Randomized clinical trial

Multicentre randomized clinical trial to investigate the cost-effectiveness of an allogeneic single-donor fibrin sealant after coronary artery bypass grafting (FIBER Study)

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Background: Reduction of blood transfusion in cardiac surgery is an important target. The aim of this study was to investigate the cost-effectiveness of the use of CryoSeal®, an allogeneic single-donor fibrin sealant, in patients undergoing coronary artery bypass grafting (CABG).

Methods: This randomized clinical study involved seven cardiac surgery centres in the Netherlands. Patients undergoing elective isolated CABG with the use of at least one internal thoracic artery (ITA) graft were assigned randomly to receive either CryoSeal® (5 ml per ITA bed) or no CryoSeal®. Primary efficacy endpoints were units of transfused red blood cells, fresh frozen plasma and platelet concentrates, and duration of intensive care unit stay. Secondary efficacy endpoints were 48-h blood loss, reoperation for bleeding, mediastinitis, 30-day mortality and duration of hospital stay.

Results: Between March 2009 and January 2012, 1445 patients were randomized. The intention-to-treat (ITT) population comprised 1436 patients; the per-protocol (PP) population 1292. In both the ITT and the PP analysis, no significant difference between the treatment groups was observed for any of the primary and secondary efficacy endpoints. In addition, no significant difference between the groups was seen in the proportion of transfused patients. Estimated CryoSeal® costs were €822 (95 per cent c.i. €808 to €836) per patient, which translated to €72 000 per avoided transfusion (unbounded 95 per cent c.i.).

Conclusion: The use of the fibrin sealant CryoSeal® did not result in health benefits. Combined with the high cost per avoided transfusion, this study does not support the implementation of routine CryoSeal® use in elective isolated CABG. Registration number: NTR1386 (http://www.trialregister.nl).

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Introduction

Transfusion of blood products is a common intervention in cardiac surgery but is not without risk. It is associated with increased in-hospital morbidity, including increased rates of renal failure, serious infection, prolonged ventilator support, atrial fibrillation and stroke, as well as increased in-hospital mortality[1]. In addition, blood transfusion has been associated with increased long-term mortality[2]. The relationship with early risk for adverse outcome appears to be dose-dependent, with transfusion of no more than 1–2 units of red blood cells (RBCs) already increasing risks after isolated coronary artery bypass grafting (CABG). Any reduction in blood transfusion during cardiac surgery is thus an important target to improve outcome and reduce healthcare costs[3].

During the past two decades, fibrin sealants have gained popularity as an adjunct to achieve haemostasis and reduce RBC transfusion in many surgical fields, including cardiac surgery[4]. Fibrin sealants are indicated for control of surgical bleeding when conventional interventions such as compression, ligation, clipping, suturing or electrocoagulation are insufficient. The application of fibrin sealants is generally considered clinically safe[5]. However, there are still concerns regarding the antigenicity of bovine thrombin or aprotinin used in the majority of commercially available fibrin sealants[6]. Furthermore, most fibrin sealants are produced from pooled plasma, which is associated with an increased viral or prion risk. The use of an autologous fibrin sealant in cardiac surgery, on the other hand, may be associated with variable quality arising from co-morbidities.

The fibrin sealant CryoSeal® (Sanquin Blood Supply Foundation, Amsterdam, The Netherlands) is produced from an allogeneic, single, non-remunerated volunteer donor without the addition of antifibrinolytics, and may therefore have potential advantages[7]. CryoSeal® fibrin sealant has not been studied in cardiac surgery previously. In CABG, use of the left internal thoracic artery (ITA) is universally accepted. Evidence from several studies suggests that bilateral ITA grafting prolongs survival[8,9]. However, not only has the use of a single ITA graft been associated with increased mediastinal drainage compared with the exclusive use of saphenous vein grafts[10], but also bilateral ITA grafting is associated with increased postoperative blood loss compared with single ITA grafting[11]. The aim of this study was to investigate the cost-effectiveness of the use of CryoSeal® in patients undergoing elective isolated CABG with the use of single or bilateral ITA grafts.

Methods

The FIBER (Fibrin sealant Induced Blood Exposure Reduction) Study was a multicentre randomized clinical study involving seven cardiac surgery centres in the Netherlands. The trial was performed in accordance with the Declaration of Helsinki, the ethical principles of the International Conference on Harmonization Good Clinical Practice and relevant Dutch laws, and was approved by the ethics committee of the Leiden University Medical Centre, followed by the relevant local ethics committees. All patients provided written informed consent before entering in the study. A steering committee was responsible for organizing the study, executing data analysis and writing the paper.

