# Original Article

# Utility of Urine Reagent Strips in CSF Analysis as An Aid to Rapid Diagnosis of Meningitis

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## ABSTRACT

**Background:** Bacterial Meningitis is a medical emergency and timely intervention has an implication on the prognosis and outcome. Examination of the CSF for leucocytes, glucose and proteins are the cornerstones in the diagnosis of meningitis in general and to arrive at the cause. Hence, this study is done to evaluate the usefulness of urinary reagent strip for rapid diagnosis of meningitis.

**Methods:** This is a prospective single blinded study on 100 CSF samples subjected to index test (Urine reagent strip test-Dirui H10) and definitive test comprised of CSF microscopy and biochemical analysis for proteins and sugar. The diagnostic accuracy of each index test at different cut off levels tabulated in the form of sensitivity, specificity, PPV and NPV.

**Result:** The sensitivity and specificity for leukocytes by the strip method for ≥15 cells/cumm were 92% and 98.66%, and for protein levels >30 mg/dl were 84.33% and 94.11% respectively. The test showed high specificity (100%) but less sensitivity for glucose <50mg/dl. It was observed that the accuracy of the tests increased with increase in the values of cell counts and proteins and decrease in sugar reaching 100% accuracy for higher cut-offs.

**Conclusion:** Urine reagent strip can be utilized for the rapid analysis of CSF in both rural areas as well as in centres where the facility is available as it reduces turnaround time.

*Keywords: Cerebrospinal Fluid, Meningitis, Urine Reagent Strip, Accuracy.*

## Introduction

Globally, meningitis accounts for about 180,000 deaths annually.[1] Even after introduction of vaccine, bacterial meningitis continues to be a cause for concern about mortality and morbidity in socially and economically backward population.[2]

Global mortality from meningitis has declined and Substantial disparities in geographical distribution and age groups are seen. In 2016, nearly 0·6% of all ages deaths and close to 3% of the total in children younger than 5 years were due to meningitis. The peak age of incident meningitis is during the neonatal period, deaths are highest in children younger than 5 years, and meningitis death rates are highest in many of the same locations where overall younger than 5 years mortality is highest.[3]

Bacterial Meningitis is a medical emergency and prompt diagnosis of meningitis is fundamental for early treatment to prevent permanent neurological deficits and death.[4] While Neonatal meningitis continues to contribute substantially to neurological deficits worldwide, febrile seizures make allusions to meningitis, resulting in a diagnostic dilemma for the clinicians.[5]

Examination of the cerebrospinal fluid (CSF) for leucocytes, glucose, proteins, and culture are the cornerstones in the diagnosis of meningitis.[6] CSF analysis requires trained personnel and an equipped laboratory, which are not available in rural areas.[6] Even in the settings where they are available, the turnaround time period for laboratory based CSF analysis is long.[5,6,7]

The use of urine reagent strips for quick cerebrospinal fluid (CSF) tests has been described in few studies[8] but the results are variable and the method has not gained popularity.

If proven useful these strips help the clinician in rapid bedside diagnosis of meningitis and initiate treatment as these tests do not require expertise and can be easily performed and interpreted.[4]

## Materials and Methods

This study was conducted in the Department of Pathology at S. Nijalingappa Medical College, Bagalkot. The study was prospective, conducted for a period of 7 months between November 2018 and July 2019, on 100 CSF samples remaining after biochemical tests and microscopic examination within 1 hour of tap.

A semi quantitative urinary reagent strip test (index test) for analysis of CSF leukocytes, proteins, and sugar and CSF microscopy and biochemical analysis of proteins and sugar (definitive test) were performed on all 100 samples. If the quantity of the CSF sample was insufficient for performing the index test, then those samples were excluded.

Index test was done using urinary reagent strips which can detect ten parameters including protein, glucose, and leukocyte esterase. With the help of a pipette, 2–3 drops of undiluted CSF were added to patches of proteins, glucose, and leukocyte esterase, and the color change was recorded and interpreted using the manufacturer provided color grading. Reagent strip Dirui H10 was used for the study.

