The efficacy of dexamethasone treatment in adult patients with acute bacterial meningitis

Celal Ayaz, MD, Mustafa K. Celen, MD, Mehmet F. Geyik, MD, Mehmet Ulug, MD.

ABSTRACT

الأهداف: تقييم فعالية استعمال عقار الكورتيكوستيرويدات في علاج المرضى البالغين المصابين بالتهاب السحايا البكتيري.

الطريقة: تم تقييم 144 مريضاً بشكل عشوائي من أجل تحديد كفاءة المعالجة بالديكساميثازون في المرضى البالغين المصابين بالتهاب السحايا البكتيري الحاد بمستشفى دايكل الجامعي بتركيا في الفترة ما بين يناير 2000م الى ديسمبر 2004م. بينما تلقت المجموعة الأولى عقار سيفترياكسون بمقدار 4gr/اليوم بالإضافة إلى عقار ديكساميثازون وتلقت المجموعة الثانية عقار سيفترياكسون 4gr/اليوم فقط. تم إعطاء عقار ديكساميثازون من 10–15 دقيقة فقط قبل تلقي الجرعة الأولى من المعالجة بالمضادات الحيوية بمقدار 8mg. استمرت 16mg/في اليوم لمدة ثلاثة أيام.

النتائج: شملت الدراسة عدد 144 مريضاً شخصت حالتهم بالتهاب السحايا البكتيري الحاد. تم تحليل السائل النخاعي الشوكي عند وقت الدخول للمستشفى وبعد 24 ساعة و48 ساعة وفي نهاية المعالجة. وفقاً لمستوى كريات الدم البيضاء في سائل النخاع الشوكي تبين أنها $1710\pm2140/mm^3$ في المجموعة الأولى التي تلقت المعالجة بعقار ديكساميثازون مقارنة ب $1950\pm2244/mm^3$ أي المجموعة الثانية (p=0.001). تحسنت العواقب لدى المجموعة التي تلقت عقار ديكساميثازون بشكل ملحوظ ومطرد أكثر من مجموعة التحكم (p=0.001). بينما كانت نسبة الوفيات 9.7% في مجموعة المرضى التي تلقت عقار ديكساميثازون وكانت 16.7% لدى مجموعة التحكم ولكن لم يتبين هنالك وجود دلالة ملحوظة (p=0.093).

خاتمة: استعمال ديكساميثازون في المرضى البالغين لا يزال تحت النقاش واستعمال ديكساميثازون من 10–15 دقيقة قبل العلاج بالمضادات الحيوية للمرضى فاقدي الوعي والذين حالتهم الصحية ضعيفة يعد فعالاً في التحسن السريري للمريض.

Objectives: To evaluate the efficacy of dexamethasone added to the treatment of adult patients with bacterial meningitis in our region.

Methods: One hundred and forty-four patients were randomized prospectively and evaluated to determine the efficacy of dexamethasone treatment in adult patients with acute bacterial meningitis at Dicle University Hospital, Diyarbakir, Turkey between January 2000 and December 2004. While the first group received ceftriaxone 4 gr/day plus dexamethasone, the second group received ceftriaxone 4 gr/day only. Dexamethasone was given 10-15 minutes before the first 8 mg dose of antibiotic treatment. It was continued at 16 mg/day for 3 days.

Results: The study included 144 patients with the diagnosis of acute bacterial meningitis. Cerebrospinal fluid (CSF) was analyzed at the time of admission, after 24-48 hours (**Table 1**), and at the end of treatment. Accordingly, CSF leukocyte level was found to be $1710\pm2140/mm^3$ in group 1 receiving dexamethasone treatment compared to $1950\pm2244/mm^3$ in group 2 (p=0.001). The consciousness in the group receiving dexamethasone improved significantly more rapidly than the control group (p=0.001). While mortality was 9.7% in the patient group receiving dexamethasone it was 16.7% in the control group, however, it was not significant (p=0.093).

Conclusion: The use of dexamethasone in adult patients is still under debate, and the administration of dexamethasone 10-15 minutes before antibiotherapy to unconscious patients in a poor state of health, is effective in the clinical improvement of the patient.

