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RESEARCH ARTICLE

EFFECTIVENESS OF PALIVIZUMAB IN PREVENTING RSV HOSPITALIZATION IN HIGH RISK INFANTS WITH CHD & PREMATURE INFANTS.

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Abstract

Respiratory syncytial virus (RSV) is the major cause of bronchiolitis and viral pneumonia in children younger than 1 yr of age.

Infection with respiratory syncytial virus (RSV) is one of the major causes of childhood respiratory morbidity and hospitalization. Palivizumab, a humanized monoclonal antibody, has been recommended for high risk infants to prevent severe RSV-associated respiratory illness.

Key ward: palvizumab + bronchiolitis + RSV

A randomized clinical trial was done in Karballa Teaching Hospital For Pediatrics from October 2015-march 2017 to studies the protective effect of palivizumab prophylaxis for reducing RSV-associated hospitalizations in infants with congenital heart disease and premature infants.

We studied 84 patients divided to 2 groups (group A & B): 30 patients with congenital heart disease their age less than 1 year considered group A and 54 premature neonates who are delivered at the season of RSV (October – March) considered group B.

Group A (30 patients): subdivided to 2 subgroups: A1 & A2, both had hemodynamically significant CHD (large VSD & PDA, complete AV canal with heart failure and on medical treatment, TOF and D-TGA). 18 patients who received 5 doses of palvizumab monthly (from October- March) considered as group A1 and 12 patients who received 3 doses monthly considered as group A2, with monthly follow up for signs of any respiratory illness.

Group B (54 patients): subdivided to 2 subgroups: B1 & B2 both were premature neonates their gestational age less than 35 weeks of gestation and their body weight less than 1500 gm. 25 patients they were received 5 doses of palvizumab monthly for 5 months from October-March considered as group B1 and 25 patients they were received 3 doses of palvizumab monthly considered as group B2. 2 patients received 2 doses only and developed irritability & cough therefore we stopped palvizumab injection, 2 patients received one dose and escape from follow up (therefore those 4 patients were excluded from the study). premature neonates with severe sepsis, severe jaundice, severe congenital malformation, history of birth asphyxia and complex congenital heart disease also were excluded from the study.

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All 4 groups were received palvizumab 15mg/kg intramuscular monthly with regular follow up each months for any sign of respiratory distress.

For each group we select control group C1(30 patients with CHD)&group C2(50 premature infants) :they didn't received palvizumab ,both groups were taken from cardiology clinic,outpatients clinic &premature department &compared with each group.

The results for group A1, 3 patients developed mild bronchiolitis without hospitalization,for group A2 only one patient(8.33%) need hospitalization .

The results for group B1, 7 of them they developed mild bronchiolitis and they didn't need hospitalization,for groupB2, 8 of them they developed mild bronchiolitis and one of them(4%) need hospitalization for 2 weeks.no death was reported.

Regarding control group: 30 patients with CHD(group C1) who didn't received palvizumab,21(70%) patients they were need hospitalization &1 death was reported . and from 50 patients premature infants(group C2) ,39 patients(78%) developed bronchiolitis and they need admission &4 death was reported.

In this study we found breast feeding had significant factor that contribute to the reduction of severity of bronchiolitis and rate of hospitalization.

From this study we recommend :the usage of palvizumab as prophylaxis against RSV for premature infants & hemodynamically significant CHD because its effectiveness in reduction of morbidity &mortality. And encourage breast feeding for its effectiveness against severe disease in infants below 1 year.

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..... **Introduction:-**

Respiratory syncytial virus (RSV) is the major cause of bronchiolitis and viral pneumonia in children younger than 1 yr of age.

RSV is an enveloped RNA virus with a single-stranded negative-sense genome that replicates entirely in the cytoplasm of infected cells and matures by budding from the apical surface of the cell membrane.Because this virus has a nonsegmented genome, it cannot undergo antigenic shift by reassortment like the influenza viruses do.(1)

Infection with RSV does not grant permanent or long term immunity. Reinfections are common and may be experienced throughout life. Other viruses identified as causing bronchiolitis are human metapneumovirus, influenza, adenovirus, and parainfluenza.(2).

The virus can live for a half an hour or more on hands. The virus can also live for up to 5 hours on countertops and for several hours on used tissues.(3).

Epidemiology:-

RSV is distributed worldwide and appears in yearly epidemics. In temperate climates, these epidemics occur each winter over 4-5 mo.During the remainder of the year, infections are sporadic and much less common. In the Northern hemisphere, epidemics usually peak in January, February, or March. RSV outbreaks often overlap with outbreaks of influenza and human metapneumovirus but are generally more consistent from year to year and result in more disease overall, especially among infants younger than 6 mo of age.

RSV is one of the most contagious viruses that affect humans. Infection is nearly universal among children by their 2nd birthday. Reinfection occurs at a rate of at least 10-20% per epidemic throughout childhood, with a lower frequency among adults. In situations of high exposure, such as daycare centers, attack rates are nearly 100% among previously uninfected infants and 60-80% for second and subsequent infections.

Asymptomatic RSV infection is unusual in young children. Most infants experience coryza and pharyngitis, often with fever and frequently with otitis media caused by a virus in the middle ear or bacterial super infection.

