Serum and cerebrospinal fluid levels of Ceftriaxone in Children with viral meningoencephalitis and Clinical Implications

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Abstract

Central nervous system infections are common pediatric emergencies with significant morbidity and mortality. While specific infectious etiological agent being investigated and established which takes time and technical expertise, often empirical anti bacterials are started. Escalation and de-escalation follow depending on the microbiological workup, culture positivity. Knowledge of pharmacokinetic/pharmacodynamic principles of commonly used antibacterial drugs helps selection, proper dosage and duration and enables antibacterial stewardship. Different age groups of children have predictable pattern of infectious agents on epidemiological and previous microbiological work up. Forty children with aseptic meningitis/ viral meningoencephalitis with median age 15 months (95% CI 6.7 to 31.9 months) and range 1 month to 11 years are studied. There is no significant difference in the proportion of males 62.5% (95% CI 45.8 to 77.3%) and females 37.5% (95% CI 22.7 to 54.2%). All the children received Ceftriaxone I.V in a dose of 50 mg/kg 12th hourly (100 mg/kg/d). The serum and CSF Ceftriaxone levels observed are after a mean number of doses of 2.2±0.9 (range: 1 to 4 doses).

Keywords: aseptic meningitis, CSF analysis, serum and CSF ceftriaxone levels.

INTRODUCTION

Central Nervous System infections in children are common medical emergencies with significant morbidity, mortality and residual sequalae.1 Global burden of disease network (WHO) estimated that in 2010 meningitis caused approximately 422,900 deaths and encephalitis, 143,500 deaths.2 The precise epidemiology of CNS infections differs by age ,geography and in many children determining an exact microbiological diagnosis is challenging particularly in resource limited settings. A recent multinational study of community acquired CNS infections found that 8.8% people died, and 18.5% were left with sequelae. It is often difficult for a treating pediatrician in such emergency situations to differentiate between bacterial meningitis, aseptic meningitis and viral meningoencephalitis.

Unsurprisingly treatment protocols in such situations include empirical antibiotic regimens with antibiotics like ceftriaxone, cefotaxime, ampicillin and amikacin and other antibiotics.

Ceftriaxone is one of the important anti bacterial drugs used in children immediately after clinical suspicion of meningoencephalitis. In standard practice it is administered intra venously in a dose of 50mg/kg every 12 hours or 100 mg/kg once daily. The drug levels reaching in CSF and brain tissue have to be appropriate, reaching MBC levels against common bacterial organisms causing meningoencephalitis in children, to effectively cure the child if there is a bacterial etiology.3

Ceftriaxone is a third-generation cephalosporin antibiotic, it has broad spectrum activity against Gram-positive and Gram-negative bacteria. Pharmacokinetic details of ceftriaxone are metabolism negligible, half-life 5.8 to 8.7 hours and excretion 33-67% renal and 35-45% biliary route.4

In the clinical background explained above and available laboratory settings, there is a need to use knowledge of a pk/pd model of commonly used antibacterial drugs whenever a child arrives at PICU with a possibility of multiple infectious agents

as cause and treatment fit the needs of this child. Present study is planned to determine the serum and ceftriaxone levels of ceftriaxone, percent of ceftriaxone reaching cerebrospinal fluid in forty children and draw clinical and management implications .

AIMS & OBJECTIVES

1. To study the CSF ceftriaxone levels in children with meningoencephalitis/aseptic meningitis especially penetration of ceftriaxone independently with minimal meningeal inflammation and influence of the disease process.
2. To observe serum free ceftriaxone levels after intravenous administration of ceftriaxone in a dose of 50mg/kg every 12 hours
3. To observe relation between CSF or serum ceftriaxone levels with host characteristics.

SUBJECTS AND METHODS

SAMPLE SIZE

Forty children from age 1month to 12 years with a diagnosis of aseptic meningitis/ viral meningoencephalitis in PICU, Department of Pediatrics, Dr. DY Patil Medical College Hospital &Research Centre, Pune, Maharashtra, India are study subjects.

INCLUSION CRITERIA

1.Children age 1 month to 12 years diagnosed clinically as case of aseptic meningitis/viral meningoencephalitis, and whose parents consented for the study.