Inclusion and randomization

Patients undergoing elective isolated CABG (either on-pump or off-pump) with the use of at least one ITA graft were eligible. Exclusion criteria were: CABG with exclusive use of saphenous vein grafts; any concomitant procedure including ablation for atrial fibrillation; emergency surgery; history of bleeding diathesis or coagulopathy; Jehovah's Witness; participation in any other study involving an investigational drug or device; and inability of the patient to understand the study information. Once patients had signed a consent form, they were randomized by calling the trial manager. In this telephone call, information about the intended procedure (use of single or bilateral ITA) was requested in order to receive a sufficient amount of CryoSeal® fibrin sealant (5 ml for each ITA bed) if randomized to CryoSeal® treatment. Patients were assigned randomly at a ratio of 1 : 1 to either treatment with CryoSeal® fibrin sealant or no CryoSeal® treatment (control group), stratified according to study site.

Investigational product

CryoSeal® is an allogeneic single-donor fibrin sealant produced from fresh frozen quarantined plasma from donations of non-remunerated volunteers. It is produced by the Sanquin Blood Bank[12] using disposables provided by Recuperate Medical (Recuperate Medical, Haren, The Netherlands). CryoSeal® consists of two components: cryoprecipitate and thrombin. Cryoprecipitate is the fraction of human plasma that contains concentrated coagulation factors, such as fibrinogen, fibronectin, plasminogen, factor VIII, factor XIII and von Willebrand factor. Owing to the low levels of plasminogen, CryoSeal® does not require an artificial fibrinolysis inhibitor (such as aprotinin, sourced from bovine lung tissue, or tranexamic acid).

Safety and toxicology

The single-donor plasma was tested routinely for hepatitis C virus, hepatitis B virus, human immunodeficiency virus 0–2, human T-lymphotropic virus 1/2, *Treponema pallidum* haemagglutination assay, and parvovirus B19 at donation. It was retested after a quarantine period of at least 6 months before processing to CryoSeal®, thereby virtually excluding the plasma as a source of infectious disease transmission to the recipients.

Given the origin of CryoSeal® (no pooled plasma and no addition of bovine or chemical fibrinolysis inhibitors), no toxicity was expected. However, CryoSeal® is a blood product and adverse transfusion reactions may occur.

Feasibility in coronary artery bypass grafting

To study the feasibility of CryoSeal® use in CABG, a pilot study was done in the Department of Cardiothoracic Surgery, Leiden University Medical Centre. The study included 40 consecutive patients who had elective isolated CABG, either on-pump or off-pump. It was concluded that CryoSeal® can best be applied to the ITA bed in this population. No side-effects or postoperative complications were reported in the feasibility study.

Surgical procedure and application of CryoSeal®

Surgical techniques were used according to the local standards. After sternotomy, harvesting of the ITA, pedicled or skeletonized, was carried out simultaneously with saphenectomy (if applicable). Cardioplegic arrest, when applicable, was done either by use of cold crystalloid solution or by warm or cold blood cardioplegia. The surgeon was blinded to treatment group allocation until near the end of the operation. For each randomized patient, a cooling box was delivered to the operating room containing either CryoSeal® or no CryoSeal®. The handling of CryoSeal® was taught by video instruction before the study. The cooling box was not opened until 30 min before use of CryoSeal®, which had to be applied after the administration of protamine. In this way, the routine achievement of haemostasis during surgery was influenced minimally. CryoSeal® had to be thawed at 40°C for at least 20 min before use. After the administration of protamine, patients assigned to the study group were treated with a maximum of 15 ml CryoSeal® each. For each ITA bed, 5 ml CryoSeal® was used. CryoSeal® was applied with the use of a spray tip mounted on a 5-ml syringe. Any remaining fibrin sealant could be used on anastomoses, cannulation sites and any other part of the surgical field, at the discretion of the surgeon. The chest was then closed routinely. All CryoSeal® not used during the operation was returned to the local Hospital Blood Transfusion Services to record the amount of fibrin sealant applied to each patient. Surgeons had the discretion to use additional tranexamic acid, but use of other fibrin sealants was not allowed.

Transfusion policy

Blood transfusion practice was based on the transfusion guidelines of the American Society of Anesthesiologists[13] and the Dutch Institute for Healthcare Improvement[14]. The Dutch guidelines support a fairly restrictive transfusion policy. They recommend RBC transfusion when the haemoglobin level is less than 7 g/dl, and advise against transfusion when the level is above 9 g/dl. When the haemoglobin concentration is above 7 g/dl and less than 9 g/dl, the transfusion trigger is determined by blood loss, cardiopulmonary reserve, age and/or co-morbidity. Management was at the discretion of the treating physician.

Efficacy endpoints

The primary efficacy endpoints were number of transfused blood products (RBCs, fresh frozen plasma (FFP) and platelet concentrates (PCs)) up to 48 h after surgery and duration of stay in the intensive care unit (ICU). Secondary efficacy endpoints included the amount of blood loss within 48 h after surgery, reoperation for bleeding, mediastinitis, 30-day mortality and duration of hospital stay.

