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Vitamin-D Levels in Neonates with and without Sepsis: A Case Control Study

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Abstract:

BACKGROUND:Neonatal sepsis is a syndrome comprising of non-specific symptoms and signs of infection accompanied by bacteraemia in first 28 days.vitamin D is a hormone which is steroid and fatsoluble vitamin. It has a vital importance in the active function of the innate immune system by activating anti-microbial peptides .There are few epidemiological evidence showing a relation between low levels of vitamin d levels and its association with neonatal sepsis.Vitamin D not only plays a role in calcium and phosphorous homeostasis but also in immune function. Vitamin D receptors are present in epithelial cells and cells of immune system.

AIM:To study the role of vitamin d levels in neonates with sepsis.

OBJECTIVE:The objective is to measure vitamin D levels in neonates with probable sepsis and culture proven sepsis and neonates without sepsis and correlate levels of vitamin D in neonates with and without sepsis.

METHODOLOGY:This will be a case control study which will be done in NICU ,department of Pediatrics in Jawaharlal Nehru Medical College and AVBRH hospital ,Sawangi,Wardha from Nov 2020 to oct 2022.Neonates with probable sepsis and culture positive sepsis will be considered as cases .Neonatal and maternal details ,examination and required investigations will be recorded and relation , between vitamin d levels and neonatal sepsis will beassessed.

EXPECTED RESULT: We expect that vitamin D deficiencymight predispose to neonatal sepsis

CONCLUSION:There might be significant relationship between low levels of vitamin D levels and neonatal sepsis.

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Keywords:Neonates,vitamin D and sepsis

INTRODUCTION:

Neonatal sepsis is the first most common cause of neonatal mortality rate and neonatal admissions in India. As much as 40 percent of deaths below the age of one year occur during first 7 days of life because of neonatal septicaemia[1]. The incidence of neonatal sepsis is less than 1 per 1000 live births.The same in premature babies is 2 cases per 1000 live births. The increasing incidence of neonatal sepsis in premature babies is because of multiple factors. Immunological differences between neonates and grownup child and adult makes them vulnerable to various infections. The incidence of infection increases with decrease in weight and gestation of neonates.

A rigorous analysis of neonatal causes and risk factors revealed that the low birthweight babies have propensity to develop and acquire infections. Other risk factors of neonatal sepsis are preterm, PROM, Intrapartum fever and other signs of chorioamnionitis documented maternal colonisation with group b streptococcus and multiple per vaginal examination [2]. These are the majorfactors responsible for the manifestation of early onset sepsis[3]. Late onset sepsis usually occurs after 3 days of life and can be divided into two different clinical entities namely disease occurring in other wise term healthy infants in the community and the disease effecting the premature infants in the NICU. Later type of LOS is termed as hospital acquired sepsis as the risk factors are prevalent in ICU care example that is presence of central lines, use of broad-spectrum antibiotics, endotracheal ventilation and mechanical ventilation, feeding tube insertion, multiple blood samplings and routine care in the NICU[4]. The infection in the healthy term and nearterm neonates is caused by group b streptococcus and gram negative species such as Ecoli and klebsiellaWhile in community acquired infections streptococcus pneumoniae,Hemophilusinfluenzae,Neisseriameningitides occur although less frequently. Gram negative bacteria are common cause of neonatal septicaemia.E.coli, Klebsiellapneumoniae, pseudomonas species and Acinetobacter species often complicate neonatal stay [6].Gram negative bacteraemia is usually found in UTI in neonates[5]. In neonates itcan cause generalised septicaemias. LOS usually acquired from community has not been poorly defined when risk factors are considered but be likely due to prematurity, colonisation of new born with mother and community organisms, gestational age, lack of maternal derived protective antibodies and primary immunodeficiencies.In developing countries customs like shaving head in particular communities, applying specific routine for cord care and skin care are associated with the development of LOS. The incidence of group b streptococcus LOS was reported to be 0.7 cases for 1000 live births. The median gestational age of LOS is around 30 weeks. This indicates premature babies are more risk of LOS.LOS is not limited to generalised infection, but involves organ specific infection like meningitis,pneumonia,septic arthritis,UTI and skin infections. The incidence of infection of newborn both LOS and EOS can be reduced by use of antibiotics in the mother before delivery [6].