Neurosciences 2008; Vol. 13 (2): 146-150

From the Department of Clinical Microbiology and Infectious Diseases, Dicle University Hospital, Diyarbakir, Turkey.

Received 6th June 2007. Accepted 25th November 2007.

Address correspondence and reprint request to: Associate Professor Mustafa K. Celen, Department of Clinical Microbiology and Infectious Diseases, Dicle University Hospital, 21280 Diyarbakir, Turkey. Tel. +90 (412) 2488006. Fax. +90 (412) 2488440. E-mail: mkcelen@hotmail.com

Acute bacterial meningitis causes deaths and important sequelae in many parts of the world.[1] Despite the improvements in antimicrobial agents and in the medical intensive care techniques, the rate of morbidity and mortality observed in bacterial meningitis is not negligible. In a study performed in our area on 206 cases, mortality in acute bacterial meningitis

was reported as 27.1%.[2] Three major bacteria causing meningitis in developed countries are *Streptococcus pneumoniae (S. pneumoniae)* (15.3%), Neisseria meningitidis (7.5%) and *Haemophilus influenzae type B (Hib)* (3.8%). In other studies long term survival rates range between 2.5-27.7%.[3] Animal studies and clinical experience on meningitis, mentioned that the addition of a glucocorticoid, dexamethasone, to antibiotherapy decreased mortality and morbidity. Dexamethasone decreases the synthesis of many inflammatory mediators, the aggregation of adhesion molecules, and provides the stabilization of lysosomes in the CSF.[3,4] Therefore, the inflammatory response, and the development of neurological sequelae are decreased especially in the *Hib,* and *S. pneumoniae* meningitis of infants and children. In controlled studies performed in adult patients with acute bacterial meningitis, it was mentioned that there are contrary ideas on the efficacy of dexamethasone treatment.[5] While it was pointed out that the beneficial effects of dexamethasone treatment should not be underestimated, some experts do not recommend dexamethasone treatment in cases of bacterial meningitis.[6-9] The objective of our study was to evaluate the efficacy of dexamethasone added to the treatment of adult patients with bacterial meningitis in our region.

Methods. Dicle University Hospital is a 1050-bed, primary and tertiary referral hospital, which serves a population of almost 5.5 million in the Southeast region of Turkey. The University Hospital has most types of medical and surgery units. This prospective randomized study included all cases of community-acquired acute bacterial meningitis diagnosed, and treated in Dicle University Hospital between January 2000 and December 2004. Patients were analyzed in 2 separate groups. While ceftriaxone 4 gr/day+ dexamethasone were given to the first group, ceftriaxone 4 gr/day only was given to the second group. Equal numbers of patients were included in both the groups, namely, 72 in the ceftriaxone+ dexamethasone group and 72 in the ceftriaxone only group. Randomization was carried out by odd and even number of patients. Odd numbered patients were included in the dexamethasone group, and the even numbered in the ceftriaxone only group. Dexamethasone was given 10-15 minutes before the first 8 mg dose of antibiotic treatment. It was continued at 16 mg/day for 3 days. In this study, children, patients with a history of allergy to beta-lactam antibiotics, patients with complaints longer than 48 hours, people with congenital and acquired CNS abnormalities, patients with ventriculoperitoneal shunt, and people with liver/renal insufficiency were excluded from the evaluation. The diagnoses of patients included in the study were considered according to the history, and physical examination findings supporting meningitis with the laboratory data. Diagnosis was made with the evaluation of CSF obtained with lumbar puncture (at least 100/mm^3 leucocytes), the determination of bacteria in gram staining or the presence of growth in CSF culture. We examined samples of CSF microscopically for total cell count, and white cell differential. After centrifugation, deposits were cultured on sheep blood agar and hemophilus test medium, both were incubated in a candle jar at 37°C for 48 hours. Five ml brain-heart infusion broth with 1% Vitox was added to the remaining deposit for enrichment culture. This broth was incubated for 48 hours, and the centrifuged deposit was then cultured on plates of sheep blood agar and hemophilus test medium, which were also incubated for 48 hours. Blood was cultured manually, a maximum of 5-10 ml blood was added to a single culture bottle. Bottles were incubated overnight at 37°C before venting. We examined cultures macroscopically every day, which were then gram stained if turbid or hemolyzed. Subcultures and direct susceptibility testing were carried out as directed by the gram-stain findings. All plates were incubated in a candle jar, and examined after 24 and 48 hours of incubation. All patients and their blood relatives were informed of the study, and its protocol was approved by the Local Ethical Committee of Dicle University Hospital.