EXCLUSION CRITERIA

1. Children with bacterial meningitis
2. Above 12 years
3. Parents not giving consent
4. Children not fit for lumbar puncture
5. Febrile convulsions and epilepsy

In the 40 children with a diagnosis of aseptic meningitis enrolled for the study following clinical and laboratory variables were recorded: age, sex, weight, height, BMI, cerebrospinal fluid analysis – total and differential cell count, protein and sugar estimation in CSF and hemoglobin, serum ceftriaxone levels and CSF ceftriaxone levels.

Statistical analysis done using EpiInfo software.

Venous blood sample collection: Venepuncture done and 3 ml of venous blood collected in sterile tube under aseptic precautions between 31/2 hours to 4 hours after intra venous administration of ceftriaxone dose. Serum separated by centrifuging the blood sample, and stored in eppendroffs tubes, at -20 deg centigrade till analysis.

Serum samples were analysed for ceftriaxone levels in two sessions between 1-2 months after collection.

CSF collection

Lumbar puncture was performed by one of the pediatric residents, under strict aseptic precautions, after obtaining written consent from parents. CSF was collected in 1ml sterile plastic tube, stored at -20 deg till analysis. CSF was collected within 15- 30 minutes of venous blood sample collection in all children.

CSF cell count and analysis done immediately and biochemical analysis done within 2 hours. Serum and CSF ceftriaxone levels were estimated by High Pressure Liquid Chromatography (HPLC)

Technical Details of Ceftriaxone estimation in serum and CSF UV –Visible Spectrophotometer - Elico SL 164; Colorimeter Ensure Biotech Ltd, Hyderabad, India; Centrifuge Remi Motors Ltd, Mumbai, India ;Water bath Thermostatic Biotechnics, India; pH Meter Elico LI 120 ; CycloMixer Remi Equipment Ltd, India Accupippettes (100 µl, 1000 µl) : Himedia Labs Ltd, Mumbai, India, Eppendroff`s tubes Test tubes, Sterile needles & syringes, Lumbar puncture trays

RESULTS & OBSERVATIONS

Table 1. Age & Sex Distribution

AGE GROUP	N	MALE			FEMALE		
		FREQUENCY	PERCENT	95% CI (%)	FREQUENCY	PERCENT	95% CI (%)
0-2	03	3	100	100-	0	0	0-

months				100			70.8
3 – 12 months	17	12	70.6	44-89.7	5	29.4	10.3-56
1year-5years	14	7	50	23-77	7	23	23-77
6-12 years	06	3	50	11.8-88.2	3	50	11.8-88.2
	40	25	62. 5%		15	37.5%	

In the four age groups 0-2 months; 3-12 months; 1year to 5 years and 6 years to 12 years 3, 17, 14 and 6 children are distributed respectively. Boys and girls are equally distributed.

Median weight of age group 0-2 months was 3 kilos (min 2.8, max 3), 3mo-12 mo 6 kilos (min 4, max 9), 1 -5 years 10 (min 6, max 9) 6- 12 years 20.5 kilos (min 15, max 26).

Median recumbent length or height of study subjects in the 4 age groups was 0-2 months 53 cm (min 51 , max 53) , 3months to 12 months infants 66 cm (min 55 max 74), 1 year to 5 year 76 cm(min 63 max 94) and 6 -12 years age group 104 cm (min 83 , max 114)

Mean BMI in age group 0 – 2 months was 10.1± 0.5, 3-12 months 14.7±1.4 , 1 -5 years 17.9 ± 1.4 and 6-12 years was 19.4 ±1.3. The BMI is significantly more in older age group children.

