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ROLE OF PROPHYLACTIC ANTIBIOTICS IN PREVALENCE OF SEPSIS IN ACUTE LIVER FAILURE

Medicine

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ABSTRACT

The major cause of death in ALF is sepsis accounting for 24-49% of deaths in Indian patient population which is common. Hence we aimed to study the prevalence of sepsis in ALF and the role of prophylactic antibiotics in limiting the incidence of infections in ALF and improving related mortality. Total 46 patients of ALF were divided into 2 main groups with SIRS>=2 and SIRS<2 at the time of admission based on the number of SIRS components. Patients with SIRS>=2 were studied for the prevalence of sepsis in ALF. Group of patients with SIRS<2 were studied for the incidence of sepsis and the role of prophylactic antibiotics in ALF dividing both the groups into further control group who received prophylactic antibiotics and the test group who were treated with antibiotics only on deteriorating due to sepsis and on every episode of worsening. Role of prophylactic antibiotics was studied by documenting serial infections and mortality in control group and comparing with the test group without prophylactic antibiotics.

KEYWORDS

INTRODUCTION:

ALF is most common condition composing of both fulminant and sub fulminant hepatic failure with rapid impairment of liver function which is characterized by jaundice and subsequent altered mental state and coagulopathy by prolongation of prothrombin time ≥ 15 secs or INR ≥ 1.5 and presenting any degree of mental alteration in a patient with clinical evidence of liver disease less than 26 weeks of duration in the absence of pre-existing liver disease (2,3,4). Various studies in India suggestive of, liver failure occurring after 4 weeks of onset of jaundice usually presents with ascites, encephalopathy. These patients were different from ALF cases and were identified as sub-acute liver failure and these patients do not survive more than 6 months(8,9). The cause of death has been identified as sepsis in 24%-49% of Indian patients with ALF and is documented as second most common cause of death after cerebral edema. Various studies on ALF had reported sepsis in 11% of patients, but recent studies have proved a 50% association with bacteremia(5,15). Around 10-37% of mortalities in ALF could be attributed to bacterial infections and 10-80% experience bacterial infections sometimes in course of illness(8). Prophylactic antibiotics role in ALF has always been debatable. Some studies have supported prophylactic antibiotics use and some groups do not suggest its use, as it may lead to resistant infections in about 10% of cases. Sepsis is suspected with clinical evidence based on fever, tachycardia, leukocytosis and patients are investigated based on signs and symptoms of sepsis(20,21). An analysis of 50 patients for prospective study of bacterial infections in ALF showed 80% of patients with infection rate and with 70% gram positive infections commonly seen in respiratory tract, urinary tract and indwelling central venous line catheters(5,8)

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Aims and Objectives:

Patients with ALF the integrated multidisciplinary supports involving liver transplant is not easily available/affordable in the country, hence intensive medical management including prevention and treatment of sepsis and its deleterious outcome emphasizes in the early diagnosis and treatment of ALF.

Pathophysiology of Sepsis in ALF:

Decrease in complement levels, impaired phagocytic functions which increased need for invasive procedures make patients of ALF more susceptible to infections. Gram negative sepsis with endotoxaemia resulting in microcirculatory failure and tissue hypoxia contribute to multiorgan failure(13,17).

Concept of prophylactic antibiotics in ALF

The criteria for SIRS are fulfilled by about 60% of patients with ALF though 1/3rd of patients fail to express SIRS even when clinical sepsis is evident. Majority of bacterial infections occurred early within 72 hours of admission(19,24). Pneumonia is common in sepsis, accounting for 50% of the infections developed at a median of 5 days after onset of ALF whereas bacteremia and urinary tract infections occurred at a median of 3 and 2 days respectively(5,21).

MATERIALS AND METHODS:

A small prospective case control study was carried out on 46 patients of ALF who fulfilled the diagnostic criteria of ALF as formulated by O'Grady and colleagues (10,14). Period of study was done between December 2015 till August 2017 at SVIMS; Tirupati, A.P.

