The Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) study: a randomised, controlled, multicentre clinical trial

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Summary

Background No consensus exists on whether preoperative blood transfusions are beneficial in patients with sickle-cell disease. We assessed whether perioperative complication rates would be altered by preoperative transfusion.

Methods We did a multicentre, randomised trial. Eligible patients were aged at least 1 year, had haemoglobin SS or Sβ⁰thalassaemia sickle-cell-disease subtypes, and were scheduled for low-risk or medium-risk operations. Patients were randomly assigned no transfusion or transfusion no more than 10 days before surgery. The primary outcome was the proportion of clinically important complications between randomisation and 30 days after surgery. Analysis was by intention to treat.

Findings 67 (96%) of 70 enrolled patients—33 no preoperative transfusion and 34 preoperative transfusion—were assessed. 65 (97%) of 67 patients had the haemoglobin SS subtype and 54 (81%) were scheduled to undergo medium-risk surgery. 13 (39%) of 33 patients in the no-preoperative-transfusion group had clinically important complications, compared with five (15%) in the preoperative-transfusion group (p=0·023). Of these, 10 (30%) and one (3%), respectively, had serious adverse events. The unadjusted odds ratio of clinically important complications was 3·8 (95% CI 1·2–12·2, p=0·027). 10 (91%) of 11 serious adverse events were acute chest syndrome (nine in the no-preoperative-transfusion group and one in the preoperative-transfusion group). Duration of hospital stay and readmission rates did not differ between study groups.

Interpretation Preoperative transfusion was associated with decreased perioperative complications in patients with sickle-cell disease in this trial. This approach could, therefore, be beneficial for patients with the haemoglobin SS subtype who are scheduled to undergo low-risk and medium-risk surgeries.

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Introduction

Many patients with sickle-cell disease require surgery, particularly abdominal, orthopaedic, or ear, nose, and throat procedures, because of disorders such as obstructive sleep apnoea, adenotonsillar hypertrophy, cholelithiasis, splenic sequestration, and avascular necrosis. The rate of perioperative complications varies according to the clinical severity of the disorder and the type of operation but, overall, complications related and not related to sickle-cell disease are common.[1–4]

Preoperative blood transfusion, which decreases the proportion of sickle red blood cells, suppresses erythropoiesis, and improves anaemia, has been associated with decreased risk of complications related to sickle-cell disease, but is also associated with acute transfusion reactions, alloimmunisation, and delayed haemolytic transfusion reactions. One view is that transfusion is immunosuppressive and might increase the risk of postoperative infections.[4] Although the risks of post-transfusion HIV or hepatitis infections are low in the developed world, they remain high in sub-Saharan Africa.[5] With potential new transfusion hazards, such as variant Creutzfeldt-Jakob disease[6,7] and West Nile virus,[8,9] the risks of transfusion need to be balanced against its benefits.

A randomised controlled trial showed no significant difference in postoperative complication rates between two groups of patients with sickle-cell disease who received either intensive (exchange) or conservative (top-up) preoperative transfusion,[10] but the trial did not include a no-transfusion group. Several observational studies have shown benefits with transfusion, but others have shown no benefits, and studies from countries with low availability of blood for transfusion or from centres that do not routinely offer preoperative blood transfusion do not show increased perioperative complication rates.[2,11–16] Improved surgical and anaesthetic techniques have led to decreases in perioperative complication rates.[17] A UK survey of surgery done in 2002–03 in patients with sickle-cell disease showed large variation in transfusion practice, with 43% of patients receiving no preoperative transfusion.[3] Similar variations in practice have been reported in the USA.[18]

Owing to the lack of conclusive evidence about the benefit of preoperative blood transfusion,[4] we did the Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) study to investigate whether routine

preoperative transfusion would affect the overall perioperative complication rate in patients with sickle-cell disease.

Methods

Study design and patients

TAPS was a multicentre, randomised, controlled clinical trial with a group sequential superiority design.[19] The study involved 22 sites in Canada, Ireland, the Netherlands, and the UK, between November, 2007, and March, 2011.

Eligible patients had haemoglobin SS (HbSS) or haemoglobin Sβ⁰thalassaemia (HbSβ⁰thal) sickle-cell-disease subtypes, were aged at least 1 year, and were scheduled to undergo low-risk or medium-risk elective surgery (under general or regional anaesthesia) within the next 28 days. Surgeries were classified according to the Co-operative Study of Sickle Cell Disease criteria (appendix p 1).[2] Low-risk surgery included adenoidectomy and inguinal-hernia repair, and medium-risk surgery included cholecystectomy and joint replacement. Operations not on the Co-operative Study of Sickle Cell Disease list were classified after discussion with the trial investigators. Patients scheduled to undergo high-risk operations, such as cardiovascular or brain surgery, were excluded. Other exclusion criteria were haemoglobin levels lower than 65 g/L, blood transfusion within the previous 3 months, history of acute chest syndrome within the previous 6 months or intubation and mechanical ventilation ever for the treatment of acute chest syndrome, oxygen saturation lower than 90%, current renal dialysis, and a history of stroke in children. All patients or their parents or guardians provided written informed consent.

