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ORIGINAL ARTICLE

Effects of Blood Donation Frequencies and types of Blood Donors on Storage Lessions as assessed by the level of antioxidants and Lipid Peroxidation

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Abstract

Introduction: Influence of Blood storage lesions on Red Blood Cells transfusion recovery and therapeutic efficacies have been well documented. Several stabilizing additives to counteract or minimize these untoward changes have been formulated. Despite these stabilizers, detectable hemolysis occurs in the blood stored in the blood bank hence, need for search on other contributing factors. Assessment of the effects of Blood Donation Frequencies and Types of Blood Donors on Storage Lesions as Assessed by the Level of Antioxidants and Lipid Peroxidation.

Materials and Methods: Ethically approved cross sectional experimental research on a total numbers of 120 recruited male of family replacement donors (n=30) and Remunerated donors (n=90). Remunerated donors were grouped into three (3) based on the frequency of donation per year as mild (n=30), moderate (n=30) and high frequency (n=30) donors. Four hundred and fifty milliliters (450 ml) of blood drawn from each donor into double blood bag containing CPDA-1 anticoagulant. 100 ml of well mixed blood was transferred into the satellite bag, detached and stored in the blood bank at 2-6 C for 35 days. The blood samples analyzed for MDA, TAP, URIC, and GSH at 0, 7, 14, 21, 28 and 35 days of storage.

Results: In the recruited donors, majority were above 40 years of age where family donors had secondary education, government employed; feed majorly on carbohydrate, none alcohol drinkers, none cigarette smokers with history of donating more than four years before the study and less than four times donation frequency per year. Remunerated blood donors had primary education, self-employed, moderate alcohol drinkers and moderate cigarette smokers donating more than four times a year and more than four years donation experience. In this study, the GPX, TAP and Uric acids for family were higher than remunerated at baseline and the values decrease across the week for both categories. MDA value for family was lower than remunerated donors at baseline and the

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values increase across the week for both categories.
Discussion: The current findings demonstrate evidences significant level of literacy and moderately balanced diet in all categories of donors but bad social life predominantly among remunerated donors. Also, an unacceptably low activity of antioxidants, high oxidative stress and high lipid peroxidation in high frequency blood donors. Conversely, family replacement donors in this study revealed evidence of increase activity of antioxidants, decrease oxidative stress and decrease lipid peroxidation.
Conclusion: This study established variation in oxidant and antioxidants levels in whole blood stored up to 5 weeks influenced by Blood Donation Frequencies and Types of Blood Donors on Storage Lesions.

INTRODUCTION

Red blood cells (RBCs) are the most frequently transfused blood product. As a result, effective ex vivo storage of RBCs is an essential requirement for medical practice. However, RBC functionality and viability are progressively impaired during storage in blood banks(1) RBCs undergo numerous structural and biochemical modifications during this period that are likely to affect their recovery and tolerance to the transfusion therapy at clinical level (2). Although the mechanisms underlying storage lesion remain uncertain, altered metabolism, increased oxidative stress, and the so called “donor variation effect,” which refers to substantial donor-to-donor differences in blood storage quality, represent currently established contributing factors (3). Well documented that both in-bag hemolysis and 24-hour in vivo recovery, namely, the “gold quality standards” for the developed storage systems, have been associated with donor-related factors (3). Inter-donor variation appears to have a genetic component related to blood homeostasis (4). Similarly, cell fragility (5), metabolites (6) and micro-particle (MP) accumulation (7), oxidative stress sensitivity, and antioxidant capacity (8,9) have also been suggested as donor-related attributes of RBC storage lesion. The contribution of donor variation in hemoglobin (Hb) levels (10), RBC metabolic rate, Micro Particles (MP) production and other factors to the quality of stored RBCs has now been extensively examined (11).

