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Comparative evaluation of thyroid hormone abnormalities in septic neonates from Darbhanga, Bihar

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Abstract

The role of thyroid hormones in neurologic development of newborn has been elucidated & absence of adequate hormones as occurs in congenital hypothyroidism result in adverse neuro-developmental outcome. Currently the neonatal screening for congenital hypothyroidism is performed in all developed countries as well as few developing countries. Advances in diagnostic techniques and therapeutic intervention are designed to enhance the overall outcome of the ever-increasing number of surviving premature and critically-ill infants. According to National Neonatal Perinatal Database (NNPD) 2000 neonatal sepsis is the most common cause of deaths in the country followed by prematurity & birth asphyxia. Hence based on the above findings the present study was planned for Comparative Evaluation of Thyroid Hormone Abnormalities in Septic Neonates from Darbhanga, Bihar.

The present study was planned in Department of Paediatrics, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India. The two groups of neonates of diagnosed with the neonatal sepsis and Control neonates were enrolled in the present study during the period of July 2019 to december 2019. The 25 neonates diagnosed with the neonatal sepsis were enrolled in Group A as Cases group. The Control group consist of 25 neonates without any complications.

The data generated from the present study concludes that Sick newborns have significantly increased TSH levels compared to the healthy newborns, indicating a subclinical Hypothyroidism in the former groups. Further studies are required on larger sample size to substantiate the findings and should aim to clearly establish the strength of the above-mentioned association in neonates with sepsis whether thyroid supplementation during initial course of NICU stay can affect the outcome, among neonates with severe sepsis need to be systematically evaluated.

Keywords: thyroid hormone, abnormalities, septic neonates, Bihar region, etc

Introduction

Neonatal sepsis may be categorized as early onset (day of life 0-3) or late onset (day of life 4 or later). Of newborns with early-onset sepsis, 85% present within 24 hours (median age of onset 6 hours), 5% present at 24-48 hours, and a smaller percentage present within 48-72 hours. Onset is most rapid in premature neonates. Early-onset sepsis is associated with acquisition of microorganisms from the mother. Infection can occur via hematogenous, transplacental spread from an infected mother or, more commonly, via ascending infection from the cervix. Organisms that colonize the mother's genitourinary (GU) tract may be acquired by the neonate as it passes through the colonized birth canal at delivery. The microorganisms most commonly associated with early-onset infection include the following [1]: Group B Streptococcus (GBS), Escherichia coli, Coagulase-negative Staphylococcus, Haemophilus influenza, Listeria monocytogenes.

Trends in the epidemiology of early-onset sepsis show a decreasing incidence of GBS disease following the widespread adoption of prenatal screening and treatment protocols [2, 3, 4].

In a study involving 4696 women, prenatal cultures showed a GBS colonization rate of 24.5%, with a positive culture rate of 18.8% at the time of labor. As many as 10% of prenatally culture-negative women were found to have positive cultures at the time of labor. In the study, intrapartum antibiotic prophylaxis occurred appropriately in 93.3% of cases, with 0.36 of 1000 infants developing early-onset GBS disease [5].

Trends in late-onset sepsis show an increase in coagulase-negative streptococcal sepsis, with most isolates showing susceptibility to first-generation cephalosporins [2]. The infant's skin, respiratory tract, conjunctivae, gastrointestinal tract, and umbilicus may become colonized via contact with the environment or caregivers. Pneumonia is more common in early-onset sepsis, whereas meningitis and bacteremia are more common in late-onset sepsis. Early-onset sepsis is 10 to 20 times more likely to occur in premature, very low birthweight infants [6]. Premature infants often have nonspecific, subtle symptoms; considerable vigilance is therefore required in these patients so that sepsis can be identified and treated in a timely manner.

The infectious agents associated with neonatal sepsis have changed since the mid-20th century. During the 1950s, S aureus and E coli were the most common bacterial pathogens among neonates in the United States. Over the ensuing decades, Group B Streptococcus (GBS) replaced S aureus as the most common gram-positive organism causing early-onset sepsis. Currently, GBS and E coli continue to be the most commonly identified microorganisms associated with neonatal infection. Additional organisms, such as

coagulase-negative Staphylococcus epidermidis, L monocytogenes, Chlamydia pneumoniae, H influenzae, Enterobacter aerogenes, and species of Bacteroides and Clostridium have also been identified in neonatal sepsis.

Meningoencephalitis and neonatal sepsis can also be caused by infection with adenovirus, enterovirus, or coxsackievirus. Additionally, sexually transmitted diseases (eg, gonorrhea, syphilis, herpes simplex virus [HSV] infection, cytomegalovirus [CMV] infection, hepatitis, human immunodeficiency virus [HIV] infection, rubella, toxoplasmosis, trichomoniasis, and candidiasis) have all been implicated in neonatal infection.

