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Review Article

Therapeutic Phlebotomy Revisited: A Review

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Abstract

Therapeutic phlebotomy is the removal of red blood cells or serum iron from the blood. It is one of the preferred treatments for blood disorders. In ancient times this process was known as bloodletting. Generalized method included were venesection and arteriotomy and systemic methods included were cupping and by leeches. It stimulates bone marrow stem cells to generate new red blood cells (RBCs). Iron for hemoglobin synthesis is taken from the body thus reducing serum iron. Different indications of therapeutic phlebotomy include Polycythemia Vera, Hemochromatosis, Porphyria cutanea tarda, Sickle cell disease, Non-Alcoholic Fatty liver disease (NAFLD) with hyperferritinemia. Other methods available for reducing RBC and iron level include apheresis and administration of desferroxamine. Phlebotomy can cause rare adverse effects, such as thrombosis, mostly seen in patients with polycythemia Vera. Other adverse effects include Hematoma at phlebotomy site. Usually hematoma is mild but in severe cases can cause damage in nerves and surrounding tissue. Haemoconcentration, extravasation, Syncope and Fainting, petechiae, Excessive Bleeding, edema, arterial puncture, pain and anemia are some of the adverse effects caused by therapeutic phlebotomy. Unsafe phlebotomy can expose patients and health workers to various infections like Hepatitis B virus (HBV), Hepatitis C virus (HCV) and Human Immunodeficiency virus (HIV); syphilis and malaria. Different countries have approved allogenic use of blood units obtained from therapeutic phlebotomy. Mostly blood collected from patients with hemochromatosis is permitted. The article also discusses criteria for initiating therapeutic phlebotomy and various regimen followed in different diseases.

Keywords: Therapeutic phlebotomy, hemochromatosis, polycythemia Vera, porphyria cutanea tarda, sickle cell disease, Non-Alcoholic Fatty liver disease with hyperferritinemia.

INTRODUCTION

The term phlebotomy suggests "lancing (*tomia* from *témno*) a vein (*fléba* from *flés*)". *Sensu strictu*, which suggests bloodletting (a practice of removing blood).This practice is performed for therapeutic purposes [*1*]. It is used for treating disorders of blood by removal of RBC s or serum iron done. This is one of the most efficient methods in management of symptoms and complications. The usual indication for phlebotomy is an abnormally high hematocrit (primary or secondary polycythemia).

History of Blood letting

In ancient times therapeutic phlebotomy was known as bloodletting. It began with Egyptians around 3000 years back. In 19th century in Europe it reached its peak. Galen was able to propagate ideas of bloodletting. Generalized method included venesection and arteriotomy, .Localized method were done by scarification with cupping and leeches. The main instruments for this technique were called lancets and fleams [2].

Dr Pierre Louis (1787–1872) scientific physician in Paris assessed efficacy of bloodletting. He examined clinical presentation and outcomes of 77 patients of acute pneumonia taken from hospital

records. He compared the results in patients treated with bloodletting before and after the procedure and concluded that the effect of this procedure "was actually much less than has been commonly believed but he didn't condemn bloodletting" [3]. In ancient times Phlebotomy was performed with different procedures like cupping, acupuncture, or leeches.

Phlebotomy and Wet Cupping

Phlebotomy is a procedure which takes place using inserted needles and it is different from wet cupping (Al-hijamah). While performing Al hijamah procedure, at selected areas local suction is created using special cups, which are applied for some time and then these cups are removed. After this scratching of skin is done from surgical tool. The cups are at a point supplanted to draw out little blood amounts and removal of toxins.

Cupping therapy is done in conditions like facial paralysis, Herpes zoster cervical spondylosis, acne, rheumatoid arthritis, carpal tunnel syndrome brachialgia paraesthetica nocturna, acute gouty arthritis, fibromyalgia, persistent nonspecific lower back pain, acute trigeminal neuralgia, and migraines [4-6].

Physiology of Therapeutic Phlebotomy

By bloodletting stimulation of Bone marrow is done which causes generation of red blood cells. New red blood cells require iron transport from stores of body for hemoglobin production. Hence diminishing patient's by large iron levels. This makes restorative phlebotomy as the favored option for blood clutters leading to evacuation of red blood cells and iron. It's one of foremost useful strategy for overseeing side effects [7].