See Online for appendix

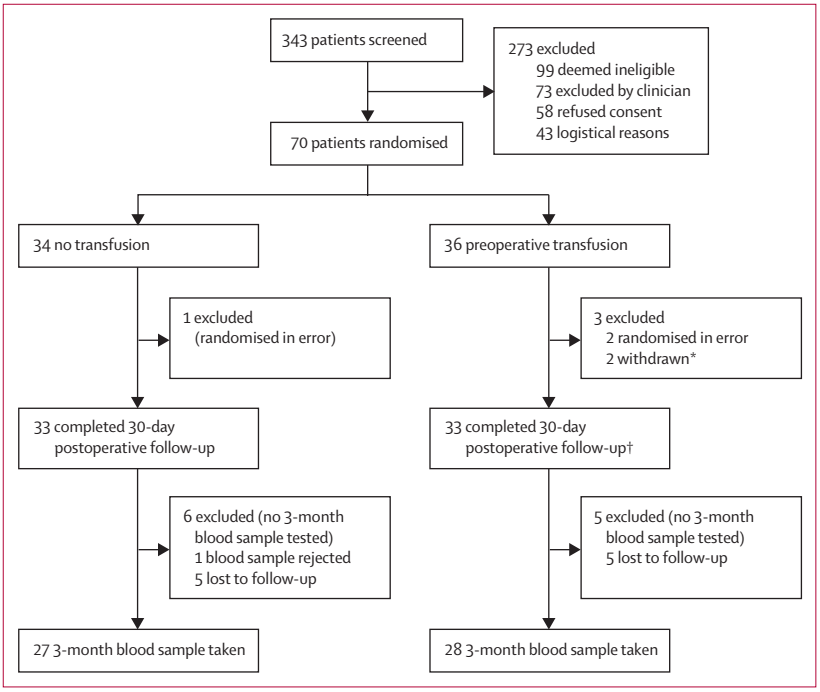

Figure: **Trial profile**
*Both withdrawn patients were included in the intention-to-treat analysis. Postoperative data were available on one withdrawn patient. †Included one withdrawn patient.

Randomisation

Patients were allocated treatment by an independent, centralised online randomisation service. Block randomisation was used to avoid centre effects, and patients were stratified by surgical risk (low or medium), age (1–6, 7–16, 17–39, or 40 years or older), and history of complications related to sickle-cell disease (no or yes), defined as more than three admissions to hospital requiring opioid analgesia in the previous 12 months, steady-state oxygen saturation of 90–94%, previously diagnosed pulmonary hypertension, creatinine concentration higher than 100 μmol/L, or history of stroke as an adult. Patients could be randomised up to two times provided that procedures were at least 6 months apart. Patients having additional procedures were excluded to avoid the risk of within-patient bias.

The randomisation groups were no preoperative transfusion or a preoperative red-cell transfusion within 10 days before surgery, with transfusion aimed at increasing haemoglobin concentration to 100 g/L. In patients who presented with haemoglobin concentrations lower than 90 g/L, a top-up transfusion was used, whereas in those with baseline haemoglobin levels of 90 g/L or higher, partial exchange transfusion was used to achieve an estimated haemoglobin S percentage of less than 60%. Standard prestorage leucocyte-depleted red blood cells were used, and blood was fully matched for ABO, full-Rhesus phenotype (Cc/D/Ee), and K1 antigen, plus any other antigens to which the patient had antibodies. Doctors and patients were aware of treatment allocations.

Perioperative care

A care protocol developed for the trial was given to study centres for guidance; its use was not mandatory and centres could follow their own standards of perioperative care to ensure maximum applicability of results to the usual-care setting.[20] Recommendations included intravenous fluids if the patient was nil by mouth for more than 2 h before surgery, and to continue after surgery until oral administration of fluids could be tolerated; careful monitoring of oxygenation to maintain oxygen saturation at more than 96% on air; and thromboprophylaxis if the patient was immobile for longer than 24 h. We placed no restrictions on concurrent medication or enrolment in other studies while patients were in the trial.

Assessment of alloimmunisation

A blood sample was taken from each patient at trial entry for measurement of red-cell alloantibodies. Samples were assessed in local laboratories by standard methods but stored centrally during the study. Another blood sample was taken from each patient at 3 months

after surgery and was tested in central laboratories (Reference Laboratory, Colindale, in the UK, and the local central laboratory in each of the other countries). If red-cell antibodies were identified in the postoperative sample, it was tested again in parallel with the preoperative sample to assess whether or not the antibody was newly formed. Information on previous alloantibodies was not captured for the trial because there was no central source of such data and many patients were treated at multiple hospitals.

Assessment of quality of life and cost-effectiveness

We assessed quality of life with the EQ-5D health outcomes questionnaire. Scores were collected at baseline and at 1–3 months after surgery for patients aged 12 years and older. On the basis of the responses, we calculated quality-adjusted life-years to assess cost-effectiveness.

