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Original Research Article

Study of Magnitude and Outcome of Hepato-Biliary Dysfunction in Neonatal Septicemia

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Abstract

Background: Hepatobiliary dysfunction is one of the most usual clinical conditions manifesting in neonatal medicine. The huge majority of cases of unconjugated hyperbilirubinemia entail non pathological causal factors, whereas cholestatic jaundice generally reflects underlying pathologies which can be very serious. Few cases of neonatal cholestasis need quick, specific medical or surgical treatment, so it is rapidly vital to recognize the cause and treat the specific pathology.

Material & Methods: The study was carried out in all out born and inborn newborns having blood culture positive sepsis. Investigations done in this study were complete blood count (CBC), C- Reactive Protein (CRP), Peripheral blood films, blood culture sensitivity, liver function test (LFT) which includes SGOT, SGPT, serum bilirubin (total, direct and indirect), serum total protein, serum albumin, serum alkaline phosphatase, PT/INR and USG abdomen. Blood levels for estimation of total and direct bilirubin, serum alkaline phosphatase, SGOT, SGPT, serum proteins, prothrombin time were taken after 72 hours of clinical suspicion of sepsis. These investigations (LFTs) were repeated between days 10 to 14.

Results: In our study Hepatobiliary dysfunction was found to be present in 61.67% Conjugated Hyperbilirubinemia was seen in 11.67%.

Significant association was observed between Hepatobiliary Dysfunction with Elevated SGPT (P<0.001S). Significant difference was observed between the Hepatobiliary Dysfunction with SGPT and SGOT.

Conclusion: Neonatal Sepsis is an important cause of hepato-biliary dysfunction in newborns. Septicemia must be ruled out by necessary investigations in newborns with cholestasis at the earliest before planning for other investigations and work up as it is(NNS) treatable by appropriate antibiotics and supportive treatment.

Introduction

Neonatal sepsis is explained as a clinical syndrome distinguished by signs & symptoms of infection with or without bacteremia in the 1st month of life and encircles various systemic infections of the new born [1].

Neonatal sepsis has 25% contribution in the total neonatal mortality in developing countries [2] & accounts for about 0.52 million deaths yearly in the world [3] Gram-negative organisms are mostly responsible for sepsis in developing countries & are frequently linked with multi-organ dysfunction, resulting in high mortality & poor prognosis in the neonates.

The load of disease attributed to neonatal infections differs by geographic region and maternal and neonatal risk factors. Globally, it is evaluated that more than 1.4 million neonatal deaths yearly are the outcome of invasive infections [4]

Currently, many infants with sepsis have been hospitalized in neonatal intensive care units for weeks or months due to extreme prematurity, or due to congenital malformation or surgical conditions [5]. Sepsis is often associated with cholestasis, Hyperbilirubinemia & liver enzyme abnormalities [6].

The key is to differentiate between the newborns having cholestatic jaundice due to septicemia from those having obstructive, hereditary, or metabolic disorders. The exact course, pattern of abnormalities, and outcome of sepsis associated Hepato-biliary dysfunction in neonates have not been described. The present study was conducted to determine the prevalence, pattern, and outcome of Hepato-biliary dysfunction in neonatal sepsis, and to evaluate its effect on the survival and growth [7].

Aims and Objectives

- To determine the magnitude of Hepato-biliary dysfunction in neonatal sepsis.

Material & Methods

This was a hospital based prospective study conducted in the department of Neonatalogy of a tertiary care hospital from January 2020 to July 2021.

Study subjects-All newborns admitted in wards and NICU of the department of pediatrics with suspicion of sepsis and blood culture positive were the subjects for the present study as per following inclusion and exclusion criteria.

Inclusion criteria:

All symptomatic newborns having blood culture positive bacterial sepsis for pathogenic bacteria were included in the study.