Safety and safety reporting

Prespecified serious adverse events (SAEs) were myocardial infarction, stroke, mediastinitis, reoperation for ischaemia and 30-day mortality. Myocardial infarction was defined as presence of at least two of the following: ischaemic chest pain lasting for more than 20 min; changes in serial electrocardiogram (ECG) tracings; and troponin T level above 1 μg/l. Stroke was defined as a new persistent cerebrovascular event leading to a neurological deficit being diagnosed by a neurologist. Diagnosis of mediastinitis required positive substernal tissue cultures. Reoperation for ischaemia was defined when there was a need for reoperation based on changes in serial ECG tracings and troponin T level above 1 μg/l. Each SAE had to be recorded on a SAE form and sent to the coordinating principal investigator. SAEs were reported to the local ethics committee, according to local requirements.

Other recorded adverse events (AEs) included low cardiac output syndrome, ventilation for more than 48 h, sepsis, pneumonia, renal insufficiency, atrial fibrillation, ventricular fibrillation, transient ischaemic attack, superficial wound infection and reoperation for bleeding.

Data safety monitoring board

An independent data safety monitoring board (DSMB) was established to protect the safety and welfare of the patients. The DSMB was blinded to group allocation when assessing the interim report data.

Statistical analysis

To demonstrate CryoSeal® to be cost-effective, a treatment effect of a 50 per cent reduction in the number of RBC transfusions and a 0·4-day reduction in duration of ICU stay was needed. The power calculation based on this treatment effect, a power of 90 per cent, and an α level of 0·05 (two-sided test), showed that the minimum size per treatment group should be 500 patients. It was planned to enrol approximately 750 patients per group to allow for violations of the protocol, non-evaluable patients, patient withdrawal from the study, and reliable preplanned subgroup analysis.

A planned interim analysis was conducted by the DSMB after 1000 patients had been randomized and complete ICU data had been recorded for at least 90 per cent of those patients. The interim analysis was intended as both a safety assessment and a superiority analysis. For statistical stopping boundaries, the Haybittle–Peto approach was used, which requires $P < 0{\cdot}001$ as evidence required to consider stopping the trial[15]. A futility analysis was not considered in order to ensure an adequate sample size to perform planned subgroup analyses.

Efficacy and safety analyses

Efficacy and safety analyses were conducted for all randomized patients (intention-to-treat (ITT) population) and for randomized patients who completed the study according to the protocol (per-protocol (PP) population).

Heterogeneity in treatment effect across the seven study sites was examined for all primary efficacy endpoints using ANOVA or logistic regression analysis, as appropriate. These analyses were conducted by including interaction terms for treatment and study site. Heterogeneity was assumed to be present in case of a statistically significant treatment × study site interaction effect. Once no heterogeneity had been demonstrated, differences in efficacy outcomes between the two treatment groups were tested for continuous variables using Student's t test for independent samples. Comparison of categorical variables was performed with Pearson's χ^2 test or Fisher's exact test, as appropriate.

The robustness of results for alternative population specifications (subgroup analysis) was tested in a similar way to that for study site. There were four predefined subgroup variables: sex, preoperative use of antiplatelet medication within 5 days of surgery (yes or no), use of cardiopulmonary bypass (CPB; yes or no), and use of single *versus* bilateral ITA. When a significant treatment × subgroup interaction was detected, a subgroup analysis was conducted for the respective primary efficacy endpoint.

For safety analysis, the treatment effect on safety measures was tested by univariable binary logistic regression analysis. Odds ratios and 95 per cent c.i. were computed with the no-CryoSeal® treatment group as reference.

All statistical tests were two-sided. $P < 0{\cdot}050$ was considered statistically significant.The statistical analyses were performed using SPSS® software version 20.0 (IBM, Armonk, New York, USA).

Economic evaluation

The economic evaluation consisted of a cost-minimization analysis, from the hospital perspective and with a time frame from the day of surgery to discharge. No detectable cost differences were expected in non-hospital or other societal costs, or beyond the duration of hospitalization. Included cost categories were CryoSeal® use, blood products, hospitalization and reoperations.

Costs of CryoSeal® use were estimated at €705 and €1080 for surgery with one and two ITAs respectively (based on the use of 9 and 14 ml of CryoSeal®, a market price of €75 per ml, and 2 additional min of operating time, valued at €15 per min[16]). The product costs were counted regardless of whether the patient received the CryoSeal®; additional operating time was included only if the patient actually received the CryoSeal®.

Costs of blood products were estimated using unit prices in the Netherlands in 2012: €215 for RBCs, €185 for FFP and €519 for PCs[17,18]. To account for compatibility tests and hospital handling costs, the unit price for RBCs was multiplied by a factor of 4, and the unit prices of FFP and PCs by a factor of 2[19].

Costs of hospitalization were estimated using standard prices, at €2288 per ICU day and €490 per non-ICU day[13]. Reoperation for ischaemia, reoperation for bleeding and treatment of mediastinitis were valued at €4000, €2000 and €3000 respectively.

Average costs were compared according to ITT, using unequal-variance t test, multiple imputations to account for missing data (rendering slight differences compared with the efficacy analysis), and at 2012 price level. A cost-effectiveness analysis was performed using cost-effectiveness acceptability curves, comparing the difference in the proportion of transfused patients with the difference in costs[20].

