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Research Article

Clinical Profiling With Therapeutic Phlebotomy As An Adjunct Therapy In Symptomatic Patients At A Tertiary Care Hospital.

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Abstract

Background: Therapeutic phlebotomy is a medical procedure that involves removing blood, particularly red blood cells or serum iron, as a treatment for specific blood disorders. Historically known as bloodletting, this ancient practice had two primary methods: generalized techniques, such as venesection (vein cutting) and arteriotomy (artery cutting), and systemic techniques, including cupping and the use of leeches. The procedure was believed to stimulate the bone marrow to produce new red blood cells while simultaneously reducing serum iron levels. In modern medicine, therapeutic phlebotomy is used to manage conditions by decreasing red blood cell mass, lowering hematocrit (the proportion of red blood cells in the blood), reducing blood viscosity, or inducing iron deficiency. This approach helps alleviate symptoms and complications associated with various diseases.

Objectives: Therapeutic phlebotomy allows for a controlled and gradual decrease in red cell mass leading to improved blood flow and symptomatic relief in polycythaemia. The present study was aimed to determine the impact of serial fixed volume therapeutic phlebotomy protocol on the symptoms in patients of polycythemia.

Material and Method: This prospective longitudinal study was conducted over 37 months. The desired haematocrit for polycythemia vera and secondary polycythemia was 45% and 52% respectively. A fixed volume of 250 ml phlebotomy was performe. Presenting symptoms was evaluated before and after each procedure quesnarried based assement like mild ,moderate severe relif in symptoms

Volume to reduced= initial Hct-Desired Hct/79 X blood volume/kg X body weight/kg.

Results: From 2019 to 2024, a total of 151 therapeutic phlebotomy (TP) procedures were performed on 44 patients. Since the introduction of TP in 2019, the mean interval between procedures has been approximately 22 days. Polycythemia vera was the predominant indication for TP, followed by congenital heart disease. Platelet counts varied among patients, with some exhibiting levels exceeding 400,000/μL, while the average platelet count was 340,000/μL.Uncommon presentations for TP included polycythemia with optic neuritis, acute appendicitis, obesity with nasal obstruction, chronic obstructive pulmonary disease (COPD), sarcoidosis, and coronary artery disease with hypertension. Pre-procedure and post procedure symptoms of patient compared with paired T test and chi squared test (The two-tailed P value equals 0.6657) with mild and moderate symptoms group.

Conclusion: Our protocol yielded rapid and marked improvement in patients of primary and secondary polycythemia with minimal adverse events and significant amelioration of clinical parameters.

Keywords: Therapeutic phlebotomy, hemochromatosis, polycythemia Vera, porphyria cutanea tarda, sickle cell disease.

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INTRODUCTION

Therapeutic phlebotomy is a medical procedure that involves removing blood, particularly red blood cells or serum iron, as a treatment for specific blood disorders. Historically known as bloodletting, this ancient practice had two primary methods: generalized techniques, such as venesection (vein cutting) and arteriotomy (artery cutting), and systemic techniques, including cupping and the use of leeches[1]. The procedure was believed to stimulate the bone marrow to produce new red blood cells while simultaneously reducing serum iron levels. In modern medicine, therapeutic phlebotomy is used to manage conditions by decreasing red blood cell mass, lowering hematocrit (the proportion of red blood cells in the blood), reducing blood viscosity, or inducing iron deficiency. This approach helps alleviate symptoms and complications associated with various diseases[2]. It serves as an effective adjunct therapy for conditions such as polycythemia vera, hemochromatosis, porphyria cutanea tarda, sickle cell disease, and non-alcoholic fatty liver disease (NAFLD) with hyperferritinemia, among others[3,4,5]. Alternative methods for reducing red blood cells and serum iron include apheresis and the administration of desferroxamine, a medication that binds to iron. The efficacy of therapeutic phlebotomy has been well established, with evidence suggesting it can improve life expectancy in patients suffering from certain disorders. Although phlebotomy is generally considered safe, rare complications can arise. For example, patients with polycythemia vera are at increased risk of thrombosis. Other potential side effects include hematomas at the phlebotomy site, which can range from mild to severe, possibly leading to nerve and tissue damage. Additional adverse effects may include hemoconcentration, extravasation, syncope (fainting), petechiae (small red or purple spots on the skin), excessive bleeding, edema, arterial puncture, pain, and anemia. Unsafe phlebotomy practices pose a risk of transmitting infections such as hepatitis B (HBV), hepatitis C (HCV), HIV, syphilis, and malaria to both patients and healthcare workers. In some countries, blood collected from therapeutic phlebotomy, particularly from patients with hemochromatosis, is approved for allogeneic use (donated blood for other patients).[6]

