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### RESEARCH ARTICLE

#### THERAPEUTIC ERYTHROCYTAPHERESIS VERSUS TRADITIONAL PHLEBOTOMY IN THE TREATMENT OF PATIENTS WITH ERYTHROCYTOSIS.

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#### Abstract

**Background:** - Traditional phlebotomy is the most commonly used therapy for erythrocytosis. After the introduction of the new modality of therapy of cell separators, erythrocytapheresis has been also introduced. The aim of the study was to compare the two kinds of treatment.

**Patients and methods:-** This study was conducted in National center of Hematology, on 70 patients with erythrocytosis. Most of the patients were male, 54 males with 16 females, with male to female ratio of 3.3:1. 70 patients with erythrocytosis with hematocrit (Hct) equal to or above 50% in males and equal to or above 48% in females, the patients were divided to three groups for comparison: Group (1):24 patients were treated with phlebotomy. Group (2):24 patients were treated with therapeutic erythrocytapheresis (TEA) only. Group (3): 22 Patients were treated with phlebotomy then switched to erythrocytapheresis (TEA). Applying (TEA), by discontinuous flow cell separator machine, MCS+(Haemonetics). The time interval between two successive treatments in each patient was recorded for all patients in the three groups of therapy.

**Results:-** 79.15% of group-1 patients treated with phlebotomy required a short time: 2 weeks-2 months for the next phlebotomy, while only 5/24 (20.83%) of patients required longer time interval 3-4 months. In group-2 treated exclusively with TEA the majority 21 out of 24 patients (87.5%) had prolonged time interval for the next session of therapy from 3-7 months, with P value <0.002. Patients of Group-3 after switching to the new modality of therapy TEA, the time interval in the majority of patients had prolonged time interval for the next therapy from 3-7 months, 19 out of 22 patients (86.36%), with P value <0.002. No serious side effects noticed in patients treated with both types of treatments. TEA is more expensive, with longer working time.

**Conclusion:-** Erythrocytapheresis (TEA) is more efficient than traditional phlebotomy with prolongation of the treatment interval in treating patients with erythrocytosis. Well tolerated by the patients, but it is more expensive, with relatively more technician working time.

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**Introduction:-**

Erythrocytosis and polycythemia they represent related but distinct terms that usually but not always coexist. Polycythemia (many cells) which may be called absolute erythrocytosis indicates increase in the red cell mass while erythrocytosis may be a result of increased red cell mass or a reduced plasma volume which may be called relative or a spurious erythrocytosis, which leads to increase red cell concentration that does not reflect increase quantity of red blood cell (RBC) in the body[1]. Absolute erythrocytosis may be secondary to many congenital or acquired conditions which lead to hypoxia, as cyanotic heart disease, chronic lung diseases, smoking or high altitude result in physiological polycythemia with increased level of hormone erythropoietin, or tumors, renal cysts and endocrine diseases with adrenocortical dysfunction that produce erythropoietin [2]. The second type of absolute erythrocytosis is polycythemia Vera (PV) associated with excessive proliferation of RBC with white blood cells WBC and/or platelets increase in many affected patients, PV is considered as a myeloproliferative disorder [3]. The third type of absolute erythrocytosis which account for 20 to 30% of patients are categorized as idiopathic polycythemia with unknown etiology, which is a heterogeneous group found in a significant proportion of patients who do not full fill the criteria of diagnosis of either polycythemia Vera or secondary polycythemia, which is diagnosed by exclusion[4]. Erythrocytosis is associated with high blood viscosity and increased blood volume which lead to certain symptoms and signs related to the degree of the increase and the resulting effects on blood flow and oxygen transport, so cyanosis observed in patients with polycythemia Vera is due to the dilatation of cutaneous vessels by increased blood volume and sluggish local circulation due to increased blood viscosity[1]. Patients with erythrocytosis with hematocrit of 50% and more are at high risk of developing thromboembolic events such as stroke a heart attack, pulmonary embolism or deep vein thrombosis. Published data indicate that thrombosis was the presenting symptom in 12%-49% of patients with polycythemia Vera and was the cause of death in 20%-40%, usually central nervous system thrombosis [5]. In patients with erythrocytosis secondary to respiratory causes which leads to respiratory failure as chronic obstructive lung diseases COPD, hyper viscosity symptoms are presented earlier with Hct levels less than 50% because there is scleroerythrocytosis, which is a morphological changes of the red blood cells that further slows the blood flow[6].