Neonates present with nonspecific and variable signs and symptoms due to septicemia .In cases of EOS they have decreased activity, breathing difficulty, feeding difficulty, rash,

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apnoea, seizures, grunting, chest retractions and tachypnoea,lethargy, irritability, temperature, instability, poor perfusion and hypotension.[7] DIC in neonates can manifest with purpura, petechiae, melena and altered gastric aspirate. Gastrointestinal symptoms include distension of abdomen, poor feeding, vomiting, ileus, decreased bowel sounds. LOS has signs and symptoms like altered sensorium, seizures, high pitched cry, apnoea, sclerema, cyanosis,decreased urine output, pyodermagangrenosum and shock. The presentation of sepsis in the neonates cannot be easily differentiated from transient tachypnoea of new born, respiratory distress syndrome, congenital heart diseases, congenital viral infections, meconium aspiration syndromes, persistent pulmonary hypertension of new born, intestinal obstruction and diaphragmatic hernia and in born errors of metabolism.

The antibiotics are started with the suspicion of sepsis and investigations are ordered in high-risk cases and clinical sepsis. [8]The evaluation of sepsis include septic screen, blood culture, CSF examination,blood glucose level. In severely ill neonates particularly preterm can have thrombocytopenia and evidence of DIC (elevated PT, APTT, INR and decreased fibrinogen levels. In cases of LOS CSF examination is advised for cell count, proteins,glucose concentration,gram stain and culture. X ray chest is necessary to evaluate pneumonia which might reveal pulmonary infiltrates, atelectasis, fluffy shadows, pleural effusions. Arterial blood gas analysis is indicative of hypoxia, hypercarbia and metabolic acidosis in cases of severe sepsis and pneumonia.

The main stay of treatment of sepsis of neonates is use of antibiotics which should be started as fast as possible in high risk and doubtful cases of septicemia.[9] Initially a broad spectrum antibiotics according to local institutional antibiotic policy is started. The usual antibiotics are ampicillin and gentamycin as an initial therapy with the addition of third generation cephalosporin like cefotaxime in cases of severe sepsis and meningitis is started[10].

The role of vitamin D in neonatal sepsis in recent studies have been postulated. The actions of vitamin D are not just limited to calcium and phosphorous metabolism in skeletal system but include in wide systemic manifestations.[11] Development of cardiovascular diseases, insulin resistance,allergic disorders,metabolic diseases,autoimmune disorders and cancers have been implicated with the deficiency of vitamin D .Some of the studies indicate that vitamin D deficiency associated with IUGR and low birth weight babies. Poor neuro cognitive development and behavioral disorders are more in neonates with vitamin D deficiency. The development of immunological system is linked with vitamin D levels during fetal and neonatal period. Synthesis of immunoglobulins, activation of T cell lymphocytes, differentiation of killer and T helper cells, migration of neutrophils and augmentation of antimicrobial peptides has been suggested to be affected by vitamin D levels.[12] In a recent study new bornwith low cord blood vitamin D had susceptibility to neonatal septicaemia. Only few studies observed role of vitamin D in early onset sepsis. Hence the current study is undertaken to find out role of vitamin D levels and the occurrence of neonatal sepsis.

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AIM AND OBJECTIVES OF THE STUDY

AIM: To study the role of vitamin D levels in neonates with sepsis.

OBJECTIVES:

1]To measure vitamin D levels in neonates with probable sepsis and culture proven sepsis

2]To measure vitamin D levels in neonates without sepsis

3]Correlate levels of vitamin D in neonates with and without sepsis

METHODS:

Study design: Case control study

Settings:AVBRH,Sawangi is attached to a rural medical college located in Maharashtra .This study will be conducted in NICU ,Department of Pediatrics ,in Jawaharlal Medical college and AVBRH Hospital ,Sawangi ,Wardha from Nov 2020 to Oct 2022

Participants:

INCLUSION CRITERIA:

Cases:Neonates with probable sepsis and culture positive sepsis

Controls :Healthy Neonates staying with mothers in the post-natal wards

EXCLUSION CRITERIA

1.Neonates with major congenital abnormality

2.Neonate on formula feeds

3.Neonates who have received vitamin D supplementation

Variables: vitamin d levels

Data sources and measurements: vitamin d levels will be assessed in ng/ml.serum 25 OH D levels less than 10 ng/ml is severe deficiency ,insufficiency is 11 to 32 ng/ml ,adequacy is 32 to 100 ng/ml .