Statistical methods

The primary outcome was the proportion of patients with clinically important complications between randomisation and 30 days after surgery. This timeframe was deemed sufficient to capture all complications triggered by the surgery or preoperative transfusions. Clinically important complications were classified as being related to sickle-cell disease, infection, surgery, or transfusion, and definitions were provided to study centres (appendix p 5).[21] Detailed reports of complications were scrutinised by an independent endpoint review panel that was unaware of treatment allocations to assess whether events satisfied the trial definitions. Complications that were life threatening or resulted in death, permanent or severe disability, or other important medical outcomes (appendix p 5) were additionally reported as serious adverse events (SAEs) and were reviewed by the independent data monitoring committee.

Secondary outcomes were total number of inpatient days, number of red-cell units received during and after surgery, and readmission or non-discharge by 30 days after surgery. We also assessed a composite outcome of the primary outcome plus alloimmunisation at 3 months after surgery.

In a national survey of practices in the UK, 26% of transfused patients with sickle-cell disease had complications.[3] We therefore set a baseline complication rate of 25% for this study. We aimed to detect a difference of at least 10% in either direction in the complication rates of the two study groups. For a double-triangular group sequential design, we calculated that to achieve power of 90% and a 5% significance level, to be assessed by interim analyses after every 40 patients, the required overall sample size would be 405 patients. We used PEST software (version 4.4) to make the calculations, as it adjusts for multiple analyses of data.

Odds ratios (ORs) and 95% CIs for the primary outcome in the intention-to-treat population were calculated with an unadjusted logistic regression model that excluded patients randomised in error. The robustness of study results was checked by performing a per-protocol analysis that also excluded patients randomised in error as well as withdrawn patients, those who did not receive their allocated treatment, and those who underwent transfusion more than 10 days before surgery. Additionally, we did an intention-to-treat analysis of the primary outcome with adjustment for stratification factors (age at randomisation, risk level of surgery, and history of sickle complications). This trial is registered with ClinicalTrials.gov and ISRCTN Register, numbers NCT00512577 and ISRCTN00862331.

Role of funding sources

Five authors were employed by the study sponsor, NHS Blood and Transplant. The study was run on behalf of the sponsor by the NHS Blood and Transplant/MRC Clinical Studies Unit, who undertook the study design, data collection, data analysis, and data interpretation, overseen

	No preoperative transfusion (n=33)	Preoperative transfusion (n=34)	Overall (n=67)*
Sex			
Male	17 (52%)	16 (47%)	33 (49%)
Female	16 (48%)	18 (53%)	34 (51%)
Sickle-cell-disease subtype			
HbSS	33 (100%)	32 (94%)	65 (97%)
HbSβ°thal	0	2 (6%)	2 (3%)
Median (IQR) percentage HbF (%)	7·7 (5·2–11·0)	7·3 (4·2–9·8)	7·5 (4·6–10·8)
Median (IQR) age at randomisation (years)	13·3 (6·4–21·4)	15·1 (7·6–37·4)	13·4 (6·4–26·5)
Age group (years)			
1–6	10 (30%)	8 (24%)	18 (27%)
7–16	11 (33%)	11 (32%)	22 (33%)
17–39	11 (33%)	10 (29%)	21 (31%)
≥40	1 (3%)	5 (15%)	6 (9%)
Scheduled surgery			
Medium-risk surgery			
All	28 (85%)	26 (77%)	54 (81%)
Abdominal	13 (39%)	10 (29%)	23 (34%)
ENT	9 (27%)	7 (21%)	16 (24%)
Orthopaedic	4 (12%)	6 (18%)	10 (15%)
Other	2 (6%)	3 (9%)	5 (8%)
Low-risk surgery	5 (15%)	8 (24%)	13 (19%)
History of sickle-cell-disease complications			
No	23 (70%)	19 (56%)	42 (63%)
Yes	10 (30%)	15 (44%)	25 (37%)
ASA risk score[22,23]			
2 (mild systemic disease)	20 (61%)	24 (73%)	44 (67%)
3 (severe systemic disease)	13 (39%)	9 (27%)	22 (33%)
Hydroxycarbamide at trial entry	4 (12%)	3 (9%)	7 (11%)

Data are number (%) unless stated otherwise. HbSS=haemoglobin SS. HbSβ°thal=haemoglobin Sβ°thalassaemia. HbF=fetal haemoglobin. ENT=ear, nose, and throat. ASA= American Society of Anesthesiologists. *Three patients randomised in error were not included in the primary intention-to-treat analysis as they had no follow-up data.

