ORIGINAL ARTICLE

Cost-effectiveness analysis of preoperative transfusion in patients with sickle cell disease using evidence from the TAPS trial

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Abstract

The study's objective was to assess the cost-effectiveness of preoperative transfusion compared with no preoperative transfusion in patients with sickle cell disease undergoing low- or medium-risk surgery. Seventy patients with sickle cell disease (HbSS/Sß^{0}thal genotypes) undergoing elective surgery participated in a multicentre randomised trial, Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS). Here, a cost-effectiveness analysis based on evidence from that trial is presented. A decision-analytic model is used to incorporate long-term consequences of transfusions and acute chest syndrome. Costs and health benefits, expressed as quality-adjusted life years (QALYs), are reported from the 'within-trial' analysis and for the decision-analytic model. The probability of cost-effectiveness for each form of management is calculated taking into account the small sample size and other sources of uncertainty. In the range of scenarios considered in the analysis, preoperative transfusion was more effective, with the mean improvement in QALYs ranging from 0.018 to 0.206 per patient, and also less costly in all but one scenario, with the mean cost difference ranging from −£813 to £26. All scenarios suggested preoperative transfusion had a probability of cost-effectiveness >0.79 at a cost-effectiveness threshold of £20 000 per QALY.

Patients with sickle cell disease (SCD) often require surgery, and peri-operative complications are common (1, 2). Preoperative blood transfusion has been associated with decreased peri-operative complications, but is also associated with increased acute transfusion reactions, alloimmunisation and delayed haemolytic transfusion reactions. Preoperative transfusions are usually given to patients undergoing high-risk surgery, but there is no consensus about the role of transfusion in patients undergoing low- or medium-risk surgery.

A multicentre randomised trial, Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS), was undertaken to assess whether routine preoperative transfusion increases or decreases the risk of peri-operative complications in patients undergoing low- or medium-risk surgery (3). The primary outcome was the proportion of patients with clinically important complications between randomisation and up to and including 30 d postsurgery. Complications were classified as related to SCD, infection, surgery or transfusion. Complications, which were life-threatening or resulted in death, permanent or severe disability, or other important medical outcomes, were also reported as serious adverse events (SAEs). A significant imbalance in SAEs resulted in early trial closure in March 2011.

This trial showed a statistically significant increase in complications, predominantly acute chest syndrome (ACS), in untransfused SCD patients having low- or medium-risk surgery. Although limited by early closure and a small number of participants, this evidence suggests that patients with SCD have better outcomes if they receive a blood transfusion before surgery. However, the published trial results do not weigh the positive short-term outcomes of transfusion vs. the risk of transfusion complications, nor do they consider the costs associated with the alternative forms of management.

Therefore, a cost-effectiveness analysis was undertaken to compare preoperative blood transfusion with no transfusion for patients with SCD (HbSS/Sß^{0}thal genotypes) undergoing low- or medium-risk elective surgery using data from the TAPS trial. The analysis incorporated the short-term costs and benefits, and long-term implications of transfusion complications.

Methods

Overview

The cost-effectiveness analysis was undertaken from the perspective of the UK National Health Service (NHS), with outcomes expressed as quality-adjusted life years (QALYs). Two linked analyses were undertaken. Firstly, a 'within-trial' analysis was undertaken which used trial resource-use and outcome data over a period of 1-year follow-up. Secondly, a decision-analytic model was used to extrapolate the estimated costs and outcomes over the longer term. In particular, the model was used to capture the prognostic implications of complications observed in the trial.

Trial design

Full details of TAPS are available elsewhere (3). Briefly, it was a multicentre, pragmatic, randomised controlled trial, with a group sequential superiority design. It was carried out between November 2007 and March 2011 at 22 sites in England, the Netherlands, Ireland and Canada, with appropriate ethical approval and written patient/parental consent. An interim analysis was scheduled after every 40 patients. Secondary outcomes included health-related quality of life [using the EQ-5D instrument (4)] and resource use: number of days in hospital; units of blood transfused; the use of heparin, antibiotics or pain medication; and other peri-operative treatments such as oxygen, spirometry and blood warming.

