arrival. Patient was immediately started on intravenous antiviral medications and antibiotics with a presumed diagnosis of viral meningoencephalitis. CT scan of the head was done within 20 minutes of arrival and showed no abnormality. Spinal Tap was done soon after. Blood cultures were negative in 48 hours; we believe this could have resulted due to cultures being drawn after antibiotic administration in the ED. CFS smear showed gram negative diplococci consistent

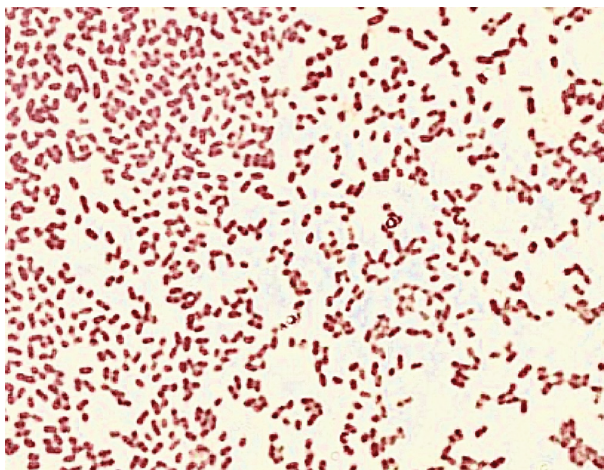


Figure 1: Gram Negative Diplococci

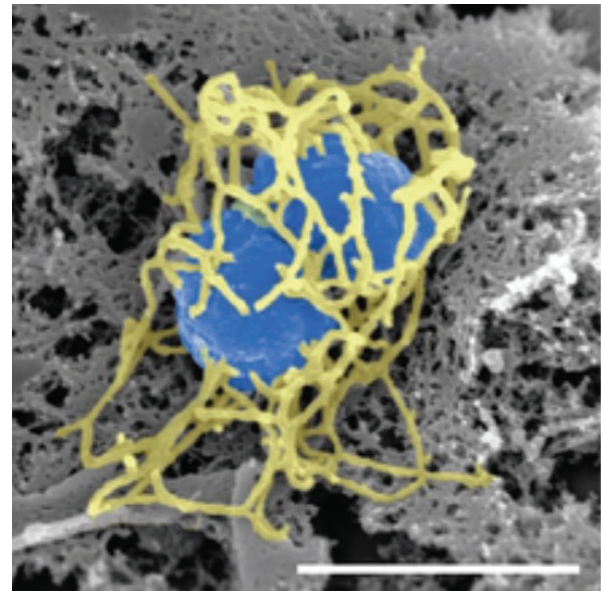


Figure 3: Scanned Electron Micrograph of a single *N. meningitidis* cell (colored in blue) with its adhesive pili (colored in yellow).

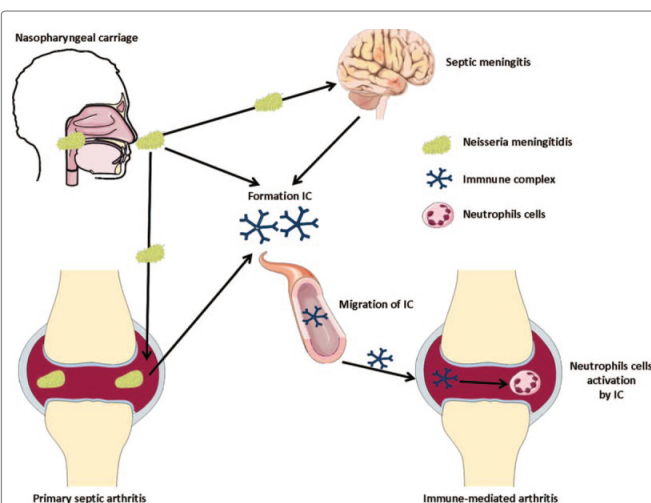


Figure 2: Scheme representing the supposed pathophysiology of meningococcal-related arthritis. Migration of the bacterial agent (*Neisseria meningitidis*) in the central nervous system causes meningitis or in other organs such as joints leads to primary septic arthritis. Production of immune complexes and migration via circulation in other organs such as joints and stimulation of neutrophils leads to inflammation and immune-mediated arthritis [19].

