The Age of BLood Evaluation (ABLE) randomised controlled trial: description of the UK-funded arm of the international trial, the UK cost–utility analysis and secondary analyses exploring factors associated with health-related quality of life and health-care costs during the 12-month follow-up

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Scientific summary

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Scientific summary

Background

Donated red blood cells (RBCs) can be stored for up to 35 days in the UK (and up to 42 days in some countries). Historically, the shelf life of RBCs was established based upon biochemical standards and RBC survival studies were conducted in healthy volunteers. Despite the daily use of RBCs in hospitals worldwide, there was no high-quality clinical research to determine whether or not older stored RBCs deliver oxygen to tissues as effectively as fresher RBCs. Current standards for approval of RBC products are based on characteristics of the product, especially RBC survival in vivo at 24 hours, but not on the ability of cells to transport oxygen to tissues. Prior to the Age of BLood Evaluation (ABLE) trial, an accumulating body of laboratory and clinical research had raised the possibility that stored RBCs may be ineffective or may even have harmful effects on patients. None of this evidence was conclusive, but the signals seen in some uncontrolled observational clinical studies, together with the widespread use of RBC transfusions, meant that this research question was of vital importance to ensure RBCs are used safely and effectively in the future. The ABLE study was an international trial, led from Canada, which recruited patients in Canada, the UK, the Netherlands and France. The Health Technology Assessment (HTA) programme funded a UK-based arm of the study with the intention of contributing to international recruitment and undertaking a UK-specific health economic evaluation.

Objectives

The primary objective of the international ABLE trial was to determine whether or not, in critically ill adult patients requiring RBC transfusion, transfusing fresher RBCs stored for ≤ 7 days compared with standard-issue RBCs stored for up to 35 days decreases mortality, organ failures and new infections.

Additional objectives for the UK arm of the trial were to:

- establish whether or not, in critically ill adult patients, the use of RBCs stored for ≤ 7 days compared with standard-issue RBCs stored for up to 35 days improves health-related quality of life (HRQoL)
- establish the cost-effectiveness of transfusion using RBCs stored for ≤ 7 days compared with standard-issue RBCs stored for up to 35 days
- undertake a substudy comparing two measures of HRQoL, the EuroQol-5 Dimensions (EQ-5D), three-level version (EQ-5D-3L) and the five-level version (EQ-5D-5L), at 6 and 12 months post randomisation among survivors
- undertake an exploratory study of factors associated with HRQoL and health-care costs during 12 months' follow-up following critical illness.

Methods

Study design

The ABLE study was an international double-blind, multicentre, randomised clinical trial. Follow-up was to 6 months for survival only across the international cohort, but in the UK, follow-up was to 12 months post randomisation for survival; HRQoL and health-care resource use data were collected.

Study end points

Primary end point

Ninety-day all-cause mortality.

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Secondary end points

1. Intensive care unit (ICU) and hospital mortality; 28-day, 6- and 12-month mortality; survival times.
2. Number of organ failures developing; multiple organ dysfunction score; time to development of organ failure; highest number of organ failures per patient.
3. New infections (including nosocomial pneumonia, deep-tissue infections and bacteraemia).
4. Duration of respiratory, haemodynamic and renal support.
5. Length of hospital and ICU stay.
6. Adverse event rates, including transfusion reactions.
7. Health-related quality of life at 6 and 12 months, measured using the EQ-5D questionnaire.

Population

Inclusion criteria

All admissions to the ICU were potentially eligible for up to 7 days following admission and were tracked using screening logs for the following criteria.

1. The patient had a request for a first RBC unit transfusion in the ICU.
2. The patient had an anticipated length of invasive and/or non-invasive mechanical ventilation (MV) of at least 48 hours once enrolled, as estimated by the attending physician.

Exclusion criteria

Exclusion criteria were classified into clinical criteria and transfusion laboratory criteria.

Clinical criteria

1. Patients who were aged < 16 years.
2. Patients previously enrolled in the ABLE study.
3. Patients who had already been transfused with RBCs during the current hospitalisation.
4. Patients who had an obvious terminal illness documented in the medical record with a life expectancy of < 3 months.
5. Patients who had undergone routine cardiac surgical care.
6. Patients in whom a decision to withdraw/withhold critical care had been made (including patients with probable or proven brain death).

Transfusion laboratory criteria

1. No RBCs with a storage time of ≤ 7 days were available in the transfusion laboratory or could not be supplied for other reasons at the time of eligibility and potential randomisation.
2. Patients requiring urgent transfusion of > 1 unit of uncross-matched RBCs.
3. Patients who had a known objection to blood transfusions.
4. Patients who planned to receive autologous-donated RBCs.
5. Patients who posed difficulties in securing blood products (having a rare blood type) and were difficult to match.