It has long been known that RBCs from some donors store well while others store poorly (12,13). Evidence of donor-related variability is seen by the hemolysis profiles obtained from large datasets of RBC component quality control information (14), *in vivo* 24-hour post-transfusion RBC recovery data (13,15), as well as studies in twins and different strains of inbred mice (14). Donor-related variability may be an unaccounted for confounder in the “age of blood” clinical studies reported to date (14). Oxidative stress occurs if there is an imbalance of free radicals and antioxidants in the body, which can lead to cell and tissue damage. Oxidative stress occurs naturally and plays important role in the aging process (16). Factors contributing to oxidative stress include: Diets high in fat, sugar, and processed foods; Physical Inactivity; Obesity; Exposure to radiation; Smoking cigarettes or other tobacco products; Alcohol consumption; Pollution; Exposure to pesticides or industrial

chemicals and Occupation (16). RBCs also have to deal with oxidative stress due to their constant exposure to oxygen fluctuations. Erythrocytes assist with maintaining circulatory antioxidant levels, particularly by recycling oxidized forms of plasma ascorbic acid (17), and contributing to the extracellular pool of GSH (18). Despite their characteristic absence of mitochondria, RBCs can also act as ROS generators. Indeed, oxy-hemoglobin dissociation to deoxy-hemoglobin through oxygen release can promote iron electron capture by oxygen. Due to its ferric (Fe^{3+}) iron state, met-hemoglobin cannot bind oxygen, but the enzyme met-hemoglobin reductase can convert met-hemoglobin back to Fe^{2+} normal hemoglobin (Hb). This Hb autoxidation occurs at a rate of 3%, and leads to formation of the superoxide radical $O_2^{\bullet}$, further producing the highly reactive hydroxyl radical $HO^{\bullet}$ through the Fenton reaction (19). Such radicals are extremely reactive, possessing a very short half-life of approximately 10^{-9} seconds (20). Hence, they can non-specifically affect all types of macromolecules within their immediate environment. This can lead to several types of RBC storage lesion, include lipid peroxidation, protein amino acids modifications, and protein backbone breaks (21). Which take place in both family and remunerated blood donors but probably at different degrees

The oxidative lesion is of particular interest, since such damage is not reversed through the transfusion process, in contrast to biochemical modifications. Since erythrocytes are unable to perform protein synthesis, no protein turnover is possible. Damaged proteins accumulate until they are degraded or eliminated from the cell. Redox proteomic studies performed on stored RBCs show increasing hallmarks of oxidative stress throughout the storage period. Several protein carbonylation investigations have indicated that increased storage duration is related to increased carbonylated protein contents associated with the RBC membrane and cytoskeleton (22,23), or with entire erythrocytes (24). Blasi *et al.*, further demonstrated that protein carbonylation was due to increasing oxidative stress concomitant with over-activation of the oxidative phase of the PPP recruited to counteract ROS. Protein oxidation can also be investigated in terms of cysteine redox status, but such an approach has not yet been employed in the transfusion field. Oxidation reportedly results in hemoglobin crosslinking, forming hemi-chromes that covalently bind the cytoplasmic domain of the major integral glycoprotein of the erythrocyte membrane (band 3), inducing its clustering (25,26). The induced conformational change creates a neo-antigen site at the erythrocyte surface (27,28), allowing *in vivo* recognition by naturally occurring auto-antibodies (29). In turn, this leads to RBC clearance from circulation through complement activation (30) and phagocytosis by Kupffer liver cells (31). This is known as the band 3 clustering model.

Biological macromolecules can be damaged by oxidative insult, leading to oxidized products that act as biomarkers of oxidative stress status. Methods have been developed to measure these biomarkers as a means of evaluating oxidative stress (32,33). The commonly studied markers are products of lipid peroxidation such as malondialdehyde (MDA), 4-hydroxynonenal, and iso-prostanes (34), oxidized amino acidic residues (such as cystine, methionine sulfoxide, 3-nitrotyrosine, and 3-Cl-tyrosine), or protein carbonyls (PCO) (32,35). A different approach to evaluation of oxidative stress is the analysis of antioxidant concentrations. An ROS attack can lead to a major depletion of antioxidants such as vitamin E, vitamin C, reduced glutathione (GSH), and urate (36). GSH can be oxidized, mainly to glutathione disulfide (GSSG), or can form glutathionylated proteins (PSSG). The measurement of GSH, GSSG, PSSG, and their relative ratios may therefore give fundamental information on the intracellular redox status (37).

RBC storage lesion, including lipid peroxidation, protein amino acids modifications, and protein backbone breaks (21) accumulate until they are degraded or eliminated from the cell. Redox proteomic studies performed on stored RBCs show increasing hallmarks of oxidative stress throughout the storage period.

