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A Study on Estimation of Cortisol Levels in Cerebropinal Fluid for Differentiating Bacterial from Non Bacterical Meningitis

Dr.P.Vishnuram[1], Dr. Kumar Natarajan[2], Dr.N.Karuppusamy[3], Dr. Manjunath Bv[4], Dr. Mithra Prasad[5], Dr.Barathiraja[6]

[1,3] *Assistant Professor, Department Of General Medicine, Coimbatore Medical College & Hospital, Coimbatore.*
[2]*Professor & HOD, Department Of General Medicine, Coimbatore Medical College & Hospital, Coimbatore.*
[4-6] *Post Graduates, Department Of General Medicine, Coimbatore Medical College & Hospital, Coimbatore.*

Abstract**:** *Meningitis remains serious clinical problem in developing countries. Delayed diagnosis and treatment result in significant morbidity and mortality. Case fatality can be as high as 25 % in bacterial meningitis. Early antibiotic therapy is crucial for improving the outcome of bacterial meningitis. There is a need for a reliable and cost effective method to differentiate among various types of meningitis. There is also a need for a test which can distinguish bacterial meningitis from aseptic meningitis during the acute phase of the disease, so as to avoid complications due to delayed treatment. Thus, determination of unstimulated endogenous CSF-cortisol activity may be an early diagnostic and valuable marker in differentiating bacterial from nonbacterial meningitis[7].This is an observational cross-sectional study conducted in a tertiary care hospital over a one- year period to evaluate the effectiveness of CSF cortisol levels in differentiating bacterial from aseptic meningitis and to determine the cutoff level of cortisol for the diagnosis of bacterial meningitis. The results of our study showed that CSF cortisol levels were significantly higher in bacterial meningitisgroup compared to non-bacterial meningitis group with a cutoff value of 10microg/dl and that the levels significantly reduced following specific treatment.*

Keywords**:** Cortisol, Neutrophilic, Lymphocytic, Aseptic meningitis, CSF.

I. Introduction

Meningitis remains serious clinical problem in developing countries. Delayed diagnosis and treatment result in significant morbidity and mortality. Case fatality can be as high as 25 % in bacterial meningitis. Long-term sequelae such as hearing loss, palsies and personality changes affect approximately 40% of survivors. Early antibiotic therapy is crucial for improving the outcome of bacterial meningitis. This necessitates the presence of a diagnostic test which has high sensitivity and can prognosticate the severity of the disease process.

Signs and symptoms, results of routine CSF analysis and radiological imaging are often inadequate in reaching a definitive diagnosis. Rapid methods of detection of organism like Gram's stain and AFB stain of CSF lack sensitivity, whereas, culture of CSF is time consuming. PCR test is a highly sensitive and specific test but is costly and not widely available. Therefore, for differentiation among various types of meningitis, a reliable and cost effective test should be available. There is also a need for a test which can distinguish bacterial meningitis from aseptic meningitis during the acute phase of the disease, so as to avoid complications due to delayed treatment. On the other hand in patients with aseptic meningitis, unnecessary antibiotic use can be avoided. Several studies in the paediatric population have shown elevated serum cortisol levels to correlate with a complicated course of bacterial meningitis [4,5]. Moreover, unstimulated high cortisol levels in serum correlate with an unfavourable outcome of sepsis [6]. Thus, determination of unstimulated endogenous CSF-cortisol activity may be an early diagnostic and valuable marker in differentiating bacterial from nonbacterial meningitis[7].

II. Aim Of The Study

1. To evaluate the utility of CSF Cortisol levels in differentiating Bacterial and Non-Bacterial meningitis.
2. To study CSF Cortisol levels in Bacterial (neutrophilic) and Non-Bacterial (lymphocytic and aseptic) meningitis.

III. Materials and Methods

Design: Cross sectional observational study in patients of suspected meningitis during August 2013 to July 2014.

Sample Size: 50 Patients Which Includes 40 Study Patients And 10 Control Subjects.

Case Definitions: Patients with clinical suspicion of meningitis presenting with fever, vomiting, altered sensorium and nuchal rigidity.

Inclusion Criteria
1. Age of patients more than 16 years
2. Patient with clinically suspected meningitis, confirmed with CSF analysis.

Exclusion Criteria
1. Partially treated cases with antibiotics before admission.
2. Patients treated with corticosteroids before admission.
3. Traumatic lumbar punctures for CSF collection.

Control Group
Ten patients without any pre-existing neurological disorders will be included as controls.

Working Indices: Investigation
1. Hematological
a) Complete haemogram.
2. Hepatic function tests
3. Renal function tests
4. Serum electrolytes
5. Random blood sugar: at the time of lumbar puncture
6. Chest X-ray PA view
7. Blood culture
8. CSF
a) Cytochemical analysis including- cell count, cell type, protein, sugar
b) CSF- CORTISOL estimation by chemiluminescent assay.
c) CSF- gram stain and Zeil Nelson stain
d) CSF- culture for mycobacteria and pyogenic organisms
e) CSF - TB PCR, HSV PCR, India ink, Cryptococcal Ag, ADA as and when required.
9. Serum cortisol.

Analysis Of CSF:
A fresh sample of CSF collected in heparinised vial obtained by the lumbar puncture. The different types of meningitis will be categorized as follows, according to cytochemical parameters.

1) Bacterial Meningitis:
Protein: more than 45 mg /dl
White blood cells: 10/microliter to 10000 /microliter: neutrophil predominate
glucose: < 40mg/dl
CSF/ serum glucose: < 0.4
Cloudy or turbid appearance
Gram's stain and culture were done

2) Tubercular Meningitis:
Protein: 0.1-0.5 g/L.
Cell counts: 10-500 cells/microL; lymphocytic pleocytosis.
Glucose: 20 - 40 mg/dl.
AFB and culture will be done.

3) Aseptic Meningitis:
Protein: 20-80 mg/dl.
Glucose: normal to decrease.
Cell counts: 25-500 cells/microliter
Cell types: lymphocytic pleocytosis.

Csf Cortisol Activity:
CSF-Cortisol activity was estimated in all 40 cases by direct chemiluminescent assay and comparison was made among neutrophilic meningitis, lymphocytic meningitis, aseptic meningitis and controls.

Method: For in vitro diagnostic use in the quantitative determination of cortisol levels in CSF using the ADVIA Centaur CP system by direct chemiluminescent assay.

