COMPARISON OF SERUM PROCALCITONIN AND C-REACTIVE PROTEIN IN DIAGNOSIS OF BACTERIAL MENINGITIS

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ABSTRACT

Objective: The diagnostic accuracy of Procalcitonin (PCT) as compared with C - reactive protein (CRP) for early diagnosis of bacterial meningitis in children was evaluated.

Design: Descriptive diagnostic study.

Place on Duration of Study: This study was conducted in Pathology department of Army Medical College Rawalpindi from September 2007 to September 2008.

Material and Methods: Descriptive diagnostic accuracy study was conducted in Pathology Department of the Army Medical College, Rawalpindi. Total 77 subjects consisted of 31 patients of bacterial meningitis and 46 healthy children were included as controls from the Military hospital, Rawalpindi. The patients comprised of 18 (58 %) male and 13 (42 %) female with mean age 6 years. Patient's investigations including cerebrospinal fluid (CSF) examination and culture were carried out at admission. PCT and CRP were analyzed on Vidas analyzer and Immulite 1000 respectively.

Results: PCT levels were significantly high median (range) of 4.5 ng/ml (0.10-19.00) ng/ml than controls 0.45 ng/ml (0.10-3.00). Serum CRP levels were moderately elevated with median (range) 11 mg /L (0.30 – 23.00) as compared with 0.30 mg/L (0.30-9.5) controls. The Area under receiver characteristic curve of PCT 0.86 (95 % CI: 0.76-0.93) was significantly higher than CRP 0.72 (95% CI: 0.61-0.82). The optimum diagnostic cutoff point for PCT and CRP were 2 ng/ ml and 6 mg/L respectively by ROC analysis. PCT had maximum sensitivity 74% and specificity 84% at cutoff > 2 ng/ ml while CRP revealed sensitivity 58% and specificity 83% at cutoff > 6mg/ L.

Conclusion: This study has demonstrated PCT as a more reliable diagnostic marker than CRP for early diagnosis of bacterial meningitis and can be used in combination with clinical evaluation for proper management of the seriously ill children.

Keywords: Procalcitonin, C- Reactive Protein, Bacterial Meningitis, Sensitivity, Specificity, Children

INTRODUCTION

Meningitis is an important cause of mortality and morbidity in children [1]. It carries a risk of fatal outcome or severe neurological deficit, especially when the diagnosis and the antibiotic administration are delayed [2, 3]. Distinguishing between bacterial and viral meningitis is sometimes difficult due the overlapping signs and symptoms. Timely collection of CSF and isolation of an organism, allows optimization of choice of antimicrobial therapy [4, 5]. The practice of giving empirical treatment to all children, with suspected meningitis result in unnecessary and indiscriminate use of antibiotics and is associated with high medical costs [6, 7]. Routinely, bacterial meningitis is confirmed on clinical suspicion, positive gram stain and bacterial culture of cerebrospinal fluid is highly specific but not 100% sensitive [8, 9]. Moreover the lumbar puncture (LP) may be contraindicated in small children who are irritable with seizures, or due to other cause of raised intracranial pressure, and occasionally infection at the lumbar puncture site [10].

Keeping in view the limitations and drawbacks associated with the use CRP intensive research has been carried out for the past decade to find new and rapid diagnostic methods for diagnosis of bacterial meningitis.

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CRP is an acute-phase reactant synthesized by the liver in response to the inflammation but elevated CRP concentration also occurs in viral infections and other inflammatory conditions. Due to its nonspecific nature, it has limited utility in differentiating bacterial from viral meningitis [11, 12]. Procalcitonin (PCT) is 116-amino acid prohormone of calcitonin. Microbial infection induces a ubiquitous release of PCT from all parenchymal tissues throughout the body [13].

The role of PCT in diagnosis of bacterial meningitis in adults and children has been investigated since 1993 [14]. Serum PCT appears to be more sensitive and specific for early prediction of bacterial infections [15, 16]. In a Chinese study by Li et al (2006) demonstrated high diagnostic value in children suffering from bacterial meningitis (16). However, there are studies with mixed results in children with bacterial meningitis [17]. Some studies recommend the use of PCT; however there are reports with negative results as well.

The role of PCT in diagnosis of bacterial infections remains controversial and in the present scenario its use is yet to be established. This is first study of its kind to determine the diagnostic role of PCT in bacterial meningitis in our region. This study aimed to evaluate the diagnostic value of serum PCT in comparison with CRP for early diagnosis of bacterial meningitis in children. This study will help in improvement of diagnostic process of meningitis and better management in pediatric clinical practice.