Results

Between March 2009 and January 2012, a total of 1445 patients were included in the study (*Fig. 1*). Nine patients withdrew consent or had incomplete data. Thus, the ITT population comprised 1436 patients: 722 (50·3 per cent) were randomized to CryoSeal® and 714 (49·7 per cent) to no CryoSeal®. There were 144 protocol violations: 113 in the CryoSeal® group and 31 in the no-CryoSeal® group, resulting in a PP population of 1292 patients: 609 and 683 respectively. Protocol violations included treatment with less than the required amount of fibrin sealant (98 patients), treatment with CryoSeal® although randomized to no sealant (6), other than isolated CABG surgery (32) and other reason (8). The two groups were similar with respect to baseline demographic, clinical and surgical characteristics, except for the use of CPB ($P = 0{\cdot}011$ and $P = 0{\cdot}005$ in the ITT and PP population respectively) (*Table 1*).

Primary and secondary efficacy outcomes

In both the ITT and the PP analysis, no significant difference between the treatment groups on any of the primary and secondary efficacy endpoints was observed. In addition, no significant difference between the groups was seen in the proportion of patients transfused with blood products (*Table 2*).

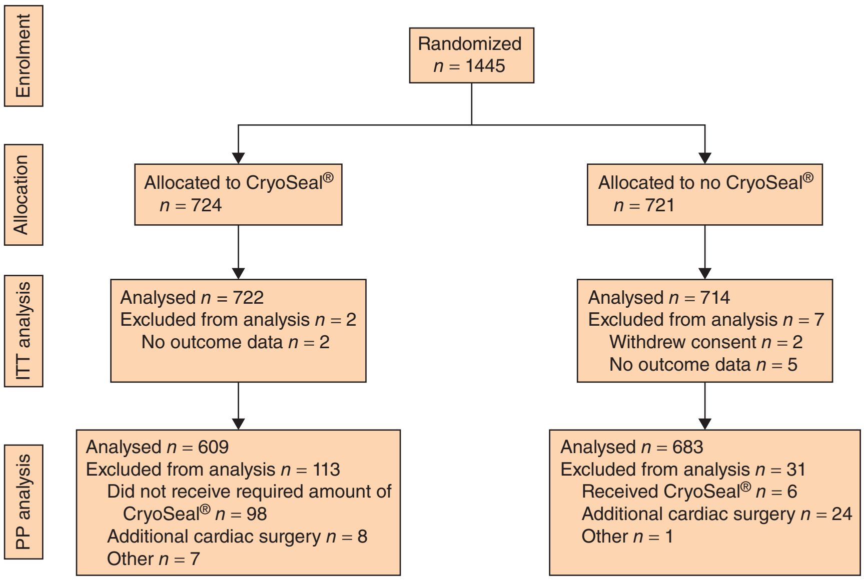

Fig. 1 CONSORT diagram for the trial. ITT, intention-to-treat; PP, per-protocol

Table 1 Baseline demographic, clinical and surgical characteristics

	Intention-to-treat analysis		Per-protocol analysis		
	CryoSeal® (*n* = 722)	No CryoSeal® (*n* = 714)	CryoSeal® (*n* = 609)	No CryoSeal® (*n* = 683)	*P*‡
Demographics					
Age (years)*	65·7(9·7)	65·1(10·0)	65·4(9·8)	65·1(9·9)	0·554§
Female sex	126 (17·5)	136 (19·0)	110 (18·1)	128 (18·7)	0·754
Co-morbidity					
Myocardial infarction	277 (38·4)	272 (38·1)	232 (38·1)	255 (37·3)	0·778
LV function < 30%	17 (2·4)	17 (2·4)	16 (2·6)	17 (2·5)	0·875
Previous cardiac surgery	18 (2·5)	13 (1·8)	13 (2·1)	12 (1·8)	0·623
Previous PCI	148 (20·5)	133 (18·6)	127 (20·9)	125 (18·3)	0·248
Hypertension	409 (56·6)	398 (55·7)	344 (56·5)	378 (55·3)	0·680
Diabetes	192 (26·6)	174 (24·4)	160 (26·3)	169 (24·7)	0·529
COPD	65 (9·0)	67 (9·4)	54 (8·9)	66 (9·7)	0·623
Renal insufficiency	45 (6·2)	37 (5·2)	36 (5·9)	37 (5·4)	0·701
Logistic EuroSCORE*	3·4(3·5)	3·3(3·3)	3·4(3·5)	3·3(3·3)	0·634§
Preop. medication					
Anticoagulants within 5 days	20 (2·8)	12 (1·7)	14 (2·3)	11 (1·6)	0·370
Antiplatelets within 5 days	463 (64·1)	460 (64·4)	395 (64·9)	439 (64·3)	0·826
Preop. laboratory data					
Haemoglobin (mmol/l)*	8·7(0·9)	8·7(0·9)	8·7(0·9)	8·7(0·9)	0·799§
Haematocrit (%)*	41·5(4·2)	41·4(4·1)	41·4(4·1)	41·5(4·1)	0·767§
Platelets ($\times 10^9$/l)*	243·5(73·6)	243·6(72·5)	245·0(73·7)	243·5(72·3)	0·702§
Prothrombin time (s)*†	13·6(3·2)	13·4(2·7)	13·6(2·8)	13·4(2·6)	0·179§
APTT (s)*†	31·5(7·4)	31·0(5·8)	31·7(7·4)	31·0(5·8)	0·112§
Surgery					
Use of 2 ITAs	292 (40·4)	298 (41·7)	242 (39·7)	294 (43·0)	0·228
Use of CPB	615 (85·2)	640 (89·6)	514 (84·4)	612 (89·6)	0·005
Time for CPB, when used (min)*	97·6(33·9)	100·2(36·4)	97·4(31·6)	99·2(34·8)	0·380§
Use of tranexamic acid	610 of 708 (86·2)	620 of 699 (88·7)	517 of 599 (86·3)	593 of 669 (88·6)	0·210

