Role of Plasmapheresis in Waldenström’s Macroglobulinemia

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Abstract
Despite the absence of randomized trials, plasmapheresis has consistently demonstrated efficacy in treatment of Waldenström’s macroglobulinemia (WM) patients with hyperviscosity syndrome (HVS). This procedure can promptly reverse most clinical manifestations of serum HVS. Early diagnosis is crucial and usually can be made from the funduscopic exam. Serial viscosity measurements can be monitored by the Ostwald tube method which is simple, reproducible, and for which there is substantial clinical correlation. The concept of a symptomatic threshold, whereby each WM patient has a distinct viscosity threshold for the development of HVS, seems valid. Maintaining serum viscosity below each patient’s symptomatic threshold effectively prevents recurrent HVS. Plasmapheresis is sometimes necessary as an emergency procedure and is useful maintenance therapy in selected patients. Prophylactic plasmapheresis should be considered in patients at risk for HVS after rituximab therapy. Vigorous plasmapheresis in WM patients with syndromes because of autoreactive immunoglobulin M antibodies requires further study.

Introduction
Therapeutic plasmapheresis (plasma exchange) is a procedure involving the separation of plasma from circulating blood cells to remove a disease substance. One major indication is to treat patients with hyperviscosity syndrome (HVS), a common manifestation of Waldenström’s macroglobulinemia (WM). HVS was described by Jan Waldenström in his original 1944 report of 2 patients with the disease that bears his name.1 Most patients with HVS have WM.

Methods to Measure Viscosity
Viscosity refers to flow resistance of a liquid and comes from the Latin word ‘Viscum alba’ for mistletoe.2,3 Whole blood viscosity does not directly correlate with plasma viscosity. Although HVS is caused by hyperviscous blood, clinical laboratories generally only measure serum or plasma which display Newtonian properties. This practical effect of measuring a Newtonian fluid is that the method of measurement will not dramatically affect the test result. By contrast, whole blood viscosity also includes the viscosity because of blood cellular elements resulting in non-Newtonian behavior. The method of measurement can dramatically affect the assay result when measuring whole blood. In WM, serum or plasma viscosity measurements reflect the concentration and properties of the immunoglobulin M (IgM) paraprotein. IgMs display a wide range of intrinsic viscosity values (0.106–0.162 dL/g), each protein having individual properties.4 This might account, in part, for the varying viscosity values seen in patients with the syndrome.

Because IgM is a pentamer with molecular size of 925 kDa, this giant molecule can exert profound effects on blood cells and blood flow, especially when present in high concentrations often found in WM patients. Whereas serum viscosity rises linearly with increasing IgG levels, the increase in viscosity with rising IgM concentration can become exponential above a concentration of 3 g/dL.5 Serum viscosity can be accurately measured with an Ostwald viscometer (Figure 1).5 Normal serum or plasma viscosity is approximately 1.4–1.8 relative to that of water. Viscosity of serum and plasma are comparable unless the IgM M-protein complexes with fibrinogen or the fibrinogen is abnormal. College of American Pathologists (CAP) data for 2010 reveal that approximately 75% of clinical laboratories use a ‘capillary tube’ (eg, Ostwald tube) or similar type of viscometer.6,7 Viscosity is measured by the time required for a serum or plasma sample to flow through the tube under the influence of gravity. Viscous samples flow more slowly. Hence, viscosity is proportional to time. Although the Ostwald method is widely used, it lacks standardization and controls commonly employed for other hematology or chemistry assays. Laboratories report their results in 1 of 2 ways: (1) a ratio, comparing the measurement with the patient sample to the measurement with water, or (2) in units of viscosity, such as centipoise (cp). Because the viscosity of water at 20°C approximates 1.0 cp, the viscosity ratio will be similar to the sample’s viscosity in cp at this temperature. CAP data (2010) indicate that clinical laboratories measure viscosity at 1 of 2 temperatures: room temperature or 37°C. For most clinical laboratories, the Ostwald method is ideally suited for measurement of serum (or
plasma) viscosity because of its simplicity, reproducibility, and clinical correlation.8

