Urticarial Reactions In Multi-Transfused Patients In University Of Maiduguri Teaching Hospital, Maiduguri, Borno State.

***Dr SG AHMED, MBBS, FWACP**
DEPARTMENT OF HAEMATOLOGY, UNIVERSITY OF MAIDUGURI TEACHING HOSPITAL, PMB 1414, MAIDUGURI.
Dr UA IBRAHIM, MBBS
DEPARTMENT OF MEDICINE, UNIVERSITY OF MAIDUGURI TEACHING HOSPITAL, PMB 1414, MAIDUGURI.
**CORRESPONDENCE TO Dr SG AHMED, DEPT OF HAEMATOLOGY*

ABSTRACT

Objectives: The study was aimed at determining the pattern of urticarial transfusion reactions (UTR) among patients who received multiple blood transfusions at the University of Maiduguri Teaching Hospital (UMTH) from 1997-2001.

Materials and Methods: A total of 154 multi-transfused patients who received transfusions during the period 1997-2001 at the UMTH were studied with respect to the incidence, time of onset and clinical severity of UTR in relation to the cumulative number of previously transfused units of blood.

Results: The overall incidence of UTR among all patients irrespective of number of previous transfusions was 7%. However, analyzing the data with respect to the number of previously transfused units of blood, the incidence of UTR were 0%, 3%, 10%, 17% and 27% among patients who were previously transfused with 3-7, 8-12, 13-17, 18-22 and 23-27 units of blood respectively. All cases of UTR in the affected patients were clinically mild manifesting with urticarial rashes and pruritis without any features of anaphylaxis irrespective of the number of previous transfusions. The mean duration of time between the start of transfusion and onset of UTR among all affected patients was 35 minutes. However, the mean duration of time between the start of transfusion and onset of UTR varied with number of previous transfusions where patients who had previous transfusions with 8-12, 13-17, 18-22 and 23-27 units of blood reacted after a mean time of 53, 40, 27 and 17 minutes respectively.

Conclusion: This data would suggest that blood transfusion is an important sensitizing event in the development of UTR and the risk increases with the number of previous transfusions. Therefore, multi-transfused patients need closer observation during transfusion therapy.

KEY WORDS:
URTICARIAL REACTION, MULTIPLE TRANSFUSIONS

INTRODUCTION

Urticarial transfusion reaction (UTR) is one of the common types of non-haemolytic immune transfusion reactions encountered in clinical blood transfusion therapy [1]. UTR is predominantly mild and the clinical manifestation typically includes generalized pruritis with widespread urticarial lesions consisting of circumscribed areas of cutaneous oedema[2]. Rarely, UTR may be severe in which case there will be associated features of anaphylaxis including bronchospasms, angioneurotic oedema, abdominal cramps and hypotension[1,2,3]. The urticarial lesions are due to allergic reactions caused by sensitivity to antigenic determinants on plasma proteins present in donor blood that react with the corresponding IgE antibodies in the recipient plasma[3,4]. The plasma proteins in the donor plasma could be endogenous proteins such as the immuno-

globulins such as IgG, IgM and IgA, or exogenous proteins such as milk or egg proteins usually derived from food stuff that were recently ingested by the blood donor [1,5,6]. Antibodies to leucocytes and platelets antigens do not appear to be associated with urticarial reactions in transfused patients[7]. Immune complexes are formed between antigenic determinants on immunoglobulins and the corresponding IgE antibodies, which become adsorbed via the IgE receptors on the membranes of cutaneous mast cells and basophilic leucocytes in the circulating blood leading to degranulation and release of histamine resulting in cutaneous vascular dilatation, increased permeability and oedema that manifest as urticaria [1,3].

Previous exposure to blood by transfusion or pregnancy is thought to be responsible for sensitizing patients to produce reagenic IgE antibodies against plasma proteins in the blood of the donor or foetus leading to urticarial reactions during subsequent exposures to blood or blood products[1]. In pregnancy, sensitization to various antigens, including plasma proteins in the foetal blood is thought to follow foeto-maternal transplacental haemorrhage leading to maternal exposure to foetal blood during the course of pregnancy or labour[1]. In patients who received blood transfusions, sensitisation is thought to occur as a result of direct exposure of the recipient to allogenic donor antigens, including plasma proteins in the transfused blood or blood products[1].

In this paper we intend to evaluate the frequency and pattern of UTR among multi-transfused patients with respect to the number of previously transfused units of blood as seen in the University of Maiduguri Teaching Hospital (UMTH), Maiduguri, Borno State, North East Nigeria.