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †Data were collected as part of standard care and are missing for 91–117 patients. LV, left ventricular; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; APTT, activated partial thromboplastin time; ITA, internal thoracic artery; CPB, cardiopulmonary bypass. ‡Pearson's χ^2 test, except §Student's *t* test.

Table 2 Primary and secondary efficacy endpoints

	Intention-to-treat analysis				Per-protocol analysis			
	CryoSeal® (*n* = 722)	No CryoSeal® (*n* = 714)	Difference in mean values or OR†	*P*‡	CryoSeal® (*n* = 609)	No CryoSeal® (*n* = 683)	Difference in mean values or OR†	*P*‡
Primary endpoints								
Blood product usage								
RBCs (units)*	0·57(1·38)	0·59(1·52)	−0·02 (−0·17, 0·14)	0·844§	0·57(1·37)	0·54(1·38)	0·03 (−0·13, 0·18)	0·741§
RBCs (patients transfused)	179 (24·9)	179 (25·1)	0·99 (0·78, 1·25)	0·915	153 (25·2)	166 (24·4)	1·05 (0·81, 1·35)	0·730
FFP (units)*	0·27(0·82)	0·32(1·10)	−0·05 (−0·15, 0·05)	0·345§	0·25(0·77)	0·28(0·97)	−0·03 (−0·13, 0·06)	0·496§
FFP (patients transfused)	93 (12·9)	92 (12·9)	1·00 (0·74, 1·36)	0·994	75 (12·4)	81 (11·9)	1·04 (0·75, 1·46)	0·800
Platelets (units)*	0·19(0·50)	0·20(0·55)	−0·01 (−0·06, 0·05)	0·787§	0·20(0·50)	0·18(0·48)	0·02 (−0·04, 0·07)	0·561§
Platelets (patients transfused)	117 (16·3)	115 (16·2)	1·01 (0·76, 1·34)	0·951	105 (17·3)	107 (15·7)	1·12 (0·84, 1·51)	0·444
Any blood product	249 (34·6)	252 (35·4)	0·97 (0·78, 1·20)	0·763	212 (34·9)	237 (34·8)	1·01 (0·80, 1·27)	0·963
Duration of ICU stay (h)*	31·4(46·9)	34·5(58·9)	−3·1 (−8·6, 2·4)	0·267§	31·2(44·7)	34·5(60·0)	−3·3 (−9·1, 2·4)	0·251§
Secondary endpoints								
Blood loss within 48 h (ml)*	809(542)	817(692)	−8 (−73, 56)	0·796§	802(508)	810(684)	8 (−73, 58)	0·823§
Reoperation for bleeding	21 (2·9)	23 (3·2)	0·90 (0·49, 1·64)	0·731	19 (3·1)	19 (2·8)	1·13 (0·59, 2·15)	0·719
Mediastinitis	10 (1·4)	5 (0·7)	1·99 (0·68, 5·85)	0·203	9 (1·5)	5 (0·7)	2·03 (0·68, 6·09)	0·197
30-day mortality	7 (1·0)	8 (1·1)	0·86 (0·31, 2·40)	0·779	6 (1·0)	8 (1·2)	0·84 (0·29, 2·43)	0·747
Duration of postoperative hospital stay (days)*	5·99(3·95)	6·07(4·21)	−0·08 (−0·51, 0·34)	0·710§	5·81(3·44)	6·01(4·23)	−0·20 (−0·62, 0·23)	0·362§

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.) and †values in parentheses are 95 per cent c.i. Data are missing for some variables, for a maximum of three patients. OR, odds ratio; RBCs, red blood cells; FFP, fresh frozen plasma; ICU, intensive care unit. ‡Pearson's χ^2 test, except §Student's *t* test.