Cost analysis

Costs were assessed from the perspective of the UK NHS. In the within-trial analysis, mean costs per treatment arm were calculated by applying unit costs taken from routine NHS sources and the published literature, to resource-use

Table 1 Unit costs

Resources	Costs (£ 2011)			Source
	Base case	Low	High	
Cost per unit of blood	136.50	124.52	329.94	(8, 15, 16)
Heparin (per day)	3.56	2.82	4.04	BNF (tinzaparin sodium, 4500 units)
Antibiotics (per day)	7.83	4.70	10.96	BNF (ampicillin, 500 mg injection)
Pain medication (per day)	14.64	8.78	20.50	BNF (codeine phosphate, 60 mg, every 4 h)
Active warming (per procedure)	20.15	12.09	28.20	Guys and St Thomas NHS foundation trust
Blood warming (per procedure)	11.85	7.11	16.59	Guys and St Thomas NHS foundation trust
Incentive spirometry (per procedure)	90.00	54.00	126.00	Clinical opinion
CPAP (per procedure)	2.00	1.20	2.80	Cost of mask and tubing
Supplemental O$_2$ (per procedure)	2.00	1.20	2.80	Cost of mask and tubing
Chest X-ray (per procedure)	88.92	53.35	124.49	(17, 18)
Cost of day in ICU	1234.06	635.08	1833.04	(8, 17)
Cost of day in HDU	873.22	757.12	989.32	(15, 17)
Additional bed day	246.33	186.62	277.07	(8, 15, 17)

CPAP, central positive airway pressure.

data from the trial (Table 1). In the decision-analytic model, costs were extrapolated to the lifetime of the patient by summing the within-trial costs and the expected costs of transfusion complications. All costs are reported in 2011 UK sterling adjusting for inflation using the Health and Community Health Services price index (PSSRU 2011).

Health outcomes

In TAPs, EQ-5D data were collected at baseline and at 30-day postsurgery follow-up. At the time of trial set-up in 2005, no reliable tool similar to the EQ-5D was available for patients younger than 12 yr of age. Therefore, EQ-5D data were only collected for those aged 12 yr and older at entry. For the within-trial analysis, QALYs were calculated using area under the curve methods (5) based on EQ-5D responses at baseline and at 30 d follow-up. In the base case, it was assumed that patients' follow-up responses were sustained until the end of the year. Sensitivity analysis was used to assess the effect of assuming that all patients

returned to normal health by the end of the year if their follow-up EQ-5D score was below that of normal health. The decision model considered the health consequences of potential transfusion complications.

'Within-trial' analysis

Seemingly, unrelated regression was used to take into account the correlation between estimates of mean costs and QALYs (6), and controlling for baseline EQ-5D (7). Further analyses also controlled for age, sex and surgery risk. A complete case analysis was undertaken on all trial patients without missing data. This analysis does not include patients <12 yr as no EQ-5D were collected. For subsequent analyses, QALYs were estimated for patients less than age 12 yr using multiple imputation regression analysis to control for age, sex, surgery risk, surgery type as well as surgery outcomes and indicators for presurgery health.

Decision model analysis

Transfusion complications are rare, but the consequences can be costly (8). TAPs is likely to have been too small a trial with too short a follow-up to provide reliable estimates of the long-term implications of these complications. Therefore, additional costs of transfusion complications are calculated using published lifetime cost estimates, which are estimated to be more than £180 000 in the case of HIV (Table 2).

Table 2 Long-term costs of blood transfusions

Transfusion complications	Probability of event[1]	Cost (£ 2011)	Source of costs
Transfusion-related graft vs. host disease	0.000002	11 057	(8)
Incorrect blood component transfused	0.000244	2221	(8)
Haemolytic transfusion reaction	0.000081	8547	(8)
Post-transfusion purpura	0.000008	1796	(8)
Transfusion-related acute lung injury	0.000025	3486	(8)
Fatal air embolism	0.00003	3082	(8)
Variant Creutzfeldt–Jakob disease	0.0000012	179 730	(8)
Human immunodeficiency virus	0.0000001	181 825	(8)
Human T-cell lymphotropic virus	–	178 688	(8)
Malaria	0.0000012	1419	(8)
Hepatitis A	0.0000012	3030	(8)
Hepatitis B	0.0000001	34 119	Assumption
Hepatitis C	–	34 119	(19)
Total expected additional cost		1.69	Calculation

[1]The probability of an event after having a transfusion (8).