Table 1: **Baseline characteristics of patients assessed for primary outcome**

by an independent trial steering committee. The writing of the report was undertaken by the trial writing group. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

343 patients were screened, of whom 86 (25%) were scheduled to undergo low-risk surgery and 257 (75%) medium-risk surgery. Of these patients, 273 (80%) were excluded (figure). Among these, 99 (36%) were deemed ineligible, mainly because of transfusion within the past 3 months (58 [59%]), haemoglobin levels lower than 65 g/L (16 [16%]), and acute chest syndrome within the past 6 months (12 [12%]). Other reasons were history of stroke (n=7), oxygen saturation lower than 90% (n=5), and already having been entered into the trial twice (n=1). Of the 99 ineligible patients, the intended transfusion plan was available for only 55 (56%), of whom 40 (73%) were scheduled to receive a preoperative transfusion. Of 73 patients excluded by clinicians, 32 (44%) were scheduled to undergo orthopaedic surgery, 11 (15%) abdominal procedures, and 14 (19%) ear, nose, and throat procedures; the remaining 16 patients were due to have other low-risk surgeries. Clinicians excluded 23 (32%) of these 73 patients because they definitely wanted them to have a preoperative transfusion, 13 (18%) because they did not want to give preoperative transfusion at all, but in 37 (51%) no transfusion plan was stated. Of 58 patients who refused consent, 21 (36%) did so because they did not wish to undergo transfusion and four (7%) did so because they wanted preoperative transfusion, with the remainder refusing for other reasons.

The first interim analysis, done in September, 2010, after 40 patients had completed 30-day postoperative follow-up, indicated that the trial should continue, as no stopping boundaries had been crossed on the basis of the primary outcome. An emerging imbalance in SAEs that had become increasingly marked by February, 2011, was noted between the two groups by the independent data monitoring committee. At this point, therefore, the committee requested an unscheduled interim analysis, which was undertaken for 61 patients with complete data. The proportion of patients with clinically important complications did not differ significantly between groups (11 [37%] of 30 in the no-preoperative-transfusion group *vs* five [16%] of 31 in the preoperative-transfusion group; difference 20·5%, 95% CI –0·1 to 42·1, p=0·068). The proportion of patients with SAEs in each group at this point, however, did differ significantly (10 [33%] of 30 *vs* one [3%] of 31; difference 30·1%, 95% CI 12·1–48·1, p=0·002). In view of the potential risk to patients' safety, the independent data monitoring committee recommended that the trial steering committee consider early closure of the study, to which they agreed in March, 2011. At trial closure, 70 patients had been recruited.

Of the 70 patients enrolled, 13 (19%) were scheduled to have low-risk operations and 57 (81%) to have medium-risk operations. Three patients were randomised in error and, therefore, only 67 patients were included in the intention-to-treat analysis (33 in the no-preoperative-transfusion and 34 in the preoperative-transfusion group; figure), including six for whom we did not have postoperative data at trial closure because they had been followed up for less than 30 days. Two patients were entered into the trial twice, and had different study numbers each time. Two patients in the transfusion group withdrew from treatment, but only one had no postoperative data and, therefore, outcomes were assessed in 33 patients in each group (figure).

The baseline characteristics of patients in the two groups were similar (table 1). Haemoglobin concentrations were similar overall, but were higher in the

	No preoperative transfusion (n=33)	Preoperative transfusion (n=34)	Overall (n=67)
Median (IQR) haemoglobin concentration (g/L)			
Baseline	77 (71–84)	80 (74–86)	79 (73–86)
Preoperative	77 (71–82)	97 (91–105)*	87 (75–97)
Postoperative†	75 (67–83)	88 (81–98)	82 (73–90)
Number (%) of patients who received red-cell transfusions			
Preoperatively			
Top up	1 (3%)‡	26 (76%)	27 (40%)
Partial exchange	0	5 (15%)	5 (7%)
Intraoperatively§	4 (12%)	1 (3%)	5 (7%)
Postoperatively§	9 (27%)	3 (9%)	12 (18%)
Total number of red-cell units received	38	71	109

*Post-transfusion data are missing for two patients (one withdrawal, one protocol deviation). †Postoperative haemoglobin concentrations reported for 35 patients (no-transfusion group n=19, preoperative-transfusion group n=16). ‡Patient given transfusion because haemoglobin concentration fell to less than 65 g/L between randomisation and surgery. §One patient in each study group had intraoperative and postoperative transfusions.

Table 2: **Haemoglobin concentrations and blood-transfusion details**

	No preoperative transfusion (n=33)	Preoperative transfusion (n=34)	Overall (n=67)
Number of patients with clinically important complications (%)	13 (39%)	5 (15%)	18 (27%)
Number of clinically relevant complications			
All related to sickle-cell disease	12	3	15
Acute chest syndrome	9	1	10
Acute pain crisis	3	1	4
CNS	0	1	1
Surgery-related	4	1	5
Infection-related	0	1	1
Transfusion-related	0	0	0
Other	0	1	1
Total	16*	6†	22
Number of patients with complications classified as SAEs (%)	10 (30%)	1 (3%)	11 (16%)

CNS=central nervous system. SAEs=serious adverse events. *Three patients had two complications. †One patient had two complications.