Table 2A: Hemoglobin, CSF parameters & Ceftriaxone levels between Age groups

VARIABLE	AGE GROUPS				Statistical test	Statistics	p-value
	0-2 M (N=3)	B3-12 M (N=17)	1y-5 y M(N=14)	6y -12 y (N=6)			
Hemoglobin (gm/dL) mean±S.D	10.7±0.8	9.7±1.8	10.7±1.2	11.5±1.2	ANOVA	F-stat: 2.55	0.1
CSF TLC Median (range)	15 (7-400)	10 (2-60)	12 (2-180)	33 (2-96)	Kruskal-Wallis test	Kruskal-Wallis H:2.23	0.5
CSF Ploys Median (range)	2 (0-40)	0	0	0	Kruskal-Wallis test	Kruskal-Wallis H: 3.6	0.31
CSF Lymphs Median (range)	98 (60-100)	100 (80-100)	100 (85-100)	100 (98-100)	Kruskal-Wallis test	Kruskal-Wallis H: 3.6	0.31
CSF Protein (mg/dL) Median (range)	63 (45-580)	48 (12-102)	16 (4-100)	35 (4-70)	Kruskal-Wallis test	Kruskal-Wallis H: 7.6	0.06
CSF Sugar (mg/dL) mean±S.D	50.7±11	59.3±11.8	68.8±19.6	62.2±14.1	ANOVA	F-stat: 1.63	0.2
CSF Ceftriaxone (ug/mL) Mean±S.D	5.5±1.1	5.9±0.8	6.2±0.9	5.7±0.6	ANOVA	F-stat: 0.7	0.5
% Serum Ceftriaxone in CSF Mean±S.D	3.9±0.7	4.2±0.6	4.3±0.7	3.8±0.4	ANOVA	F-stat: 1.0	0.4
Serum Ceftriaxone (mg/dL) Median (range)	139.5 (135.5-153.5)	143.7 (129.7-155.4)	140.6 (131.4-188.4)	150.3 (144.3-152.5)	Kruskal-Wallis test	Kruskal-Wallis H: 2.5 Df:3	0.5

Mean hemoglobin in age group 0 – 2 months was 10.6± 0.76, 3-12 months 9.7±1.80, 1 -5 years 10.7 ± 1.25 and 6-12 years was 11.4 ±1.2. The mean hemoglobin is similar in all age groups (Bartlett's chi square 3.2307 df 3, p value 0.35)

Median cell count in cerebrospinal fluid of study subjects in the 4 age groups was 0-2 months 15 cells (min 7 , max 400) , 3months to 12 months infants 10 (min 2 max 60), 1 year to 5 year 12 (min 2 max 180) and 6 -12 years age group 33 cells (min 2 , max 96 ;Bartlett's chi square -44.0076 df 3 and p value 0.0000)

Median protein levels estimation in cerebrospinal fluid of study subjects in the 4 age groups was 0-2 months 63 mg/dl (min 45, max 580) , 3months to 12 months infants 48 mg/dl (min 12 max 102), 1 year to 5 year 16 (min 4 max 100) and 6 -12 years age group 35 mg/dl (min 4 , max 70; Bartlett's Test for Inequality of Population Variances : Bartlett' chi square 57.3741 df =3 p value 0.0000)

Mean sugar levels in CSF in age group 0 – 2 months were 50.6± 11.0, 3-12 months 59.2±11.8, 1 -5 years 68.7 ± 19.5 and 6-12 years was 62.1 ±14.1.(Bartlett's chi square 3.7180 df =3, p value 0.29)

Polymorhs in cerebrospinal fluid of study subjects in the 4 age groups(median values) was 0-2 months 63 mg/dl (min 45 , max 580) , 3months to 12 months infants 48 mg/dl (min 12 max 102), 1 year to 5 year 16 (min 4 max 100) and 6 -12 years age group 35 mg/dl (min 4 , max 70; Bartlett's Test for Inequality of Population Variances : Bartlett' chi square 57.3741 df =3 p value 0.0000)

Lymphocytes in cerebrospinal fluid of study subjects in the 4 age groups (median values)was 0-2 months 98(min 60, max 100) , 3months to 12 months infants 100 (min 80 max 100), 1 year to 5 year 100(min 85 max 100) and 6 -12 years age group 100 (min 98 , max 100; Bartlett's Test for Inequality of Population Variances : Bartlett' chi square 36.6447 df =3 p value 0.0000. Lymphocytic pleocytosis is observed in all 4 age groups suggesting the viral etiology.

CSF parameters are similar among age groups.