MATERIAL AND METHOD

This prospective longitudinal study was conducted over 37 months. The desired haematocrit for polycythemia vera and secondary polycythemia was 45% and 42% respectively. A fixed volume of 250 ml phlebotomy was performed. Presenting symptoms was evaluated before and after each procedure quesnarried based assessment like[mild ,moderate and severe]relief in symptoms

Volume to reduced= initial Hct-Desired Hct/79 X blood volume/kg X body weight/kg. In general, each unit of blood (500 ml) that is removed represents about 200 to 250 mg of iron, depending on the hemoglobin by Zubair et al.[6]

PHYSIOLOGY OF THERAPEUTIC PHLEBOTOMY

Therapeutic phlebotomy (TP) stimulates the bone marrow to generate new red blood cells, a process that necessitates iron mobilization from the body's stores for hemoglobin synthesis. This effectively depletes excess iron levels, making TP a cornerstone in the management of polycythemia vera (PV). In PV patients, regular TP is administered to maintain hematocrit levels below 45%, a key measure to mitigate the risk of thrombotic events.[7,8] However, due to the periodic nature of these treatments, patients may experience prolonged periods where their hematocrit exceeds 45%, inadvertently increasing their thrombosis risk. A significant challenge in PV management is symptomatic iron deficiency, which is often present at the time of diagnosis and exacerbated by frequent or repeated phlebotomy sessions. Hepcidin, the central regulator of iron homeostasis, plays a critical role in this dynamic. Suppression of hepcidin enhances iron absorption and bioavailability, facilitating erythropoiesis in PV patients undergoing TP.[9] This regulation is crucial in balancing iron levels while managing disease symptoms effectively.

uncommon presentation for TP noticed with ,polycythemia with optic neuritis, acute appendicitis, obesity with nasal obstruction, COPD, Sarcodiosis, coronary artery diseases with complication of HTN, Hypothyroidism and polycythemia, cardiac disorder (TOF,VSD,TOF+PS)[7,8,10].

RESULTS

Symptoms observed among patients Pre-procedure

From 2019 to 2024, a total of 151 therapeutic phlebotomy (TP) procedures were performed on 44 patients. Of these, 26 procedures were conducted on female patients, while male patients accounted for 121. Polycythemia vera was the predominant indication for TP(61%), followed by congenital heart disease(21%) (see **Figure 1**). Uncommon presentations for TP included polycythemia with optic neuritis, acute appendicitis, obesity with nasal obstruction, chronic obstructive pulmonary disease (COPD), sarcoidosis, and coronary artery disease with hypertension. Other rare cases involved hypothyroidism, complex cardiac conditions (e.g., Tetralogy of Fallot [TOF], ventricular septal defect [VSD], TOF with pulmonary stenosis [TOF+PS]), and associated polycythemia. Notably, only 14 patients underwent TP once, with the majority requiring multiple sessions. Since the introduction of TP in 2019, the mean interval between procedures has been approximately 22 days. The highest number of TP procedures occurred in 2021, with the lowest

