

Original Research Article

Serum procalcitonin in pediatric bacterial meningitis versus pediatric non bacterial meningitis: open label prospective study

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ABSTRACT

Background: Several studies have shown potential value of serum Procalcitonin level (SPCT) for diagnosing and differentiating bacterial meningitis (BME) from other, but the results were inconsistent.

Methods: Children from birth to 12 years, with clinical suspicion of meningitis were enrolled. Clinical and laboratory information was collected and cases were classified according to pre decided case definition (based on clinical and laboratory) as bacterial or non-bacterial meningitis (NBME).

Results: Out of 4393 admission (2016-17) 60 patients were selected for final study (on basis of case definition) which were equally distributed in both group (BME and NBME) in terms of age and sex (p 0.97). 29/41 (70%) patients of pyogenic meningitis had high level of SPCT which was significant, whereas only 2/19 (10.5%) patients of NBME had high level of SPCT. Although SPCT seems to be the good marker in differentiating between BME and NBME, SPCT level specificity (89%) in the diagnosis of BME was not higher than CSF protein level (94%) and CSF glucose level (94%).

Conclusions: Measurement of plasma SPCT levels are of value in differentiating BME & NBME in children. However, SPCT should not be used as single sole diagnostic marker of BME if CSF protein and glucose are available. CSF WBC Count alone should not to be used in diagnosis of BME as specificity is low. This study needs to be validated with a larger sample size and microbiological confirmation of bacterial disease.

Keywords: Bacterial Meningitis, CSF Glucose, CSF Protein, Non Bacterial Meningitis, Procalcitonin

INTRODUCTION

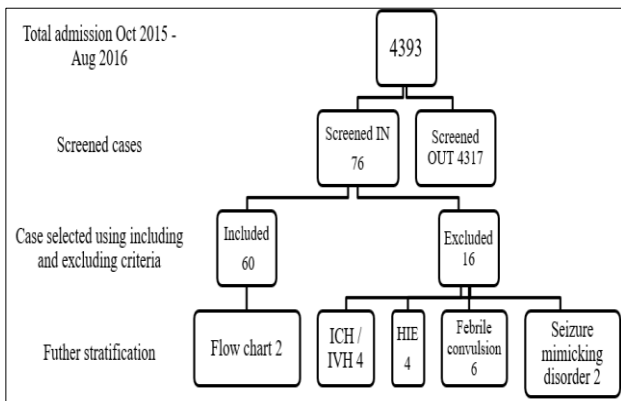
Bacterial meningitis (BME) and Serum Procalcitonin (SPCT). In spite of advances in diagnosis and treatment of BME they still remain important causes of mortality and morbidity. Early diagnosis and starting immediate empirical therapy are the key factors to reduce it in BME, but may result in unwanted antibiotic administration for NBME (Non Bacterial Meningitis), with the associated morbidity and economic burden.¹ Therefore, distinguishing BME and NBME early on could help to limit unnecessary antibiotic use and hospital admissions. The consequences of delayed diagnosis of BME can be severe. So any proposed diagnostic tool must achieve

near 100% sensitivity.² Clinical criteria, gram staining, and bacterial antigen testing of CSF as well as biological markers in the blood (CRP, white blood cell count (WBC), and neutrophil count) or CSF (protein, glucose, WBC count and neutrophil count) used alone do not offer 100% sensitivity with high specificity for distinguishing BME and NBME.² Also CSF culture for bacterial/non-bacterial growth takes 2 to 8 days.³ Research has been carried out to find new and rapid diagnostic methods for differential diagnosis of bacterial and NBME.⁴ One among them is an acute phase reactant like SPCT: a calcitonin pro-peptide. It is synthesized in C cells of the thyroid gland and secreted from leukocytes of the peripheral blood. The secretion of SPCT was found to

increase in the presence of bacterial lipopolysaccharides and cytokines associated with sepsis.^{5,6} SPCT levels increase during the course of bacterial, infections, but remain normal or slightly increased in viral infections and inflammatory reactions that are not infectious.^{6,7} The aim of the present study was to measure serum SPCT levels and effective role in the early diagnosis of BME and to document their efficacy in the differential diagnosis of BME and NBME.

