ORIGINAL PAPER

Dexamethasone as adjuvant therapy in the treatment of invasive meningococcal diseases

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Purpose: With this study we want to evaluate the role of dexamethasone adjuvant treatment in different clinical forms of invasive meningococcal diseases. **Work Methods:** This was a randomized, open label trial that was conducted in 147 individuals with meningococcal sepsis. All of the cases have been divided in two groups: (1) Cases with meningococcal disease and CNS infection, and (2) Cases with meningococcal disease and no affection of the CNS. Cases from both groups were treated with dexamethasone, 0.15 mg/kg, every 6 h, for 4(four) days, as adjuvant therapy. Cases which were not treated with dexamethasone were used as control group. **Work Results:** From overall number of cases**,** in 130 of them, the meningococcal disease was accompanied with meningitis; in other 17 cases only signs of sepsis were present. In both clinical forms, the dexamethasone was used in 92 cases. The higher mortality rate is registered among the cases without meningitis, 17.65%, compared with 6.92% which is registered among cases with meningitis. The overall mortality rate among all cases was 8.2%. The significant difference was recorded only on CSF sugar level between two groups (treated or not with dexamethasone) on the day 1-4 of the hospitalization. **Discussion**: Our epidemiological data are in correlation with data from other epidemiological studies. Most of the cases 69.4%, were more than 12 hours sick at home before the hospitalization, 7.5 % of cases were hospitalized within 12 hours from the onset of the diseases, while 23.1% of cases data are missing. This is in correlation with similar data from other studies. **Conclusion:** Dexamethasone has a limited effect on outcome of the invasive meningococcal disease. Dexamethasone had some effect only during the days of administration in cases with clinical form of sepsis with meningitis, by normalizing the values of CSF sugar earlier. Key words: dexamethasone, meningococcal sepsis, therapy

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1. INTRODUCTION

Neisseria meningitidis, an encapsulated, oxidase positive, Gram-negative coccus, is solely a human pathogen [1,2,3]. It is an etiological cause of meningococcal disease. Meningococci may cause different clinical syndromes, but in clinical practice, meningitis or sepsis, or more often in combination of both, is the most life threatening clinical conditions (1).

Meningococcal disease remains an important health problem that occurs worldwide as endemic infection. The incidence of meningococcal disease varies from 1-3/100.000 in most industrialized nations to 10-25/100.000 in some third-world countries, [1]. During epidemics peaks, the disease incidence may approach 1000/100.000 inhabitants, (1,2).

At least four conditions have to be met before the invasive disease can occur: exposure to a pathogenic strain, colonization of the naso-oropharyngeal mucosa, passage through that mucosa, and survival of the meningococcus in the bloodstream (3,4). Once viable meningococci have reached the bloodstream, different manifestation can develop (1,2,5). The most common presentation in Europe is with features of both meningitis and septicemia (around 60%). One-fifth presents with features of meningitis alone, and one –quarter present with septicemia alone (2).

Antibiotics do not halt the meningeal inflammatory processes immediately. Some studies show even a transient worsening of the inflammation after antibiotic administration, possibly due to the enhancement of endotoxin release. In sepsis the antibiotic-induced endotoxin release has never been observed (1). A possible explanation for this discrepancy is that the clearance of endotoxin and/or the regulation of the production of cytokines in the CSF differ from that in the bloodstream.

In population based studies, including all ages, the overall mortality for meningococcal disease was found to be around 7%. The reported mortality of children who were admitted to intensive care with meningococcal disease varies between 14.5% and 35% (4). The mortality of meningococcal septicemia is consistently higher than the mortality from meningococcal meningitis. When features of both septicemia and meningitis are present, the mortality rate is intermediate (2).

Aggressively early treatment of meningococcal disease can reduce mortality. Routine use of steroids remains

controversial (6). New treatments continue to be evaluated, but none has so far proven to be effective in further reducing morbidity or mortality. Simple, timely therapeutic maneuvers may greatly improve the prospects for survival (6).

The aim of a study is to evaluate the role of dexamethasone adjuvant treatment in different clinical forms of invasive meningococcal diseases.

2. METHODS

This was a randomized, prospective, open label trial that was conducted in individuals with meningococcal sepsis treated at the Department of Infectious Diseases, University Clinical Center in Prishtina in a five year time period.

Meningococcal sepsis (MS) is identified as bacteriemia with or without meningitis, caused by *Neisseria meningitides* isolated by blood and/or CSF culture, or confirmed by latex agglutination or on direct microscopic examination on blood and/or CSF. Cases with no etiological confirmation but with clinical picture of sepsis with skin petechial hemorrhages are also included in this study.

