Use of urine reagent strip to evaluate CSF for bedside diagnosis of pyogenic meningitis in paediatric age group: A Hospital Based observational study

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| KEYWORDS	ABSTRACT
Cerebrospinal fluid, meningitis, reagent strip.	**Background**: Cerebrospinal fluid (CSF) analysis is required to make a diagnosis of meningitis to aid in the proper management of patients. In urban areas with good health-care facilities, it is easy to get a CSF analysis done. However, in rural and remote areas with no proper transport facilities, such a simple point of care test will definitely be useful. We conducted a study and compared the results of reagent strip test with the biochemical tests and microscopic examination. **Aims and Objectives:** The aim of the study was to determine the utility and efficacy of reagent strip test on CSF .**Materials and Methods:** A prospective, time-bound study was carried out department of pediatrics Institute of Medical Science and SUM Hospital, Bhubaneswar, Odisha, India on the CSF sample remaining after the biochemical tests and microscopic examination. The values of both the methods were compared. Using Chi-square and Fischer's exact test, data were analysed. **Results:** Leukocyte esterase positivity by test strip had a sensitivity of **84.6%** and specificity of **51.9%** , **Positive predictive value=25.6%, Negative predictive value= 94.5%** for detection of CSF granulocytes more than 10 cells/mm^3 . The association of CSF cell count at cut off more than 10 cells/ul was found to statistically significant with presence of bacterial meningitis (p-value =0.005). The sensitivity of glucose strip with trace reading in detection of bacterial meningitis was found to be 92.3%, specificity was 56.4%, positive predictive value was 29.3% and negative predictive value was 97.4% **Conclusion:** This test will be useful in remote areas as a point of care test for early patient management.

INTRODUCTION

Globally, meningitis is a significant cause of morbidity and mortality in the paediatric population accounting for about 180,000 deaths annually[1].Prior to introduction of vaccines, *Haemophilus influenzae* type *b* (Hib), *Streptococcus pneumoniae*, and *Neisseria meningitidis* were reported to be the commonest causes for bacterial meningitis with their relative contributions varying by time, location and age group in different parts of the world[2] The burden of bacterial meningitis due to *Hib* and *S. pneumoniae* decreased significantly following the introduction of the respective vaccines in high income nations. However, bacterial meningitis continues to be a cause for concern in low and middle income countries either due to low level of vaccine coverage or non- availability of these vaccines in their national immunization programs [3, 4]. Population based
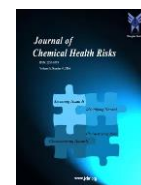
studies from South Asian countries and retrospective hospital based studies from these regions have reported that 12.8% and 28% of the confirmed cases of invasive bacterial disease were due to *S. pneumoniae*, respectively [5]. In urban areas with good health-care facilities, it is easy to get a CSF analysis done. However, in rural and remote areas with no proper transport facilities, such a simple point of care test will definitely be useful. CSF studies have been determined in the past with the help of reagent strips, but the results are variable, and the method has not gained popularity. If proven useful these strips can be used as an excellent test to help clinicians make a rapid bedside diagnosis of meningitis and initiate treatment [6] This would greatly benefit health professionals working in areas with limited resources [7] Besides, these tests do not require any expertise and can be easily performed bedside [8] and interpreted. Despite its usefulness, this study is not gained importance because of lack of interpretation using proper cut-off values [9] In our study, we have compared the results of reagent strip test with the biochemistry and microscopy to know if this simple test can be used as a point of care test in diagnosing bacterial meningitis.

AIMS & OBJECTIVES

To evaluate CSF using a standard urine dip strip (glucose, proteins, leucocytes) and to compare the results with the clinical course and outcome and the local standard methods. Biochemical values (proteins and glucose) and microscopic examination (leukocyte number) were considered gold standard.

METHODOLOGY

A single blinded diagnostically clinical trial (laboratory technicians were not aware of the results of the reagent strip) was conducted in paediatric wards of the Institute of Medical Science and SUM Hospital, tertiary hospital in Bhubaneswar. We included children from 2 months to 14 years of age, which presented at the paediatric emergency department at the Hospital from November 1st 2018 to August 30th 2020.

