The Clinical Indications for Cryoprecipitate Use
A Critical Review
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Historical
Although the first report of a successful therapeutic transfusion for hemophilia appeared in 1840 [16], sound clinical use of blood for this purpose paralleled the elucidation of blood group serology. Plasma fractionation, spurred mostly by the need for preservable factors came into its own around 1946 [6] and the commercial application of these techniques followed shortly thereafter. Problems relating to volume overload were largely answered by the development of cryoprecipitate [27] and, risk of viral infection notwithstanding, cryoprecipitate became a standard product for supplying factor VIII, von Willebrand factor, fibrinogen and, more recently, fibronectin.

As component therapy became more widely used, the specific indications for this therapy became more muddled. In a review of the problem by Braunstein and Oberman [4] it was concluded that most fresh frozen plasma use was based on anecdotal, unreferenced information and that there was a distinct paucity of controlled clinical data. This situation, as judged by guidelines published this year for component therapy [24][5], has had little more substantial improvement than a well-attended consensus conference [2] during which guidelines for fresh frozen plasma use were agreed upon. In the absence of large-scale controlled trials, these consensus recommendations form the basis for FFP use.

There has been no similar conference over the use of cryoprecipitate; either due to the relatively less frequent use of the product or to the even more sketchy information pertaining to its indications. This paper is an attempt to consolidate some of what has been established on the specific indications for cryoprecipitate use.

Use in Classic Hemophilia
Although the use of cryoprecipitate for the treatment of classic hemophilia has been largely superceded by more highly purified factor concentrates, there are features which still make it the therapy of choice in some situations. It is more easily stored than some preparations which must be kept at very low temperatures and, when dose size is not a limiting factor, is a very economical source of factor VIII. Its main disadvantages are the high variability of actual factor VIII content, which ranges between 70 and 150 units per bag [18], and the necessity of transfusing the product immediately upon thawing due to its relative instability. Since each unit is a single-donor product, infectious exposure for one unit is lower than for pooled concentrates [1] but this consideration cannot take precedence over dosing requirements.

The amount of factor VIII required varies by the clinical situation. Minor bleeds can respond to as little as 10u/Kg as a one time dose. More extensive hemarthroses may require multiple 20u/Kg doses as frequently as every 8-12 hours. A preparatory dose of 30 to 50u/Kg is suggested before major surgery, followed by a constant infusion of 3u/Kg/Hr for 3-5 days [26]. In doses such as these, the volume of cryoprecipitate required may be prohibitively high.

Recently, a pharmaceutical alternative to small dose factor VIII therapy has appeared. It is a synthetic analog of vasopressin, DDAVP (1-deamino-8-D-arginine-vasopressin) and is capable of stimulating the release of stored factor VIII and von Willebrand factor [18]. When given in
a dose of 0.3μg/Kg, it produces a two- to four-fold increase in the levels of factor VIII in persons with mild hemophilia. Response to the drug is variable between patients and may decrease with successive doses; a monitored trial is advisable before relying on its efficacy. It may, however, substantially replace cryoprecipitate in the treatment of mild hemophilia.

Treatment of von Willebrand's Disease

The appropriate therapy for von Willebrand disease (vWD) is a more complex issue than for other factor deficiencies, owing to the clinical variability of the disease. In consideration of this, a brief review is in order.

The von Willebrand factor (vWF) is a multimeric glycoprotein consisting of up to 15 or more protomers of about 220,000 molecular weight [17][36]. It forms a stable complex in plasma with factor VIII [38] and binds to platelets [9], facilitating platelet aggregation. This latter feature forms the basis for an in vitro test of vWF activity, the ristocetin-induced platelet aggregation assay. The ristocetin assay is sensitive to vWF multimericity and is useful in defining specific types of vWD [37].