Principle: The ADVIA Centaur CP Cortisol assay is a competitive immunoassay using direct chemiluminescent technology. Cortisol in the patient sample competes with acridinium ester labeled cortisol in the Lite Reagent for binding to polyclonal rabbit anti-cortisol antibody in the Solid Phase. The polyclonal rabbit anti-cortisol antibody is bound to monoclonal mouse anti-rabbit antibody, which is covalently coupled to paramagnetic particles in the Solid Phase.

Specimen Collection and Handling:

The following recommendations for handling and storing CSF samples are furnished by the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS):5

1. Universal precautions are taken for collecting all CSF samples.
2. Allow samples to clot adequately before centrifugation
3. Samples tubes are stoppered and always kept upright.
4. Do not use samples that have been stored at room temperature for longer than 8 hours.
5. The CSF are refrigerated at 2° to 8o C if the assay is delayed and is not completed within 8 hours.
6. The CSF samples are freezed at or below -20°C in case sample is not assayed within 48 hours of collection.
7. Freeze samples only once and mix thoroughly after thawing. Before placing samples on the system ensure that samples have the following characteristics:
   A. Samples are free of fibrin or other particulate matter. If present remove particles by centrifugation.
   B. Samples are free of bubbles or foam.

Loading Reagents:

Ensure that the system has sufficient primary and ancilliary reagent packs. Mix all primary reagent packs by hand before loading them onto the system. Visually inspect the bottom of the reagent pack to ensure that all particles are dispersed and suspended. Load the primary reagent packs in the primary reagent area. You can use the arrows on the end label as a placement guide. However, left , center, and right placement of the primary reagent packs is not required , because the ADVIA Centaur CP system has only one probe. The system automatically mixes the primary reagent packs to maintain the homogenous suspension of the reagents.

Test Procedure

The System Automatically Performs The Following Steps:

1. Dispenses 20 microliter of sample into a cuvette.
2. Dispenses 50 microliter of Lite Reagent and 250 microL of Solid Phase and incubates for 9 .66 minutes at37°C.
3. Separates, aspirates, and washes the cuvettes with Wash 1.75
4. Dispenses 300 microliters each of Acid Reagent (R1) and Base Reagent (R2) to initiate the chemiluminescent reaction.
5. Reports results according to the selected option, as described in the system operating instructions.

Table 1: Reference Values for CSF-Cortisol:

NORMAL	< 2 microgram/dl
NONBACTERIAL	2-10 microgram/dl
BACTERIAL	>10 microgram/dl

It is recommended that each laboratory establish its own normal range representing its patient population.

Study Design: Cross sectional observational study.

Ethical clearance:

Ethical clearance was obtained from the Institutional Ethical Committee.

IV. Statistical Analysis

Mean, Median, Standard Deviation are estimated, in order to know the association between CSF cortisol levels, cytochemical analysis and culture results. In all the tests "p" value less than 0.05 and 0.01 are accepted as statistically significant and highly significant, respectively. SPSS16 software is used.

V. Results

Table -2: Age and percentage distribution

Age-wise Distribution	No: of cases	% Distribution
16-20	14	35%
21-25	5	13%
26-30	3	8%
31-35	4	10%
36-40	4	10%
41-45	2	5%
46-50	3	8%
>50	5	13%
Total	40	100%

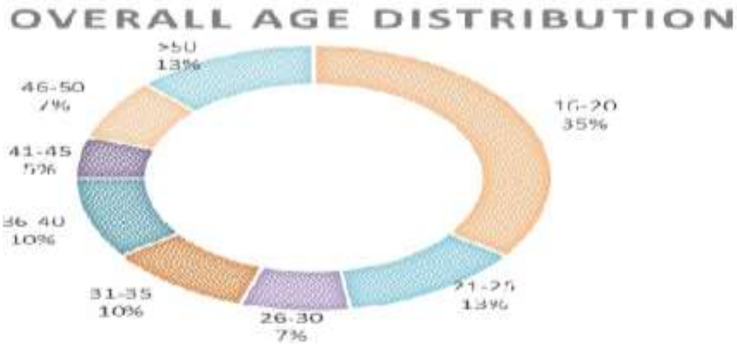


Figure 1: Age distribution

In our study the peak incidence of meningitis is seen in 16-20 years of age.

Table 3: Distribution among gender

Gender	No: of Cases	Percentage
Female	14	35%
Male	26	65%
Total	40	100%

In the present study male were 65% and female cases were 35%. Male to Female ratio is 1.85:1

Table 4: Gender distribution

	Gender (%)		
Meningitis Diagnosis	Male	Female	Total
Non Bacterial	35%	23%	58%
Bacterial	30%	13%	43%
Total	65%	36%	100%

In our study, in 65% were male patients and 35% were female patients suffering from meningitis. Out of this, 23% and 35% for non-bacterial meningitis respectively. In case of bacterial, male: female incidence was 30% and 13% respectively.

Figure 2: Gender distribution across meningitis sample

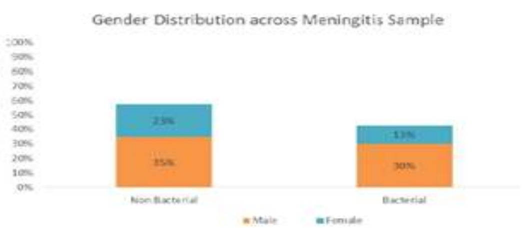


Table 5: Meningitis diagnosis.

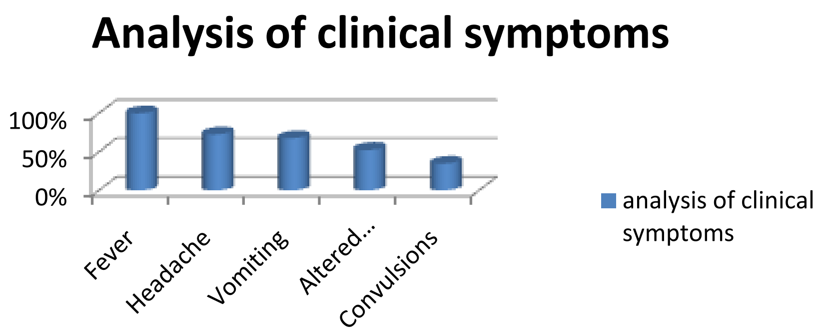
	Gender		
Meningitis Diagnosis	Male	Female	Total
Neutrophilic	12	5	17
Lymphocytic	9	7	16
Aseptic	5	2	7
Total	26	14	40

In our studies out of 40 patients 17 cases had neutrophilic meningitis, 16 cases had lymphocytic meningitis and 7 cases had Aseptic meningitis.

