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A CLINICAL PHARMACIST ROLE IN EVALUATION OF RISK FACTORS, COMPLICATIONS, ADVERSE REACTIONS DURING BLOOD TRANSFUSION AND THEIR PREVENTION, MANAGEMENT IN BETA THALASSEMIA MAJOR PATIENTS IN THALASSEMIA AND HEMOPHILIA DAY CARE CENTER, NELLORE, ANDHRA PRADESH, INDIA.

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ABSTRACT:

Background: Blood transfusions are life saving procedure in Beta Thalassemia Major patients. These are increase the life span of the patients. But chronic transfusions can leads to Acute and delayed transfusion adverse reactions, some of complications. An adverse transfusion reaction (ATR) is an unfavorable reaction in the blood transfusion, the severity of these reactions may be different among individuals depending upon the type of reaction and the patient's susceptibility. Transfusion adverse reactions are may be immediate or delayed type depending on the onset and immune or nonimmune type depending on the pathogenesis. Early detection of adverse transfusion and complications will help in taking step to reduce their incidence and make Safe blood transfusion. This study has been undertaken to evaluate adverse reactions and their cause, prevention and management procedures to improve the transfusion safety and patient's Quality of life.

Methods: A prospective observational study was performed in the Indian Red Cross Society Thalassemia and Hemophilia Day Care Centre, Nellore from December 2020 – January 2022.. in order to evaluate Beta Thalassemia Major patients from 6 months to 39 years old. Based on the inclusion criteria patients were enrolled.

Results: From a total of 96 patients 65 patients were identified as (Her parents marriages are Consanguineous marriages) as a Risk factors for the disorder and some of the complications were observed in that mainly 64 patients faced iron overload complications and other complications also. 52 patients were experienced with Acute transfusion Adverse Reactions, incidence was 0.38% and 66 patients were experienced with Delayed transfusion adverse reactions during in their transfusions incidence was 0.46%. Total 13,673 units of blood transfused in this study period. These were assessed by ISBT Severity criteria and Imputability levels.

Conclusion: Clinical pharmacist role is essential in health care settings by promoting health care services to doctors and health care professionals. Patient & Pharmacist relationship improves the patient's knowledge on disease and can improve the patient's Quality of Life. This study is useful for identification of Adverse Reactions and their prevention, management is useful for reduce the patient disease burden and improves Transfusion safety.

Keywords: Adverse Transfusion Reactions, Transfusion safety, Clinical Pharmacist.

INTRODUCTION:- Thalassemia is genetic blood disease, inherited from a person's parents which will end in the abnormal formation of hemoglobin. The name Thalassemia derived from a mixture of two Greek words: "Thalassa" meaning "the sea" and "Haema" means (blood). Thalassemia refers to disorders related to defective synthesis of "α or β -globin" subunits of hemoglobin (Hb)A(α2;β2), inherited as pathologic alleles of 1 or more of the globin genes located on chromosomes 11 (β) and 16 (α). [1] Risk factors of Thalassemia is Hereditary transmission,[3] Consanguinity, Ancestry, Some Communities, Thalassemia is particularly in Malaria prevailing areas, but the exact mechanism is still not known. In areas where malaria was prevalent, humans underwent a small genetic change in their DNA, it makes chages occurs in RBC. [33] Complications are Iron Overload, Growth retardation, Hepatic complications, Renal complications, cardic complications, Transfusion related infections(Hepatitis - B), Endocrine , splenomegaly, Bone Damage etc., Regular blood transfusions and chelation therapy will increased the anticipation of thalassemics into 4th & 5th decades of life. Transfusion reactions are defined as adverse events associated with the transfusion of whole blood or one of its components. These may range in severity from minor to life-threatening [2]. Reactions can occur during the transfusion (acute transfusion reactions) or days to weeks later (delayed transfusion reactions) and may be immunologic or non-immunologic.[3] Common blood reactions associated with blood transfusions are non-hemolytic reactions, hypotensive transfusion reactions, allergic reactions, Post Transfusion Purpura, acute hemolytic reactions, autoimmune hemolytic anemia, delayed transfusion reactions, transfusion related acute lung injury (TRALI), TACO and graft vs. host disease (GVHD).[4] The ISBT has laid down criteria for 'severity' and 'imputability' of transfusion reactions. [27] and definitions for classifications (type of reations). [31,32] The transfusion reactions in a recipient are generally subdivided as acute (within 24 hours) or delayed (after hours to days of transfusion) reactions.[4]

The main aim and objective of our study is to Identify transfusion-related adverse reactions, risk factors and complications is useful for the patient to avoid extra burden associated with the transfusions. Premedication before transfusion also helpful for reducing Transfusion related adverse reactions. Creating awareness, guidence, premarital and prenatal screening are the simplest preventive measures in future avoid the disease occurrence in children.

