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Does Dexamethasone Helps in Meningococcal Sepsis?

Ilir Tolaj, Hamdi Ramadani, Murat Mehmeti, Hatixhe Gashi, Arbana Kasumi, Visar Gashi, Haki Jashari

Department of Infectious Diseases, University Clinical Centre in Pristina, Kosovo

Corresponding author: Hamdi Ramadani, MD, PhD, Director of the ID Department, UCC Pristina, Mob. +383 44 137 050, E-mail: ramadanidrhamdi@live.com

ABSTRACT

Purpose: Prompt recognition and aggressive early treatment are the only effective measures against invasive meningococcal disease (IMD). Anti-inflammatory adjunctive treatment remains controversial and difficult to assess in patients with IMD. The purpose of this study was to evaluate the effect of dexamethasone (DXM) as adjunctive treatment in different clinical forms of IMD, and attempt to answer if DXM should be routinely used in the treatment of IMD. ***Methods:*** In this non-interventional clinical study (NIS), 39 patients with meningococcal septicaemia with or without of meningitis were included, and compared regarding the impact of dexamethasone (DXM), as an adjunctive treatment, on the outcome of IMD. SPSS statistics is used for statistical processing of data. ***Results:*** Thirty (76.9%) patients with IMD had sepsis and meningitis, and 9 (23.1%) of them had sepsis alone. Dexamethasone was used in 24 (61.5%) cases, in both clinical groups. The overall mortality rate was 10.3%. Pneumonia was diagnosed in 6 patients (15.4%), arthritis in 3 of them (7.7%), and subdural effusion in one patient (2.6%). The data showed a significant statistical difference on the length of hospitalization, and WBC normalization in groups of patients treated with DXM. ***Conclusion:*** The use of DXM as adjunctive therapy in invasive meningococcal disease has a degree of proven benefits and no harmful effects. In fighting this very dangerous and complex infection, even a limited benefit is sufficient to recommend the use of DXM as adjunctive treatment in invasive meningococcal disease.

Keywords: N. meningitidis; sepsis; meningitis; dexamethasone (DXM).

1. INTRODUCTION

Invasive meningococcal disease (IMD) represents a public health problem and is a leading cause of morbidity and mortality worldwide. It can occur as an endemic disease with sporadic cases or epidemics with outbreaks. The clinical spectrum of IMD is broad (1). These clinical aspects of meningococcal infection are a consequence of the close interaction of meningococci with host endothelial cells. A low level of bacteraemia is likely to favour the colonization of brain vessels, leading to bacterial meningitis, whereas the colonization of a large number of vessels by a high number of bacteria is responsible for one of the most severe forms of shock observed (2). Prompt recognition and aggressive early treatment are the only effective measures against IMD (3). Anti-inflammatory adjunctive treatment remains controversial and difficult to assess in patients, especially when it comes to septicaemia with or without meningitis caused by *Neisseria meningitidis* (4). Our earlier study showed that the use of dexamethasone has a limited effect on the outcome of the condition, primarily in re-establishing the functions of the blood–brain barrier in the cases of meningococcal sepsis with meningitis by normalizing the values of CSF sugar in comparison to cases in which no dexamethasone was used (5).

2. PURPOSE

The purpose of this study was to evaluate the effects of dexamethasone as adjunctive therapy in different clinical forms of IMD, and attempt to answer if DXM should be routinely used in the treatment of IMD.

3. METHODS

This non-interventional clinical study was performed on patients with IMD hospitalized at the Department of Infectious Diseases, University Clinical Centre in Pristina, from 2001 to 2016. IMD is identified as bacteraemia with or without meningitis, caused by *Neisseria meningitidis*, confirmed either by blood culture, CSF culture, Latex agglutination, or

direct microscopic identification of the pathogen. Cases with no etiological confirmation but with typical skin petechial haemorrhages were also included in the study. A wide range of information was collected including demographic data, the time of onset of the disease, time of hospitalization and discharge, and diagnostic evaluation. Cases were divided in two groups:

- Cases with meningococcal sepsis and CNS affection, and
- Cases with meningococcal sepsis and no affection of the CNS.

