Cryoprecipitate versus commercial fibrinogen concentrate in patients who occasionally require a therapeutic supply of fibrinogen: risk comparison in the case of an emerging transfusion-transmitted infection

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ABSTRACT

A probabilistic model was used to compare cryoprecipitate to viral inactivated, commercial fibrinogen concentrate to evaluate with regard to the recipient's risk of exposure to an emergent AIDS-like epidemic. In patients who occasionally need a therapeutic dose of fibrinogen, commercial fibrinogen would be marginally safer than cryoprecipitate if the new pathogen were sensitive to inactivation. But there is a potential high risk of exposure if the emerging agent withstands inactivation. In most of the analyzed scenarios, cryoprecipitate is safer than commercial fibrinogen as long as the odds that the new agent is sensitive to inactivation are lower than 1.000 to 1.

Key words: transfusion, cryoprecipitate, fibrinogen, infection, risk.

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Transfusion of cryoprecipitate is controversial because of the risk it poses due to lack of viral inactivation and the availability of alternative, viral inactivated, commercial coagulation factor concentrates. On the one hand, although the risk for transfusion-transmitted HIV, HBV and HCV has fallen to negligible levels[1] and cryoprecipitate can be made from quarantined plasma, which makes it safe against these viruses,[2] it still poses the threat of exposing recipients to any emerging infectious agent that could enter into the blood supply. On the other hand, commercial factor concentrates are manufactured from plasma pools that include several tens of thousands of individual donors. This means they have the potential to spread any infectious agent present in just a few donors if the agent can pass the pre-donation screening undetected and withstand the inactivation procedure.[3,4]

Mathematical models show that multiple independent infusions of plasma products, as in the case of patients with congenital coagulation factor deficiency, raises the lifetime risk of exposure to nearly 100%, even when pools are made from only a few donors each.[3] This has led some authors to discourage the use of cryoprecipitate in patients with mild hemophilia,[5] von Willebrand disease[6] or congenital afibrinogenemia,[7] and to rely instead on viral inactivated, commercial factor concentrates. At present, however, most cryoprecipitate is used as a therapeutic supply of fibrinogen in patients with hemorrhage and acquired fibrinogen deficiency because of DIC, transient hyperfibrinolysis, massive transfusion or severe liver failure. In most such patients, transfusion of cryoprecipitate is a once-in-a-lifetime event, so that the criterion for choosing between cryoprecipitate and commercial fibrinogen must be different from that applied to chronic transfusion. To help decide which product should be used in these patients, we compared cryoprecipitate to commercial fibrinogen to evaluate and quantify exposure to a hypothetical, emerging transfusion transmitted agent.

Design and Methods

We modeled a 15-year period over which hypothetical cohorts of 10,000 patients per year who require a single dose of fibrinogen are given either a 2-gram infusion of commercial fibrinogen or a 10-unit pool of cryo-

precipitate. In the reference-case, we assumed that each lot of commercial fibrinogen is made up of 30,000 plasma donors (range 1,000–75,000 in sensitivity analyses) and provides 2,000 therapeutic doses (range 67–5,000).

A hypothetical scenario involving an emerging, AIDS-like epidemic was simulated. The likelihood of collecting an infectious plasma donation was modeled according to the estimates by Busch *et al.*[8] for the San Francisco area in the late 1970's and early 1980's with two modifications: annual risk figures were reduced by 100-fold to make them comparable to the incidence rates that were observed in most western countries, and time was compressed so that the whole epidemic unfolds over a 5-year period. The probability of such an AIDS-like epidemic arising anytime over the next 15 years was assumed to range between 0.0001 and 0.1 *per annum* (Figure 1).

The probability that a lot of commercial fibrinogen or a pool of cryoprecipitate harbored at least one infectious donation was $pL = 1 - (1 - p)^n$, where p is the risk of collecting an infectious donation and n is the number of different donors included in the lot or pool. The number of contaminated lots or pools in any year over the 15-year period was modeled by extracting random integers from a binomial distribution, $B(nL,pL)$, where nL is the number of different lots of commercial fibrinogen or pools of cryoprecipitate used each year. As the demand for commercial fibrinogen was fixed at 10,000 doses per year, the smaller the lot size, the greater the number of different lots that needed to be manufactured each year. The model was run on Excel spreadsheets and the @Risk add-in (*www.palisade.com*) was used to generate the random variates. Results were the mean of 10 simulations with 10,000 iterations each.