Table 2B. Summaries of Ceftriaxone levels in CSF and serum in different age groups (n=40 total)

Age group (n)	Mean CSF ceftriaxone levels (ug/mL)	% of Serum Ceftriaxone in CSF	Median Serum Ceftriaxone levels (ug/mL)
0-2 months (3)	5.5±1.14	3.8±0.66	139.5 (135.5-153.5)
3-12 months (17)	5.9±0.85	4.1±0.60	143.7 (199.7-155.4)
1-5 years (14)	6.1±0.92	4.2±0.65	140.5 (131.4-188.3)
6-12 years (6)	5.7±0.62	3.8±0.40	150.3 (144.3-152.5)

Mean CSF ceftriaxone levels were between 5.5±1.14 ug/ml to 6.1±0.92 ug/ml and there is no influence of age. Similar levels of ceftriaxone found id CSF of all age groups.

3.8±0.40 to 4.2±0.65 percent of ceftriaxone reached CSF in different age groups. Similar levels achieved in all age groups.

Serum ceftriaxone levels in different age groups was similar and 139.5 (135.5-153.5) ug/ml to 150.3 (144.3-152.5)

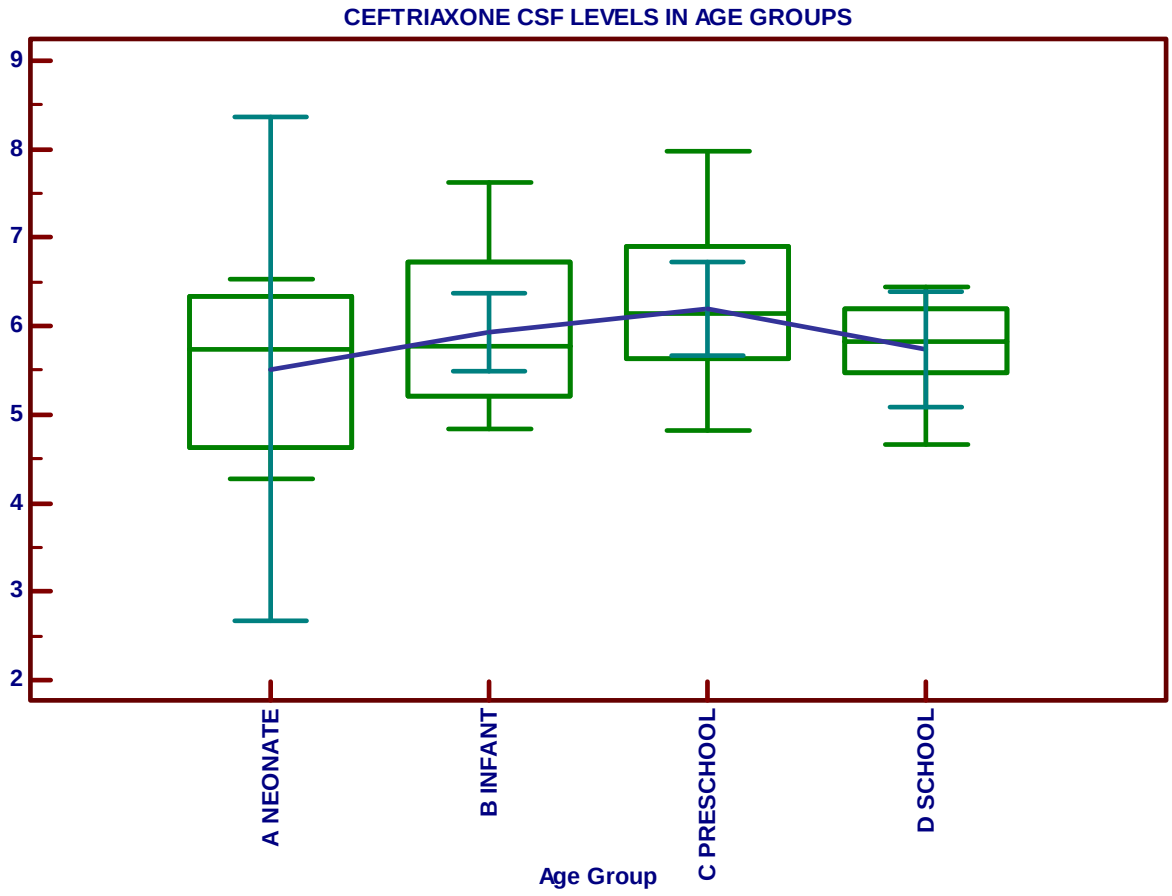


Figure 1: CSF Ceftriaxone levels in different Age Groups

Mean CSF Ceftriaxone levels are not different between age groups.