Transplacentally acquired anti-RSV maternal immunoglobulin G serum antibodies, if present in high concentration, appear to provide partial but incomplete protection. These immunoglobulin Gs may account for the lower severity of RSV infections during the 1st 4-6 wk of life, except among infants born prematurely, who receive less maternal immunoglobulin. Breastfeeding provides substantial protection against severe disease, an effect that may pertain only to female infants and not male infants.(1)

Clinical manifestation:-

Typically, the first sign of infection in infants with RSV is rhinorrhea.

Cough may appear simultaneously but more often does so after an interval of 1-3 days, at which time there may also be sneezing and a low-grade fever. Soon after the cough develops, the child who experiences bronchiolitis begins to wheeze audibly. If the disease is mild, the symptoms may not progress beyond this stage. Auscultation often reveals diffuse fine inspiratory crackles and expiratory wheezes. Rhinorrhea usually persists throughout the illness, with intermittent fever. Chest radiograph findings at this stage are frequently normal.

Signs of severe, life-threatening illness are central cyanosis, tachypnea of >70 breaths/min, listlessness, and apneic spells. At this stage, the chest may be significantly hyperexpanded and almost silent to auscultation because of poor air movement.

Chest radiographs of infants hospitalized with RSV bronchiolitis have normal findings in approximately 30% of cases, with the other 70% showing hyperexpansion of the chest, peribronchial thickening, and interstitial infiltrates. Segmental or lobar consolidation is unusual and pleural effusion is rare.

Fever is an inconstant sign in RSV infection. In young infants, particularly those who were born prematurely, periodic breathing and apneic spells have been distressingly frequent signs, even with relatively mild bronchiolitis. RSV infections in profoundly immunocompromised hosts may be severe at any age of life.(1)

Bronchiolitis and pneumonia resulting from RSV are more common in boys than in girls by a ratio of approximately 1.5 : 1. Other risk factors with similar impact include 1 or more siblings in the home, white race, rural residence, maternal smoking, and maternal education <12 yr. The medical factors in infants associated with highest risk are chronic lung disease of prematurity, congenital heart disease, immunodeficiency, and prematurity.(1).

The incubation period from exposure to first symptoms is approximately 3-5 days. The virus is excreted for variable periods, probably depending on severity of illness and immunologic status. Most infants with lower respiratory tract illness shed infectious virus for 1-2 wk after hospital admission. Excretion for 3 wk, and even longer, has been documented. Spread of infection occurs when large, infected droplets, either airborne or conveyed on hands or other fomites, are inoculated in the nasopharynx of a susceptible subject.(1).

Nosocomial infection during RSV epidemics is an important concern. Virus is usually spread from child to child on the hands of caregivers or other fomites. Adults undergoing reinfection also have been implicated in spread of the virus. Contact precautions are sufficient to prevent spread when compliance is meticulous, as the virus is not usually spread by small particle aerosol.(1).

Pathogenesis:-

Bronchiolitis is caused by obstruction and collapse of the small airways during expiration. Airway narrowing likely is caused by virus-induced necrosis of the bronchiolar epithelium, hypersecretion of mucus, and round-cell infiltration and edema of the surrounding submucosa. These changes result in formation of mucus plugs obstructing bronchioles, with consequent hyperinflation or collapse of the distal lung tissue.(1).

Bronchiolitis is a disorder most commonly caused in infants by viral lower respiratory tract infection. It is the most common lower respiratory infection in this age group. It is characterized by acute inflammation, edema, and necrosis of epithelial cells lining small airways, increased mucus production, and bronchospasm.(2)

A large number of soluble factors, such as cytokines, chemokines, and leukotrienes, are released and may predispose some individuals to more severe disease. There is also evidence that genetic factors may predispose to more severe bronchiolitis.(1)

Diagnosis:-

Bronchiolitis is a clinical diagnosis. RSV can be suspected with varying degrees of certainty on the basis of the season of the year and the presence of the virus in the community.(1)

RSV plays a causative role in an estimated 40-75% of cases of hospitalized bronchiolitis.(1)

History & physical examination: Clinicians should diagnose bronchiolitis and assess disease severity on the basis of history and physical examination. Clinicians should not routinely order laboratory and radiologic studies for diagnosis.(2)

Clinical signs and symptoms of bronchiolitis consist of rhinorrhea, cough, wheezing, tachypnea, and increased respiratory effort manifested as grunting, nasal flaring, and Clinical signs and symptoms of bronchiolitis consist of rhinorrhea, cough, wheezing, tachypnea, and increased respiratory effort manifested as grunting, nasal flaring, and intercostal and/or subcostal retractions preceded by viral upper respiratory tract prodrome.(2) Older children most often have only mild, cold-like symptoms, such as croupy cough (often described as a "seal bark" cough), stuffy nose, or low-grade fever. (3). Rarely, RSV infection can cause death in infants. However, this is unlikely if the child is seen by a health care provider in the early stages of the disease. Children who have had RSV bronchiolitis may be more likely to develop asthma(3)

The course of bronchiolitis is variable and dynamic, ranging from transient events such as apnea or mucus plugging to progressive respiratory distress from lower airway obstruction. Young infants with bronchiolitis may develop apnea, which has been associated with an increased risk for prolonged hospitalization, admission to intensive care, and mechanical ventilation.(2) Apnea can be the first sign of bronchiolitis in an infant. This occurs more commonly in infants born prematurely and infants who are younger than 2 months. Difficulty feeding related to nasal congestion and rapid breathing, which can result in dehydration.(4)

risk factors for severe disease include prematurity, hemodynamically significant congenital heart disease, chronic lung disease (bronchopulmonary dysplasia, cystic fibrosis, congenital anomaly), and the presence of an immunocompromised state.(1)(2)(3)(4).