Exclusion criteria:

1. All those with congenital hepato-biliary malformations. i.e. choledochal cyst on USG.
2. Newborns with Apgar score < 3 at 1 minute i.e. HIE III
3. Newborns who are on total parenteral nutrition.
4. Those who were not signing informed written consent.
5. Age > 28 days of life

The study was carried out in all out born and inborn newborns having blood culture positive sepsis. This study was approved by the Research Ethics Committee After taking informed written consent from selected patients (as per exclusion and inclusion criteria) thorough history about maternal fever, diarrhea, vomiting, leaking or bleeding per vaginum, multiple per vaginum examinations, difficult or prolonged labor and meconium aspiration

and history of consanguineous marriage or family history of jaundice/cholestasis/liver disease was taken. Details on the mode of delivery and resuscitation at birth was recorded. Gestational age of the neonate was calculated from the first day of the last menstrual period of the mother. In case if last menstrual period is not known, gestational age was calculated by modified Ballard score.

The symptoms that suggest infection such as poor feeding, pre-feed gastric residues, respiratory distress, fever, hypothermia, apnea, bleeding etc. also was recorded.

Investigations done in this study were complete blood count (CBC), C- Reactive Protein (CRP), Peripheral blood films, blood culture sensitivity, liver function test (LFT) which includes SGOT, SGPT, serum bilirubin (total, direct and indirect), serum total protein, serum albumin, serum alkaline phosphatase, PT/INR and USG abdomen.

A septic screening was done on all admitted newborns with clinical suspicion of sepsis and those with maternal risk factors. A BD Bactec was to be sent of septic screen positive patients. Septic screen includes TLC, CRP, Band forms on PBF. Positive septicemia criteria mean TLC count >5000 with ANC <2000, positive CRP and band forms >20% of total neutrophil count [8].

Blood levels for estimation of total and direct bilirubin, serum alkaline phosphatase, SGOT, SGPT, serum proteins, prothrombin time were taken after 72 hours of clinical suspicion of sepsis. These investigations (LFTs) were repeated between days 10 to 14. HEPATO-BILIARY DYSFUNCTION - Hepato-biliary dysfunction has been defined as SGPT>50 IU/L and/or direct bilirubin level > 20% of the total serum bilirubin when it is > 5 mg/dl or absolute direct bilirubin value >1mg/dl when total serum bilirubin level is < 5 mg/dl. [9]

Neonates were started on intravenous antibiotics and other supportive management as soon as sepsis was suspected on the basis of either clinical signs and symptom or a positive sepsis screen.

The data were collected in a preformed proforma

The qualitative data were expressed in percentage and proportion and the quantitative data were expressed in mean and standard deviation. The qualitative data were analyzed using chi square test and the quantitative data were analyzed using student‘t’ test. The level of significance was taken significant $p < 0.05$.

Results

The Study of magnitude of hepato-biliary dysfunction in neonatal septicemia was carried out in all out born and inborn newborns having blood culture positive sepsis. The goals of the study were to find out the magnitude of Hepato-biliary dysfunction in neonatal sepsis.

- In our study hepatobiliary dysfunction was found to be present in 61.67% Conjugated Hyperbilirubinemia was seen in 11.67%.
- Significant association was observed between Hepatobiliary Dysfunction with Elevated SGPT (P<0.001S).Significant difference was observed between the Hepatobiliary Dysfunction with SGPT and SGOT.
- Significant difference was observed between the Hepatobiliary Dysfunction with Serum Bilirubin. Higher values of serum bilirubin were observed in cases with Hepatobiliary dysfunction.
- The mean values of Investigations of total bilirubin, direct bilirubin, and indirect bilirubin in babies was as follows: Serum Bilirubin Total at 3rd day was 6.95 ± 3.84., at 10th to 14th Days 5.40 ± .3.25, after 15 days of 2nd time of Investigations 3.59 ± 191. Mean ± value of Direct bilirubin at 3rd

day was 0.82 ± 0.42, at 10th to 14th Days 0.77 ± 0.38 and after 15 days of 2nd time of Investigations 0.72 ± 0.38, Mean ± value of Indirect bilirubin at 3rd day was 6.13 ± 3.71, at 10th to 14th Days 4.62 ± 3.17, after 15 days of 2nd time of Investigations.