recorded in 2020 (**Figures 3 and 4**). Patients frequently reported symptoms such as headaches, malaise, dizziness, lethargy, and facial plethora during the pre TP process. Moderate symptoms, including thrombotic events, strokes, venous thrombosis, visual disturbances, and transient ischemic attacks, were also observed with some regularity. In addition, severe complications, such as pain crises, cardiac and neural dysfunction, severe respiratory distress, and chronic kidney disease, were noted.[n=101] patient observed with mild,[n=52] moderate and [n=6] severe symptoms observed[**Fig-5**]. Post procedure of TP symptoms has subsided and improved that was considered accordingly simple questionarried based study, improved or not improved. Mild and moderate procedure showed there is improvement in TP symptoms which accounted by physical examination of patients while severe symptoms was insignificant improvement [**Table**]. Pre-procedure and post procedure symptoms of patient compared with paired T test and chi squared test (The two-tailed P value equals 0.6657) with mild and moderate symptoms group. Single frequency of TP observed in n-14 patients, whilst rest attended more than one TP procedure.(n-15) patients attended >9 times TP procedures and mean interval was 28 days among them[**Fig-6**]. Platelet counts varied among patients, with some exhibiting levels exceeding 400,000/μL, while the average platelet count was 340,000/μL (**Figure 7**). The majority of TP procedures were performed in patients aged 31-40, with only 9 procedures in older age groups. Hemoglobin levels averaged 18.1 g/dL, with 10 patients presenting with exceptionally high levels exceeding 20 g/dL. Moreover, 23 patients experienced episodes of fever accompanied by elevated total leukocyte counts above 12,800/μL, while 11 patients had critically high hematocrit levels over 70%, with a pre-procedure mean of 55%[**table-3**].. Fear was the most common complication noted during primarily first procedure of TP among (n-15) person.(n-2)patients complained about pain and one patient hematoma over the site of procedure which was subsides by compression of cold sponging.

Symptoms observed pre - Phlebotomy procedure [Table-1].

symptoms	Male(121)	Female(30)
Mild symptoms 101(headache, malaise, dizziness, lethargy, plethora)	90	11
Moderate symptoms 52(thrombotic event, stroke, venous thrombosis, visual disturbance, transient ischemic attack	36	16
Severe symptoms6(pain crisis, cardiac malfunction, neural malfunction ,severe respiratory distress, chronic kidney disease)	3	3

VAS questionnaire were assessed for symptoms study, which has four 10-cm horizontal lines that corresponded to headache, dizziness, fatigue, and gastrointestinal discomfort. They marked a single slash in the corresponding position of the questionnaire that best represents their worst feeling for the four symptoms. . The left end of the line is 0 mm with the word "none", and the right end is 100 mm with the word "severe". Intermediate points along the line represent varying degrees of symptoms. Then, we transformed the corresponding tag into a score.

symptoms	headache	dizziness	fatigue	Gastric symptoms
Pre-procedure score (mean)	7(mean)	6	8	9
Post-procedure score(mean)	4	3	3	4

Symptoms followed post - Phlebotomy procedure [Table-2].

symptoms	Male(121)	Female(30)
Mild symptoms 101(headache, malaise, dizziness, lethargy, plethora)	(improvement)85	(improvement)10
Moderate symptoms 52(thrombolic event, stroke, venous thrombosis, visual disturbance, transient ischemic attack	(improvement)30	(improvement)16
Severe symptoms6(pain crisis, cardiac malfunction, neural malfunction ,severe respiratory distress, chronic kidney disease)	(improvement)3	(improvement)2

Stats:

P-value-0.2056, t-1.4545, Sample size (n)-6, Average of differences ($\bar{X}_d$)-23.8333, SD of Differences (S_d)-40.1368 Normality p-value-0.01438, A priori power-0.1707 ,Post hoc power-0.2208Skewness-1.9313, Skewness Shape  Asymmetrical, left/negative(pval=0.022)Excess kurtosis-3.5929, Kurtosis Shape  Leptokurtic, long heavy tails (pval=0.039) Outliers-101

Results of the paired-t test indicated that there is a significant medium difference between Before (M = 43.2 ,SD = 46.5) and After (M = 19.3 ,SD = 20.3), t(5) = 1.5, p = .206.