Von Willebrand disease may be characterized as belonging to one of four general types as follows [7]. Type I is the "classic" autosomal codominant type with moderate to severe reductions in all factor VIII/vWF complex activities. Crossed immunoelectrophoresis reveals a full array of vWF multimers, but all in reduced amounts. Close analysis of the vWF present does not reveal any qualitative abnormality, thus the disease seems to be exclusively one of quantitatively. Type II vWD is characterized by a striking reduction in the high molecular weight multimers of vWF. As might be expected, platelet aggregation assays in type II disease are consistently abnormal, while total amounts of vWF measured antigenically may be normal. This disease type is further subdivided into types II A, B and C. The vWD type IIA patient shows deficiency in the high and intermediate molecular weight forms of vWF. vWF antigen is typically normal or higher than normal. Type IIB is characterized by a reduction in only the highest molecular weight forms of vWF, with the concomitant finding that platelet vWF multimeric structure is normal. vWF from these patients has an inexplicably high affinity for platelets. Type IIC has clinical features similar to type IIA, except that it demonstrates an autosomal recessive mode of inheritance. Type III vWD is the most severe clinically, with barely detectable levels of vWF and factor VIII. It shows an autosomal recessive mode of inheritance; offspring of two parents with type I vWD fall into this category. Finally, a "platelet-type" of vWD exists (also referred to as "pseudo vWD") in which the patient's platelets have an abnormal affinity for vWF, leaving the plasma vWF depleted. Platelets from these patients are exquisitely sensitive to ristocetin aggregation.

The appropriate therapy of vWD depends to a great extent on the specific type of vWD to be treated. Even with this knowledge, treatment is largely empiric, based on poorly understood laboratory findings such as bleeding time. Since patients with vWD severe enough to reduce factor VIII levels are subject to the same type of bleeds as factor VIII deficient patients, it is reasonable to follow factor VIII levels as a guide to replacement therapy, even though infusions of pure factor VIII are understandably of little benefit [36]. Cryoprecipitate is the replacement of choice, except in cases when DDAVP may suffice, as follows. Patients with type I disease tend to have the best responses to this drug; cryoprecipitate usually yields good results in the refractory patients. Type II disorders usually have poor response to the drug, consistent with the qualitative defect in these patients. In type IIB disease, the use of DDAVP is to be avoided, as severe thrombocytopenia has been reported [13], although cryoprecipitate
can be used effectively. Cryoprecipitate can also be used successfully in type III vWD, although pre-treatment levels in these patients are so low that repeated therapy can lead to the production of anti-vWF antibody production. Platelet-type vWD is the most troublesome form of the disease to treat, as treatment with DDAVP or cryoprecipitate may lead to severe thrombocytopenia. In such cases, cryoprecipitate infusion is best begun cautiously [33][34].

**Congenital Fibrinogen Deficiency**

Congenital afibrinogenemia was first described in 1920 [28] with about 150 cases subsequently being reported. These patients may present at birth with abnormal umbilical stump bleeding, but bleeding episodes are generally attributed to trauma. Hemarthroses are unusual and spontaneous bleeding episodes quite rare. Cryoprecipitate has been recognized as a reliable source of fibrinogen [10][25]. There are anecdotal reports of successful treatment of traumatic bleeds with cryoprecipitate [19][3], but no study has documented the need for a particular level of fibrinogen. Indeed, the only report which compared the post-transfusion fibrinogen level with clinical course (an unprecedented case of the "prophylactic" use of cryoprecipitate for afibrinogenemic children [29]), indicates that fibrinogen levels as low as 10 mg/dl are not associated with any increased bleeding tendency. Another author [3] concluded "...A virtually complete lack of fibrinogen is compatible with survival.". Such findings may have profound implications in the treatment of less well-understood syndromes of acquired fibrinogen deficiency. This is especially true in light of a paper by Mason and Ingram [22], later cited by Mammen [19] and many others, where the figure of "50-100 mg/dl" is offered as the fibrinogen level to be achieved in post surgical patients who congenitally lack fibrinogen. No primary data or reference is offered to substantiate this figure.

**Aquired Fibrinogen Deficiency**

One of the most challenging situations that one encounters in clinical medicine in acute disseminated intravascular coagulation (DIC). It is defined as a "...pathological syndrome resulting from the formation of thrombin, subsequent activation and consumption of certain coagulant proteins and production of fibrin thrombi." [21]. It may be seen in a variety of clinical situations, including sepsis and related shock, obstetric complications such as amniotic fluid embolism and retained abortion, severe hemolysis, neoplastic disease and many others. Of all the conflicting advice written about this disease, one could summarize all the universally agreed-upon features of its management in one sentence: It is usually triggered by underlying pathology, resolution of which is key to resolution of the coagulopathy.