Results and Discussion

In the reference-case, and assuming that the emergent pathogen is sensitive to inactivation, 2.4 out of 150,000 patients transfused with cryoprecipitate are exposed to the new agent. If the new agent is assumed to withstand inactivation, the magnitude of exposure is nearly 1,000-fold higher in patients infused with commercial fibrinogen than in those transfused with cryoprecipitate (Table 1). This difference is maintained over the whole range of probabilities of emergence of the new agent (*data not shown*). Figure 2 shows the magnitude of exposure according to the size of the plasma pool from which commercial fibrinogen is made. Under the assumption that the new infectious agent withstands inactivation, the number of patients exposed though commercial fibrinogen increases steeply by one order of magnitude as the size of the plasma pool grows from 1,000 to about 15,000 donors, and continues to rise more steadily thereafter. In response to raised concerns about the large pool

Table 1. Magnitude of exposure to an emerging pathogen through cryoprecipitate or viral inactivate, commercial fibrinogen concentrate in the reference-case.

	Commercial fibrinogen concentrate		*Cryoprecipitate*	
Sensitivity of the new agent to inactivation	*No. Patients*	*Risk per patient*	*No. Patients*	*Risk per patient*
Sensitive	0	0	2.40	0.000016
Resistant	2,217	0.015	2.40	0.000016

Over a period of 15 years, 150,000 hypothetical patients received a single dose of either cryoprecipitate pooled from 10 donors or commercial fibrinogen concentrate made up from 30,000 donors. The probability of emergence of the AIDS-like epidemics was assumed to be 0.01 per year.

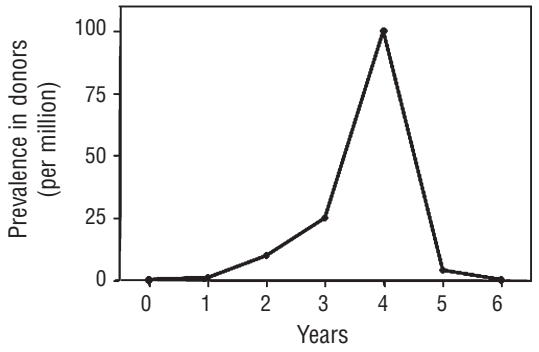

Figure 1. Simulated epidemic of an AIDS-like transfusion-transmitted infection in blood and plasma donors. The epidemic may emerge at any time over the 15-year period according to an assumed annual probability. After the outbreak, the epidemic unfolds autonomously and does not reappear within the same 15-year period.

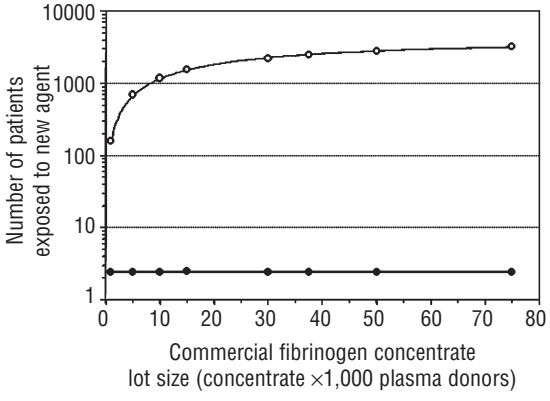

Figure 2. Magnitude of exposure in recipients to an emergent pathogen according to the number of plasma donors included in each lot of commercial fibrinogen concentrate. Cryoprecipitate (filled circles) is compared to commercial fibrinogen (open circles) under the assumption that the new agent withstands inactivation. If the new agent is sensitive to inactivation, there will be no exposure through commercial fibrinogen.