Porphyria Cutanea Tarda (PCT)

It's one of the commonest types of poryphria. It causes insufficiency of uroporphyrinogen decarboxylase, enzyme valuable in heme biosynthesis. The enzyme comes about in collection of photosensitive by items like uroporphyrinogen, driving to the delicacy and rankling of sun uncovered skin [8] Porphyria cutanea tarda large amounts of Porphyrins get accumulated in liver over a period of few months [**9].** Porphyria cutanea tarda can result in development of Hepatocellular carcinoma, liver fibrosis and liver cirrhosis.

Estimates Prevalence has ranged from 1 in 5000 to 25000 People. Porphyria cutanea tarda is characterized by photosensitive dermatosis, photosensitivity, hyperpigmentation, dark coloured urine and liver damage. The cutaneous photosensitivity takes place by uroporphyrin and decarboxylated porphyrins. The compound is found in liver where activity of uroporphyrinogen decarboxylase is diminished. The accumulation of compound takes place in liver, this compound circulate in plasma, and finally excreted in urine [10].

It was first described by Waldenstrom in 1937. He first correlated Porphyria cutanea tarda (PCT) and iron overload, UROD activity and the possible link to hereditary hemochromatosis [11]. Onset of Porphyria cutanea tarda is after 30 years. Its occurrence in childhood is rare. It is acquired but sometimes genetic also [12].

The low Uroporphyrinogen-decarboxylase activity in Porphyria cutanea tarda promoted its subdivision as follows:-

1. Sporadic Porphyria cutanea tarda (type I, symptomatic or acquired).
2. Porphyria cutanea tarda (familial).
3. Porphyria cutanea tarda (Type III).
4. Toxic Porphyria cutanea tarda.
5. Environmental factors like alcohol usage and Hepatitis C or HI, medications like estrogen and cyt P- 450 inhibitors, tobacco etc.

Therapeutic phlebotomy is the management for Porphyria cutanea tarda, until Hb levels <20ng/mL is attained. It should be used for a period and recurring every 2weeks. Hydroxychloroquine is an alternative treatment of this disease [13]

Polycythemia Vera

Polycythemia Vera is a blood disorder. It is related to critical erythrocytosis and generating erythrocytes in bone marrow leading to increment in number of cells and high blood consistency [14].

According to Italian Societies of Hematology and Blood Transfusion recommendations for phlebotomy in Polycythemia Vera is hematocrit <45% [15]. In Polycythemia Vera, where Red Blood Cell production is autonomous, with increasing red cell mass, the plasma volume remains unchanged or increases unless the Hematocrit is >60% [16, 17]. The aim of Therapeutic Phlebotomy is to reduce Red Blood Cell mass and blood viscosity improving tissue perfusion, oxygen delivery.

Murugesan M, Das conducted a study on Effect of Therapeutic Phlebotomy on Plasma Volume in Polycythemia [18]. Therapeutic Phlebotomy procedures in 134 patients undergoing 236 episodes were studied prospectively. Plasma volume changes were calculated based on the difference between the pre- and post-collection blood volume. A progressive reduction in hematocrit and hemoglobin in relation to volume removed and frequency was observed. There was a progressive increase of 2.5 mL/kg in plasma volume with respect to the frequency of Therapeutic Phlebotomy. Symptomatic improvements following Therapeutic Phlebotomy were noted in 60% of patients. Therapeutic Phlebotomy though commonly performed for reducing red cell mass in polycythemia had poor

compliance from patients, resulting in failure to achieve desired levels.

Hemochromatosis

Hereditary hemochromatosis is caused due to increase of iron absorption in duodenum mediated via HFE gene leading to overload of iron in blood leading to end organ damage as an end stage .If proper treatment is not given on time. Few studies have reported hemochromatosis has also resulted in Neuropsychiatric complications [19, 20].

NewhaN B, Khanna R (2018) [21] conducted a study on 52-year-old where the effect of therapeutic phlebotomy on non-suicidal injury was connected in a converse way causing antagonist results when phlebotomy was poised . This was the primary report distributed which potrayed relationship in nonself-destructive, self -injury and Therapeutic Phlebotomy. They consider telling almost they require of hazard evaluation and observing of self -harm among patients who have experienced Therapeutic Phlebotomy to prevent or diminish adverse outcomes.