From a practical point of view, the underlying problem will frequently require more time to resolve than the patient's hemodynamic instability will allow. Thus, initial management may center on fluid replacement and pressor support and may, in fact, supercede confident establishment of the diagnosis. A "gold standard" for the diagnosis does not exist, but summarizing information that is generally available ([21][23][8]), the diagnosis rests on demonstrating a decreasing fibrinogen level in the presence of a prolonged protime. A dropping platelet count helps to establish the diagnosis, but is not always present. Products of fibrin degradation will be present, but this sensitive finding is sufficiently non-specific that it is primarily helpful, when negative, to rule out DIC.

It is after addressing the emergent issues of cardiopulmonary support that the more elusive questions present themselves. First, a decision must be made as to whether or not to anticoagulate. There is evidence on both sides of this issue. The advice given by Miale [23] is
that such therapy is only helpful after the initiating event has been resolved. Colman [21] suggests a 10,000 unit dose of heparin IV, unless massive bleeding is evident. A great deal of clinical judgement is allowed on this point; appropriate consideration of the patient’s actual condition is essential.

At this point, the issue of replacing coagulation factors must be addressed. The two sides of this argument are (1) if microthrombi are, in fact, forming within small vessels, one only worsens the situation by providing more "fuel to the fire". On the other hand (2), if massive hemorrhage is evident and platelets and coagulation factor levels are very low, one is hard pressed to explain how the patient will resolve a severe bleeding episode without the basic coagulation hardware necessary to do so. Since each unit of cryoprecipitate contains between 200 and 250 mg of fibrinogen; transfusion of 10 units into a 70 kilogram person can be expected to raise the fibrinogen level by 60 to 70 mg/dL. If the inciting event is known to be curtailed (i.e. evacuating a retained abortion), then little argument can be made against furnishing coagulation proteins, through infusions of fresh frozen plasma and cryoprecipitate, although in the absence of obvious bleeding such replacement may be unnecessary. Similarly, if heparin anticoagulation is in effect, fibrinogen replacement seems unlikely to worsen the DIC cycle. There is no literature available to support either point of view securely [32][15][20]. In a recent review of a small number of obstetric patients [35], a sudden drop in fibrinogen during a severe bleed correlated with poor prognosis, but the effect of replacing fibrinogen with cryoprecipitate could not be associated with improved outcome.

A third therapeutic measure which has been advocated by some is the use of fibrinolytic inhibitors. This is done with the intent of reducing the plasma concentration of fibrin degradation products which in and of themselves could, at least in theory, create a hemorrhagic diathesis. A loading dose of 4-6g epsilon-amino caproic acid has been suggested, followed by 1 g every one to two hours [21]. It is of utmost importance to recognize the danger of administering this drug without first anticoagulating the patient. To do so risks worsening some of the sequelae of DIC, such as microthrombi-related renal ischemia.

Use of Cryoprecipitate as a Replacement for Fibronectin.

Of all the potential uses of cryoprecipitate, this is the one perhaps most in need of study. Fibronectin is involved in maintaining the integrity of the endothelial barrier to tissues. Its lack is associated with tissue edema, most strikingly in the lung, and this fact has been used to justify its use for burn patients who may be fibronectin depleted [31]. Studies in sheep demonstrate the effectiveness of this approach [12], and single case studies even go so far as to suggest that the beneficial effect of cryoprecipitate in amniotic fluid embolism is due to its fibronectin content [30]. A second activity of fibronectin, that of enhancing reticuloendothelial endocytosis has been established [14]. In light of the fact that septic patients are fibronectin deficient, attempts have been made to resore this protein by infusing cryoprecipitate. Results so far are not encouraging [11], but further study will help establish which clinical circumstances, if any, appropriately mandate its use.
REFERENCES

16) Lane, S. (1840) "Hemorrhagic Diathesis: Successful Transfusion of Blood" Lancet 1 pp185-188.


