Comparison of cryoprecipitate and intermediate purity concentrate for the treatment of haemophilia

Cryoprecipitate offers comparative security of local supply for Haemophilia Centres and, until NHS concentrate became more widely available, the question of its efficiency was academic. During 1975 and 1976 this position was changed by the greater availability of commercial concentrates at a potency of 15-20 iu/ml and by attempts by the RTCs to reach targets for FFP production; it has been difficult for some RTCs simultaneously to maintain earlier levels of cryo-precipitate production, and the comparative returns of concentrate and cryo-precipitate are now an immediate issue.

I will put the view that intermediate purity concentrate should progressively replace all cryoprecipitate, and that planning for the provision of factor VIII should reflect only temporary acceptance of cryoprecipitate as a second-rate therapeutic material. Cryoprecipitate cannot compete with concentrate in safety, reliability, or convenience for the patient, and claims that it is cheaper or more economical of plasma resources have doubtful validity.

Haemophilia Centres use more than half their supply of factor VIII for treatment of minor bleeds, at home or at the Centre, and using a dosage of about 5 iu/kg. It is generally conceded that surgical cases should be accorded priority where higher potency concentrates are in limited supply. The debate is therefore largely about the relative merits of cryoprecipitate and concentrate for self-administration or brief out-patient treatment at Haemophilia Centres.

1. Stability

Concentrate may be kept for one year at +5° and transported at normal temperature; cryoprecipitate must be kept below -30°, even during transport, and is considered to have a storage life of one to three months.

2. Wastage

There is therefore little overall wastage of concentrate by loss of potency during storage and transport or by outdating, whereas all these sources of waste are already significant in treatment centres using cryoprecipitate, and would become more severe if cryoprecipitate were widely used for home treatment.

3. Dose preparation

Even if cryoprecipitate is redissolved at the RTC or Haemophilia Centre, and even if the work is simplified by the use of pooling sets, reconstitution and pooling of cryoprecipitate is time-consuming and wasteful. Few studies have convincingly illustrated how much cryoprecipitate factor VIII reaches the patient. Concentrates should dissolve and be ready for injection within 15 minutes and incur less loss in solution by virtue of a higher volume/surface area ratio and more accessible containers.

4. Potency

The potency and purity of normal 8IP concentrate and cryoprecipitate are similar, but 8IP should give way in 1977 to a more potent concentrate containing approximately 15 iu/ml, sufficient for virtually all uses, including surgery, and possibly near the best compromise between potency and wastage.

5. Hepatitis risk

Concentrates made from large pools of plasma carry a greater risk of transmitting hepatitis B than does cryoprecipitate. For severe haemophiliacs, this increased risk can be minimised by careful allocation of batches, and improvements are likely as a result of more effective screening of donations and the replacement of the anonymous professional donor with the UK voluntary donor as the major source of plasma for factor VIII.

6. Quality control

Although clinicians tend to take for granted the safety and consistency of clinical materials, the reassurance of a quality controlled concentrate must be accorded a definite value. How many units of cryoprecipitate are contaminated with bacteria, pyrogenic or carry a high concentration of blood group antibodies or immunogens? How often is the residue available for investigation of unwanted side effects? How easy is it to determine whether an unwanted reaction is related to an idiosyncrasy of the patient or the dose? How promptly can a clinician distinguish a poor haemostatic response from a poor dose of cryo-precipitate? Unless local availability (a logistic matter) or hepatitis risk

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are accorded overwhelming weight, concentrate must be seen by the patient and the clinician to be preferable to cryoprecipitate.

7. Economy of plasma resources

Before freezing and storage, cryoprecipitate made with constant attention from carefully collected plasma can probably yield about 70% of the activity present in the original plasma. The proportion of factor VIII received by the patient is usually much less than this for the following reasons:

(i) Most of the cryoprecipitate in the UK is made in large quantities by inadequately trained, motivated and supervised staff, without continuing quality control. Specification and maintenance of refrigeration and other equipment is seldom in the hands of engineers. The level of investment in partially automated equipment to standardise freezing, thawing and pooling is inconsistent with the high value of the product.