METHODS

A prospective, open label study was undertaken in the pediatric ward of Sir T. General Hospital Bhavnagar from during the period of 15/10/2015 to 15/08/2016 (Figure 1).



ICH- intracranial hemorrhage
IVH- intraventricular haemorrhage
HIE- hypoxic ischemic encephalopathy

Figure 1: Study design.

Children between age group of 1 day to 12 years were screened based on symptoms and signs.

Presenting complaints like Fever, Vomiting/nausea, Headache, Convulsion, Excessive crying, Restlessness, Bulging anterior fontanelle, not breast feeding well, behavioral changes, altered sensorium, Irritability.

Presenting signs like signs of meningeal irritation (Neck rigidity/ Kernig’s sign/ Brudzinski sign), any cranial nerve palsy suggestive of meningitis, admitted in the ward.

Above were included in the study if they met with the study criteria.

Inclusion criteria

Children in the age group from 1st day of life to 12 year of age with meningitis (bacterial+ non-bacterial) having any Clinical criteria

- Convulsion + fever
- Excessive crying + fever + anterior fontanel bulging

- Altered sensorium
- Meningeal signs positive
- Already diagnosed meningitis with <18hr initiation of antibiotic therapy.

And any laboratory criteria

- CSF Gram/ZN stain positive
- Or CSF culture positive for pathogenic organism
- Or CSF routine & micro analysis shows WBC ≥20cells/cu.mm with Protein elevated/ Glucose depleted

Written informed consent was taken from caregiver of each patient. In this manner 76 subjects were selected and 16 were excluded.

Exclusion criteria

- Preadmission diagnosed as partially treated BME with >18 hour of duration of antibiotic therapy before admission
- Trauma induced convulsion
- Intracerebral/ intraventricular hemorrhage induced convulsion
- Bleeding disorder/ electrolyte imbalance/ hypoglycemic/ vasculitis and infarcts/ any other apparent cause other than meningitis

Following which Lumbar puncture CSF for Cell count, glucose and protein and blood were collected for serum SPCT level (Chemiluminescent Immunoassay for Antigen Detection, CLIA) and C- reactive protein (CRP).

And the analysis was conducted on 60 subjects, According to below criteria, the patients were divided into two groups: BME and NBME.

Case definition

BME defined as when

- CSF gram stain/ Zn stain yielded pathogenic bacteria.^{8,9} OR
- Culture yielded pathogenic bacteria OR
- CSF routine & micro shows WBC >20cells/cu.mm with Polymorph neutrophils predominance, Protein >50 mg/dl (elevated), Glucose 0-40mg/dl (depleted) and CRP positive

NBME defined as

CSF gram stain/Zn stain culture yielded no pathogenic bacteria.

CSF may show cells but does not show glucose or protein change as above.

Data were expressed as mean, Standard Error of Mean (SEM) (Normal value of SPCT was <0.01ng/ml).

Differences between groups were analyzed by nonparametric tests, p <0.05 was considered significant. Specific statistical tests like fisher exact test and comparative test were applied as needed.

Note: CSF Procalcitonin was not raised in bacterial meningitis in similar previous studies and so CSF Procalcitonin was not done.¹⁰

RESULTS

The present study was carried out on 60 patients. 29 (48.3%) were male and 31 (51.7%) were female. Male: Female Ratio was 0.9:1.1 (X2=0.0011, p 0.9724 not significant). Age group of study population was mean 3.25 yrs. ±SD 3.675 (X2=0.06810, p 0.7941 not significant). There was no significant association between sex or age and serum SPCT.

Two cases were confirmed (CSF culture positive) case of BME whose SPCT level was 2.85ng/ml and 0.05ng/ml. Six of the eight confirmed cases (bacterial blood culture positive) had SPCT level >0.5ng/ml (though not significant). And two had bacterial UTI, whose SPCT level were 0.06ng/ml and 3.6ng/ml (p NS). SPCT level is significantly raised in BME (Table 1).

Table 1: Serum procalcitonin and types of meningitis.