Non-Alcoholic Fatty Liver Disease (NAFLD) with hyperferritinemia

Non-Alcoholic Fatty Liver Disease causes liver disease. It's a multisystem disease involving hepatic and extra- hepatic organs. It can lead to cirrhosis, liver failure. It increases risk of various diseases like diabetes mellitus type II, cardiac diseases. It also affects kidney leading to chronic kidney diseases. Non-Alcoholic Fatty Liver Disease starts from lipid accumulation in liver, and fat accumulation in liver. It is one of the risk factor which causes disease progression. In spite of the fact that major chance components which causes fibrosis in liver improvement is seen in Non-Alcoholic Fatty Liver Disease patient above 50 years, increased weight resistance of insulin, Type 2 Diabetes mellitus (T2DM), increased ferritin levels [22-24]. It affects iron metabolism also and leads to hyperferritinemia and hemochromatosis. Free radicals formation and damage to cellular function occurs due to accumulation of iron [25]. Glucose metabolism is also affected by iron and act as insulin secretion modulator by pancreatic β cells [26].

Jaruvongvanich V, Riangwiwat T *et al.,* (2016) [27] conducted a meta-analysis on outcomes of four interventional trials on phlebotomy outcome in Non-Alcoholic Fatty Liver Disease cases versus the outcomes of Non- Alcoholic Fatty Liver Disease patients who did not undergo phlebotomy was done. The study demonstrates that phlebotomy improved insulin resistance and the Alanine transaminase (ALT) and High density lipoprotein (HDL-C) levels in Non-Alcoholic Fatty Liver Disease patients. Physicians may consider phlebotomy as an alternative option in Non-Alcoholic Fatty Liver Disease patients in addition to lifestyle interventions.

Khodadoostan M, Zamanidoost M *et al.,* (2017) [28] conducted a study on thirty-two patients who had NAFLD and after lifestyle changes was done for 6 months, cases who still had Non-Alcoholic Fatty Liver Disease, whose ferritin serum was above 250 mg/dl, were enrolled in this clinical trial study. Aspartate tranaminase (AST), ALT, Alkaline phosphatase (ALK-P), Complete blood count (CBC), Total iron binding capacity (TIBC), iron, and ferritin levels were correlated. Liver biopsy was taken. After that patients underwent phlebotomy, giving 350 cc bloods monthly. Before every phlebotomy, hemoglobin and ferritin were checked. If they were in the goal range, phlebotomy was discontinued and the patient underwent liver biopsy. The results before and after phlebotomy were compared. Phlebotomy improved liver enzymes and histology of liver significantly and induced reduction of ferritin. From the study it was concluded that Phlebotomy is effective for the improvement of liver profile and histology of liver.

Adams L, Crawford D *et al.,* (2015) [29] conducted a 6-month controlled randomized trial on impact of phlebotomy on the foundation of a way of life counsel in patients with Non-Alcoholic Fatty Liver Disease was performed. Essential endpoints were taken such as hepatic steatosis and liver harm (recognized by ALT and CK-18). Auxiliary endpoints taken were insulin resistance which was measured utilizing affront affectability file (ISI). Homeostasis show of appraisal (HOMA) and lipid peroxidation methods were also used. 74 subjects (33 phlebotomies and 41 controls) were taken. They experienced a middle (extend) of 7 venesection sessions and had an essentially more prominent decrease in levels of ferritin in 6 month duration, comparing with controls. After 6 months phlebotomy and control bunches got to be same in HS, serum ALT, or CK-18 levels got to be same after 6 months. End-of-study ISI , homeostatic model assessment (HOMA), or F2- isoprostane levels between phlebotomy and control bunches got to be same .Out of patients experiencing phlebotomy no correlation was found in between number of sessions of phlebotomy and change in HS, liver harm, or IR from baseline. From the paper it was concluded that ferritin which is decreased after phlebotomy poses no change or improvement in liver enzymes, hepatic fat, or IR in Non-Alcoholic Fatty Liver Disease subjects, Due to discrepancy in results of different studies further prospective, controlled trials should be carried out to investigate outcomes and histological improvement in Non-Alcoholic Fatty Liver Disease patients after phlebotomy.