PATIENTS AND METHODS

A total of 154 multi-transfused patients (94 males and 60 females) within the ages of 31-73 years who suffered from various types of chronic anaemic disorders and received blood transfusion on more than one occasion during a 5-year period (January 1997-December 2001) were studied with respect to the frequency and clinical severity of UTR as it related to the cumulative number of previously transfused units of blood. All of the female patients included in this study had no history of pregnancy thus excluding the possible effect of previous pregnancies1 on the causation of UTR. All patients were registered with the UMTH, which is a tertiary reference centre for the North East sub-region where they received medical care including blood transfusion for various types of chronic anaemic disorders including sickle cell disease, aplastic anaemia, lymphomas, myelodysplastic syndrome, myelofibrosis, acute and chronic leukaemias, inherited bleeding disorders and chronic renal diseases.

In each case, the cumulative number of previously transfused units of blood were determined and documented at the instance of the first episode of UTR. The duration between the start of transfusion and onset of UTR were also documented and the clinical severity of the reactions were assessed as mild if the urticarial skin rashes were accompanied by pruritis only, or severe if any features of anaphylaxis such as bronchospasm, angio-oedema, abdominal cramps or hypotension accompanied the urticarial skin rashes1,2,3.

The data were analyzed using the chi-square test and a probability level of $p<0.05$ was taken as significant.

RESULTS

The total number of transfused units of blood per individual patient varied from 3 to 27 units and the overall incidence of UTR among the patients studied was 7% as shown on Table 1. Analyzing the data with respect to the cumulative number of previously transfused units of blood, it can be seen that none of the patients who received only 3-7 units of blood experienced any form of UTR. However, the incidence of UTR among patients who received 13-17 units was 10%, which was significantly ($p< 0.05$) higher than 3% found among patients who received 8-12 units. Similarly, the incidence of UTR of 17% found among patients who have had 18-22 units of blood was significantly ($p< 0.05$) higher than the incidence of 10% seen among recipients of 13-17 units. Patients who received 23-27 units of blood had the highest incidence of UTR of 27%, which was significantly ($p< 0.05$) higher than the incidence of 17% seen among the recipients of 18-22 units.

Table 2 showed that all patients studied in this report had the mild form of UTR. The mean duration of time between the start of transfusion and onset of UTR among all affected patients was 35 minutes. However, the mean duration of time between the start of transfusion and onset of UTR showed an inverse correlation with the cumulative number of previously transfused unit of blood. The patients who received

13-17 units had a mean reaction time of 40 minutes, which was significantly ($p< 0.05$) shorter than 53 minutes for patients who received 8-12 units. Similarly, the mean reaction time of 27 minutes found among patients who have had 18-22 units of blood was significantly ($p< 0.05$) shorter than 40 minutes seen among recipients of 13-17 units. Patients who received 23-29 units of blood had the shortest mean reaction time of 17 minutes, which was significantly ($p< 0.05$) higher than 27 minutes seen among the recipients of 18-22 units.

Table1: Incidence of urticarial transfusion reactions (UTR) among 154 multi-transfused patients.

No of Previously Transfused Units	No of Subjects Studied	No of Subjects with UTR	Incidence of UTR (%)
3-7	52	0	0
8-12	38	1	3
13-17	31	3	10
18-22	18	3	17
23-27	15	4	27
Total	**154**	**11**	**7**

Table2: Pattern of clinical severity and mean reaction time of UTR among 11 affected multi-transfused patients.

No of Previously Transfused Units (Minutes)	No of Subjects with *Mild UTR	No of Subjects with**Severe UTR	***Mean Reaction Time
8-12	1	0	53
13-17	3	0	40
18-22	3	0	27
23-27	4	0	17
Total	**11**	**0**	**35**