Erythrocytosis, an increase of the red blood cell count above the threshold value of 6,000,000/ $\mu$ L, with established criteria recommended by World Health Organization in 2001, haemoglobin (Hb) 18.5 g/dL and above or hematocrit (Hct) 52% in men and Hb 16.5g/dL and or Hct of 48% in females suggest that there is erythrocytosis, with elevated red cell mass 125% above mean normal predicted value [7]. An Hct value of 60% or greater always has an increased red cell mass[8]. In primary erythrocytosis, there are a number of erythropoietin receptor mutations either congenital mutations or acquired as seen in acquired polycythemia Vera. In primary erythrocytosis with congenital EPO receptor mutations, the cytokine EPO binds to RBC through EPO receptor, which is followed by cascade of phosphorylation. Janus Kinase 2 (JAK2) is auto-phosphorylated and latter phosphorylates cytoplasmic tyrosine's of EPO receptor, these tyrosines act like a docking site for the signal transducer and activator of transcription factor 5 (STAT5) protein, which homodimerizes and translocates to the nucleus, where it initiates gene transcription, proliferation of erythroid precursors and finally RBCS production. This process is regulated by a mechanism to turn off red cell production. About 30 minutes after EPO binds, the phosphatase SHP1 is recruited to the receptor and dephosphorylates the receptor and JAK2. The receptor then goes on to be ubiquitinated and degraded in the proteasome[9]. There are several mutations leading to loss of 57-127 amino acids from EPO receptor, leading to preservation of JAK2-binding site but loss of SHP 1-binding site. Consequently those mutations result in (switching on) to stimulate RBCS production with the loss of (switching off) mechanism, leading to continued RBCS with resulting erythrocytosis despite low level of EPO [10]. While in acquired Primary erythrocytosis which is the classical acquired polycythemia Vera, the acquired abnormal clone, an erythrocytosis with increased both white blood cells and platelets. Those patients have a clone of cells with mutated JAK2 with a gain-of-function mutation in exon 14, Val1617Phe, leads to activated JAK2[11]. Minority have mutations in exon 12 of JAK2, clinically mainly have increase in RBCS and were diagnosed wrongly as idiopathic erythrocytosis before the discovery of this clone[12,13].

Regarding therapy of erythrocytosis traditional phlebotomy is the most common practice applied, with certain drugs as hydroxyurea and busulphan [14]. The introduction of the new modality of therapy, erythrocytapheresis, applying cell separators, these instruments allow sophisticated type of phlebotomy, since they considerably remove only red blood cells, not whole blood, with preservation of blood volume and so hemodynamic balance is unchanged [15].

Erythrocytapheresis is an alternative way of therapy, which has been evaluated by several randomized [16, 17] and nonrandomized studies [18].

### **Patients and Methods:=-**

This study was conducted in National Center of Hematology, on 70 patients with erythrocytosis consulting the center from 1<sup>st</sup> April 2014 to the 1<sup>st</sup> April 2015. Most of the patients were male, 54 males with 16 females, with male to female ratio of 3.3:1. The age of the patients ranges between 20 to 77 years old. The most age presented were those between 40-50 years (17 patients), followed by group 50-60 years (14 patients). Thirty nine patient out of seventy had secondary erythrocytosis : 17 patients heavy smokers, 10 patients secondary to chronic lung disease, 8 patients secondary to renal disease, 2 patients were secondary to hepatic cause, while two with androgen administration. Nineteen patients with polycythemia Vera. Finally twelve patients with idiopathic erythrocytosis.

Study design: We conducted a three –treatment-arms, randomized study, involving 70 patients with erythrocytosis with Hct equal to or above 50% in males and equal to or above 48% in females the patients were divided to three groups for comparison:

Group (1): 24 patients were treated with phlebotomy.

Group (2): 24 patients were treated with therapeutic erythrocytapheresis (TEA) only.

