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RESEARCH ARTICLE

EFFECT OF GRAM NEGATIVE BACTERIAL INFECTIONS ON LIVR AND RENAL FUNCTIONS BEFORE AND AFTER ANTIBIOTIC TREATMENT.

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Abstract

Gram negative bacterial infections are predominant in tropical countries. Studies done in the past have observed the effect of gram negative bacterial infections on liver, renal and cardiac functions. Marked elevation of inflammatory markers PCT, CRP and TNF-α are observed in all types of gram negative bacterial infections. The purpose of this study is to find out the effect of antibiotic on gram negative bacterial infections on liver and renal markers before and after treatment. The outcome of this study has confirmed that liver markers showed elevations both during infection and after antibiotic treatment showing highly significant correlation on the 8th day before and after treatment with antibiotic; further significant correlations were also observed between normal and patients before and after antibiotic treatment. Haematological markers ESR and WBC also showed similar significant correlations as observed for liver markers. Renal markers urea &creatinine also showed similar correlations.

Introduction:-

Infectious diseases are still dominating in developing countries and the environment plays a powerful role in the transmission of infectious diseases including vector-borne diseases such as malaria, dengue, Kala Agar, Plague, Filarasis, Chickungunya and yellow fever to name a few. Each year infectious diseases kill 3.5 million people world wide affecting mostly the poor and young children who live in low and middle income countries. Research can change this and bring health to many more. The poorest in developing countries face a burden of communicable diseases. Disease that have re-emerged may be due to evolution of antimicrobial resistance by pathogens or due to insecticidal resistance by vector, human migration, HIV/AIDS and changes in transmission strategies. The aim of this research is to highlight the various organs affected due to infection by a host of organism by evaluating biochemical changes at different stages according to the degree of infection, and to highlight the role of biochemistry in the diagnosis of Infectious diseases along with clinical microbiology.

The majority of pathogens that cause abdominal infection in patients with liver cirrhosis are gram negative, and drug resistance is significantly higher in nosocomial infections than in non-noscomial infections.[(1)]E. coli bacteraemia rates have risen due to rising rates of resistant organisms; little change occurred in susceptible E. coli. Although the severity of resistant infections, and their outcome, appear similar to susceptible E. coli in the setting studied, the increasing burden of highly resistant organisms is alarming and merits on-going surveillance.[(2)] Sustained Gram-negative sepsis induced a hyperdynamic state and hyperaemic Acute Renal Failure (ARF). Despite increased renal perfusion, Urine Sodium concentration (UNa), Fractional excretion of Sodium (FeNa) and fractional excretion of Urea nitrogen (FeUn) decreased significantly. These findings suggest that, in sepsis, these urinary biochemical changes are not reliable markers of renal hypoperfusion.[(3)]

Rheumatoid Factor (RF) induced by E.coli glycolipoprotein correlated with 'protection' from liver damage, indicating that RF autoimmune response does not necessarily exacerbate liver disease.[4]E. coli + bile peritonitis rats had significantly elevated levels of bilirubin, Alkaline Phosphatase (ALP), Aspartate Transaminase (AST) and Alanine Transaminase (ALT) as compared with both controls and rats with peritonitis induced by E. coli alone. Hepatic dysfunction as revealed by routine laboratory tests is seen early in experimental peritonitis in the rat, but this is not accompanied by a reduced ALP clearance rate.[5]There was an increase in the number of E. coli in the proximal small intestinal flora in Non Alcoholic Steato Hepatitis (NASH) group than in control group and Tumor Necrosis Factor Alpha (TNF-α) level was significantly higher in NASH group than in control group.[6]Procalcitonin (PCT), and C-reactive Protein (CRP) serum levels for differentiating sepsis from Systemic Inflammation Response Syndrome (SIRS), identifying new fever caused by bacteremia and assessing prognosis. On Intensive Care Unit day 1, the sepsis group had higher serum Soluble Triggering Receptor Expressed on Myeloid Cells (sTREM-1), PCT, and CRP levels compared with the SIRS group.[7] Although CRP levels are reduced in response to acute infection, production is nevertheless maintained even in patients with advanced liver dysfunction.[8]