METHODS AND MATERIALS:-

- **Place of Study:** This study was conducted at Indian Redcross Society Thalassemia and Hemophilia Day Care Centre, Nellore.
- **Study method:** A prospective observational study. This study is condected by after obtaining the permission from the institutional ethical committee. The patients will be enrolled in the study after taking informed consent from them.
- **Study Population:.** 96 Beta Thalassemia Major Patients under maintenance of Blood Transfusions and Chelation therapy.
- **Inclusion Criteria:** Patients who takes blood transfusions and chelation therapy.
- **Exclusion criteria:** Hemophilia, Anemia, Cancer patients, Sickle cell Anemia patients.
- **Study duration:** December 2020 to January 2022..
- **Study materials:**

1. Patient informed consent form.
2. Patient data collection Proforma.
3) Transfusion Reactions Reporting form.
4) Used ISBT Severity and Imputability Scale used to Assessment of Transfusion Adverse Reactions.
5) The following variables were calculated:-
1) ATR frequency - based on Total number of patients.
2) ATR Incidence - ATRs observed in patients / Total number of Transfusions *100.
3) Overall ATR Incidence – Number of patients experienced ATR/Total number of Transfusions*100.
4) Severity and grading – ISBT Severity and grading criteria.
5) Imputability Levels – ISBT Imputability Levels.

RESULTS :

During the study period December 2020 to January 2022 in Indian Redcross Society Thalassemia and Hemophilia Day care center total 96 patients [49 (51.04 %) males and 47 (48.95 %) were females. Age of the patients between 6 months to 39 years. In those 2 female (02.08 %) patients are married and their children and their partners are healthy individuals. Diagnosed age of patients were 1 (01.04%) was diagnosed at the age of 19 years, 2 (2.08%) patients were diagnosed at the age of< 15 years, 22 (22.91%) patients were diagnosed at the age of< 10 years 08 (08.33%) patients were diagnosed at<5 years and 63 (65.62%) patients were diagnosed at the age of<1 year. Risk factors were mentioned in **(Table .1)** and Complications were mentioned in **(Table.2).** Their Blood groups are (O +Ve – 41 (42.70 %), B +ve – 32 (33.33%), A +ve – 13 (13.54%), AB +ve- 05 (05.20%), B – ve - 03 (05.20%). 16 (16.66%) patients were transfused thrice, 13 (13.54%) patients were transfused thrice, 47 (48.95 %) patients were transfused twice, 20 (20.83%) patients were transfused once in a month. Total 13,673 units of blood transfused in this study period. Out of 96 patients 52 patients were experienced with Acute transfusion Adverse Reactions, incidence was 0.38% and 64 patients were experienced with Delayed transfusion adverse reactions during in their transfusions incidence was 0.46%. **(Table.3)**. Type wise distribution and incidence of Transfusion Adverse Reactions **(Table.3,4).** The severity of these Adverse Reactions as per ISBT Criteria were Non Severe, Grade – 1-[313(75.97 %)reactions] and Severe Grade -2 [99 (24.02 %) reactions] **(Table. 3)** and their Assessment as per Imputability levels wise Definite [Certain] – 259 (27.50 %), Probable [Likely] – 121 (29.36 %) and Possible – 32 (07.76 %) **(Table. 3)**.

Table.1. Risk factors wise distribution of Beta Thalassemia Major patients:

SL. NO.	Risk factors	NO. OF Patients (n = 96)	PERCENTAGE (%)
1.	Consanguinity	65	67.70 %
2.	Non - Consanguinity	31	32.29 %

Table. 2. Complications wise distribution of Beta Thalassemia Major patients:

SL. NO.	Complications	NO. OF Patients (n = 96)	PERCENTAGE (%)
1.	Iron Overload	64	66.66 %
2.	Growth Retardation	04	04.16 %
3.	Infections	09	09.37 %
3.	Hepatic Complications	61	63.54 %
4.	Cardiac Complications	01	01.04 %
5.	Renal Complications	01	01.04 %
6.	Endocrine Complications	06	06.25 %
7.	Bone Complications	01	01.04 %
8.	Splenomegaly	45	46.87 %
9.	Respiratory Complications	03	03.12 %