Taking into account the low probability of occurrence of transfusion complications, the mean additional cost of all transfusion complications is estimated to be £1.69 per transfusion.

To understand the potential long-term health effects of transfusion complications, the median survival of patients with SCD was assumed to be 55.8 yr, calculated as a weighted average according to the male/female split of TAPS (9). The average age of a patient in TAPS was 17.3 yr. The calculated life expectancy used in the model was 38.5 yr.

The additional loss of QALYs for those living with transfusion complications was calculated by assuming a 0.05 health-related quality of life (HRQoL) decrement (8) for 38.5 yr for hepatitis B and HIV and for 1 month for a haemolytic transfusion reaction, post-transfusion purpura, vCJD, hepatitis A or malaria. The probabilities of death from transfusion complications (Table 3) were those used in previous analyses (8). It was assumed that death resulted in the loss of 0.93 QALYs per year for 38.5 yr. No QALY decrements were calculated for hepatitis C or HTLV as the probability of these events was considered to be vanishingly small (8). On this basis, the health outcome was estimated to be a loss of 0.0016 QALYs per transfusion.

In the TAPS trial, no patients died from ACS or other causes (3). However, previous trials have shown an increased risk of death from ACS (10). The base-case analysis is conservative as it excludes the long-term consequences of ACS, the most common adverse event, and was lower in patients with preoperative transfusions. We estimated that 0.64 QALYs are lost per occurrence of acute chest syndrome (probability of death $0.018 \times$ length of life lost $38.5 \times$ health-related quality of life lost 0.93), which was used in a further scenario analysis.

Economic analysis

The economic statistic used is the incremental cost-effectiveness ratio (ICER). This is calculated as the difference in costs divided by the difference in effect, in this case QALYs.

Table 3 Probability of death due to complications from blood transfusions

Complications	Probability of death	Source
Transfusion-related graft vs. host disease	1	(8)
Incorrect blood component	0.012	(8)
Haemolytic transfusion reaction acute	0.043	(8)
Haemolytic transfusion reaction delayed	0.038	(8)
Post-transfusion purpura	0.046	(8)
Transfusion-related acute lung injury	0.237	(8)
Fatal air embolism	1	(8)
Acute chest syndrome	0.018	(10)

$$ICER = \frac{Cost_A - Cost_B}{QALYs_A - QALYs_B}$$

Treatment A is said to be dominated by Treatment B if Treatment A is less effective but more costly. Treatment A is said to be cost saving if it is more effective and less costly. When $Cost_A > Cost_B$ and $QALYs_A > QALYs_B$, this ratio represents the additional cost for each additional QALY produced by Treatment A. To determine whether a treatment which is more effective but also more costly is cost-effective, we compare it to a threshold. The threshold represents the opportunity costs of the National Health Service (NHS) or the health expected to be forgone elsewhere as other NHS activities are displaced. The National Institute of Health and Care Excellence (NICE) decision threshold is currently £20 000–£30 000 per QALY gained, although recent research suggests the threshold might actually be lower (11). This suggests that NICE is likely to accept new treatments with an ICER <£20 000 per QALY. This is because the QALYs produced by the new treatment will be less expensive than the QALYs displaced elsewhere in the NHS by the additional cost of the new treatment.

Uncertainty in the parameters estimated in the trial was combined with uncertainty in parameters from the literature using probabilistic sensitivity analysis (PSA) (12). Inputs were defined using appropriate probability distributions to reflect their full uncertainty, taking into account known correlations between parameters. Monte Carlo simulation was undertaken to estimate the combined uncertainty of the parameters within the model. The probability of each form of management being more cost-effective was calculated from 1000 simulations.