MATERIALS AND METHODS

Descriptive diagnostic accuracy study was conducted in Pathology Department of the Army Medical College, Rawalpindi. The present study was approved by the Ethics Committee of the Army Medical College, Rawalpindi, Pakistan.

Subjects

Total 77 subjects consisted of 31 patients of bacterial meningitis and 46 healthy children included as controls from the Military Hospital, Rawalpindi. Fifty one children of suspected meningitis were included after informed parental consent on a prospective sequential basis. They were admitted from September 2007 to September 2008 in the pediatric unit of in Military Hospital Rawalpindi, Pakistan. However, 20 patients were excluded from the final analysis because of incomplete characterization of bacterial meningitis in 17, and 3 had already taken antibiotic. Therefore, the total study population comprised 31 patients of bacterial meningitis with age ranging from 1 to 12 years were included. Forty six (n=46) aged and sex matched healthy children were included from Rawalpindi as controls.

Diagnosis of bacterial meningitis

All children of meningitis of bacterial origin were diagnosed by qualified pediatrician on the basis of clinical symptoms i.e. meningitis was diagnosed according to evaluation of history, physical examination, CSF laboratory findings, (increased protein >2 g/l, decreased CSF: plasma glucose ratio < 0.4, and leukocyte count >1500 x 109/L and polymorph nuclear leukocyte domination. The children who had known neurosurgical disease, traumatic lumbar puncture, recurrent meningitis, pretreated meningitis or referral from another hospital were not enrolled in the study.

Laboratory Methods

All samples were collected in separator vacutainer tubes (BD, NJ USA) when the patients arrived in the wards. Blood samples were allowed to clot and then centrifuged for 10 min at 1,000 G. The serum was separated and stored at – 80 0C until assayed for PCT and CRP. All the routine investigations including blood count were carried out in the Pathology Department of the Army Medical College, Rawalpindi. Blood cultures and CSF cultures were set up immediately; pathogens were identified by positive staining and culture.

Serum hS- CRP was analyzed by solid-phase, two-site sequential chemiluminescent immunometric high sensitivity C-reactive protein assay kit based on [18] on Immulite-1000 (Immulite, Diagnostic Product Corporation, L A, USA). Serum PCT levels were measured by two monoclonal antibodies, by a VIDAS BRAHMS PCT. It is an automated test for use on the VIDAS instrument (BRAHMS Diagnostica, Berlin, Germany) for the determination of human procalcitonin in human serum using the ELFA (Enzyme-Linked Fluorescent Assay) technique. Two levels controls of Immulite CRP of DPC (Seimen, USA) LCRC 100B with mean (Range) of 1.43 (1.25-1.61 ng/L) and 72 (58-86 ng/L) were analyzed. PCT control of B.R.A.H.M.S (Biomerieux, France) at concentration of .5 and 2 ng/ml were also run with each batch. Coefficient of Variance (CV) for PCT and CRP were 3.8 and 5 percent respectively.

Statistical Analysis

Statistical analysis was performed by SPSS version 16 (Chicago IL). Exploratory data analysis revealed that PCT and CRP concentrations were not normally distributed. Therefore, the results are presented as medians and ranges. The area under receiver operator curves (AUROC) of serum PCT and CRP were calculated for diagnosing bacterial meningitis in children. Receiver operator characteristic curves were used to evaluate the diagnostic values and AUROC were compared by Hanley and McNeil test [19]. The diagnostic accuracy values of sensitivity (SN), specificity (SP) and likelihood ratio (LR) were calculated. We set the optimal cut-off value for diagnosis of bacterial meningitis. The concentrations of PCT and CRP at admission in the patients were compared with controls by Mann-Whitney U test. A p value of less than 0.05 is considered significant.

RESULTS

Thirty one children were diagnosed as bacterial meningitis in the pediatric unit of tertiary care hospital with reference tests. They consist of 18 (58 %) male and 13 (42 %) female with median age of 6 ranged from 1 to 12 years. Baseline clinical characteristics of the study patients are shown in (Table-1). At admission, all children had temperature above 38°C fever (100 %), nausea or vomiting (39 %), headache (35 %) and convulsion (29 %). Causative pathogens were Streptococcus pneumoniae (n=18), Neisseria meningitidis (n=9), Haemophilus influenzae (n=3) and Escherichia coli (n=1).

Early Diagnosis of Bacterial meningitis by Procalcitonin

The children with bacterial meningitis had significantly high median (range) serum PCT levels of 4.5 ng/ml (0.10-19.00) as compared with controls 0.45 ng/ml (0.10-3.00) at admission (Fig-1a). Serum CRP levels were

Table-1: Demographic characteristic of children with bacterial meningitis (n=31)

Parameters	Median (Range)
Age (years)	6 (1-12)
Sex (M/F)	18/13
Fever n (%)	31(100.0)
Nausea or vomiting n (%)	12(39)
Headache n (%)	11 (35.0)
Convulsion n (%)	9 (31.8)
Leukocyte count /µ L	16.2×10^{3}

moderately elevated at admission with median (range) 11 mg /L (0.30 – 23.00) as compared with controls 0.30 mg/L (0.30-9.5) (Fig-1b).