	Male	male	Marginal row
Mild symptoms	90	85	177
Moderate symptoms	36	30	66
	126	115	241

Chi-square without Yates correction ,Chi squared equals 0.187 with 1 degrees of freedom.
The two-tailed P value equals 0.6657 ,The association between rows (groups) and columns (outcomes) is considered to be statistically significant.

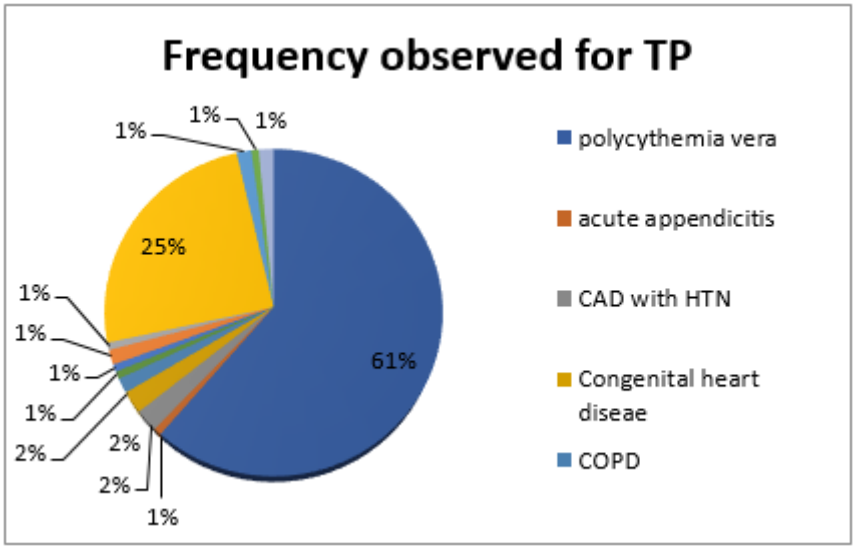
Complications observes during procedure among patients [Table-3].

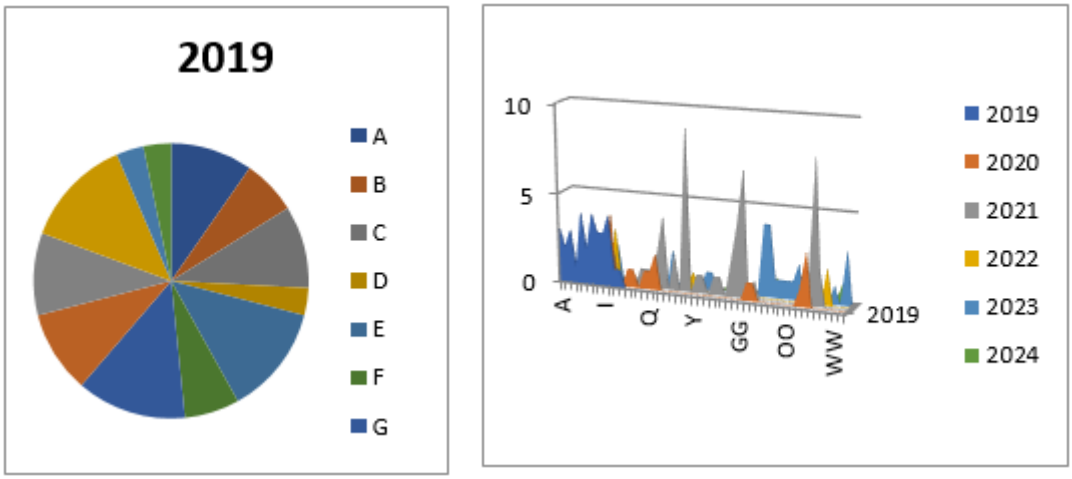
Complications(rare)	Male(9)	Female(7)
hematoma	1	
edema		
fear	9	6
hypersensivity		
thrombosis		
Arterial puncture		
petechial		
Excessive bleeding		
Vaso-vagal		
vomiting		
Pain	1	1

Table present frequency in different variable [Table-4].