Student's t test was used to compare means between groups, and the x^2 test and Fisher's exact test were performed to analyze qualitative data. Parametric data are expressed as mean ± standard deviation. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 10 (SPSS Inc, Chicago, IL).

Results. The study included 144 patients with the diagnosis of acute bacterial meningitis. Ninety-six of the cases included in the study were male (66.7%) and 48 (33.3%) were female. Patients were divided into 2 groups. The mean age of the first group was 32± 13.1; 54 of the cases (75%) were male and 18 (25%) were female. The mean age of the control group was 31.9±13.2, 42 of the patients (58.3%) were male, and 30 (41.7%) were female. The clinical states of both patient groups were similar at the time of admission (**Table 1**). The Glasgow coma score at the time of admission was 7.79±1.4 in group 1 and 8.04±1.3 in group 2.[10] One hundred and one of the patients (70.1%) were admitted to our clinic from a center at least 60 km away. Ninety-two of the cases (63.8%) had received at least one dose of parenteral antibiotic before admission. There was no significant correlation between the patients with or without previous antibiotic treatment by means of

mortality (p=0.121). Seventy-eight of the 144 cases that were diagnosed with acute bacterial meningitis had bacterial causes (**Table 1**). The CSF of the patients was analyzed on admission, after 24-48 hours, and at the end of treatment. Accordingly, the leukocyte levels of CSF in the first 2 days in group 1 were significantly low compared to group 2 (p=0.001) (**Table 2**). On the contrary, although CSF protein was quantitatively low compared to group II, this was not found statistically significant (p>0.084). The CSF glucose was quantitatively high compared to control group, but this was also not significant (p=0.079). As a conclusion, the CSF leukocyte in the dexamethasone treated group in the first 48 hours of treatment was found low compared to the control group. The patient group treated with dexamethasone became conscious significantly faster compared to the control group (p=0.001). Two patients from group 1, and 3 patients from group II died in the first 48 hours of treatment. Seven patients from group 1, and 12 patients from group 2 died during the whole treatment (p=0.091). While the causative agent was *S. pneumonia* in 2 of the dead patients, *N. meningitidis* was the cause in one patient of group 1. In group 2, in 4 of the dead patients the causative agent was *S. pneumonia* while it was *N. meningitidis* in 2. There was no correlation between mortality and the causative agent in acute bacterial meningitis (p>0.05). While there was cerebral edema in 23.6% of the dexamethasone treated group, cerebral edema occurred in 37.5% of the group treated only with antibiotics. Eight of the 19 dead patients were lost due to cerebral edema and hydrocephaly, 4 of them due to circulatory insufficiency, others due to respiratory insufficiency, and multi organ failure. The association between the developing complications and dexamethasone use is shown in **Table 3**. Body temperature returned to normal faster in the dexamethasone treated group compared to the control group (p=0.089). Prophylactic sucralfate was started in the dexamethasone treated patients. There was no gastrointestinal system bleeding in any of the patients.

Table 1 - Clinical and laboratory characteristics of treatment groups.

Characteristics	Group 1	Group 2
Age (year)	32±13.1	31.9±13.2
Male	54	42
Female	18	30
Features on admission		
Temperature ≥ 38°C	67	62
Meningeal signs	65	63
Impaired consciousness	58	56
Coma	3	2
Respiratory failure	2	2
CRP	112±29.3	109±41.4
Infected with		
Streptococcus pneumoniae	13	11
Neisseria meningitidis	11	10
Staphylococcus aureus	9	8
Staphylococcus epidermidis	8	5
Pseudomonas aeruginosa	2	1
No isolate	29	37