Radiography: may be useful when the hospitalized child does not improve at the expected rate, if the severity of disease requires further evaluation, or if another diagnosis is suspected. (2)

Routine laboratory tests are of minimal diagnostic use in most cases of bronchiolitis or pneumonia caused by RSV.

The white blood cell count is normal or elevated, and the differential cell count may be normal with either a neutrophilic or mononuclear predominance. Hypoxemia as measured by pulse oximetry or arterial blood gas analysis is frequent and tends to be more marked than anticipated from the clinical findings. A normal or elevated blood CO₂ value in a patient with a markedly elevated respiratory rate is a sign of respiratory failure.

Definitive diagnosis of RSV infection is based on the detection in respiratory secretions of live virus by cell culture. The presence of viral RNA (detected by a molecular diagnostic test using reverse transcription PCR) or viral antigens (detected by a rapid diagnostic test, usually a membrane blotting test incorporating antibody detection of viral proteins) is strongly supportive in the right clinical setting. Endotracheal tube lavage fluid from patients intubated for mechanical ventilation can be tested. The specimen should be placed on ice, taken directly to the laboratory, and processed immediately for culture, antigen detection, or PCR analysis (1)

Treatment:-

Treatment at home usually includes antipyretic, increased oral fluid, Parents should encourage their child to drink an adequate amount of fluids. and saline nose drops (with bulb suctioning for infants). Monitoring at home periodically for signs or symptoms of worsening. Specifically, this includes monitoring for an increased rate of breathing, worsening chest retractions, nasal flaring, cyanosis, a decreased ability to feed or decreased urine output. Parents

should contact their child's healthcare provider to determine if and when an office visit is needed, or if there are any other questions or concerns. Smoking in the home should be avoided.(4)

Recovery — Most children with bronchiolitis who are otherwise healthy begin to improve within two to five days. However, wheezing persists in some infants for a week or longer, and it may take as long as four weeks for the child to return to his or her "normal" self.(4).

The treatment of uncomplicated cases of bronchiolitis is symptomatic. Humidified oxygen and suctioning are usually indicated for hospitalized infants who are hypoxic. Intravenous fluid can be given for moderately dehydrated infants. NG tube feeding is helpful when sucking is difficult because of tachypnea.(1)

Ribavirin is an antiviral agent delivered through an oxygen hood, face mask, or endotracheal tube with use of a small-particle aerosol, indicated for:

- ❖ Infants younger than 1 yr of age with hemodynamically significant congenital heart disease
- ❖ Children 24 mo of age or younger with profound immunocompromising conditions during RSV season
- ❖ Infants in the 1st yr of life who have either congenital abnormalities of the airway or neuromuscular disease that compromises handling of respiratory secretions
- ❖ Administration in the 2nd yr of life is recommended for children who required 28 or more days of oxygen after birth and who have on going treatment for chronic pulmonary disease (oxygen, steroids and diuretics)(1).

In 2006, the AAP, in conjunction with the American Academy of Family Physicians (AAFP), the American College of Chest Physicians (ACCP), and the American Thoracic Society (ATS), published guidelines for the diagnosis and management of bronchiolitis in children 1 through 23 months of age. These guidelines were updated in 2014 and include the following recommendations (5) :

- Diagnosis and severity should be based on history and physical findings and not on laboratory and radiologic findings
- Bronchodilators should not be routinely used
- Corticosteroids should not routinely be used
- Ribavirin should not be used
- Risk of serious bacterial infection, especially in infants 30-90 days old with bronchiolitis is low. Antibacterials should be used only upon proven coexistence of bacterial infection
- Nutrition and hydration should be assessed.
- Supplemental oxygen should not be routinely used for patients with saturations above 90% on pulse oximetry; continuous pulse oximetry monitoring may not be necessary
- Chest physiotherapy has not shown to benefit infants with bronchiolitis
- Deep suctioning may provide temporary relief
- Nebulized hypertonic (3%) saline may improve symptoms of bronchiolitis when length of stay is expected to exceed 3 days
- Palivizumab prophylaxis should only be administered to selected children
- Hand decontamination is indicated to prevent nosocomial spread
- Infants should not be exposed to passive smoking
- Breastfeeding is recommended.