Table 6: Analysis of clinical symptoms

Clinical symptoms	No:of cases	Percentage
Fever	40	100%
Headache	29	72.5%
Vomiting	27	67.5%
Altered sensorium	21	52.5%
Convulsions	14	35%

Figure 3: Analysis of clinical symptoms



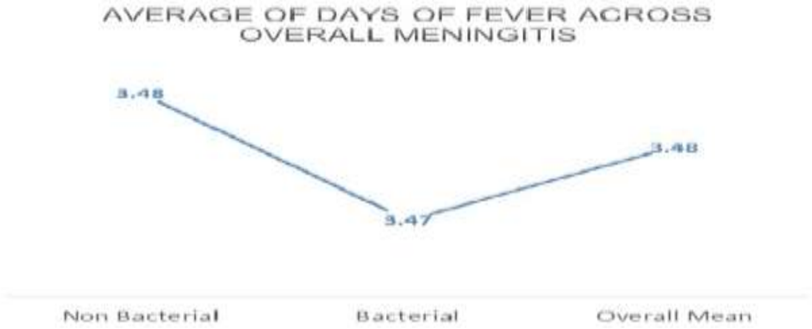
In our studies among 40 patients of meningitis,all patients had fever (100%). Headache was present in 29 patients (72.5%), vomiting was seen in 27 patients (67.5%), various stages of altered sensorium is seen in 21 patients (52.5%), convulsions in 14 cases (35%).

Table 7: Analysis of clinical signs

Signs	No:of cases	Percentage
Signs of meningeal irritation	40	100%
Altered sensorium	21	53%
Drowsiness	15	37.85%
Irritability	4	10.09%
Stupor	2	5.04%
Coma	0	0
Cranial nerve involvement	4	10%
6^{th} nerve palsy	3	7.5%
7^{th} nerve palsy	1	2.5%
Motor system involvement		
Hemiparesis	1	2.5%

Among the 40 cases of meningitis, signs of meningeal irritation were seen in all (100%) of cases. Altered sensorium was seen in 21 cases (53%). Cranial nerve palsies were present in 4 cases, 3 were 6^{th} nerve palsy and 1 was facial nerve palsy.

Figure 4: Analysis of clinical signs



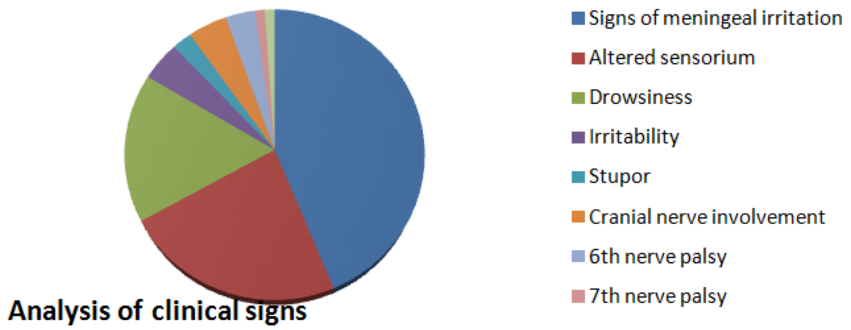
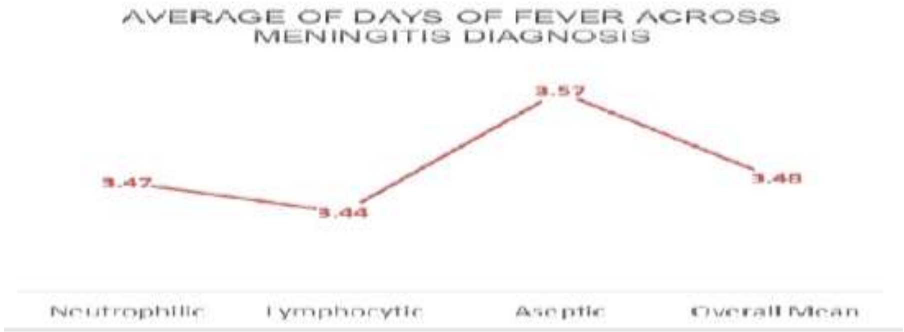


Table 8: Average of days of fever across overall meningitis



Overall Meningitis	Mean
Non Bacterial	3.48
Bacterial	3.47
Overall Mean	3.48

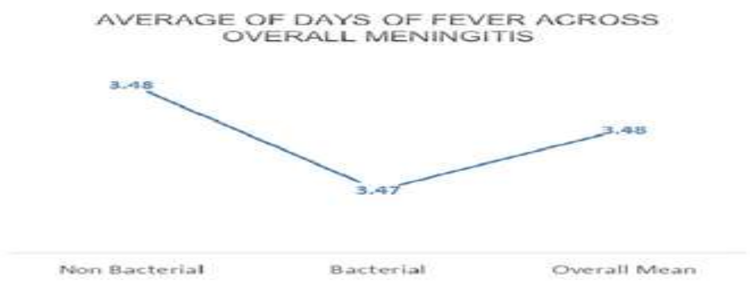


Figure 5: Fever across overall meningitis

In the present study there was no significant correlation between the total of days of fever in bacterial and nonbacterial meningitis.