CRP - C-reactive protein

Discussion. The use of systemic corticosteroids in addition to antibiotics in adult patients with acute bacterial meningitis is still under debate. The dosage and efficacy of steroids have been compared in many studies.[11] In this study, by giving half of the patients ceftriaxone+dexamethasone and ceftriaxone only to the other half, the effect of dexamethasone on morbidity and mortality was investigated. In previous studies, the dose and duration of dexamethasone use was reported as 2-7 days, being at least 2 days. However, the efficacy of 2 days of dexamethasone, and 4 days of dexamethasone was found similar in the studies performed in children.[12] In many studies, 4 days of dexamethasone regimen was used. It was shown in various studies that starting steroid therapy before, or with the first dose of antibiotics is more effective than starting after the first dose. Although the duration of steroid usage has been indicated between 2-7 days, it is not clear yet.[13,14] In another study, dexamethasone has been administered 5-10 days before antibiotic treatment or together with the first dose.[15,16]

Table 2 - Cerebrospinal fluid (CSF) results on hospital admission, and after 24 to 48 hours of therapy.

CSF finding	Group 1		Group 2	
	Admission	24-48 hours	Admission	24-48 hours
Leucocytes (cells/mm^3)	8921±3616	1710±2140	8874±2954	1950±2244
Glucose (mg/dl)	24±21	56±26	27±19	46±19
Protein (mg/dl)	250±52	149±40	247±49	191±52
Chlorine (mmol/L)	108±11	107±8	104±12	105±9

Table 3 - Complications or adverse events during treatment according to treatment groups.

Complication or event	Group 1	Group 2	*P*-value
Death at 48 hours	2	3	$p>0.05$
Death	7	12	$p>0.05$
Prolonged fever*	23	34	$p>0.05$
Subdural effusion	3	5	$p>0.05$
Subdural empyema	2	1	$p>0.05$
Hyponatremia	4	1	$p>0.05$
Hydrocephalus	34	41	$p>0.05$
Hemiparesis	12	7	$p>0.05$
Hemiplegia	3	1	$p>0.05$

*Fever lasting 7 days or more after the beginning of therapy

In our study, the patients in the first group started dexamethasone treatment 10-15 minutes before the first antibiotic dose. This treatment was continued for 3 days at 16 mg/day. Dexamethasone has been used for 2-7 days in the studies. We used a 3 days regimen to decrease the risk of gastrointestinal bleeding. In a study including 200 patients where the efficacy of dexamethasone in acute bacterial meningitis was investigated, the level of glucose in CSF in the dexamethasone treated group raised significantly, compared to the untreated group. Similarly, the level of CSF protein in the dexamethasone treated group was found significantly low compared to the untreated group.[17]

In our study, although it was detected that the glucose levels increased compared to controls at 24-48 hours, on CSF analysis it was not statistically significant (p=0.079). In a study including 115 cases performed in Switzerland, it was observed that dexamethasone did not cause any adverse effect on the clinical, and laboratory prognosis of the patient. In none of the analysis, while blood in the stool or apparent bleeding was observed, there was also no decrease in hemoglobin levels. It was concluded that dexamethasone would be efficient in adults and children, and it would be useful in routine use.[18] In our study while there was no decrease in hematocrit levels, we did not observe any gastrointestinal bleeding. In a study performed in India including 40 patients, the first group from the 2 groups with 20 patients, was given ceftriaxone + dexamethasone, and the control group was administered ceftriaxone + placebo treatment. While the CSF values significantly improved, there was no significant difference between the groups by means of fever, nausea, and vomiting.[19] Although it was observed in our study that fever more rapidly decreased in the dexamethasone treated patient group, this difference was not statistically significant. In another study including 68 patients with acute bacterial meningitis,[20] the dexamethasone added group improved more rapidly compared to placebo by means of clinical prognosis of fever, nausea, and consciousness. Development of neurological complications and mortality was observed significantly low in the dexamethasone treated group. In our study patients treated with dexamethasone became conscious more rapidly compared to the control group (p=0.001). Although neurological complications, such as hydrocephaly were less in the dexamethasone treated group, the difference was not statistically significant ($p>0.05$). In a larger series of studies, it was concluded that steroid treatment was useful in adult patients with acute bacterial meningitis. While the development of complications and mortality was found significantly low in the dexamethasone treated group compared to placebo in a study performed in Holland with 301 adult patients with acute bacterial meningitis, there was no gastrointestinal bleeding due to steroid use.[21,22] In our study, 7 of the 72-dexamethasone treated patients, and 12 of the 72 control patients were lost. Although it seems different numerically, there was no statistical difference. In a study including 429 patients with acute bacterial meningitis, it was determined that dexamethasone use decreased the number of neurological sequelae. It was noted that dexamethasone decreased mortality especially in patients with pneumococcic meningitis.[23] In our study, the causative agent in 2 of the dead patients from the first group and in 2 of the dead patients from the second group, were pneumococci, however, there was no significant difference. It was considered that the lower number of grown causative agents was effective in this issue. It was determined at the end of many studies that the addition of steroids to the treatment of meningitis decreased mortality in adult patients. As it has a beneficial effect on acute bacterial meningitis, it was noted that dexamethasone treatment before the first antibiotic dose in adult patients would be beneficial for all patients.[24] There are also contrary ideas concerning this issue. Although routine dexamethasone use was found effective in some studies, the efficacy of this treatment has not been accepted in many studies as it was suggested that randomization was not appropriate in the studies. The compliance of patients with meningitis to treatment in an area may vary from another area.[25-27] In our study, patients with 48-hour complaints were included. Although the proportional difference was determined in mortality, it was not statistically significant. In a study performed in Pakistan, dexamethasone was added to the treatment of 48 of 89 patients with acute bacterial meningitis, and placebo was given to the remaining 41. While the rate of neurological sequelae and death in the dexamethasone treated group were 42% and 25%, these rates were 30% and 12% in the placebo treated group.