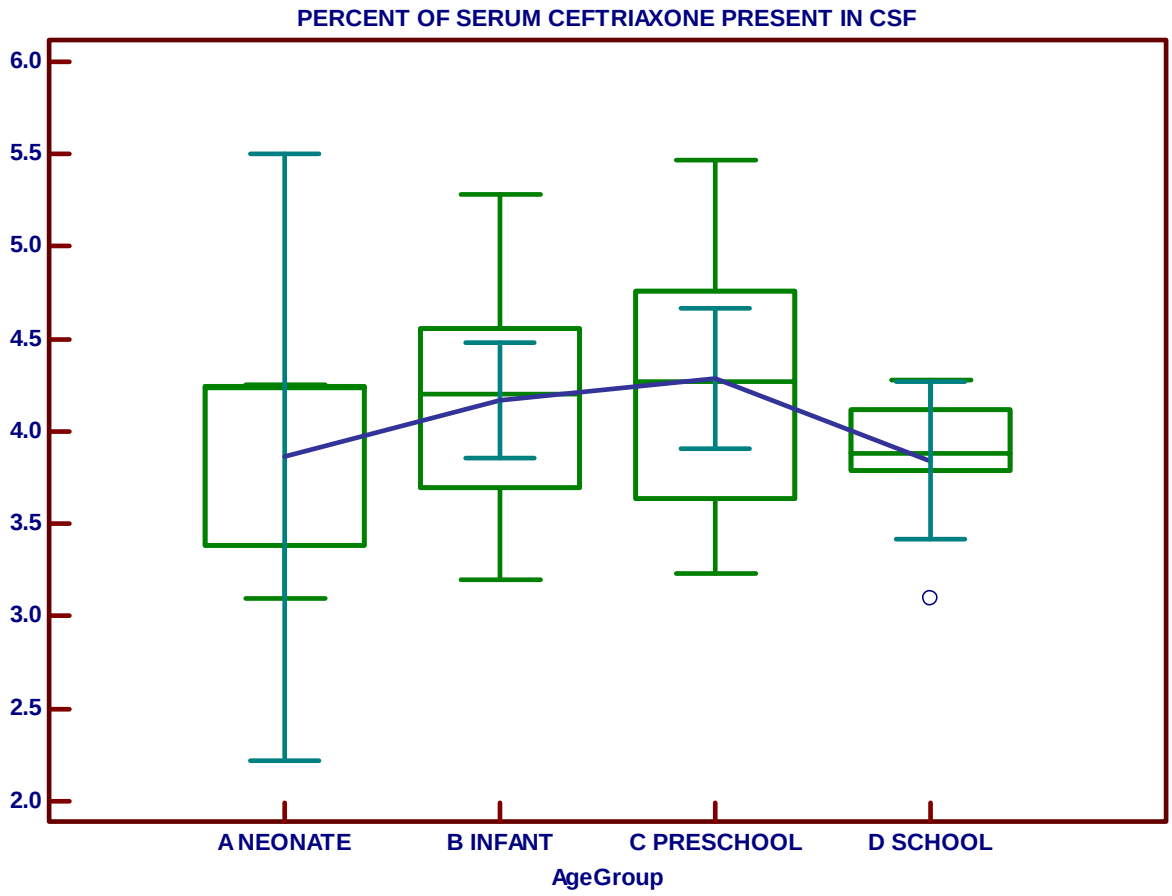


Figure 2: Percent of Serum Ceftriaxone present in CSF in different Age Groups

The percentage of serum Ceftriaxone reaching CSF is also not different between age groups