Both groups of cases with meningococcal sepsis, with and without meningitis, were treated with dexamethasone, 0.15mg/kg, q6h, for 4 days, as adjunctive treatment. Cases with meningococcal sepsis not treated with dexamethasone were used as the control group. SPSS was used for processing of the statistical data. P values <0.05 were considered significant.

4. RESULTS

Thirty-nine patients with invasive meningococcal disease were identified during the period of this follow up study. Females predominated with 25 cases (64.1%), and the median age of the patients was 4.9 (0 – 43) years old. Most of the cases, 27 of them (69.3%) were from 0 – 4 years old. Patients were hospitalised ≤ 24 hours after the onset of first symptoms. In 29 (74.4%) cases, the meningococcal sepsis was accompanied with meningitis. Dexamethasone, as adjunctive treatment, was used in 24 (61.5%) cases (18 cases with sepsis and meningitis, and in 6 cases with sepsis and no CNS affection). The median time of hospitalization was 19.62 (1 – 45) days. There were four deaths (10.3%), all of which occurred on the first 24 hours of hospitalization and were related to septicaemia with cardiovascular and coagulation disturbances. The etiological diagnosis was made in 28 (71.7%) cases. Pneumonia was diagnosed in 6 patients (15.4%), arthritis in 3 of them (7.7%), and subdural effusion in one patient (2.6%).

Compared data between different groups of patients (sepsis with and without meningitis, treated or not with dexamethasone) showed statistical differences between different clinical forms of invasive meningococcal disease only on the length of hospitalization, highlighting the positive effects of DXM in the studied groups where DXM was used (Table 1).

Several data taken on different time periods (separated by 5 -7 days each) for different laboratory variables (ESR, WBC, CSF cells, CSF glucose and CSF proteins)

Variable	S+M+ DXM+	S+M+ DXM-	P	S+M- DXM+	S+M- DXM-	P
Cases/nr	20	10		4	5	
Age/years	5.9 (0–43)	5.5 (2–12)	0.237	2.25 (0-6)	1.2 (0–3)	0.53
Male / Female	8/12	5/4		2/3	0/5	
Hosp/days	18.7 ± 20.0	19.9 ± 4.7	0.02	10.5 ± 11.2	14.4 ± 5.5	0.01
ESR 1/mm/h	31.0 ± 26.7	20.4 ± 17.9	0.39	21.2 ±21.1	21.7± 19.8	0.54
ESR 2	39.2 ± 25.5	39.5 ± 32.9	0.3	50	48.0 ± 17.0	
ESR 3	35.3 ±19.9	24.3 ±9.9	0.09	40	20.7 ± 21.1	
WBC 1/x10^9/L	22.6 ± 9.9	20.3 ± 16.8	0.4	14.6 ± 6.4	12.9±2.1	0.37
WBC 2	14.9 ± 7.2	7.6 ± 2.6	0.19	11.6 ± 3.5	5.2±2.6	0.39
WBC 3	7.3 ±2.1	8. 4 ± 3.0	0.16	8	10.3 ±3.5	
Gran 1/%	75.7 ±12.4	75.5 ±5.9	0.12	66.3 ± 6.7	57.4 ± 8.9	0.91
Gran 2	68.4 ± 12.5	59.0 ± 12.1	0.16	77.0±12.7	46.5 ± 12.3	
Gran 3	60.7 ± 10.2	55.1 ± 18.3	1.76	70.0 ± 3.5	41.5 ± 11.5	
CSF 1/cells/ml	5436 ± 4826	2425 ± 4146	0.05			
CSF 2	610 ± 848	616 ±934	0.99			
CSF 3	26 ± 29	29 ± 25	0.63			
CSF Gluc1/mmol/L	2.9 ± 1.53	3.77 ± 1.03	0.07			
CSF Gluc 2	3.62 ± 0.66	3.2 ± 0.52	0.21			
CSF Gluc 3	2.94 ± 0.52	2.57 ± 0.99	0.99			
CSF Prot 1/mg/ml	1.91 ± 2.57	1.77 ± 2.48	0.63			
CSF Prot 2	0.69 ± 0.55	0.59 ± 0.23	0.47			
CSF Prot 3	0.43 ± 0.34	0.52 ± 0.12	0.4			