Definitive tests were done by an independent blind observer. The tests done were cell count by Neubauer's chamber followed by differential counting on two centrifuged smears: one stained with hematoxylin and eosin stain and the other with Leishman stain along with protein and sugar estimation by an automated analyzer (Erba Mannheim).

The values of both the methods were compared. Normal CSF values used were leukocytes: 0–5 cells/micro 1 (adults) and 0–30 cells/micro l (neonates), glucose: 50–80 mg/dl, and proteins: 15–45 mg/dl.

The parameters were analyzed using relevant statistical tools.

## Result

This is a Prospective study conducted in the Department of Pathology at S. Nijalingappa Medical College Bagalkot on 100 CSF samples, remaining after biochemical tests and microscopic examination within 1 hour of tap.

The distribution of males (55%) and females (45%) were almost equal. 83% of cases were in the pediatric age group and 17% of cases were adults. 29% of the cases were neonates. The age wise and Gender wise distribution is as shown in Table 1.

Three cardinal parameters, leukocytes, proteins, and glucose tests of the reagent strip, were compared with those of the reference standard. The sensitivity for leukocytes by the strip method for cut-off of ≥15 cells/cumm was 92% and specificity was 98.66%. The Accuracy was 97% for cut-off for ≥15cells/cumm which increased to 100% with higher cutoffs of cell count [Table 2].

The sensitivity for the protein levels >30mg/dl by reagent strip was 84.33% and the specificity was 94.11%. For a cutoff level of the proteins of >300mg/dl, both the sensitivity and specificity increased to 100% [Table 2].

The reagent strip test for glucose at cutoff level of <50mg/dl was highly specific with a specificity of 100% but it was less sensitive with a sensitivity of 50%[Table 2].

**Table 1: Age wise and Gender wise distribution.**

| Age | Male | Female | Total |
|---|---|---|---|
| 0 Days-2 Month | 15 | 14 | 29 |
| ≥2 Months-2 Year | 12 | 11 | 23 |
| ≥2years- 6 Years | 7 | 3 | 10 |
| ≥6 Years- 16 Years | 11 | 10 | 21 |
| ≥16 Years | 10 | 7 | 17 |
| **Total** | **55** | **45** | **100** |

**Table 2: Diagnostic accuracy of urinary reagent strips.**

| Index Test | Cutoff value | TP | FP | FN | TN | SN | SP | PPV | NPV | Accuracy |
|---|---|---|---|---|---|---|---|---|---|---|
| Leucocytes (cells/ µ l) | >15 | 23 | 1 | 2 | 74 | 92% | 98.66% | 95.83% | 97.36% | 97% |
| | >70 | 10 | 0 | 0 | 90 | 100% | 100% | 100% | 100% | 100% |
| | >125 | 5 | 0 | 0 | 95 | 100% | 100% | 100% | 100% | 100% |
| Protein (mg/dl) | >30 | 70 | 1 | 13 | 16 | 84.33% | 94.11% | 98.59% | 44.82% | 86% |
| | >100 | 15 | 1 | 1 | 83 | 93.75% | 98.80% | 93.75% | 98.80% | 98% |
| | >300 | 1 | 0 | 0 | 99 | 100% | 100% | 100% | 100% | 100% |
| Sugar (mg/dl) | <50 (Neg) | 12 | 0 | 12 | 76 | 50% | 100% | 100% | 86.36% | 88% |

**Table 3: Age wise and Gender wise distribution.**

| Author | Sample size | Age Range | Neonates | Pediatric | Adults | Male | Female | M:F ratio |
|---|---|---|---|---|---|---|---|---|
| Gupta A et al[9] | 360 | 11-78yrs | | | | 174 | 186 | 1:1 |
| Mazumder et al[5] | 100 | | 41 | 77 | 23 | 52 | 48 | |
| Chikkannaiah et al[6] | 103 | 2D-75Yrs (14cases-<1yrs; 27cases-<12yrs) | | 41 | 62 | | | 1.86:1 |
| Joshi et al[10] | 75 | 1D-75 yrs | | | | | | |
| Present study | 100 | 1 day- 61 yrs | 29 | 83 | 17 | 55 | 45 | |