Materials and Methods

The study is a random, cross-sectional and non-interventional research comprises of 120 apparently healthy male prospective blood donors within the age of 18-55yr residents in Ilorin metropolis, Kwara State using the serial recruitment method.

Study Population

The study population included family donors and remunerated blood donors of different categories based on their blood donation interval in major hospitals (UITH and State General hospitals) and private laboratories within Ilorin metropolis.

Ethical consideration

Clearance was obtained from the Ethical and Research Committee of the Kwara State Ministry of Health. Institutional research and ethics committees were approached for permission with full compliance with the institutional research policies during sample collection.

Informed Consent

An informed verbal and written consent was obtained from the prospective participants using a consent form after clearly explaining the aim of the study including the procedures and possible risks that may be associated.

Subject Grouping:

A total numbers of 120 male donors were recruited as blood donors, family Replacement blood donors (n=30) and Remunerated donors (n=90). Remunerated blood donors were grouped into three (3) based on the frequency of donation per year as mild (n=30), moderate (n=30) and high frequency (n=30) donors.

Blood donors screening

Blood donors were assessed from blood donor pool of the institution screened for Hepatitis B virus, Hepatitis C virus, Syphilis and HIV according to National Guideline of Federal Government of Nigeria (NBTS, 2006) and found suitable and fit before blood donation.

Blood Bag

Satellite double blood bag having capacity of 450 ± 10 ml containing Citrate Phosphate Dextrose Adenine (CPDA-1) solution with a shelve life of 35 days for whole blood storage at 2-6 C was used to store the collected blood.

Bleeding of donors

Four hundred and fifty milliliters (450 ml) of blood was drawn each from 120 healthy donors (age range from 21-55years) into double blood bag containing CPDA-1 anticoagulant. Blood was collected with adequate safety precautions to avoid contamination and infection. 100 ml of well mixed blood was transferred into the satellite bag, detached and stored in the blood bank at 2-6 C for 35 days.

Sample collection

The effect of storage was analyzed at 0, 7, 14, 21, 28 and 35 days of storage by withdrawing 10 ml blood each time from the satellite blood bag. The blood samples collected were analyzed for hematological parameters before being centrifuged at 5000 rpm for five minutes to obtain the plasma which was stored at -20

C for further biochemical investigations. The sample analyzed on day 0 served as baseline control.

Laboratory Procedures:

Estimation Of Total Antioxidant Potential (Tap) (Benzie and Strain, 1999).

Principle of the Assay

At low pH, ferric tripyridyltriazine (Fe III TPTZ) complex reduced to ferrous form, an intense blue color which was measured at 593nm. The change in absorbance is directly proportional to the combined or "total" reducing power of the electron donating antioxidants present in the reaction mixture.

Estimation of Malondialdehyde (MDA) (Varshey and Kale, 1990)

Principle

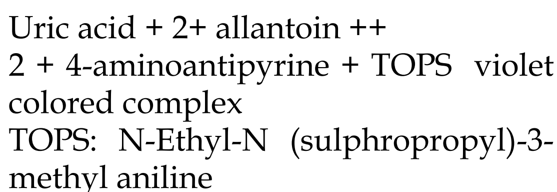
Malondialdehyde react with 2-thiobarturic acid (TBA) in acidic pH to form a pink complex and was measured spectrophotometrically at 532nm.

Uric Acid: Uricase TOPS method

Principle

Uricase transforms uric acid into allantoin, with formation of hydrogenperoxide. In presence of peroxidase (POD) it reacts with ethyl-sulphopropyl toluidine (ESTP) and 4-aminophenazone, to produce a colored complex whose color intensity is directly proportional to the uric acid concentration in the sample.

Enzymatic determination of uric acid according to the following reactions.



Uric acid + 2+ allantoin ++
2 + 4-aminoantipyrine + TOPS violet colored complex
TOPS: N-Ethyl-N (sulphropropyl)-3-methyl aniline

Human Glutathione Peroxidase- GSH-PX

Assay Principle

This kit is an Enzyme-Linked Immnosorbent Assay (ELISA). The plate has been pre-coated with Human GSH-PX antibody. GSH-PX present in the sample is added and binds to antibodies coated on the wells. And then biotinylated Human GSH-PX antibody is added and binds to GSH-PX in the sample. Then Streptavidin-HRP is added and binds to the Biotinylated GSH-PX antibody. After incubation, unbound streptavidin-HRP is washed away during a washing step. Substrate solution is then added and color develops in proportion to the amount of Human GSH-PX. The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450 nm.