Interventions

Patients were randomised to one of two groups, receiving either of:

1. Standard-issue RBCs (average storage age: 18–21 days). In this group, the blood bank provided RBCs according to its usual practice, which was typically to use group-specific blood towards the end of the stocked RBC age in order to minimise wastage.
2. Red blood cells stored for ≤ 7 days. In this group, the blood banks controlled the storage age of RBCs to provide the freshest available RBCs in the storage range of 2–7 days whenever possible.

The intervention lasted until hospital discharge or death, and RBCs were provided whenever blood transfusion was prescribed by clinicians.

Screening and consent

Patients were screened in the ICU by clinicians and research staff. The recruitment window started from the decision to transfuse RBCs, and its duration was largely determined by the urgency of transfusion. Consent required a flexible approach because the majority of participants lacked mental capacity, and included the consent of relatives, welfare guardians and professional consultees, in accordance with English and Scottish legal frameworks.

Randomisation and blinding

Randomisation was undertaken by research staff within the participating ICUs via a remote randomised system based in the Ottawa Health Research Centre. Group allocation was restricted to the hospital transfusion laboratory in order to maintain blinding of clinical and research teams in the ICU throughout the intervention. Allocation was stratified by trauma versus other critically ill patients, and by study centre. Randomisation comprised a computer-generated random listing of the treatment allocations using a pre-established minimisation algorithm. Only the study statistician and designate at the co-ordinating centre had knowledge of the randomisation codes.

All RBC units issued to patients had the expiry date (and date bled) concealed by application of an adhesive label by the transfusion laboratory technician/biomedical scientist prior to issue to patients. Accompanying documentation also had any expiry dates obscured.

Data collection

Baseline data included age, sex, hospital and ICU admission dates, type of admission, most responsible ICU admission diagnosis, Acute Physiology and Chronic Health Evaluation II (APACHE II) score at ICU admission, transfusion history during the 4 weeks prior to admission and significant comorbidities. Co-interventions administered at randomisation were recorded, including MV, dialysis/renal replacement therapy and cardiovascular support.

Hospital-based outcomes were collected by research staff from clinical records during hospitalisation. Outcomes at 6 and 12 months were collected via postal and telephone contacts using questionnaires for HRQoL (EQ-5D) and health resource use questionnaires. UK ICUs were randomised to use either the EQ-5D-3L or the EQ-5D-5L questionnaire for the evaluation of these different measurement tools in the critically ill population.

Results

The international trial cohort was recruited between March 2009 and May 2014 (with extension to October 2014 for UK patients included in the health economic evaluation). In the international trial, 2510 patients underwent randomisation; 80 (3.2%) had no primary outcome data, leaving 2430 patients (1211 in the group allocated to receive fresh blood and 1219 in the group allocated to receive standard-aged blood) in the intention-to-treat analysis. In total, 359 patients were recruited in the UK; 357 patients were included in the economic evaluation.

Baseline data were available for 2412 of the 2430 patients with primary outcome data. Of these 2430 patients, 94 (3.9%) did not receive any RBC transfusions. The mean age was 61.2 years [standard deviation (SD) ± 16.7 years] and 42.5% of patients had coexisting illnesses. The illness severity, based on the APACHE II score and requirement for organ support, was high [mean 21.8 (SD ± 7.6)] and the majority of patients had significant levels of organ dysfunction based on the multiple organ dysfunction syndrome [MODS; mean MODS score of 4.9 points (SD ± 3.1 points); 97.4% of patients were receiving MV, 28.1% were receiving renal replacement therapy and 62.8% were receiving vasoactive support]. Almost all

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patients were non-elective ICU admissions. The majority had a medical diagnosis (71.0%), most likely to be consistent with the non-eligibility of patients receiving blood transfusion prior to ICU admission, which excludes many surgical and trauma patients.

The mean pre-transfusion haemoglobin concentration was 7.69 g/dl (SD ± 1.28 g/dl) and 7.64 g/dl (SD ± 1.09 g/dl) for the groups receiving fresh and standard-aged blood, respectively. Patients received 4.3 RBC units (SD ± 5.2 RBC units) and 4.3 RBC units (SD ± 5.5 RBC units) in the groups receiving fresh and standard-aged blood, respectively. There was excellent separation of storage age profile: 6.1 days (SD ± 4.9 days) in the group allocated to receive fresh blood versus 22.0 days (SD ± 8.4 days) in the group allocated to receive standard-aged blood. The UK cohort was similar to the international cohort.

Primary outcome

In the international trial, at 90 days after randomisation, 37.0% (448/1211) of patients in the group allocated to receive fresh blood and 35.3% (430/1219) of patients in the group allocated to receive standard-aged blood had died {unadjusted absolute risk difference of 1.7% [95% confidence interval (CI) –2.1% to 5.5%; $p = 0.38$]; adjusted absolute risk difference 1.7% [–1.6% to 4.9%]}. Outcomes restricted to the UK cohort were similar: 32.4% (58/179) in the group allocated to receive fresh blood and 34.9% in the group allocated to receive standard-aged blood (61/175).