Serum procalcitonin	Type of illness		Total
	Bacterial meningitis (pyogenic + tuberculosis)	Non Bacterial meningitis	
>0.5ng/ml	25+4=29	2	31
<0.5ng/ml	12	17	29
Total	41	19	60

Fisher's exact Test: OR:20.54 (95% CI: 4.10-103.04); RR:2.26 (CI: 1.45-3.52); Sensitivity: 70.73%, Specificity: 89.47%, PPV: 93.55, NPV: 58.62, LR: 6.72; p<0.0001.

OR-Odd's Ratio, CI- Confidence Interval, RR-Relative Risk, PPV-Positive Predictive Value, NPV-Negative Predictive Value, LR-Likelihood Ratio

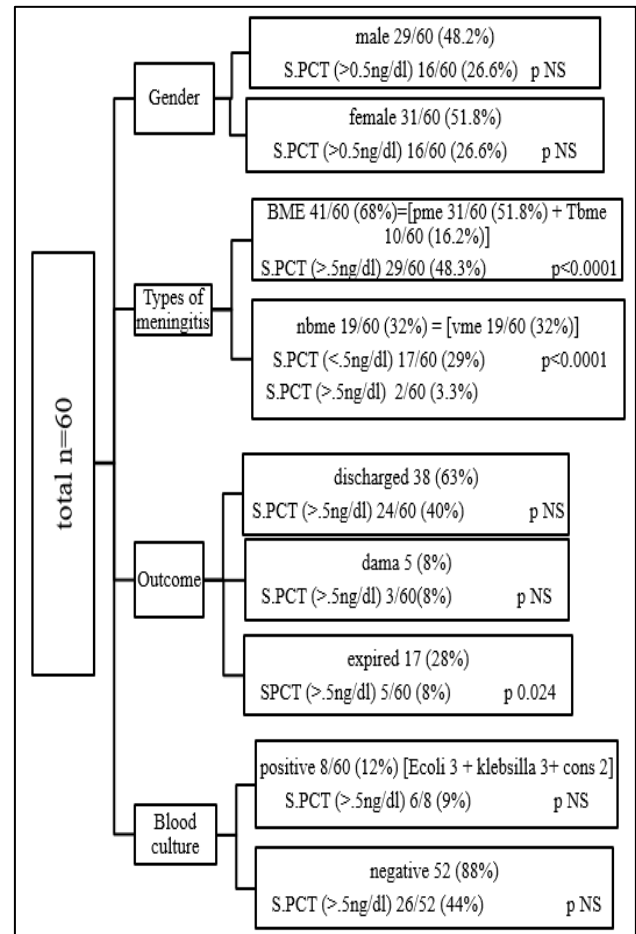
Table 2: Bacterial meningitis predictors and types of meningitis (quantatively).

	Bacterial meningitis (pyogenic + tuberculosis) n=41					Non Bacterial meningitis n=19				
	mean	median	SEM	min	max	Mean	median	SEM	Min	Max
WBC in CSF/mm ³	3723	280	3015	100	124000	100	40	31	4	550
	Values obtained after excluding extreme 1,24,000 value (n=40)									
	793	280	284	100	6912					
CSF glucose mg /dl	34.4	31	3.21	5	98	68.47	67	4	36	96
CSF protein mg/dl	124	116	5.63	43	241	41	67	7.6	19	158
CRP mg/dl	3.49	4.8	0.22	0	4.8	1.23	1.2	0.26	0	4.8
PCT ng/ml	2.8	2.65	0.49	0.01	18.48	0.2	0.11	0.05	0.01	0.9

SEM = Standard Error of Mean

In present study, outcome wise, 38 were discharged of whom 24 had >0.5ng/ml SPCT level (p NS) and 17 expired of whom only 5 had >0.5ng/ml SPCT level (p 0.024).

Remaining observation is as per Figure 2, Table 2, 3 and 4.



SPCT = Serum Procalcitonin, PME = Pyogenic meningitis, TBME = Tuberculosis Bacterial Meningitis, BME = Bacterial Meningitis, NBME = Non Bacterial Meningitis, VME = Viral Meningitis, NBME = Non Bacterial Meningitis, DAMA = Discharged against medical advice, NS = not significant

Figure 2: Serum procalcitonin level compared with various aspects and significance.