Sickle Cell Disease

Hemoglobin SS i.e. homozygous sickle cell disease contribute frequent infection, low fetal hemoglobin, and cold weather. These correlate with increase in cases of vaso-occlusive pain crises and increased mortality. Patients with heterozygosity of

hemoglobin S (i.e. Hb SC and Hb S/+-thalassemia) have mild clinical course with less vaso-occlusive episodes. Even though the hematocrit values are high as compared to that of Hb SS.

SS or SA variants take advantage from phlebotomy or when given with hydroxyurea [30]. The procedure reduces blood's viscosity as it reduces Hb levels [31].

Bouchaïr *et al.*, [32] described on repeated phlebotomies there was a reduction in hospitalization duration even with low Hb levels and was not associated with adverse events.

Rombos *et al.*, [33] showed that performing phlebotomy weekly lead to improvement in time scale, prevelance, and pain crises. From the study it was suggested that on performing phlebotomy regularly it showed placebo effect.

Summarell and Sheehan [34] conducted a study on HbSC has different pathophysiology, in comparison to hb SS. HbSC instead of sickling shows dehydration of cells potentiating sickling of HbSS. In this study HbSC patients didn't show any clinical improvement after taking maximum amount of tolerated dose of hydroxyurea. From the study it was concluded combination therapy of hydroxyurea and phlebotomy is fruitful treatment in HbSC sufferer.

Aygun B, Mortier N conducted a study on [35]. 927 therapeutic phlebotomy were done on 60 children out of all phlebotomy procedure 33 had adverse events, of grade 2. 23 in kids who had covered 30 months treatment given in this work showed favorable net iron balance (−8.7 mg Fe/kg) with drop in ferritin levels which was significant, concentration of liver iron remained unchanged. From the study it was concluded that it is a safe procedure, leading to iron expulsion in children who follow 30 months protocol.

Treatment

Phlebotomy is carried out at blood center, on apheresis unit. It is not carried out at home or at physician office [36].

Therapeutic Phlebotomy Consent

To perform any procedure consent form is required. The procedures requirement must include Documented Informed Consent. For therapeutic phlebotomy following details should be included in the consent form.

Physician Order Must Include:

a. Patient's Full Name.
b. Date of Birth.
c. Procedure requested.
d. Expected date of collection Therapeutic Phlebotomy.
e. Amount of blood to be collected.
f. Desired Hgb/Hct.
g. Patient Diagnosis.
h. Frequency of donation.

Physical assessment is necessary before starting a phlebotomy procedure. It includes patient vitals.

Physical Assessment (Record on Consent Form):

a) Blood pressure.
b) Pulse.
c) Hemoglobin.
d) Respiration.
e) Temperature.
f) Hematocrit.
g) Arm inspection.

Supplies required performing Therapeutic phlebotomy

a) Documentation.
b) Consent for procedure.
c) Capillary tubes [2].
d) Chloraprep swabstick.
e) Gauze.
f) Transfer device vial.
g) Tape.
h) Devices for personal protection.
i) Blood bag with labeling as for Therapeutic Phlebotomy.
j) Alcohol swabs with 70% isopropyl.

Treatment regimen of different indications in Therapeutic Phlebotomy

- Hereditary hemochromatosis: It is performed weekly till time hypoferritinemia (ferritin level reaches 50-100 ng/ml), hb less than 11 mg/dl [37, 38] are achieved.
- Secondary iron overload: Depending on etiology treatment is different.
- Polycythemia Vera: In this case recommendation is for phlebotomy in weeks to months. Till time iron reserve are depleted. Hematocrit levels are maintained at < 50% [39, 40].

When to give Therapeutic Phlebotomy

Subject	**S. Ferritin (ng/ml)**
age less than 18 years for both male and female	Above 200
Women	
Women not pregnant but of child bearing age	Above 500
Women pregnant and of child bearing age	Above 200
Men	
Age abve 18 years	Above 300

Adverse Effects caused by unsafe phlebotomy

The adverse effects include pain can even cause bruising at the site of pierce, nerve damage and haematoma.

Poor blood transfusion services, due to untrained professionals which cause poor venepuncture practice or any anatomical abnormality can cause haematoma and injure anatomical structures at the site or in the vicinity of needle entry, destitute infection control hones can lead to bacterial contamination at the location where the needle was embedded into the skin [41].