Results

Table 1 above shows that there was a statistically significant association that existed between age and category of donor revealing majority of family donors were age above 40 while non-family donors were in age groups between 31 and 40. There was an equally significant relationship between income, type of food year donation started between family and non-family donors.

Table 2 shows that there was significant relationship in alcohol consumption rate, Cigarette smoking and Frequency of donation/Year between family and non-family blood donors while table 3 shows the Malondialdeyhde (MDA) among different categories of donors throughout the storage of whole blood units under standard blood bank conditions. Values obtained with independent samples t-test and expressed as Mean±Standard deviation, bold p-value indicates statistical significance at $p < 0.05$.

Table 4 above shows the antioxidant potential among different categories of donors throughout the storage of whole blood units

under standard blood bank conditions. Values obtained with independent samples t-test and expressed as Mean±Standard deviation, bold p-value indicates statistical significance at $p < 0.05$.

Table 5 above shows the glutathione peroxidase (GPX) among different categories of donors throughout the storage of whole blood units under standard blood bank conditions. Values obtained with independent samples t-test and expressed as Mean±Standard deviation, bold p-value indicates statistical significance at $p < 0.05$.

Table 6 above shows the Uric acid among different categories of donors throughout the storage of whole blood units under standard blood bank conditions. Values obtained with independent samples t-test and expressed as Mean±Standard deviation, bold p-value indicates statistical significance at $p < 0.05$.

Table 1: Association between socio-demographic characteristics and categories

Variables	Category		χ^2	p-value
Age groups	Family (%)	Remunerated (%)	13.377	0.001
21–30	9 (18.8)	39 (81.2)		
31–40	0 (0.0)	19 (100.0)		
> 40	21 (39.6)	32 (60.4)		
Educational level			4.773	0.189
None	3 (37.5)	5 (62.5)		
Primary	0 (0.0)	7 (100.0)		
Secondary	15 (31.9)	32 (68.1)		
Tertiary	12 (20.7)	46 (79.3)		
Sources of income			17.083	0.001
Self employed	21 (39.6)	32 (60.4)		
Government employee	25 (73.5)	9 (26.5)		
Private employee	0 (0.0)	25 (100.0)		
Unemployed	0 (0.0)	8 (100.0)		
Type of food taken			4.785	0.029
Carbohydrate	24 (31.6)	52 (68.4)		
Protein	6 (13.6)	38 (86.4)		
Year Donation Starts			12.379	0.001
≤ 4	21 (41.2)	30 (58.8)		
> 4	9 (13.0)	60 (87.0)		

Table 2: Association between socio-demographic characteristics and categories

Variables	Category		χ^2	p-value
	Family (%)	Remunerated (%)		
Alcohol consumption			32.698	0.001
None	9 (75.0)	3 (25.0)		
Low	6 (35.3)	11 (64.7)		
Moderate	6 (8.3)	66 (91.7)		
Heavy	9 (47.4)	10 (52.6)		
Cigarette smoking			35.819	0.001
None	9 (75.0)	3 (25.0)		
Low	3 (75.0)	1 (25.0)		
Moderate	9 (47.4)	10 (52.6)		
Heavy	9 (10.6)	76 (89.4)		
Frequency of donation/Year			24.183	0.001
≤ 4	24 (48.0)	26 (52.0)		
> 4	6 (8.6)	64 (91.4)		

Table 3: Malondialdeyhde (MDA)

Categories	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5
Family	1.21±0.17	1.37±0.18	1.68±0.11	2.40±0.19	3.69±0.19	5.29±0.26
Remunerat-ed	1.37±0.25	1.52±0.26	1.98±0.23	2.77±0.21	4.09±0.24	5.56±0.29
t-test	-3.259	-2.593	-6.873	-8.495	-8.281	-4.597
P-value	0.002	0.011	0.001	0.001	0.001	0.001

Table 4: Total Antioxidant Potential

Categories	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5
Family	2143±168	2093±168	1945±126	1836±124	1668±86	1538±78
Remunerated	1361±199	1335±186	1252±165	1182±162	1059±158	934±131
t-test	19.335	19.755	20.944	20.186	20.111	23.704
P-value	0.001	0.001	0.001	0.001	0.001	0.001