Receiver operator characteristic curves at admission for serum PCT for bacterial meningitis are shown in (Fig. 2). The Area under receiver characteristic curve (AUROC) at admission for the PCT was 0.86 (95 % CI: 0.76-0.93) was significantly high (p= <0.01) as compared with CRP that was 0.72 (95% CI: 0.61-0.82). The optimum diagnostic cutoff point for PCT levels in this study population was > 2 ng/ ml by ROC analysis (Fig. 2). Diagnostic accuracy parameters of PCT revealed maximum sensitivity 74% and specificity 84% at cutoff > 2 ng/ ml.

The optimum diagnostic cutoff point for CRP levels in this study population was 6 mg/L by ROC analysis (Fig. 2). Diagnostic accuracy of CRP demonstrated a sensitivity of 58 and a specificity of 83% for diagnosis of bacterial meningitis at cutoff 6 mg/L.

Comparison of diagnostic accuracy parameters of PCT and CRP at two different cut off for diagnosis of bacterial meningitis are shown in Table.2. The study has demonstrated that PCT had maximum likelihood ratios and diagnostic odds ratio for diagnosis of bacterial meningitis at cutoff > 2 ng/ ml. Total of 23 children out of 31 were correctly identified as having bacterial meningitis by PCT at the time of admission in the hospital. Serum CRP correctly identified 18 children out of 31 patients of bacterial meningitis at admission. Thus, PCT had better diagnostic odds ratio for diagnosis of bacterial meningitis than CRP. Diagnostic values of PCT were better than the serum CRP for diagnosis of bacterial meningitis.

Table-2: Diagnostic accuracy of serum Procalcitonin (PCT) and serum C- reactive protein (CRP) in children admitted with bacterial meningitis (n=31)

Biochemical markers (Cut off value)	SE (%)	SP (%)	LR+	LR-	DOR
PCT ≥1.5 (ng/ ml)	77	80	3.85	0. 29	13.3
PCT ≥ 2 (ng/ ml)	74	84	4.62	0.31	15
CRP ≥ 4 (mg/ L)	65	78	3.0	0.45	6.7
CRP ≥ 6 (mg/ L)	58	83	3.41	.51	6.7

Diagnosis c

SE =Sensitivity, SP=Specificity, LR = Likelihood ratio, DOR= Diagnostic Odds ratio
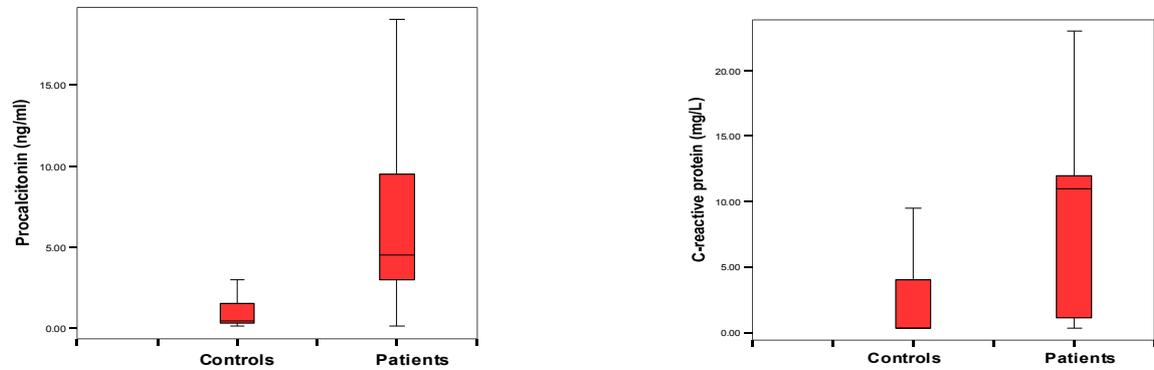
Fig. 1: Distribution of Procalcitonin and CRP in the study participants (p=<0.01)
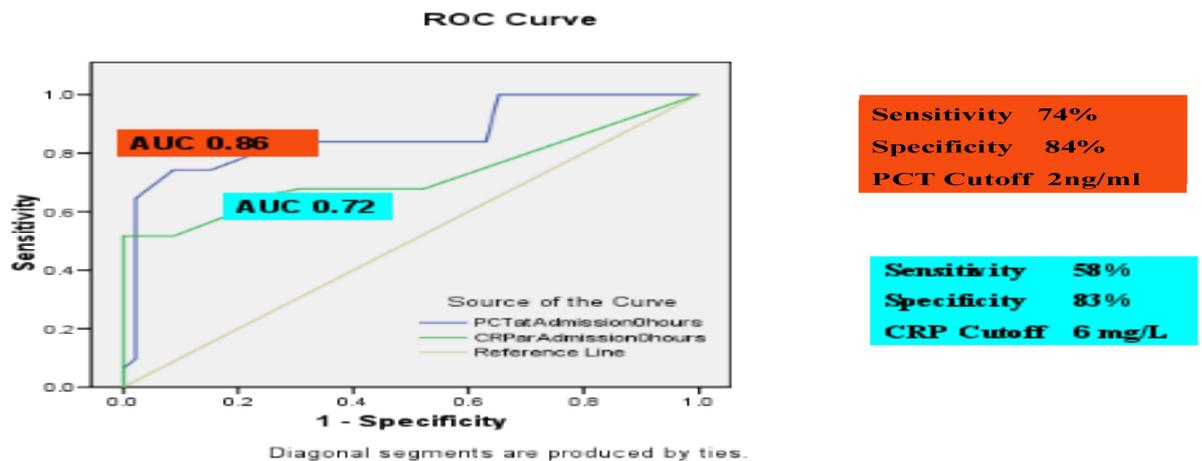
Fig. 2: Receiver operator characteristic (ROC) curves of serum PCT (AUC 0.89; 95 % CI= 0.83-0.96) and CRP (AUC 0.79; 95 % CI= 0.70-0.88) concentration at admission