Bacterial organisms with increased antibiotic resistance have emerged and have further complicated the management of neonatal sepsis [7]. The colonization patterns in nurseries and personnel are reflected in the organisms currently associated with nosocomial infection. In neonatal intensive care units (NICUs), infants with lower birth weight and younger gestational ages have an increased susceptibility to these organisms. S epidermidis, a coagulase-negative Staphylococcus, is increasingly seen as a cause of nosocomial or late-onset sepsis, especially in the premature infant, in whom it is considered the leading cause of late-onset infections. Its prevalence is likely related to several intrinsic properties of the organism that allow it to readily adhere to the plastic mediums found in intravascular catheters commonly required for the care of these infants.

The bacterial capsule polysaccharide adheres well to the plastic polymers of the catheters. Also, proteins found in the organism (AtlE and SSP-1) enhance attachment to the surface of the catheter. The adherence creates a capsule between microbe and catheter, preventing C3 deposition and phagocytosis [8, 9].

Biofilms are formed on indwelling catheters by the aggregation of organisms that have multiplied under the protection provided by the adherence to the catheter. Slimes are produced at the site from the extracellular material formed by the organism, which provides a barrier to host defense as well as to antibiotic action, making coagulase-negative staphylococcal bloodstream infection (BSI) more difficult to treat. The toxins formed by S epidermidis have also been associated with necrotizing enterocolitis. In addition to being a cause of neonatal sepsis, coagulase-negative Staphylococcus is ubiquitous as part of the normal skin flora. Consequently, it is a frequent contaminant of blood and cerebrospinal fluid (CSF) cultures. When a culture grows this organism, the clinical presentation, colony counts, and the presence of polymorphonuclear neutrophils (PMNs) on Gram staining of the submitted specimen often help differentiate true infection from contaminated culture specimens.

In addition to the specific microbial factors mentioned above, numerous host factors predispose the newborn to sepsis [10]. These factors are especially prominent in the premature infant and involve all levels of host defense, including cellular immunity, humoral immunity, and barrier function. Immature immune defenses and environmental and maternal factors contribute to the risk for neonatal sepsis, morbidity, and mortality, particularly in preterm and/or very low birthweight (VLBW) infants [10, 11]. There may also be a genetic association [10].

PMNs are vital for effective killing of bacteria. However, neonatal PMNs are deficient in chemotaxis and killing capacity. Decreased adherence to the endothelial lining of blood vessels reduces their ability to marginate and leave the intravascular space to migrate into the tissues. Once in the tissues, they may fail to degranulate in response to chemotactic factors.

Furthermore, neonatal PMNs are less deformable and thus are less able to move through the extracellular matrix of tissues to reach the site of inflammation and infection. The limited capacity of neonatal PMNs for phagocytosis and killing of bacteria is further impaired when the infant is clinically ill. Finally, neutrophil reserves are easily depleted because of the diminished response of the bone marrow, especially in the premature infant [12].

Neonatal monocyte concentrations are at adult levels; however, macrophage chemotaxis is impaired and continues to exhibit decreased function into early childhood. The absolute numbers of macrophages are decreased in the lungs and are likely decreased in the liver and spleen as well. The chemotactic and bactericidal activity and the antigen presentation by these cells are also not fully competent at birth. Cytokine production by macrophages is decreased, which may be associated with a corresponding decrease in T-cell production [13].

Although T cells are found in early gestation in fetal circulation and increase in number from birth to about age 6 months, these cells represent an immature population. These naive cells do not proliferate as readily as adult T cells do when activated, and they do not effectively produce the cytokines that assist with B-cell stimulation and differentiation and granulocyte/monocyte proliferation. Formation of antigen-specific memory function after primary infection is delayed, and the cytotoxic function of neonatal T cells is 50%-100% as effective as that of adult T cells. At birth, neonates are deficient in memory T cells. As the neonate is exposed to antigenic stimuli, the number of these memory T cells increases.

Natural killer (NK) cells are found in small numbers in the peripheral blood of neonates. These cells are also functionally immature in that they produce far lower levels of interferon gamma (IFN-γ) upon primary stimulation than adult NK cells do. This combination of findings may contribute to the severity of HSV infections in the neonatal period. The fetus has some preformed immunoglobulin (Ig), which is primarily acquired through nonspecific placental transfer from the mother. Most of this transfer occurs in late gestation, such that lower levels are found with increasing prematurity. The neonate's ability to generate immunoglobulin in response to antigenic stimulation is intact; however, the magnitude of the response is initially decreased, rapidly rising with increasing postnatal age [14].