Total sample size is 63 cases and 63 controls. 126(63/63)

METHODOLOGY:

Inclusion criteria –

- Cases are neonates with probable sepsis and culture positive sepsis
- Controls are healthy neonates staying with the mothers in postnatal wards

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Exclusion criteria –

- Neonates with major congenital abnormalities,
- neonates on formula feeding and
- neonates who have received vitamin d supplementation will be excluded from the study.

The mother and neonate demographic details , examination findings and required investigations will be noted in predesigned validated proforma.Gestational age will be assessed by last menstrual period and new Ballard'sscore .investigationssent for all the neonates like Hemoglobin(Hb),TLC,CRP ,blood culture will be noted .Vitamin d levels of the neonates will be measured in the study. The neonate will be managed according to the present NICU protocols.Probable sepsis is defined as - when clinical and laboratory (Sepsis screen) are consistent with bacterial infections but blood culture is sterile.

When the initial screen is negative it should be repeated after12 to 24 hours when clinical suspicion of infection is strong. When repeat sepsis screen is also negative the diagnosis of sepsis can be excluded with reasonable certainty.
Culture proven sepsis:Blood culture will be taken before starting antimicrobial therapy. The venepuncture site overlying a peripheral vein will be thoroughly sterilised before obtaining specimen of blood for culture.Alcohol povidone iodine-alcohol will be applied and 1 ml of blood in 10 to 20 ml of broth for blood culture will be taken.

Septic screen:

PARAMETER	**ABNORMAL VALUE**
Total leukocyte count	<5000/mm3
Absolute neutrophil count	Low count as per Manroe chart for term infants and Mouzinho chart for VLBW infants
Immature or band cells to the total neutrophil ratio	>0.2
Micro ESR	>10mm 1st hour
CRP	>6mg/dl

Sepsis screen is considered as positive when 2 or more parameters are positive.

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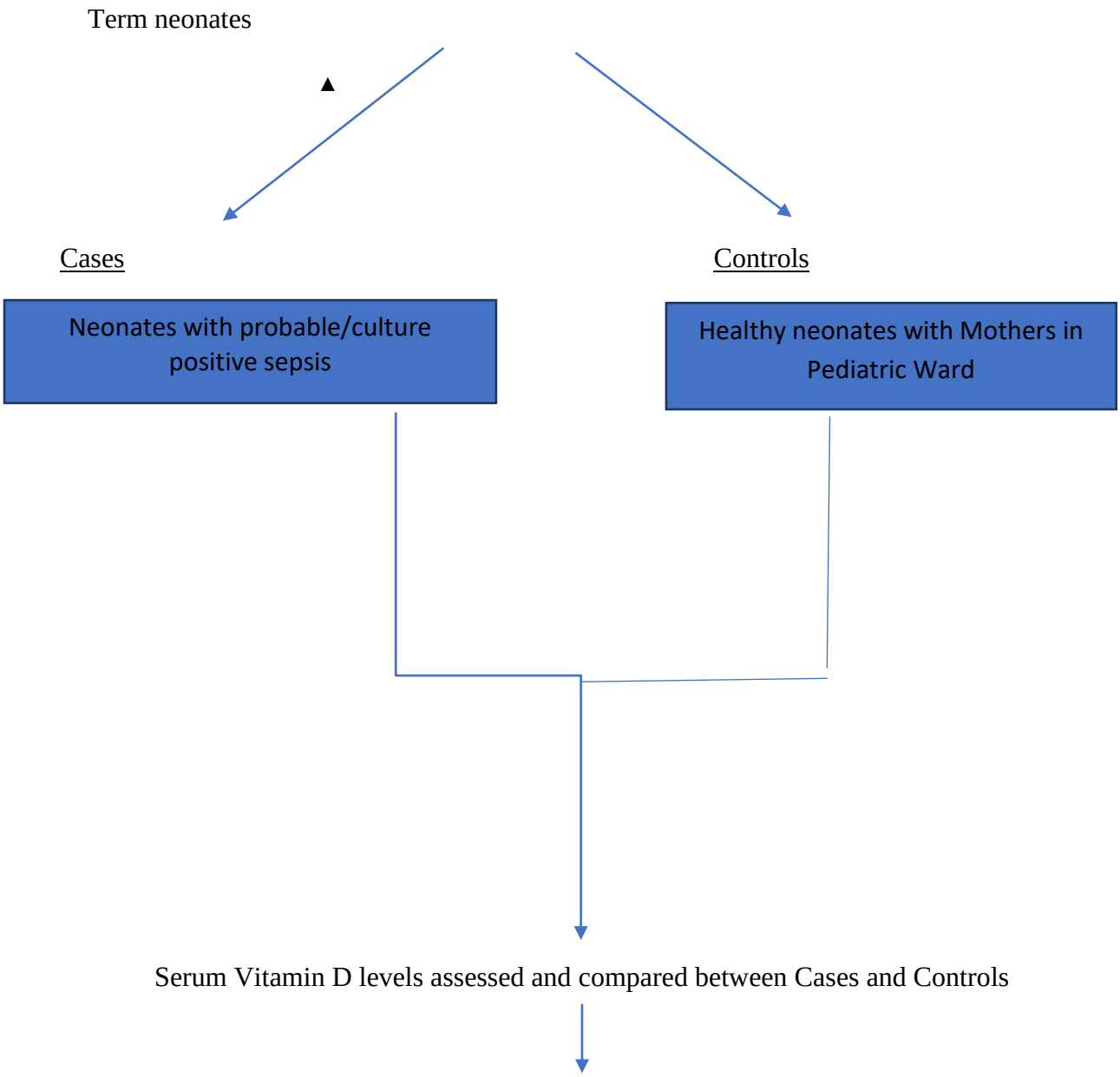
DESIGN :