Prevention : There are several ways to prevent severe bronchiolitis:

- ❖ Avoid smoking in the child's home because this increases the risk of respiratory illness.
- ❖ Wash hands frequently with soap and water, especially before touching an infant. Hands should ideally be wet with water and plain or antimicrobial soap, and rubbed together for 15 to 30 seconds. Hands should be rinsed thoroughly and dried with a single-use towel.
- ❖ Use alcohol-based hand rubs.
- ❖ Avoid other adults and children with upper respiratory infection.
- ❖ A yearly vaccination for influenza virus is recommended for everyone older than 6 months, especially for household contacts of children younger than five years.
- ❖ Infants who are younger than 24 months with specific types of chronic lung disease and infants who are younger than 12 months who were born before 29 weeks, have specific types of heart disease, or have other risk

factors for severe respiratory syncytial virus (RSV) infection may be given a special medication (palivizumab) to prevent severe RSV infection requiring hospitalization.(4).

Breastfeeding and avoidance of cigarette smoke are also presumed to decrease the incidence and/or severity of viral respiratory tract infections (5)(6).

Immunoprophylaxis: Palivizumab(synagis):-

Palivizumab, a humanized murine monoclonal immunoglobulin G-1 directed against an epitope on the F glycoprotein of RSV, is produced by recombinant DNA technology, and has 95% human and 5% murine amino acid sequences. Rare cases of anaphylaxis are the only recognized serious adverse event. Standard dosing is 15 mg/kg administered intra muscularly every 30 days during RSV season for a maximum of five dose. Palivizumab is available in 50 mg or 100 mg vials.(6).

Palivizumab was licensed in June 1998 by the Food and Drug Administration for the reduction of serious lower respiratory tract infection caused by respiratory syncytial virus (RSV) in children at increased risk of severe disease.(7).

The American Academy of Pediatrics has updated its guidance for the use of palivizumab in infants and young children at greatest risk of hospitalization attributable to RSV infection:

Preterm Infants Without Chronic Lung Disease of Prematurity or Congenital Heart Disease:

Palivizumab prophylaxis may be administered to infants born before 29 weeks, 0 days' gestation who are younger than 12 months at the start of the RSV season. For infants born during the RSV season, fewer than 5 monthly doses will be needed. Infants 29 weeks, 0 days' gestation or later may qualify to receive prophylaxis on the basis of congenital heart disease (CHD), chronic lung disease (CLD), or another condition. Palivizumab prophylaxis is not recommended in the second year of life on the basis of a history of prematurity alone.(7).

Infants With Hemodynamically Significant CHD:

Certain children who are 12 months or younger with hemodynamically significant CHD may benefit from palivizumab prophylaxis. Children with hemodynamically significant CHD who are most likely to benefit from immunoprophylaxis include infants with acyanotic heart disease who are receiving medication to control congestive heart failure and will require cardiac surgical procedures and infants with moderate to severe pulmonary hypertension.(7)

Decisions regarding palivizumab prophylaxis for infants with cyanotic heart defects in the first year of life may be made in consultation with a pediatric cardiologist.(7)

Children younger than 2 years who undergo cardiac transplantation during the RSV season may be considered for palivizumab prophylaxis.(7)

Because 5 monthly doses of palivizumab at 15 mg/kg per dose will provide more than 6 months (>24 weeks) of serum palivizumab concentrations above the desired level for most children, administration of more than 5 monthly doses is not recommended within the continental United States. For qualifying infants who require 5 doses, a dose beginning in November and continuation for a total of 5 monthly doses will provide protection for most infants through April and is recommended for most areas of the United States.(7).

Discontinuation of Palivizumab Prophylaxis Among Children Who Experience Breakthrough RSV Hospitalization: If any infant or young child receiving monthly palivizumab prophylaxis experiences a breakthrough RSV hospitalization, monthly prophylaxis should be discontinued because of the extremely low likelihood of a second RSV hospitalization in the same season (<0.5%).(7).

Use of Palivizumab in the Second Year of Life: Hospitalization rates attributable to RSV decrease during the second RSV season for all children. A second season of palivizumab prophylaxis is recommended only for preterm infants born at <32 weeks, 0 days' gestation who required at least 28 days of oxygen after birth and who continue to require supplemental oxygen, chronic systemic corticosteroid therapy, or bronchodilator therapy within 6 months of the start of the second RSV season.(7).

Lack of Therapeutic Efficacy of Palivizumab: Passive antibody administration is not effective in treatment of RSV disease and is not approved or recommended for this indication.(7)

Effect of Palivizumab Prophylaxis on Subsequent Wheezing:

Prophylaxis is not recommended for primary asthma prevention or to reduce subsequent episodes of wheezing.(7) Clinicians may administer palivizumab prophylaxis in the first year of life to certain infants with hemodynamically significant heart disease.

Clinicians may administer up to a maximum of 5 monthly doses of palivizumab (15 mg/kg per dose) during the RSV season to infants who qualify for prophylaxis in the first year of life. Qualifying infants born during the RSV season may require fewer doses. For example, infants born in January would receive their last dose in March.(7) palivizumab reduced the risk of hospitalization due to RSV infection by 55% and 45%. Via monthly intramuscular (IM) injection, to be administered throughout the duration of the RSV season.

Palivizumab targets the fusion protein of RSV, inhibiting its entry into the cell and thereby preventing infection.(8)

Other potential target groups for palivizumab prophylaxis include:(9)

1. Children younger than one year of age with neuromuscular disorders impairing the ability to clear secretions from the upper airways or pulmonary abnormalities.
2. Children younger than two years of age who are immunocompromised (e.g. those with severe combined immunodeficiency; those younger than two years of age who have undergone lung transplantation or hematopoietic stem cell transplantation) during the RSV season.
3. Children with Down syndrome who have additional risk factors for lower respiratory tract infections.