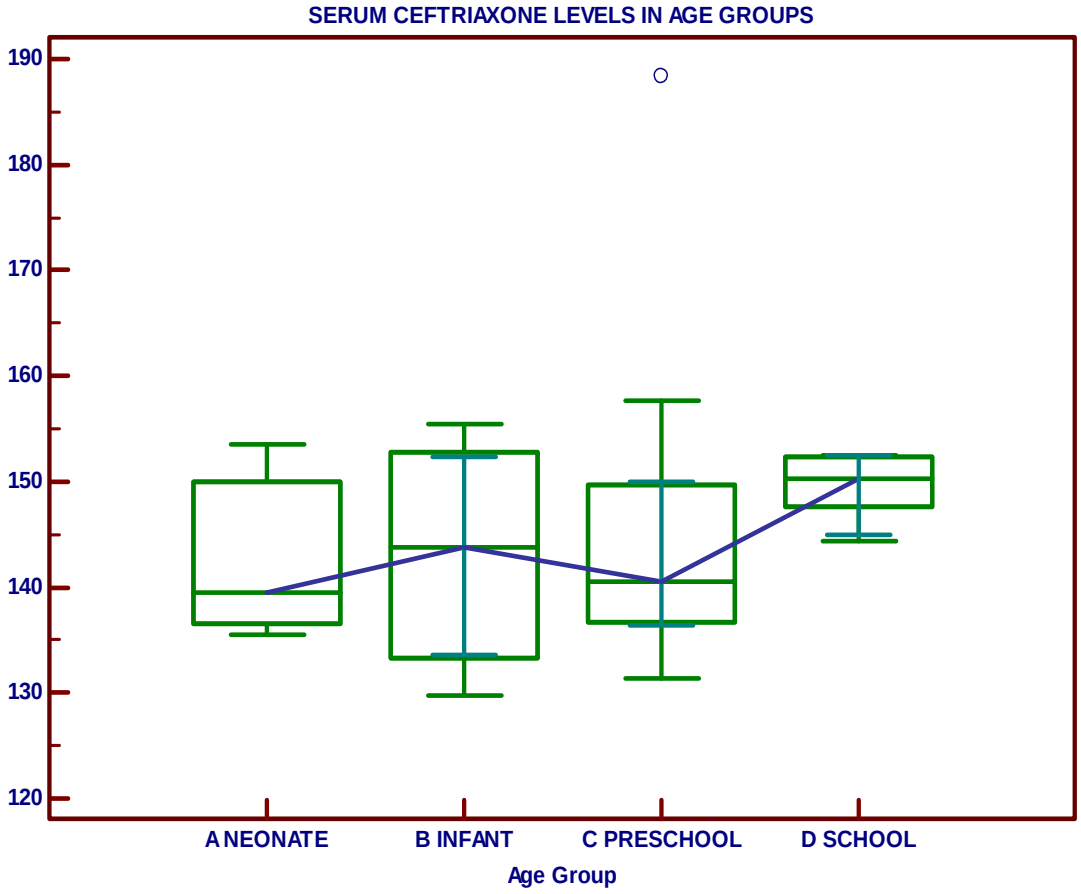


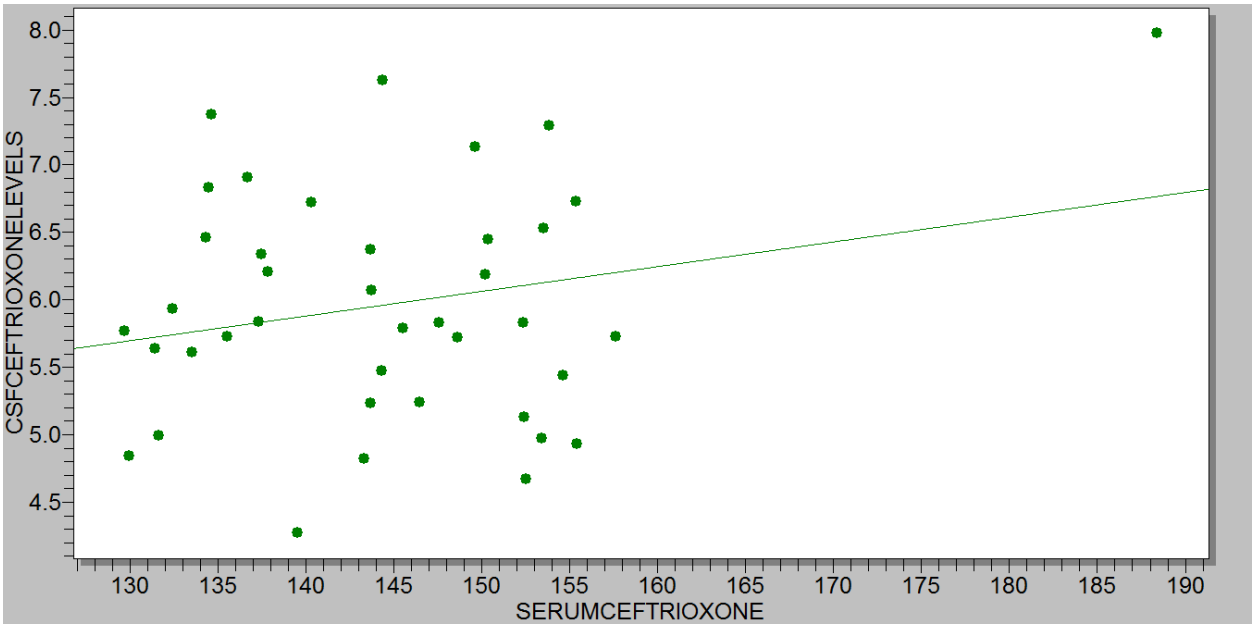
Fig 3 Serum Ceftriaxone levels in different Age Groups

Table 3: Correlation between Ceftriaxone level and Patient & CSF Characteristics

		Age	CSF Ceftriaxone	CSF Serum %	Serum Ceftriaxone	No. Doses Given	Duration Therapy	Height	Weight	BMI	Hemoglobin	CSF Proteins	CSF Sugar	CSF Cells	CSF Polymorphs	CSF Lymphocytes
CSF Ceftriaxone	R	-.044	1.000	.879**	.055	.118	.118	-.133	-.087	-.050	.009	.032	.023	.123	-.042	.042
	P	.788	.	.000	.737	.469	.469	.413	.593	.761	.955	.845	.886	.451	.795	.795
	N	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
CSF Serum %	R	-.170	.879**	1.000	-.373*	.101	.101	-.273	-.213	-.128	-.068	-.071	.155	-.026	-.047	.047
	P	.294	.000	.	.018	.534	.534	.089	.186	.430	.677	.662	.339	.873	.775	.775
	N	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
Serum Ceftriaxone	R	.242	.055	-.373*	1.000	.010	.010	.252	.220	.147	.157	.101	-.144	.109	-.146	.146
	P	.132	.737	.018	.	.949	.949	.117	.172	.365	.333	.536	.376	.504	.368	.368
	N	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40

Spearman rank correlation coefficient=r, significance level=P, study sample size=n

Serum and CSF Ceftriaxone levels didn't show any correlation with age, BMI, cell count ,sugar and protein in CSF indicating independent reach of the drug not influenced by age, sex or meningeal inflammation.



Discussion

Meningoencephalitis/aseptic meningitis is one of the common pediatric emergencies. It causes significant mortality and morbidity in children.

Forty children with aseptic meningitis/ viral meningoencephalitis with median age 15 months (95% CI 6.7 to 31.9 months) and range 1 month to 11 years are studied. There is no significant difference in the proportion of males 62.5% (95% CI 45.8 to 77.3%) and females 37.5% (95% CI 22.7 to 54.2%). All the children received intravenous ceftriaxone in a dose of 50 mg/kg 12th hourly (100 mg/kg/d). The serum and CSF Ceftriaxone levels observed are after a mean number of doses of 2.2±0.9 (range: 1 to 4 doses).

There is no statistically significant difference in hemoglobin and CSF parameters (total cell count, polymorphs, lymphocytes, protein, and sugar levels) or serum, CSF ceftriaxone levels and percentage of serum drug reaching CSF between 4 age groups of study subjects.