The most common predisposing factors associated with klebsiella (K) pneumonia were diabetes mellitus (58%), urolithiasis (25%) and immunosuppression (17%). All patients with K pneumoniae renal abscesses should receive empiric antibiotics and percutaneous drainage or aspiration, and surgical intervention as necessary for patients with intractable disease.[9] In K pneumonia laboratory data showed raised enzyme levels of ALP, AST, ALT, increased direct bilirubin, White Blood Count (WBC) with neutrophilia.[10]K pneumoniae bacteremia was commonly associated with elevated liver enzymes, whereas none of the infants with Pseudomonas aeruginosa bacteremia had elevated liver enzymes. Gram-negative bacteremia is commonly associated with cholestasis in premature neonates. Liver enzyme abnormalities are more common than elevated conjugated bilirubin and not all gram-negative bacteria have the same effect and the lack of enteral feeding seems to play a more significant role than the administration of parenteral nutrition.[11]

Many bacteria among the Enterobacteria family are involved in infectious diseases and diarrhoea. Significant increase of some biochemical parameters such as ALP, AST, ALT and creatinine were found.[12] Patients with biochemical evidence of liver disease generate significantly lower serum CRP concentrations during bacteraemia than patients without liver dysfunction. Serum CRP concentrations should be interpreted with caution in patients with liver disease to diagnose and monitor bacterial sepsis.[13]

The serum PCT level correlates well with the severity of Pseudomonas pseudomallei infection and is comparable with other acute-phase markers. However, this prognostic indicator and marker of continuing disease activity is not specific to melioidosis and could be applied to other severe infections.[14]A PCT value greater than or equal to 7 ng/mL obtained at the time of admission to the ICU is a predictor of short-term mortality and thus may allow the identification of those septic patients at increased mortality risk and help improve their treatment.[15]PCT is a useful biomarker for early and accurate prediction of sepsis in severe trauma patients. If used in adjunct to clinical findings, it proves to be a good biomarker for early diagnosis, treatment and for monitoring response to therapy in confirmed cases of sepsis. It will prove to be a good supportive indicator of sepsis in early stages for the trauma patients in a low resource country like India.[16]

Material and methods:-

A total of 50 gram negative bacteria infected patients in the age group of 9- 75 years (Males and Females) who were investigated for blood culture, liver function tests and blood counts were enrolled for this study. An equal number of non-infectious normal populations were also enrolled and all the analytes were tested as for patients group. The sole aim of this study was to find out the effect of gram negative bacteria infections on liver function before and after antibiotic treatment. Blood samples were collected on the 8th day after antibiotic treatment to assess liver and renal functions.

Inclusion Criteria :

- All patients in the age group of 18 to 65 years, both Male and Females
- Patients who do not have previous history of Renal, Cardiac and Liver diseases
- Patients who are not on any antibiotics.
- Patients who were diagnosed to have Infection due to bacteria like Klebsiella, Pseudomonas, Enterobacter, Escherichia coli.

- Temperature should not be more than 100^0F
- Patients should not have taken any steroids for the last 1 month

Exclusion Criteria :

- All patients in the age group below 18 and above 65 years, both Male and Females
- Patients with previous history of Renal, Cardiac and Liver diseases.
- Patients who are on antibiotics
- Patients who were diagnosed to have Infection due to bacteria like Klebsiella, Pseudomonas, Enterobacter, Escherichia coli.
- Patients having chronic illness.
- Female patients with confirmed pregnancy and Lactating woman.
- Patients whose temperature are normal.
- Patients who are on any medication for the last 1 month.
- Patients whose Liver enzyme – AST or ALT > 60 U/L upper limit of normal 40U/L.

Results:-

Table – I Mean & SD for Patient groups: Before and After antibiotics (n=50).