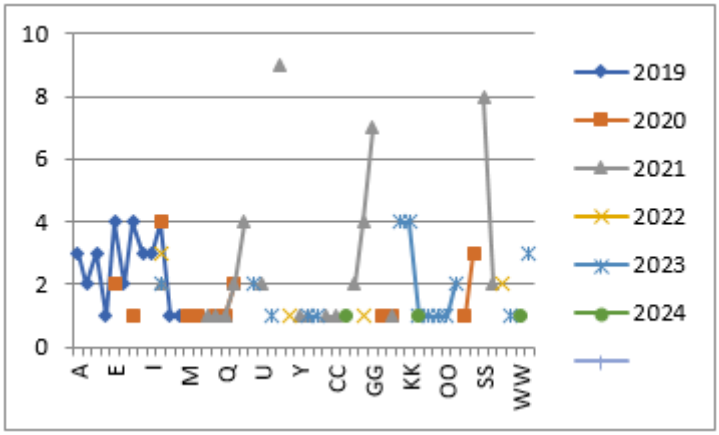
Age	Hb(g/dl)	TLC(U/L)	Hct(%)
10 to 19=19	12 to 14=4	<12.1=139	40 to 45 =14
20 to 30=27	14.1 to 16=23	>12.2 to 18=10	45.1 to 50=10
31 to 40=54	16.1 to 18=62	>18.1 to 20=20	50.1 to 55=46
41 to 50=26	18.1 to 20=37	>20.1 to 23=3	55.1 to 60=40
51 to 60=20	21.1 to 23=4		60.1 to 65=17
61 to 73=9	23.1 to 23.9=7		65.1 to 70=6
			70.1 to 75=11

CAD with HTN (coronary artery disease with hypertension),COPD(chronic obstructive pulmonary diseases)[Figure-1].

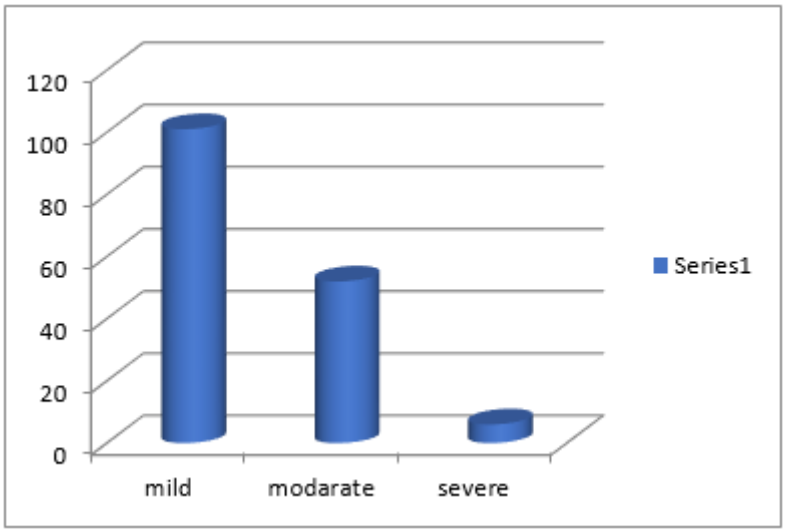




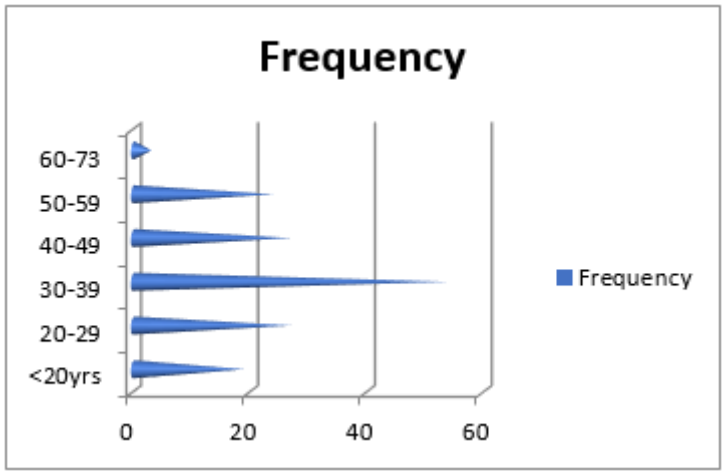
TP procedure among patient as annuls presentation [Figure-2], &Trend [Figure-3].