with diagnosis of *Neisseria meningitidis*. CSF cultures confirmed *Neisseria meningitidis*, sensitive to Ceftriaxone. Patient received Ceftriaxone, Dexamethasone, pantoprazole, and Dilantin while in the hospital. Although, there was no history of seizures or peptic ulcer disease, Dilantin and Pantoprazole were administered prophylactically. Within 4 hours of initiation of antibiotics and IV Dexamethasone patient woke up confused, she was given mild sedation. Patient woke up five hours later and was completely oriented and talking normally. She developed no neurological deficits. Upon discharge from the hospital after 48 hours, patient was continued on Ceftriaxone, tapering doses of Dexamethasone, pantoprazole, and Dilantin for two week period. Patient regained full function at home. One year follow up revealed no neurological sequelae.

Gram negative diplococci were noted in cerebral spinal fluid resembling *Neisseria meningitidis* (Figure 1).

Discussion

Neisseria meningitidis induced acute meningitis has relatively

less neuronal involvement compared with *S. Meningitidis* and *H. Meningitidis*. Adjuvant Dexamethasone therapy prior to antibiotics improves outcomes significantly in a severe case of bacterial meningitis when given much before onset of severe neurological complication with Glasgow coma scale between 3-8 along with fever 101.5 F. In this case the use of dexamethasone for 72 hours prior to the onset of severe symptoms, improved outcome. Majority of bacterial meningitis cases present to the ED with fever, neck rigidity and altered mental state without having been administered with dexamethasone or antibiotics. Oligoarticular or polyarticular involvement of large joints is the most common presentation [15-17] (Figure 2).

Immune-mediated arthritis seems to be related to immune complexes (ICs) [18]. The pathophysiology is unclear, but *N meningitidis* may promote the formation of ICs. These ICs can migrate to other organs such as the pericardium or joint, thereby leading to immune-mediated pericarditis or arthritis (Figure 2) [19].

In our case, patient had large joint fleeting pain 72 hours prior to onset of coma (GCS 4). This was most likely due to immune mediated arthritis related to *Neisseria meningitidis* as patient was afebrile till one hour before GSC 4 coma. Arthritis secondary to meningococcal disease was reported to be septic and/or immune-mediated [17]. Immune-mediated arthritis can involve the same joint site or a joint site other than that initially involved by septic arthritis, as seen in the patients in the study done by Masson-Behar et al. [19]. Joint pain was alleviated by the use of NSAID and dexamethasone daily for 72 hours prior to coma.

Bacterial meningitis is still a worldwide major infectious disease. About 1.2 million cases of bacterial meningitis are estimated to occur annually worldwide with 135,000 deaths [5].

Meningococcal meningitis (Figure 3) and sepsis are potentially fatal diseases which affect people around the world, disproportionately affecting certain areas.

Compared with *S. Meningitidis* and *H. Meningitidis*, *Neisseria meningitidis* induced acute meningitis has relatively less neuronal involvement. According to several studies, adjuvant Dexamethasone therapy prior to antibiotics improves outcomes significantly in a severe case of bacterial meningitis when

given much before onset of severe neurological complication with Glasgow coma scale between 3-8 along with fever. In fact, Dexamethasone, before or within one hour of the first dose of antibiotics is likely to be one of the most significant practice changes that will benefit many adults and children in common types of acute bacterial meningitis and has great value in the developed world. This stands in contrast with the findings of an individual patient data meta-analysis study that included 2029 patients from 5 randomized control trials. [7]. Despite continued controversy, current evidence does show that the use of steroids has been shown to improve the overall outcome of patients with certain types of bacterial meningitis, including *H influenzae*, *tuberculosis*, and *pneumococcal meningitis*.