Table 3 Serious adverse events and adverse events

	Intention-to-treat analysis				Per-protocol analysis			
	CryoSeal® (*n* = 722)	No CryoSeal® (*n* = 714)	Odds ratio*	*P*†	CryoSeal® (*n* = 609)	No CryoSeal® (*n* = 683)	Odds ratio*	*P*†
Serious adverse events								
Myocardial infarction	18 (2·5)	26 (3·6)	0·68 (0·37, 1·24)	0·208	14 (2·3)	24 (3·5)	0·65 (0·33, 1·26)	0·199
Stroke	4 (0·6)	3 (0·4)	1·32 (0·29, 5·91)	0·718	4 (0·7)	3 (0·4)	1·50 (0·33, 6·71)	0·599
Mediastinitis	10 (1·4)	5 (0·7)	1·99 (0·68, 5·85)	0·212	9 (1·5)	5 (0·7)	2·03 (0·68, 6·09)	0·197
Reoperation for ischaemia	2 (0·3)	4 (0·6)	0·49 (0·09, 2·70)	0·451	2 (0·3)	4 (0·6)	0·56 (0·10, 3·07)	0·503
30-day mortality	7 (1·0)	8 (1·1)	0·86 (0·31, 2·40)	0·779	6 (1·0)	8 (1·2)	0·84 (0·29, 2·43)	0·747
Adverse events								
Low cardiac output syndrome	15 (2·1)	18 (2·5)	0·82 (0·41, 1·64)	0·573	13 (2·1)	18 (2·6)	0·81 (0·39, 1·66)	0·555
Ventilation time > 48 h	12 (1·7)	3 (0·4)	4·00 (1·12, 14·24)	0·032	7 (1·1)	3 (0·4)	2·63 (0·68, 10·22)	0·162
Sepsis	2 (0·3)	2 (0·3)	0·99 (0·14, 7·03)	0·990	1 (0·2)	2 (0·3)	0·56 (0·05, 6·18)	1·000
Pneumonia	16 (2·2)	15 (2·1)	1·06 (0·52, 2·15)	0·884	11 (1·8)	13 (1·9)	0·95 (0·42, 2·13)	0·894
Renal insufficiency	19 (2·6)	13 (1·8)	1·46 (0·71, 2·97)	0·302	16 (2·6)	13 (1·9)	1·39 (0·66, 2·91)	0·385
Atrial fibrillation	212 (29·4)	213 (29·9)	0·98 (0·78, 1·23)	0·845	167 (27·5)	201 (29·5)	0·91 (0·71, 1·16)	0·427
Ventricular fibrillation	11 (1·5)	4 (0·6)	2·75 (0·87, 8·67)	0·085	9 (1·5)	4 (0·6)	2·55 (0·78, 8·31)	0·121
Transient ischaemic attack	0 (0)	3 (0·4)	–	0·122‡	0 (0)	3 (0·4)	–	0·252‡
Wound infection, superficial	5 (0·7)	9 (1·3)	0·55 (0·18, 1·64)	0·279	3 (0·5)	9 (1·3)	0·37 (0·10, 1·37)	0·137
Reoperation for bleeding	21 (2·9)	23 (3·2)	0·90 (0·49, 1·64)	0·731	19 (3·1)	19 (2·8)	1·13 (0·59, 2·15)	0·719

Values in parentheses are percentages unless indicated otherwise; *values in parentheses are 95 per cent c.i. Data are missing for some variables, for a maximum of two patients. †Univariable binary logistic regression analysis, except ‡Fisher's exact test.

Subgroup analysis

ANOVA or logistic regression analysis for the primary efficacy outcomes revealed only significant treatment × subgroup interaction effects for the subgroup variable use of CPB. For this subgroup variable, significant interaction effects were found for the proportion of patients transfused with FFP ($P = 0·027$), units of transfused PCs ($P = 0·038$), the proportion of patients transfused with PCs ($P = 0·014$) and duration of ICU stay ($P = 0·035$). In the subgroup of patients who had surgery off-pump, significant differences between treatment groups were found for the proportion of patients transfused with FFP ($P = 0·020$), units of transfused PCs ($P = 0·036$) and the proportion of patients transfused with PCs ($P = 0·014$) in the ITT analysis. In the PP analysis, however, these significant differences disappeared. No significant differences between the treatment groups were found in the on-pump CABG subgroup.

Table 4 Estimated postoperative hospital costs (by randomization and intention-to-treat analysis)

	Volumes of care		Costs (€)		
	CryoSeal® (*n* = 722)	No CryoSeal® (*n* = 714)	CryoSeal® (*n* = 722)	No CryoSeal® (*n* = 714)	*P*†
Use of CryoSeal®	642 (88·9)	6 (0·8)	822	0	< 0·001
Blood products					
RBCs	181 (25·1)	180 (25·2)	1200	1208	0·896
FFP	95 (13·2)	93 (13·0)	443	459	0·342
Platelets	119 (16·5)	116 (16·3)	1123	1141	0·380
Proportion of transfused patients	252 (34·9)	253 (35·5)			
Hospitalization (days)*					
ICU care	1·32	1·45	3010	3307	0·272
Non-ICU care	7·04	7·09	3454	3478	0·818
Interventions during hospitalization					
Reoperation for ischaemia	2 (0·3)	4 (0·6)	11	22	0·407
Reoperation for bleeding	21 (2·9)	23 (3·2)	58	64	0·731
Treatment of mediastinitis	10 (1·4)	5 (0·7)	42	21	0·201
Total costs (€)			10 163	9702	0·202

Values in parentheses are percentages unless indicated otherwise; *mean values. RBCs, red blood cells; FFP, fresh frozen plasma; ICU, intensive care unit. †Unequal-variance *t* test.