- Cases with deranged SGPT were almost half 30/60 (50%), the onset was seen by day 3 of sepsis, and in 6 /12 babies by day 10 of sepsis

Discussion

Systemic and extra hepatic infectious diseases can be the leading cause of biochemical changes indicative of hepatic involvement. In majority cases hepatic involvement is overlooked or even neglected. In the case of a viral infection, misconstruing the illness as hepatic rather than systemic would not affect therapy significantly but bacterial infection as a cause of jaundice cannot be overlooked as it can receive appropriate therapy [10].

In our study any hepatobiliary dysfunction was found to be 61.67%. Cases having both values raised were 23.33 %. [11]

Sumaira Khalil et al (2012) [12] observed that any hepatobiliary dysfunction (direct bilirubin >20% of total with a minimum level of 2 mg/dL or ALT > 50 U/L) was found in 83 (54.2%) subjects. Cases of Cholestatic jaundice were 65 (42.5%), whereas those of deranged ALT were 57 (37.3%). One-fourth (25.4%) of septicemic babies had cholestatic jaundice as well as derangement of ALT.

In our study, the mean values of Investigations of total bilirubin, direct bilirubin, and indirect bilirubin in babies were: Serum Bilirubin Total at 3rd day was 6.95 ± 3.84., at 10th to 14th Days 5.40 ± .3.25, after 15 days of 2nd time of Investigations 3.59 ± 191

Mean ± value of Direct bilirubin at 3rd day was 0.82 ± 0.42, at 10th to 14th Days 0.77 ± 0.38 and after 15 days of 2nd time of Investigations 0.72 ± 0.38 , Mean ± value of Indirect bilirubin at 3rd day was 6.13 ± 3.71, at 10th to 14th Days 4.62 ± 3.17 &after 15 days of 2nd time of Investigations 2.86 ± 1.88, this result is in concordance with Sumaira Khalil et al (2012) [12]observed that the highest cases of direct bilirubin was achieved by day 10 of onset of sepsis in 68% babies. In our study, the mean value of SGOT was 69.39 ± 72.31 at day 3rd day , 35.26 ±12.59 at Investigations at 10th to 14th Days and 33.00 ± 7.78 this result is in concordance with Sumaira Khalil et al (2012) [12] where, in almost two-thirds (68.4%), the onset was seen by day 3 of sepsis, and in another 26.3% babies by day 10 of sepsis. The ALT normalized by 1 month (day 31) in about half (49.2%) of the babies, whereas in the remaining half (50.8%) the raised levels persisted for variable periods up to 3 months.

In our study ,cases with deranged SGPT were almost half 30/60 (50%), the onset was seen by day 3 of sepsis, and in 6 /12 babies by day 10 of sepsis this result is in concordance with Sumaira Khalil et al (2012) [12] who found that in almost two-thirds cases 68.4% the onset was seen by day 3 of sepsis, and 26.3% babies by 10th day of sepsis. The serum glutamate-pyruvate transaminase values normalized by day 31 of life in about half (49.2%) of the neonates, whereas in the remaining half (50.8%) the raised levels persisted for variable periods up to 3 months. In our study, Mean ± value of Serum Bilirubin Total at 3rd day was 6.95 ± 3.84, at 10th to 14th Days 5.40 ± .3.25 And after 15 days of 2nd time of Investigations 3.59 ± 191 significantly decrease with the time. Sumaira Khalil et al (2012) (18) observed that Serum Bilirubin Total day 3 of sepsis 2.44±0.50 Day 10 of sepsis 2.42±0.58, Peak value 2.18±0.48.

This study documented that hepato-biliary dysfunction is common early in the course of neonatal septicemia and is transient. In sepsis without direct hepatic infection, bile flow becomes markedly reduced, leading

to cholestasis and conjugated hyperbilirubinemia without transaminase elevation. Also, cholestasis is considered to be a consequence of the hepatocyte response to sepsis-associated cytokines. These cytokines are responsible for the aggravated response to the normal physiologic cholestasis in neonates. It also has been theorized that mild hemolysis caused by micro-organisms also contributes to the increased serum bilirubin levels in the neonate [13].