**Table 4: Comparison of Present Study with Similar Previous Studies:**

| Cut Off | Sensitivity | Specificity | PPV | NPV | Accuracy | Author |
|---|---|---|---|---|---|---|
| Leucocyte >15 cells/mm$^3$ | 92% | 98.66% | 95.83% | 97.36% | 97% | Present study |
| Leucocyte >70 cells/mm$^3$ | 100% | 100% | 100% | 100% | 100% | |
| Leucocyte >125cells/mm$^3$ | 100% | 100% | 100% | 100% | 100% | |
| Protein >30mg/dl | 84.33% | 94.11% | 98.59% | 44.82% | 86% | |
| Protein >100mg/dl | 93.75% | 98.80% | 93.75% | 98.80% | 98% | |
| Protein >300mg/dl | 100% | 100% | 100% | 100% | 100% | |
| Glucose< 50mg/dl | 50% | 100% | 100% | 86.36% | 88% | |
| Leucocyte ≥10 cells/mm$^3$ | 100 | 96 | | | 92 | Gupta A et al[9] (2019) 360 cases |
| Protein ≥30mg/dl | 99 | 54 | | | 89 | |
| ≥100mg/dl | | | | | | |
| Glucose≤ 40mg/dl | | | | | | |
| ≤ 50mg/dl | 98 | 92 | | | 100 | |
| Protein ≥30mg/dl | 89.28 | 98.61 | 96.61 | 95.94 | 96 | Mazumder et al[5] (2018) 100 cases |
| ≥100mg/dl | 100 | 100 | 100 | 100 | 100 | |
| Glucose≤ 40mg/dl | 100 | 100 | 100 | 100 | 100 | |
| ≤ 50mg/dl | 85.71 | 95.65 | 98.50 | 66.66 | 88 | |
| >100mg/dl | 95.83 | 98.68 | 95.83 | 98.68 | 98 | |
| >300mg/dl | 100 | 100 | 100 | 100 | 100 | |
| Glucose< 40mg/dl | 71.42 | 100 | 100 | 95.5 | 96 | |
| < 50mg/dl | 48.2 | 100 | 100 | 82.55 | 85 | |
| Leucocyte ≥10 cells/mm$^3$ | 96.6% | 94.5 | 87.8 | 98.5 | | Chikkannaiah et al[6] (2016) 103 cases |
| Protein ≥30mg/dl | 94.9 | 45.8 | 85.2 | 73.3 | | |
| ≥100mg/dl | 96 | 87.1 | 70.5 | 98.5 | | |
| Glucose≤ 40mg/dl | 28.5 | 100 | 100 | 89.8 | | |
| ≤ 50mg/dl | 14.2 | 100 | 100 | 75.7 | | |
| Leucocyte ≥10 cells/mm$^3$ | 85.2 | 89.6 | 82.1 | 91.5 | | Joshi et al[10] (2013)75 cases |
| Protein ≥30mg/dl | 98.1 | 57.1 | 85.5 | 92.3 | | |
| ≥100mg/dl | 92.6 | 87.5 | 80.6 | 95.5 | | |
| Glucose≤ 40mg/dl | 61.1 | 96.5 | 84.6 | 88.7 | | |
| ≤ 50mg/dl | 46.2 | 98 | 92.3 | 77.4 | | |

## Discussion

The distribution of males (55%) and females (45%) were almost equal. 83% of cases were in the pediatric age group and 17% of cases were adults. 29% of the cases were neonates

