DOUBLE FILTRATION PLASMAPHERESIS IN THE SYMPTOMATIC HYPERVISCOSITY RELATED TO WALDENTROM'S MACROGLOBULINEMIA

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OBJECTIVES

Hyperviscosity syndrome (HVS) in Waldenstrom's macroglobulinemia (WM) is a rare life-threatening complication due to increased plasma viscosity, typically associated with monoclonal IgM. Guidelines of the American Society for Apheresis (ASFA 2016) recommends Plasmapheresis as first-line therapy in the symptomatic HVS and the prophylaxis for Rituximab with grade of evidence 1B and 1C, respectively [1].

We used Double Filtration Plasmapheresis (DFPP) as semi-selective plasmapheresis technique to treat HVS in WM, because it is safer than plasma-exchange (not selective). A problem of DFPP is the loss of useful substances like fibrinogen; infact an important loss of fibrinogen increased hemorragic risk. In this study, we evaluated the percentage of reduction of immunoglobulins and the more significant factor involved in the reduction of fibrinogen.

METHODS

We describe our experience in the apheretic treatment of 6 patients (3 XY and 3 XX) affected by symptomatic HVS in WM. Patient's characteristics: mean age 68 years (range 40-74); mean body weight 85.3 Kg (range 65-107); mean Hct 27 % (range 24-30); mean plasma volume 3.7 L (range 2.8-5); mean Hb 8,86 g/dl (range 8,1-10); mean PLT 133x10^3/ml (30-180x10^3), mean Total proteins (TP) 10,6 g/dl (range 9,4-13,9), mean IgM 6,6 g/dl (range 4891-12265). Patients showed paresthesia, headache, somnolence, visual impairment, hearing loss, anemia and splenomegaly. They underwent 3 to 7 sessions of Double Filtration Plasmapheresis (DFPP), performed every other day, with the Diapact CRRT B-Braun, the plasmaseparator Plasmaflo OP-05W (Asahi Kasei Tokyo) and the secondary filter EC-50W (Asahi Kasei Tokyo) (Fig 1).

After DFPP, 4 patients were treated with 6 sessions of Rituximab, Dexamethasone, and Cyclophosphamide [2]; while 2 patients were treated with Rituximab, Dexamethasone and Bendamustine [2].

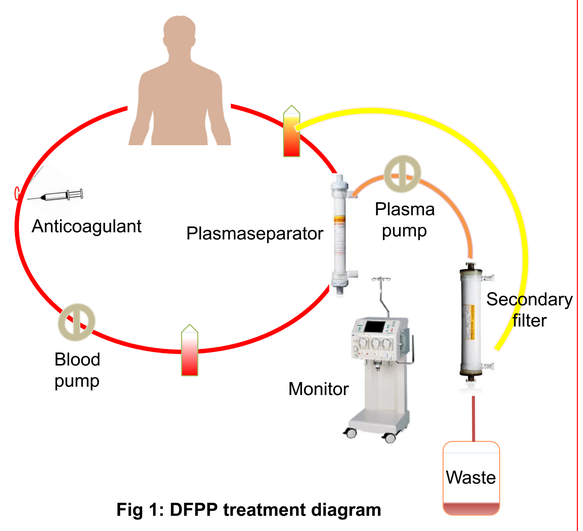

Fig 1: DFPP treatment diagram

DFPP setup

Vascular access: peripherical vein arm-arm

Low molecular weight heparin: 20UI/kg in bolus

Blood flow: 80-90ml/min

Plasma flow: 25-28ml/min

Volume treated:1TPV

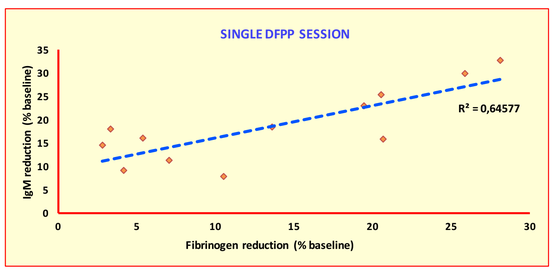

Fig 2A : Relation between reduction of Fibrinogen (%baseline) and IgM (%baseline) after single DFPP session

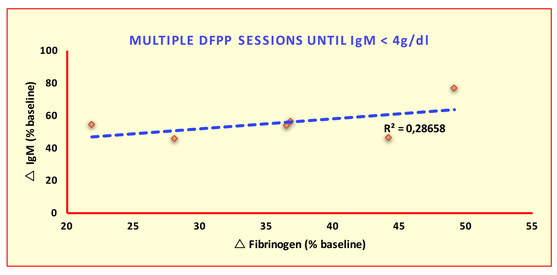

Fig 3A: Relation between △ Fibrinogen (% baseline) and △ IgM (% baseline) after multiple DFPP sessions