Table 1. Base-line data on four different groups of patients with IMD. (S: sepsis; M: meningitis, DXM+: treated with dexamethasone, DXM-: not treated with dexamethasone)

Variables (Mean)	(I)	(J)	Mean Diff. (I–J)	Std. Error	Sig	95% Conf. Int.	
						Low	Upp
ESR 2	M+D+	M+D-	-7.062	14.789	0.722	-55.361	41.237
ESR 3	M+D+	M+D-	6.795	12.114	0.599	-24.345	37.936
WBC 2	M+D+	M+D-	5.579	5.14	0.306	-6.049	17.207
WBC 3	M+D+	M+D-	-1.537	1.8	0.416	-5.609	2.536
CSF cells 2	M+D+	M+D-	-246.266	576.726	0.676	-1492.675	999.675
CSF cells 3	M+D+	M+D-	-4.051	17.345	0.819	-41.522	33.419
CSF Gluc 2	M+D+	M+D-	-0.176	0.378	0.659	-1.101	0.75
CSF Gluc 3	M+D+	M+D-	0.115	0.377	0.771	-0.807	1.037
CSF Prot 2	M+D+	M+D-	0.105	0.209	0.649	-0.559	0.769
CSF Prot 3	M+D+	M+D-	0.058	0.202	0.794	-0.701	0.586

Table 2. Pairwise comparisons of different IMD laboratory variables. (S – sepsis; M – meningitis; D – dexamethasone, M+D+: sepsis with meningitis treated with dexamethasone; M+D-: sepsis with meningitis not treated with dexamethasone)

Variances		Sum of Squares	df	Mean Square	F	Sig.
ESR 1	BG	791.231	1	791.231	1.47	0.233
	WG	19918.358	37	538.334		
	Total	17268.618	20			
ESR2	BG	15.766	1	15.766	0.26	0.875
	WG	9240.47	15	616.031		
	Total	9256.235	16			
ESR3	BG	469.444	1	469.444	1.498	0.239
	WG	9240.47	15	616.031		
	Total	9256.235	16			
WBC1	BG	125.873	1	125.873	0.931	0.341
	WG	4869.461	36	313.462		
	Total	5484.334	37			
WBC2	BG	285.153	1	285.153	9.83	0.006
	WG	522.169	18	29.009		
	Total	807.322	19			
WBC3	BG	12.581	1	12.581	2.073	0.166
	WG	115.317	19	6.069		
	Total	127.898	20			
CSF cells1	BG	88100242.6	1	88100242.6	4.486	0.042
	WG	667759894	34	19639996.9		
	Total	7555860137	35			
CSF cells2	BG	15930.449	1	15930.449	0.22	0.884
	WG	15315883.5	21	729327.784		
	Total	15331813.9	22			
CSF cells3	BG	36.75	1	36.75	0.47	0.832
	WG	11061	14	790.071		
	Total	11097.75	15			
CSF Gluc1	BG	3.497	1	3.497	2.043	0.163
	WG	86.922	30	2.483		
	Total	126.763	31			
CSF Gluc2	BG	0.404	1	0.404	1.035	0.323
	WG	6.64	17	0.391		
	Total	7.044	18			
CSF Gluc3	BG	0.335	1	0.335	0.891	0.362
	WG	4.878	13	0.375		
	Total	5.212	14			
CSF Prot1	BG	1.663	1	1.663	0.294	0.593
	WG	124.394	22	5.654		
	Total	126.058	23			
CSF Prot2	BG	0.036	1	0.036	0.24	0.63
	WG	2.727	18	0.152		
	Total	2.764	19			
CSF Prot3	BG	0.019	1	0.019	0.193	0.668
	WG	1.204	12	0.1		
	Total	1.224	13			

Table 3. IMD laboratory data compared only on the basis of treatment with DXM. (BG-between groups, WG-within groups)

were compared between groups of patients with clinical form of sepsis with meningitis, depending on the type of treatment, with or without DXM as adjunctive therapy (Table 2). A comparison of each of the parameter values between two groups (DXM or no DXM) showed no significant statistical difference between them.