*Mild UTR= Urticarial rashes with pruritis only

**Severe UTR= Urticarial rashes with pruritis accompanied by features of anaphylaxis

***Mean Reaction Time= Mean Time between start of transfusion and onset of UTR

DISCUSSION

The data on Table 1 showed that the overall incidence of UTR among all patients irrespective of the number of previous pregnancies was 7%. Analyzing the data with respect to the cumulative number of previously transfused units of blood, we found that none of our patients who had only 3-7 units of blood experienced any form of UTR. However, the incidence of UTR among patients who had 8-12, 13-17, 18-22 and 23-27 units of blood showed significant increase in magnitude from 3% to 10%, 17% and 27% respectively as shown on Table 1. Urticarial reaction is therefore a commonly encountered clinical problem in patients who received multiple transfusion therapy. Our data revealed a rising incidence of UTR in proportion to the number of previously transfused units of blood. This trend would suggest that the frequency with which patients receiving transfusion therapy become sensitized and develop antibodies against plasma proteins is proportional to the number of antigenic exposures, and higher number of transfusions will invariably result in greater number of such exposures. In fact, a similar trend was seen among patients with non-haemolytic febrile transfusion reactions due leucocytes antibodies in which the incidence of the reactions was found to be directly proportional to the number of antigenic exposures due to previous transfusions8. Hence, the absence of UTR among our patients who received only 3-7 units of blood in this report (Table 1) would suggest that this amount of blood transfusion did not provide sufficient antigenic exposure for sensitization and development of antibody against plasma protein antigens.

The pattern of clinical severity did not correlate with number of previously transfused units of blood as all patients irrespective of the number of transfusions and antigenic exposures had only the clinically mild form of UTR characterized by generalized pruritis and urticaria with no accompanying symptoms of anaphylaxis such as bronchospasms, angioneurotic oedema, abdominal cramps or hypotension (Table 2). The overall mean reaction time among all patients with UTR irrespective of the number of previous transfusions was 35 minutes (Table 2). However, there was an inverse correlation between the number of previously transfused units of blood and the mean reaction time, which ranged from 17 minutes for patient who had 23-27 units of blood to 53 minutes for those who had only 8-12 units of blood as shown on Table 2. This data revealed significant shortening of mean reaction times in proportion to the cumulative number of previously transfused units of blood as shown on Table 2. This is interpreted to suggest that the shortening of reaction times among patients who have had

higher number of previous transfusions could be due to the presence of plasma protein antibodies with greater avidity produced as result of boosted anamnestic secondary immune response generated by repeated antigenic exposures[1] as a result of the previous multiple transfusions. Hence, patients who had higher number of previously transfused units would produce very avid antibodies, which lead to more efficient and faster antigen-antibody interactions and shorter reaction times.

Fortunately, all of our patients studied in this report had the clinically mild form of UTR (Table 2), which could be effectively managed by simply slowing down the rate of transfusion and supplementing with parenteral administration of anti-histamines such as chlorpheniramine 10mg intramuscularly or intravenously[1,3], following which the urticarial rashes would usually disappear within 30 minutes in all such cases and the transfusion could be safely completed slowly[1]. However, many such cases of mild UTR are often incorrectly assessed leading to unnecessary termination of transfusion. Clinicians must assess and manage all mild cases of UTR appropriately in order to avoid unnecessary terminations of transfusion that would result in undue delay in the clinical progress of patients. Further more, unnecessary terminations of transfusions often have distressing financial implication on the patient, and this is particularly so in our environment where voluntary donor blood is scarce and most units of blood are usually obtained from commercial donors[10,11], this situation being a direct consequence of the lack of a functional National Blood Transfusion Service in the country[1,10,11,12]. In our experience, many patients have experienced such financial distress as a result of unnecessary termination of their transfusion due to mild forms of urticarial transfusion reactions.

It is important for the clinicians to bear in mind that UTR tend to recur in affected patients, therefore such patients must be offered pre-transfusion preventive measures before any future or subsequent transfusions[1,3]. Fortunately, UTR can easily be successfully prevented if an anti-histamine such as chlorpheniramine at a dose of 10mg is given either 1-2 hours orally before onset of transfusion or more conveniently, intravenously at the start of the transfusion[1,3]. In addition, such patients should be transfused with red cell concentrate rather than whole blood so as to minimize the quantity of the antigenic plasma proteins in the donor blood thereby reducing the chances of UTR[13].