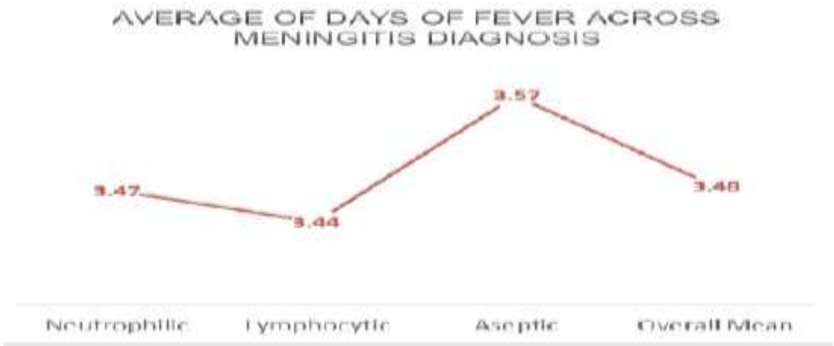
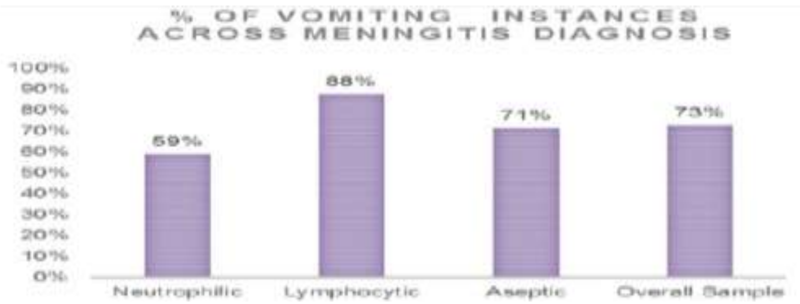


Figure 6: Average of days of fever among Neutrophilic, Lymphocytic, and Aseptic meningitis

In the study there was no correlation between the days of fever and neutrophilic, lymphocytic and aseptic meningitis.

Figure 7: Distribution of Vomiting Instances across overall Neutrophilic, Lymphocytic, and Aseptic meningitis

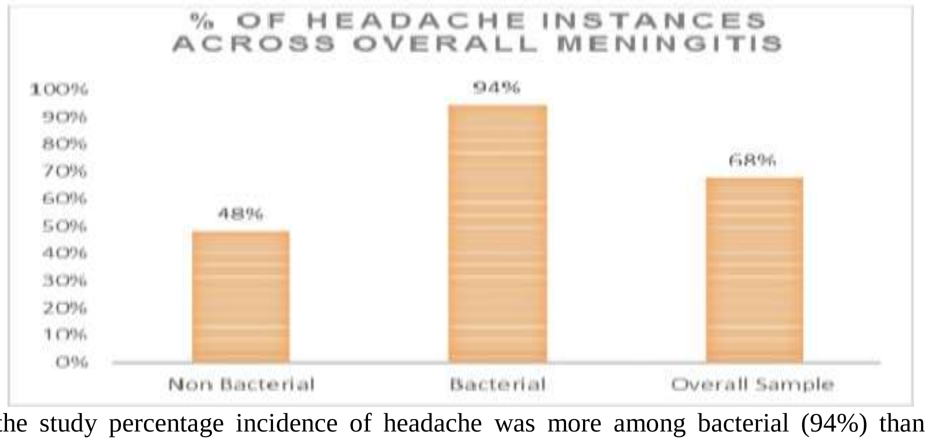


In our present study incidence was more among lymphocytic meningitis (88%) compared to neutrophilic (59%) meningitis and aseptic (71%) meningitis.

Table 9: Distribution of headache instance across overall meningitis

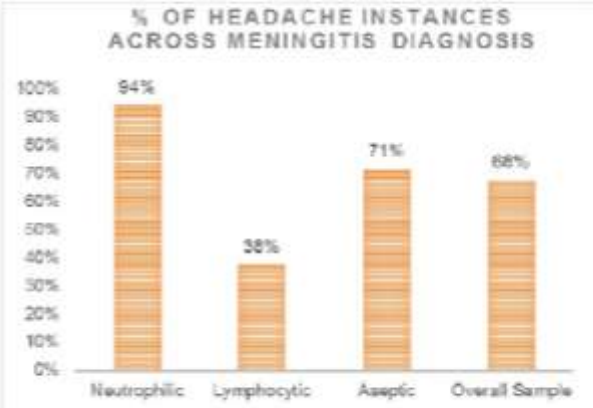
Overall Meningitis	Percentage
Non Bacterial	48%
Bacterial	94%
Overall Sample	68%

Figure 8: Percentage of headache instances across overall meningitis



In the study percentage incidence of headache was more among bacterial (94%) than nonbacterial (48%) meningitis.

Figure 9: Percentage of headache instances across meningitis diagnosis

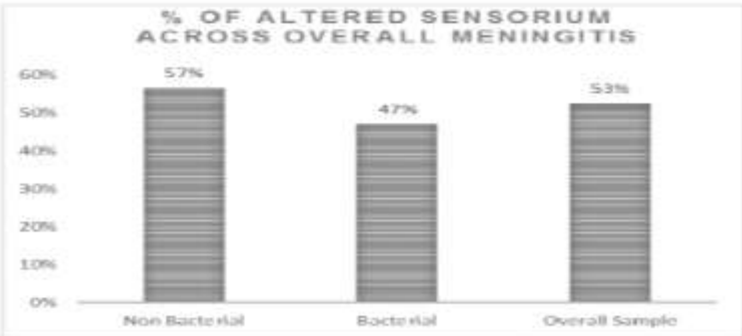


In the study headache was common was present in 94% of neutrophilic meningitis. In case of lymphocytic meningitis and aseptic meningitis the headache was present in 38% and 71% patients respectively.

Table 10: Distribution of ALTERED SENSORIUM Instances across: Distribution

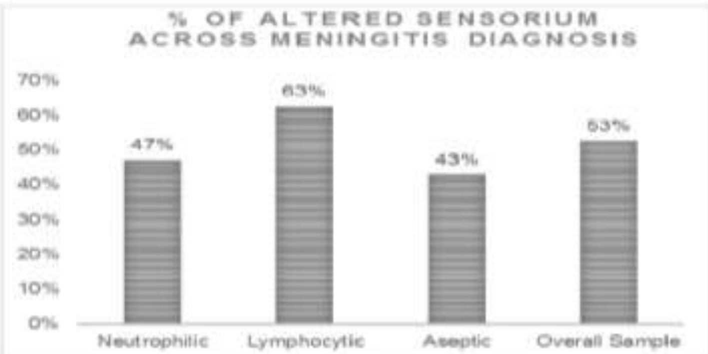
Overall Meningitis	Percentage
Non Bacterial	57%
Bacterial	47%
Overall Sample 53%	53%

Figure 10: Percentage of altered sensorium across overall meningitis



Over incidence of altered sensorium was 53%. Nonbacterial meningitis (57%) incidence was more in comparison with no bacterial (47%) meningitis.