Side effects of palvizumab: (10)

- Sore throat
- Runny nose
- Redness or irritation at injection site
- Vomiting
- Diarrhea

Some more serious side effects include:

- Severe skin rash
- Itching
- Hives (urticaria)
- Difficulty breathing

Adverse events such as injection site reactions (2.3%), fever (1.5%), diarrhea (<1%), and nervousness/irritability (<1%).(11)

palivizumab, a humanized monoclonal antibody that binds RSV F protein, have been shown to reduce RSV-associated hospitalization. Palivizumab the preferred choice of RSV immunoprophylaxis because of its lack of concern with fluid overload, particularly in children with pre-existing cardiac or pulmonary disease, ease of administration, lack of interference with immunization schedules.(11)

palivizumab was able to neutralize both subtype A and B strains of RSV

and it was safe and well-tolerated, there were no significant changes in urinalysis, hematological values, blood urea nitrogen, creatinine, and transaminase levels.(11)

Monthly prophylaxis resulted in a 55% relative reduction in RSV hospitalization. Significant decreases in hospitalizations were seen in children greater than 5 kg (51%), less than or equal to 5 kg (57%), and in infants born

before 32 weeks gestation (47%). Palivizumab recipients also had significantly reduced hospital days, days with supplemental oxygen requirement, moderate/severe lower respiratory tract infections, and intensive care unit (ICU) admissions.(11)

Risk factors for RSV hospitalization:

Reported host risk factors include the following: congenital malformations, congenital airway anomaly, neuromuscular impairment, birth weight, gender, lack of breastfeeding, duration of breastfeeding, cord serum anti-RSV antibody concentration, small for gestational age, Down syndrome, epilepsy, cord blood vitamin D concentration, family history of atopy, viral load, malnutrition, multiple births, and singletons versus multiple birth subjects.

Environmental risk factors include the following: environmental pollution, crowded living conditions, living at increased altitude, meteorological conditions, low parental education, low socioeconomic status, child care attendance, size of child care facility, month of birth, smoke exposure, maternal smoking during pregnancy, and proximity to hospital care. One publication suggested that malformations of the urinary tract increase the risk of RSV hospitalization.(7)

A study was done in Spain for premature infant found that, age ≤ 10 weeks at start of RSV season, breast-feeding ≤ 2 months, at least 1 school age sibling, at least 4 people living in the household (excluding the infant and school-age siblings), and a family history of wheezing were significantly associated with an increased risk of RSV hospitalization .(11)

Storage and administration of palivizumab:-

The storage must be in the refrigerator, not allowed to be freeze and must be used within 6 hours once you mix it. Palivizumab can be used after dilution with 1 mL of sterile water, should be added slowly to the palivizumab vial and then gently swirl the vial (do not shake it) for 30 seconds. then let the vial sit at room temperature for 20 minutes until the solution becomes clear. The solution should be clear and free of floating material. (12).

Palivizumab is administered intramuscularly at a dosage of 15 mg/kg once a month. The drug is packaged in single-dose liquid solution vials at 50 mg/0.5 mL and 100 mg/1.0 mL and does not contain preservative. A vial cannot be stored once it is opened. Anaphylaxis has occurred after palivizumab administration after initial exposure or reexposure, with some cases of severe hypersensitivity reactions reported.(13).

Palivizumab does not interfere with the immune response to live or inactivated vaccines. The childhood immunization schedule should be followed for all children, regardless of palivizumab use.(13)

Material and Methods:-

A randomized clinical trial was done in Karballa Teaching Hospital For Pediatrics from October 2015-march 2017 to studies the protective effect of palivizumab prophylaxis for reducing RSV-associated hospitalizations in infants with congenital heart disease and premature infants.

The study included 84 patients with CHD and premature infants, 2 premature infants were received 2 doses only and developed irritability & cough therefore we stopped palvizumab injection and 2 premature infants received one dose and escape from follow up (therefore those 4 patients were excluded from the study).

The remaining 80 patients were divided to 2 groups (group A & B) : 30 patients with congenital heart disease their age less than 1 year considered group A and 54 premature neonates who are delivered at the season of RSV (October – March) considered group B. Group A (30 patients) : subdivided to 2 subgroups: A1 & A2, both had hemodynamically significant CHD (large VSD & PDA, complete AV canal with heart failure and on medical treatment, TOF and D-TGA) . 18 patients who received 5 doses of palvizumab monthly (from October- March) considered as group A1 and 12 patients who received 3 doses monthly considered as group A2, with monthly follow up for signs of any respiratory illness.

Group B (50 patients): subdivided to 2 subgroups: B1 & B2 both were premature neonates their gestational age less than 35 weeks of gestation and their body weight less than 1500 gm . 25 patients they were received 5 doses of

palvizumab monthly for 5 months from October-March considered as group B1 and 25 patients they were received 3 doses of palvizumab monthly for 3 months considered as group B2.