Majority of bacterial meningitis cases present to the ED with fever, neck rigidity and altered mental state without having been administered with dexamethasone or antibiotics. In populations with meningitis, the frequency of arthritis is rare, with incidences ranging from 2% to 12.5% [9,10,15,16]. In our case, patient had large joint fleeting pain 72 hours prior to onset of coma (GCS 4). This was most likely due to immune mediated arthritis related to *Neisseria meningitidis* [19] as patient was afebrile till one hour before GSC 4 coma. In septic arthritis, patients harbor symptoms of infections such as fever, leukocytosis and synovial effusion, which was absent in our case.

In this case the use of dexamethasone for 72 hours prior to the onset of severe symptoms, improved outcome. Oral dexamethasone was given for fleeting large joint pain and swelling possibly related to sepsis culminating into meningitis and coma. This case shows earliest use of dexamethasone in a patient with acute meningitis with earliest recovery within 13 hours of admission. Joint pain was alleviated by the use of NSAID and dexamethasone daily for 72 hours prior to coma. Similar cases have been reported; where polyarticular immunologically mediated arthritis was noted up to 72 hours prior to presentation in ED for *N. meningitidis* [20].

The delay of appearance, the absence of improvement with antimicrobial agent treatment, and the negative synovial fluid cultures are helpful for the diagnosis of immune-mediated arthritis. As in our patient, treatment with NSAIDs usually leads to complete resolution of symptoms. Dexamethasone administered on day one of the arthritis, further accelerated relief of pain. Some patients required prolonged NSAIDs therapy to achieve resolution, especially the ones older than 50 [15]. We believe if dexamethasone was used as in our case along with NSAIDs, relief of pain would have been much quicker.

Immunological mediated arthritis has been reported in meningococcal meningitis [19], septic arthritis in this study. Out of 7 patients, 5 had septic arthritis, 4 had immune-mediated arthritis and 2 had septic arthritis followed by immune-mediated arthritis. In this study arthritis was noticed 3-7 days after manifestation of meningitis. There are several studies conflicting this, in some cases arthritis was noted before or during active meningococcal infection. Septic arthritis is related to invasive meningococcal disease, with isolation of *Neisseria meningitidis* in the joint fluid or concomitant proven infection in another site [19]. Functional outcome of arthritis in bacterial meningitis is generally good because meningococcal arthritis is usually immune-mediated, and pneumococcal arthritis is generally less deforming than staphylococcal arthritis [16].

In patients older than 55 years, dexamethasone reduced risk of death or severe neurological sequelae [20]. Brouwer et al., found a more pronounced beneficial effect of corticosteroids in patients aged >55 years than in other age groups [22]. No study has been done to evaluate benefits of administration of

Dexamethasone on 72 hours prior to manifestation of meningitis. A four day regimen is recommended, with Dexamethasone therapy started before or with the first dose of antibiotics [6]. We believe the early use of dexamethasone may be found beneficial in all types of bacterial meningitis. Dexamethasone appears to be more effective in patients aged older than 55 years. This is contrasted with the findings of a recent individual patient data meta-analysis including 2029 patients from 5 randomized control trials [6].

Eight weeks after enrollment, the percentage of patients within unfavorable outcome was significantly smaller in dexamethasone group than in placebo group. Predictors of unfavorable outcome were coma on admission, hypotension, and meningitis due to *S. pneumonia* [6]. The benefit of dexamethasone remained substantial in an analysis adjusted for the other risk factors [6].

As shown in this article, several studies have demonstrated clearly the benefits of early use of Dexamethasone before and in continued conjunction with antibiotics. In developed countries, the mortality in adults suffering from meningitis is 6 to 37% depending on microbial aetiology [23]. Adoption and incorporation of upcoming evidenced based treatments should be encouraged at all levels.

Conclusion

As shown in our patient, early treatment with Dexamethasone lead to complete resolution of symptom and a remarkable recovery with no long standing neurological or systemic sequelae. No study has been done to evaluate benefits of administration of Dexamethasone on 72 hours prior to manifestation of meningitis. We believe the early use of dexamethasone may be found beneficial in all types of bacterial meningitis.

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