Table 3: Bacterial meningitis predictors and bacterial meningitis (qualitatively).

	Normal values	BME Predicting Values ^{8,9}	BME (n=41)				p value
			Sensitivity%	Specificity%	PPV	NPV	
WBC in CSF	0-20/mm ³	>100	100	73	89	100	0.0283 [significant]
CSF glucose	45-85 mg/dl	≤40	68	94	96	58	<0.0001*
CSF protein	15-45 mg/dl	≥100	78	94	96	66	<0.0001*
		≥80	95	89	95	89	<0.0001*
CRP	0.6>mg/dl	≥2.4	92	57	82	78	<0.0001*
		≥4.8	51	73	80	41	0.0953 ns
PCT	0.01ng/ml	≥0.5	70	89	93	58	<0.0001*

NOTE: * = [extremely significant]

Table 4: CSF cells and protein, C-reactive protein and procalcitonin in present study (n).

	(n)	BME			NBME		
		Present study (41)	Alain viallon ¹⁰ (23)	Dominique Gendrel ¹¹ (18)	Present study (19)	Alain viallon ¹⁰ (57)	Dominique Gendrel ¹¹ (41)
Serum	CRP	3.49±0.22* (0-4.8) mg/dl	166±37 [∞] (18-662) mg/l	144±69 (28-311) mg/l	1.23±0.26 (0-4.8) mg/dl	14±4 (2-60) mg/l	14.8±14.1 (0-48) [£] mg/l
	PCT ng/ml	2.8±0.49* (0.01-18.48)	3.8±5.2 [∞] (0.22-101)	54.5±35.1 (4.8-110)	0.2±0.05 (0.01-0.9)	0.03±0.003 (0.01-0.1)	0.32±0.35 (0-1.7) [†]
CSF	Cells/mm ³	3723± 3015* (100-124000)	1,483±427 [∞] (105-6,336)	5,156±4,336 (250-17,500)	100±31 (4-550)	83±21 [£] (19-624)	391±648 (20-3,200) [£]
	Protein g/l	12.4±0.563* (4.3-24.1)	5.1±0.9 [∞] (0.4-22)	2.3±1.2 (0.4-4.74)	4.1±0.76 (1.9-15.8)	0.95±0.1 [£] (0.3-5)	0.62±0.47 (0.12-2.72) [£]
	Glucose mmol/L	3.44±0.321 [#] (0.5-9.8)	2.5±0.5 [∞] (0.5-5) mmol/L		6.847±0.4 (3.6-9.6) mmol/L	3.7±0.2 (2.4-6.8) mmol/L	

Present study: Data are mean±SEM (range). CRP=C-reactive protein, * = p<0.0001 extremely significant, # = p 0.0283 significant, Note: glucose from mg/dl converted to mg/l, CSF protein from mg/dl converted to mg/l, In our hospital CRP level above 4.8 mg/dl are not measured given as >4.8mg/dl. A Viallon study¹⁰: Values for blood and CSF parameters in patients with bacterial or viral or no meningitis¹⁰, NOTE. Data are mean±SEM (range). PMN-polymorph nuclear cell, ∞ = P 0.05, bacterial meningitis vs. the other two groups, £ = P 0.05, viral meningitis vs. controls. D Gendrel study¹¹: Data are mean±SD (range), CRP=C-reactive protein, £ = p < 0.001, † =p < 0.0001.

DISCUSSION

Serum SPCT level has been reported to be useful in the diagnosis of severe bacterial infections and in the follow up of treatment. However, there have been only a few reports about serum SPCT in the differential diagnosis of meningitis in childhood.¹⁰

In present study various aspect of level of serum SPCT and various types of meningitis in relation to various factors like age, sex, clinical diagnosis and pathological conditions ,laboratory parameter have been studied and compared with similar other studies.^{10,11}

The mean, median, SEM, minimum and maximum values and ranges for C-reactive protein levels and for CSF parameters (polymorph nuclear cell counts, protein levels, glucose in CSF, and SPCT levels) had statistically significant differences for all of these tests between BME

and NBME. However, a wide area of overlapping individual values for cellular predominance, level of glucose in CSF, and protein levels in CSF were found between patients with bacterial and NBME. In the group with BME; 6 (13%) had a lymphocytic predominance in CSF at admission; 14/41 (35%) had a normal CSF glucose and 2/41 (5%) had normal CSF protein.

