

PLASMAPHERESIS IN WALDENSTRÖM'S MACROGLOBULINEMIA

by Marvin J. Stone, MD



Marvin J. Stone, M.D.

Plasma is the fluid portion of the blood. Plasmapheresis or plasma exchange is a procedure involving the separation of plasma from the circulating blood cells in order to remove a disease substance. The red cells, white cells, and platelets are then returned to the patient along with prescribed replacement fluid. Plasma exchange is performed with a machine that uses centrifugation to divide plasma from the cellular blood components. Blood is drawn from a patient's arm vein and anticoagulant is added to keep the blood from clotting. The blood enters the blood cell separator where the plasma is removed from the cells and pumped into a collection bag. The cells and the replacement fluid ordered by a physician are returned to the patient through a needle in the opposite arm. Usually, the plasmapheresis procedure is completed in about two hours. The sterile tubing and needles are used only once. Sometimes a catheter is inserted in order to gain venous access. Side effects from the procedure are few, but sometimes patients feel lightheaded or develop numbness or tingling. These symptoms can be managed by increasing the fluid flow that is returned to the patient and giving calcium. Approximately 300,000 plasma exchange procedures are performed worldwide each year.

Plasmapheresis is performed to treat hyperviscosity syndrome (HVS), a common manifestation of Waldenström's macroglobulinemia (WM). Patients with HVS have skin and mucosal bleeding, retinopathy with visual disturbances, and a variety of neurological disorders. HVS can be diagnosed from physical examination by identifying the characteristic retinal venous engorgement ("sausaging") in the eye on fundoscopic inspection. HVS can be accurately monitored with an Ostwald tube and usually corrected by plasmapheresis.

HVS was described by Jan Waldenström in his original 1944 report of two patients with macroglobulinemia. Viscosity refers to resistance to flow or stickiness. IgM exists as a pentamer with a molecular size of 925 kilodaltons (IgG is 150 kd and albumin 65 kd). It is thus not surprising that this giant molecule can exert profound effects on blood cells and blood flow, especially when present in the high concentrations of IgM often found in WM patients. In addition to bleeding, visual disturbances and other neurologic problems frequently occur in HVS. Heart failure and other cardiovascular manifestations are less common. Approximately 80% of patients with HVS have WM. Normal viscosity measured with an Ostwald tube is 1.4 to 1.8 relative to water. HVS is unlikely unless the serum viscosity is greater than 4. When IgM level rises above 3g per deciliter, the risk of HVS increases. Viscosity levels in HVS vary significantly between patients but correlate closely with signs and symptoms in the same patient ("symptomatic threshold"). Prompt diagnosis of HVS from the eye exam enables appropriate therapy, i.e., plasmapheresis, to be instituted. In addition to affecting plasma viscosity, macroglobulin coats red cells leading to the characteristic stacking appearance (rouleaux) on peripheral blood smear in Waldenström patients. Protein coating also causes a platelet functional defect which contributes to the bleeding tendency in patients. The presence of cryoglobulinemia, whether single or multiple component, strikingly elevates serum viscosity in WM patients.

The rise in viscosity with increasing serum concentration of IgG is roughly linear. However, above a concentration of 3g per deciliter, IgM relative viscosity rises steeply. The Ostwald tube used by Waldenström in his initial study remains a simple, reliable method for measuring relative serum viscosity in patients. During the last 5 years at Baylor-Dallas, 499 serum viscosity determinations were ordered, 297 of which (59.5%) were elevated. The majority (60.5%) of these patients had monoclonal IgM. Results are usually available within one hour from the time the blood specimen is received in the laboratory.

Plasmapheresis, first carried out for macroglobulinemia in the late 1950s, was demonstrated to reverse retinopathy and other clinical manifestations in most patients. This procedure remains an effective short-term treatment for HVS because of the demonstrated relationship between serum viscosity and IgM levels and also because IgM is 80% intravascular. Chemotherapy is often begun concomitantly with plasma exchange. Some WM patients can be managed predominately with plasmapheresis.