Serum, CSF Ceftriaxone levels and percentage of serum drug reaching CSF are similar in both sexes.

Present study shows that serum and cerebrospinal fluid ceftriaxone levels are independent of age, sex, nutritional status, meningeal inflammation. Michael M Millner et al 5 reported similarly; adequate CSF ceftriaxone levels in aseptic meningitis with once daily ceftriaxone dose.

The CSF levels of drug in present study are comparable to or more than the CSF levels found in children with bacterial meningitis in other studies.6,7,8 It indicates ceftriaxone reaches CSF without much influence of meningeal inflammation which is clinically useful. In the study by J.L. Gaillard et.al6 and Gaillard 9 CSF drug levels have correlation with CSF glucose or protein or cell count whereas in present study such association is not observed . The variability in the levels observed may be due to some variation in time of CSF collection after drug administration and sample sizes between studies. Our study is having larger sample compared to many studies.

The mean CSF ceftriaxone levels observed in different age groups in present study are 5.5 to 6.1µg/ml similar to observations by Paul N Goldwater3 Thomas P. Lodise, Roland Nau, Martina Kinzig et al 10 Present study demonstrated CSF ceftriaxone therapeutic levels in different age groups is almost similar. But serum ceftriaxone levels observed between different studies including present study are showing more variability. This could be due to the variation in the drug dose given and timing of the blood sample taken from the time of drug administration between studies.

The percent of serum Ceftriaxone 3.8±0.40 to 4.2±0.65 reaching CSF is almost same within a serum Ceftriaxone range of 129.7µg/ml to 188.4µg/ml (table 3) similar observations made by others .

Table 4 Comparisons between present study and by Different Authors

Name of author	Study Subjects	n	CSF Ceftriaxone Mean	Serum Ceftriaxone Mean or Median	% Serum drug in CSF mean	CSF Ceftriaxone level influenced by	Post-dose interval (h)	Dose mg/kg	Post-Rx	AGE
Present Study, 2022	Aseptic meningitis	40	6±1 ug/mL	144 ug/mL (95% CI:	4.1±0.6 (95% CI:			50 BD		1mo - 12 y

			(95% CI: 5.7-6.2)	138.4-149.3)	3.9-4.3)					
Tadashi Hoshino et.al, 2010	Meningitis bacterial	12	5.54±4.39 mg/L	136.1±85.2 mg/L			0.25 to 3.5	50 BD	2-10 d	
Paul N Goldwater, 2005	Meningitis bacterial some + Dexamethasone	57	0.58 to 35 ug/mL			early infection, timing of dose	0.75 to 24	100 OD		3w-12Y
J.L.Gaillard, V.Abadie, G.Cheron, F.Lacaille,	Meningitis bacterial +Dexamethasone	11	4±2.9 mg/liter	301±90 mg/liter		CSF glucose-negative correlation	4.5	50 BD or 100 OD	1-2 d	4m-8y
Michael M. Millner et.al	Aseptic meningitis	22	4 ± 1.8 mg/liter	114 ± 62 mg/liter			12	70-100 OD	10 d	99±47 m
Martin et al.,	Meningitis	14	2.8 mg/L in bacterial		17% in bacterial & 4% in Aseptic			50-100	24	4d-9m
Russell W Steele et.al,	Meningitis bacterial	30	6.4 ug/mL	295±76 ug/mL	3.5-4.8		1 to 6	50-75		d
E. Gould Chadwick,	Meningitis bacterial	17	2.4 to 13.5 ug/ml	267±36 ug/mL	4.8±3.5	CSF glucose-negative correlation&CSF WBC and Protein Positive Correlation	1 to 4.5	50-75		0.6-52m
Razia Latif & Adnan S. Dajani,	Meningitis	27	5.7 ± 4.7 µg/ml	137 ± 39µg/ml	4.4 (range: 0.83-11)		3	75 OD	1-3 d illness	1m-16.5y
			2.1±1.3 ug/mL	158±32 ug/mL	1.5 (range: 1.0-4.4)				13-30 d illness	
H M Grubbauer et al,	Meningitis bacterial	33			6.6			100		

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