Exclusion criteria:-

1. Premature infants with severe sepsis ,severe jaundice,severe congenital malformation and history of birth asphyxia.
2. complex congenital heart disease

All 4 groups were received palvizumab 15mg/kg intramuscular(antrolateral aspect of the thigh) monthly with regular follow up each months for any sign of respiratory distress and side effects.the vial of palvizumab was diluted with 0.5ml of steril water for 50 mg vial and 1ml for 100mg , the sterile water was added slowly to the palvizumab vial and then gently swirl the vial for 30 seconds. then the vial was left at room temperature for 20 minutes until the solution becomes clear and then injected by well trained nursing staff.the patients was observed for any sign of allergy or anaphylaxis for half an hour.

For each group we select control group(group C)80 patients :30 patients with CHD(group C1) &50 premature neonats(group C2) was taken from cardiology clinic,outpatients clinic &premature department &compared with each group.

For each patient and control there was a list of information that include: the name of patient,age,body weight,date of palvizumab injection(first,second,3rd,4th and fifth dose),amount of palvizumab,side effects,type of feeding(breast,mixed and artificial),diagnosis(premature or CHD),if the patient developed bronchiolitis,if the patient need hospital admission,phone or mobile number.

The patients were followed monthly and examined for any signs of respiratory illness and asked the parents for any noticeable side effects.

For all patients we asked them to continue their routine vaccination according to the vaccination program in Iraq,because the palvizumab not interfere with routine vaccination.

THE RESULTS: we in ruled in this study 80 patents with the following results:

For group A1:

The hospital admission was zero percent

The number of patients that developed mild bronchiolitis was 3 patients and no death was reported.

For group A2:

The hospital admission was 8.3%

The number of patients that developed mild bronchiolitis were 4 patients and no death was reported.

For group B1:

The hospital admission was zero percent.

The number of patients that developed mild bronchiolitis were 7 patients and no death was reported.

For group B2:

The hospital admission was 4%

The number of patients that developed mild bronchiolitis were 8 patients and no death was reported.

For group C1:hospital admission was 21(70%) and one death was reported(3.3%),as shown in table (1).

For group C2: Hospital admission was 39(78%) and 4 death was reported(8%).as shown in table (2).

No significant side effects was reported.

Palvizumab didn't interfere with routine vaccination program

Breast feeding had significant factor that contribute to the reduction of severity of bronchiolitis and rate of hospitalization as shown in table(3).

Table (1):- the effectiveness of palvizumab in reduction hospital admission between congenital heart disease group and control group:

Patients group	Total No.	No.of patients developed mild bronchiolitis	No.of hospital admission	No. of death
Group A1	18	3 ¥ #	zero ¥ *	Zero ¥ #
Group A2	12	4 #	1(8.3%) *	Zero #
Control group(C1)	30	3	21(70%)	1(3.3%)

¥ No significant difference ($p>0.05$) as compare with group A2 .

#No significant difference ($p>0.05$) as compare with control group

* Significant difference ($p<0.05$) as compare with control group

Table (2):- the effectiveness of palvizumab in reduction hospital admission between premature group and control group:

Patients group	Total No.	No.of patients developed mild bronchiolitis	No.of hospital admission	No. of death
Group B1	25	7 ¥ *	Zero ¥ *	Zero ¥ #
Group B2	25	8 *	1(4%) *	Zero #
Premature infants(C2)	50	1	39(78%)	4(8%)

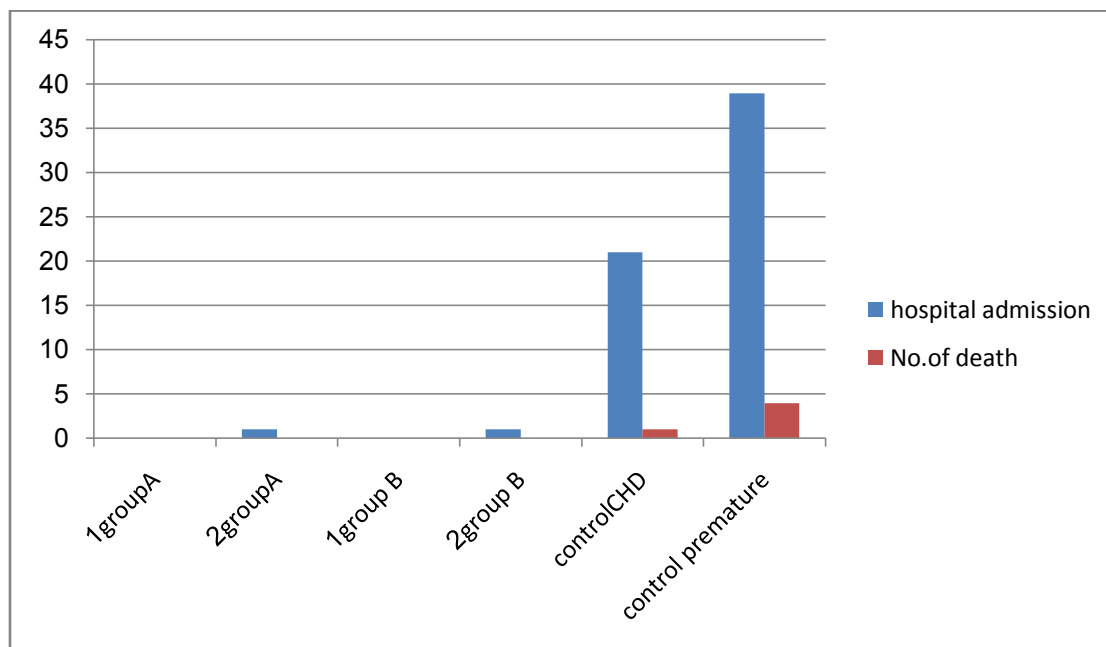
¥ No significant difference ($p>0.05$) as compare with group B2 .