All of the cases have been divided in two groups:

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

Cases from both groups were treated with dexamethasone, 0.15 mg/kg, every 6 h, for 4(four) days, as adjuvant therapy. The first dose of dexamethasone was given up to 30 minutes before the initiation of the antibiotic treatment. Cases from both groups which were not treated with dexamethasone are used as control group.

The comparing of the continuous variables between two groups and subgroups is done by using the one way variant analysis –ANOVA. The values $p < 0.05$ are considered significant.

3. RESULTS

The etiological diagnosis was made based on direct microscopic examination of the CSF (52/112–44.07%), latex agglutination test of the CSF (66/88–77.0 %), CSF culture (5/9- 55. 55%). The number of positive blood cultures was very low, only about 10%, (12/114).

Males predominated with 87 cases (59.18%), the median age was 4.76 years old (0 – 33) (males 4.05, females 5.62, (Table 1).

Age-group		F		M			
		N	%	N	%	N	%
<=2		23	38.33	42	48.28	65	44.22
4-Mar		12	20	18	20.69	30	20.41
8-May		13	21.67	11	12.64	24	16.33
12-Sep		4	6.67	9	10.34	13	8.84
>12		8	13.33	7	8.05	15	10.2
Total	N	60	100	87	100	147	100
	%	40.82	-	59.18	-	100	-

Table 1. Cases according to age group and gender

Diagnosis			Dexamethasone		Total
			Yes	No	
	All cases	N	84 (M49 F35)	46 (M25 F21)	130
Sepsis with meningitis		%	64.60%	35.40%	100
	Exitus	N	7 (M4 F3)	2 (M2 F0)	9
		%	8.33	4.34	6.92
	All cases	N	8 (M6 F2)	9 (M7 F2)	17
Sepsis without meningitis		%	47.00%	53.00%	100
	Exitus	N	3 (M1 F2)	0	3
		%	37.5	0	17.64
Total	All cases	N	92 (M55 F37)	55 (M32 F23)	147
	Exitus	N	10 (M5 F5)	2 (M2 F0)	12
		%	10.86	3.63	8.16

Table 2. Mortality rate according to clinical form and treatment

Group cases	Nr.	Ave.	SD	SEM	Med.	Lower 95%CI	Upper 95%CI	Min -Max
First day D+	24	1.3	0.5	0.1	1.3	1	1.5	0.2–1.9
1- 4 days D+	20	3.8	1.3	0.3	3.6	3.2	4.4	1.4–6.3
5 – 8 days D+	15	3.3	1.2	0.3	3.1	2.6	4	1.5–5.7
9+ days D+	6	2.5	0.6	0.3	2.6	1.8	3.1	1.7–3.3
First day D-	15	1.1	0.5	0.1	1	0.8	1.4	0.3–2.1
1- 4 days D-	12	2.7	0.7	0.2	2.7	2.2	3.1	1.4–3.6
5 – 8 days D-	10	2.4	0.5	0.2	2.6	2	2.8	1.5–3
9+ days D-	7	2.5	0.5	0.2	2.5	2	3	1.9–3.6

Table 3. CSF sugar data

In 130 (88.40%) of the cases, the meningococcal disease was accompanied with meningitis, in other 17 (11.60%) cases only signs of sepsis were present.

In 84/130 (64.6%) cases of meningococcal disease with meningitis and in 8/17 of cases with meningococcal disease without meningitis the dexamethasone was used. From overall 147 cases, no matter of the clinical form, the dexamethasone was used in 92 cases (62.6%), and in other 55 cases (47.4%) the dexamethasone was not used, (Table 2).

The normalization of CSF sugar and proteins was analyzed for different group of cases, on the day of hospitalization (day 0), day 1-4, day 5-8, and day 9 and more of hospitalization. Only the cases with pathological values of the CSF sugar and proteins on the day of hospitalization are included.

The median values of the CSF sugar for the group of cases with sepsis and meningitis treated with dexamethasone, were: on the day of hospitalization 1.3 mmol/L, on days 1-4 , 3.8 mmol/L, on days 5-8 3.3 mmol/L and on days 9+ 2.5 mmol/L.

The medial values of the CSF sugar for the group of cases with sepsis and meningitis but not treated with dexamethasone were: on the day of hospitalization was 1.1 mmol/L, on days 1-4, 2.7 mmol/L, on days 5-8, 2.4 mmol/L and on days 9+, 2.5 mmol/L, (Table 3).

The cross comparing of the data show significant difference on CSF sugar level between two groups (treated

or not with dexamethsaone) on the day 1-4 of the hospitalization ($p<0.05$ ANOVA), (Table 4).