Safety

Except for the duration of mechanical ventilation exceeding 48 h in the ITT analysis ($P = 0·032$), there were no significant differences between the groups in the rate of SAEs and AEs (*Table 3*).

Economic evaluation

Of 722 patients randomized to CryoSeal®, 642 (88·9 per cent) actually received this intervention. Estimated CryoSeal® costs were €822 (95 per cent c.i. €808 to €836) per patient. Other cost categories showed no statistically significant differences, in line with the lack of impact that CryoSeal® use had on clinical outcome (*Table 4*). The overall cost difference was estimated at €461 (95 per cent c.i. €−247 to €1170) per patient.

Whether use of CryoSeal® in CABG is cost-effective depends on the willingness to pay to avoid blood transfusion. Use of CryoSeal® resulted in a 0·6 per cent estimated decrease in the proportion of transfused patients (from 35·5 to 34·9 per cent), which translates the estimated cost difference to €72 000 per avoided transfusion (with unbounded 95 per cent c.i.). *Fig. 2* shows the probability that use of CryoSeal® is cost-effective compared with no CryoSeal®, conditional on the willingness-to-pay per avoided transfusion. For willingness-to-pay of up to €10 000 per avoided transfusion, CryoSeal® is, at most, 21 per cent likely to be cost-effective. Restricting the cost analysis only to the costs of CryoSeal® (the only significantly different cost category), CryoSeal® use is even less likely to be cost-effective (*Fig. 2*).

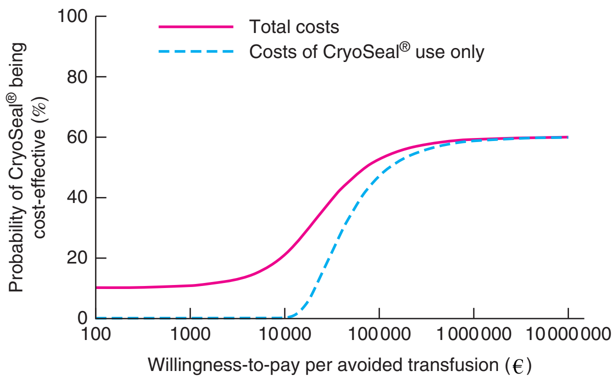

Fig. 2 Cost-effectiveness acceptability curves: probability that CryoSeal® is cost-effective compared with no CryoSeal®, conditional on the willingness-to-pay per avoided transfusion

Discussion

In this multicentre study performed in the Netherlands, use of the fibrin sealant CryoSeal® as an adjunct to achieve haemostasis in patients undergoing elective isolated CABG with ITA grafting was not associated with a reduction in blood transfusion. The numbers of transfused units of RBCs, FFP and PCs were not significantly different between the patients randomized to treatment with CryoSeal® and patients randomized to no fibrin sealant. The duration of ICU stay and the secondary efficacy outcomes also showed no significant differences between the two treatment groups. In line with this lack of impact of CryoSeal® on outcomes, there was no significant difference between the groups for any of the predefined cost categories (blood product usage, hospitalization, reoperation for ischaemia or bleeding, and treatment of mediastinitis), other than the costs of the sealant itself.

The sample size calculation was based on a treatment effect of a 50 per cent reduction in RBC transfusion. The control group, however, showed a mean number of only 0·6 RBC units transfused per patient. The mean numbers of units of transfused FFP and PCs were even lower. Studies on blood transfusion usage in CABG continue to show considerable variation. An average of approximately 2 units of RBCs transfused per patient has been reported in studies[21–23] from different continents, whereas the mean blood loss in these studies appeared to be similar to that in the present study. This obvious difference in transfusion practice for CABG may reflect an enhanced implementation of blood conservation techniques in the Netherlands. Here, intraoperative blood salvage and blood-sparing interventions, as well as restricted blood transfusion algorithms, have become standard practice recently. This raises the question of how the complementary use of a fibrin sealant could be cost-effective when effective blood conservation strategies are used. It should be noted, however, that the effectiveness of CryoSeal® could not be demonstrated by comparing postoperative blood loss between the treatment groups in the present study.

Risk factors for postoperative blood loss and transfusion in CABG include female sex, use of antiplatelet drugs within 5 days before surgery, use of CPB and use of bilateral ITA[24,25]. Planned subgroup analyses were undertaken in subgroups based on these four variables. Only in the subgroup of patients who had surgery off-pump did the ITT analysis show significant differences in blood transfusion between the treatment groups, in favour of CryoSeal®. This potential effectiveness of the fibrin sealant in off-pump CABG procedures might be explained by the fact that during CPB the coagulation profile is more severely affected. CPB is known to be associated with haemodilution by the pump prime, resulting in anaemia, reduced fibrinogen and platelet levels, and platelet dysfunction[26]. Furthermore, an increase in thrombin formation has been described after the release of the aortic cross-clamp by liberating blood from the myocardium and pulmonary vascular bed[27]. The coagulation profile in on-pump patients might be so disturbed that CryoSeal® cannot compensate. In off-pump patients, on the other hand, the coagulation profile is changed minimally[28], and the use of fibrin sealant may have contributed to preventing postoperative haemorrhagic complications. It should be noted, however, that the significant effects in the ITT analysis were not confirmed by the PP analysis.