The likelihood of making a wrong decision (one minus the probability of being cost-effective) was combined with the potential health and cost consequences of a wrong decision to calculate the expected value of perfect information (EVPI), the value of avoiding all consequences of a wrong decision, equivalent to the value of being able to resolve all decision uncertainty and indicating the maximum value a health system attaches to further research. A value of EVPI higher than the anticipated cost of further research is a necessary condition for further research to be good value. To estimate the EVPI, it was necessary to estimate the number of SCD patients likely to undergo surgery and who would be eligible for this treatment. In a survey of 31 of the 41 hospitals that were known to treat patients with SCD, 136 procedures were reported between May 2002 and May 2003 (1). We assumed 175 procedures would occur each year assuming the number of SCD patients has increased in the UK since 2002 and that the survey was a representative sample of UK hospitals. We assumed that if preoperative transfusion is taken up as routine practice over the next 10 yr, approximately 1750 SCD patients could be treated with preoperative transfusions.

Results

'Within-trial' analysis

Of the 70 patients randomized in TAPS, 67 were included in the clinical analysis. The three patients excluded were randomized in error: one with high-risk surgery and two for having had a transfusion within 3 months of scheduled surgery not declared at enrolment.

Complete resource-use data were collected for 64 patients, one patient had missing information on whether they had received blood warming, one patient had missing information on whether they had received peri-operative heparin and one patient withdrew, and no resource-use data were collected.

Resource-use estimates were similar across treatment arms. Patients with no preoperative transfusion received a mean of 0.85 fewer units of blood per patient and were more likely to use incentive spirometry (Table 4). Costs were higher in the no preoperative transfusion arm, including scenarios based on low and high estimates of unit costs (Table 5).

Of the 36 patients 12 yr or older, 35 completed the baseline EQ-5D, 29 completed the follow-up EQ-5D and 14 from each arm completed both. Patients who had no preoperative transfusion had higher baseline and follow-up HRQL and higher unadjusted QALYs (Table 6). Adjusting for baseline HRQL, patients receiving preoperative transfusion had 0.018 higher mean QALYs and £735 lower mean costs (Table 7). There was a 0.79 probability of preoperative transfusions being cost-effective at a cost-effectiveness threshold of £20 000 per QALY.

Table 4 Within-trial analysis: resource-use estimates by treatment

Treatment	No preoperative transfusion	Preoperative transfusion
	% of patients receiving	
Heparin	9.4	15.1
Antibiotic	97.0	90.9
Patient warmed	84.8	84.8
Blood warmed	9.4	6.0
Incentive spriometry	36.4	6.0
CPAP	3.0	3.0
Supplemental O_2	78.8	81.8
Chest x-ray[1]	12.1	2.9
	Mean (SD)	
Length of stay days	4.7 (3.7)	4.1 (3.6)
ICU days	0.3 (1.3)	0.0 (0.0)
HDU days	0.1 (0.4)	0.1 (0.3)
Units of blood[2]	1.2 (2.3)	2.1 (1.5)

[1]Collected from complication reports, associated with ACS.
[2]Includes all blood transfusions reported in the trial.

Table 5 Within-trial analysis: estimated treatment costs

| Treatment Type of cost | No preoperative transfusion | | | Preoperative transfusion | | |
| | Mean (SD) per patient | | | | | |
	Base case	Low cost	High cost	Base case	Low cost	High cost
Blood	£157 (£307)	£143 (£280)	£380 (£743)	£273 (£211)	£249 (£193)	£660 (£511)
Other	£1766 (£2515)	£1233 (£1548)	£2200 (£3539)	£1405 (£1062)	£1115 (£833)	£1965 (£1414)
Total	£1924 (£2762)	£1377 (£1773)	£2583 (£4148)	£1447 (£1050)	£1148 (£823)	£2023 (£1394)

Table 6 Complete case unadjusted health-related quality of life and QALYs

| Trial results | No preoperative transfusion | | | | | Preoperative transfusion | | | | |
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max
Baseline EQ-5D	17	0.793	0.298	0.055	1	18	0.76	0.236	−0.016	1
Follow-up EQ-5D	15	0.864	0.190	0.516	1	14	0.854	0.166	0.516	1
QALYs[1]	14	0.857	0.186	0.520	1	14	0.849	0.164	0.525	1

[1]Not adjusted for baseline EQ-5D.

