

Cost-effectiveness of solvent/detergent-treated fresh-frozen plasma

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Vox Sanguinis

Background and Objectives Although transfusion-transmitted infections are rare, non-infectious complications occur relatively frequently. Solvent/detergent-treated fresh-frozen plasma (SD-FFP) has been shown to reduce the frequency of both types of complication, although previous economic evaluations failed to consider non-infective events and subsequently underestimated the benefits of SD-FFP.

Materials and Methods A time-series analytical model was used to estimate the incremental cost/life year saved for SD-FFP compared with untreated FFP, having controlled for post-transfusion mortality and patient age. Various infective and non-infective transfusion-related complications were considered.

Results The discounted cost/life year saved for SD-FFP use in the UK was £22 728 [95% confidence interval (95% CI): £22 604–22 853] for neonates and £98 465 (95% CI: £97 924–99 005) for patients aged 70. The cost-effectiveness ratio was below £50 000/life year saved for patients ≤ 48 years of age, and below £30 000/life year saved for those ≤ 21 years of age. In transfusion recipients with no significant morbidity, the cost-effectiveness ratio was £12 335 for neonates and £61 692 for 70-year olds. The most important driver of cost-effectiveness was transfusion-related acute lung injury (TRALI), on account of its relatively high incidence and mortality rate.

Conclusions Previous analyses greatly underestimated the cost-effectiveness of SD-FFP. Inclusion of non-infectious complications suggests that SD-FFP is cost-effective in patients ≤ 48 years of age and in older patients with good clinical prognosis, which may justify the wider use of this technology.

Key words: cost-effectiveness analysis, fresh-frozen plasma, solvent/detergent-treated fresh-frozen plasma, transfusion reactions.

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Introduction

Plasma transfusion is an effective and generally well-tolerated treatment for microvascular bleeding in patients with coagulation deficiencies, although a proportion of patients experience adverse effects, some of which can be fatal. The incidence of transfusion-related complications may be underestimated owing to the under-reporting of incidents

and a tendency to overlook non-infectious adverse events [1,2].

Solvent/detergent-treated fresh-frozen plasma (SD-FFP) [3] is an alternative to untreated fresh-frozen plasma (FFP), which virtually eliminates the risk of transmission of enveloped viruses, such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) [4,5]. Other manufacturing processes involved in the production of SD-FFP reduce the risk of bacterial contamination and non-infectious complications, such as transfusion-related acute lung injury (TRALI) and non-haemolytic febrile reactions [3,6].

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Several studies have assessed the cost-effectiveness of SD-FFP, producing a wide range of cost/quality-adjusted life year (QALY) estimates (\$289 000 [7], \$2 156 000 [8] and \$9 743 000 [9]), which suggest that the increased safety of SD-FFP does not justify its additional cost. However, these studies considered only rare infective complications (HIV, HBV and HCV) and ignored several relatively common non-infective events. These include TRALI – a life-threatening condition characterised by pulmonary oedema occurring within 6 h of transfusion [10,11]. The incidence of TRALI is ≈ 0.02–0.05% per plasma-containing unit transfused [1,12–14]. It is associated with a 5–14% mortality rate [10,12,15–17] and is also costly to treat, as patients require intensive care treatment for 2–7 days [10,11,18].

In this study, the cost-effectiveness of SD-FFP was evaluated using a comprehensive and robust economic model, which incorporated the relative risks, costs and mortality rates associated with transfusion-related complications. Unlike previous studies, we considered both infective and non-infective conditions.

Methods

Description of the model and cost-effectiveness calculations

The life expectancy of hypothetical patients aged up to 70 years was evaluated using a simple decision-tree time-series model. In one arm of the model, patients received FFP, while SD-FFP was administered in the other. A proportion of the patients in each arm experienced a transfusion-related adverse event (Fig. 1): the probability of these events differed between the two treatment groups, as indicated by the literature. For each event, short- and long-term costs were accrued and any associated mortality was applied.

As there was insufficient utility data relating to transfusion-related adverse events to conduct a cost/QALY analysis, we calculated the cost/life year saved (LYS) using the formula below:

$$\text{Cost/LYS} = \frac{[(\text{incremental cost of SD-FFP}) - (\text{costs saved by avoiding events})]}{[(\text{life years of FFP recipients}) - (\text{life years of SD-FFP recipients})]}$$

The analysis was performed from a health service budget perspective.