Table. 3 : Total number of Adverse Transfusion Reactions and their Nature (Type), [32]Severity, [27] Imputability Levels [27]

ADVERSE TRANSFUSION REACTIONS	No. Of Reactions (n=412)	Nature (Type)of the reaction	Severity Grade	Imputability Levels
Facial flushing and eye lid flushing	05	Anaphylactic Reaction	Grade-1(Non Severe)	Definite
Fever	39	Febrile non Hemolytic Reactions	Grade-1(Non Severe)	Definite
Chills	39	Febrile non Hemolytic Reactions	Grade-1(Non Severe)	Definite
Rigors	39	Febrile non Hemolytic Reactions	Grade-1(Non Severe)	Definite
Sweating	07	Febrile non Hemolytic Reactions	Grade-1(Non Severe)	Possible
Urticaria	42	Allergic reaction	Grade-1(Non Severe)	Definite
Infusion site edema	02	Acute hemolytic Reaction	Grade-1(Non Severe)	Possible
Infusion site pain	08	Anaphylactic Reaction	Grade-1(Non Severe)	Possible
Itching (Pruritus)	29	Allergic reaction	Grade-1(Non Severe)	Definite
Vomiting	33	Anaphylactic Reaction	Grade-1(Non Severe)	Probable
Throbocytopenia	04	Post Transfusion purpura	Grade-2(Severe)	Probable
Abdominal pain	14	Anaphylactic Reaction	Grade-1(Non Severe)	Probable
Back/Flank pain	19	Anaphylactic Reaction	Grade-1(Non Severe)	Probable
Headache	22	Anaphylactic Reaction	Grade-1(Non Severe)	Probable
Cough	09	Anaphylactic Reaction	Grade-1(Non Severe)	Possible
Hypotension	29	Hypotensive Transfusion Reaction	Grade-2(Severe)	Probable

Haematuria	06	Delayed hemolytic TransfusionReaction	Grade-1(Non Severe)	Possible
Iron Overload	66	Delayed transfusion reaction	Grade-2 (Severe)	Definite

Table. 4 : Type wise distribution of Adverse Transfusion Reactions[32] and their frequency, frequency percentage and incendence.

Type Of Adverse Transfusion Reactions	Frequency	Frequency%	Incidence
❖ **Acute Transfusion Adverse Reactions**			
Febrile Non Hemolytic Transfusion Reactions	113	27.42 %	0.82 %
Allergic reactions	71	17.23 %	0.51 %
FNHTRs and Allergic reactions	11	02.66 %	0.08 %
Anaphylactic Reactions	110	26.69 %	0.80 %
Hypotensive transfusion reactions	29	07.03 %	0.21 %
Acute Hemolytic Transfusion Reactions	02	0.48 %	0.01 %
Delayed Hemolytic Trafusion Reactions	06	01.45 %	0.04 %
❖ **Delayed Transfusion Adverse Reactions**			
Iron overload	66	16.01 %	0.48 %
Post Transfusion Purpura (Thrombocytopenia)	**04**	**0.97 %**	**0.02 %**

DISCUSSION: Beta Thalassemia Major patients requiring a lifelong blood transfusions to stay alive. Every blood transfusion carries a minute risk of Reactions and Complications. The frequency of transfusion adverse reactions in our study almost equal in males and females at the same point of view Prakash et al [6] study also shown almost equal frequency of reactions in males and females. It was contrast with other studies of Shajil et al [5], Sinha et al [7] Sharma et al [14], Akhter N et al [9] was shown higher incidence of transfusion reactions in females than male. Other studies Kumar et al [10] and Bhattacharya et al [11] shown lower incidence of transfusion reactions in females. In our study 2 female patients were married and having healthy children it was quite different to other's studies.

In this study all patients are transfused only with antigen present washed PRBCs in their blood transfusions and Bed side Leukocyte Reduction filters were not used during transfusion. Clerical errors are common causes of adverse reactions during transfusions but in our study blood group checking and cross matching conducted by technicians before blood transfusion. So clerical errors detection omitted in this study.