The use of fibrin sealants in cardiac surgery is generally considered to be safe, and their use has increased substantially since their commercial introduction 20 years ago. Recently, however, concerns about early graft occlusion after CABG have been reported based on clinical studies. In these studies[29,30], an increased risk of myocardial infarction and even 30-day mortality after the use of Tissucol® fibrin sealant (Baxter, Vienna, Austria) was observed. These deleterious effects were thought to be associated with inadequate application of Tissucol® – insufficient mixing of its components and spray application directly on to bypass graft anastomoses. The retrospective character of these studies, however, precluded a definitive conclusion on the safety of Tissucol®. Although safety was not the main purpose of the present study, no significant differences were found between the treatment groups in the occurrence of SAEs and AEs, except that with CryoSeal® the duration of mechanical ventilation more frequently exceeded 48 h in the ITT analysis.

Related specifically to use in CABG, the application site of fibrin sealant and the amount given are often not clearly documented in the literature. In the present study a standard treatment regimen was followed, requiring 5 ml CryoSeal® per ITA bed. The rationale for this was that the ITA graft is a risk factor for haemorrhage after CABG. It has been reported[31] that, in patients having an ITA harvested, the ITA or its bed was the main cause of bleeding in 43 per cent. Not only has single ITA grafting been linked to an increased bleeding risk compared with the use of only saphenous vein grafts[10], but also bilateral ITA grafting increases the risk of bleeding compared with single ITA grafting[11]. Furthermore, based on the pilot study, it was established that the application of 5 ml CryoSeal® was the optimal amount to cover the entire ITA bed.

Whether a strategy of blood management is cost-effective depends on willingness to pay to avoid transfusion. The present cost analysis was performed from a hospital perspective, including costs of CryoSeal®, blood products, hospital stay and complications related to postoperative bleeding. Prices vary by country and by centre; the present study used prices for blood products and hospitalization that are specific to the Dutch context, which may not be representative elsewhere. Yet, the study showed no differences between the treatment groups in the respective types of care; therefore, the conclusion of the analysis would not change if other prices were used. For the CryoSeal® fibrin sealant, a price was used that may underestimate the true costs: it included a realistic price for the product itself, but only a relatively small surcharge of €30 to account for the approximately 2 min additional surgery time. Implementation and other in-hospital handling costs were neglected, so the economic evaluation is biased in favour of CryoSeal®. For reasonable willingness-to-pay per avoided transfusion, the fibrin sealant CryoSeal® is unlikely to be cost-effective.

A limitation of this study was the lack of blinding with the possible risk of surgeons' performance bias. This limitation seems unavoidable, as the use of a placebo fibrin sealant is hardly feasible. However, to minimize the influence on routine haemostasis, a cooling box was used in every patient that was opened only 30 min before the end of surgery. Furthermore, although number of blood transfusions required is an objective efficacy measure, it is influenced by transfusion policy. Using a restrictive transfusion policy, as has become standard practice in the Netherlands, effectiveness of CryoSeal® treatment may not be detected. However, even if blood loss had been used as an endpoint in this study, there would be no evidence for the effectiveness of CryoSeal®.

There is limited research on the use of fibrin sealants in cardiac surgery. The majority of controlled studies suggest that fibrin sealants are efficacious in reducing postoperative blood loss and RBC transfusion. However, previous large studies in this area were retrospective, and prospective studies had small numbers[32]. Evidence of efficacy is only a first step in evaluating whether fibrin sealants are appropriate for clinical use[33]. So far there are no large randomized clinical studies on the cost-effectiveness of a fibrin sealant in CABG.

This multicentre randomized clinical trial demonstrated that the use of the fibrin sealant CryoSeal® in elective isolated CABG procedures was not cost-effective. There were no health benefits. In combination with the high costs per avoided transfusion, this study does not support the implementation of routine CryoSeal® use in elective isolated CABG.

Collaborators

Local principal investigators in the FIBER study were: G. Tavilla (Leiden University Medical Centre, Leiden; 565 randomized patients; Radboud University Medical Centre; 275 patients), R. C. A. Meijer (University Medical Centre Utrecht; 199 patients); M. A. Keyhan-Falsafi (Haga Hospital, The Hague; 179 patients), P. S. Eggens, M. Bentala (Amphia Hospital, Breda; 141 patients), J. G. Maessen (University Hospital Maastricht; 77 patients) and R. Cocchieri (Academic Medical Centre, Amsterdam: 9 patients).

Members of the DSMB were: H. R. Büller (chair); R. J. de Haan and A. P. Kappetein; for interim analysis only, R. Brand (statistician).

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