Figure 11: Percentage of altered sensorium across meningitis diagnosis



The presence of altered sensorium was more in Lymphocytic meningitis (63%) compaosed to neutrophilic meningitis in the present study

Table 11: Distribution of Instances of seizure across overall meningitis

Percentage of Instances of SEIZURES	Non Bacterial (%)	Bacterial (%)	Total
0	70%	59%	65%
1	22%	6%	15%
2	4%	29%	15%
3	0%	6%	3%
6	4%	0%	3%
Total	100%	100%	100%

In our study, 30% of non-bacterical meningitis and 41% of bacterial meningitis had seizures.

Figure 12: Instances of seizure across overall meningitis

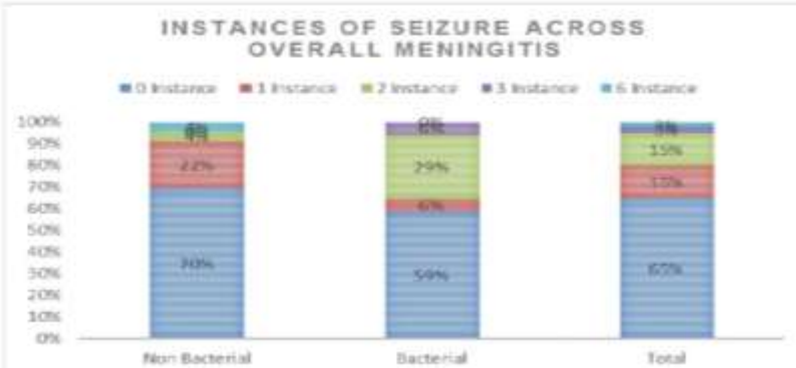
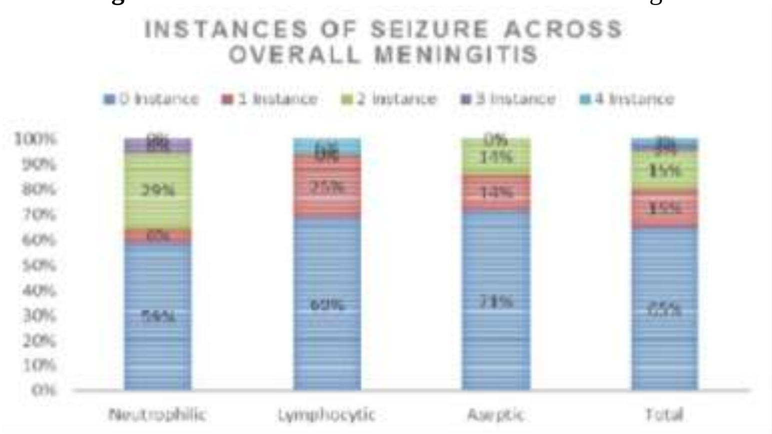


Figure 13: Instances of seizure across overall meningitis



Furthermore 22% of non bacterial and 6% bacterial had one non-bacterial episode of seizure respectively. 35% of bacterial meningitis group had more than one episode of seizure as compared to non bacterial meningitis non bacterial group (8%).

Table 12: Cytological and bio chemical parameters of blood and CSF in different group of meningitis patients.

Parameters	Normal ranges	Neutrophilic Meningitis	Lymphocytic Meningitis	Aseptic Meningitis
Blood				
WBC Count (cells/mm3)	4000-11000	14900	7350	6950 (3630-7950)
CSF				
Cell Count (cells/mm3)	<5	210(90-400)	182(85-300)	32 (20-40)
Cell type (predominant)	Usually lymphocytes	Neutrophils	Lymphocytes	Lymphocytes
Protein (mg/dl)	20-45mg/dl	120(80-165)	119(90-160)	39(30-50)
Glucose (mg/dl)	>2/3of blood glucose	40(26-69)	42(26-86)	74(60-82)
CSF/Serum Glucose ratio	>0.6	0.28(0.288-0.34)	0.3(0.28-0.42)	0.64(0.62-0.66)

In the present study among 40 meningitis cases, the WBC count in neutrophilic meningitis is high compared to lymphocytic meningitis and aseptic meningitis. Among the neutrophilic cases mean CSF cell count is 210 cells/mm3, mean protein level is 120 mg/dl, mean CSF glucose is 40 mg/dl and mean CSF/Serum glucose ratio is 0.28.

Table 13: Average of protein, Sugar and RBS across Neutrophilic, Lymphocytic, Aseptic meningitis

Meningitis Diagnosis	Protein	Sugar	RBS
Neutrophilic	119.94	40.00	140.76
Lymphocytic	119.56	42.81	140.13
Aseptic	39.29	74.00	118.57
Overall Sample	105.68	47.08	136.63

In the present study neutrophilic and lymphocytic meningitis mean and protein was 119.94/dl and 119.56mg/dl respectively. There was significant difference when compared with aseptic meningitis. Similarly the CSF glucose was low in neutrophilic and lymphocytic meningitis (≈40mg/dl) in comparison with aseptic meningitis (74mg/dl).

Figure 14: Mean levels of protein, sugar and across meningitis diagnosis

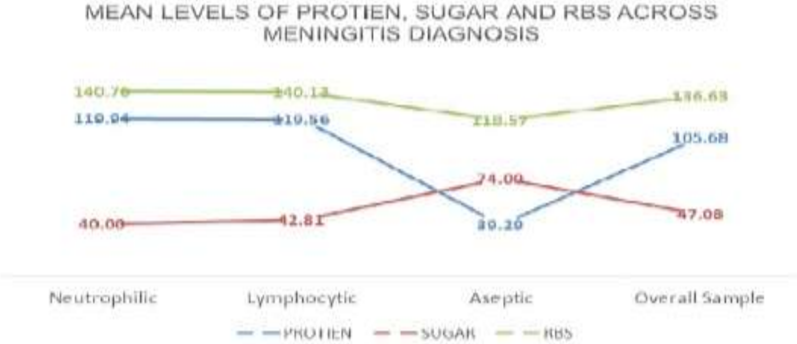


Table 14: Overall meningitis diagnosis

Overall Meningitis Diagnosis	Statistics	CSF Cortisol Levels
Non Bacterial	Mean	3.8
	Median	4.0
	Maximum	5.0
	Minimum	2.0
	No: of cases	23
Bacterial	Mean	13.1
	Median	14.0
	Maximum	17.0
	Minimum	4.0
	No: of cases	17
Total	Mean	7.7
	Median	5.0
	Maximum	17.0
	Minimum	2.0
	No: of cases	40.0

Mean CSF cortisol level in bacterical meningitis (13.1 g/dl) group was siginificantly higher as compared to non-bacterial meningitis (3.8 g/dl) and control group (1.05 g/dl).