It is usually not necessary to plasmapherese patients down to normal viscosity to relieve symptoms. A potential exception is illustrated by a patient with documented macroglobulinemia for 37 years who developed peripheral neuropathy associated with an anti-MAG antibody (myelin-associated glycoprotein; the IgM that causes peripheral neuropathy is labeled the anti- MAG antigen). Because her neurological symptoms reproducibly recurred above a serum viscosity of 2.5-3, we sought to keep her viscosity close to normal with frequent plasmaphereses. Over a 23 year period, this patient underwent approximately 400 plasmapheresis procedures with little chemotherapy other than corticosteroids. She died abruptly in 2003 six weeks after knee surgery. Her prolonged course raises the possibility that patients with monoclonal macroglobulin antibodies that produce neuropathy or other organ dysfunction may benefit from a more aggressive effort to maintain serum viscosity near normal. Prospective clinical trials will be necessary to confirm this possibility.

Transient increases in IgM levels after rituximab therapy (“flares”) occur in 30%-70% of WM patients and have been well described. It has been recommended that plasmapheresis be carried out in advance of rituximab therapy if serum viscosity is above 3.5 or IgM level is greater than 50 grams/liter. Because of the relationship of serum viscosity to IgM concentration, it may be wise to consider plasmapheresis in advance if serum viscosity is above 3 or the IgM level is above 30 grams/liter. The mechanism of the flare phenomenon is unclear. The rise in IgM levels may occur disproportionately to the increase in serum viscosity. The flare phenomenon has become less of a problem with use of combination regimens that utilize chemotherapy prior to giving rituximab.

Plasmapheresis remains a valuable adjunct to the treatment of some patients with WM.

Baylor Sammons Cancer Center

Dallas, Texas

REFERENCES

1. Fahey JL, Barth WF, Solomon A: Serum hyperviscosity syndrome. JAMA 1965;192: 464-7.
2. Menke MN, Fekete GT, McMeel JW, Treon SP: Effect of plasmapheresis on hyperviscosity-related retinopathy and retinal hemodynamics in patients with Waldenström's macroglobulinemia. Investigative Ophthalmology & Visual Science 2008;49: 1157-60.
3. Stone MJ: Waldenström's macroglobulinemia: Hyperviscosity syndrome and cryoglobulinemia. Clinical Lymphoma & Myeloma in press 2009.

Marvin J. Stone, a native of Columbus, Ohio, attended Ohio State University. He received his M.D. degree with Honors from the University of Chicago. A residency in internal medicine followed at Barnes Hospital in St. Louis and at Parkland Memorial Hospital in Dallas. He subsequently served as a clinical associate at the National Institutes of Health in Bethesda. In 1976 Dr. Stone was appointed as Chief of Oncology at Baylor University Medical Center in Dallas and Director of the Baylor Charles A. Sammons Cancer Center. Stepping down from these appointments in 2008, he now heads the Internal Medicine Clerkship for third-year medical students and the Medical Oncology Fellowship Program. Dr. Stone is also Clinical Professor of Internal Medicine at the University of Texas Southwestern Medical School. In 1980, he started the first bioethics course for medical students at Southwestern.

Dr. Stone has received Outstanding Teacher Awards from the house staff at Baylor and from medical students at UT Southwestern. The author of over 200 articles and book chapters on various aspects of hematology, oncology, and immunology, Dr. Stone was honored in 1999 when the Baylor University Medical Center created the Marvin J. Stone Library at the Baylor Institute for Immunology Research. Dr. Stone is a Master of the American College of Physicians and received the Distinguished Service Award from the University of Chicago in 2002. He is a past president of the American Osler Society and was the first chair of the American Society of Clinical Oncology's Career Development Committee. In 2004 Dr. Stone received the Lifetime Achievement Award in Waldenström's Macroglobulinemia from the International Society for the Study of Waldenström's Macroglobulinemia. He contributed an essay on monoclonal antibodies to The Lancet's special issue on Medicine and Creativity in 2006.

This article was published in the IWMF *Torch*, [volume 10.2](#) (April 2009) pages 4-5.