In the present study Febrile non Hemolytic Transfusion adverse reactions, Allergic reactions, Allergic and FNHTRs, Anaphylactic Reactions Acute Hypotensive transfusion adverse reactions, Thrombocytopenia and Iron overload were occurred due to the Packed Red blood cells transfusion. Most of the studies shown that majority of reactions were occurred due to PRBCS [14,5,16,6,15,17.] It was contrast to the others reported in their studies high frequency of transfusion reactions were due to whole blood transfusions.[9,7,6,18,19.] In Another studies reported that Acute transfusion adverse reactions were less commonly occurred through the Leuko

reduction PRBCs. [15,30.] In this study Delayed transfusion adverse reactions were also observed. Gente et al [14] study reported 85% of the FNHTRs occurred due to the 8-14 days age of RBCs, it is quite different from our study. In our study reactions are not correlation to age of RBCs. Patients receiving multiple transfusions, transfusion reaction is usually caused by PRBCs due to more amount of leftover plasma during component preparation in products collected with no additive solution. Standardization in the component preparation will help in reducing the incidence of FNHTRs to PRBCs.[14] Febrile non hemolytic transfusion reactions (FNHTRs) and allergic reactions are the most common acute adverse reactions to blood component transfusions. These are less harmful and reversible. [22.] In our study majority of Acute transfusion adverse reactions were FNHTRs and followed by allergic reactions. (**Table**.**2**) It was similar to other studies. [14,9,,6,23,19,30,21.] In the present study, transfusion-associated sepsis were not observed because our blood bank maintaining proper storage methods with out contamination of blood products.

1. **Febrile Non Hemolytic Transfusion Reactions:**

Most of the studies reported that high incidence of FNHTRs were due to PRBCs. Premedication was not taken by so many patients, so this is also may be one of the reason of higher incidence of FNHTRs. in our study. Some studies shows that pre medication did not reduce the incidence of FNHTRs. [24.] FNHTRs are caused by the presence of antibodies (anti-HLA or anti-leukocytes) in recipient plasma that react against leukocytes present in donor components or the presence of biological response modifiers (BRMs) that accumulate in donor plasma during product storage and Antigen-Antibody reactions in cytokines. In both cases, there is an increase in circulating cytokines that results in fever, chills, or rigors. So many studies reported that the incidence of FNHTRs can be decreased through leukocyte reduction [8,23.] LR- PRBCs are not available in our blood bank and Bed side Leuko reduction filters were not used these are also responsible for higher incidence of FNHTRs. Another reason for higher frequency of FNHTRs in this study was 13 patients had previous history of sensitisation to blood transfusion FNHTRs. A comparative study on incidence of FNHTR in leukoreduced and nonleukoreduced blood components showed that high incidence in nonleukoreduced and low incidence in prestorage leukoreduced blood. [15,30.] **Prevention**: Leucocyte depleted (Leukocyte reduced) PRBCs and Usage of Bedside Leukocyte Reduction Filters usage in transfusions. 30 mins before pre medication with Antipyretics, Antihistamines and Meperidine.

The pre-storage laboratory leucoreduction is useful and more effective than bedside leucoreduction.[18]

Management: Antipyretics and Antihistamines. Meperidine for Rigors.

2. **Allergic Reactions:** In the present study after FNHTRs followed by Anaphylactic reactions and next Allergic reactions in higher incidence. Out of 96 patients 14 patients had a previous history of allergic reactions and allergic to other substances/transfusion. Other studies reported that allergic reactions were higher incidence to the Packed Red blood cells.[28,5,16,29,17.] Histamines and leukotrines are responsible for these reactions. Allergic reactions occur owning to antibodies against donor plasma proteins. These reactions are common in IgA deficient individuals although they may occur in normal IgA levels individuals. The incidence of these reactions couldn't reduced by Leukocyte Reduction in RBCs.[15] Allergic reactions result of recipient IgE and donor antigen interactions triggering the release of histamine and denovo synthesis of leukotrines and platelet activating factor.[15]

Prevention: 30 mins before Premedication with Antihistamines and hydrocortisone. Plasma deficient blood.

Management: Symptomatic treatment with Antihistamines and Hydrocortisone.

3. **Allergic and FNHTRs:**

11 patients Were experienced with both febrile and FNHTRs. These patients have previous history of (both reactions to the blood transfusions.) sensitisation to the blood transfusions. These patients recovered with medication management. These reactions incidence is higher than Gente et al [14] study.

Prevention: Pre medication with Antipyretics, Antihistamines, Hydrocortisone and Meperidine. Pre – Storage Leuko reduction like LR- PRBCs and Bed side Leukocyte reduction filters can reduce the occurrence of these reactions

Management: Symptomatic treatment with Antipyretics, Antihistamines, Hydrocortisone and Meperidine.

