TRANSFUSION AND APERHERESIS

Rationales for therapeutic apheresis

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Introduction

Bloodletting seems to have held tremendous appeal for practitioners of the past. It was a treatment favored by barbers, physicians and naval surgeons from medieval times through the Renaissance, through the Enlightenment and well into the 19th century. It’s likely that the trust and confidence it inspired were based in part on its compelling rationale (the depletion of evil humors), while additional support may have come from its obvious effects on complexion and vital signs, plus a generous amount of placebo value. The advent of the scientific method exposed the theoretical basis for bloodletting for what it was — preposterous — and revealed that, with a very few exceptions, the benefits attributed to it for centuries were pure fiction. There are lessons here for contemporary physicians; namely to be clear about reasons for implementing a therapy and cautious about claims for clinical benefit.

Therapeutic apheresis may be fairly described as the modern descendant of bloodletting. Providers of this service/treatment often encounter expectations among patients and other physicians that differ very little from those associated with bloodletting in the past; i.e.; they expect that “cleaning the blood” in some vaguely understood manner will be good for what ails them. Such expectations are sometimes met in individual patients, resulting in case reports suggesting efficacy, but many of these claims have not stood the test of time.

Systematic approach to evidence

It is desirable that medical therapies have a rational basis. A framework is presented here for analyzing the appropriateness and effectiveness of therapeutic apheresis (TA) for a given application. It is argued that TA is most rational where three conditions are met: 1) the disease or symptom is caused by a blood constituent that TA can reasonably be expected to deplete; 2) TA has in fact been shown to meaningfully deplete it; and 3) documented meaningful depletion has been shown to be accompanied by clinically significant benefit.

Firm pathophysiological basis

First, there will ideally be a clear understanding of the pathophysiology of the disease in question that provides a strong rationale for TA. Since TA is usually a “subtractive” therapy, this generally requires that there be compelling evidence that the disease, or at least the targeted manifestation of it, is related to the presence of a blood constituent, preferably an abnormal blood constituent. Furthermore, classic metabolic data (e.g.; half-life, volume of distribution) should support the notion that the pathogenic constituent can be meaningfully depleted by the appropriate TA technique. Often the goal is depletion of a plasma constituent, in which case it is well to bear in mind that therapeutic plasma exchange (TPE) can only be considered reasonable for macromolecules having a relatively long half-life (preferably a week or more) and a substantial fraction of total body content (preferably at least half) in the vascular space.

Documented depletion by TA

Second, the expectation that the pathogenic blood abnormality will be corrected or meaningfully improved by TA should be confirmed by appropriate measurements. In practice, documented utility of TPE to bring about lasting depletion has been limited to antibodies (half-life of IgG =4 weeks) and low density lipoproteins [1]. Expectations of benefit from “cleansing” the blood of smaller, shorter-lived molecules, including various mediators of inflammation, have never been substantiated by data showing
meaningful depletion or borne out by clinical experience.

These first two conditions might be called “rationale criteria.” A good example of an application having a strong rationale might be red cell exchange for complications of sickle cell disease (SCD). There is ample evidence linking the vaso-occlusive pathology observed in SCD to the presence of abnormal red cells. This provides good reason to suppose that removal of these cells and replacement with normal cells might be beneficial. Furthermore, since the lifespan of a normal red cell is measured in months, there is good reason to expect that a corrective effect of TA would persist for at least several weeks; in fact, serial electrophoretic analyses have repeatedly shown a preponderance of circulating hemoglobin A for many weeks following a red cell exchange. Thus, the rationale criteria are clearly met for this application.

Clinical efficacy

The third criterion requires analysis of clinical data and assessment of its strength. In a few illnesses in which the rationale factors are very strong, efficacy has been considered proven when TA is consistently followed by dramatic and unprecedented clinical improvement, preferably in the absence of any other therapy but at least in the absence of any other new therapy. Examples of this would include the hyper-viscosity syndrome (TPE), the leukostasis syndrome (therapeutic leukapheresis) and symptomatic thrombocytosis (therapeutic platelethpheresis). Ideally, however, it is preferable that clinically (vs. statistically) significant benefit be documented in a disorder with a reasonable rationale by properly conducted, randomized controlled trials [2,3]. These can be especially important when TA is employed in conjunction with other therapies and/or used in an illness characterized by spontaneous remissions or fluctuations in activity.