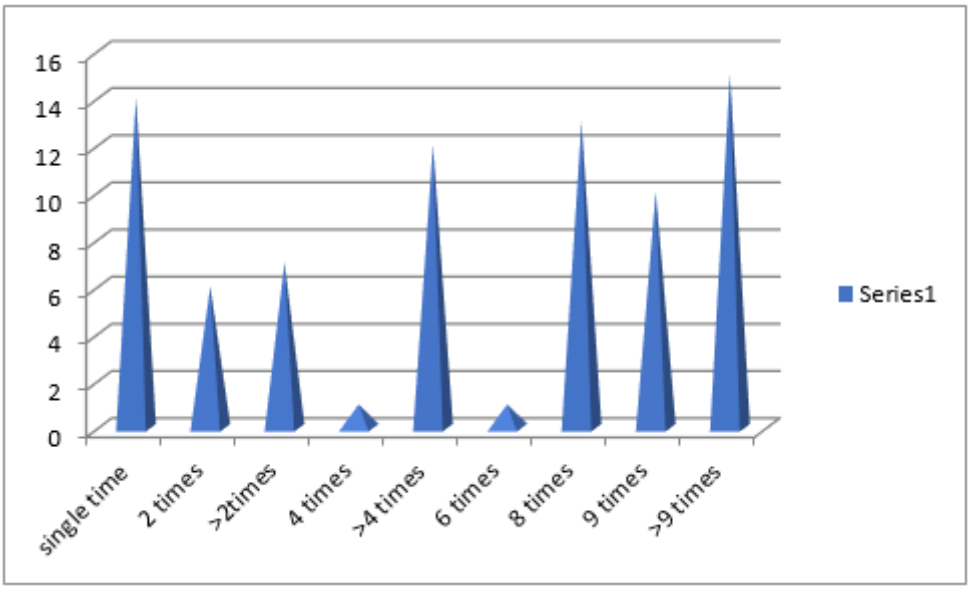
TP procedure among patient as annul presentation [Figure-4].



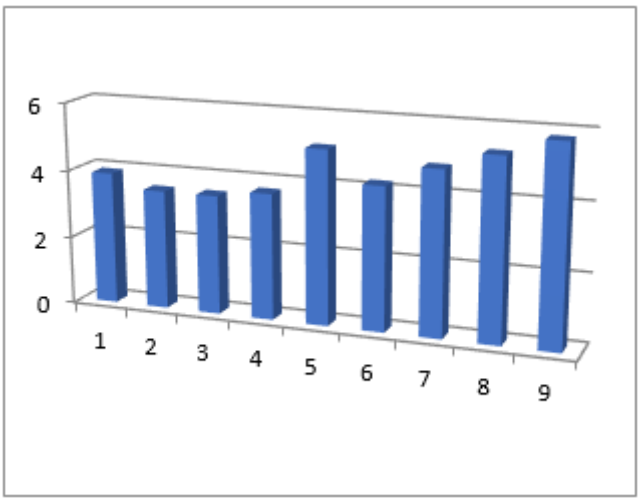
Frequency of symptoms among patients [Figure-5].



Frequency of TP among different age groups [Figure-6].



Frequency of TP among per patients [Figure-7].



Frequency platelet among patients [Figure-8].