Anshu Gupta et al in 2019 [9], used Combur-10 urinary reagent strip for a rapid analysis of the CSF on 360 cases. It showed high sensitivity and specificity for leucocytes >10 cells/cumm i.e. 100% and 96% respectively whereas for CSF proteins the strip test was more sensitive (99%) and less specific (54%). With respect to glucose, the strip was highly specific (92%) and highly sensitive (98%). Lower cut-off for proteins in the urine is 30 mg/dl and for the CSF is 15 mg/dl. So, it can give high false positive results by showing 1 + in reagent strip even when the value of CSF protein is in normal range (15–45 mg/dl). This could be the reason for low specificity for protein in this study. [9]

In the study by Mazumder S et al[5] in 2018, 100 CSF samples were analyzed using Combur-10 urinary reagent strip for a rapid analysis and followed by definitive tests. It showed sensitivity of 89.28% and specificity of 98.61% for leucocytes >15 cells/cumm and sensitivity of 85.71% and specificity of 95.65% for CSF proteins for >30mg/dl. For glucose<50 mg/dl, the sensitivity was 48.2% and specificity was 100%. They also observed that the accuracy of the tests increased with increase in the values of cell counts and proteins and decrease in sugar reaching 100% accuracy for very high test results. This is significant as bacterial meningitis shows very high CSF cell counts and protein levels with very low sugars as compared to aseptic meningitis and thus the strip test proves to be of great relevance in identifying these cases. They got 11 false negative cases (<30mg/dl as per strip method), 10 out of which actually had laboratory values of proteins <45mg/dl, which is the standard biochemical cut off for normal CSF proteins. [5]

Chikkannaiah et al in 2014, [6] used Combur-10 urinary reagent strip for rapid analysis of the CSF on 103 cases. The strip had a high sensitivity and specificity for leucocytes ≥10 cells/cumm. With respect to proteins, the results are acceptable for a higher cut-off level of ≥100 mg/dl, where the sensitivity and specificity were 96% and 87.1%, respectively, while at ≥30 mg/dl, the strip was more sensitive and less specific. With respect to glucose, the strip was highly specific (100%) and less sensitive at both the cut-off levels. Observations of this study were comparable to those reported in this study. [6]

Joshi et al[10] using the same reagent strip, observed a sensitivity of 85.2% and a specificity of 89.6% for leucocytes >10 cells/cumm. For proteins, at a cut-off of ≥30 mg/dl, the sensitivity was high (98.1%) but the specificity was low (57.1%); however, at a cut of ≥100 mg/dl, both the sensitivity and specificity were high and acceptable. The strip based analysis for glucose at a cut-off of ≤40 mg/dl was more specific (96.5%) than sensitive (61.1%); and, even at a cut-off level of ≤50 mg/dl, the test was more specific (98%) than sensitive (46.2%).[10]

In the present study, we used Dirui H10 urine reagent strips to study three cardinal parameters, leukocytes, proteins, and glucose results which were compared with those of the reference standard. The sensitivity for leukocytes by the strip method for ≥15 cells/cumm was 92% and specificity was 98.66%. The Accuracy was 97% which increased to 100% with higher cut-offs of cell count. The sensitivity for the protein levels >30mg/dl by reagent strip was 84.33% and the specificity was 94.11%. For a cut-off level of the proteins of >300mg/dl, both the sensitivity and specificity increased to 100%.

The reagent strip test for glucose at cut-off level of <50mg/dl was highly specific with a specificity of 100% but it was less sensitive with a sensitivity of 50%. These results were comparable with the above studies which used Combur 10 reagent strips for index test.

## Conclusion

In light of observations of our study and with reference to the results obtained in similar studies by various observers, we can conclude that urinary reagent strips can be used for rapid diagnosis of CSF for meningitis. If this method is used in routine clinical practice, the rapidity of diagnosis will considerably decrease the morbidity and mortality that occurs due to meningitis both in rural areas as well as in centres where the facility is available as it reduces turnaround time. Further studies with larger numbers and comparison with different manufacturer strips can be undertaken. If standardized, this method can re-establish the entire diagnostic protocol of meningitis.

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