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Plasma exchange for treating cryoglobulinemia: A descriptive analysis

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ABSTRACT

Background: Cryoglobulinemia is an immune-complex-mediated systemic vasculitis involving small-to-medium-sized vessels. Plasmapheresis transiently removes the circulating cryoglobulins and has been advocated (in conjunction with immunosuppressive therapy) to be effective in reducing morbidities associated with cryoglobulinemia. The goal of this paper was to review over the past 20 years the medical literature for evidence supporting or refuting the reported use of plasmapheresis for cryoglobulinemia (January 1988 through June 2008).
Methods: We included all reported literature of the use of plasma exchange for the treatment of cryoglobulinemia that included at least five patients. Electronic searches were performed using MEDLINE (January 1988 through June 2008) and Cochrane Central Register of Controlled Trials (January 1988 through June 2008).
Results: Of the 11 articles included in this review, there were a total of 156 patients studied. Two studies used cryofiltration, one compared plasma exchange to double cascade filtration and the other eight dealt with plasma exchange only. Outcome measures were often not clearly defined.
Conclusions: Although plasma exchange is an accepted treatment for cryoglobulinemia, there are no large multicentre randomized controlled trials of plasma exchange versus placebo or versus immunosuppressive therapy. Of the 11 studies from our literature search, none had a clear report of the apheresis procedures and clearly defined quantitative outcomes. The quality and variability of the evidence precludes a meta-analysis or even a systematic analysis. However, these studies weakly support the use of plasma exchange largely on a mechanistic basis.

1. Introduction

Cryoglobulinemia is an immune-complex-mediated systemic vasculitis involving small-to-medium-sized vessels. High levels of cryoprotein may be found in the blood. Cryoproteins are a group of abnormal circulating proteins that precipitate or form a gel if exposed to cold temperatures (about 4 °C) and they usually resolubilise at body temperature (about 37 °C) [1]. Renal manifestations include proteinuria and renal insufficiency [2]. Other clinical manifestations include arthralgias, mylagias, vascular purpura, Raynaud's, peripheral neuropathy, and cardiac disease [3]. The clinical conditions that may be associated with cryoglobulinemia include viral infections (hepatitis A, B, C, and cytomegalovirus), autoimmune disease (systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, Sjogren syndrome, scleroderma, polymyositis, cold agglutinin disease), and lymphoproliferative disorders (macroglobulinemia, lymphoma, chronic lymphoid leukemia) [4]. There are three types of cryoglobulinemia. Type I contains only a monoclonal immunoglobulin (usually IgM) while the other two types are mixed. Type II is characterised by a monoclonal Ig, usually IgM, with rheumatoid factor activity against IgG, with which it is mixed. In Type III, there is a mixture of two types of polyclonal Ig, one of which has rheumatoid factor activity [5].

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Treatment for systemic vasculitis with corticosteroids remarkably improved the prognosis for patients versus no treatment [6,7]. Further studies have demonstrated a better prognosis with cyclophosphamide and the combination of corticosteroids plus cyclophosphamide [7,8]. However, steroids and cytotoxic, or immunosuppressive, medications (such as azathioprine, cyclophosphamide, methotrexate, and penicillamine) have also been reported as having little success in some cases [5,9–11]. Since hepatitis C virus is often associated with cryoglobulinemia, interferon-alpha has been added to the treatment possibilities [3,7,12]. Three prospective trials have shown good short term results in essential mixed cryoglobulinemia with interferon-alpha [3,13,14] but tolerance may be poor and long term outcomes have not been uniformly promising [3,15]. However, 15 of the 27 patients that received interferon-alpha for 6 months in Misiani's randomized control study in contrast to the control group had undetectable HCV RNA and significant decreases in cutaneous vasculitis, anti-HCV antibody, cryoglobulin and serum creatinine levels at 6 months of follow-up [15].