Group (3): 22 Patients were treated with phlebotomy then switched to erythrocytapheresis (TEA).

Inclusion criteria were as follows: patients with erythrocytosis with Hct equal to or above 50% in males and equal to or above 48% in females, age 18 years and older, weight 50 Kg or more, signed informed consent and willing to answer questionnaires. Exclusion criteria were: age below 18 years, excessive overweight (BMI more than 35Kg/m<sup>2</sup>) pregnancy and malignancy, cardiac arrhythmias, heart failure and epilepsy. The ethical comity of our center approved the study.

In traditional phlebotomy 450 mL of whole blood which is equivalent to 200-250 mL RBCS, were withdrawn in about 10 minutes after puncturing a superficial vein in the forearm with a sterile strait needle gauge-16 connected to a sterile disposable collecting bag (Demophorius LTD, Cyprus), in each occasion, with compensation of equal amount of physiological saline 0.9%, in order not to cause volume imbalance.

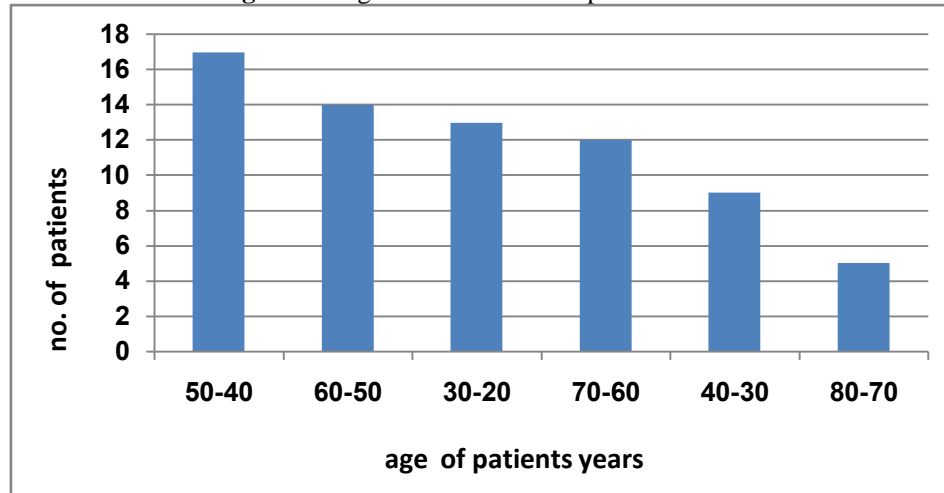
Applying therapeutic erythrocytapheresis (TEA), the new modality of therapy, by discontinuous flow cell separator machine, Haemonetics MCS+ was used, each procedure was divided to two or three cycles, the removed RBCS based on the patient, sex, height, weight, Hct, the instrument software calculated precisely the whole blood volume and the Hct at the end of the procedure set at 40%, with the removal of around 400 mL of concentrated RBCS, using citrate-phosphate-dextrose anticoagulant (ACD) at a ratio of 16:1 (blood: anticoagulant) and after removal of RBCS, the autologous platelet rich plasma of the patient was returned with 400 mL 0.9% saline as fluid compensation. By this technique a personalized amount of RBCS were removed with automated isovolaemic compensation. For each patient one disposable set was used for each procedure specific for erythrocytapheresis. The procedures were performed by a well trained staff at the cell separation unit in our center.

Complete blood count (CBC) was done 2 days after each procedure, and CBC was repeated every 3-4 weeks to follow Hct, if it reached 50±1% in males or 48%±1% in females, a new therapeutic procedure underwent either phlebotomy or TEA according to their group of therapy. Our aim was to maintain the patient with Hct to below 45% and to keep it at this value for as long as possible. The period between two consecutive therapies were observed and recorded in each patient in all groups of therapies. Beside that we estimated the a proximate cost of the procedures, depending on the cost of the phlebotomy bag, apheresis set, human resources, taking into account the time of each procedure.

**Statistics:-** All data analysis was done with computer software (SPSS-pc Version 16.0, SPSS, Inc., Chicago, IL). Univariate analysis on baseline differences in Metric is done with the Mann-Whitney test.