EXPECTED RESULT:

There might be a significant correlation between low levels of vitamin d and neonatal sepsis. In the current study the vitamin D Levels in the neonates in neonatal sepsis may correlate with duration of stay and neonatal mortality. Neonatal sepsis is often associated with many complications like DIC, shock etc , the vitamin D level may influence development of such complications. The vitamin D levels of neonates are dependent on maternal diet, socioeconomic , cultural aspects and religion. All these factors will be correlated with the vitamin D levels and the occurrence of neonatal sepsis in both cases and controls.

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DISCUSSON:

Vitamin D levels are associated with immunocompromised status. Low vitamin d in the mother and the neonates are associated with the development of neonatal sepsis[9].Neonates with strong immunological response have tendency to resist sepsis. Vitamin D induces fetal programming of immunological peptide genes through toll like receptors and increase strong immunological response against invading bacteria. Vitamin D is involved in modulation of inflammatory response in the event of overwhelming septicemia. Vitamin D inhibits the growth of gram positive and gram negative bacteria and some viruses through alteration of immunological signalling pathway,release of immunoglobulins and activation of T lymphocytes.[12]

In a case control study conducted by Centinkaya et al found that vitamin D levels were low in cases of neonatal septicemia as compared to the healthy controls. The vitamin D levels were drawn on first three days of life to assess impact of vitamin D on early onset sepsis. The mean vitamin D levels were around 8 ng/dl in case population while control population had 19ng/dl in significant proportion to conclude the role of vitamin D in neonatal sepsis[13]. A correlation of cord blood level of vitamin D and early onset sepsis was done by Cizmeni et al and it was observed that a significant lower levels of vitamin D in cases of neonatal septicemia as compared to controls.[14]. The positive effect of vitamin D is not just limited to early onset sepsis ,as observed in the study by Dhandai et al that the newbornwere more prone to develop Los if deficient in vitamin D levels.A significant population($p=0.001$)of neonates with LOS had vitamin D levels of 15.37 ng/ml than the control group.21.37ng/ml [15].

The effect of vitamin D on neonatal sepsis has been studied by Sachan et al and concluded that neonatal septicemia was common when associated with hypovitaminosis D. Those mothers with low vitamin D had neonates with sepsis as compared to normal vitamin D levels in mother. This substantiates impact of vitamin D on the early fetal development of immunological function and blood levels of vitamin D in early neonatal life for continued beneficial effect against infection.Studies on sepsis [16-18] and role of vitamin-D[19,20] in various conditions were reported. Other related studies on neonates were reviewed[21,22].

LIMITATIONS :

1. As pointed out earlier the current study will estimate vitamin D levels in neonates and not of mothers also. An appropriate method would be to measure maternal, neonatal blood levels of vitamin D in cases and controls to have a linear correlation of data on neonatal sepsis.

CONCLUSION:

Our study might suggest that low levels of vitamin d levels is associated with neonatal sepsis and hence could guide research for improving the levels by administering vit d to mothers.

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