Table 3: **Numbers of clinically important complications and serious adverse events**

preoperative-transfusion group than in the no-preoperative-transfusion group before surgery, as expected (table 2). One patient in the no-preoperative-transfusion group received a preoperative transfusion because the haemoglobin concentration fell to lower than 65 g/L between randomisation and surgery (table 2). In the preoperative-transfusion group, 26 (76%) of 34 patients received top-up transfusions, and five (15%) received partial exchange transfusions (median preoperative percentage of haemoglobin S achieved 47·2%, IQR 43·1–50·4). The three remaining patients were not transfused preoperatively, including the two who withdrew (table 2). The interval between transfusion and surgery was more than 10 days in five patients, 5–10 days in four, and less than 5 days for 22 (five within 24 h before surgery, two on the previous day, and precise timings unknown for 15). Perioperative management was similar in the two groups, and involved intravenous fluids, heparin, antibiotics, and supplemental oxygen. The median haemoglobin concentration after surgery was higher in the preoperative-transfusion group than in the no-preoperative-transfusion group (table 2). Only 13 operations were classified as low risk—five in the no-preoperative-transfusion group and eight in the preoperative-transfusion group.

Overall, 18 patients had 22 clinically important complications, among whom 14 patients had 15 events related to sickle-cell disease (table 3). The most frequent event related to sickle-cell disease was acute chest syndrome, which was seen in nine patients in the no-preoperative-transfusion group and in one in the preoperative-transfusion group (tables 3, 4). Four patients had postoperative acute vaso-occlusive pain, and one had a transient complication of the central nervous system with no sequelae (table 3). No complications occurred between randomisation and surgery. The median time between surgery and any complication was 2·5 (IQR 1·5–4·5) days. The proportion of patients with clinically relevant complications was higher in the no-preoperative-transfusion group than in the preoperative-transfusion group (table 3). The OR for clinically important complications was 3·8 (95% CI 1·2–12·2), which indicates significantly higher risk of complications without preoperative transfusion (p=0·027).

The per-protocol analysis for the primary outcome included 58 patients, 32 in the no-transfusion group and 26 in the preoperative-transfusion group. Nine patients from the intention-to-treat cohort were excluded from this analysis: two in the preoperative-transfusion group withdrew from treatment and seven patients with protocol deviations (five in the preoperative-transfusion group who underwent transfusion more than 10 days before surgery and one who had no transfusion because of clinician reluctance, and one in the no-preoperative-transfusion group who received a preoperative transfusion because of a fall in haemoglobin concentration). The per-protocol analysis corroborated the intention-to-treat findings (OR 3·8, 95% CI 1·0–13·5, p=0·042).

When adjustment was made for stratification factors at baseline in the intention-to-treat cohort, the risk of clinically important complications remained similar (OR 3·4, 95% CI 1·0–11·8, p=0·049). None of the stratification factors showed a significant effect on the proportion of patients who had clinically important complications.

	Brief description	Intraoperative or postoperative transfusion	Surgery risk	Surgery	Time spent in ITU/HDU (days)	Hospital stay pro-longed	Readmitted
Preoperative transfusion	Acute chest syndrome	5 RBC units postoperatively	Medium	Shoulder arthroplasty and subacromial decompression	0	Yes	No
No transfusion	Acute painful crisis (postoperative ileus/ girdle syndrome)	2 RBC units postoperatively	Medium	Total hip replacement	0	Yes	No
No transfusion	Acute chest syndrome	2 RBC units postoperatively	Medium	Laparoscopic cholecystectomy	0	Yes	Yes
No transfusion	Intraoperative bleeding and acute chest syndrome*	4 RBC units intraoperatively and 2 RBC units after second surgery	Medium	Laparoscopic cholecystectomy converted to open because of bleeding and readmission for surgical removal of pack inserted to control bleeding	3 ICU 2 HDU	Yes	No
No transfusion	Acute chest syndrome	9 RBC units postoperatively	Low	Umbilical hernia repair	7 ICU	Yes	No
No transfusion	Acute chest syndrome	8 RBC units postoperatively	Medium	Laparoscopic cholecystectomy	0	Yes	No
No transfusion	Acute chest syndrome	No	Medium	Adenoidotonsillectomy	0	No	Yes
No transfusion	Acute chest syndrome	No	Medium	Adenoidotonsillectomy	0	Yes	Yes
No transfusion	Acute chest syndrome	1 RBC unit intraoperatively	Medium	Laparoscopic splenectomy	0	Yes	No
No transfusion	Acute chest syndrome	2 RBC units postoperatively	Medium	Tonsillectomy	0	Yes	Yes
No transfusion	Acute chest syndrome	1 RBC unit postoperatively	Medium	Adenoidotonsillectomy	0	Yes	No

ITU=intensive-care unit. HDU=high-dependency unit. RBC=red blood cell. *Acute chest syndrome occurred after second surgery.