Table 5: GLUTATHIONE PEROXIDASE -GPX

Categories	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5
Family	43.9±1.4	42.6±1.5	40.6±1.5	37.6±2.1	34.0±2.0	30.4±1.6

Remunerat-ed	35.4±3.7	34.3±4.0	32.4±3.9	29.5±4.0	25.9±4.2	22.1±4.1
t-test	12.298	11.126	11.318	10.541	10.160	9.281
P-value	0.001	0.001	0.001	0.001	0.001	0.001

Table 6: URIC ACID

Categories	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5
Family	0.47±0.02	0.45±0.02	0.40±0.03	0.34±0.01	0.27±0.02	0.22±0.02
Remunerat-ed	0.43±0.02	0.39±0.02	0.33±0.03	0.25±0.02	0.19±0.02	0.14±0.01
t-test	9.487	14.230	11.068	23.634	18.974	28.790
P-value	0.001	0.001	0.001	0.001	0.001	0.001

DISCUSSION:

Out of a total numbers of 120 adult male recruited as blood donors, family donors were 30 and remunerated donors were 90. In the recruited family donors, majority were above 40 years of age; had secondary education, government employee; feed majorly on carbohydrate and were none alcohol drinkers, none cigarette smokers with history of donating more than four years before the study and less than four times donation frequency per year. These findings on family donors aligned with previous studies on voluntary blood and were found to be employed, educated and had correct knowledge of anemia and its preventive measures (38). This study reinforces why the international society of blood transfusion and WHO regarded blood donation as voluntary in all circumstances and financial benefit must never be a motive.

Contrarily, remunerated blood donors were majorly young individual of age between 31-40 years having primary education, self-employed, moderate drinkers and moderate cigarette smokers donating more than four years before the study and more than four times a year. These observations probably can be due to increasing rate of poverty, joblessness and bad social life. This study reinforces the evidence from previous studies that alcohol and cigarette consumption have risks of addiction and have adverse effects on the metabolic quality of remunerated high frequency blood donors.

In this study, the GPX, TAP and Uric acids for family were higher than remunerated donors at baseline and the values decrease across the week for both categories. This finding implies reduction in the antioxidant defense systems, protein oxidation and lipid peroxidation during storage however, family blood donors have increased antioxidant defense systems with low protein oxidation and lipid peroxidation. Contrarily, MDA value for family was lower than remunerated donors at baseline and the values increase across the week for both categories. The findings aligned with previous researchers which corroborate increased possibility of vesiculation and loss of deformability in cellular constituents of stored blood.

In assessing oxidant biomarkers in the four studied groups: Malondialdehyde (MDA) was lower in family donors than other categories of remunerated donors and progressively increasing during cold storage but mildly low in mild frequent donors, high in moderate and highest in heavy/high donors with progressive increase that showed statistical significance in mild, moderate and high donors from baseline to week five when compared with family category of blood donors. MDA is an indirect marker of lipid peroxidation, which modifies membrane proteins and lipid causing damage to erythrocyte membranes and subsequent hemolysis (39).Findings in this study showing a significant increase in plasma MDA, and is in agreement with that of (40) who reported increase plasma MDA concentrations during storage.

In assessing anti-oxidant biomarkers in the four studied groups: TAP for family were higher than remunerated donors at baseline and the values decrease across the week for both categories. TAP, Uric acid and GPX in family donors from baseline to week-5 were higher than remunerated non-family donors and progressively decreasing during cold storage. The decrease that showed statistical significant p-value for mild, moderate and high donors from baseline to week-5 when compared with family donors**.** Contrarily, MDA value for family was lower than non-family at baseline and the values increase across the week for both categories. Findings in this study aligned with previous research which revealed that the activities of GPX and SOD enzymes are significantly decreased throughout the period of storage (41,42). Findings in this study also aligned with previous research in which (43) reported statistically significant decrease in plasma Uric acid during the storage period when compared with the values of those antioxidants at donation state. Also, these findings implied increased reduction in the antioxidant defense systems, increased protein oxidation and increased lipid peroxidation during storage in remunerated non-family blood donors however, family blood donors have increased antioxidant defense systems, decreased protein oxidation and decreased lipid peroxidation. The findings aligned with previous researchers which corroborate increased vesiculation and loss of deformability in cellular constituents of stored blood.

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