The neonate is also capable of synthesizing IgM in utero at 10 weeks' gestation; however, IgM levels are generally low at birth, unless the infant was exposed to an infectious agent during the pregnancy, which would have stimulated increased IgM production [15].

IgG and IgE also may be synthesized in utero. Most IgG is acquired from the mother during late gestation. The neonate may receive IgA from breastfeeding but does not secrete IgA until 2-5 weeks after birth. Response to bacterial polysaccharide antigen is diminished and remains so during the first 2 years of life. Complement protein production can be detected as early as 6 weeks' gestation; however, the concentration of the various components of the complement system varies widely from one neonate to another. Although some infants have had complement levels comparable to

those in adults, deficiencies appear to be greater in the alternative pathway than in the classic pathway [16].

The terminal cytotoxic components of the complement cascade that lead to the killing of organisms, especially gram-negative bacteria, are deficient. This deficiency is more marked in preterm infants. Mature complement activity is not attained until infants reach 6-10 months of life. Neonatal sera have reduced opsonic efficiency against GBS, E coli, and Streptococcus pneumoniae because of decreased levels of fibronectin, a serum protein that assists with neutrophil adherence and has opsonic properties. The physical and chemical barriers to infection in the human body are present in the newborn but are functionally deficient. Skin and mucous membranes are broken down easily in the premature infant. Neonates who are ill, premature, or both are at additional risk because of the invasive procedures that breach their physical barriers to infection. Because of the interdependence of the immune response, the individual deficiencies of the various components of immune activity in the neonate conspire to create a hazardous situation when the neonate is exposed to infectious threats.

The intestines are colonized by organisms in utero or at delivery through swallowing of, and exposure to, amniotic fluid and genitourinary tract secretions. The immunologic defenses of the gastrointestinal tract are not mature, especially in the preterm infant. Lymphocytes proliferate in the intestines in response to mitogen stimulation; however, this proliferation is not fully effective in responding to a microorganism, as antibody response and cytokine formation are immature until approximately 46 weeks' gestation. Necrotizing enterocolitis has been associated with the presence of a number of species of bacteria in the immature intestine. Overgrowth of these organisms in the neonatal lumen can be a component of the multifactorial pathophysiology of necrotizing enterocolitis.

The role of thyroid hormones in neurologic development of newborn has been elucidated & absence of adequate hormones as occurs in congenital hypothyroidism result in adverse neuro-developmental outcome. Currently the neonatal screening for congenital hypothyroidism is performed in all developed countries as well as few developing countries. Advances in diagnostic techniques and therapeutic intervention are designed to enhance the overall outcome of the ever-increasing number of surviving premature and critically-ill infants. According to National Neonatal Perinatal Database (NNPD) 2000 neonatal sepsis is the most common cause of deaths in the country followed by prematurity & birth asphyxia [17]. Hence based on the above findings the present study was planned for Comparative Evaluation of Thyroid Hormone Abnormalities in Septic Neonates from Darbhanga, Bihar.

Methodology

The present study was planned in Department of Paediatrics, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India. The two groups of neonates of diagnosed with the neonatal sepsis and Control neonates were enrolled in the present study during the period of July 2019 to december 2019. The 25 neonates diagnosed with the neonatal sepsis were enrolled in Group A as Cases group. The Control group consist of 25 neonates without any complications.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria: Neonates of diagnosed with the Perinatal asphyxia & neonatal sepsis and Control neonates

Exclusion criteria: Babies having features of overt congenital hypothyroidism and babies born to mothers having history of thyroid related dysfunction.

Results & Discussion

Central hypothyroidism is characterized by impaired secretion of thyroid hormone due to defect in the hypothalamic-pituitary-thyroid (HPT) regulatory system. Congenital central hypothyroidism due to maternal hyperthyroidism is not an uncommon entity, but often remains unrecognized unless specific attention is given. Exposure of fetal HPT system to a higher thyroid hormone concentration might impair its physiological maturation leading to central hypothyroidism in neonates born to thyrotoxic mothers.

Changes in thyroid hormone levels in critically sick patients, including neonates, in the absence of primary thyroid pathology has been termed Euthyroid sick syndrome [18]. It is characterized by reduction in tri-iodothyronine (T3) in moderately sick patients, and reduction in thyroxine (T4) in severe disease. Among children with septic shock, non-survivors have lower thyroid hormone levels compared to survivors [19]. In addition, preterm infants are predisposed to transient hypothyroxinemia of prematurity, characterized by low levels of T3 and T4 [20]. Unlike adults who may not have any long-term consequences of transient hypothyroidism, preterm neonates suffer from neurodevelopmental disabilities [21, 23]. Thus, septic preterm neonates are under a double jeopardy, both by virtue of sepsis and prematurity.