The available data was compared, depending on the treatment with DXM as adjunctive therapy, without regard to the clinical form of IMD (sepsis alone, or sepsis with meningitis), prior to introduction of the DXM, after the finishing of the treatment with DXM (day 5) and again 5-7 days after (Table 3). These data show the significant difference between two groups of patients, on the second measurement of the WBC (P=0.006), by faster normalization of the WBC count in the group of cases treated with DXM.

Presentation of the same data as figures show a more positive outcome of various variables from the DXM use, although statistical significance was not reached for most of them (Figures 1-4).

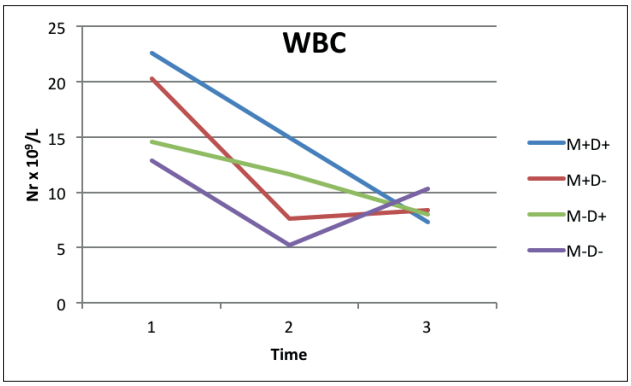

Figure 1. Correlation between WBC and the use of DXM as adjunctive treatment in different clinical forms of IMD. (M+: sepsis with meningitis, M-: sepsis with no meningitis, D+: treated with dexamethasone, D-: no dexamethasone used as adjunctive treatment)

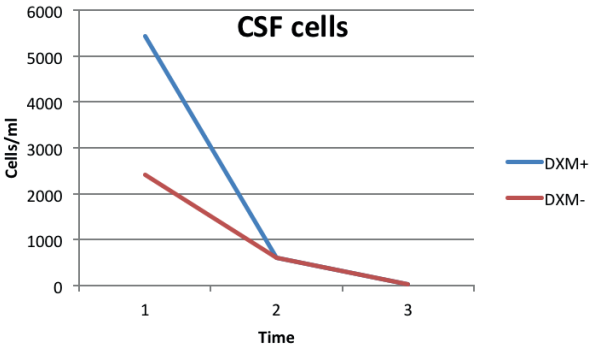

Figure 2. Correlation between CSF cell elements and the use of DXM as adjunctive treatment (DXM+: with dexamethasone; DXM-: without dexamethasone)

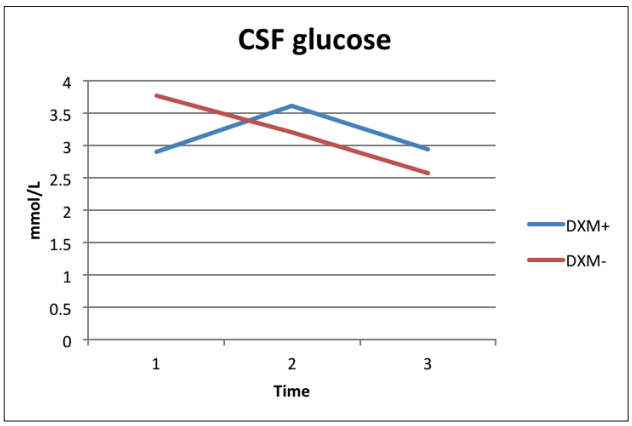

Figure 3. Correlation between CSF glucose and the use of DXM as adjunctive treatment. (DXM+: with dexamethasone; DXM-: without dexamethasone)