- ► STUDY DESIGN : Descriptive observational study
- ► STUDY GROUP : All suspected pyogrnic meningitis children admitted in paediatrics ward from 2 month to 14 years age group
- ► STUDY DURATION : 24 Months
- ► SAMPLE SIZE :All children of 2 month – 14 Year diagnosed with pyogenic meningitis admitted during data collection periods will be included for our study which is expected around 159
- ► STATISTICAL METHOD AND TOOL USED IN THE STUDY: Chi-square and Fischer's exact test,
- ► ETHICAL CLEARANCE: Institutional ethical clearance was obtained for the study

The values of both the methods were compared. Normal CSF values used were leukocytes: 0–5 cells/micro l (adults) and 0–30 cells/microl (neonates), glucose: 50–80 mg/dl, and proteins: 15–45 mg/dl. Cut-off values used for diagnosing bacterial meningitis were CSF protein of >30 mg/dl, CSF glucose of <50 mg/dl, and CSF neutrophils of >10 cells/mm.^{3}

Table1: Study parameters with index test values and their corresponding biochemical values and microscopy

Index test	Gold standard
Leukocyte reagent strip No color	Microscopic examination
Anycolor1+	<10 leukocytes/mm^3
2+	10–75 leukocytes/mm^3
3+	75–500 leukocytes/mm^3

>500 leukocytes/mm^3

Glucose reagent strip	Biochemistry value
No color	<50 mg/dl
1+	50–100
2+	100–300
3+	300–1000
4+	>1000
Protein reagent strip test	Biochemistry value
No color	<30 mg/dl
1+	30–100
2+	100–500
3+	>500

RESULTS

CSF samples of 159 patients were included in the study. 69.8% [111/159] were male and 30.2% [48/159] were females with a median age of 4.9 years [range 2 months-14 years].

We estimated the diagnostic accuracy of the key indicator tests with reagent strip testing as the index test and CSF microscopy or biochemical laboratory-based values (CSF proteins and CSF glucose) as reference standards. Leukocyte esterase positivity by test strip had a sensitivity of **84.6%** and specificity of **51.9%**, **Positive predictive value=25.6%, Negative predictive value= 94.5%** for detection of CSF granulocytes more than 10 cells/mm^3

TABLE - 2

CSF cell count	Bacterial Meningitis (yes=1, no=0)		Total	P-value	Odd's ratio (C.I.)
	0	1		0.00	5.93 (1.93-18.14)
<10 cells/ul	69	4	73		
>10 cells/ul	64	22	86		
Total	133	26	159		

The association of CSF cell count at cut off more than 10 cells/ul was found to statistically significant with presence of bacterial meningitis (p-value =0.00). The odd's ratio for the association was 5.93 with 95% confidence interval of 1.93-18.14. (Table -2)

TABLE 3: Cross tabulation demonstrating accuracy of leukocyte strip in detection of bacterial meningitis among study participants.

TABLE- 3

Leucocyte strip	Bacterial Meningitis (yes=1, no=0)		Total	p-value
	No	Yes		
Negative	61	1	62	
Trace	10	12	22	
1 cross	40	8	48	0.00

2 cross	15	4	19	
3 cross	7	1	8	
Total	133	26	159	

The readings of leukocyte strip when compared against the diagnosis of bacterial meningitis were found to be significant (p-value=0.00)). Total 13 patients with bacterial meningitis were found to have leucocyte strip reading of 1 cross and higher

Table 4: Cross tabulation demonstrating accuracy of protein strip in detection of bacterial meningitis among study participants.

TABLE-4

Protein strip		Bacterial Meningitis		Total	p-value	Odd's ratio (C.I.)
		No	Yes		0.00	4.54(1.87-11.02)
	Negative/1 cross	109	13	122		
	2 cross/3 cross	24	13	37		
Total		133	26	159		

Sensitivity= 61.5%, Specificity=97.7%, Positive predictive value=84.2%, Negative predictive value= 92.9% .

The reading obtained from protein strip when segregated into negative, 1 cross and 2 cross findings in one group and 3 cross finding in another group, showed a significant association of protein strip readings with detection of bacterial meningitis (p-value=0.00). The odd's ratio (95% CI) for this association was 69.33 (17.25-278.58). The sensitivity of protein strip at cut off point of 3 cross and above reading was found to be 61.5%, specificity was 97.7%, positive predictive value was 84.2% and negative predictive value was 92.9%.

Table 5: Cross tabulation demonstrating accuracy of glucose strip in detection of bacterial meningitis among study participants.

TABLE-5

Glucose Strip Reagent		Bacterial Meningitis (yes=1, no=0)		Total	p-value	Odd's ratio (C.I.)
		0	1		0.00	15.5(3.52-68.34)
	negative	75	2	77		
	Trace	58	24	82		
Total		133	26	159		

Sensitivity=92.3%, Specificity=56.4%, Positive predictive value=29.3%, Negative predictive value= 97.4%