Data sources

The incremental cost of SD-FFP was calculated by subtracting the cost of FFP (UK National Health Service, Blood Transfusion Service 2002–3 list price, £20.72 per unit) from the cost of Octaplas® (Octapharma, average UK selling price, £46.30 per unit), indicating an incremental cost of £25.58 per unit.

The high mortality of transfusion recipients had to be taken into account, as patients who die soon after transfusion would not lose any life years if they contracted hepatitis or HIV. Post-transfusion mortality was modelled using the weighted average of three population cohort studies [19–21], which indicated that 22.8% of transfusion recipients would die within 1 year following transfusion, 27.7% within 2 years, 34.1% within 5 years and 52.0% within 10 years. Patients who survived for 10 years after transfusion were assumed to have the normal life expectancy for their age (UK 1999 figures [22]). Adverse event-specific mortality rates or life expectancies appropriate to each complication were applied to the patients experiencing transfusion-related complications (Table 1) in addition to the post-transfusion mortality rates applied to all patients. A separate sensitivity analysis was undertaken to assess the cost-effectiveness of SD-FFP in patients with good prognosis at the point of transfusion. In this analysis, it was assumed that all patients experienced a

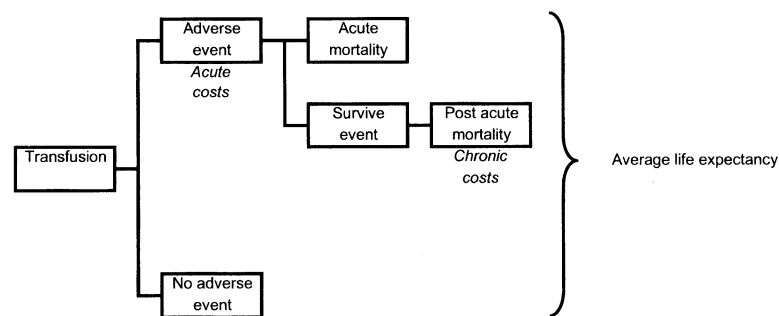


Fig. 1 Decision-tree model used to evaluate the cost-effectiveness of solvent/detergent-treated fresh-frozen plasma (SD-FFP). A proportion of patients undergoing transfusion will experience adverse events, such as transfusion-related acute lung injury (TRALI) or human immunodeficiency virus (HIV) and will therefore incur additional costs and mortality either immediately or over a period of several years. Those who survive the acute incident will experience mortality as a result of their underlying condition or age. It is assumed that only those who survive for longer than 10 years lose life years as a result of HIV or hepatitis. For simplicity, only one such event is illustrated.

Table 1 Incidence, costs and mortality associated with transfusion reactions

	TRALI		HIV		Hepatitis B		Hepatitis C	
	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.
No units transfused for one event	5000 [1,12-14]	2000 [12]	2 778 000 [46,47]	202 000 [46,47]	200 000 [46-49]	20 000 [46-49]	625 000 [46]	312 500 [46]
Reduction in risk with SD-FFP	100% ^a	100% ^a	100% [4,5]	100% [4,5]	100% [4,5]	100% [4,5]	100% [4,5]	100% [4,5]
Acute costs	£0	£6719	£0	£8630 [24]	£0	£1000 [27]	£0	£4800 [27]
Postacute costs	-	-	£0	£12 940 [8]	-	-	-	-
Costs in last year of life	-	-	£0	£54 670 [25]	-	-	-	-
Mortality - first year (%)	10% (± 20%) [10,12,15-17]	-	12 years (± 20%) [28]	0%	Reduced by 1.75 years (± 20%) [29]	0%	Reduced by 1.75 years (± 20%) [29]	0%
Life expectancy for those surviving to 10 years	Normal	-	-	-	-	-	-	-

The mortality rate for transfusion-related acute lung injury (TRALI) was varied by ±20% of the baseline value during the probabilistic analysis, as was the life expectancy for those infected with human immunodeficiency virus (HIV) and the reduction in life expectancy caused by hepatitis.