**Results:-**

The total numbers of the patients with erythrocytosis enrolled in this study were 70 with 54 males, 16 females with male to female ratio of 3.3:1. The age of the patients ranges between 20 to 77 years old. The most age group presented were those between 40-50 years (17 patients), followed by group 50-60 years (14 patients). The range of the age of the patients is showed in Figure-1.

**Figure 1:-** Age distribution of the patients treated.

According to age groups group 40-50 years (17/70 total patients) was the most represented group, followed by age group 50-60 years (14/70), then age group 20-30 years (13/70) years, age group 60-70 (12/70) years, then age group 30-40 years (9/70), and lastly group 70-80 years (5/70).

The time interval between two successive treatments in each patient was recorded for all patients in the three groups of therapy. Table -1 showed the difference in the time interval between group-1 treated with classical phlebotomy and group-2 treated with TEA exclusively. In group-1 most of the patients required repeated phlebotomy after a short period of time, 5 out of 24 patients (20.83%) the time interval was 2 weeks, 10 out of 24 (41.66%) the time interval from 2 weeks to one month, while 4 out of 24 (16.66%) the time interval was from 1-2 months. Which means that 79.15% of group-1 patients treated with phlebotomy required a short time = 2 weeks-2 months for the next phlebotomy, while only 5/24 (20.83%) of patients required longer time interval 3-4 months. In comparison with group-2 treated exclusively with TEA the majority 21 out of 24 patients (87.5%) had prolonged time interval for the next session of therapy from 3-7 months, with P value < 0.002. While 3 out of 24 (12.5%) had a shorter time interval of 1-2 months.

**Table 1:-** The difference in time interval in Group-1 treated with phlebotomy and Group-2 treated with TEA.

Time interval	Group-1 Phlebotomy No.24	Group-2 TEA No. 24
2 weeks	( 5/24) 20.83%	0
2 weeks-1 month	(10/24) 41.66%	0
1-2 months	( 4/24) 16.66%	(3/24) 12.5%
3 months	(3/24) 12.5%	( 4/24) 16.66%
4 months	(2/24) 8.33%	( 4/24) 16.66%
5 months	0	(5/24)20.83%
6 months	0	(5/24)20.83%
7 months	0	(3/24) 12.5%
Mean	46.66	142.5
Median	45	126
standard deviation	57.86	63.3

P value : <0.002

Regarding group-3, 22 patients with erythrocytosis were treated with traditional phlebotomy then switched to erythrocytapheresis TEA. In those patients also they have prolonged time interval between to the next therapeutic procedure, with P value <0.002 as showed in Table.2

**Table 2:-** The changes in the time interval in Group- 3, treated with phlebotomy, and then switched to TEA.

Time interval	Group-3 phlebotomy No.22	Group-3 TEA No.22
2 weeks	(4/22)18.18%	0
2 weeks-1 month	(9/22) 40.9%	0
1-2 months	(4/22)18.18%	(3/22) 13.6%
3 months	(3/22) 13.6%	(3/22) 13.6%
4 months	(2/22) 9.09%	(4/22)18.18%
5 months	0	(5/22) 22.72%
6 months	0	(4/22)18.18%
7 months	0	(3/22) 13.6%
Mean	48.9	134.09
Median	41	115
standard deviation	20.3	58.02

P value: < 0.002.

Similar to the results noticed in Table-1, data in Table-3 showed, the majority of patients of Group-3 treated with phlebotomy required repeated phlebotomy after a short period of time, 4 out of 24 (18.185%) patients the time interval was 2 weeks, 19 out of 22 (40.9%) patients the time interval from 2weeks to one month, while 4 out of 22 (18.18%) the time interval was from 1-2 months. Which means that 77.37% of Group-3 patients treated with phlebotomy required a short time: 2 weeks-2 months for the next phlebotomy, while only 5/22 (22.69%) of patients required longer time interval 3-4 months. Meanwhile patient of Group-3 after switching to the new modality of therapy TEA, the time interval in the majority of patients had prolonged time interval for the next therapy from 3-7 months, 19 out of 22 patients (86.36%) , with P value <0.002. While only 3 patients out of 22 (13.6%) had a shorter time interval of 1-2 months.