Table 4: **Summary of patients with serious adverse events**

A notable overlap was seen for clinically important complications and SAEs, with the difference between study groups in the proportions of patients who had complications being attributable largely to an excess of SAEs, which were reported in ten patients in the no-transfusion group and only one in the preoperative-transfusion group (difference 27·4%, 95% CI 10·7–44·0, p=0·003; tables 3, 4). All but one of the 11 patients with SAEs had acute chest syndrome, of whom two required admission to intensive care, and eight required intraoperative or postoperative transfusions. One patient in the no-transfusion group had acute chest syndrome after low-risk surgery, whereas all other patients with this complication had undergone medium-risk operations. One patient had two SAEs: severe intraoperative bleeding and acute chest syndrome (table 4). All patients with SAEs recovered fully.

Owing to the limited number of patients, the analysis of secondary outcome measures was descriptive. Only one patient in the preoperative-transfusion group developed a red-cell alloantibody (anti-S) 3 months after surgery. This patient also had a clinically important complication. The length of stay did not differ between study groups (mean 5·4 [SD 3·7] days in the no-preoperative-transfusion group *vs* 4·8 [SD 3·6] days in the preoperative-transfusion group, 95% CI –1·2 to 2·4, p=0.521). All patients were discharged within 30 days of surgery. The rate of readmission was higher in the no-preoperative-transfusion group than in the preoperative-transfusion group (five patients *vs* one patient), but this difference was not significant (difference 12·2%, 95% CI –1·3 to 25·7, p=0·08). 12 patients in the no-preoperative-transfusion group required blood transfusion intraoperatively or postoperatively compared with only three patients in the preoperative-transfusion group (difference 27·5%, 95% CI 8·6–46·5, p=0·007; table 5). Transfusions were required because of complications in 11 of these 15 patients, of whom eight had acute chest syndrome and one had a severe postoperative painful crisis, and, therefore, was related to complication rate rather than study group allocation.

Complete EQ-5D data were available for 29 patients. Mean health-related quality-of-life scores were higher in the preoperative-transfusion group than in the no-preoperative-transfusion group when baseline EQ-5D was controlled for (difference 0·024, 95% CI –0·093 to 0·141, p=0·675). Data on use of resources were available for 64 patients. Patients in the preoperative-transfusion group spent a mean of 0·64 fewer days in hospital than did patients in the no-transfusion group (95% CI –1·16 to 2·44, p=0·478) but received an average of 0·85 more units of blood (95% CI –0·07 to 1·77, p=0·071). The overall cost of resources during the study was lower for the preoperative-transfusion group, with the difference between groups being UK£440 (95% CI –595 to 1476, p=0·399). Preoperative transfusions, therefore, had a 79% probability of being cost effective at a cost-effectiveness threshold of £20 000 per quality-adjusted life year.

	No preoperative transfusion (n=13)	Preoperative transfusion (n=5)	Overall (n=18)
Sex			
Male	4 (31%)	1 (20%)	5 (28%)
Female	9 (69%)	4 (80%)	13 (72%)
Sickle-cell-disease subtype			
HbSS	13 (100%)	3 (60%)	16 (89%)
HbSβ°thal	0	2 (40%)	2 (11%)
Median (IQR) percentage HbF (%)	6·1 (4·4–7·9)	4·6 (4·2–8·8)	5·1 (4·2–8·4)
Median (IQR) age at randomisation (years)	12·1 (5·5–20·3)	23·5 (11·5–27·5)	12·8 (9·7–26·3)
Age group (years)			
1–6	4 (31%)	0	4 (22%)
7–16	4 (31%)	2 (40%)	6 (33%)
17–39	5 (39%)	2 (40%)	7 (39%)
≥40	0	1 (20%)	1 (6%)
Scheduled surgery			
Medium-risk surgery			
All	12 (92%)	4 (80%)	16 (89%)
Abdominal	6 (46%)	2 (40%)	8 (44%)
ENT	4 (31%)	0	4 (22%)
Orthopaedic	1 (8%)	2 (40%)	3 (17%)
Other	1 (8%)	0	1 (6%)
Low-risk surgery	1 (8%)	1 (20%)	2 (11%)
History of sickle-cell-disease complications			
No	10 (77%)	3 (60%)	13 (72%)
Yes	3 (23%)	2 (40%)	5 (28%)
ASA risk score[22,23]			
2 (mild systemic disease)	6 (46%)	4 (80 %)	10 (56%)
3 (severe systemic disease)	7 (54%)	1 (20%)	8 (44%)
Hydroxycarbamide at trial entry	2 (15%)	0	2 (11%)

Data are number (%) unless stated otherwise. HbSS=haemoglobin SS. HbSβ°thal=haemoglobin Sβ°thalassaemia. HbF=fetal haemoglobin. ENT=ear, nose, and throat. ASA=American Society of Anesthesiologists.