^aNo confirmed cases of TRALI have been observed following transfusion of more than 3 000 000 Octaplas[®] units.

normal life expectancy unless they incurred a life-threatening post-transfusion complication.

To ensure robust results, a probabilistic analysis (Monte Carlo technique) was performed, whereby the incidence and costs associated with each event were allocated minimum and maximum values based on the literature (Table 1). The model generated random data points between these minimum and maximum values (assuming a rectangular distribution) and analysed 10 000 combinations of variations to calculate mean values, standard deviations and confidence intervals.

Recurring annual costs were allocated for each year of survival. Acute and recurring costs were based on either published UK cost surveys or published studies. The minimum value for all costs was set to zero to encompass patients who would not incur any extra costs as a result of the transfusion-related complication - for example dying shortly after transfusion as a result of their underlying condition. The maximum cost of TRALI was based on 80% of patients requiring 3 days of intensive care (at a cost of £1193/day [23]) and 20% needing 6 days [10,11]. Patients were also assumed to require an average of 10 additional days in a general hospital ward at a cost of £242 per day [23]. Annual costs of HIV were taken from published cost-analysis studies [24,25], converted from US dollars, at a rate of £0.65/dollar where applicable. All post-acute costs were increased by 3% per annum to account for inflation [26]. Hepatitis costs were based on interferon therapy alone [27].

The baseline mortality rate for TRALI (10% [10,12,15-17]) was varied by ±20% of its default value in order to obtain the adverse event-related mortality for each simulation. All people infected with HIV through transfusion with infected blood products who were still alive after 10 years were assumed to die 12 years after transfusion. This life expectancy (based on published studies [28]) was varied ±20% during probabilistic generation of simulations. Infection with hepatitis was assumed to take 1.75 years [29] (±20%) off the normal life expectancy of all those surviving for 10 years or more after transfusion.

As the SD virus-inactivation process removes virtually all risk of transmission of enveloped viruses [4,5], the risk of HIV, HBV and HCV was assumed to be zero in patients transfused exclusively with SD-FFP. We also assumed the risk of TRALI from SD-FFP to be zero, as data on > 3 000 000 units of Octaplas[®] identified no confirmed cases of the condition (Octapharma, data on file).

In line with current UK recommendations [30], health benefits and costs were discounted at a rate of 3.5%. An undiscounted analysis was also conducted for comparability.

Complications excluded from the model

There is evidence suggesting that the incidence of febrile and urticarial reactions, anaphylaxis and donor-derived bacterial

infection is lower for SD-FFP than for FFP [3,6]. One large observational study found no plasma-related adverse events among the recipients of 5064 units of SD-FFP [6]. However, in order to be as conservative as possible, SD-FFP was assumed to have no effect on the risk of febrile reactions, urticaria, anaphylaxis or bacterial infection.

Acute and delayed haemolytic reactions and post-transfusion purpura (PTP) were not considered, as there is little data comparing the relative risk for SD-FFP and FFP and as these complications are rarely caused by FFP [2]. Cytomegalovirus (CMV) and human T-cell lymphoma viruses (HTLV-I and HTLV-II) were not included in the model as these leucocyte-associated viruses are not thought to be transmissible by plasma [31–33]. The clinical significance of hepatitis G and transfusion-transmitted virus (TTV) is unknown [34,35], while the risk of transmission of malaria, babesiosis and Chagas' disease is very low in Europe and North America [31].

Creutzfeldt–Jacob disease (CJD) and variant Creutzfeldt–Jacob disease (vCJD) were excluded from the model as no case of transfusion-transmitted infection has been reported in humans to date [36]. Hepatitis A virus (HAV) was excluded owing to the low risk of transmission, while parvovirus B19 infection was omitted as the condition causes little or no mortality and as there is little data on the risk posed by FFP and SD-FFP [31].

The Pearson correlation coefficient (r) was used as an indicator of the significance of correlations, while the Student's independent sample t -test was used to test the difference between means.