Figure 15: Mean CSF Cortisol Levels in Meningitis patients

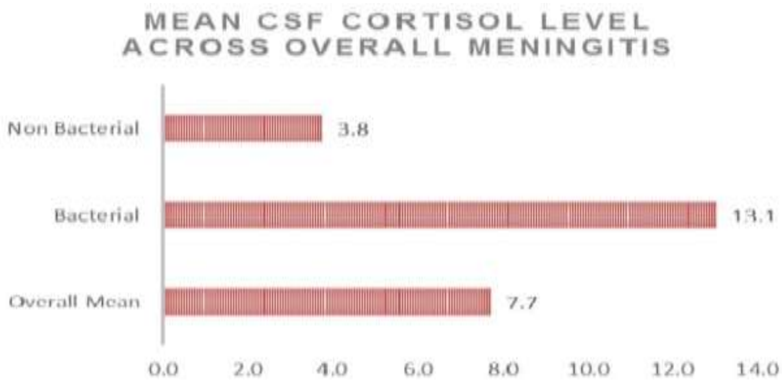
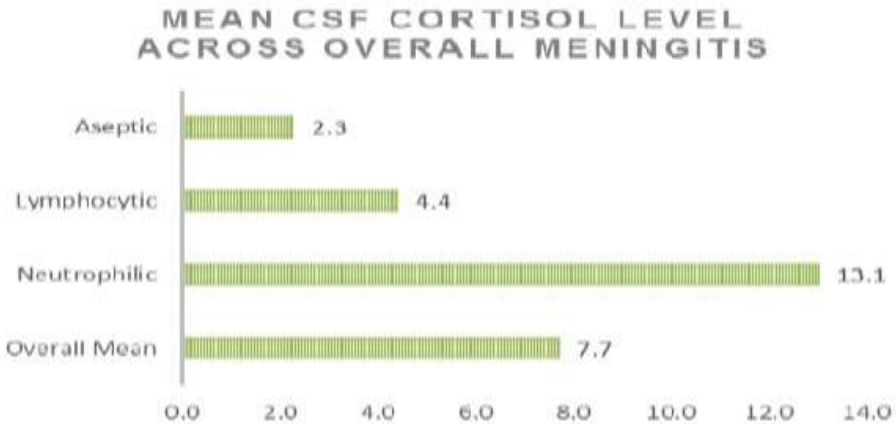


Table 15: CSF cortisol level across neutrophilic, lymphocytic, aseptic memingitis

Meningitis Diagnosis	Statistics	CSF Cortisol Levels [ug/dl]	F value	P value
Neutrophilic	Mean	13.06	110.721	0.000
	Median	14		
	Maximum	17		
	Minimum	4		
	No:of cases	17		
Lymphocytic	Mean	4.44		
	Median	5		
	Maximum	5		
	Minimum	3		
	No:of cases	16		
Aseptic	Mean	2.29		
	Median	2		
	Maximum	3		
	Minimum	2		
	No: of cases	7		
Controls	Mean	1.05		
	Median	-		
	Maximum	1.7		
	Minimum	0.2		
	No: of cases	10		

The P value indicates that the means are different. Mean CSF cortisol level in neutrophilic meningitis was significantly high as compared with lymphocytic, aseptic meningitis and control group. It is statistically significant with p value of 0.000.

Figure 16: Mean CSF cortisol level across overall meningitis



The mean CSF cortisol levels in neutrophilic meningitis are 13.1 g/dl, lymphocytic meningitis is 4.4 g/dl and aseptic meningitis is 2.3 g/dl.

Table 16: Comparison of CSF cortisol levels and neutrophilic, lymphocytic and aseptic meningitis

CSF Cortisol Levels Tukey HSD						
			Mean Difference (I-J)	Std Error	Sig (P value)	95% Confidence Interval
					Lower Bound	Upper Bound
Neutrophilic	Lymphocytic	8.621*	0.688	0.000	6.94	10.3
	Aseptic	10.773*	0.887	0.000	8.61	12.94
Lymphocytic	Neutrophilic	-8.621*	0.688	0.000	-10.3	-6.94
	Aseptic	2.152	0.895	0.054	-0.03	4.34
Aseptic	Neutrophilic	-10.773*	0.887	0.000	-12.94	-8.61
	Lymphocytic	-2.152	0.895	0.054	-4.34	0.03

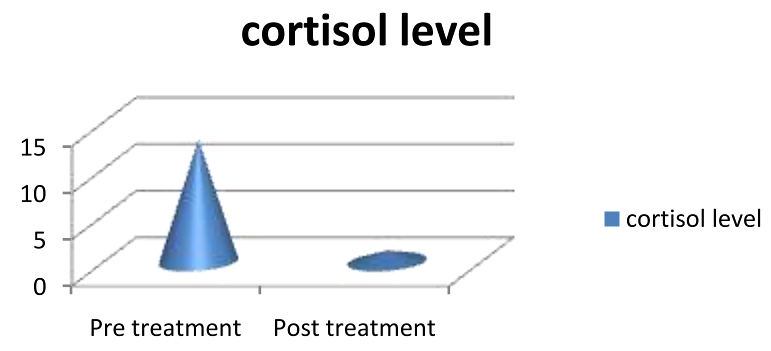
The tukey test confirms that average levels of CSF cortisol is significantly higher for neutrophilic when compared to the average levels of CSF cortisol is not significantly different between lymphocytic and aseptic meningitis.