The median values of the CSF proteins for the group of cases with sepsis and meningitis treated with dexamethasone were: on the day of hospitalization 2.1g/L, on days 1-4, 0.9 g/L, on days 5-8, 0.7 g/L and on days 9+, 0.5 g/L.

The medial values of the CSF proteins for the group of cases with sepsis and meningitis but not treated with dexamethasone were: on the day of hospitalization was 2.0 g/L, on days 1-4, 0.6 g/L, on days 5-8, 0.5 g/L and on days 9+, 0.4 g/L.

The cross comparing of the data show no significant difference on CSF proteins level between two groups (treated or not with dexamethsaone ($p>0.05$ ANOVA), (Table 5).

Compare	Medium difference	t	P value
0 D+ vs 0 D-	0.129	0.46	p > 0.05
1-4 D+ vs 1-4 D-	1.128	3.622	p < 0.05
5-8 D+ vs 5-8 D-	0.883	2.536	p > 0.05
9+ D+ vs 9+ D-	-0.028	0.06	p > 0.05

Table 4. Compare of CSF sugar data according to the dexamethasone treatment

Group cases	Nr	Average	SD	SEM	Med	Lower 95%CI	Upper 95%CI	Min-Max
First day D-	29	2.1	1.2	0.2	0.9	1.7	2.6	0.6-5
1-4 days D-	26	0.9	0.3	0.07	0.8	0.7	1	0.4-1.9
5 -8 days D-	30	0.7	0.4	0.6	0.6	0.6	0.9	0.3-1.2
9+ days D-	13	0.5	0.3	0.3	0.4	0.3	0.6	0.1-1.2
First day D+	37	2	1.2	0.2	2	1.6	2.4	0.5-5
1- 4 days D+	26	0.6	0.3	0.05	0.6	0.5	0.7	0.1-1.5
5- 8 days D+	17	0.5	0.2	0.04	0.4	0.4	0.6	0.2-0.9
9+days D+	12	0.4	0.1	0.04	0.5	0.4	0.5	0.3-0.7

Table 5. CSF proteins data

4. DISCUSSION

Epidemiological data regarding our cases are in correlation with data from other epidemiological studies (1, 2,3,10, 11, 12). The incidence of the meningococcal diseases in our trial is higher among younger age – groups, average age 4.76 and younger than 2 years old 44.33 % of all cases, and among the families with more than 4 family members (70%), which tend to be the families from the rural areas.

The latex agglutination test of the CSF and direct microscopic examination of the CSF were the most often diagnostic procedures used in terms of making etiological diagnosis. The positive results (77% and 44.07% respectively) of these procedures are presented to be an auxiliary diagnostic methods, rapid and easy practicable for the diagnosis of meningococcal disease (17).

The beginning of the sepsis in all our cases was abrupt, with fast progressive development in all the cases (13, 14, 15). Fever, vomitus, petechial bleeding, positive meningeal sings, and somnolence were the most frequent initial symptoms and signs in our cases with meningococcal sepsis. Most of the cases 69.4%, were more than 12 hours sick at home before the hospitalization, 7.5 % of cases were hospitalized within 12 hours from the onset of the diseases, while 23.1% of cases data are missing. This is in correlation with similar data from other studies, [16,20].

In 130 (88.40%) of the cases, the sepsis was accompanied with meningitis, in other 17 (11.60%) cases of sepsis, the meningitis didn't developed. The mortality rate for cases with meningococcal sepsis and meningitis was 6.92%, while in those cases in which the meningitis didn't developed this rate was 17.64%, showing the development of the meningitis during the meningococcal sepsis is important predictive sign in terms of fatal outcome.

Dexamethasone decreases brain edema, intracranial pressure and increases cerebral pressure to prevent regional hypoxia and focal ischemia of brain tissue along with reduction of inflammatory response in subarachnoid space in bacterial meningitis (6,7). In meningococcal meningitis, statistically significant benefit has not been demonstrated for any outcome, but there is also no evidence of a detrimental effect (19,20).

5. CONCLUSION

The use of dexamethasone has a limited effect on outcome of the meningococcal sepsis.

Dexamethasone had some effect only during the days of administration in cases with clinical form of sepsis with meningitis, by normalizing the values of CSF sugar earlier, showing the positive effect on the normalization of the brain barrier permeability.

Dexamethasone decreases brain edema, intracranial pressure and increases cerebral pressure to prevent regional hypoxia and focal ischemia of brain tissue.

The eventual effect of dexamathasone on the mortality was not possible to evaluate, because of the fact that all the cases in this study terminated with death in the first 24 hours after the hospitalization.

Abbreviations:

CSF = Cerebrospinal fluid

MS = Meningococcal sepsis

CNS = Central nervous system

D+ = treated with dexamethsaone

D–= not treated with dexamethasone

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