**Hyperviscosity Syndrome**

Hyperviscosity syndrome seldom occurs until relative serum viscosity is $\geq 4.0$ and might be considerably higher in individual patients. However, the viscosity level at which the syndrome appears is generally reproducible within the same patient (symptomatic threshold).5,8–12 Patients with HVS have skin and mucosal bleeding, retinopathy with visual disturbances, and a variety of neurologic disorders varying from headache to coma.8 Heart failure and other cardiovascular manifestations are less common. HVS can be diagnosed from the physical examination by identifying characteristic retinal venous engorgement (‘sausaging’) on funduscopic inspection (Figure 2).8,13,14 Hemorrhages, exudates, microaneurysms, papilledema, and an appearance indistinguishable from central retinal vein occlusion might be seen in later stages. HVS can be accurately monitored with an Ostwald viscometer.5,14

**Plasmapheresis**

Plasmapheresis (plasma exchange) was first carried out for macroglobulinemia in the late 1950s and shown to promptly reverse retinopathy and other clinical manifestations of HVS in most patients.5,9–16 Accurate diagnosis of HVS from the eye exam enables appropriate therapy, that is, plasmapheresis, to be instituted promptly.17,18 Plasmapheresis does not affect the underlying disease process and so chemotherapy is often begun concomitantly. However, some patients with WM can be managed predominately with plasmapheresis.9–11,13,14,19,20 This procedure remains effective short-term treatment for HVS because IgM is 80% intravascular and serum viscosity rises steeply with increasing IgM levels. Thus, a relatively small reduction in IgM concentration has a significant effect on lowering serum viscosity. Plasma exchange reduces viscosity approximately 20%–30% per session. Because bleeding is the most common sign of HVS, urgent plasmapheresis using a cell separator should be carried out for patients with visual symptoms to reduce the likelihood of blindness from retinal hemorrhages and/or retinal detachment.21

As noted, HVS can be diagnosed from the physical exam (funduscopic), treated effectively with plasmapheresis, and monitored with the Ostwald tube. Plasmapheresis is usually well tolerated and safe.8–18 Generally 1–1.5 plasma volumes are exchanged per session. Fluid replacement usually consists of albumin and saline in various proportions. Serum viscosity can be monitored serially and the procedure can be repeated on successive days. It is usually not necessary to achieve normal viscosity to relieve symptoms. The management of HVS in WM remains one of the most effective uses of this procedure. When patients are maintained at a level under their symptomatic threshold, clinical manifestations of the syndrome usually are prevented.

**Aggressive Plasmapheresis for Special Conditions**

Some clinical circumstances might call for aggressive plasmapheresis: (1) visual findings (hemorrhages); (2) cryoglobulinemia; (3) prevention of rituximab flare; and (4) treating autoantibody syndromes causing organ dysfunction (eg, peripheral neuropathy).
As noted, urgent plasmapheresis might be indicated in patients with retinal hemorrhages to lessen the chance of blindness. In our experience, 70% of cryoglobulins are mixed (monoclonal IgM–polyclonal IgG) that precipitate at lower concentration and higher temperatures than single-component cryoglobulins.\textsuperscript{13,14,22,23} The presence of cryoglobulinemia can result in a strikingly temperature-sensitive elevation of serum viscosity.\textsuperscript{19,22} A transient increase in IgM levels, sometimes dramatic, after rituximab therapy (flares) has been reported in 30%–70% of patients.\textsuperscript{17,24} Plasmapheresis should be considered before giving rituximab if serum viscosity $>3.5$ or IgM level $>4$ g/dL. More data are required to determine whether prophylactic plasmapheresis might be better considered if serum viscosity $>3.0$ or IgM $>3$ g/dL. Peripheral neuropathy is sometimes associated with M-proteins, especially IgM, which have autoantibody activity to various peripheral nerve antigens.\textsuperscript{25,26} Plasmapheresis has limited efficacy in treatment although randomized trials are lacking. Acquired von Willebrand disease has been reported in WM; low von Willebrand factor levels are associated with higher concentration of IgM and hyperviscosity.\textsuperscript{27} Whether patients with IgM proteins having autoantibody activity and consequent immunemediated organ damage should receive more aggressive plasmapheresis is unknown, but this approach warrants a prospective therapeutic trial.

**Conclusion**

Plasmapheresis remains a valuable adjunct in the treatment of some patients with WM. It should be carried out as an emergency procedure in high-risk HVS patients. Observational studies have consistently demonstrated that plasmapheresis can promptly reverse most clinical manifestations of serum HVS. Thus, early diagnosis is crucial. Maintaining serum viscosity below each patient’s symptomatic threshold effectively prevents recurrent HVS. Aggressive plasmapheresis might be indicated in some circumstances.

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