Four combinations of rationale and clinical factors

The remainder of this paper will examine the role of TA in several specific diseases. The examples chosen will encompass four possible combinations of rationale and clinical data and will illustrate how both rationale factors and uncontrolled clinical data can be misleading. They will support the argument that TA is most clearly rational when all three criteria are met.

Rationale and clinical evidence both strong

Guillain-Barre syndrome (GBS) is a good example of a disease for which there is both a strong rationale for TPE and convincing evidence of clinical benefit. Studies in the 1970s showed that the disease could be reproduced in experimental animals by injection of patient plasma, thereby suggesting that a plasma factor was pathogenic [4]. Later studies have established that anti-myelin antibodies circulate during the illness [5]. These antibodies probably arise from a “cross-reactive” immune response to microbial antigens encountered in a recent infection, particularly an enteritis due to Campylobacter jejuni [6]. Furthermore, clearance of anti-myelin antibody has been shown to be more rapid in patients who receive TPE [7]. Finally, several large randomized controlled trials have shown that TPE shortens the time to recovery by a substantial margin [8–10]. Thus there is a complete package of evidence supporting use of TPE in GBS.

Strong rationale with no clinical benefit

Systemic lupus erythematosus (SLE) is an example of a disease that offers a strong rationale for TPE but for which the results of controlled trials show a lack of efficacy. SLE has long been considered the prototype of an autoimmune disease mediated by autoantibodies. Enthusiasm for treating SLE was thus understandably high in the early days of automated TPE [11]. There was also no shortage of data confirming the expectation that plasma levels of antinuclear antibodies and immune complexes could be lowered by TPE [12]. Thus, the rationale factors strongly support the use of TPE in SLE. There were also observational reports suggesting that TPE was beneficial for lupus patients [13]. However, these were inadequate to establish efficacy because the patients inevitably received other effective therapies and because spontaneous fluctuations in disease activity are common in SLE. It was nevertheless surprising when a randomized, controlled trial of TPE in lupus nephritis showed no benefit [14]. This conclusion was confirmed by a subsequent international controlled trial in patients with a variety of severe lupus syndromes [15]; the latter trial was stopped early when interim analysis showed no benefit from TPE and an increased risk of death from central venous catheter sepsis in patients randomized to TPE. This experience with SLE illustrates the pitfalls of accepting conclusions about efficacy without controlled data in an illness in which improvement is not unprecedented.

Weak rationale and weak clinical data

There are also diseases in which TA has been used extensively despite a rather weak rationale. Controlled trials in some of these, when finally performed, have shown little or no evidence of benefit. Multiple sclerosis (MS) is a good example of this combination of findings.
TPE has been used extensively in MS, beginning in the 1980’s. Interest in trying it in a central demyelinating disorder may have arisen from the favorable outcomes neurologists were reporting with TPE in peripheral demyelinating disorders such as GBS. Whatever the reason, early advocates of TPE in MS chose to ignore the absence of evidence that an autoantibody or any other humoral factor had a pathogenic role in MS. Rather, past and current evidence implicates cellular immune mechanisms as the major cause of demyelination in MS [16]. Absent a causative plasma factor, there can obviously be no documentation of depletion of such a factor by TPE, and this has never been done in MS.

Clinical use of TPE in MS produced many observational studies suggesting benefit. These were not convincing, however, because the patients were receiving other therapies and because the disease is characterized by spontaneous remissions. When randomized controlled trials of TPE were done, the evidence for benefit was not convincing [17,18]. Although there remain pockets of enthusiasm for TPE within the MS treatment community, most neurologists have abandoned it [19]. In the case of MS, then, the lack of a compelling rationale was overlooked until controlled studies showed no clinical benefit. A similar sequence of events can be found in the early use of TPE for renal transplant rejection.

Rationale weak but clinical data supportive

The most perplexing scenario for the analytic approach advocated herein is a disease in which the rationale for TA is unclear or uncertain, but clinical evidence has nevertheless been adduced and interpreted to show efficacy. Some diseases that would formerly have fallen into this category have been reassigned to the previous one when unfavorable clinical data from controlled trials became available. On the other hand is the example of thombotic thrombocytopenic purpura, which moved from this category to the first one (rationale and clinical data both strong) when its pathophysiology was finally worked out. There are others, however, in which controlled trials have been done and appear to support efficacy in spite of a weak rationale. It is curious that several such diseases are treated with a proprietary TA device provided by a single manufacturer. Because this is the most challenging category, and the one in which critical analysis is most needed, several examples will be offered.