4. **Anaphylactic Reactions:** Anaphylactic Reactions are another form of allergic reactions. Histamine and Leukotrines are the mediators of these reactions. These are commonly seen in IgA deficient recipients, it is caused by antibodies against donor IgA. [17.] In the present study patients were experienced with Facial flushing and eye lid flushing, cough, Infusion site pain , vomiting, Abdominal pain, Back pain, Headache.

Prevention: Use of IgA deficient blood components. Premedication with Corticosteroids, Antihistamines.

Management: Corticosteroids, Antihistamines.

5. **Acute Hypotensive transfusion adverse reactions:** Incidence of these reactions are slightly higher than other studies. Hypotension within the first four hours of transfusion with out any evidence of other conditions causing hypotension [9,15]. It responds quickly to cessation of the transfusion and supportive therapy. [20.] Patients with otherwise unexplained hypotensive transfusion reactions should be given a trial of washed blood products. Bedside leucoreduction filters have been implicated more often in acute hypotensive transfusion reaction although it has also occurred with prestorage leucofilters. [25] The frequency of Hypotensive reactions in our study is high than compared to the other studies. Sreedhar babu et al study reported that one patient had experienced hypotension after transfusing PRBCs which is preserved in additive solution – saline adenine glucose mannitol (SAGM). [16.] Some authors reported that mannitol act as an Acetylcholine esterase (ACE) Inhibitor there by slowing down catabolism of bradykinin and leading to its accumulation in the stored RBCs. Some studies shown that hypotension developed in patients who received blood components by bed side leuko reduction filters. [16, 25,26.] But our patients were not used such Bed side leuko reduction filters.In our blood bank SAGAM wasn't used. Those are used Citrate Phosphate dextrose adenine in their blood collecting bags.

Prevention and Management: Cessation of transfusion and supportive therapy with ORS or Ringer's lactate solution (RL), also known as sodium lactate solution and Hartmann's solution, is a mixture of sodium chloride, sodium lactate, potassium chloride, and calcium chloride in water.

Delayed Hemolytic Transfusion Adverse Reactions: Presence of antibodies, auto antibodies, allo antibodies or both complicates pre-transfusion and compatibility testing and auto-antibodies poses difficulties in detection of alloantibodies by pan reactivity. The blood banks provide only ABO- and Rh (D) - antigens matched blood, which increases risk of alloimmunization to minor blood group antigens. Majority of these alloantibodies are of Rh blood group specificity, extended antigen matching (C, E, c, e, K) which can prevent RBC alloimmunization to great extent. Patients who have WAAs in their serum have a higher rate of alloimmunization. Monitoring of evidence of RBC destruction due to alloantibodies is difficult in patients, who already have AIHA. It is vital to detect the appearance of new alloantibodies or disappearance of old alloantibodies to prevent hemolytic transfusion reaction during or after allogeneic transfusion.[13]

1. Post Transfusion Purpura (Thrombocytopenia):

It occurs when the recipient develops antibodies against the platelets. This results in the destruction of platelets. It occurs between 1 and 24 days after blood transfusion. It is commonly associated with the Transfusion of RBCs or whole blood. Antibodies against HPA- 1a, HPA -1b, other platelet antigens and HLA antigens are responsible for PTP. [18]

Prevention and Management: Plasmapheresis, Intravenous immune globulin. Platelet transfusions are usually ineffective in raising the platelet counts in these patients [18].

2. Iron overload: out of 96 patients, 66 patients have iron overload. It's not mentioned in other studies. It is also one of the delayed transfusion reaction. Regularly transfused patients have risk for iron overload. A unit of RBCs contains approximately 250 mg of iron. Majority of the released iron can't be excreted and is stored in the body as haemosiderin and ferritin and causing tissue damage leads to heart failure, liver failure etc.,[18]

Management: Iron chelators.

Conclusion: Clinical pharmacist plays a vital role in health care settings to provide better patient care. Patient education is important to reduce disease burden. Patient & Pharmacist relationship improves the patient's knowledge on disease can improve the patient's Quality of Life. In our blood bank majority of the reactions were FNHTRs. Those are common for PRBCs transfusion. Introduction of Pre storage Leukocyte Reduction or Bed side Leucocyte reduction filters can reduce the occurrence of these reactions. Pre medication also useful to avoid transfusion related adverse reactions. In our study sepsis reactions were not observed because our blood bank maintaining proper storage conditions. Identification of Adverse Reactions in blood transfusions and their prevention, management is useful for reduce the patient disease burden and improves transfusion safety, quality of life of patients.

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