Inclusion Criteria:

- Patients above 10 years of age
- Jaundice with subsequent encephalopathy within 8-28 das
- Coagulopathy with INR ≥ 1.5

Exclusion Criteria

- History of illness>4 weeks
- Pre-existing liver disease
- Alcoholism>10 years
- Encephalopathy due to non-hepatic causes
- Evidence of portal hypertension

Sampling strategy:

Total of 46 patients were initially categorized into groups with SIRS ≥ 2 and SIRS<2. Out of 46 patients, 20 patients of SIRS ≥ 2were considered to have clinical sepsis and were studied for prevalence of sepsis. Patients with SIRS<2 the remaining 26patients formed the study group who were further divided into (I) Control (13 patients), on prophylactic antibiotics (II) Test (13 patients), who were not given prophylactic antibiotics.

SIRS Components are studied under these parameters
Pulse rate >90/min
Total leucocyte count<4000/>12000
Temperature <36^{0}c/>38^{0}c
Respiratory rate>24/min

Aim and Objectives:

Our aim was to observe whether SIRS can be considered as a true representation of clinical sepsis to justify the use of prophylactic antibiotics in the presence of more than 2 SIRS components.

Of the 20 patients with SIRS≥ 2, 70% (14/20) patients had evidence of either radiological or microbiological infections. Patients with SIRS<2, 42.3(11/26) had evidence of infection whereas 27.3% (3/11) with clinically documented infections expressed only 0-1 SIRS components as laid by O'Grady and colleagues. Out of 26 patients with SIRS< 2 of the study group, subsequent observation and monitoring of SIRS components showed that by day 2-3, 12 patients (8 from the test group without prophylactic antibiotics and 4 from the control group on antibiotic prophylaxis) developing more than 2 SIRS components,

50% (6/12) had become infected as compared to 14.3% (2/14) infections in the remaining 14 patients who never expressed more than 1 SIRS components (significant at p≤0.05 after following Z test). Therefore initial SIRS assessment did not correlate with prevalence of infection in the study group but subsequent increase in SIRS components correlated well with acquisition of infections.

Events of ongoing sepsis as observed in SIRS≥ 2 were 80% and SIRS < 2 was 57.7%. A statistically significant observation was that, presence of worsening factors was associated with 67.8% infections whereas in absence of such factors only 26.6% were infected.

Infections in ALF

Infection rate was observed was 54.3% (25/46). In SIRS≥ 2, 70% (14/20) were infected with 64.3% (9/14) mortality was in infected patients. In SIRS <2, 42.3% (11/26) were infected with 54.5% (6/11) mortality in the infected. Non-infected patient Mortality rate was 30% which is not significant at p≤0.05. Prevalence of infections in ALF as determined by observing day 1 infections was 64% (16/25) of which 93% infections was prevalent in SIRS≥ 2 and 27.3%(3/11) in SIRS <2 (Significant at p≤0.05 after performing the Z test).

Patients with ALF, respiratory tract infections accounted for 64%(17/25) and 41.2%(7/7) had microbiological documentation as Klebsiella 57%(4/7); E.coli28.5%(2/7) and Acinetobacter 14%(1/7) isolated from sputum and Et-tube cultures.

In our study, the most significant organism was Pseudomonas 33.3%; E.coli 27.8%; Klebsiella 22.2%; Staphylococcus, Acinetobacter and Candida was 5.5% each. Urosepsis 44.4% (8/18) were predominantly caused by E.coli 62.5%(5/8) and Pseudomonas and Staphylococcus. E.coli infections were documented in first 2 days of illness suggesting E.coli prevalence in ALF.

Infections and Mortality in ALF:

Mortality in ALF is multifactorial. Therefore in this study we compared mortality in infected to non-infected with or without prophylactic antibiotics.

Mortality in the study group of ALF was 52.2% and Mortality in SIRS <2 was 42.3% and SIRS≥2 was 60%. In SIRS ≥ 2, microbiologically documented infections were reported in 25% (5/20) and evidence of chest infections clinically and imaging without microbiological confirmation was present in 65% (13/20).