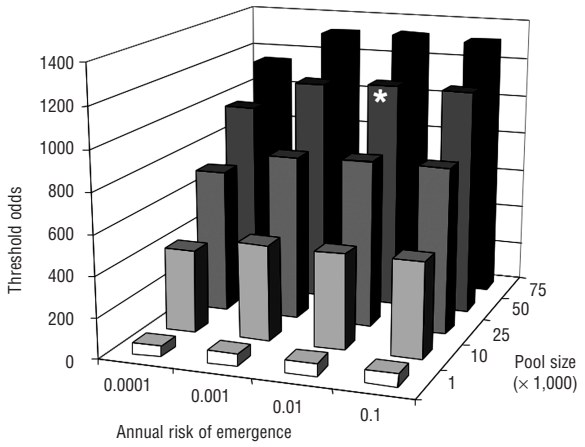

Figure 3. Threshold odds for the new agent's sensitivity to inactivation that makes the number of patients exposed though commercial fibrinogen concentrate equal to the number exposed through cryoprecipitate.

sizes involved in the manufacture of commercial factor concentrates, major plasma fractionators have voluntarily committed to limit pool size to 60,000 donors.[4] The above results, however, show that this measure will have little effect on the magnitude of exposure to emerging pathogens that withstand inactivation unless the pool size is decreased to below 15,000 donors, a degree of reduction that is probably unrealistic given the economic constraints. Indeed, the main reason for large fractionation pools is to reduce production costs by exploiting economies of scale and scope during the manufacture of plasma derivatives. Consequently, smaller pools would translate into a reduced supply and higher selling prices not only for commercial fibrinogen but also for other plasma-derived medicinal products.

A critical factor which must be taken into account when evaluating the relative protection provided by commercial fibrinogen or cryoprecipitate is the likelihood that the new agent is sensitive to viral inactivation. Sensitivity to inactivation would make commercial fibrinogen safe, but not cryoprecipitate. We can, therefore, calculate the threshold odds for the new agent to be inactivated that could make commercial fibrinogen equivalent to cryoprecipitate as far as the number of exposed patients is concerned. Such threshold odds can be represented by the quotient of the proportion of patients that would be exposed through commercial fibrinogen if the new pathogen withstood inactivation to the proportion of patients exposed though cryoprecipitate if the pathogen were sensitive to inactivation. Figure 3 shows the threshold odds for several assumptions on the annual risk of emergence of the new agent and the size of the plasma pool from which commercial fibrinogen is made. For instance, for a plasma pool of 50,000 donors and an annual risk of emergence of 0.01, the estimated value for the threshold odds is 1,120 to 1 (asterisk). This means that commercial fibrinogen is a safer choice than cryoprecipitate only if we assume that the odds for the new pathogen to be sensitive to inactivation are 1,120 to 1 or higher. There is little evidence to support this assumption. The genera enterovirus, parvovirus, circovirus and polyomavirus, all of which have been identified as potential threats to the safety of the blood supply, are very resistant to the current inactivation procedures.[9] Emerging retroviruses are also of great concern to the safety of the blood supply.[10] Though retroviruses bear lipid envelopes and are therefore sensitive to physicochemical inactivation, an emerging agent for which, for the moment, there is no laboratory screening assay, might reach a concentration in donor plasma so high as to overcome the capacity of the inactivation procedures. For instance, plasma levels as high as 10^9 RNA copies/mL have been found in experimental infections with a chimeric simian-human immunodeficiency virus.[11] Also, prions, which are the paradigm of a previously unknown infectious agent, cannot be routinely screened in donors and are insensitive to the inactivation procedures currently used in the manufacture of plasma derivatives.

It should be noted that we analyzed risk of exposure rather than risk of infection. The latter depends on other variables in addition to exposure, such as the infectiveness of the agent, its quantity in the final product, whether it is inactivated or attenuated during manufacturing, and the susceptibility of the recipient population.[3] Since all these variables are specific for the agent in question, and the present analysis deals with a hypothetical, unknown emerging pathogen, we made no attempt to further characterize risk of infection once the agent is assumed to withstand the inactivation process. Anyway, risk of infection would always be less than risk of exposure.

Instead of using the more traditional model that represents an already established blood-borne infection,[3,5] we modeled an AIDS-like epidemic that may or may not unfold anytime over the coming years. This modeling approach allows any external knowledge on the risk of emergence of a new pathogen to be incorporated into the decision-making in addition to the *best guess* on the likelihood that it withstands inactivation. For instance, under the belief that risk of emergence is high, the main factor in deciding between cryoprecipitate and commercial fibrinogen is the estimated likelihood that the emerging agent will be sensitive to inactivation. In contrast to what is commonly thought, our results show that cryoprecipitate would be the safer alternative unless this likelihood was almost certain.

Conflict of Interest

The author reported no potential conflicts of interest.

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ERRATA CORRIGE

On Haematologica 2006; 91(suppl 4):192-3, we published the article "Fatigue:è un problema per gli adolescenti affetti da patologia onco-ematologica?" with a wrong list of authors. Correct article is now published below.