The reading obtained from glucose strip when segregated into negative and trace findings showed a significant association of glucose strip readings with detection of bacterial meningitis (p-value=0.00). The odd's ratio (95% CI) for this association was 15.5(3.52-68.34). The sensitivity of glucose strip with trace reading in detection of bacterial meningitis was found to be 92.3%, specificity was 56.4%, positive predictive value was 29.3% and negative predictive value was 97.4%
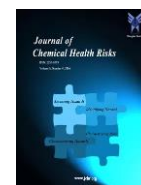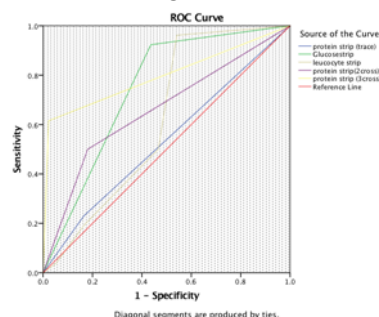
Figure -1

Table-6

Variable(S)	Area Under The Curve	Asymptotic Sig.B	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
Protein Strip(>=Trace +)	.533	.599	.408	.657
Glucose Strip	.743	.000	.655	.832
Leucocyte Strip	.623	.048	.528	.717
Protein Strip (>=2 Cross)	.660	.010	.536	.784
Protein Strip (>=3 Cross)	.796	.000	.679	.914

The ROC curve shown here depicts the diagnostic role of strip reagent findings in bacterial meningitis.

The significant diagnostic clinical features were found to be presence of positive glucose, leucocyte, and protein strip (2 cross and above) findings. The area under curve (AUC) was highest for positive protein strip at 3 cross (0.8) followed by positive glucose strip (0.74), positive protein strip at 2 cross and above (0.66) and positive leucocyte strip (0.62) (Figure -1).

DISCUSSION

There is a good correlation between the results of reagent strip test and laboratory methods of CSF protein, sugar, and leukocyte estimation.Romanelli *et al*.[6] conducted a study on CSF samples of 164 children and obtained a sensitivity, specificity, positive and negative predictive values, and accuracy of 90.7, 98.1, 95.1, 96.4, and 96.1, respectively. They found a good correlation between the reagent strips and cytological and biochemical assays.Moosa*et al*. [7] observed a sensitivity of 97% in the diagnosis of meningitis by reagent strip testing of CSF samples of 234 children with clinically suspected meningitis. In another study involving 75 samples, sensitivity and specificity for testing CSF proteins by reagent strip was 77.8% and 100%, respectively, while that for CSF granulocytes was 92.6% and 100%, respectively. [4]

Study by Joshi et *al*. [9] involving 75 patients found a sensitivity and specificity of 98.1% and 57.1%,respectively,for detection of CSF proteins>30 mg/dl. While the leukocyte esterase positivity had a sensitivity and specificity of 85.2% and 89.6%, respectively. In another study by Joshi*etal*. Sensitivity and specificity for CSF protein at 1 cross (>30 mg/dl) was 95% and 57%, respectively. They were of the opinion that the sensitivity and specificity improved significantly when higher cut-off was used. Parmar*etal*.[10] reported the sensitivity and specificity of the reagent strips for the diagnosis of meningitis as 97.14% and 96.42%, respectively. They observed sensitivity, specificity for tuberculous meningitis and bacterial meningitis of 100%, and 96.55%, and of 70% and 96.55% for aseptic meningitis. Accuracy observed for the diagnosis of meningitis as a whole, bacterial, tubercular, and aseptic meningitis were 96.78%, 98.2%, 98.27%, and 83.0%, respectively .In our study of the total 159 cases,leukocytes of more than 10 were seen in 26 cases. Total 13 patients with bacterial meningitis were found to have leucocyte strip reading of 1 cross and higher. In one case, the dipstick was positive though there were no granulocytes in microscopy. This could be due to blood contamination as a result of the traumatisation a study by Bisharda*etal*.[11]14 of the total 36 cases were confirmed to have meningitis by laboratory criteria.Of these,12were picked up by the dipstick test.Five
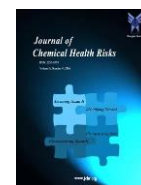
samples tested positive by dipstick al though their microscopic results were negative. They found a sensitivity of 85.26% and specificity of 77.27% in detecting pyogenic meningitis by dipstick test.In a study by Molyneux and Walsh, [12] the sensitivity of the strips was only33%,and the specificity was 83% on clear CSF samples.In our study, The sensitivity of protein strip at cut off point of 2 cross(>100mg/dl) and above reading was found to be 50%, specificity was 82%, positive predictive value was 35.1% and negative predictive value was 89.3% .

Conclusion: This test will be useful in remote areas as a point of care test for early patient management. The results of our study demonstrate. The significant diagnostic clinical features were found to be presence of positive glucose, leukocyte, and protein strip (2 cross and above) findings. Hence, these strips can be of a great positive marker to clinicians working in remote areas to reliably make a rapid diagnosis of meningitis and initiate appropriate treatment.

Limitations of This study: we need to perform a multicentre study will larger numbers of patients to get more reliable results.

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