Table 17: CSF cortisol level in bacterial meningitis in relation to treatment

Mean CSF CORTISOL levels (g/dl)

	Pre treatment	Post treatment
Bacterial meningitis	13.1	1.2

Figure 17: Cortisol level



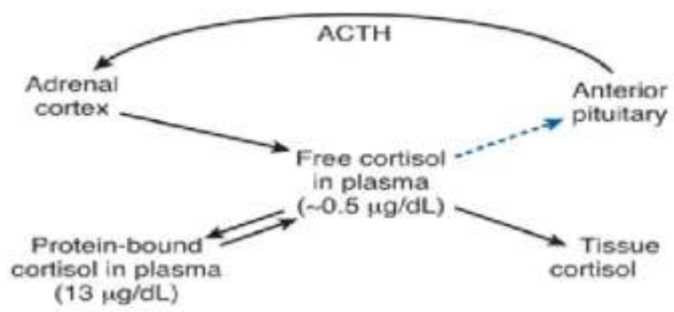
In the present study there was significant reduction in CSF cortisol levels post treatment.

VI. Discussion

Cortisol is the main corticosteroid circulating in humans.Corticosteroids are synthesized in adrenal cortex from cholesterol.The physiological actions of cortisol are:
- Maintaining electrolyte and water balance
- Regulation of carbohydrate metabolism (gluconeogenesis)
- Maintenance of vascular response to catecholamines.
- Anti-inflammatory activity and suppression of immune response.

Cortisol secretion is dependent on the integrity of the hypothalamic-pituitary-adrenal (HPA) axis and the steroid exerts a negative feedback on its own synthesis through this axis. Cortisol measurement is thus an important parameter in the investigation of apparent HPA dysfunction. Figure 18 shows interrelationship of free and bound cortisol

Figure 18: Interrelationship of free and bound cortisol



Cortisol is bound in the circulation to alpha globulin called transcortin or corticosteroid binding globulin. The half-life of cortisol in the circulation is longer (about 60-90 minutes), with approximately 1% excreted unchanged in the urine. This excreted fraction is called urinary "free cortisol" and if renal function is normal, will reflect the level of circulating non-protein bound cortisol. Most immunological methods employed for the determination of urinary free cortisol omit chromatographic steps thereby co-measuring cortisol metabolites. Aftermetabolic breakdown, mainly in the liver, cortisol is excreted into the urine as dihydrocortisol and tetrahydrocortisol derivatives conjugated to glucuronic acid[8].The circulating cortisol concentration is normally subject to acircadian rhythm, with the maximum level being reached in morning at 8-9 a.m. and the minimum around midnight(12am)[9].Cortisol is the major glucocorticoid in humans, maintaining the stress reaction of the body to all kinds of physical and psychological discomfort. Increase in cortisol secretion can take place very quickly, within minutes in acute stress conditions, and can stay at high levels for long periods, sometimes days, months, and even years in chronic disease conditions[10]. The mechanism behind increased CSF cortisol in bacterial meningitis is associated with systemic inflammation, intense stress response and compromised blood brain barrier.During critical illness, cortisol-binding globulin and albumin blood levels decrease by about 50%, leading to an increase in biologically active free cortisol.It was suggested that balance between CSF cortisol and blood cortisol levels are controlled by active efflux of the hormone from the brain. Perturbation of this mechanism by inflammation, together with reduced ability of brain cells to metabolize sterol molecules, may lead to persistent increase in CSF cortisol[7].Although it is known that exogenous corticosteroids can improve the outcome of bacterial meningitis, less is known about the role played by important endogenous anti-inflammatory mediators, such as cortisol and IL-10, in CSF during the course of bacterial meningitis. It is assumed that high levels of IL-10, as were observed in CSF from children with bacterial meningitis, can suppress the intensity of intrathecal inflammation and limit its deleterious effects [11]. Cortisol has effects similar to those of IL-10, but in contrast, elevated serum cortisol levels have shown increased incidence of complications of bacterial meningitis in several studies conducted in paediatric patients [12,13] Moreover, unstimulated high cortisol levels in serum correlate with an unfavourable outcome of sepsis[14] However, whether cortisol concentrations are also increased in CSF during bacterial meningitis and whether intrathecal levels of this hormone have prognostic value are not known.The study by Michal Holub et al concluded that serum cortisol levels were significantly elevated in bacterial meningitis as compared to aseptic meningitis and that cortisol levels could be incorporated as a biological and diagnostic marker in the meningitis panel. 7. Michal Holub et al documented an optimum cutoff value of 46.1 nmol/l for the diagnosis of bacterial meningitis and showed that the elevated levels also correlated with disease severity[7]. The peak incidence of meningitis in the present study was seen in patients in the age group between 16-20 years. In the Michal Holub et al study, the mean age was 42 years[7] in the present study the incidence in males was 65% and in females was 35%. In Michal Holub et al study the incidence in males was 61.7% and in females was 38.3%[7]. In the present study, the most common symptom was fever (100%) followed by headache (72.5%) and vomiting (67.5 %.). In van de Seek D et al study, the classic triad of fever, Nuchal rigidity and change

in mental status was present only in 44% of cases. However 95% had at least two of the four symptoms of headache, fever, neck stiffness and altered mental status[15]. In the present study, Seizures were noted in 36% and is comparable with Van de Beek et al study, the incidence of seizures was 17%[15]. In the present study, the signs of meningeal irritation were present in 100% of cases. Neck rigidity in 100% of cases, Kernig's in 35.5% of cases and Brudzinski's sign 8.7% of cases. In Khatua et al study, neck rigidity was noted in 54% case and Kernig's sign in 40% of cases[16]. In the present study, cranial nerve involvement was seen in 4 cases (10%), three sixth nerve palsy and one seventh nerve palsy which is less common compared to other studies done by Van de Beek et al(33%) .

Virmani et al (27%) and Khatua et al (25%) [14,15]. In the present study, mean CSF cortisol levels were significantly higher in neutrophilic meningitis (13.06microg/dl) as compared to lymphocytic meningitis (4.44 microg/dl), Aseptic meningitis (2.29 microg/dl) and controls (1.05 microg/dl). It is statistically significant,(p<0.0001). Similarly, in Michal Holub et al study, the mean CSF Cortisol was significant elevated in neutrophilic meningitis; (133nmol/ l) compared to aseptic (17nmo/l) and controls (10nmol/l)[7], p value being highly significant (0.001).Beran et al study showed that the mean CSF cortisol was significantly elevated in aseptic meningitis compared to controls. In the present study, similar observations were made, mean CSF cortisol level in aseptic meningitis (2.29 microg/dl) compared to controls (l.05microg/dl). In the present study, it was observed that there was no significant difference in mean CSF cortisol levels in culture positive (l6.05) and culture negative (13.51) neutrophilic meningitis, p value being <0.069.Only 8 patients; of bacterial meningitis showed culture positivity. The 8 cultures were positive and the organisms were streptococcus pneumoniae (7), Neisseria meningitidis (1) and hemophilus influenza (1). This is in controversy to the study by Michal Holub et al, in which it was observed that there was significant difference in CSF cortisol levels in culture positive(162nmol/l) and culture negative percent(103nmol/l). In the present study, a direct correlation was observed between mean CSF and serum cortisol levels (13.06), p value being 0.0001. In Michal Holub et al study similar observations were made, a direct correlation between mean CSF cortisol levels(133 nmol/l) and mean serum cortisol levels(939+/-534 nmol/l).In Singhi SC et al study, free mean cortisol levels were significantly higher in bacterial meningitis compared to aseptic meningitis[7].