There is a relationship between thyroid function tests (TFT) and cardiac function. Children who undergo cardiac bypass surgery have deranged TFTs and treatment with T3 improves myocardial function [24, 25]. On comparison of children (beyond neonatal period) with septic shock versus those with sepsis but no shock, researchers have reported lower thyroid hormone levels among the former [19, 26]. Septic shock may just reflect greater severity of sickness, as the above authors did not adjust for the level of sickness to determine whether TFTs have an independent relationship with shock.

Table 1: Thyroid Hormone Levels

Groups	Group A	Group B
Neonates of	**Neonatal sepsis**	**Control**
No. of Cases	25	25
Age in Days	4 – 7	4 – 8
Weight in Kg	2.1 – 3.2	2.4 – 3.5
Sex		
Males	15	19
Females	10	6

Table 2: Thyroid Hormone Levels

Groups	Group A	Group B
Neonates of	**Neonatal sepsis**	**Control**
No. of Cases	25	25
Age in Days	4 – 7	4 – 8
Weight in Kg	2.1 – 3.2	2.4 – 3.5
TSH (mU/L)	4.8 – 7.8	1.9 – 4.3
Free T4 (ng/dl)	0.85 – 1.93	1.1 – 1.5
Free T4 (pg/dl)	202.4 – 229.6	209.3 – 253.8

Lodha, *et al*. [27] found significantly lower thyroid hormone levels in those with septic shock. They also reported no deaths in the group without septic shock whereas 50% of the children with septic shock died [27]. Yildizdas, *et al*. [28] showed that mean (SD) total T3 levels among children with sepsis alone *vs* those with septic shock were 0.91 (0.22) nmol/L *vs* 0.64 (0.23) nmol/L and total T4 levels were 100.6 (1.93) *vs* 65.8 (19.35), respectively (P<0.05). In both the studies, children with septic shock were sicker and had higher mortality.

A positive maternal history of thyroid disease should increase suspicion regarding fetal thyrotoxicosis, and the mother's blood should be analyzed for TSIs. If the result is positive and there are clinical signs of fetal thyrotoxicosis, treatment should be started immediately by giving the mother carbimazole or propyl thiouracil, which cross the placenta to the fetus and control fetal thyrotoxicosis [29, 30]. The doses of these drugs are titrated based on fetal heart rate, and if the mother develops treatment-induced hypothyroidism, levothyroxine can be added. The fetal response to treatment is indicated by fetal heart rate control, weight improvement and, if present, goiter shrinkage.

Thyroid hormones are important for the metabolic adaptations of the body in times of stress and critical illness [31]. Alterations in the hypothalamic-pituitary thyroid axis suggest a prognostic role of thyroid hormones in neonates with sepsis and septic shock. In a study by Kurt A *et al*. [32], serum TT3 and TT4 levels of septic newborns were significantly decreased at the onset while serum TT4 level increased after the antibiotic treatment. In another prospective cohort study by B. K Das and his co-workers, low TT3, TT4 and elevated cortisol levels predicted adverse outcome in septic neonates [33]. Borkowski *et al* have shown that decreased levels of FT3 and TSH were associated with poor prognosis in patients with septic shock. [34] In another similar study, Lodha and his co-workers suggested that thyroid function derangement in children was not an important factor contributing to severity of septic shock [31]. They found lower levels of TT3, TT4, FT3, FT4 and TSH in children with septic shock compared to sepsis group.

Epidemiological studies have shown alterations in thyroid hormones levels in hospitalized patients. These alterations are more commonly observed in those with increased age or critical illness [35]. Low triiodothyronine (T3) and elevated reverse triiodothyronine (rT3) levels are commonly observed due to inhibition of 5'-deiodinase enzyme. With increasing severity of illness the levels of total thyroxin (TT4), free thyroxin (FT4) and thyroid stimulating hormone (TSH) may also decrease [36]. Few studies in critically ill children showed an association of decreased levels of TT3 and TT4 with mortality [37, 38]. In another study by Anand *et al*, no significant changes were observed in thyroid indices with CRP [39].

Conclusion

The data generated from the present study concludes that Sick newborns have significantly increased TSH levels compared to the healthy newborns, indicating a subclinical Hypothyroidism in the former groups. Further studies are required on larger sample size to substantiate the findings and should aim to clearly establish the strength of the above-mentioned association in neonates with sepsis whether thyroid supplementation during initial course of SNCU stay can affect the outcome, among neonates with severe sepsis need to be systematically evaluated.

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