(ii) Losses occur during frozen storage of cryoprecipitate. —

(iii) Re-solution and pooling of several cryoprecipitates is inherently wasteful, and must frequently be done hastily in the home, Haemophilia Centre or hospital ward.

As a result of these losses, most producers can claim average yield of only 60-80 "units" per "donation" of plasma. The bibliography of claims and counter-claims about the factor VIII yield of cryoprecipitate would itself occupy several pages and be almost worthless outside a specific context of plasma collection, volume of production and pattern of use. The recent spot-check on a dozen cryoprecipitates from each RTC probably over-estimated the amount of factor VIII reaching the average patient, since re-solution was more scrupulous and there was less pooling loss. The mean "yield" of frozen cryoprecipitate was 375 iu/kg, of which 300-350 iu/kg might reach the patient. This compares with 220-250 iu/kg which would reach the patient as intermediate-purity concentrate

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from plasma collected in the same way but pooled (usually from much "older" plasma) in 5 l packs and sent to fractionation centres. Allowing about 5.5 donations per litre, the common dose of 250 iu of factor VIII might therefore be expected to be derived from about four donations of cryoprecipitate or about six donations as concentrate.

In real life, however, the same kind of bleeding episode seems to be treated either with 250 iu concentrate or a 6-8 donation pool of cryoprecipitate. This could mean that the average amount of factor VIII delivered to the patient as cryoprecipitate is indeed significantly less than that expected from assay of frozen packs, or that the range of factor VIII yield from cryoprecipitate is so great that a 50% excess has to be used to ensure the desired effect most of the time. In either case, the "50% extra" cryoprecipitate will seldom give more effective protection, in the context of a single minor bleed, than a rival 250 iu dose of concentrate. The two materials become approximately equal in plasma economy.

8. Financial cost

Given six packs of fresh, centrifuged blood, what are the relative costs of preparing equally effective doses of 250 iu concentrate and six-donor pools of cryoprecipitate? Some of the identifiable stages and costs of cryoprecipitate production are:

(a) Separating plasma into satellite packs, and the cost of the packs (six satellite packs per six donations).

(b) Capital and running costs of e.g. Cardice-ethanol bath, or mechnical refrigeration.

(c) Recording data, including blood groups, of individual packs.

(d) Freezing, thawing, centrifuging and separation of individual packs to prepare single cryoprecipitates.

(e) Filing individual packs systematically, storing below -30°, maintaining inventory, rotation and issue records.

(f) (Optional at RTC) Pooling of cryoprecipitates on demand, and the cost of pooling equipment. Alternatively this cost of equipment is borne at the Haemophilia Centre, and the preparation absorbs the time of medically qualified staff (or nursing staff at "Sister" level).

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After stage (d) the cryosupernatant must be discarded, expressed back on to the sedimented red cells or pooled into 5 l packs for central fractionation to IgG and albumin. The first option results in the waste of valuable resources and should not be permitted on any grounds. The second option is inconsistent with the aims of modern component therapy; allows the return of only a proportion of the plasma in outdated form, suitable only for recovery of albumin; and cannot be easier to organise than pooling into 5 l packs. The latter option should be the only acceptable one in normal transfusion practice. The costs of pooling cryosupernatant into 5 l packs include:

(g) Separating the plasma into 5 l packs, and the cost of the packs (0.25 packs per six donations).

(h) Capital and running costs of Grant freezers (using a maximum of one freezer/2000 l FFP/year).

(j) Recording pack details for despatch, etc.

(k) Wrapping packs and storing below -30°, and frozen transport of packs.

If instead of preparing cryoprecipitate, the RTC sends equivalent fresh frozen plasma in 5 l packs for central fractionation to factor VIII and factor IX concentrates, IgG and albumin, the costs to the RTC are only (g) to (k) above. In any case, these costs would be incurred on a proportion of the plasma when it was recovered from out-dated blood for albumin production.