Table 5: **Baseline characteristics of patients with clinically important complications**

Discussion

Although limited by early closure and the small number of patients enrolled, our findings indicate that rates of clinically important complications and SAEs were significantly higher in patients with sickle-cell disease who received no preoperative transfusion than in those who did. Additionally, without preoperative transfusion, the need for perioperative transfusion was increased. Confirmation of this finding in other trials would be ideal, but the logistical and recruitment issues we experienced suggest that further trials are unlikely. A prospective registry to capture data is an option, but rigorous data capture would be necessary to avoid bias.

Benefits of preoperative transfusion in patients with sickle-cell disease have not been previously reported in a randomised controlled trial. Another randomised controlled trial of preoperative transfusion showed the opposite result, with fewer complications in the no-transfusion group.[24] The patients in that study, however,

	SCD subtypes studied	Procedures	Number of procedures	Number of patients with complications (%)		Number of patients with ACS (%)	
				Transfused	Not transfused	Transfused	Not transfused
TAPS, 2012							
RCT	HbSS/ HbSβ°thal	Low and moderate risk	70	5 (15%)	13 (39%)	1 (3%)	9 (27%)
Al-Jaouni et al, 2006[24]							
RCT	All	All (except cardiac surgery)	369	27 (14%)	13 (7%)	0	0
Buck et al, 2005[3]							
Prospective observational 1-year survey	All	All	127	14 (23%)	9 (18%)	1 (2%)	4 (7%)
Neumayr et al, 1998[14]							
Prospective observational study	HbSC and others*	All	92	7 (20%)	3 (18%)	0	5 (9%)
Haberkern et al, 1997[25]							
Observational (data from Vichinsky et al[10])	HbSS/HbSβ°thal	Cholecystectomy	364	128 (39%)	16 (43%)	21 (8%)	7 (19%)
Vichinsky et al, 1995[10]							
RCT	HbSS/HbSβ°thal	All	604	199 (33%)	NA	63 (10%)	NA
Koshy et al, 1995[2]							
Observational (natural history study)	HbSS	Low risk	393	43 (17%)	27 (19%)	2 (1%)	2 (1%)
Observational (natural history study)	HbSC	Low risk	80	10 (31%)	6 (13%)	0	0
Observational (natural history study)	HbSS	Moderate risk	433	93 (24%)	8 (19%)	11 (3%)	1 (3%)
Observational (natural history study)	HbSC	Moderate risk	70	12 (25%)	9 (43%)	0	3 (14%)
Griffin and Buchanan, 1993[12]†							
Observational (retrospective)	HbSS	Low and moderate risk	76	1 (10%)	17 (26%)	0	4 (9%)
Fu et al, 2005[16]†							
Observational (retrospective)	HbSS	Low risk	38	0	5 (15%)	0	0

SCD=sickle-cell disease. ACS=acute chest syndrome. RCT=randomised controlled trial. NA=not applicable. HbSS=haemoglobin SS. HbSβ°thal=haemoglobin Sβ°thalassaemia. HbSC=haemoglobin SC. *75 patients with HbSC and others with Sβ+thalassaemia, S-HPFH, S-Lepore, and SO-Arab. †Children only.

Table 6: **Data from transfusion studies in patients with sickle-cell disease**

were from an Arab population, and such populations generally have milder phenotypes than the mainly Afro-Caribbean population in our study,[25] and the report included few details of the methods, analysis, or results to support the conclusions. The benefits we found could have been related to the additional hospital visit for patients in the preoperative-transfusion group. However, this effect seems unlikely, because all patients underwent a preoperative assessment at which perioperative advice was given. The rates of clinically important complications (five [15%] of 34) and specifically of acute chest syndrome (one [3%] of 34) in preoperative-transfusion group were lower than rates reported in previous studies.[2,3,10,14,26] This difference could be due to improvements in surgical and anaesthesia techniques (table 6). Although our trial was not blinded, there is no evidence to suggest that this approach affected management decisions. The rates of total clinically important complications (13 [39%]) and acute chest syndrome (nine [27%] of 33) in our no-preoperative-transfusion group were higher than those in previous observational studies (table 6),[2,3,12,14,16] which might have been due to our trial including patients who underwent either low-risk or medium-risk operations.

Some, although not all, previous studies have identified pulmonary disease[27–29] and abdominal surgery[26,28] as risk factors for acute chest syndrome in patients with sickle-cell disease, although some groups have performed abdominal surgery successfully without preoperative transfusion.[12,29] In this trial, the high rates of acute chest syndrome might have been due to the high proportion of patients undergoing abdominal surgery (23 [34%] of 67). Low oxygen saturations and pulmonary hypertension were included as part of the stratification factor history of sickle-cell disease and no relation was found between them and the risk of acute chest syndrome.

Only one episode of alloimmunisation was seen overall, which compares favourably with a previously reported rate of 7·5% in patients transfused pre-operatively.[10] The lower rate in our study might be related to the extension of red-cell matching to full Rhesus phenotype and K1 antigens. Alternatively, it could represent a lower previous transfusion burden in our trial population than in other trials. The lengths of stay and proportions of patients readmitted did not differ significantly between the two study groups, despite the difference in rates of SAEs. Use of preoperative transfusion seemed cost effective and to result in improved quality of life. A formal cost-effectiveness analysis will be detailed in a separate paper.