Neonatal sepsis is an important cause of hepato-biliary dysfunction. Our finding in neonate with sepsis and hepato-biliary dysfunction suggests that early onset hepato-biliary dysfunction is usually transient. So it is advisable to duly follow and observe these cases for a period of time. [14] If it is due to sepsis it is treatable by appropriate antibiotics and supportive treatment as it resolved in all cases on repeating liver function tests second time in our study.

Table 1: SGOT, SGPT and S. Bill

		SGOT	SGPT	S. BIL(TOTAL)	S.BIL(D)	S.BIL(ID)
Not elevated	**N**	23	23	23	23	23
	Mean	29.18	27.35	5.52	0.58	4.94
	Std. Deviation	6.38	7.55	2.97	0.30	2.92
Elevated	**N**	37	37	37	37	37
	Mean	94.38	68.30	7.85	0.97	6.87
	Std. Deviation	82.89	36.79	4.08	0.42	3.98
P value LS		<0.001S	<0.001S	012S	<0.001S	.048S

Table 2: Serum Investigations at follow up

	3rd day	**Investigations at 10th to 14 days**	**Serum investigations at follow up(after 15 days of 2nd time of investigations)**
N	60	34	5
S. Bilirubin			
Total	6.95± 3.84	5.40 ± 3.25	3.59 ± 1.91
Direct	0.82 ± 0.42	0.77± 0.38	0.72 ± 0.20
Indirect	6.13 ± 3.71	4.62 ± 3.17	2.86 ± 1.88
STP	6.04 ± 0.51	5.88 ± 0.71	5.90 ± 0.16
Albumin	2.97 ±0.27	3.01 ± 0.22	3.00 ± 0.14

Conclusion

This prospective study on **"**Study of magnitude and outcome of hepato-biliary dysfunction in neonatal septicemia**"** was conducted on 60 symptomatic newborns having blood culture positive bacterial sepsis for pathogenic bacteria to determine the prevalence, pattern, and outcome of Hepato-biliary dysfunction in neonatal sepsis, and to evaluate its effect on the survival and growth.

Neonatal Sepsis is an important cause of hepato-biliary dysfunction in newborns. Septicemia must be ruled out by necessary investigations in newborns with cholestasis at the earliest before planning for other investigations and work up as it

is (NNS) treatable by appropriate antibiotics and supportive treatment.

This concluded that biochemical deranged parameters (Rising trend of elevated transaminases and serum bilirubin) are the important predictors on time for differentiating the hepatobiliary dysfunction in neonatal sepsis. So that they could be used to recognize the complications at very early phase & introduce effective management strategies & treatment to prevent further mortality & morbidity associated with neonatal sepsis.

Limitation of the Study

Our study was done in a tertiary care centre where most of the admitted newborns were outborn newborns, who had already received antibiotics from their referring primary care centre. This might have led to reduced blood culture positivity rate.

This study included only 60 newborns with culture positive septicemia.

Larger studies are required to confirm these observations. There should also be separate studies on extramural and intramural newborns as their bacteriological profile defers and having history/documentation of already receiving antibiotics before obtaining blood culture and sensitivity sample in case of extramural births.

Our study was done only on blood culture positive cases of neonatal sepsis and blood culture is positive only in 60% cases of neonatal septicemia.

Due to the ongoing COVID 19 pandemic many cases were lost to follow up.

Contribution

Nipun Sharma: Data collection, Statistical analysis, drafting the article, Review of literature

Saket Yadav: Critical revision, Final approval of the version of the article to be published.

Priya Marwah: Drafting the article, Review of literature, Critical revision and final approval of the version of the article to be published.

Munish Kumar Kakkar: Conceptualized and planned the study design, Final approval of the version of the article to be published.

Madhu Mathur: Final approval of the version of the article to be published.

Gaurav Agrawal: (Corresponding Author) Critical revision, Tabulation of Data, Final approval of the version of the article to be published.

Shalin Parmar: Critical revision

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