FATIGUE: È UN PROBLEMA PER GLI ADOLESCENTI AFFETTI DA PATOLOGIA ONCO-EMATOLOGICA?

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La fatigue cancro-correlata è un fenomeno multidisciplinare ed intrinsecamente soggettivo. È un complesso di sintomi che si sviluppa nel tempo nei pazienti oncologici ed ha ripercussioni negative e drammatiche sulla vita dei malati, compromettendone l'energia fisica (sensazione di stanchezza e debolezza malgrado il dovuto riposo), le capacità mentali e le condizioni psicologiche nonché relazionali. Benché l'orientamento dell'équipe oncologica si stia indirizzando verso una visione sempre più olistica, ancora poco si parla della fatigue cancro-correlata, soprattutto per quanto riguarda l'ambito pediatrico oncologico e nello specifico all'età adolescenziale. Occorre dunque indagare per scoprire se e quanto tale problema sia percepito dagli adolescenti affetti da cancro. L'obiettivo della ricerca è: indagare il percepito del sintomo fatigue in un campione di pazienti in età adolescenziale affetti da patologia onco-ematologica e sottoposti a trattamento polichemioterapico.

Disegno dello studio. Studio osservazionale di prevalenza.

Dati.(Metodologia di raccolta, dati raccolti, analisi, con specifica degli strumenti statistici ulizzati). Per questo studio il punto di partenza è stato una revisione della bibliografia (PUBMED, CINHAL) che ha permesso di conoscere lo stato dell'arte nazionale ed internazionale rispetto all'argomento (dalla quale è stato tratto per la formulazione dell'obiettivo) e per la scelta dello strumento d'indagine (*Revised Piper Fatigue Scale*).

Le caratteristiche del campione sono state: pazienti affetti da patologia onco-ematologica, con diagnosi tumorale certa, di età compresa tra i 10 ed i 20 anni, ricoverati per trattamento polichemioterapico. In totale sono stati consegnati e raccolti 11 questionari pazienti in regime di ricovero nel reparto di Degenza di Pediatria Onco-ematologica dell'Ospedale Infantile Regina Margherita di Torino. Il periodo osservazione è andato dal 01/10/04 al 30/11/04.

Conclusioni. Dall'analisi dei dati ottenuti si può dire che il fenomeno fatigue è percepito dagli adolescenti affetti da patologia tumorale in corso di trattamento polichemioterapico. È risultato essere un sintomo che si manifesta maggiormente nella prima parte della giornata (mattino e primo pomeriggio) con un'intensità media ed una frequenza associabile alla definizione *qualche volta*. La fatigue è definita dai ragazzi come *debolezza e mancanza di forza*, definizioni sovrapponibili a quelle riscontrate in letteratura. L'instaurarsi della fatigue coincide con l'inizio dei cicli chemioterapici, motivo per cui, tra i fattori citati quali cause scatenanti, tutti i ragazzi hanno menzionato le terapie e ciò che ne consegue (aplasia, ripetuti ricoveri, trasfusioni, ecc…). La fatigue interferisce solo in parte sulla sfera cognitiva (capacità di concentrazione, di ragionamento e sulla memoria) ed interferisce maggiormente sulla sfera emotiva (sull'umore, sulla tensione e sulla noia). Pare inoltre che la correlazione tra fatigue e capacità di socializzazione sia praticamente inesistente; vi è correlazione, seppur non eccessiva, con la capacità di completare le attività scolastiche. Per la riduzione del senso di stanchezza i ragazzi ricorrono al riposo, all'aumento delle ore di sonno e alla riduzione delle attività fisiche. Si tratta in ogni caso di provvedimenti suggeriti dall'ambito famigliare e non dall'équipe medico infermieristica. Questo lavoro di ricerca ha permesso di iniziare a comprenderequanto il fenomeno fatigue sia presente negli adolescenti. Ha concesso di indagare su nuovi aspetti della sfera personale dei pazienti, dando la possibilità di poter migliorare il ruolo dell'équipe oncologica orientata sempre più verso un approccio olistico.

Eventuali proposte, problemi aperti. Il periodo e il numero di pazienti osservati è esiguo e i risultati suggeriscono l'utilità di continuare ad osservare ed analizzare il fenomeno della fatigue negli adolescenti.