Costs incurred by RTCs under (a) to (f) should be compared directly with the costs to BPL and PFL of central fractionation to freeze dried factor VIII concentrate.

<u>The option of freeze dried cryoprecipitate</u>

Several European Red Cross laboratories prepare two to eight-donor freeze dried cryoprecipitate at fractionation centres incorporating blood collection facilities. The aim is to standardise cryoprecipitate production as far as possible, prepare a more stable concentrate not requiring frozen storage and to introduce an element of quality control. They expect a mean yield exceeding 300 iu/kg plasma.

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Production of cryoprecipitate at a blood processing centre eliminates some pooling and transport costs borne by our RTCs or Haemophilia Centres, and there are certain economies in pooling donations for cryoprecipitate at an early stage. Against this, equipment for aseptic transfer must be assembled and sterilised (or purchased) and a large number of aseptic transfers completed successfully. The degree of product control exercised is variable but is inferior to quality control on batches of concentrate in two major respects:

(i) For most purposes, samples from a batch of concentrate dispensed from a single large pool may be regarded as representative of the entire batch. A sample from one of many small pools prepared in one session cannot represent the products of the session in the same way. Tests e.g. for factor VIII potency or sterility do not yield the same information when carried out on 1% of a homogeneous batch as on one out of 100 separately prepared doses.

(ii) The "overdosage" waste resulting from large dose to dose variation is analogous to that of frozen cryoprecipitate.

These drawbacks are obviously reduced as the number of donations of plasma pooled is increased. In principle, many hundreds of aseptically prepared and redissolved cryoprecipitates may be pooled and dispensed into small doses, yielding quality control benefits comparable to those obtained with freeze dried concentrates. Historically, the losses and risks of large scale aseptic handling have led to its replacement with "clean" techniques and terminal sterilisation by filtration. The losses of factor VIII incurred during such a lengthy procedure cannot be expected to be less than those of processing to intermediate-purity concentrate, which includes a stabilising stage. In the last six-month period, the losses of factor VIII activity in intermediate-purity concentrate production between re-solution of cryoprecipitate and re-solution of the freeze dried product were only 14%, including 3% during filtration and 5% during freeze drying; a further 6% was lost in sampling for quality control.

The options of frozen small-pool cryoprecipitate, dried small-pool cryo-precipitate, dried large-pool cryoprecipitate and dried sterilised concentrate

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form an orderly progression in the following respects:

(a) Increasing demand on centralised plasma procurement policy, fractionation facilities and specialised skills.

(b) Decreasing process yield of factor VIII, although not necessarily decreasing effective yields to patients.

(c) Increasing standardisation of product, leading to economies.

(d) Increasing confidence in safety and efficacy of the product.

Neither the RTCs nor the Fractionation Centres are comfortable with both whole blood and plasma processing, e.g. there is no establishment in the tradition of a "Central Laboratory" dealing with all aspects of blood economy in the UK. In particular, most RTCs lack the scientific and engineering skills required to specify and maintain the procedures and equipment which might make the expedient of cryoprecipitate economically attractive for a limited period.

Any process based on pooling of single donor cryoprecipitates must be based on an RTC, but it would be uneconomic to equip every centre with accommodation, services and the following plant:

Safe equipment for control of freezing of plasma in PVC bags.

Thawing equipment for single donations of plasma.

Freezing and freeze drying plant for large vials or bottles.

The capital cost of equipping even five RTCs would not be less than £250,000 and it is not obvious how the geographical responsibilities of the RTCs could be reconciled with such selectivity. In addition to running costs (listed above) for the production of single donor cryoprecipitates, the annual cost of operating drying plant and appropriate quality control would be of the order of £10,000 per centre. The investment of such sums to produce a single inadequate product would divert resources from fractionation centres and divert attention from closely related problems of supplying other plasma fractions, notably PPF. Compromise programmes featuring small-pool or large-pool dried ~~cryoprecipitate~~ cannot therefore be recommended to the NBTS.

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