DISCUSSION

Therapeutic Phlebotomy (TP): A Comprehensive Overview of Clinical Applications and Findings

Primary Indications for Therapeutic Phlebotomy:

Therapeutic phlebotomy (TP) is widely recognized as a valuable treatment for conditions with excessive iron or red blood cell levels. It is most commonly employed for polycythemia, a condition characterized by an elevated red blood cell count, and hemochromatosis, an iron overload disorder. Our research observed that TP was utilized in 61% of cases involving polycythemia vera, a specific type of polycythemia.Van Buren NL et al. documented that polycythemia is a prevalent adverse effect associated with testosterone replacement therapy (TRT), with a reported incidence rate of 71%. This elevated red blood cell count due to TRT can increase the risk of vascular complications, highlighting the importance of TP as an adjunct therapy to manage these effects.[8]

Advantages and Efficacy of Therapeutic Phlebotomy:

TP has consistently demonstrated effectiveness in managing iron and red blood cell levels, offering improved clinical outcomes in patients when used as an adjunct therapy. Various studies have emphasized the benefits of TP, supporting its use to manage symptoms and reduce the risk of complications, especially in polycythemia and hemochromatosis. While TP is generally effective, patient-specific factors must be carefully assessed when tailoring the phlebotomy regimen. These factors include age, sex, body weight, existing comorbidities, overall health status, and the likelihood of treatment adherence.[9]

Selected Case Studies and Observations:

Familial Porphyria Cutanea Tarda: In a study by Poh-Fitzpatrick et al., TP was shown to be effective in managing iron levels in patients with childhood-onset familial porphyria cutanea tarda. The use of iron chelation via TP led to favorable outcomes, highlighting TP's role in managing iron-related conditions beyond polycythemia and hemochromatosis [10]. Obesity Hypoventilation Syndrome: Brainster GW reported a unique case involving a 12-year-old child with obesity hypoventilation syndrome who required TP. This single case also in above study report showcased how TP could be adapted to treat rare and complex conditions where traditional treatments may fall short. Polycythemia-Related Symptom Improvement: A study by Bhatia S et al. among 29 patients demonstrated notable improvements in symptoms following TP, with symptom severity grading shifting from higher to lower grades. Improvement was quantified using a visual analog scale, with a mean score of 10, indicating TP's potential to significantly alleviate symptoms in affected individuals Above study 118 patient has found improvement in their mild and moderate symptoms based on questionaried on post procedure TP while there no improvement in severe symptoms.[11]

Use of MCV and Hb as Indicators:

Bolan CD et al. emphasized the utility of mean corpuscular volume (MCV) and hemoglobin (Hb) levels as inexpensive yet reliable markers for monitoring erythropoietic iron availability.These indicators can serve as practical guides to determine the frequency and volume of phlebotomy therapy in patients with hemochromatosis, aiding clinicians in optimizing treatment regimens. [12].

Considerations in Elderly Patients:

Abyad L et al. presented the case of an 87-year-old woman with symptoms including memory loss, transient ischemic attacks, fatigue, dizziness, and frequent falls. Diagnostic investigations revealed erythrocytosis, leukocytosis, thrombocytosis, normal arterial oxygen levels, and increased red cell volume. This study, involving elderly patients aged 61 to 73 years, highlighted the benefit of TP in older populations who may experience symptoms related to erythrocytosis and polycythemia.[13]

Managing Anemia and Neutropenia in Hemochromatosis:

In cases of idiopathic hemochromatosis with concurrent anemia and neutropenia, Finch SC demonstrated that regular TP can correct moderate anemia and neutropenia, likely caused by hypersplenism. This case illustrates how TP can be an effective diagnostic and therapeutic tool in patients where liver biopsy is not feasible.[14]

The study outlined a typical TP regimen for hemochromatosis, beginning with 5 ml/kg every 4 ± 1 weeks. If tolerated well, the volume could be increased to 10 ml/kg, allowing for more efficient management of iron overload while ensuring patient safety similar manners as Aygun B et al studies. [15]

CONCLUSION

Therapeutic phlebotomy has proven effective across various clinical contexts, from managing common conditions like polycythemia and hemochromatosis to treating rare or complex cases. The evidence indicates that TP, when appropriately customized to the patient's specific needs and health status, can significantly alleviate symptoms and improve quality of life, offering a valuable tool in managing hematologic and iron overload disorders. There was significant amelioration of the clinical parameter. Our protocol yielded rapid and marked improvement in patients of primary and secondary polycythemia with minimal adverse events and significant amelioration of clinical parameters.

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