In this study, it was determined that dexamethasone use increased the rate of the development of neurological sequelae, and death.[28] Similarly, in a large study in Malawi including 598 patients,[29] no significant difference was determined between the placebo treated, and dexamethasone treated groups by means of the development of morbidity and mortality. As almost all of the patients were admitted after an admission to another health center, most received antibiotics. Thus, the number of meningitis cases in which the causative agent was grown, was found to be limited. As there was no chance of using rapid diagnostic tests due to financial difficulties, the diagnosis was performed clinically in most of the cases. As a result, CSF leukocyte level more rapidly improved in the dexamethasone treated patient group compared to the control group in this study. The consciousness of the patients in the first group became normal more rapidly compared to the control group. The routine use of dexamethasone in adult patients is still under debate, while the administration of dexamethasone 10-15 minutes before anti biotherapy to patients without consciousness and in a generally bad condition, is effective in the clinical improvement of the patient.

References

1. Murray CJL, Lopez AD. Global burden of disease and injuries Series Vol II. Global Health Statistics. Geneva: World Health Organization; 1996. p. 285.
2. Hosoglu S, Ayaz C, Geyik MF, Kokoglu OF, Ozen A. Acute bacterial meningitis in adults: analysis of 218 episodes. ***Ir J Med Sci*** 1997; 166: 231-234.
3. Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. ***Pediatr Infect Dis J*** 1993; 12: 389-394.
4. Schaad UB, Kaplan SL, McCracken GH Jr. Steroid therapy for bacterial meningitis. ***Clin Infect Dis*** 1995; 20: 685-690.
5. McIntyre PB, Berkey CS, King SM, Schaad UB, Kilpi T, Kanra GY, et al. Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1998. ***JAMA*** 1997; 278: 925-931.
6. de Gans J, van de Beek D. European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. ***N Engl J Med*** 2002; 347: 1549-1556.
7. Tunkel AR, Scheld WM. Corticosteroids for everyone with meningitis? ***N Eng J Med*** 2002; 347: 1613-1615.
8. Davis LE, Greenlee JE. Pneumococcal meningitis: antibiotics essential but insufficient. ***Brain*** 2003; 126: 1013-1014.
9. Cohen J. Management of bacterial meningitis in adults. ***BMJ*** 2003; 326: 996-997.
10. Teasdale G, Murray G, Parker L, Jennett B. Adding up the Glasgow Coma Score. ***Acta Neurochir Supp*** (Wein) 1979; 28: 13-16.
11. van der Flier M, Geelen SP, Kimpen JL, Hoepelman IM, Tuomanen EI. Reprogramming the host response in bacterial meningitis: how best to improve outcome? ***Clin Microbiol Rev*** 2003; 16: 415-429.
12. Weitzman S, Berger S. Clinical trial design in studies of corticosteroids for bacterial infections. ***Ann Intern Med*** 1974; 81: 36-42.