Regarding the adverse events of the procedure, no serious side effects were noticed in patients treated with both types of treatments, with TEA circumoral paresthesia was seen in two patient out of 46(4.3%) due to mild hypocalcemia due to administration of anticoagulant ACD (citrate effect), and it was treated easily by reducing the infusion rate of anticoagulant [20].only in 4 out of 46 patients had mild pain at the site of venipuncture (8.6%). Few patients with TEA had poor venous access 2/46(4.3%). In phlebotomy few patients had mild pain at the phlebotomy site 3/46 (6.5%), and two had mild dizziness which account to 4.3%.

### Discussion:-

Analyzing the data obtained in the current study, it is clear that modern therapy with erythrocytapheresis TEA is superior to the traditional method of phlebotomy in treating patients with erythrocytosis, through maintaining Hct below the critical levels in males and females for a longer time. In Table -1,it was showed that with TEA therapy (Group-2),the majority 21 out of 24 patients (87.5%) had prolonged time interval for the next session of therapy from 3-7 months, while with phlebotomy therapy (Group-1), only 5/24 (20.83%) of patients required longer time interval 3-4 months , with P value <0.002. Similarly in Group -3 after switching to the new modality of therapy TEA, the time interval in the majority of patients had prolonged time interval for the next therapy from 3-7 months, 19 out of 22 patients (86.36%) , with P value <0.002 as showed in Table-2. Erythrocytapheresis is not only rapid and effective and long-lasting treatment modality in depleting RBCs in erythrocytosis, it also maintains the isovolaemic balance in the patients [21], this was proved also by both, Kaboth U.[20],and Wijermans P. [18] .

D. Evers et al also concluded that TEA is more effective and reducing the duration and number of procedures needed for the treatment of patients with hereditary hemochromatosis and polycythemia Vera and secondary erythrocytosis [22].Similarly in another study conducted by Liu H. [23],he demonstrated that applying erythrocytapheresis in the treatment of polycythemia reduces RBC count, hemoglobin, and HCT, and that TEA method has advantages over the conventional therapy .P.Poullin also agreed that TEA is more effective therapy in polycythemia Vera and hereditary hemochromatosis [24].

In this study, there was no significant difference in the adverse effects of both procedures; both had a mild side effect, which was observed by other studies [22].

Phlebotomy has the advantage that it is available, cheap, a simple procedure, easily performed. The main disadvantages of erythrocytapheresis TEA were that it required a special instrument not available in all hospitals, only in the central blood banks or special centers, with well-trained medical staff, also there were a poor venous access in few patients. TEA is expensive, the cost of each disposable set about 200\$, while the cost of the disposable bag for phlebotomy is 5\$ in Iraq. D.Evers estimated that each procedure of TAE cost about three times more than the classical phlebotomy [22]. In addition the time required for TEA procedure in our study was relatively longer 20-30 minutes compared to 10 minutes for phlebotomy, which were illustrated by other studies [16, 25].

In this study Haemonetics MCS+ equipment was used, with one-needle system applying one patient arm, but also it is possible to use a two-needle system Spectra-Optia equipment (Caridian BCT). The main obstacle with TEA was poor venous access in few patients, this problem was found by other researcher [24]. This new modality of treatment is not only used in erythrocytosis but in hemochromatosis and in emergency therapy in thrombocytosis [26]. Wiltbank T. through analyzing more than one million collections by the automated apheresis equipment (2007), he conducted that using the apheresis equipment leads to reduction of side effects [27]. Yet our study illustrated no differences in the adverse events between the two therapies so as Tatjana S. [28], which might be due to low number of patients enrolled in this study. The reduction in the adverse events by applying TEA can be explained that the use of saline compensation and longer collection time during the process of therapeutic apheresis, which assess trans capillary refilling of the intravascular compartment [29, 30].

### Conclusion:-

Erythrocytapheresis (TEA) is more efficient than traditional phlebotomy with prolongation of the treatment interval in treating patients with erythrocytosis. Well tolerated by the patients, but it is more expensive, with relatively more technician working time.

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