#No significant difference ($p>0.05$) as compare with control group

* Significant difference ($p<0.05$) as compare with control group

Table (3):- the effectiveness of breast feeding between patients and control groups:

Group of patients	Total No.	Breast feeding	mixed	artificial
Group A	30	24(80%)	4	2(6.6%)
Group B	50	25(50%)	19	6(12%)
Patients with CHD(C1)	30	3(10%)	4	23(76.6%)
Premature patients(C2)	50	4(8%)	10	36(72%)

**Figure (1):-** hospital admission and death between patients whom received palvizumab and control groups.

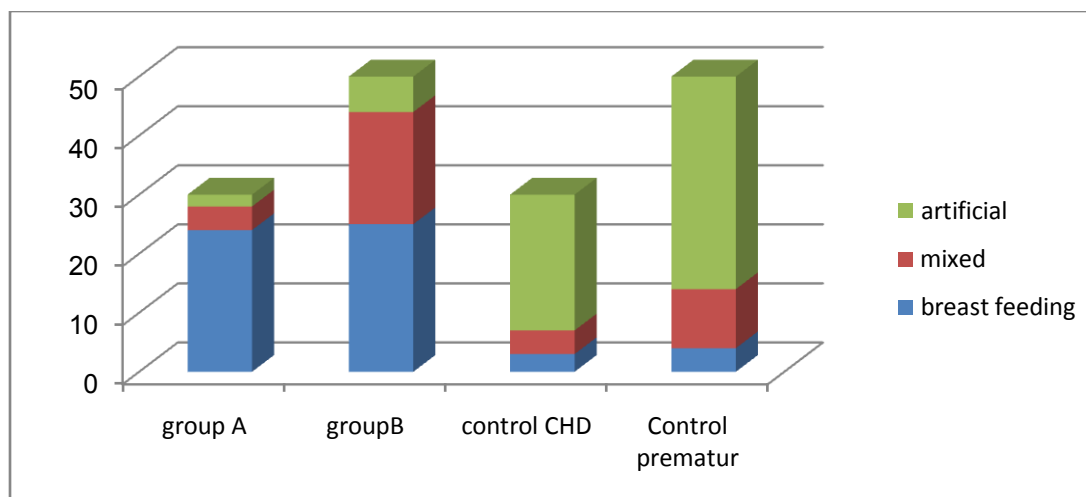


Figure (2):- effectiveness of breast feeding between group A&B and control(group C):show significant number with breast feeding didn't developed severe bronchiolitis

Discussion:-

Guidance from the American Academy of Pediatrics (AAP) for the use of palivizumab prophylaxis against respiratory syncytial virus (RSV) was first published in a policy statement in 1998. Guidance initially was based on the result from a single randomized, placebo-controlled clinical trial conducted in 1996–1997 describing an overall reduction in RSV hospitalization rate from 10.6% among placebo recipients to 4.8% among children who received prophylaxis. The results of a second randomized, placebo-controlled trial of children with hemodynamically significant heart disease were published in 2003 and revealed a reduction in RSV hospitalization rate from 9.7% in control subjects to 5.3% among prophylaxis recipients.(13).

From our study we found there is significant reduction in RSV hospitalization rate from 70% in control group to 8.33% among infants with CHD were prophylaxed with palvizumab for 3 doses and to zero percent for those infant who received 5 doses of palvizumab and no death was reported(P.value less than 0.05).regarding premature infants, the reduction rate of hospitalization was from 78% in control group to 4% among premature infants were prophylaxed with 3 doses of palvizumab and to zero percent for premature infants who received 5 doses of palvizumab .

The mortality rate was zero in both prophylaxed groups and 3.3% for patients with CHD & 8 % for premature infants whom didn't receive palvizumab.

Therefore in this study we found there is significant reduction in morbidity and mortality.

The effectiveness of palvizumab in this study indicat that RSV is the main cause of bronchiolitis in our country. From our study we found that breast feeding had significant preventive measure that contribute to decrease the incidence and severity of bronchiolitis in both groups,this result go with the guidelines were updated in 2014 and recommend the use of breast feeding is a must. (5)(6)(1).