DISCUSSION

Investigation of biochemical markers for bacterial meningitis is an important area of research in the past decades. As the morbidity and mortality in bacterial meningitis in children remains substantial despite continued advances in pediatrics, choices of novel antibiotics and availability of vaccines [20].

This is the first study utilizing serum PCT and CRP levels for early diagnosis of bacterial meningitis in Pakistani pediatric population. In our study the children with bacterial meningitis had significantly high median serum PCT levels as compared to controls at

admission (p<0.01). The same patients had their Serum CRP levels were moderately elevated at admission as compared to controls. This study demonstrated that PCT is an early biomarker as its levels were elevated at admission and has better diagnostic accuracy as compared to CRP. These findings are consistent with the previous studies, in children and adults the serum PCT level is increased in acute bacterial meningitis cases, but remains normal in viral meningitis [21, 22].

A variety of cutoff values are used in literature for PCT in meningitis (0.5-2 ng/ml) [22-24]. However, the best cutoff for this study participants was PCT > 2 ng/ ml. The results of this study are in accordance with previous Chinese study [16]. However, in our study AUROC was only higher for PCT (0.86 vs 0.72) compared to (0.984 vs 0.983 for PCT and CRP) in the above mentioned study. Recently, a Turkish study [24] reported that if used in adjunct to lumbar puncture, PCT had very high diagnostic accuracy for distinguishing between bacterial and viral meningitis in patients. Moreover, failure to perform lumbar puncture can delay the diagnosis of meningitis in young and irritable children. Serum PCT results can be obtained in 2 hours and can be conducted with only 200 µl of serum. Serum PCT measurement does not require any invasive intervention such as lumbar puncture and with its stable molecular structure in serum; it can be frequently measured in serum for the diagnosis and follow-up of bacterial meningitis, making this parameter useful in clinical practice.

The results of this study showed variation when compared with Hoffmann O et al; who reported limited diagnostic value of PCT in adults suffering from bacterial meningitis, especially in cases due to unusual agents or of nosocomial origin [17]. The reason can be difference in the population studied. We recruited children with clinically suspected meningitis and grouped them after confirmation of etiology. Secondly, we utilized CRP as well in our study for comparison with PCT. The number of participants was less in the above mentioned study (n=12) compared to our study. Moreover, the difference in age group (children vs adults), etiology of meningitis studied, difference in time of sampling and analysis could be the reasons for these dissimilar results. A limitation of this study was that it was a single-center study and numbers of subjects were relatively less. Therefore, caution must be used when attempting to extrapolate these data to general pediatric population.

The present study is an example of decision analysis to undertake large-scale studies by simulating the magnitude of the clinical effectiveness of PCT to translate into a cost-effective clinical strategy for all pediatric age groups in Pakistan. This study will aid in understanding the role of biochemical markers like CRP and procalcitonin in bacterial infection in children.

CONCLUSION

This study has demonstrated PCT as a more reliable diagnostic marker than CRP for early diagnosis of bacterial meningitis and the same can be used in combination with clinical evaluation for proper management of the disease.

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