Plasmapheresis transiently removes the circulating cryoglobulins and has been advocated (in conjunction with immunosuppressive therapy) to be effective in reducing morbidities associated with cryoglobulinemia [2–6,10,11,16–20]. The objectives of plasmapheresis are to remove the plasma's cryoglobulins, and pathogen component, thus altering the antigen–antibody ratio, to eliminate cytokines, and to increase immune complex clearance [2]. There are no large multicentre randomised controlled trials of plasmapheresis versus placebo or versus other therapies. The Canadian Apheresis Group at its annual national utilization review in 2008 noted cryoglobulinemia was the 9th most frequent indication for plasma exchange therapy. The goal of this paper was to review over the past 20 years the medical literature for evidence supporting or refuting the reported use of plasmapheresis for cryoglobulinemia (January 1988 through June 2008).

2. Methods

We included all reported literature of the use of plasma exchange for the treatment of cryoglobulinemia that included at least five patients.

Electronic searches were performed using MEDLINE (January 1988 through June 2008) and Cochrane Central Register of Controlled Trials (January 1988 through June 2008). We combined the terms "cryoglobulinemia", "cryoglobulinaemia", and "cryo", with the terms "plasmapheresis", "plasma exchange" by using the Boolean "AND" operator. We supplemented citations identified from electronic databases by reviewing the reference lists of all identified articles.

3. Results

The combined search identified 192 potentially relevant citations. By initial review, 162 articles were excluded. Thirty studies were retrieved and the full texts were reviewed. Of these, 18 were subsequently excluded (see Fig. 1). The reasons for exclusion were that there were less than five patients ($n = 5$), did not include plasma exchange as a treatment for cryoglobulinemia ($n = 2$), were review articles ($n = 3$), or did not have relevant clinical outcomes ($n = 3$) (of these, one article looked at clearance of interferon with plasmapheresis [12] another compared properties of filter membranes [21] and the third looked at amount of mononuclear blastogenesis and neutrophils [22]. Two articles were excluded because they included patients reported in other studies by the same author that we had included already. Three articles were in a language that could not be translated by the reviewers (one in Japanese, two in Russian). Of the 11 articles included in this review, there were a total of 156 patients studied. In four of the 11 studies, there was no mention of medical treatment [2,4,19,20] and in two studies no specific medication was mentioned, although the term "chemotherapy" [17] or "immunosuppression" [18] was given. The other studies gave medication names but not doses [3,5,6,11,18]. Some studies stated that the patients had failed immunosuppression as part of the inclusion criteria. One study stated that they chose patients "with severe cryoglobulinemia not responsive to immunosuppressive therapy" but did not give a definition for either "severe" or "not responsive" [18]. See Table 1 for details.

Follow-up data was often vague. Six studies did not give days or weeks or months or any specific time of follow-up [2,4,11,17–19]. For instance, Russo et al. stated that "all the patients with mild or severe symptomatology achieved regression or improvement of some clinical symptoms" but gave no indication of follow-up time [4]. D'Amico et al. "obtained rapid significant decreases in cryocrit, serum creatinine and proteinuria in all cases, while mean C3 and C4 levels did not change significantly" but did not define the time frame of "rapid" [11]. Siami and Siami, in their 1998 study [17], present a table with the number of cryofiltration apheresis treatments and end points but no exact time of follow-up. Siami et al. [18] wrote that "all seven patients showed improvement in clinical symptoms" and there is a table with a general clinical score for treatments one, five, and 10 so one presumes that the follow-up is up to treatment 10. Karmochkine et al. present a table with outcome according to the underlying disease [19]. For cryoglobulinemia, it is broken down into success (complete remission or stabilization) or failure (uncontrolled disease or death) but, again, no time of follow-up is given [19].

One study gave different time frames for different outcomes. For instance, Cohen et al. stated that for relapses after "12 months of follow-up, clinical relapses were observed in 10 of the 12 patients" and "for four patients, interferon-alpha was reinitiated and maintained but in one of them, maintenance therapy had to be stopped after 18 months" [3]. As for cryo levels, they state that four of the 12 patients had undetectable levels with initial clinical remission but they do not state the exact time of follow-up [3]. Four studies gave clear indications of follow-up, as detailed in Table 2 [5,6,16,20].

Outcome measures were often not clearly defined. Skin ulcers were followed in two studies [2,16], cryo level in one [20], and the other nine included combinations of clinical