13. Klugman KP, Friedland IR, Bradley JS. Bactericidal activity against cephalosporin-resistant Streptococcus pneumoniae in cerebrospinal fluid of children with acute bacterial meningitis. ***Antimicrob Agents Chemother*** 1995; 39: 1988-1992.
14. McIntyre P, Berkey CS, King SM, Schaad UB, Kilpi T, Kanra GY, et al. Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1988. ***JAMA*** 1997; 278: 925-931.
15. van de Beek D, de Gans J, McIntyre P, Prasad K. Corticosteroids in acute bacterial meningitis. Cochrane Syst Rev 2003; 3: CD004405. Review. Update in: Cochrane Data Base Rev. 2007; 1: CD 004405
16. Bhaumik S, Behari M. Role of dexamethasone as adjunctive therapy in acute bacterial meningitis in adults. ***Neurol India*** 1998; 46: 225-228.
17. Thomas R, Le Tulzo Y, Bouget J, Camus C, Michelet C, Le Corre P, et al. Trial of dexamethasone treatment for severe bacterial meningitis in adults. Adult Meningitis Study Group. ***Intensive Care Med*** 1999; 25: 475-480.
18. Lebel MH, Freij BJ, Syrogiannopoulos GA, Chrane DF, Hoyt MJ, Stewart SM, et al. Dexamethasone therapy for bacterial meningitis. ***N Engl J Med*** 1988; 319: 964-971.
19. Schaad UB, Lips U, Gnehm HE, Blumberg A, Heinzer I, Wedgwood J. Dexamethasone therapy for bacterial meningitis in children. Swiss Meningitis Study Group. ***Lancet*** 1993; 342: 457-461.
20. Shembesh NM, Elbargathy SM, Kashbur IM, Rao BN, Mahmoud KS. Dexamethasone as an adjunctive treatment of bacterial meningitis. ***Indian J Pediatr*** 1997; 64: 517-522.
21. Ahsan T, Shahid M, Mahmood T, Jabeen R, Jehangir U, Saleem M, et al. Role of dexamethasone in acute bacterial meningitis in adults. ***J Pak Med Assoc*** 2002; 52: 233-239.
22. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. ***N Engl J Med*** 2002; 347: 1613-1615.
23. Bennet IL, Finland M, Hamburger M, Kass EH, Lepper M, Waisbren BA. The effectiveness of hydrocortisone in the management of severe infections. ***JAMA*** 1963; 183: 462-465.
24. Lebel MH, Freij BJ, Syrogiannopoulos GA, Chrane DF, Hoyt MJ, Stewart SM, et al. Dexamethasone therapy for bacterial meningitis: Results of two double-blind placebo-controlled trials. ***N Engl J Med*** 1988; 319: 964-971.
25. Girgis NI, Farid Z, Mikhail IA, Farag I, Sultan Y, Kilpatrick ME. Dexamethasone treatment for bacterial meningitis in children and adults. ***Pediatr Infect Dis J*** 1989; 8: 848-851.
26. van de Beek D, de Gans J, McIntyre P, Prasad K. Steroids in adults with acute bacterial meningitis: a systematic review. ***Lancet Infect Dis*** 2004; 4: 139-143.
27. Odio CM, Faingezicht I, Paris M, Nassar M, Baltodano A, Rogers J, et al. The beneficial effect of early dexamethasone administration in infants and children with bacterial meningitis. ***N Engl J Med*** 1991; 324: 1525-1531.
28. Qazi SA, Khan MA, Mughal N, Ahmad M, Joomro B, Sakata Y, et al. Dexamethasone and bacterial meningitis in Pakistan. ***Arch Dis Child*** 1996; 75: 482-488.
29. Molyneux EM, Walsh AL, Forsyth H, Tembo M, Mwenechanya J, Kayira K, et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. ***Lancet*** 2002; 360: 211-218.