Control:

At the time of admission total infection rate was 53.8% (7/13). From day 2 onwards documented infections were 71.4% (5/7) with mortality 40% (2/5). In test group who were without antibiotic prophylaxis 61.5% (8/13) deteriorated from day 2-3 onwards with clinical signs of sepsis. 25% (2/8) attributed to microbiological sepsis and chest infections. 38.5% (5/13) did not deteriorate but documented Urosepsis in 40% (2/5). Documented infections were 30.7% (4/13) of which day 2 onwards infections were 75% (3/4) and associated mortality was 66.7% (2/3). This showed that prophylactic antibiotics could reduce the mortality in the infected to 40% from 66.7% when antibiotic prophylaxis was not used. (Statistically not significant at p≤0.05 after performing the Z test)

DISCUSSION:

ALF is dangerous and complicated illness involving almost all organ system. Where integrated supports involving liver transplant are lacking, prevention of sepsis and its disastrous outcome remains the mainstay of treatment. This small scale retrospective study was carried out on 46 ALF patients after they fulfilled the diagnostic criteria as laid down by O'Grady and colleagues (10,14).

When SIRS was recorded in each episode of worsening and infections, it was observed that 30.8% (4/13) from the control group and 61.5% (8/13) from the test group deteriorated and expressed more than 2 SIRS components from day3. Microbiological and radiological documented infections were present in 14.3% (2/14) in SIRS<2 and 50% (6/12) in SIRS≥2. Thus SIRS or late expression of SIRS as noted in 27% in our study and also noted in several other studies re-emphasize the fact that infections may be present in ALF without triggering the immune response.

Worsening factors and infections: The factors suggesting ongoing sepsis such as unexplained hypotension, decreasing urine output, worsening encephalopathy, severe acidosis and disseminated intravascular coagulation was observed in 80% of cases with SIRS≥2 and only 57.7% in SIRS<2. It was observed that presence of worsening factors was associated with 67.8% infections whereas in absence of such factors only 28.6% patients were infected. This association was found to be statistically significant. Prevalence of sepsis in ALF as determined by observing the infections on admission both in SIRS≥2 and SIRS <2 categories was 64%. There were 18 episodes of microbiologically documented sepsis in 13 cases out if 25 infected patients and the other 12 had clinical and radiological evident infection. A considerable number of cases had concomitant infections in 2 or more sites. Respiratory tract infections accounted for 64%(17/25). Gram negative bacteria have long been recognized as a cause of sepsis and septic shock(16,19). In our study Pseudomonas emerge as the most significant pathogen accounting for 33.3% of septicemia followed by E.coli 27.8% and Klebsiella 22.2%. Staphylococcus, Acinetobacter and Candida infections were found in 5.5% each. Candida and other fungal cultures were about 5-6%.

Role of prophylactic antibiotics in ALF was studied by documenting infections those occurred after day 1 and their outcome was compared between control group where prophylactic antibiotics were used and the test group where prophylactic antibiotics were not used. It was observed that only 2 out of 18 episodes of microbiological sepsis were documented in the first 2 days of illness and thereafter incidence of sepsis increased with increasing duration of illness. Therefore there may be a role in prophylactic antibiotics in arresting the acquisition of infection during the course of illness and the deleterious outcome of sepsis in ALF. No significant difference was observed with the use of prophylactic antibiotics used after deterioration with clinical sepsis. Therefore it may not be always wise to wait for clinical signs of sepsis to appear as it has already been shown that 27.3% of infected patients in our study never expressed more than 1 SIRS component. A recovery rate of 80% with 40% infections was seen in the control group with lower grades of encephalopathy with prophylactic antibiotic as compared to 69.2% recovery with 30.8% infections in the test group without antibiotic prophylaxis though this observation was not statistically significant. The role of prophylactic antibiotic was finally studied by comparing the outcome in subsequently acquired infections in the control and test group.

The result of this study suggests that prophylaxis against Gram negative sepsis needs to be emphasized in ALF. Daily assessment of clinical deterioration with expression of SIRS correlated well versed with infections in our study. It can thus be recommended that antibiotics in those with clinical manifestations (SIRS) may be beneficial. The observations in this study suggest an antibiotic regime of 3rd generation Cephalosporin's to curb the incidence of sepsis and related mortality in ALF. A statistical significance could not be established in this study probably owing to the small number of cases but a trend towards improvement was evident with prophylactic antibiotics.

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