ProSorba column

The ProSorba column, which contains recombinant staphylococcal protein A bound to silica particles, was originally conceived as a mean to deplete IgG antibodies and/or immune complexes from plasma separated by an apheresis instrument without the necessity for the plasma replacement fluids used in TPE. However, the IgG absorption capacity of the commercial product is quite limited – certainly less than the depletion achieved by a one-plasma-volume TPE – and it has never been shown to have a meaningful subtractive effect on any plasma constituent [20]. No other mechanism of action has ever been convincingly demonstrated for this device, though recent unpublished studies propose that leaching of protein A into patient plasma may account for some of its biologic effects.

Notwithstanding the mystery surrounding its mechanism of action, a multicenter randomized sham-controlled trial of this device was undertaken in rheumatoid arthritis (RA) and showed some temporary benefit for patients who completed 12 weekly treatments [21]. On the strength of this evidence, the device has been granted FDA approval for use in RA. In this case, then, a disease of unknown cause is being treated with a device whose mechanism of action is not clear. From an evidentiary standpoint this is suboptimal to say the least.

Photopheresis

Extracorporeal photochemotherapy (ECP), also known as photopheresis, may reasonably be mentioned in this category. In this procedure, autologous mononuclear cells separated by leukapheresis are exposed to UVA light in the presence of a psoralen and then reinfused to the patient [22]. Several theories have been proposed regarding its mechanism of action. One involves apoptosis of treated lymphocytes. Another emphasizes stimulation of monocyte differentiation into dendritic cells. A third envisions modulation of cytokine profiles from the more inflammatory Th 1 pattern to the more inhibitory Th 2 pattern [23,24]. None is proven and thus none can provide a firm rationale for any application. There seems little doubt that ECP leads to remissions in some patients with cutaneous T cell lymphoma (CTCL), an illness in which malignant lymphocytes are abundant in the blood. The ultimate effect of ECP in CTCL is down regulation of a malignant lymphocyte clone; however, down regulation of a pathogenic lymphocyte clone has not been shown in any application except CTCL and therefore the second rationale criterion has not been met for any other application. Nonetheless, ECP is widely believed to be an effective treatment for graft-versus-host disease and solid organ transplant rejection. Clinical evidence supporting these applications is almost entirely observational. A large controlled trial of prophylactic ECP in heart transplant recipients yielded conflicting signals in that mild histologic changes in routine biopsies were less frequent in ECP-treated patients but the incidence of severe, hemodynamically significant rejection was not
Plasma and blood viscosity do fall by 15%/C1 benefit from rheopheresis is far from clear [27]. Name of the procedure, the mechanism of potential “rheo” (from the Greek word for “flow”) in the name of AMD. Thus, despite the suggestive inclusion of constituents. Furthermore, it is admitted that none of is a rather extensive list of possibly harmful plasma modifiers, and cell signaling components [27].” This is a rather extensive list of possibly harmful plasma constituents. Furthermore, it is admitted that none of them has “demonstrated any causal relationship with AMD.” Thus, despite the suggestive inclusion of “rheo” (from the Greek word for “flow”) in the name of the procedure, the mechanism of potential benefit from rheopheresis is far from clear [27]. Plasma and blood viscosity do fall by 15–18% after a treatment, although published data do not allow estimation of how long this change persists.

A non-blinded controlled trial showed modest temporary improvement is visual activity in treated patients [28]. A small sham-controlled trial showed similar improvement in visual acuity in patients whose plasma did not pass through the macromolecular filter [27]. A larger multicenter trial is underway in which control patients have antecubital venipunctures done under a drape by attendants who then pretend to operate a concealed but noisy machine nearby. Interim results from this trial showed improvement in visual acuity in treated patients [27]. Since neither the cause of the disease nor the mechanism of the postulated beneficial effect is clear as yet, rationale factors for this procedure would have to be judged weak. If blood viscosity proves to be important, it is fair to point out that hematocrit is a more important determinant of whole blood viscosity than is plasma viscosity, and that phlebotomy (bloodletting) could be a simpler, cheaper and very likely a longer lasting means to achieve a lower blood viscosity.

Summary and conclusions

In summary, then, three criteria are suggested for assessment of applications of TA; two concerning rationale and one concerning clinical data. These criteria are satisfied for some of the conditions that practitioners of TA feel most confident about, but are not yet satisfied in other conditions in which it remains controversial. They may also be useful in evaluating new applications as they arise. Practitioners of TA should strive for a firm evidential basis for what they do, including the rationale criteria set forth herein. When these criteria are not met, there is a danger that a current practices will not differ in kind from bloodletting to remove evil humors.

References