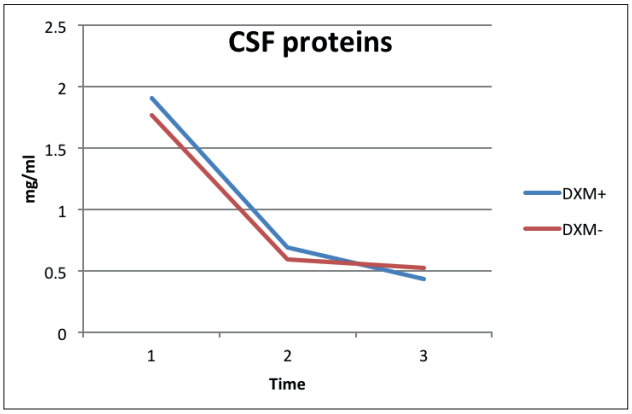

Figure 4. Correlation between CSF proteins and the use of DXM as adjunctive treatment. (DXM+: with dexamethasone; DXM-: without dexamethasone)

5. DISCUSSION

Earlier studies were more restrictive and critical regarding the use of DXM as adjunctive therapy in the treatment of IMD, and those were based on the lack of proof regarding clinical or laboratory efficacy of DXM in meningococcal meningitis (6-10), or in prevention of neurological and systemic meningococcal meningitis complications (11). The later studies on DXM as adjunctive therapy in meningococcal infections are more favourable regarding its use, stating that DXM in meningococcal meningitis has shown consistency and degree of benefits (12-14), it is not associated with any harm, and the rates of early complications like arthritis are lower (15, 16). Further more, studies on the impact of DXM on experimental meningococcal sepsis in mice showed a beneficial effect of DXM in addition to an appropriate antibiotic therapy, which is most likely due to the reduction of inflammatory response by an early induction of IL-10 cytokine (4). Our earlier study on the effect of DXM on the course of invasive meningococcal disease showed the limited effect of DXM during the days of administration in cases of sepsis with meningitis, by normalizing the values of CSF glucose and protein; showing the positive effect on the normalization of the brain barrier permeability (5). This follow up study is in correlation with our earlier study, as well as with the studies that stated positive effects from DXM use on the course of invasive meningococcal disease (5, 12-16). Most of the analysed variables in our study show more favourable outcome in patients treated with DXM, although statistical significance was not reached, except for hospitalization length and WBC (at the end of DXM treatment).

Pneumonia was diagnosed in 6 patients (15.4%), arthritis in 3 of them (7.7%), and subdural effusion in one patient (2.6%). Other studies report pneumonia as end organ manifestation of IMD in 5-15% of all cases (17), arthritis in 7.5% of the patients (18), while 5% of infections with *N. meningitidis* in infants were complicated by subdural effusion (19, 20).

The study had some limitations. We acknowledge the fact that there is a small number of cases in this study, limited lab variables collected, as well as the drop of a number of cases in terms of evaluation during the time of hospitalization, are the major limitations in properly assessing the effect of DXM use as adjunctive treatment of the invasive meningococcal disease. Another limitation is the lacks of long term follow up regarding the neurological sequels, such as hearing loss and cognitive difficulties; which may be diagnosed post-discharged. Other studies have faced similar limitations as well (7). The study could not evaluate the effect of DXM on the death rate of IMD because all four cases died on the first day of hospitalization.

The study showed a rapid decrease in the number of cases of invasive meningococcal disease hospitalized in our department compared with a previous 10-year studied period (147 patients) (5), which needs further epidemiological and social evaluation.

6. CONCLUSION

The results show that the use of DXM as adjunctive therapy in invasive meningococcal disease is with a degree of proven benefits and no proven harmful effect. In fighting this very dangerous and complex infection, even a limited benefit is sufficient to recommend the use of DXM as adjunctive treatment in invasive meningococcal disease.

- **Funding:** No funding was received for this study.
- **Conflict of Interest:** The authors declare that they have no conflict of interest.
- **Ethical approval:** For this type of study formal consent is not required.
- **Informed consent:** Informed consent was obtained from all individual participants included in the study.

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