The sensitivity and specificity respectively, for the diagnosis of acute BME at CSF protein level ≥80mg/L was 95% and 89%; and at CSF protein level ≥100mg/L it was 78% and 94%.

The sensitivity and specificity respectively, for the diagnosis of acute BME at CSF glucose level ≤40mg/L was 68% and 94%;

The sensitivity and specificity for the diagnosis of acute BME were 92% and 57%, respectively, for S. CRP level

≥ 2.4 mg/L and 51% and 73%, respectively, for S. CRP level ≥ 4.8 mg/L.

The mean SPCT level on admission in patients with acute BME was $2.8\mu\text{g/L}$, and the lower level was $0.01\mu\text{g/L}$, while the higher level in patients with NBME was $0.9\mu\text{g/L}$ (mean level, $0.2\mu\text{g/L}$). With SPCT level of $0.5\mu\text{g/L}$, the sensitivity for diagnosis of BME was 93%, and the specificity was 58%. In this study we found high serum SPCT levels exclusively in patients with BME. Children with NBME had normal or only slightly increased levels of SPCT. Use of a cut off SPCT level of $0.5\mu\text{g/L}$ in blood samples obtained at the time of admission distinguished patients with a bacterial etiology; however 12/41 (30%) BME patients had low ($<0.5\mu\text{g/L}$) serum SPCT level (Table 1).

This study demonstrated that serum SPCT levels at admission allows differentiation between acute BME and NBME with a cut off level of 0.5 ng/mL (normal <0.01). As previously reported, the increase in serum SPCT levels is low in patients with non-bacterial infection.^{10,11} Serum SPCT levels does not have higher specificity for the diagnosis of acute BME, than CSF protein level (89%) and CSF glucose level (94%) therefore, this observation is not in accordance with the literature.^{10,11}

In BME, the CSF WBC count usually is >100 and with a neutrophilic predominance, but 13% of the patients with BME had a lymphocytic predominance.

Although SPCT seems to be the good marker in differentiating between acute bacterial and NBME, twelve patients of BME had low level of serum levels of SPCT, two patients of NBME had high ($>0.5\text{ng/dl}$) serum SPCT. Three (8%) of 41 patients with BME had initial CRP levels of $<2.4\text{mg/l}$. The differences in the mean values obtained for 19 patients with NBME of our data are in agreement with those from many studies that have shown that the CRP level is valuable for distinguishing bacterial infection from non-bacterial infection, especially meningitis. As previously reported in the different studies, the SPCT level appears to be a reliable tool for early diagnosis of severe bacterial infection because this level rises rapidly and to a high degree in response to infection and because SPCT has a long plasma half-life.¹²⁻¹⁴

CONCLUSION

The results of this study suggest that measurement of SPCT levels is of value in differentiating between acute BME and NBME in children. However SPCT cannot be used as single sole diagnostic marker of BME. Also, high level of SPCT Rule's out NBME.

Also, Single sole use of CSF WBC Count should not be used in diagnosis of BME as specificity % (73), is less than CSF glucose (94), CSF Protein (94) and SPCT (89).

Recommendation

- Serum SPCT cannot be used as single sole diagnostic marker of BME.
- Study of combination of several laboratory parameters is necessary to differentiate between BME and NBME.
- Single sole use of CSF WBC Count should not to be used in diagnosis of Meningitis.

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Serum SPCT level measurement is costly. Study was conducted at single Centre with small number of subjects and Culture was positive in only 8/41 (19.5%) cases of BME.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Review Board (IRB)/ [Human Ethics Committee (HEC)]. Govt. Medical College, Bhavnagar-364001, Gujarat, India

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