Phlebotomy can expose patients as well as health workers. Putting both of them exposed to blood borne pathogens. These pathogens could be;

- Viruses like HBV, HCV and HIV;
- Bacterial infection such as syphilis;
- Parasitic eg malaria.

An example of the spread of blood borne pathogens through phlebotomy is the reporting of outbreaks of infection HBV from glucometers use (devices used to determine blood glucose concentration) [42, 43].

Complications of Phlebotomy

Hematoma

It is one of the commonest complications of phlebotomy. Hematoma is usually formed at venupunture site. Venepuncture is immediately discontinued and if patient needs physical therapy then it is immediately provided [44]. Improper sites may cause damage to nerve [45]. If patient complains severe pain the procedure is immediately stopped.

Haemoconcentration

Prolonged tourniquet application, massaging, or probing a site, intravenous fluid therapy for long time, sclerosing or occlusion of veins, dehydration can lead to haemoconcentration. It can result in untrue increment in potassium, phosphorus, and add up to proteins. These complications can result in dismalness and expanded wellbieng care costs due to hospitalization for delayed periods, utilize of intravenous antimicrobials for expanded term and surgical intercession [46].

Extravasation

It occurs due to leakage of blood. It can take place if a cannula is pulled out of vein incidently [47]. There may be blanching of the tissues and swelling at site of puncture. Symptoms like tightness, burning and discomfort can be felt [48].

Syncope and Fainting

There is a sudden fall in the blood pressure as it is an autonomic nervous system reaction triggered by fear. It is accompanied by fainting and syncope. Sight and thought of venupunture can make patient dizzy.

Petechiae and Excessive Bleeding

In case of any underlying coagulopathy patient may bleed excessively and Petechiae formation can occur in patients. Petechiae formation occurs after venepuncture. It should be made sure that bleeding of patients stops before leaving.

Edema

There may be abnormal accumulation of fluid in the intercellular spaces which may be localized or diffused. Blood collection should not be done from such sites, as it can contaminate specimen from tissue fluid.

Fear and Phobia

Fear and phobia may occur in some patients on seeing the needle. This may cause the patient to move puncturing the artery rather than the vein. The needle should be withdrawn and pressure applied.

Thrombosis

If thrombus formation occurs from blood clot .It can occlude a vein making venepuncture difficult.

Arterial Puncture

If during procedure artery is punctured instead of vein then tube is immediately removed and pressure should be applied over the site.

Allergies

The patient might develop an allergic reaction to the cleaning agent used before skin puncture. Patient can also be allergic to latex.

Therapeutic apheresis and phlebotomy

Other methods are also available to reduce RBC and iron levels. Trials have been done on using erythrocyte apheresis as an alternative of phlebotomy, [49] According to the hypothesis there is a two- to threefold increase in iron that can be removed per treatment. Minimizing the number of phlebotomies. Multiple limitations are associated with apheresis including increase in cost, prolonged time required for treatment and various restrictions in treatment.

Deferoxamine which is an iron chelator can also be given. 1 g of medication binds to approx 85 mg of iron hence reducing iron load up to 250 mg/500 mL [50]. There are few patients who cannot tolerate phlebotomy Deferoxamine is given to such patients. Interferon is given as a myelosuppressive.

Allogenic Use of Collected Blood

Different countries have different views about allogenic use of collected blood units obtained after therapeutic phlebotomy. In United States, blood units that are collected from hemochromatosis patients are permitted for allogenic use. According to FDA units

with hemochromatosis should be labeled. Units obtained from polycythemia Vera patients have risk of developing leukemia transfusion, although it has negligible risk.

CONCLUSION

Phlebotomy is a procedure of blood removal from the body. Therapeutic phlebotomy is used for treating blood disorders, in this removal of RBCs or serum iron is done. This is one of the most proficient processes in management of clinical conditions and difficulties. The usual indication for phlebotomy is an abnormally high hematocrit (primary or secondary polycythemia). This article has discussed the criteria for initiating therapeutic phlebotomy and various regimen followed in different diseases. Over the years evidence based procedures and rules, give us precise reference and guidance to conduct procedures. However, there still remains no exact formula which can tell the right vein, the right needle, the right force and the right angle that will give the perfect blood draw. Thus with further research, phlebotomy will shorten the gap between patient and laboratory.

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