In rare cases, UTR has been reported to be severe and florid features of anaphylaxis accompanied such cases resulting in life threatening cardio-respiratory instability[3]. This severe form of UTR is usually the result of a reaction between normal IgA in the donor plasma and so-called class specific anti-IgA in the recipient's plasma[3]. This antibody is found only in patients who have congenital deficiency of IgA[2,3,14], and the incidence of IgA deficiency in the Caucasian populations has been estimated to be about 1 in 10003. Such severe cases of UTR are medical emergencies and it is absolutely necessary to terminate the transfusion at once and administer adrenalin 0.5-1mg subcutaneously or intramuscularly as well as hydrocortisone 100-200mg intravenously[3] with the patient monitored in the intensive care unit. Thereafter, any future transfusion for such patients can only be undertaken using special blood collected from IgA deficient donors but if such donors are unavailable, the patients can be safely transfused with washed red cells or frozen and thawed red cells since these blood components are prepared by procedures effective in completely removing donor plasma[2,3,15]. Luckily all of our cases of UTR were mild (Table 2) with no accompanying features of anaphylaxis. The absence of severe UTR among our patients may suggest the absence or a very low prevalence of congenital IgA deficiency in the Maiduguri, North East Nigeria, but this can only be verified by conducting a survey in the sub-region. National data regarding the actual occurrence and incidence of IgA deficiency in the general Nigerian population is lacking, however, a survey conducted among school children in the Eastern Nigerian sub-region revealed an incidence rate of about 4 in 100016, a figure much higher than the incidence of 1 in 1000 in the Caucasian populations[3]. Therefore, despite the absence of anaphylaxis in all of the cases in this report (Table 2), clinicians must remain alert for the possibility of rare forms of severe UTR since there is some evidence that IgA deficiency is found in some Nigerian population groups [16].

CONCLUSION

Mild form of urticarial transfusion reaction is a common clinical problem in multi-transfused patients and the incidence increases with the number of previously transfused units of blood suggesting that blood transfusion is an important sensitizing

event in the development of these reactions. There is therefore a need for closer monitoring of multi-transfused patients during transfusion. The need for sub-regional and national surveys to ascertain the prevalence of IgA deficiency across the whole country cannot be over emphasized.

REFERENCES

1 Brozovic B, Brozovic M. Non-haemolytic Immune Transfusion Reactions. In Brozovic B, Brozovic M (eds), Manual of Clinical Blood Transfusion, 1st ed, Churchill Livingstone, London, 1986, 95-102.

2 Masouredis SP. Preservation and Clinical Use of Erythrocytes and Whole Blood. In Williams WJ, Beutler E, Erslev AJ, Lichtman MA (eds), Hematology, 4th ed, McGraw Hill, New York, 1991, 1628-1647.

3 Contreras M, Mollison P. Immunological Complications of Transfusion. Br Med J, 1990, 300: 173-176.

4 Ahmed A, Garba ES. Detrimental Effect of Blood Transfusion. Nig J Med, 1998, 7: 57-60.

5 Walter JB, Talbot IC. Blood Grouping and Blood Transfusion. In Walter JB, Israel M (eds), General Pathology, 7th ed, Churchill Livingstone, London, 1995, 897-910.

6 Heddle NM, Klama L, Singer J. The Role of the Plasma from Platelet Concentrate in Transfusion Reactions. N Engl J Med, 1994, 331: 625-628.

7 Thulstrup H. The influence of Leucocyte and Thrombocyte incompatibility on non-haemolytic Transfusion reactions. Vox Sang, 1971, 21: 233-236.

8 Ahmed SG, Obi SO. The pattern of non-haemolytic febrile transfusion reactions in multi-transfused patients. Nig J Med, 2000, 9: 13-15.

9 Weir DM. Aquired Immunity. In Weir DM (ed), Immunology: An Outline For Students Of Medicine And Biology, 4th ed, Churchill Livingstone, Singapore, 1979, 30-87.

10 Ahmed SG, Hassan AW, Obi SO. The Pattern of Blood Donation in North East Nigeria. Nig J Surg Res, 1999, 1: 76-81.

11 Ahmed SG, Hassan AW. Viral Infectivity Markers in Donor Blood: a retrospective study of Three Donor Categories. Nig J Surg Res, 2000, 2: 75-80.

12 Ukaejiofor EO. Blood transfusion and management. In Ukaejiofor EO (ed), Blood Transfusion in the Tropics, 1st ed, Salem Publications, Ibadan, 1996, 101-102.

13 Ankara-Badu GA. Blood Transfusion, Normal and Abnormal Haemostasis. In Badoe EA, Archampong EQ, Jaja MOA (eds), Principles and Practice of Surgery, including Pathology in the Tropics, 2nd ed, Ghana Publishing Corporation, Tema, 1994, 109-124.

14 Penida AA, Taswell HF. Transfusion Reactions Associated with anti-IgA antibodies. Transfusion, 1975, 57: 10-15.

15 Ahmed SG. A review of modalities of red cell transfusion in clinical practice. Nig J Med, 1997, 6: 29-32.

16 Ezeoke ACJ. Selective IgA deficiency in Eastern Nigeria. Afr J Med med Sci, 1988, 17: 17-21.