Secondary outcomes

The survival analysis of the time to death showed a hazard ratio in the group allocated to receive fresh blood, as compared with the group allocated to receive standard-aged blood, of 1.1 (95% CI 0.9 to 1.2; $p = 0.38$). No significant difference in mortality was observed between the groups on the basis of follow-up duration, age, number of units transfused, APACHE II score or admission category.

No significant differences were observed with respect to major illnesses, duration of respiratory, haemodynamic, or renal support, or length of stay in the ICU or hospital. There were also no differences in reported transfusion reactions.

The per-protocol analysis of the primary outcome that included only patients who received a transfusion showed no difference between the groups in the international trial. The sensitivity analysis of the primary outcome, in which the outcomes of patients in the group allocated to receive fresh blood who received only red blood cells that had been stored for ≤ 7 days were compared with the outcomes of patients in the group allocated to receive standard-aged blood who received red blood cells that had been stored for > 7 days, also showed no differences between the groups.

A separate analysis restricted to the patients recruited in the UK suggested that the outcomes were similar, and the effect sizes were very similar to the international cohort.

Cost–utility analysis

Taking missing data into account, the mean total costs per patient were £32,346 (95% CI £29,306 to £35,385; $n = 181$) in the group allocated to receive fresh blood, and £33,353 (95% CI £29,729 to £36,978; $n = 176$) in the group allocated to receive standard-aged blood. In both groups, approximately 85% of the total costs were incurred during the index hospital admission and 15% were incurred during follow-up. The mean utility values were similar for the two groups over time. The mean total quality-adjusted life-years (QALYs) per patient were 0.207 (95% CI 0.158 to 0.256) in the group allocated to receive fresh blood, and 0.213 (95% CI 0.170 to 0.257) in the group allocated to receive standard-aged blood.

There were no significant differences in costs between the two groups [mean incremental cost for the group allocated to receive fresh blood vs. the group allocated to receive standard-aged blood was –£231 (95% CI –£4876 to £4415)] or in outcomes [mean QALYs gained was 0.010 (95% CI –0.078 to 0.057)]. The incremental net monetary benefit for fresh blood versus standard-aged blood was not significantly

different from zero at a maximum willingness to pay for a QALY of £20,000 (mean £25; 95% CI –£4587 to £4637) and £30,000 (mean –£77; 95% CI –£4821 to £4666).

Comparison of EuroQol-5 Dimensions, three-level version and EuroQol-5 Dimensions, five-level version scores

After adjusting for patient characteristics, there were no significant differences in the conditional mean and median EQ-5D-3L and EQ-5D-5L utility scores at 6 months ($p \geq 0.17$), but there were significant differences at 12 months ($p < 0.05$): the mean EQ-5D-5L scores were 0.15 units higher than the EQ-5D-3L scores, and the median EQ-5D-5L scores were 0.20 units higher. However, the sample size was small and there were limited data to enable adjustment for potentially important confounding factors such as patient comorbidities.

Factors associated with health-care costs and health-related quality of life

None of the available covariates was a statistically significant predictor of utility scores at 6 or 12 months, or of QALYs up to 12 months, for either all patients or survivors only. However, the number of available covariates was limited, especially in relation to pre-existing and concurrent comorbidity and health status.

The majority (85%) of costs were incurred during the index hospitalisation. These were predicted by the severity of organ dysfunction and whether or not the patient died in the ICU. Controlling for whether or not the patient died, total costs increased with worsening MODS score by, on average, around £8000, £19,000 and £21,000 per patient for those with scores of 5–8, 9–12 and ≥ 13 points, respectively, compared with those with a score of 0–4 points. On average, the costs incurred by those who died were £30,000 lower costs than the costs incurred by those who survived, and those with prior chronic institutionalisation incurred total costs that were, on average, around £24,000 higher than those without chronic institutionalisation. None of the other covariates was individually statistically significant as a predictor of any of the cost measures, nor were they jointly significant when added to the models.

Conclusions

The ABLE trial found no clinically or statistically important benefit from transfusing exclusively RBCs stored for ≤ 7 days compared with the current standard practices used in blood banks for treating critically ill patients when a blood transfusion is required. There were no important differences between the UK cohort and the international cohort in patient characteristics or outcomes.

The cost–utility analysis (restricted to the UK and undertaken from a NHS perspective) showed that there were no differences in terms of costs and outcomes. The findings mean that there is no reason to prefer fresh blood to standard-aged blood on the basis of differences in quality or length of life, or on cost grounds.

Trial registration

This trial is registered as ISRCTN44878718.

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