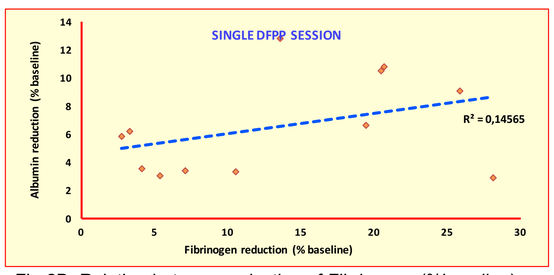

Fig 2B: Relation between reduction of Fibrinogen (%baseline) and Albumin (%baseline) after single DFPP session

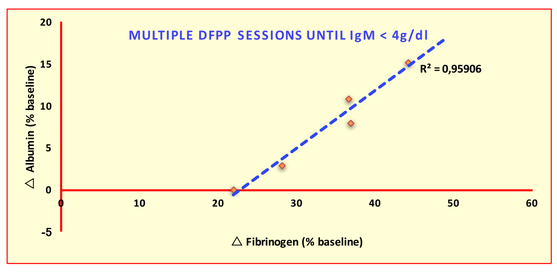

Fig 3B: Relation between △ Fibrinogen (% baseline) and △ Albumin (% baseline) after multiple DFPP sessions

Patient	IgM mg/dl (Baseline)	DFPP (n°)	IgM mg/dl (post DFPP)	Hematologic treatments	Final response
1 XX	5025	3	2203	6 sessions of Rituximab, Dexamethasone, and Cyclophosphamide	Complete response
2 XY	4891	4	2258	6 sessions of Rituximab, Dexamethasone, and Cyclophosphamide	Complete response
3 XY	5424	3	2514	6 sessions Rituximab, Dexamethasone and Bendamustine	Partial response
4 XY	6547	3	3529	6 sessions Rituximab, Dexamethasone and Bendamustine	Partial response
5 XX	12265	7	2865	6 sessions of Rituximab, Dexamethasone, and Cyclophosphamide	Complete response
6 XX	5240	2	2860	6 sessions of Rituximab, Dexamethasone, and Cyclophosphamide	Complete response

Table 1: Therapeutic response after DFPP sessions and hematologic treatment

RESULTS

After a single DFPP session, our setup removed approximately 20% of IgM, 6% of albumin and 13% of fibrinogen. For the occlusion of the secondary filter, it was not possible to treat a plasma volume steadily, so we had great variability in the percentage of IgM trapped in the secondary filter pores. After reaching the therapeutic target (plasma IgM reduction < 4 g/dl), we achieved an average reduction in IgM of 55%, TP of 50% while lower was the mean reduction for IgG (33%), IgA (31%), fibrinogen (35%) and albumin (7%). During the single session of DFPP, the amount of IgM removed was proportional to the amount of lost fibrinogen (correlation coefficient of 0.6), whereas the fibrinogen did not correlate with the loss of albumin (correlation coefficient of 0.1) (Fig 2A-2B). After repeated DFPP sessions, however, the total amount of eliminated IgM no longer correlates with the fibrinogen lost (correlation coefficient of 0.2), due to its increment. In contrast, the lost fibrinogen seems to correlate with the total amount of lost albumin (correlation coefficient of 0.9), regardless of the number of plasmapheresis sessions, for still unclear reasons (Fig 3A-3B).

After DFPP treatment, the symptomatic hyperviscosity syndrome regressed. According to Second International Workshop on WM [3] the association with DFPP and the following drugs treatment led to complete response in 4 patients; partial response in 2 patient. Patient 4XY could not undergo further treatment with RDB, due to comorbidity (Tab 1).

CONCLUSIONS

We used DFPP to treat HS in WM instead of plasma exchange to avoid loss of essential components and plasma-based reinfusion solution or substitute derivatives and to reduce the infections and allergy. More sessions of DFPP, using the cascadeflo EC-50W as secondary filter, are effective in the reduction of circulating IgM of about 55%; while they are less effective in the reduction of other immunoglobulins. The reduction of fibrinogen seems not to be associated with the rate of elimination of immunoglobulins, but with the amount of albumin lost after repeated DFPP. The normalization of plasmatic IgM concentrations induced the regression of the symptoms related to HVS and allowed the subsequent hematological treatment. The DFPP contributed to a good response to hematological therapy in all patients.

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