Table II Statistical Parameters(t & p) for Bacterial infected patients

Group	Statistics	T.BIL	D.BIL	T.PRO	ALB	AST	ALT	ALP	GGTP	UREA	CREAT
Normal	**Mean**	0.6	0.2	7.3	4.1	25	22	21	84	24	0.8
	SD	0.15	0.08	0.32	0.19	8.59	4.2	9.68	23.66	4.99	0.19
Before Antibiotics	**Mean**	1.005	0.53	6.09	3.19	65	59	119	76	51	1.18
	SD	0.701	0.471	1.08	0.70	72	50	69	79	29	1.10
After Antibiotics	**Mean**	0.647	0.353	5.845	2.95	104	52	147	140	42	1.247
	SD	0.317	0.244	1.054	0.732	268	36	87	198	34	1.312

Table III Statistical Parameters (t & p) for Bacterial infected patients before treatment n=50.

Analytes	t	p
T.Bili	3.6914	0.0004
D.Bili	3.6119	0.0005
TP	6.9373	0.0001
ALB	8.7496	0.0001
AST	4.1665	0.0001
ALT	2.1697	0.0324
ALP	2.9954	0.0035
GGTP	4.4853	0.0001
Urea	5.7073	0.0001
Creat	2.4476	0.0162
ESR	7.5231	0.0001
WBC	4.6883	0.0001

After treatment n=50.

Analytes	t	P
T.Bili	2.8790	0.0049
D.Bili	3.2734	0.0015
TP	8.3406	0.0001
ALB	10.8755	0.0001
AST	2.9529	0.0039
ALT	3.5844	0.0005
ALP	2.7038	0.0081
GGTP	5.0363	0.0001
Urea	4.3508	0.0001
Creat	3.0125	0.0033
ESR	7.5530	0.0001
WBC	4.0957	0.0001

Table IV Statistical Parameters (t & p)
Gram negative bacterial infected patients Before and After Treatment (n=50).

Analytes	t	p
B.TBili VS A.TBili	5.972	<0.000001
B.DBili VS A.DBili	13.516	<0.000001
B.TP VS A.TP	5.146	<0.000001
B.ALB Vs A.ALB	8.295	<0.000001
B.AST VS A.AST	3.417	<0.001
B.ALT VS A. ALT	4.407	<0.0001
B.ALP VS A.ALP	6.77	<0.000001
B.GGTP VS A.GGTP	3.868	<0.001
B.Urea VS A.Urea	5.415	0.000001
B.Creat VS A.Creat	1.873	<0.05
B.ESR VS A.ESR	7.953	<0.000001
B.WBC VS A.WBC	4.962	<0.000001

Table I shows the mean and SD results for the analytes studied for patients before and on 8th day of antibiotic treatment along with similar data for controls.
Table II presents the statistical parameters (t & p) between patients before antibiotic treatment and controls. All the parameters studied shows very good correlations at $p<0.001$, except ALT & ALP which showed a significant level of <0.05 and<0.01.These observations confirm that gram negative bacterial infections does indeed alter the functions of liver and kidney along with WBC & ESR.
Tables II & IV shows similar statistically data but after treatment Vs controls and before and after 8th day of antibiotic treatment for patients. The observations are similar to the one explained under Table II.

Discussion:-

Many previous studies have predicted alterations of renal and liver functions along with haematological indices due to gram negative bacterial infections. All infections generally brings out increased level of TNF-α, CRP and PCT, among which PCT is considered as gold standard.[15,16]. Previous studies have shown elevation in ALP, AST and ALT due to gram negative bacterial infections and our study has also confirmed such observations.[6,11] Alterations in blood indices were also showed in previous studies and such observations were confirmed in our study too.[12] All three types of liver functions viz synthetic (ALB), excretory (Bilirubin, ALP) and metabolic (Bilirubin, Urea) as well as blood indices (WBC) and infection marker (ESR) were all elevated on the 8th day of treatment as observed by the results shown in Table I.

Conclusions:-

The outcome of this study strongly predicts that all gram negative bacteria viz. Klebsiella, Pseudomonas, Enterobacter, Escherichia coli infections will alter /affect the functions of kidney and liver and blood total count as well as ESR. Further, highly significant correlation were obtained for all the liver function profile as well as the two principal kidney markers urea &creatinine between patients& controls before and after antibiotic treatment on the 8th day. The outcome of this study will enable future research to give more focus to evaluate other organ functions and to include liver and kidney function tests as routine for all gram negative infectious patients.

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Conflict of Interest:-None

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