The results of Farber didn't go with our study, Farber found that the effect of palivizumab administration on hospitalization for bronchiolitis with or without an RSV diagnosis among healthy preterm infants born at 29 to 36 weeks of gestation during their first RSV season occurring in 2012, 2013, or 2014, limited utilization and benefits of palivizumab were observed and no benefits were observed for those born between 33 and 36 weeks. , new diagnostic testing for a wide variety of respiratory pathogens has demonstrated that multiple viruses, such as coronaviruses, human metapneumovirus, influenza virus, parainfluenza virus, and rhinovirus, circulate at the same time as RSV and cause bronchiolitis syndromes that are indistinguishable clinically from RSV.(14)

Palivizumab, a humanized monoclonal anti-RSV antibody, was shown to reduce hospitalizations and the clinical severity of RSV infection in high risk infants and children by 55% in a randomised controlled trial. (15)

The result of our study go with (IMPact-RSV study group 1998) was a multi-center, randomized, double-blinded, placebo-controlled trial that enrolled 1502 children (500 placebo and 1002 palivizumab recipients). Eligible participants were ≤ 35 week's gestational age, they found that the monthly prophylaxis resulted in a 55% relative reduction in RSV hospitalization (10.6% placebo, 4.8% palivizumab) with significant relative reductions in premature infants (78%). (11).

My study like two studies (16, 17) which included any premature infant born at GA < 36 weeks reported a statistically significant reduction in RSV hospitalization among prophylaxed compared to nonprophylaxed infants (19–29% rate reduction), but one study (18) which included late preterm infants (GA 33 to 35 weeks) reported a non significant reduction of 0.6%.

our study go with another studies of a total of 1287 children less than or equal to 2 years of age with hemodynamically significant CHD that was uncorrected or palliated were randomized in a double-blind, placebo-controlled trial conducted in Canada, France, Germany, Sweden, United Kingdom, and the United States found that Palivizumab prophylaxis was significantly associated with a 45% relative reduction in hospitalization rates. RSV hospitalization rates were 9.7% in the placebo group and 5.3% in the palivizumab group. (11)

A similar rate of hospitalization (4.6%) was found in 108 Japanese infants with CHD who received palivizumab with no children requiring mechanical ventilation and no mortality (Saji et al 2005). Other investigators have found similar or lower incidences of RSV hospitalizations in patients with hemodynamically significant CHD than the 9.7% rate reported in the placebo arm of Feltes et al (2003) who were not given palivizumab prophylaxis (Duppenthaler et al 2004; Meberg and Bruu 2006). RSV hospitalization rates in patients with severe CHD in Norway were 9.2% (Meberg and Bruu 2006) and only 2.4% in Switzerland (Duppenthaler et al 2004). (11)

Like our study, in 3 studies (19, 20, 21) which included infants born at GA < 32 weeks, the rate of RSV hospitalization was lower in infants who received palivizumab, the reported reduction ranged between 1.2% and 12.4% and this reduction was statistically significant and this is go with my study

Like our study, a study (22) based on hospital record review investigated the effect of palivizumab among 266 children aged < 2 years with CHD, they found that the rates of RSV hospitalization in prophylaxed children were 19% lower than for nonprophylaxed infants from a different RSV season.

Another cohort study (22) among children with CHD reported a reduction in RSV hospitalizations from 7–9 cases/year when children received palivizumab ad hoc to 2–3 cases/per year when prophylaxis was administered systematically (5 doses) and in accordance with recommendations.

Like our study, a cohort study (23) that included premature infants of GA 29 to 32 weeks also reported a lower RSV hospitalization rate in children prophylaxed according to the standard recommendation of 5 doses, compared with the rate in children who received inadequate prophylaxis, that is, children who did not receive the recommended five full doses (3.3% versus 8.1%,).

Our study didn't go with the only study (24) that stratified by gestational age did not find a significant reduction in hospitalization rate in prophylaxed infants born at GA 33 to 35 weeks without CLD. The review of the studies suggests that groups of children who are likely to benefit most from palivizumab prophylaxis are premature infants born at GA ≤ 32 weeks and children with CLD.

Recommendations:-

From this study we recommend:

1. the use of palvizumab in premature infants less than 35 weeks of gestation and their body weight less than 1500 gm as immune-oprophylaxis against severe bronchiolitis
2. the use of palvizumab in hemodynamically significant congenital heart disease: large VSD, large PDA, complete AV canal with heart failure, TOF and D-TGA.
3. 5 monthly doses of pavizumab is very effective in reducing the RSV associated hospitalization.
4. 3 monthly doses of palvizumab is also effective in preventing severe bronchiolitis specially if it was given during the RSV season

5. Breast feeding is recommended in all infants less than one year because of its protective effect against severe bronchiolitis.
6. We need further studies to see the effectiveness of palvizumab in patients with chronic lung disease, cystic fibrosis, neuromuscular disease and immunocompromised patients in order to reduce the rate of hospital admission
7. No significant side effects or anaphylaxis from intramuscular injection of palvizumab.
8. Palvizumab should be supplied for each pediatric hospital to be used in high risk infants.
9. Palvizumab not interfere with routine vaccination.

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List of abbreviation:-

CHD: Congenital Heart Disease
 RSV :Respiratory Syncytial Virus
 VSD:Ventricular Septal Defect
 PDA :Patent Ductus Arteriosus
 AV Canal:AterioVentricular Canal
 TOF :Tetralogy of Fallot
 D-TGA:D-transposition of Great arteries
 CO₂ :Carbon dioxide
 NG tube:Nasogastric tube
 CLD:Chronic Lung Disease