The mean CSF cortisol pre-treatment levels (13.06) showed significant reduction post treatment (1.2). Similar observations were made in Michal Holub et al study[7]. In the present study, altogether 28 patients (80%) were admitted to Intensive Care Unit, with a median length of stay in ICU being 7 days and median length of stay in hospital was 18 days. Favorable outcomes were observed in 25patients (85.7%). Three patients (8 .5%) succumbed and two patients (5.71%) exhibited neurological sequelae. In Michal Holub et al study, altogether 40 patients (85%) were admitted toIntensive Care Unit with a median length of stay of 8 days (4-l 5) days and median length of stay in hospital being 24 days. Favorable outcomes of bacterial meningitis were observed in 17 patients (77%) and 7 patients (l 5%) succumbed within 28 days after admission, 4 patients (8%) exhibited severe neurological sequelae.

VII. Conclusion

1) CSF cortisol levels were significantly higher in bacterial meningitis group compared to non-bacterial meningitis group taking the cut off value of 10 microg/dl.
2) CSF cortisol is significantly reduced following specific treatment in bacterial meningitis group. This can be a useful guide in monitoring the response to therapy.

Bibliography

[1]. Juliet Cohen et al: "Meningitis-Definition, Cause, Symptoms and Treatment" fromEzine Articles.
[2]. Roos KL: Bacterial Meningitis. Current Treat Options Neurol 1999.1:147-156.
[3]. Tunkel AR. Hartman BJ, Kaplan SL. Kaufman BA, Roos KL.Whitley RJ:Practice guideline; for the management of bacterial meningitis. Clin Infect Dis 2004. 39:1267-12S4.
[4]. Van Woensel JB, Biezeveld MH, Alders AM, Eerenberg AJ, Endert E, Hack EC, von Rosenstiel IA, Kuijpers TW. Adrenocorticotropic hormone and cortisol levels in relation to inflammatory response and disease severity in children with meningococcal disease. J Infect Dis. 2001;184:1532–1537. doi: 10.1086/324673. [PubMed] [Cross Ref]
[5]. Singhi SC, Bansal A. Serum cortisol levels in children with acute bacterial and aseptic meningitis. Pediatr Crit Care Med. 2006;7:74–78. doi: 10.1097/01.PCC.0000192317.90862.44. [PubMed] [Cross Ref].
[6]. .Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA. 2000;283:1038–1045. doi: 0.1001/jama.283.8.1038. [PubMed] [Cross Ref]
[7]. Michal Holub, OndrejBeran,OlgaDzupova, JarmilaHnykova, Zdenka Lacinova.JanaPrihodova.BohumirProchazka and MiroslavHelcl:Cortisollevels in cerebrospinal fluid correlation with severity and bacterial origin of meningitis. Journal of Critical care 2007. 11:R41.
[8]. Suniti C Singhi. ArunBansal: pediatric critical care medicine a journal of the society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care societies 2006.7:74-7S.
[9]. McGregar AL: THE MENINGES AND CSF. A synopsis of surgicalanatomy 11thEdition,II; 5-10: 1975.
[10]. Fouad G Youssef. MD. Hammam El-Sakka. MD. Adel Azab. D et al Etiology, antimicrobial susceptibility profiles, and mortality associated with bacterial meningitis among children in Egypt.
[11]. Volume14. Issue 1. Pages 44-48(January 2004).
[12]. Narayanan S,Parandaman V, Narayanan PR, Venkatesan P et al.Evaluation of PCR using TRC-4 and IS 6110 primers in detection of tuberculous meningitis. J Clin microbial 2001;39:2M6S.
[13]. James VHT. Landon J (eds). Control of corticosteroid secretion – current views and methods of assessment. Recent Advances in Endocrinology Ed 8:50-94.1968.
[14]. Hellman L et al. Cortisol is secreted episodically by normal man. Journal ofClinical Endocrinology and metabolism. 30:411-422; 1970.
[15]. van Furth AM, Seijmonsbergen EM, Langermans JA, Groeneveld PH, de Bel CE, van Furth R. High levels of interleukin 10 and tumor necrosis factor alpha in cerebrospinal fluid during the onset of bacterial meningitis. Clin Infect Dis. 1995;21:220–222. [PubMed]
[16]. van Woensel JB, Biezeveld MH, Alders AM, Eerenberg AJ, Endert E, Hack EC, von Rosenstiel IA, Kuijpers TW. Adrenocorticotropic hormone and cortisol levels in relation to inflammatory response and disease severity in children with meningococcal disease. J Infect Dis. 2001;184:1532–1537. doi: 10.1086/324673. [PubMed] [Cross Ref].
[17]. Singhi SC, Bansal A. Serum cortisol levels in children with acute bacterial and aseptic meningitis. Pediatr Crit Care Med. 2006;7:74–78. doi: 10.1097/01.PCC.0000192317.90862.44. [PubMed] [Cross Ref]
[18]. Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA. 2000;283:1038–1045. doi: 10.1001/jama.283.8.1038. [PubMed] [Cross Ref].
[19]. Diedenk Van de Beek. MD; PhD: Jan de Gans . MD; PhD:Lodewvk Spanjaard MD. PhD: and MarinusVermeulen. MD; PhD Cluneal features and pcoHEOstic Actors m adults with BactenalMenmzits SUM
[20]. 2004; 3 51 1849- 1S59 .October 28.
[21]. Khatua SP .Bacterial meningitis in children: Analysis of 231 cases. J.Indian Med Ass 1961:37:332