Baseline characteristics showed that our study sample was typical of patients with the haemoglobin SS sickle-cell-disease subtype and did not display markedly

***Panel:* Research in context**

Systematic review

We searched Medline for full papers published from January, 1978, to December, 2011, that reported randomised clinical trials and meta-analyses. We used the search terms "sickle cell" and "transfusion", "operative", or both. We identified two randomised clinical trials[10,22] and many observational studies, plus a recently updated Cochrane review.[4]

Interpretation

The perioperative period is associated with increased risk of complications in patients with sickle-cell disease, and observational studies have shown that preoperative blood transfusion is associated with reduced risk. A randomised trial showed that top-up transfusions were as effective in preventing complications as exchange transfusions when given preoperatively,[10] but another randomised trial showed no benefit when preoperative transfusion was compared with no preoperative transfusion. We found that the use of preoperative transfusions in patients with the haemoglobin SS sickle-cell-disease subtype was associated with decreased risk of clinically important and severe complications, particularly acute chest syndrome.

severe or mild phenotypes. Only five patients had haemoglobin concentrations of 90 g/L or higher at baseline, and our findings suggest that preoperative transfusion will be of most benefit in patients with low haemoglobin concentrations. Whether patients with the haemoglobin SS subtype who present with concentrations close to 100 g/L will benefit from preoperative exchange transfusion is less clear. No benefit with preoperative exchange transfusion has been shown over simple top-up transfusion previously, which suggests that the main benefit of transfusion in this context is in the correction of anaemia rather than in the lowering of the percentage of haemoglobin S.[10]

The number of low-risk operations was too small to enable subgroup analysis by operation type, and the results in patients scheduled to undergo low-risk procedures should be interpreted with caution. Previous observational data in patients who underwent low-risk operations show opposing results, some showing a benefit from preoperative transfusion and some not.[2,16] Further evidence from randomised trials would, therefore, be required to fully clarify the extent of benefit of preoperative transfusion in patients who undergo low-risk surgery. Most cases of acute chest syndrome were seen in patients who underwent medium-risk surgery without preoperative transfusion, which suggests that this subgroup would gain the most benefit.

Observational data suggest that patients with haemoglobin SC and Sβ+thalassaemia sickle-cell-disease subtypes who undergo low-risk or medium-risk surgery (particularly abdominal) surgery benefit from preoperative transfusion.[14] Thus, preoperative transfusions might be useful in other subgroups of patients with sickle-cell disease. In this trial only two (3%) patients had the HbSβ^{0}thal genotype and we excluded patients with the haemoglobin SC and Sβ+thalassaemia subtypes because of their milder disease phenotypes. Therefore, it is difficult to apply the conclusions from this trial to subtypes other than haemoglobin SS. As patients with the haemoglobin SC subtype constitute up to 30% of all patients with sickle-cell disease, most of whom generally do not undergo preoperative transfusion,[3] a further trial in this population seems warranted.

Recruitment to this study was slower than planned, due partly to the staggered set-up of study sites, with some sites only starting recruitment in 2011. Additionally, we applied stringent inclusion criteria that led to a high rate of ineligibility among screened patients. Some clinicians decided not to enter patients, and some patients wished to avoid transfusion. The possibility of selection bias cannot be excluded, as only 20% of screened patients were recruited. Nevertheless, similar proportions of those who were recruited were scheduled to undergo low-risk and medium-risk surgery, and the reasons for exclusion across surgical-risk groups were similar, which implies no bias was related to this feature. Patients scheduled to undergo orthopaedic surgery were more likely to be excluded from the trial by clinicians than those scheduled to undergo other procedures. Only ten orthopaedic patients were recruited and, therefore, our results might not be applicable to these patients in practice.

Perioperative management of patients with sickle-cell disease is complicated and is influenced by many factors specific to individual patients and operations. This study, however, showed that preoperative transfusion was associated with decreased risk of perioperative complications, especially acute chest syndrome, in patients with the haemoglobin SS subtype who underwent low-risk or medium-risk surgery (panel). We suggest, therefore, that preoperative transfusion to a haemoglobin concentration of about 100 g/L should be part of the standard management of these patients.

Contributors

SD conceived the study. JH, MM, CL, TJ, DCR, LT, IW, and LMW designed the study. JH and MM did the literature search. JH, MM, DCR, KF, and MK-A collected the data. Data management and cleaning were done by RH and LC and data analysis by LC, with advice from TJ. Economic health analysis was done by ES. SP did the laboratory analysis. Data interpretation was undertaken by JH, CL, LC, and LMW. JH, MM, CL, LC, and RH wrote and reviewed the paper. TJ gave advice on statistical analysis. TJ, DCR, LT, IW, KF, MK-A, SD, and LMW were involved in the writing, reviewing, or both, of the paper.

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Conflicts of interest

We declare that we have no conflicts of interest.

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