Table 7 Cost-effectiveness results for multiple scenarios

Scenario	Intervention	Costs (SD)	QALYs (SD)	ICER[1]	Probability of cost-effectiveness
Complete case in trial analysis	No transfusion	£2442 (615)	0.696 (0.037)	Preoperative transfusion is less costly and more effective	0.79
	Transfusion	£1706 (615)	0.714 (0.040)		
	Difference	−£735 (869)	0.018 (0.048)		
Patients ≥12 yr old imputed trial analysis	No transfusion	£2685 (142)	0.628 (0.197)	Preoperative transfusion is less costly and more effective	0.88
	Transfusion	£1872 (135)	0.686 (0.110)		
	Difference	−£813 (196)	0.057 (0.134)		
Patients <12 yr old, imputed trial analysis	No transfusion	£961 (592)	0.569 (0.048)	£163 per additional QALY	0.86
	Transfusion	£986 (593)	0.727 (0.049)		
	Difference	£26 (838)	0.157 (0.061)		
All patients imputed trial analysis	No transfusion	£1901 (348)	0.660 (0.066)	Preoperative transfusion is less costly and more effective	0.92
	Transfusion	£1455 (343)	0.743 (0.052)		
	Difference	−£446 (489)	0.083 (0.058)		
All patients, imputed trial analysis assuming all patients return to normal health	No transfusion	£1901 (348)	0.795 (0.026)	Preoperative transfusion is less costly and more effective	0.95
	Transfusion	£1455 (343)	0.842 (0.024)		
	Difference	−£446 (489)	0.048 (0.029)		
Extrapolation of scenario 5 to long term (includes transfusion complications)	No transfusion	£1897 (359)	0.664 (0.081)	Preoperative transfusion is less costly and more effective	0.89
	Transfusion	£1481 (347)	0.744 (0.092)		
	Difference	−£416 (514)	0.080 (0.066)		
Scenario 6 additionally including mortality of ACS	No transfusion	£1901 (343)	0.498 (0.105)	Preoperative transfusion is less costly and more effective	0.99
	Transfusion	£1450 (335)	0.704 (0.094)		
	Difference	−£451 (484)	0.206 (0.091)		

[1]Incremental cost-effectiveness ratio.

'Within-trial' analysis: multiple imputation

The use of methods to impute HRQoL for patients aged under 12 yr resulted in an estimated 0.057 mean additional QALYs per patient and a mean cost reduction of £813 for preoperatively transfused patients (Table 7). In the subgroup of patients younger than 12 yr, mean QALYs were also higher by 0.157, but mean costs were £26 higher for preoperatively transfused patients giving an incremental cost-effectiveness ratio of £163 per additional QALY. Following imputation for all missing data in the study, preoperative transfusions improved mean QALYs by 0.018 per patient and lowered mean costs by £446. The probability of being cost-effective at a cost-effectiveness threshold of £20 000 per QALY was 0.92.

In a further analysis age, sex and surgery risks were included as covariates. Preoperative transfusion had higher QALYs and was less costly, with 0.090 higher mean QALYs, and a mean cost of £717 lower.

Decision model

When the costs and health effects of transfusion complications are included using the decision model, the estimated mean difference was 0.080 additional QALYs and £416 lower mean costs for patients undergoing preoperative transfusion, with a 0.91 probability of the procedure being cost-effective at a cost-effective threshold of £20 000 per QALY. The EVPI was estimated to be £138 511 (Table 7).

In a further scenario analysis, we included the QALY decrement due to death from acute chest syndrome. The probability of preoperative transfusion being cost-effective increased to 0.99 and the value of information decreased to £12 848.

Discussion

This analysis suggests preoperative transfusion is cost-effective and may be cost saving. Multiple scenario and sensitivity analyses were undertaken all suggesting preoperative transfusion has a high probability of being cost-effective at the standard cost-effectiveness threshold used by the National Institute of Health and Care Excellence (13).