Results

The discounted cost/LYS of SD-FFP in the UK was found to range from £22 728 for neonates to £98 465 for 70-year-old individuals (Table 2). Cost-effectiveness showed a significant correlation with patient age (Fig. 2, $r = 0.814$, $P < 0.01$). The cost/LYS remained below £50 000 for patients ≤ 49 years of age, and £30 000 for those ≤ 21 years of age. Not discounting future costs and outcomes had very little effect on cost-effectiveness ratios, reducing that for neonates by 4% (from £22 728 to £21 774) but having negligible impact on the cost-effectiveness ratios for older patients.

The average age for an FFP recipient is ≈ 65 years [8]. At this age, the cost-effectiveness ratio was £81 972 [95% confidence interval (95% CI): £81 521–82 423].

Sensitivity analyses

The Monte Carlo simulations underlying the analysis automatically considered all the scenarios that could occur within

Table 2 Main results: the mean incremental cost/life year saved (LYS) for solvent/detergent-treated fresh-frozen plasma (SD-FFP) is shown in addition to standard deviations (SD) and confidence intervals (CI)

Age (years)	0	20	30	50	60	70
Life expectancy (year)	77.8	58.4	48.7	29.9	21.2	13.7
<i>Baseline analysis with post-transfusion mortality</i>						
Discounted cost/LYS (costs and outcomes 3.5%)						
Mean (£)	22 728	29 653	34 548	53 154	70 181	98 465
Upper 95% CI (£)	22 853	29 815	34 740	53 444	70 563	99 005
Lower 95% CI (£)	22 604	29 491	34 355	52 863	69 799	97 924
SD (£)	6350	8281	9819	14 836	19 492	27 581
Undiscounted cost/LYS						
Mean (£)	21 774	28 760	33 907	52 651	70 247	98 512
Upper 95% CI (£)	21 895	28 920	34 095	52 938	70 631	99 055
Lower 95% CI (£)	21 654	28 600	33 718	52 363	69 862	97 970
SD (£)	6141	8156	9615	14 682	19 642	27 666
<i>Good prognosis analysis without post-transfusion mortality</i>						
Discounted cost/LYS (costs and outcomes 3.5%)						
Mean (£)	12 335	15 902	18 826	29 727	40 854	61 692
Upper 95% CI (£)	12 401	15 989	18 929	29 889	41 077	62 027
Lower 95% CI (£)	12 268	15 815	18 724	29 566	40 632	61 356
SD (£)	3385	4419	5223	8222	11 355	17 117
Undiscounted cost/LYS						
Mean (£)	10 976	14 729	17 581	28 678	40 014	61 057
Upper 95% CI (£)	11 037	14 810	17 679	28 835	40 234	61 387
Lower 95% CI (£)	10 916	14 647	17 483	28 520	39 795	60 728
SD (£)	3097	4170	5005	8032	11 178	16 811

Where indicated, costs and outcomes were both discounted at 3.5% per year. The baseline analysis considered post-transfusion mortality, while the 'good prognosis' analysis did not.

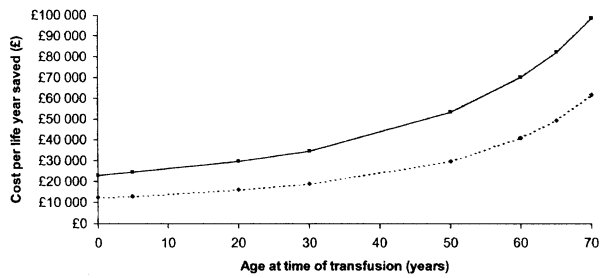


Fig. 2 Discounted cost/life year saved (LYS) by age of recipient, with and without adjustment for post-transfusion mortality. The solid line represents the baseline analysis in which post-transfusion mortality was considered, while the dotted line represents that for patients with good prognosis who experience no post-transfusion mortality except for that caused by transfusion-related complications.

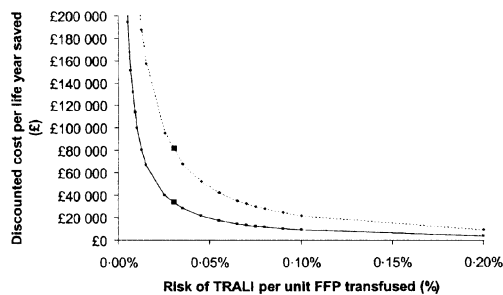


Fig. 3 Sensitivity analysis showing the effect of varying the incidence of transfusion-related acute lung injury (TRALI) on cost/life year saved (LYS) (discounted). The solid line represent patients aged 30 years, while the dotted line represent those aged 65. The baseline incidence of TRALI (1/3500) is indicated on each line by a larger black square.

specified limits. It should be noted that varying the cost of treating complications had little effect on cost-effectiveness estimates (data not shown).