The trial results are uncertain given the limited number of patients, the lack of EQ-5D data for half the trial participants and the short follow-up time. A decision model was created to explore the uncertainties of the trial data. Missing data were imputed, long-term health effects, and costs due to transfusion were modelled, and the uncertainties around the model parameter estimates were considered in a probabilistic sensitivity analysis.

EQ-5D data were only collected for those 12 yr and older, as no valid instrument was available for patients under 12 yr. Thirty-one trial participants did not complete the EQ-5D because of their age. A complete case analysis will give us an estimate of the cost-effectiveness of treatment in patients 12 yr and older. However, imputation methods taking advantage of information available in the trial on events, and patient characteristics can be used to estimate EQ-5D scores for patients <12 yr old. For this method to be reliable, we must assume that the difference in patients that completed the EQ-5D and those that did not can be explained given the other variables that have been collected in the trial, such as age, surgery risk, surgery type hospital days and comorbidities such as asthma or renal impairment. This analysis assumes those <12 yr old would have answered the EQ-5D in the same way as the respondents did and does not take into account that children's experiences and outcomes might be different. Results were presented for each age subgroup to see the incremental effect of these assumptions.

For imputation, we use truncated regressions to limit the range of possible EQ-5D scores between the instruments range and to allow the scores of those <12 yr to be different

than the scores of those >12 yr. Imputation was undertaken in a step-wise manner to assess its effect on the adoption decision. First, data were imputed to the ≥12-year-old population (scenario 2) and then to the <12-year-old population (scenario 3). Scenario 4 combined the two age groups. All in trial scenarios resulted in preoperative transfusion being cost-effective.

The population from scenario 4 was then used to extrapolate beyond the trial timeframe using decision-model analysis. Including transfusion costs and long-term consequences resulted in higher costs and lower QALYs for the preoperative transfusion group compared with scenarios 1–4, but compared with the no preoperative transfusion group costs remained lower and QALYs higher (scenario 6).

A 1988 through to 1993 multicentre randomised controlled trial compared the complication rates in sickle cell patients receiving aggressive (haemoglobin S level to <30%) or conservative (increase haemoglobin to 10 g per decilitre) preoperative transfusions (14). The authors concluded that a conservative transfusion regimen was as effective as an aggressive regimen in preventing peri-operative complications in patients will sickle cell anaemia, and the conservative approach resulted in only half as many transfusion-associated complications. No comparison was made to a no transfusion arm, and patients undergoing severe surgeries were also included. They found that 10% of patients in each arm had ACS with two of the 303 patients in the aggressive regimen dying from ACS (14).

In the TAPS study, the increased occurrence of ACS in the arm that did not receive preoperative transfusion may have longer term health effects and costs than were captured in the study. In a scenario analysis, we included the loss of QALYs associated with this increased mortality (scenario 7). These results strengthen the conclusion and the addition of long-term costs of ACS make transfusion more cost saving. However, the mortality estimates are from a 20-year-old study (10) and should be considered cautiously as it is possible that, with recent improvements in patient treatment, current mortality from ACS is lower. If the mortality estimates of ACS are lower than those used in the model, then it would be expected that the actual benefits of preoperative transfusion to be somewhere between scenarios 6 and 7.

All analyses suggested there was low decision uncertainty taking into account the small trial population. The probabilistic sensitivity analysis took into account the uncertainty around the QALYs and costs estimated in the trial and the correlation between the two as well as the uncertainty of the costs and health outcomes of the potential transfusion complications used in the extrapolation analyses. This combined uncertainty gives us a probability of the cost-effectiveness of preoperative transfusions, which in all scenarios is >79%. The EVPI was never higher than £138 511. This suggests that the value to the NHS of resolving all of the uncertainty considered in the economic model is relatively low. This

supports the decision to stop the trial early as further information was unlikely to change the conclusions of this analysis. Due to small numbers and particularly the small number of patients recruited overseas, it was not possible to take into account the differential cost-effectiveness based on country or risk of surgery as planned in the protocol.

The results of this cost-effectiveness analysis support the use of preoperative transfusion for treating patients with sickle cell anaemia undergoing low- and moderate-risk surgery.

Acknowledgements

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