The cost-effectiveness ratios for SD-FFP were significantly lower for patients with a good short-term prognosis who were likely to survive for as long as would be expected for their age ($P < 0.01$). For example, the cost/LYS for a 50-year-old patient was reduced by 44% (from £53 154 to £29 727) when the effect of post-transfusion mortality was removed. For a healthy 65-year-old patient with a good short-term prognosis, the cost/LYS was reduced to £49 157 (95% CI: £48 892–£49 422). In a further sensitivity analysis, in which 39% of patients were assumed to die in hospital, while the remainder survived to their usual life expectancy, the cost/LYS for all age groups, except for 70-year-old patients, was reduced by 2–16% (data not shown).

The cost/LYS was very sensitive to variations in the incidence of TRALI (Fig. 3). Altering the incidence or mortality of other complications had little effect on the cost/LYS: even

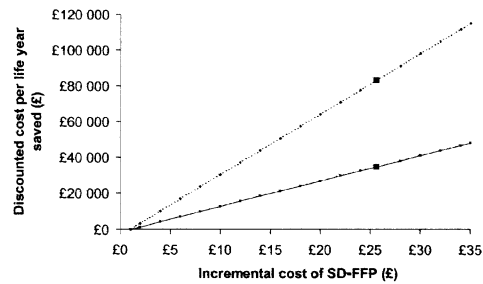


Fig. 4 Sensitivity analysis showing the effect of varying the incremental cost of solvent/detergent-treated fresh-frozen plasma (SD-FFP) on cost/life year saved (LYS) (discounted). The solid line represent patients aged 30 years, while the dotted line represent those aged 65. The baseline incremental cost of SD-FFP (£25.58) is indicated on each line by a larger black square.

when all complications other than TRALI were ignored, SD-FFP had a cost-effectiveness ratio of £35 714/LYS in 30-year-old patients (95% CI: £35 517–£35 911) and £86 624 in 65-year-old patients (95% CI: £86 141–£87 106), only 2.4–7.2% higher than the baseline ratios. The main cost element determining the cost/LYS was the cost of SD-FFP relative to FFP (Fig. 4).

Discussion

This analytical model demonstrates that when non-infectious transfusion-related complications are taken into account, SD-FFP has a cost/LYS of £22 700–£98 500 in the UK (depending upon the age of the recipient). This is substantially lower than the ratios estimated previously [7–9] by studies that ignored non-infectious events such as TRALI, which was the major driver of cost-effectiveness in our study. For patients aged 65 years (the median age of FFP recipients [8]) the cost-effectiveness ratio is £82 000/LYS. This ratio is highly sensitive to the life expectancy of the individual patient – for healthy 65-year-old patients, for example, the cost/LYS is reduced to £49 200.

It is generally accepted that a health technology is 'cost-effective' if it has a cost/QALY of less than £30 000–£50 000. However, the overall affordability of any health technology depends on political and ethical issues as well as clinical and economic ones. An example of this is leucodepletion, which became mandatory in the UK in 1999 to minimize the risk of vCJD transmission, despite cost increases of around £70 million/year and little supporting evidence [37]. Exceptions to the £30 000–£50 000 guideline are also made for technologies that have no acceptable alternative – particularly when the condition may lead to a high degree of patient dependency. Technologies safeguarding blood transfusion raise further ethical questions as the alternatives carry an indiscriminate risk of harming the patient. The cost-effectiveness ratios calculated for SD-FFP in the present report are lower than those

for many other preventative strategies, including autologous blood donation [25,38,39] and HCV nucleic acid amplification testing (NAT) [40].

If we take a value of £50 000/LYS as an 'acceptable' cost-effectiveness limit in this therapeutic context, our modelling suggests that SD-FFP is a cost-effective treatment for all patients aged 48 and under, and for older patients with good clinical prognosis. SD-FFP is most cost-effective in children, as a result of their long life expectancy. The prognosis for HBV infection in children is also much bleaker than that in adults – 90% of children infected develop a chronic infection and 40% of those develop cirrhosis [41]. Previous studies have also found cost-effectiveness ratios to be lower in younger recipients [7,8]. However, any policy recommending that different groups of patients (whether on the basis of age, predicted clinical prognosis or other criteria) should receive products with different perceived safety levels raises a number of logistical and medico-legal issues. In other situations in which an intervention is cost-effective for one age group, but not for another, policy has sometimes advised that the intervention should be given to all patients, regardless of age or prognosis.

At a national level, if all 375 000 units of FFP used in the UK each year [2] were replaced with SD-FFP, the total investment necessary would be £9.6 million/year. When the cost of treating transfusion-related complications is accounted for, this cost is reduced to around £9.2 million. This may have policy implications, as such an investment could prevent an estimated 107 cases of TRALI each year (375 000 units multiplied by an incidence of 1/3500 per unit: the midpoint between 1/2000 and 1/5000), saving around 11 lives, 386 intensive care bed-days and 1071 bed-days in general wards. It is acknowledged, however, that there is significant uncertainty surrounding the incidence of TRALI in the population, which makes any calculations of the possible benefits and cost-effectiveness of SD-FFP tentative. Our analysis may therefore have under- or overestimated the cost-effectiveness ratios. Further research on this condition is necessary to guide future clinical practice and pharmacoeconomic analysis.

As UK costs were used in this analysis, the cost-effectiveness ratios obtained are, primarily, country-specific. However, the sensitivity analysis showed that the most important cost variable driving the results was the incremental cost of SD-FFP. As the UK incremental price of this product is among the highest in the world, the cost/LYS in other countries would probably be lower than that determined by this analysis.

Although the cost-effectiveness ratios calculated in this study are lower than previously reported, this analysis was based on several conservative assumptions. Firstly, it was assumed that SD-FFP did not reduce the incidence of febrile, urticarial or anaphylactic reactions, although there is published evidence suggesting that SD-FFP does carry a reduced risk of these complications relative to untreated FFP [3,6].

Secondly, the cost of hepatitis included only drug costs for acute infection and took no account of treatment for chronic infections or resulting liver failure, which can cost as much as £30 000 per patient [29,42]. Similarly, the assumed incidence of TRALI is based on that for all blood products, although the risk may be higher for FFP than for packed red cells [1,12–14,43]. The model may also overestimate the mortality rate for young people, because a standard post-transfusion mortality was used for patients of all ages, although studies have shown that transfusion recipients < 40 years of age have substantially lower mortality rates than older patients [19,44].

Additionally, the actual UK cost of FFP may be higher than the purchase price, as a proportion of units sold will not be used before their expiry date. SD-FFP has a shelf life of 2 years compared with 1 year for FFP. The wastage that may arise from the shorter shelf life could increase the true cost of FFP, thereby reducing the incremental cost-effectiveness ratios for SD-FFP.

Finally, several transfusion-transmitted diseases were omitted because of a lack of data on pathogenicity and/or risk, including TTV, hepatitis G, malaria, babesiosis, HAV, parvovirus B19 and Chagas disease. Our present knowledge base makes it impossible to evaluate the economic impact of these diseases. This is particularly true for CJD and vCJD as the risk of transmission by blood transfusion remains theoretical. Such theoretical risks could have made the argument for using SD-FFP stronger or weaker, depending on whether the risk was found to be higher with FFP or with SD-FFP. Further research is required to assess the clinical risk and economic impact of these pathogens. Such research may also uncover other hitherto-unsuspected complications: a recent study has found an association between transplant rejection and antibodies transferred by previous blood transfusion [45].

Owing to a shortage of demographic data on FFP recipients, this study calculated the cost-effectiveness for different age groups separately, rather than assessing the overall cost-effectiveness for the population: a goal for future research would be to elucidate such demographic data and use it to model the entire transfused population.

As the information base relating to SD-FFP increases, further research will be necessary to re-evaluate its cost-effectiveness. In particular, consideration of other non-infectious complications may produce more favourable cost-effectiveness ratio estimates than those determined by this study.

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